Textbook of Epilepsy Surgery

Edited by
Hans O Lüders

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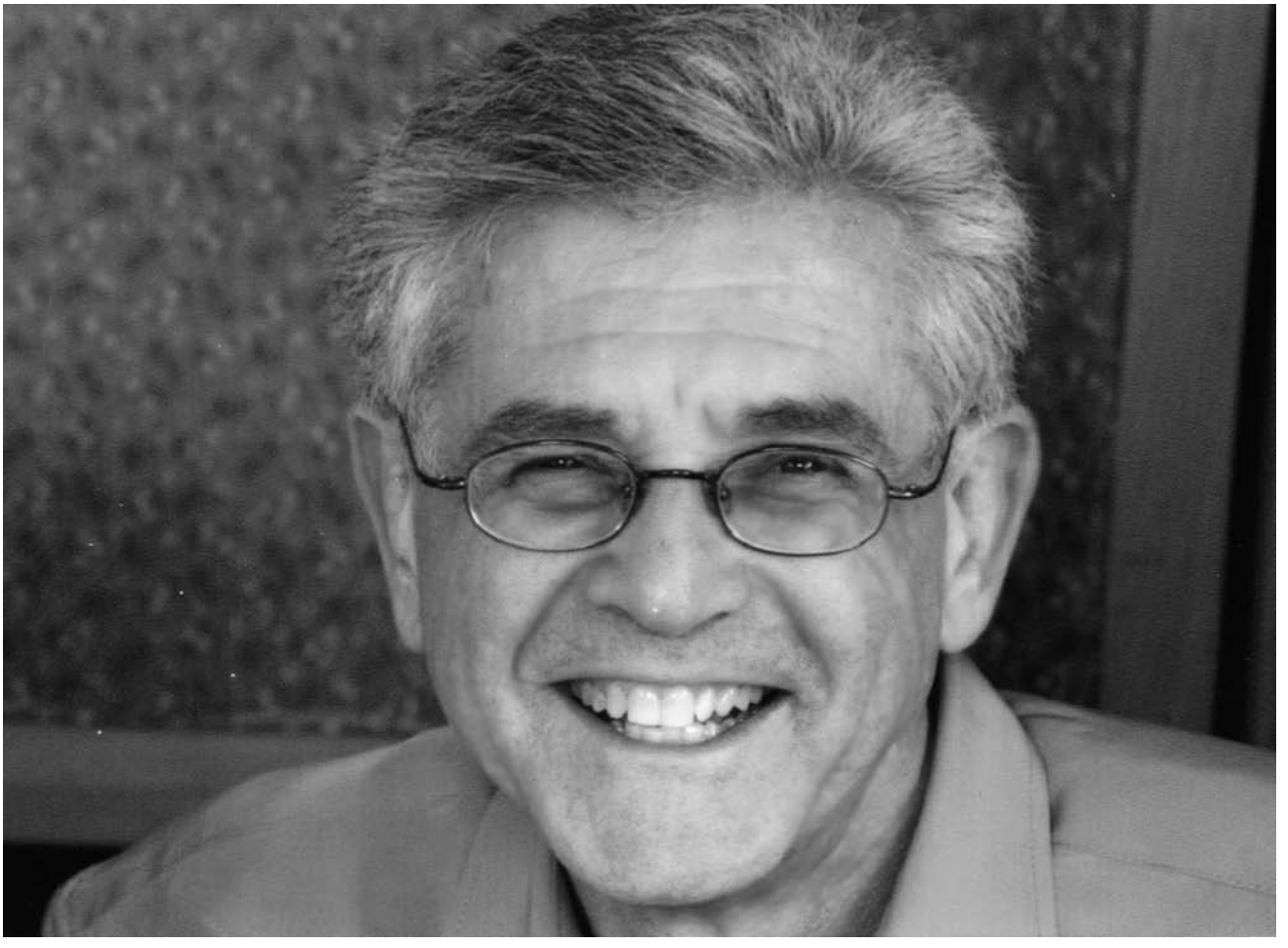

Dudley S Dinner MD
April 17, 1947 – May 1, 2007

I dedicate this book to Dudley,
my dear friend and colleague, whose contributions to epilepsy surgery
will have a permanent impact on the specialty.

Dudley joined the Cleveland Clinic Epilepsy Center as a fellow in clinical neurophysiology in 1979, shortly after I became the Director of the Center. This marked the beginning of a remarkable thirty years of extremely productive, daily collaboration. Throughout this period, Dudley participated in all major projects of the Center: contributing ideas, assisting in the organization of these projects, and managing their execution. Dudley's absolute loyalty, reliability, intellectual honesty, complete dedication, exemplary modesty, and willingness to sacrifice to achieve our objectives were essential ingredients in the development of the Epilepsy Center at the Cleveland Clinic. Dudley, as an expression of his unselfishness, never demanded recognition for his contributions. Dudley was so often the driving force behind the scenes. I would like to use this opportunity to express my deepest appreciation for Dudley's invaluable contributions, but also – and perhaps most importantly – to thank him for his friendship and unwavering support. I particularly notice his absence in my current efforts to organize an Epilepsy Center at University Hospitals. I realize now how much I relied on Dudley's help in so many of our projects. I greatly miss him as a colleague and as a dear friend.

It is a great honor to dedicate this book to Dudley.

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Preface

It was just 7 years back, in 2001, that Dr. Youseff Comair and I edited the last book dedicated to epilepsy surgery.[1] It is encouraging to note that epilepsy surgery has again made major advances, calling for a complete rewriting of essentially all the chapters of that book. Interestingly, the development of new diagnostic techniques, which certainly permit a more precise and reliable diagnosis of the epileptogenic zone, with very few exceptions, have not replaced some of the more classical diagnostic methods. In this sense, it is notorious that clinical semiology and clinical neurophysiology continue to be irreplaceable diagnostic techniques that provide a wealth of information. Moreover, modern technology, which makes recording, storage, and computer analysis of large amounts of neurophysiological data possible, gives us access to new data, such as the high-frequency oscillations or the EEG DC shifts, which promise to play important roles in the definition of the epileptogenic zone.

This *Textbook of Epilepsy Surgery* includes over 20 chapters dedicated exclusively to the history of epilepsy surgery in different countries. I felt that it was important to collect this information on a timely basis when many of the main players who actually participated in the development of epilepsy surgery, or at least directly witnessed the developments, are still active in the field.

As in our previous book on epilepsy surgery, in this book too we devote significant space to the description of the semiological seizure classification and the detailed clinical description of the epilepsies that are remediable by epilepsy surgery.

In this book, we follow a systematic approach to the diagnostic evaluation of patients who are candidates for epilepsy surgery. We first discuss the general principles of epilepsy surgery, and then divide the presurgical evaluation according to the six zones (symptomatogenic zone, irritative zone, ictal onset zone, the epileptic lesion, the functional deficit zone, and the epileptogenic zone) described in the general principles chapter. These series of chapters conclude with the description of the Epilepsy Surgery Management Meeting, an essential and indispensable part of the surgical evaluation.

The book also incorporates detailed discussions of the cortical mapping techniques and the numerous surgical techniques that can be used to surgically treat epilepsy. This is complemented by surgical outcome, the post-surgical medical management, surgical failures, and neuropathology. Finally, selected case presentations are discussed, and proposals for the establishment of an epilepsy surgery program, classification of surgical outcome, and protocols for storage and processing of brain tissue for molecular studies are presented.

I feel that epilepsy surgery is still an extremely attractive management tool for patients with medically intractable epilepsy. Unfortunately, in spite of dramatic increases in the number and mechanisms of action of modern antiepileptics, close to a third of all epileptics still suffer from uncontrolled seizures. A significant proportion of these patients are excellent surgical candidates. The extreme precision of our current presurgical evaluation methods and the recent advances in neurosurgical techniques make it imperative that all these patients get evaluated at an epilepsy center that offers epilepsy surgery. In a significant proportion of these patients, the epilepsy can be either eliminated (cured) or a significantly better seizure control can be achieved, with relatively low surgical risk. Referrals for epilepsy surgery have been continuously increasing since the pioneering efforts at the end of the 19th century. I hope that this book will contribute to making epilepsy surgery available to an even larger percentage of patients with medically intractable epilepsy.

Acknowledgments

I would like to acknowledge the help of Ms. Connie Scolaro and Ms. Autumn Semsel who, throughout the editorial process, assisted me as executive secretaries, making the editorial process so much easier.

Hans O Lüders

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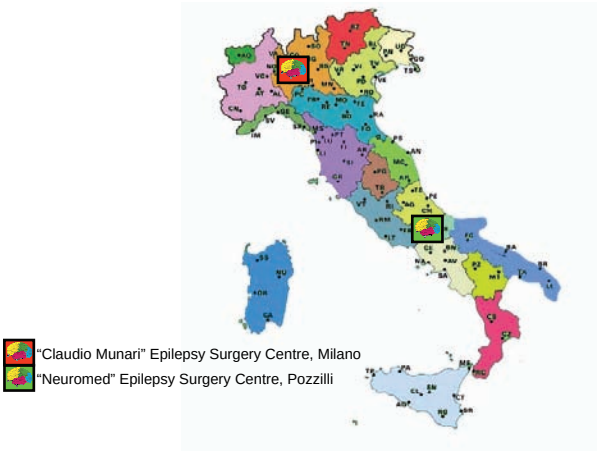

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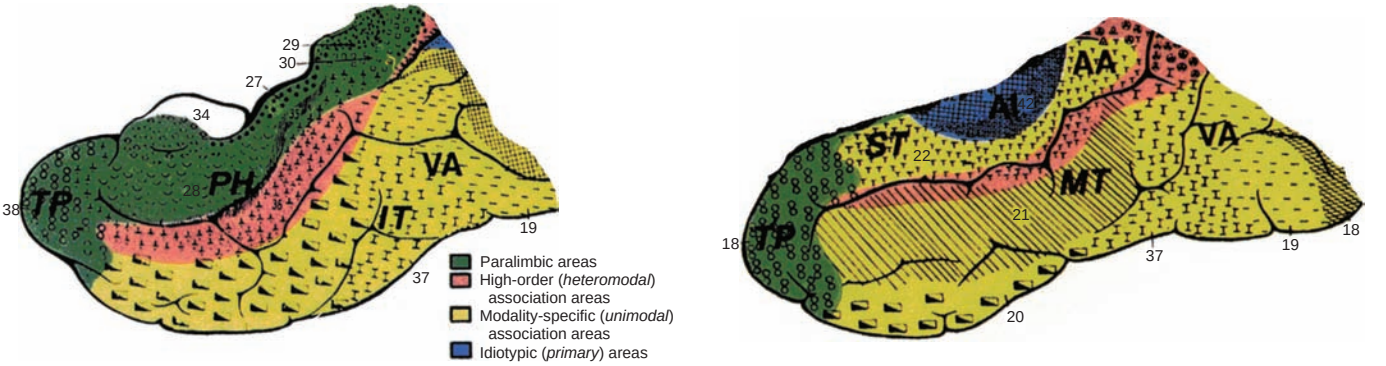

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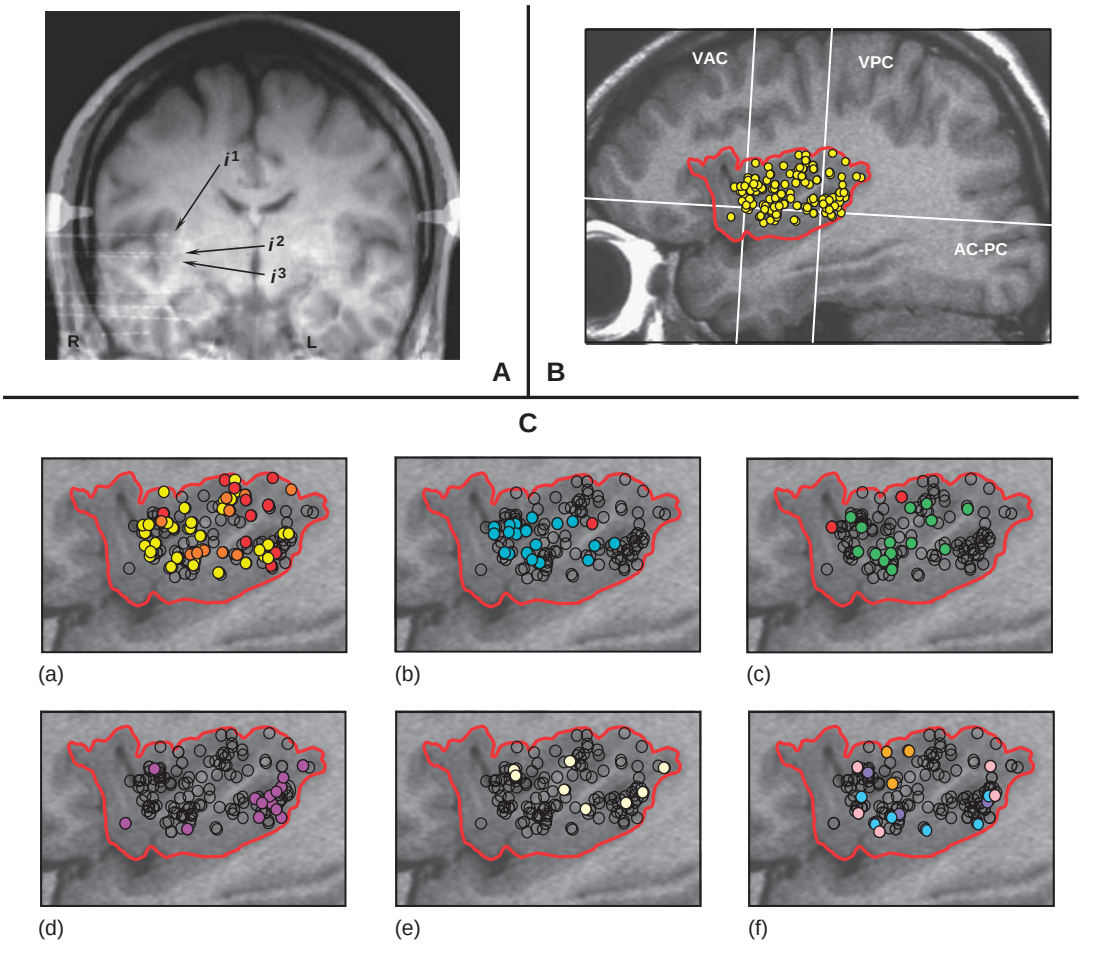

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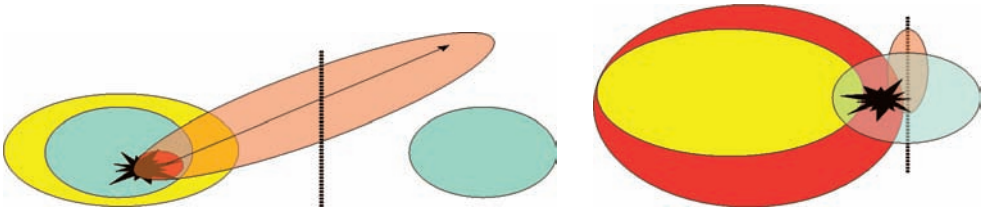

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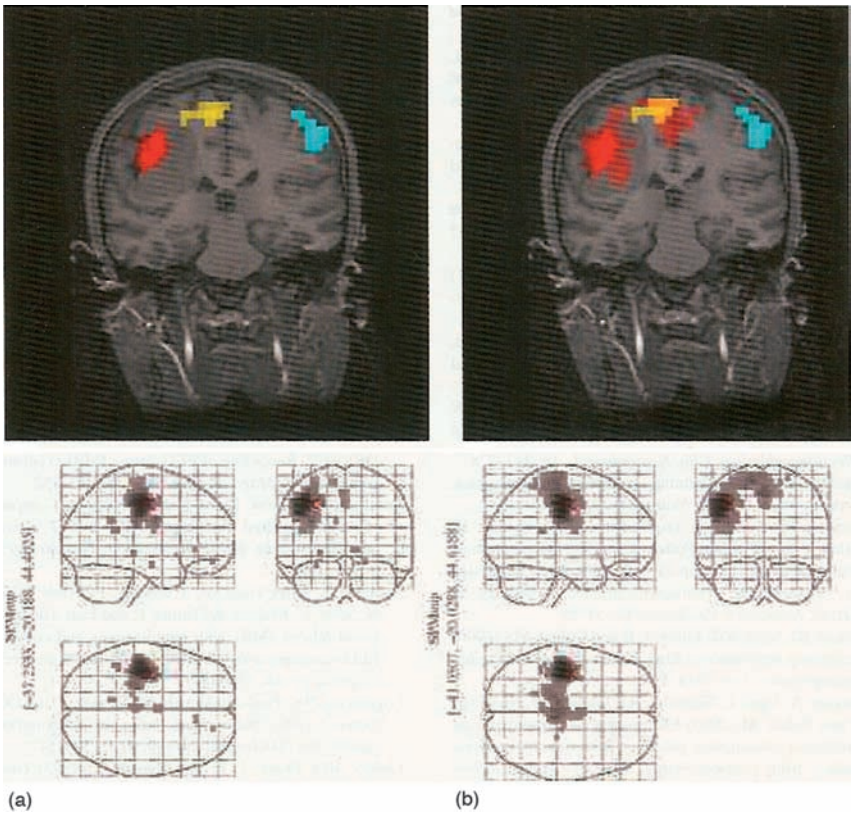

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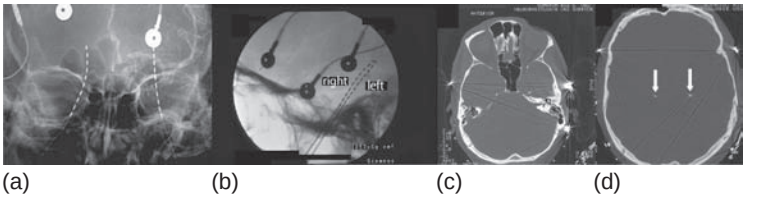

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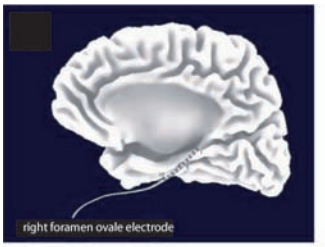

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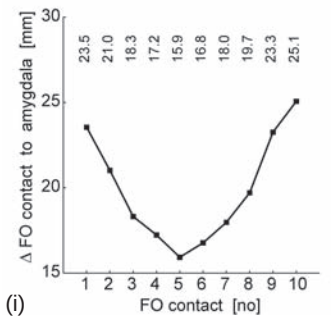

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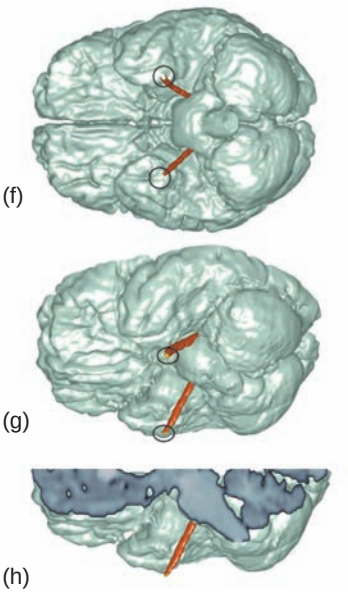

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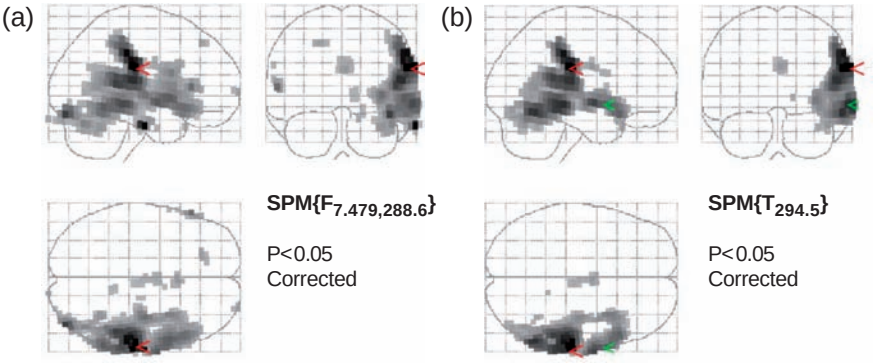

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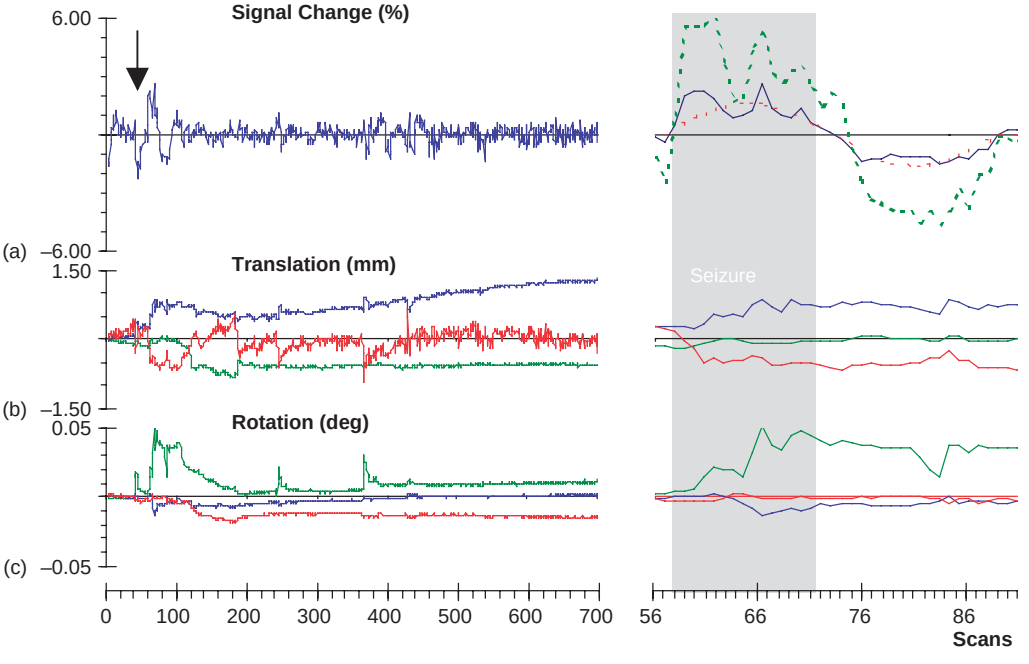

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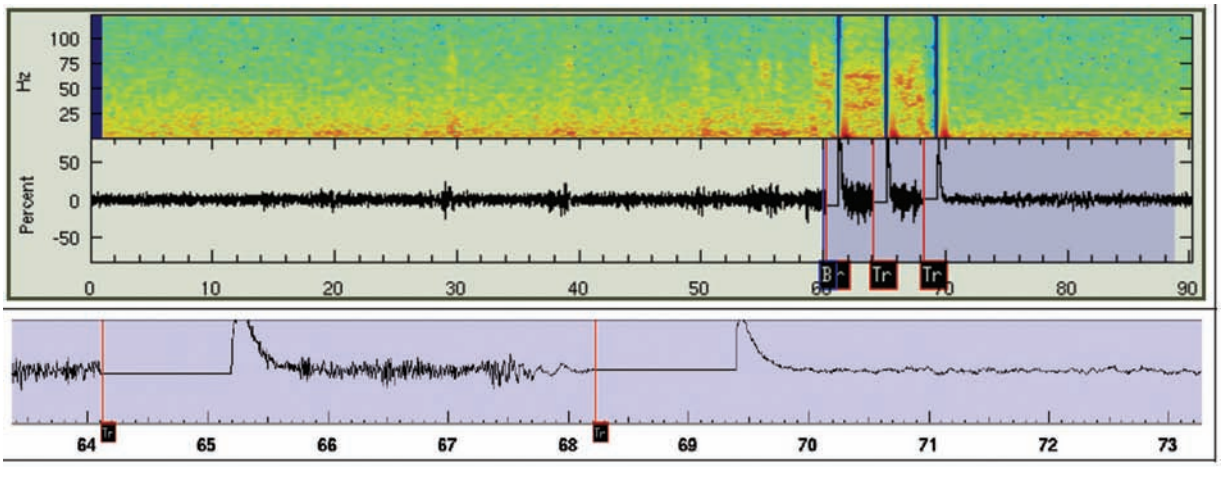

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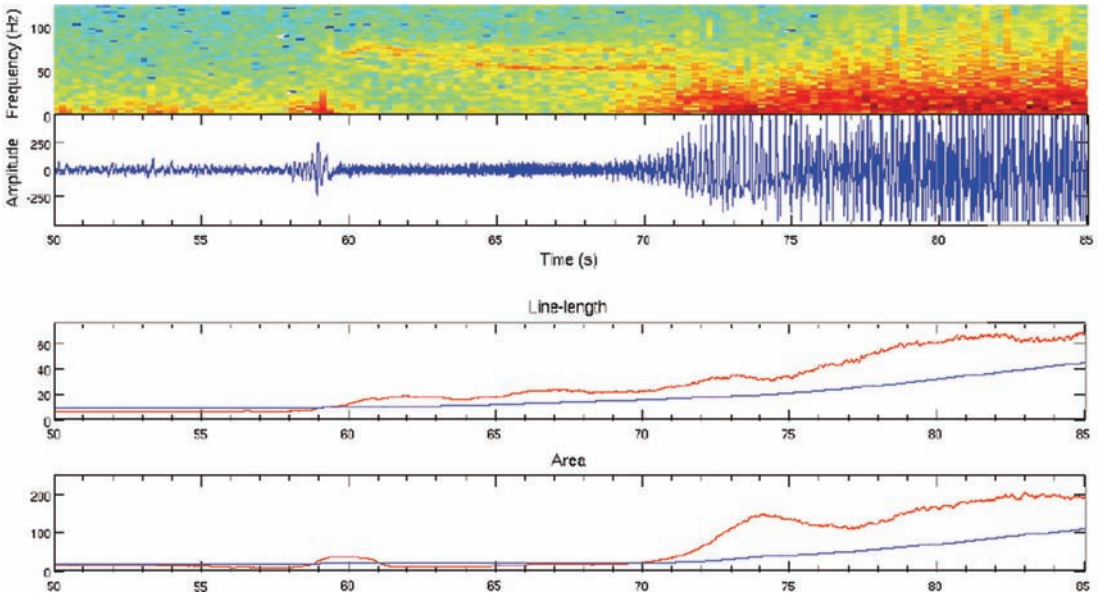

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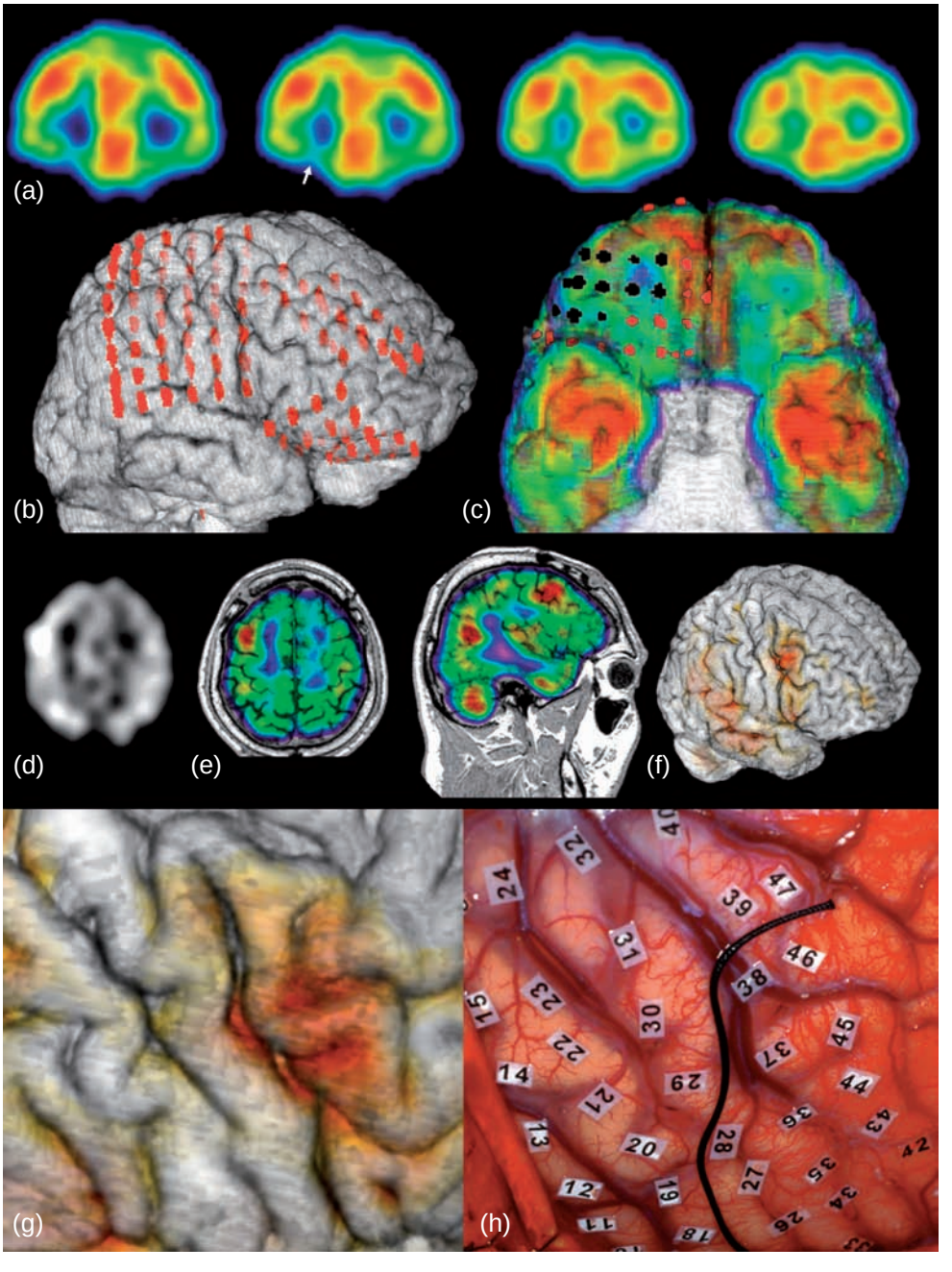

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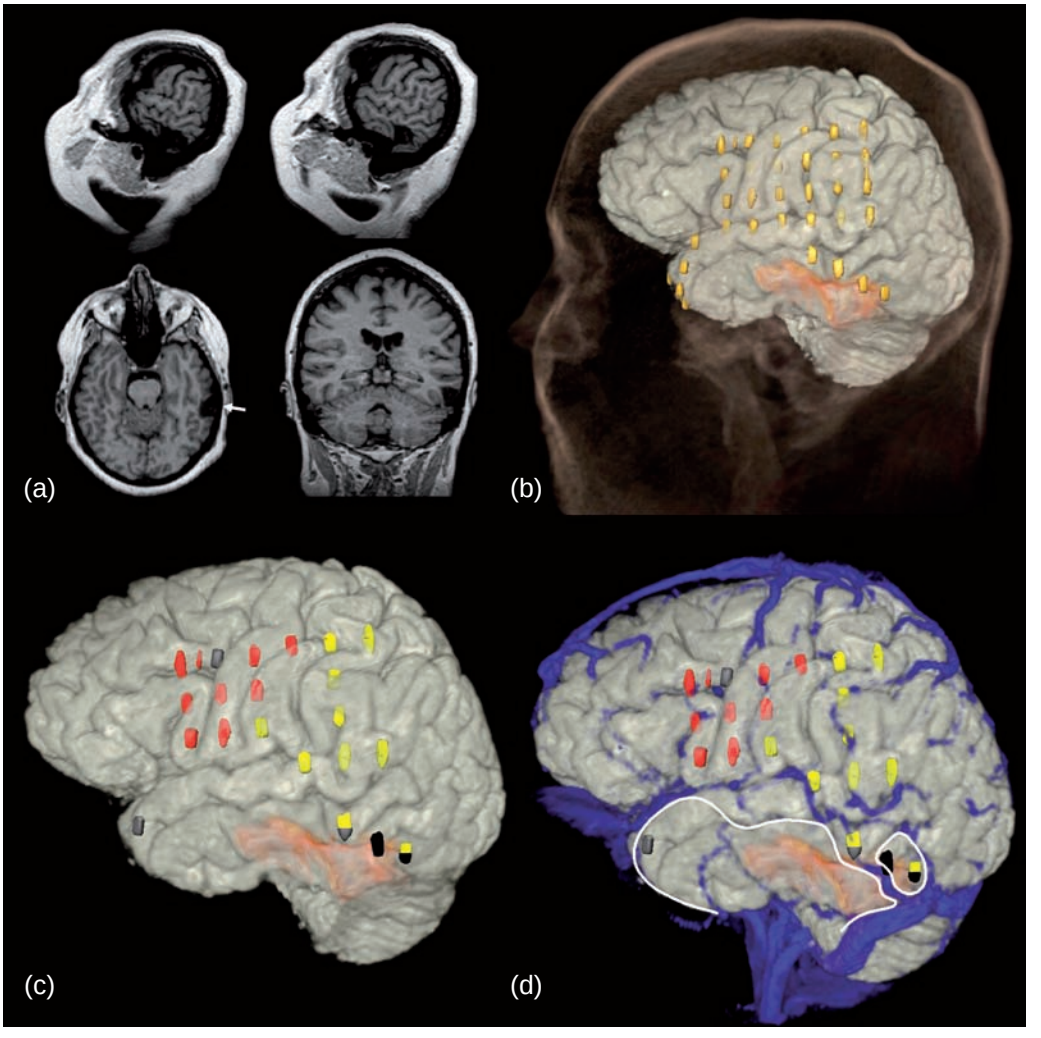

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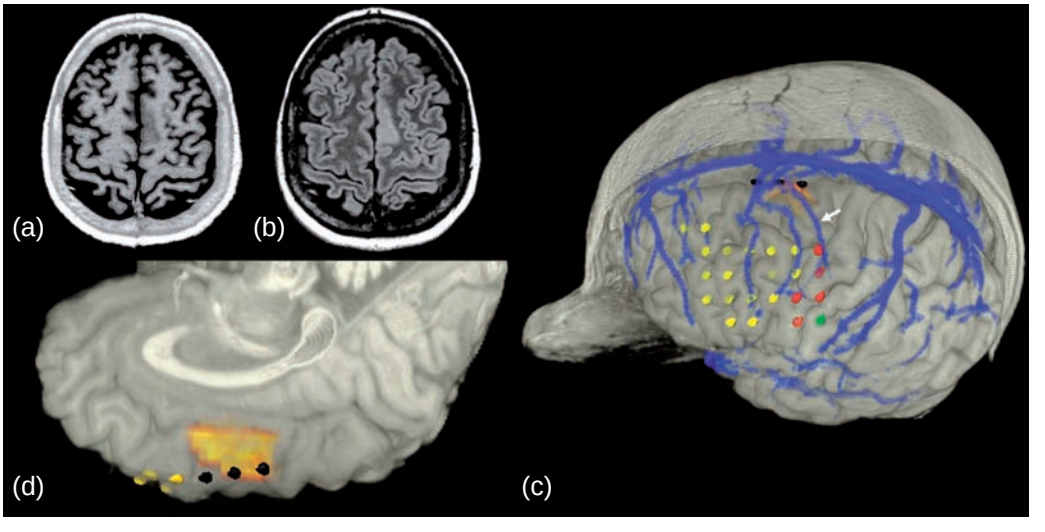

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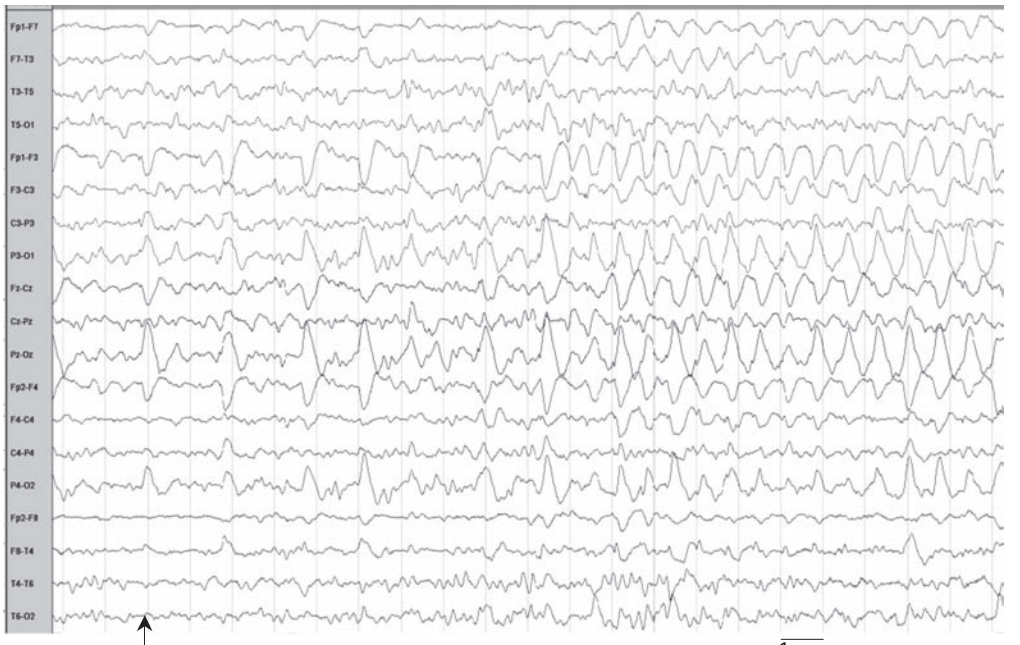

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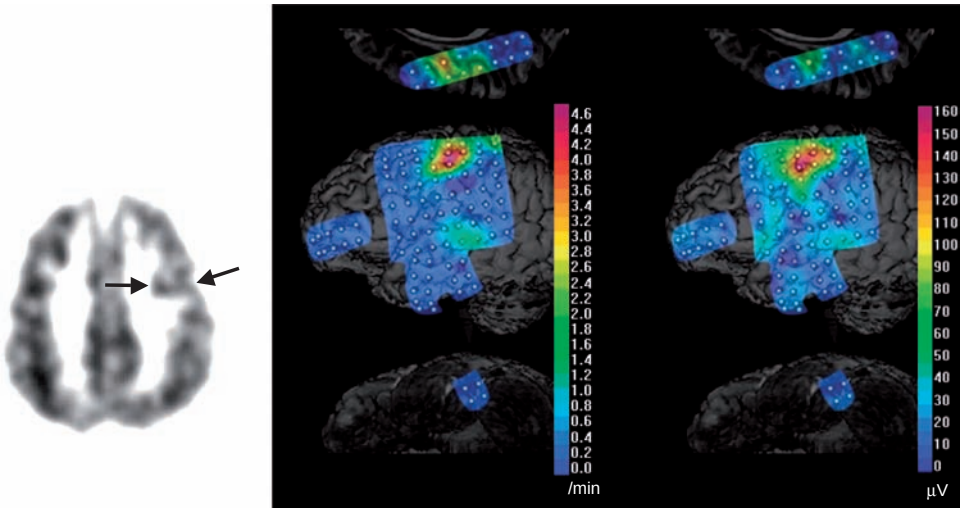

(b) (c) Interictal spike frequency (d) Ictal spike magnitude

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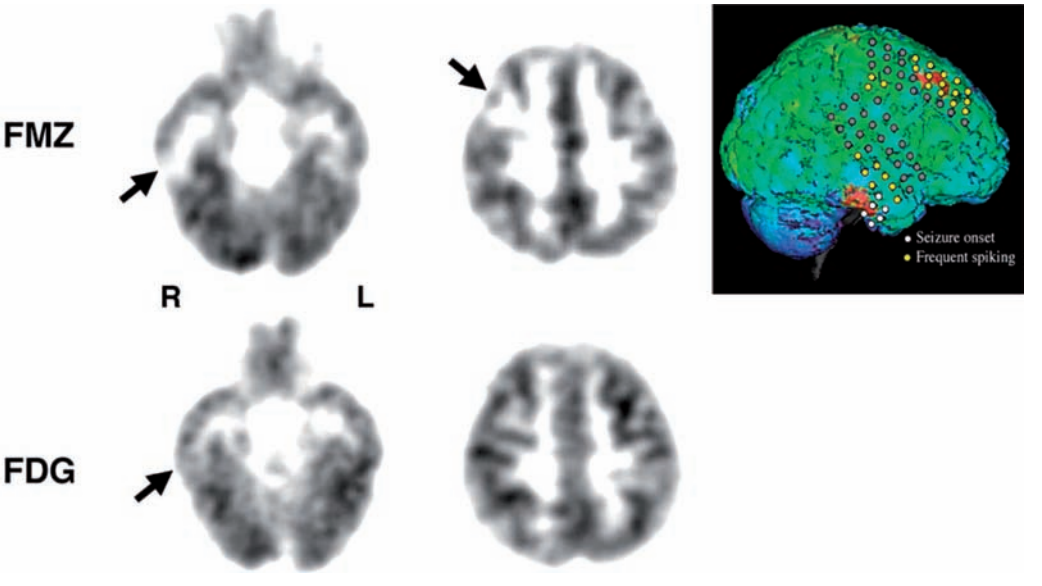

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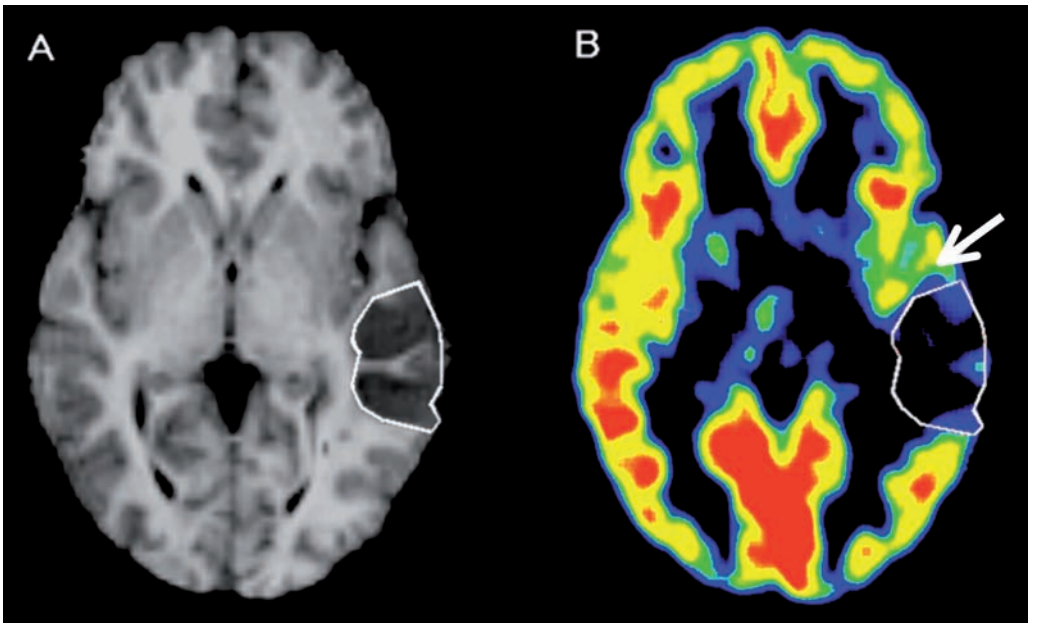

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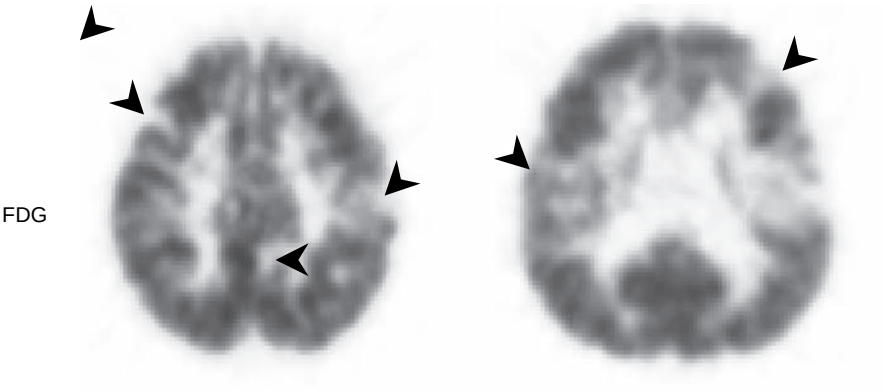

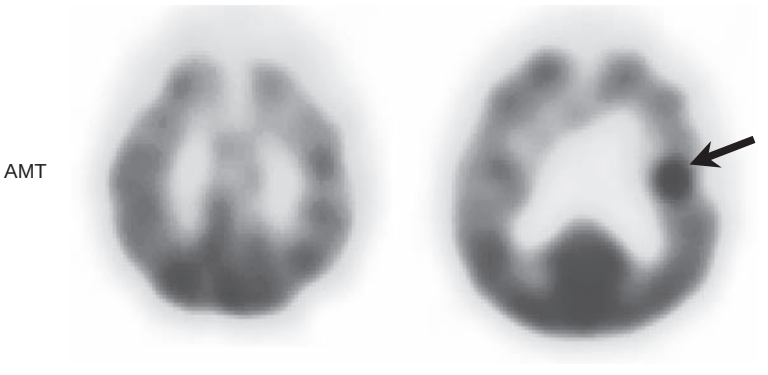

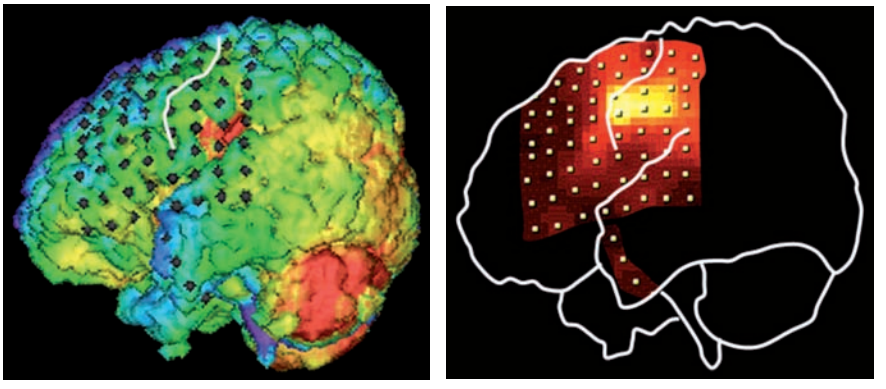

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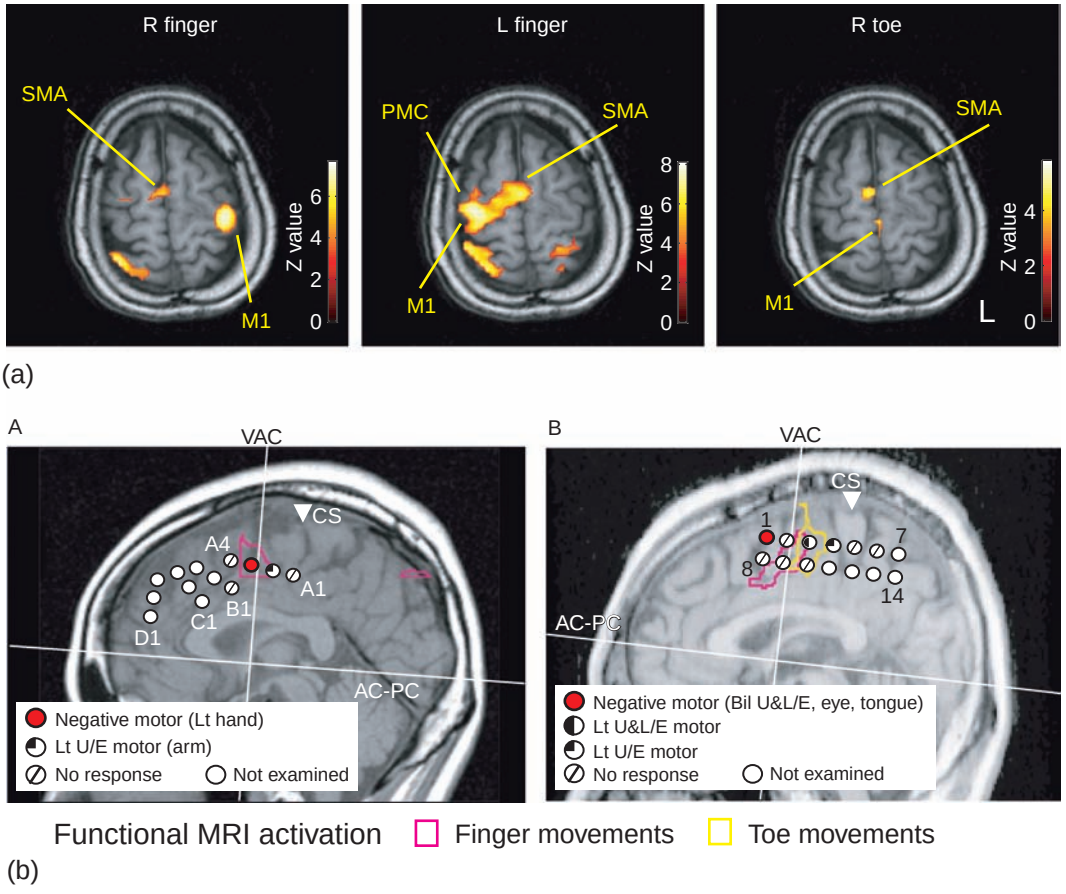

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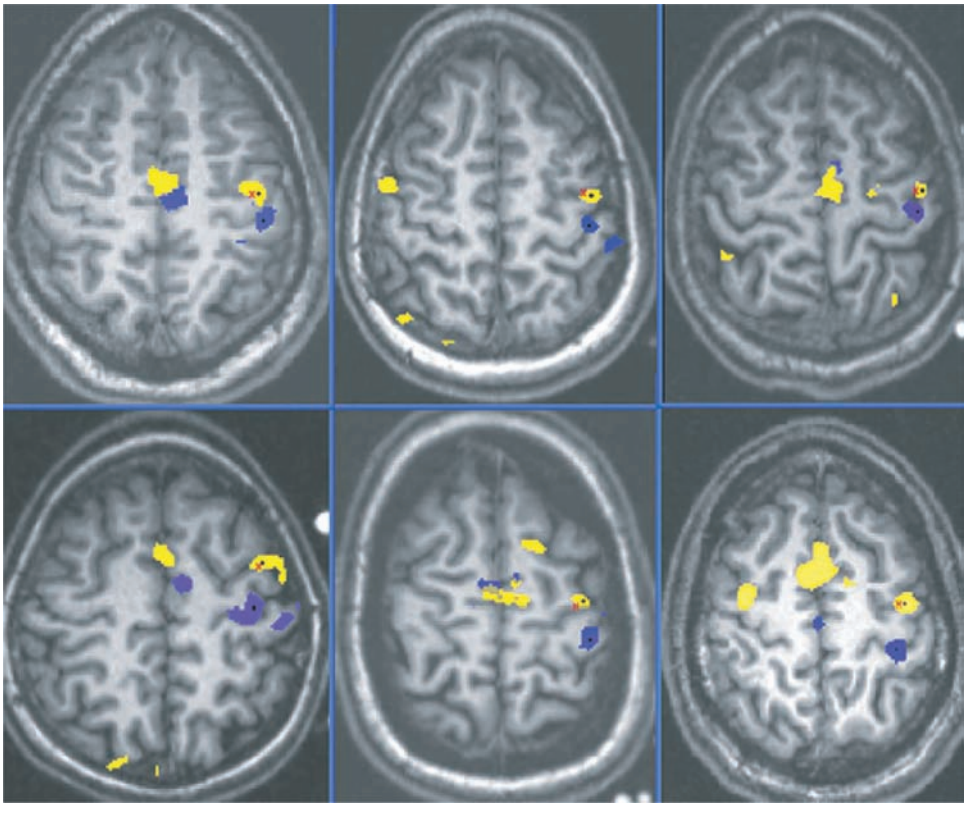

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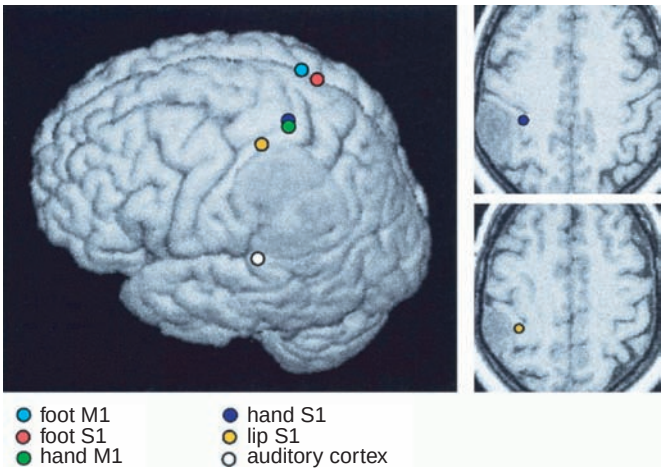

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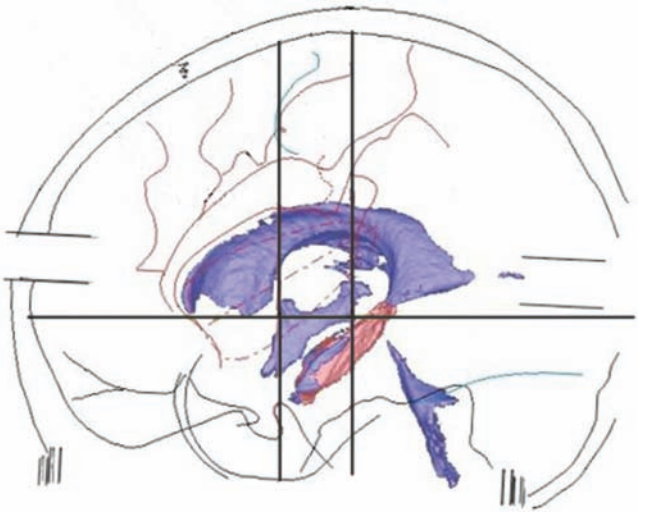

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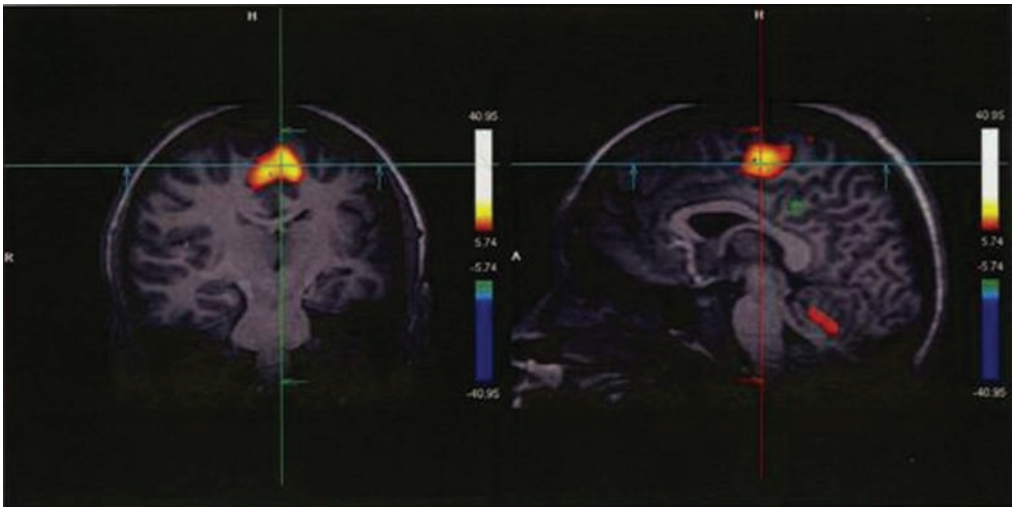

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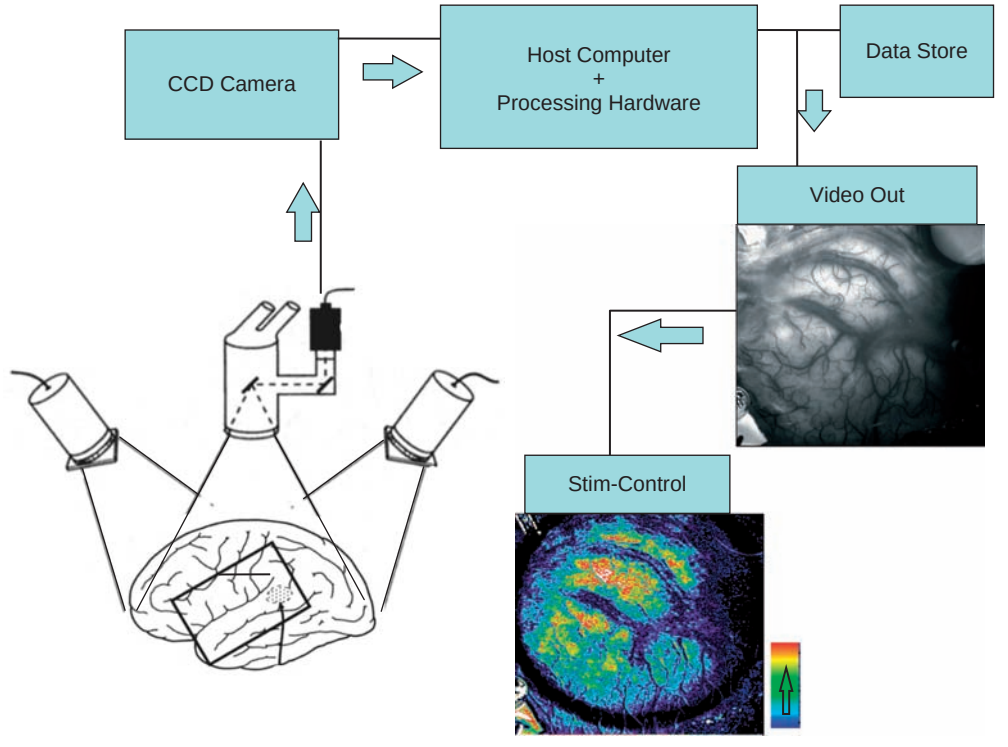

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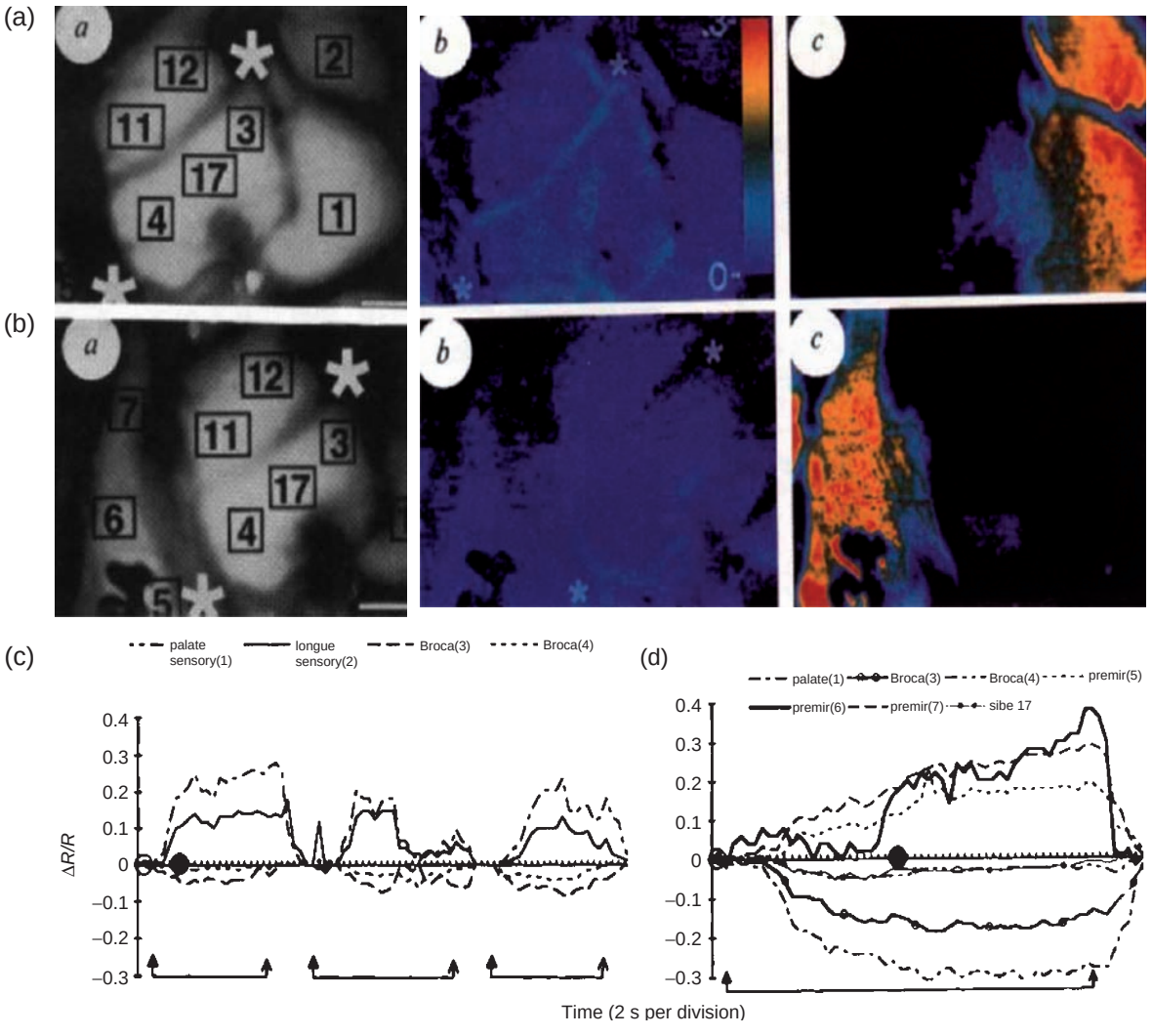

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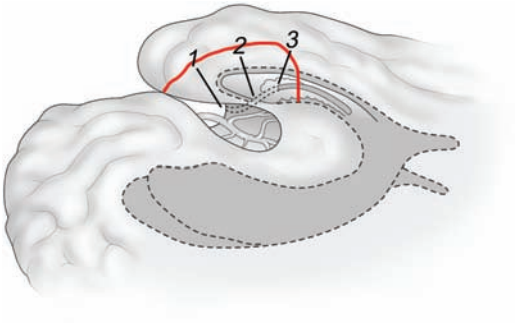

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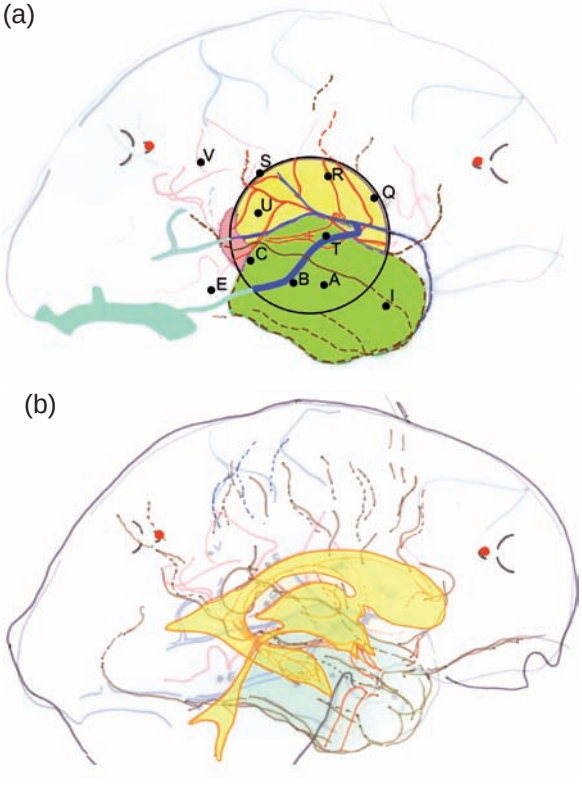

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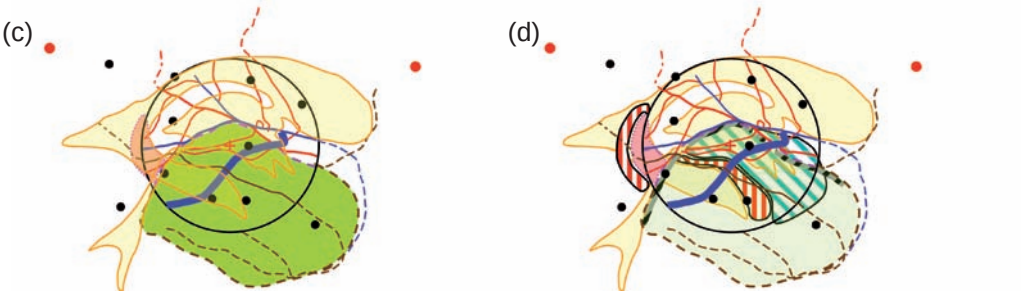

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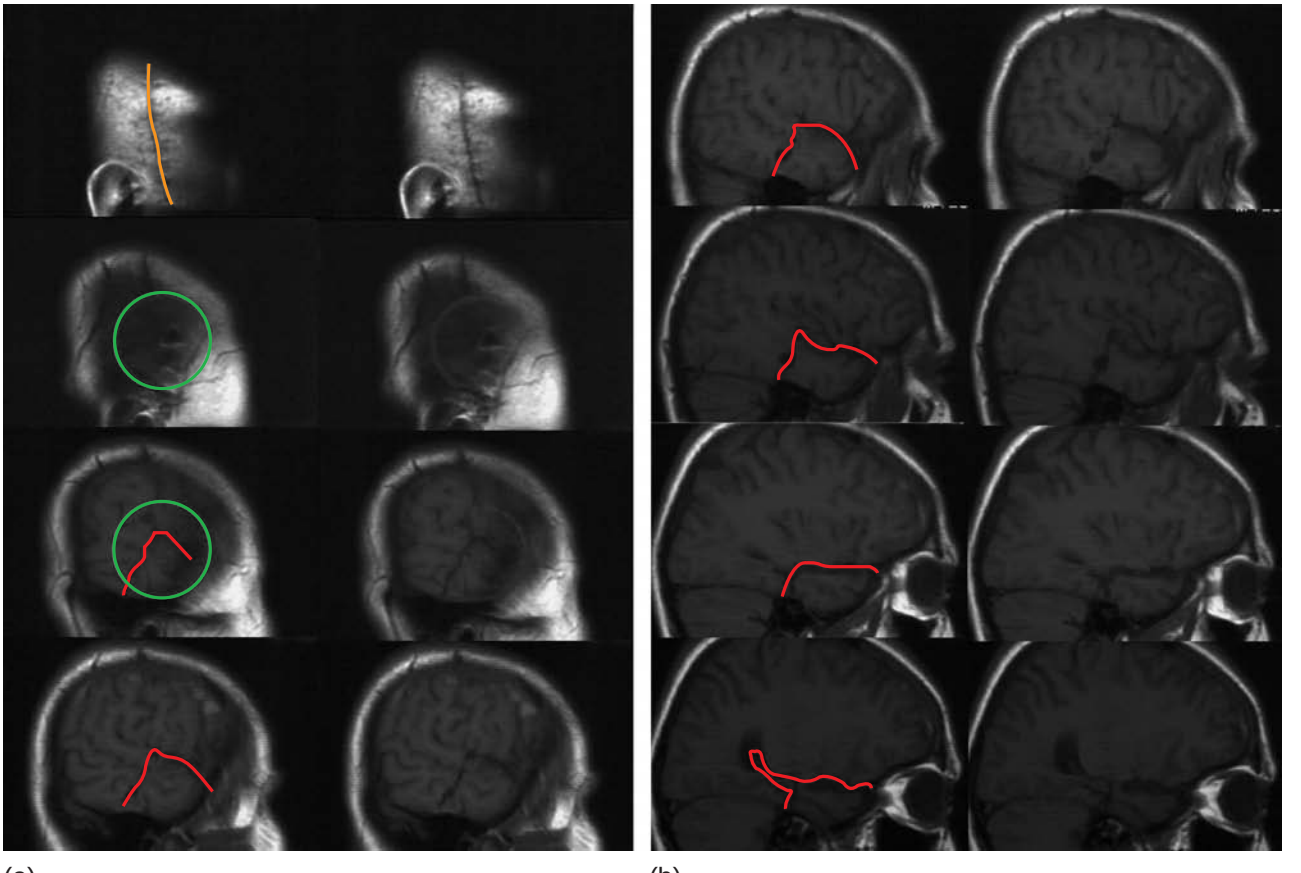

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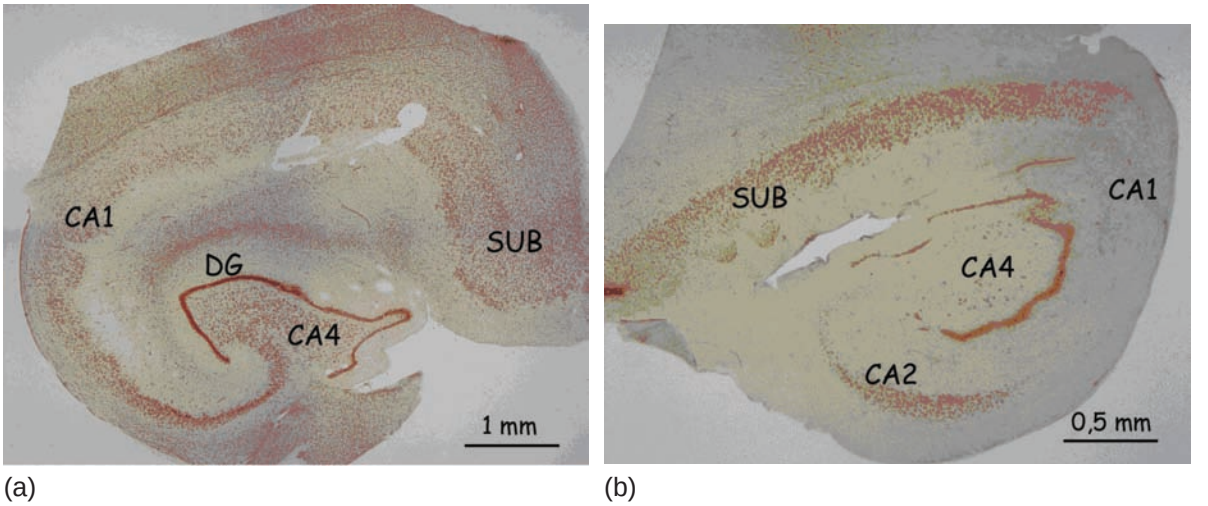

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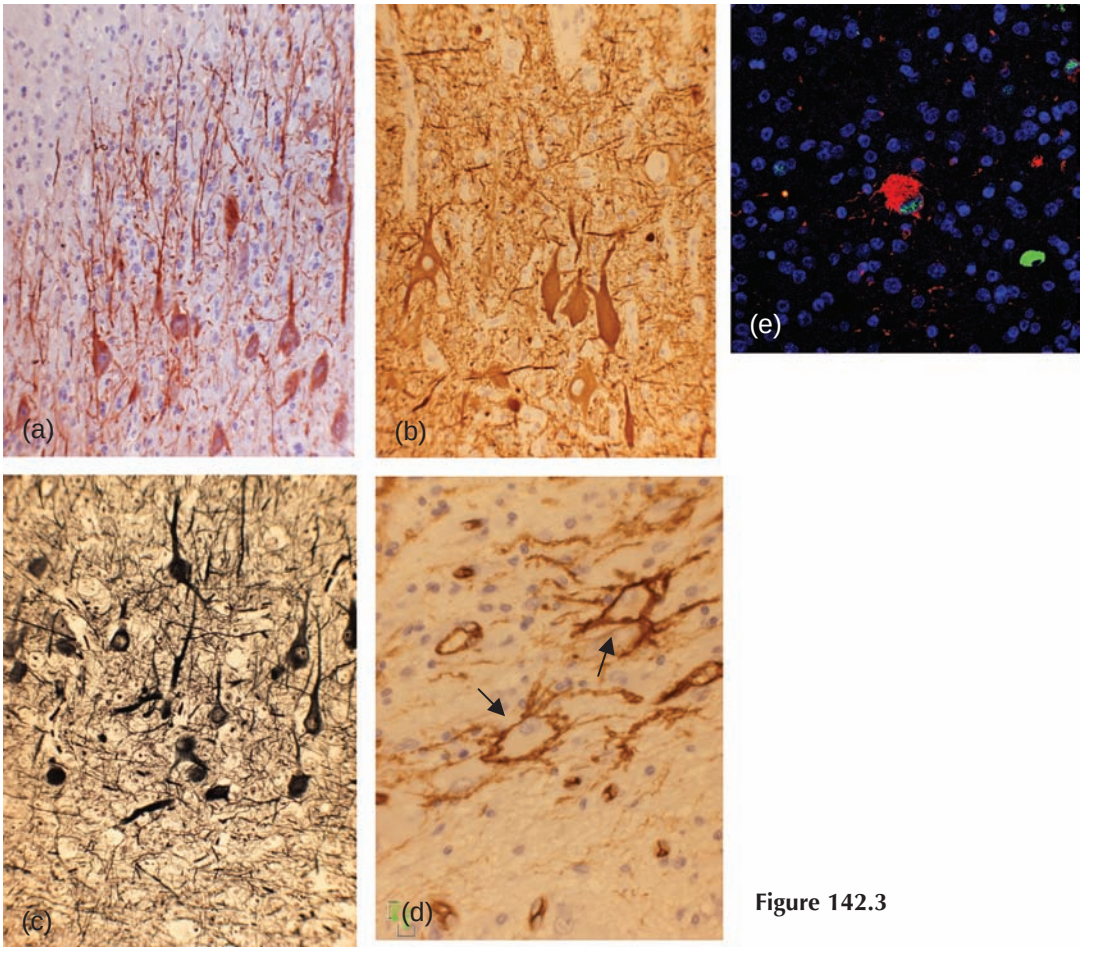

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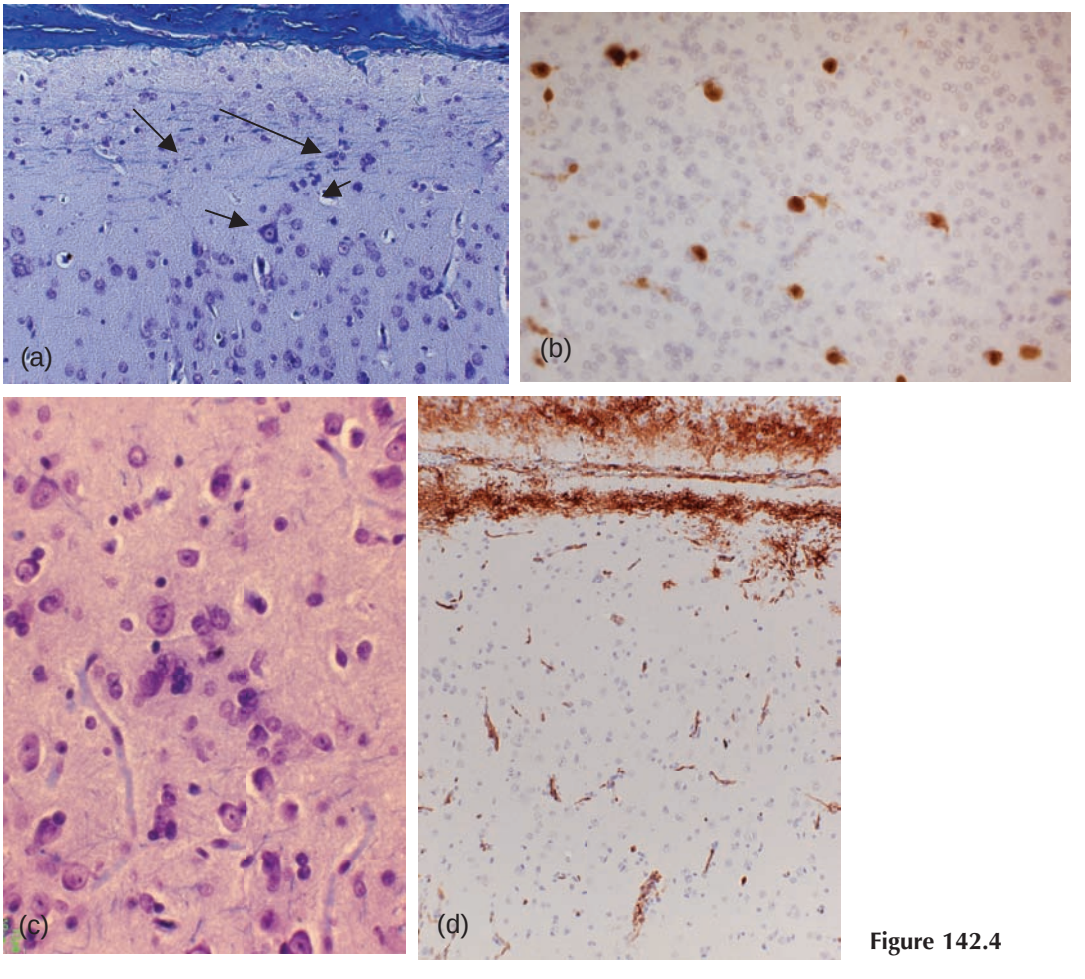

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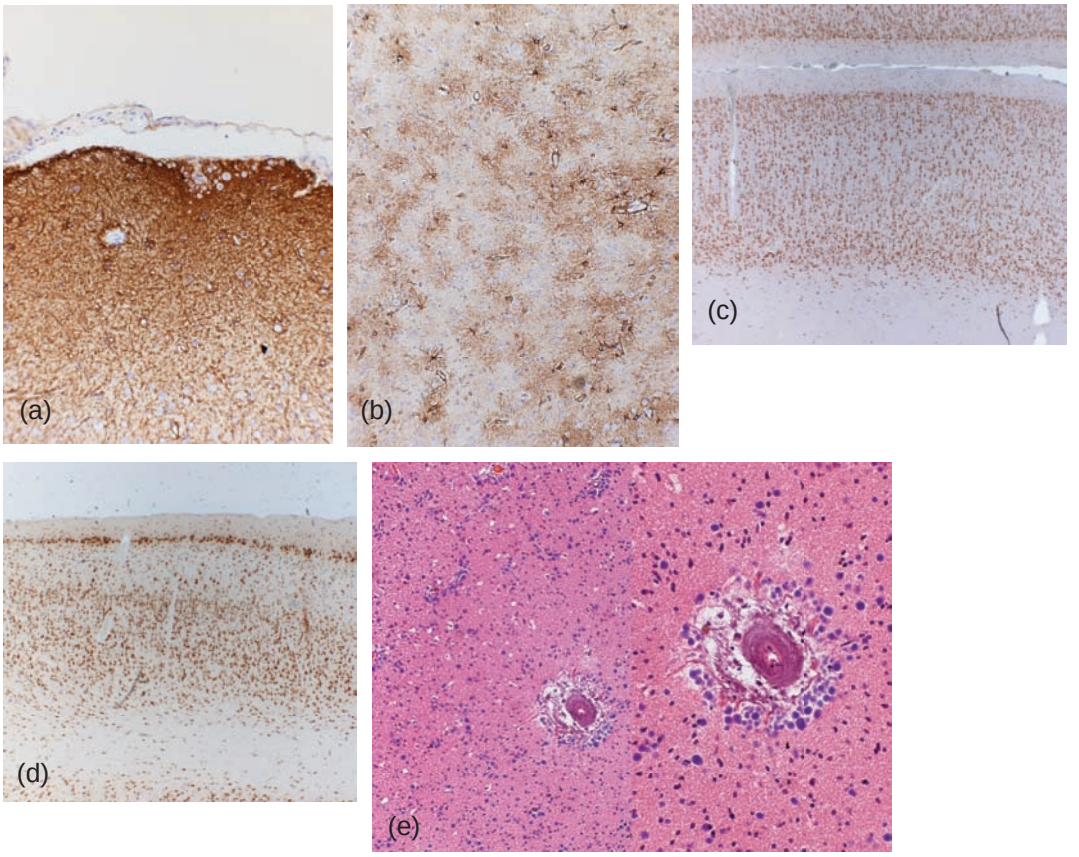

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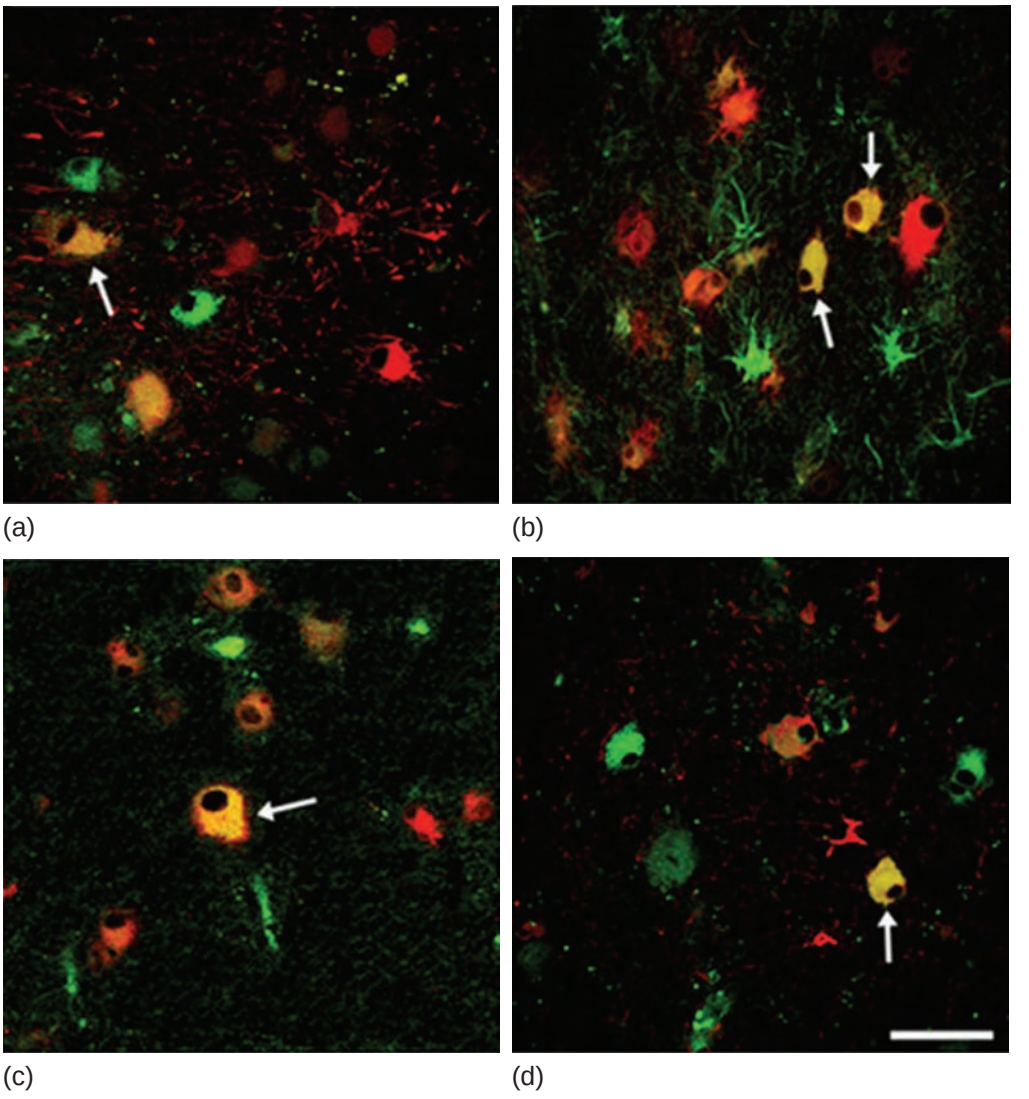

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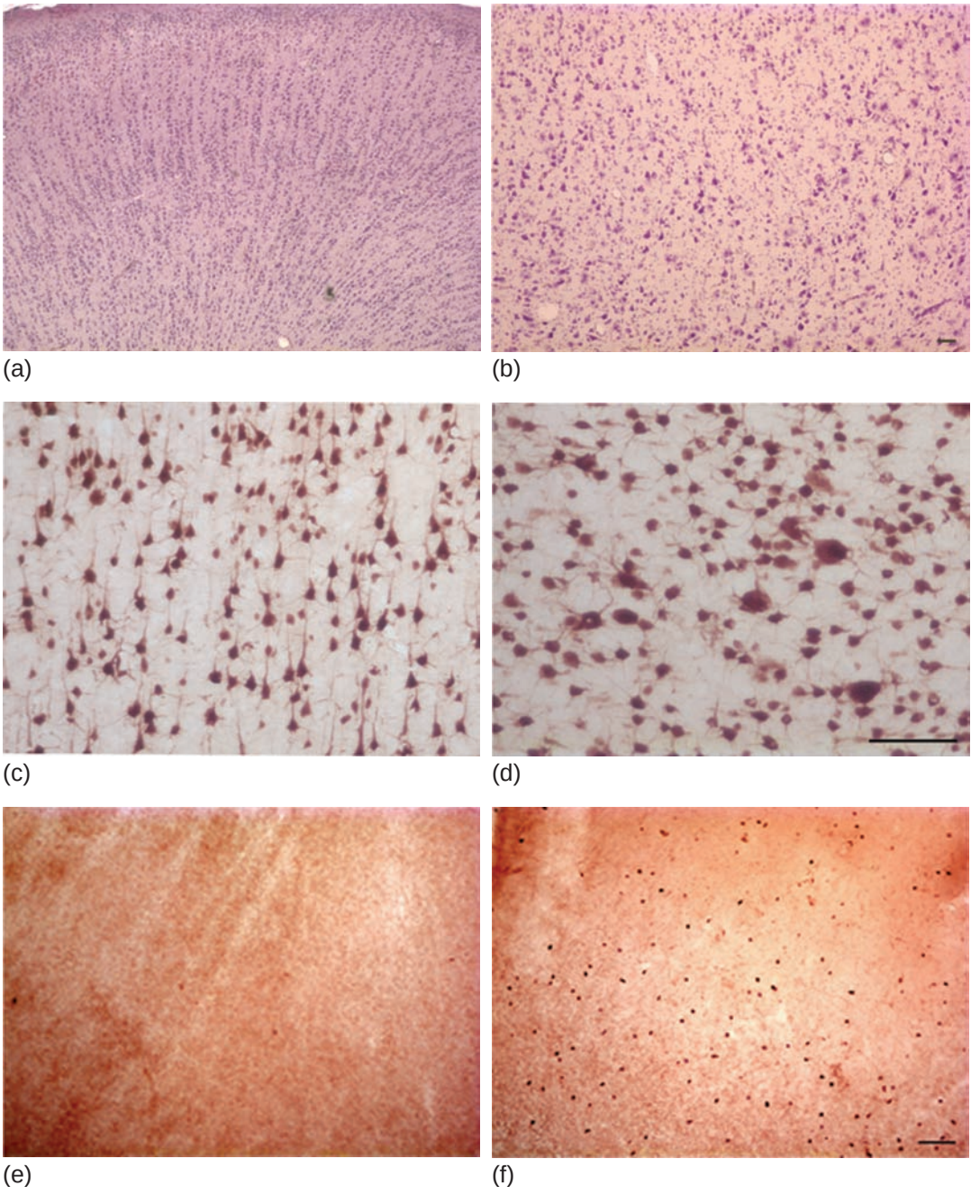

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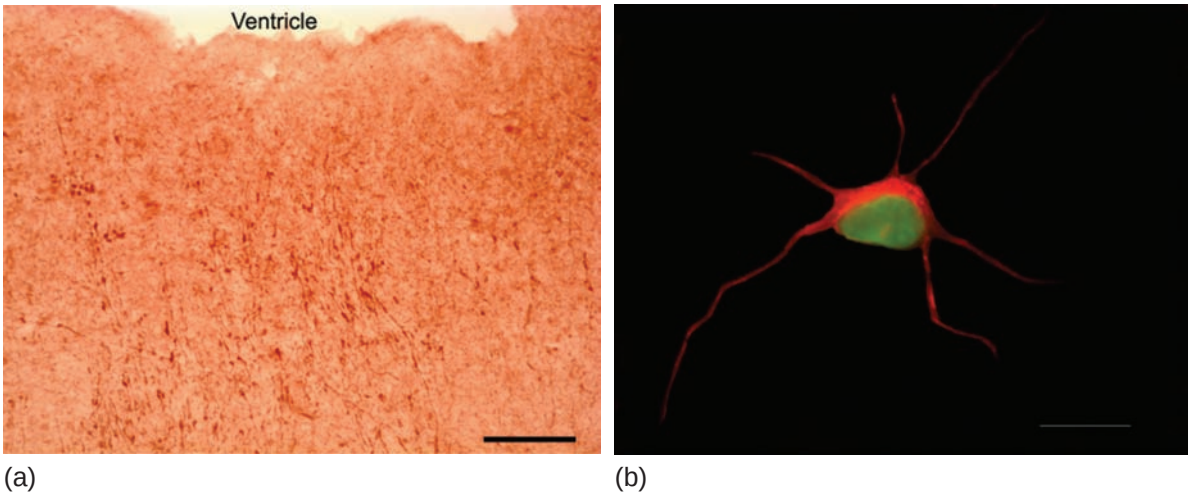

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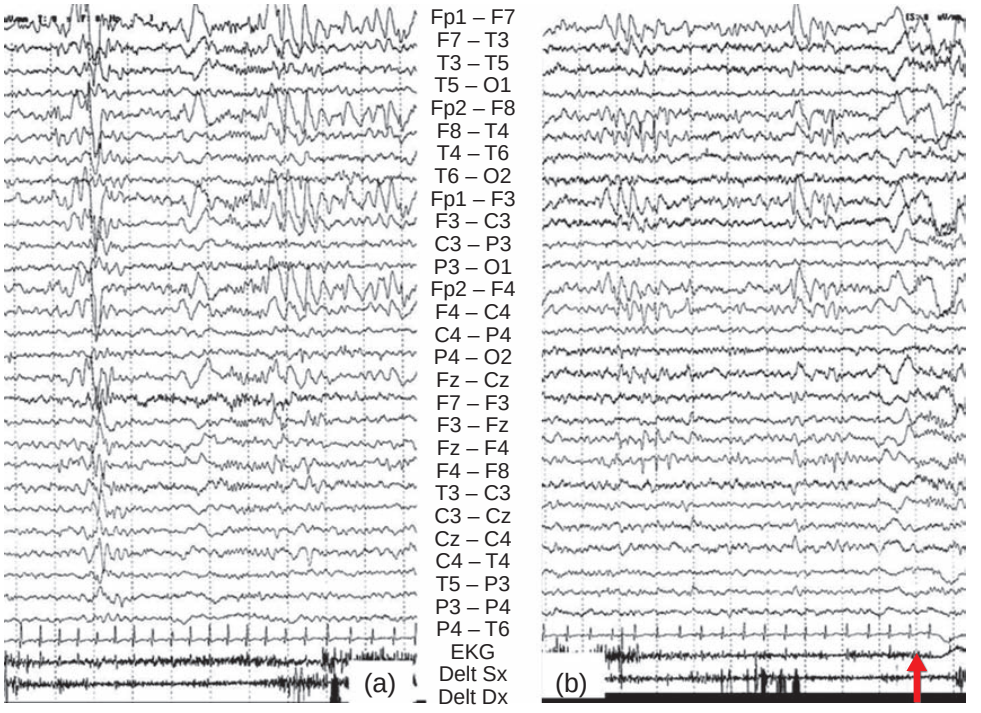

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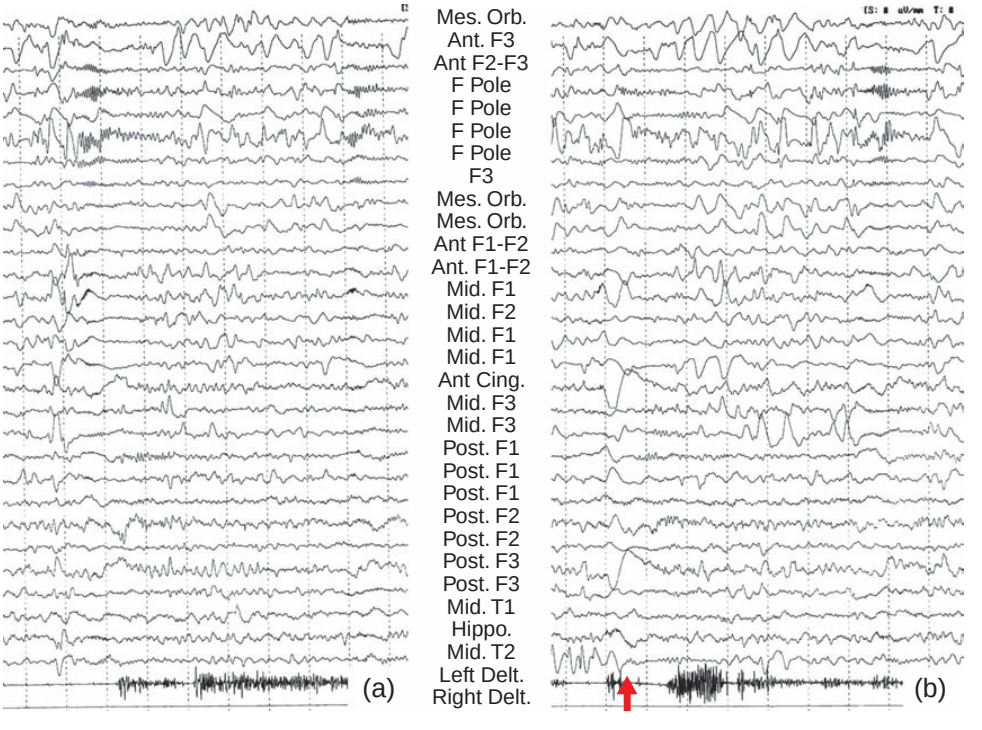

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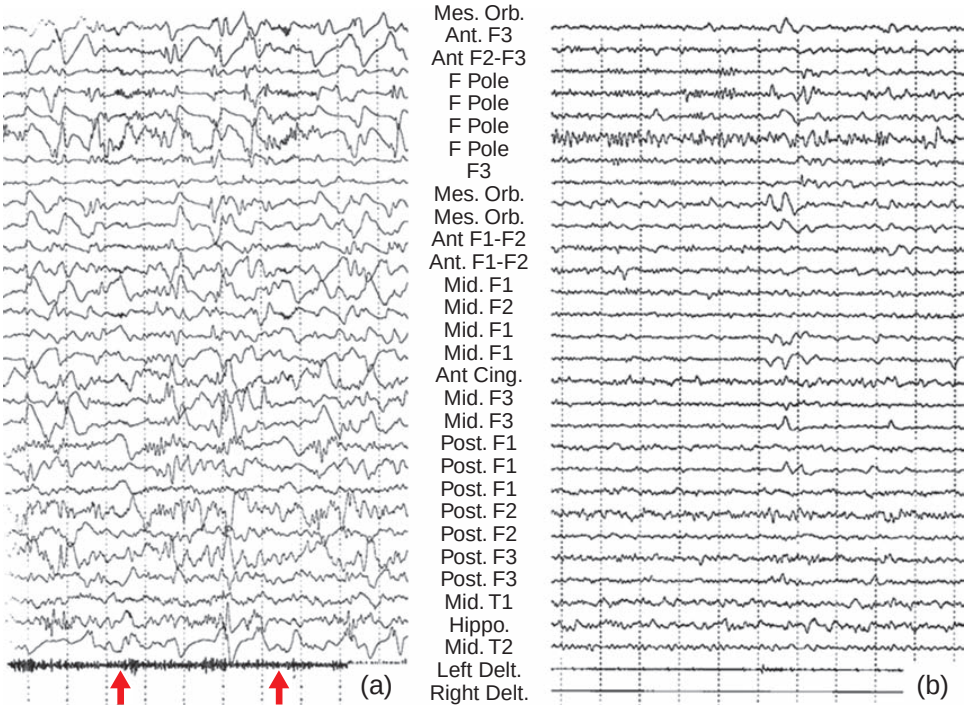

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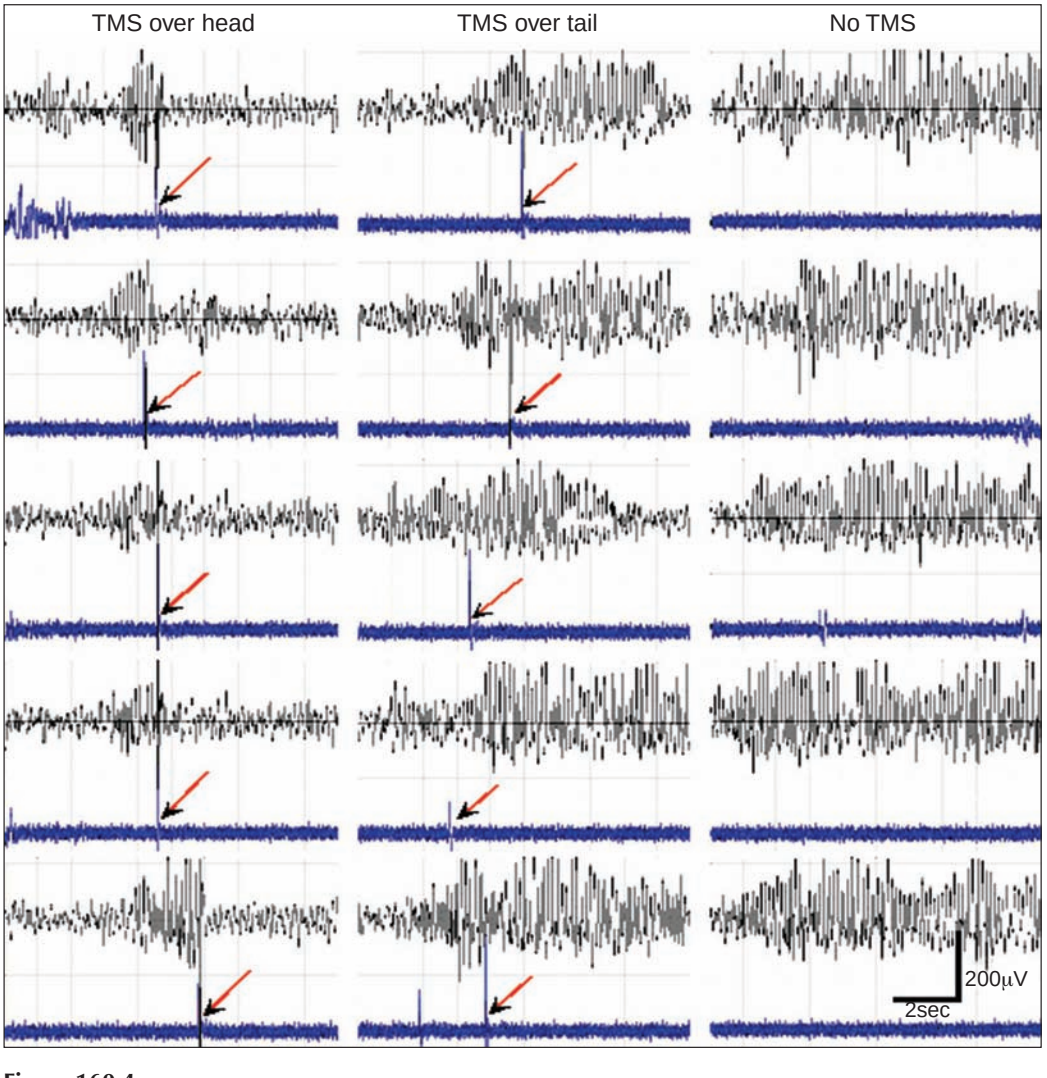

Figure 160.4

SECTION 1

History of surgery and related fields

1 Epilepsy surgery in Europe before the 19th century

D Schmidt and HJ Meencke

> ... Hippocrates, speaking generally, says, where medicine fails, steel may cure, where steel fails, fire may cure; where fire fails, the disease is incurable.
>
> Cooke, *History and method of cure of the various species of epilepsy*, 1823, p. 194

Introduction

Studying the history of epilepsy surgery from stone age cranial surgery to the emergence of brain surgery for epilepsy in the 19th century, is fraught with several difficulties. First, it may be difficult to determine if a defect found in a stone age skull is the result of a trepanation on a living person, and second, even if is clear that a trepanation has been performed, it is difficult, on the basis of archaeological skulls, to be certain why it has been performed.[1] More specifically, any effort to describe the pre-modern history of epilepsy surgery has to acknowledge that epilepsy was not always seen as a medical disorder of the brain as we do today. As elegantly summarized by Temkin,[2] the competing view held over many centuries was that epilepsy is a demonical disorder, and seizures were frequently interpreted as evidence of spiritual possession. Not surprisingly, trepanation for treatment of seizures may have been performed for medical reasons, for example in patients with underlying trauma, as well as for magical-religious, ritual, or spiritual reasons and as a dramatic miracle cure.

Although a general discussion of trepanation is beyond the scope of the chapter, it is well recognized that trepanation is the earliest form of surgery known.[3,4] Trepanation of the human skull is the removal of a piece of calvarium without damage to the underlying blood vessels, meninges and brain.[18] Trepanation of the skull is described in written records as early as 1500 BC. A human skull, recovered from a French archaeological site, carbon dated to 5100 BC, from a patient who survived trepanation (based on evidence of healing around the surgical site and age at death of 50 years) represents the oldest example of a successful neurosurgical procedure.[5] The evidence for trepanation begins in the Neolithic, and extends to the present, and comes from every corner of the world. Trepanation is intended to remove a piece of the skull by scraping, gouging, boring and sawing, sawing alone, and drilling (properly trephination). There are thousands of samples of trepanation from the ancient world, many of them from central and northern Europe, where the operation may perhaps have been most active during the Neolithic, but has been performed continuously ever since to this day.[1] Trepanation was performed in Greece, sometimes with great skill, in Bronze Age Karatas, Asine, Lernas and Mycenae, and in Early Geometric Argos (900–850 BC).[1] It is noteworthy that the different types of trepanation are not evenly distributed geographically, the scraping method was used more often in Europe, while the South Americans favored sawing.[1] Although not proven, trepanation may have been done to relieve pressure on the brain, to elevate depressed skull fractures or to remove bone fragments in the case of penetrating head injury. Since the archaeological record shows that there are signs of healing on many trepanned areas, even on prehistoric skulls, it seems that at least some patients often survived the procedure.[3–5] Many of the examples of trepanation occur on skulls that had suffered injury. It is therefore not unreasonable to consider that among those on whom trepanation was performed were victims of depression fractures who were suffering from post-traumatic seizures or epilepsy.[5] In addition, the apparent indications for trephination also included depressive symptoms, psychosis, and headaches.[4,5] General surgical procedures used in the past for treatment of epilepsy such as bloodletting, vascular litigations, or cauterization of limbs will not be discussed here. The history of modern epilepsy surgery which began in the 19th century has been covered elsewhere.[6,7] In this chapter we briefly summarize the evidence of cranial surgery for epilepsy in Europe from the Neolithic to the end of the 18th century prior to the emergence of modern epilepsy surgery.

New Stone Age trepanations for epilepsy? A controversy between Paul Broca and Victor Horsley

In 1886 large craniotomy defects were discovered in ancient skulls from France, most of which are now estimated to be late new Stone Age (Neolithic), or approximately 5000–5500 years old (Figure 1.1). These findings raised many questions in the minds of those who found them and many more in those who reported on them from then on until today.[8] Although it may be extremely difficult to conclusively identify trepanation in archaeological skull specimens, for our discussion of the history of surgery for epilepsy, we need to consider two questions. First, were the observed defects in archaeological specimens, at least in some cases, the result of trepanations performed on the living (as opposed to blade or axe or other injury, depression fractures, tumors, infections, congenital

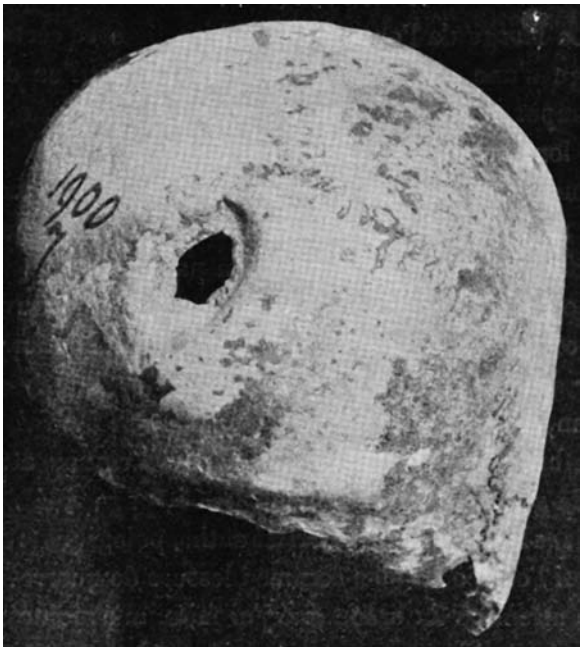

Figure 1.1 A Neolithic skull showing signs of trepanation. The skull was found in a dolmen in France by Pruniéres (with permission, Wellcome Library, London).[38] Broca concluded that this skull was trepanned before and after death.[10]

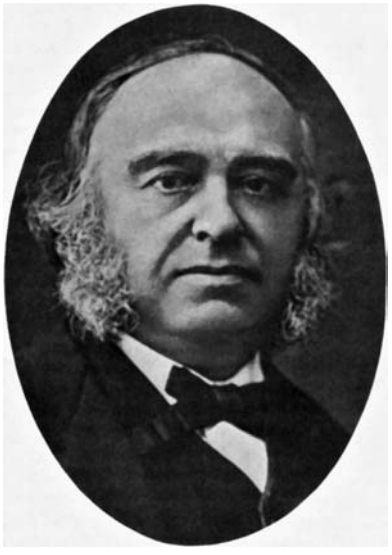

Figure 1.2 Paul Broca (1824–1880).[8]

defects, or post mortem rituals or damage)? And if so, second, was the trepanation done for treating epilepsy or convulsions?

When Prunières, a medical practitioner who had found the skulls in central France, reported his findings in 1874, he initially concluded that the skulls had been opened post mortem to transform them into drinking cups for rituals.[9] On second thought, he suggested that they may have been a therapeutic component to trepanation. Prunières now maintained surgical trepanation could have been performed to treat cranial fractures or depressed bone pieces.[9] He suggested that splinters of bone could cause bizarre behavior, including convulsions and delirium. These signs and symptoms would disappear following removal of the fractured bone. In any case, the problems would have been recognized as arising from the bone itself. Over time, he surmised, the procedure could have been extended to include the insane, the mentally ill, and even patients with convulsions without skull fractures. Now Paul Broca, Professor of External Pathology and of Clinical Surgery at the University of Paris, who later was to become famous for discovery of the motor speech area in the third frontal convolution, entered the debate (Figure 1.2). Broca was very much interested in trepanations since he had the opportunity to examine a trepanation defect in a Peruvian skull a few years earlier.

Although Broca agreed with Prunières that there was a therapeutic goal for doing trepanations, at least in some patients, he strongly disagreed about the specific malady or the theory behind it. Broca pointed out that there was no evidence for associated fractures, and furthermore he did not believe that Neolithic people had any understanding of the physiological functions of the brain nor, for that matter, anything like sophisticated surgery. He concluded: 'I think for my part that they were inspired, not by observation, but by superstition'.[10] Nevertheless, he considered a therapeutic goal for doing trepanation. In his mind, the goal was 'to avoid a danger, which could be more or less imaginary'.[10] How Broca finally ended up with the hypothesis that the goal of trepanation was to prevent infantile convulsions will be discussed in the next paragraph.

Trepanation to prevent infantile convulsions

Broca was convinced that trepanation had been a treatment for epilepsy in the past. In addition, he learned that trepanation was still performed in some parts of the world to exorcise demons thought to cause seizures. He hypothesized that Stone Age humans probably had a similar reasoning much like primitives in modern age. Broca had also read the work of Taxil from Arles who lived early in the 17th century. Taxil surmised that it was not possible to find an epileptic who was not possessed by demons and suggested that making a door in the skull would help the demons (and seizures) to elude.[2] Furthermore, Taxil also believed that an amulet made of skull bone would protect from having seizures. To Broca's delight, Taxil commented that epilepsy was very common in children. Broca himself thought that epilepsy was rare in children below age 10, and anyway, he had doubts that trepanation was able to cure epilepsy.[11] Thus by elimination, Broca was left with infantile convulsions, including febrile seizures, who, he knew, would often get better anyway, with or without trepanation. Broca's theory on Neolithic trepanation in its final form was that the cranial holes allowed the demons causing convulsions in infants to escape. In addition, as suggested by Taxil, Broca proposed that the skulls of those who survived trepanation were thought to have mystical properties and once they died, were cut out for amulets. Durin;g the mid 1880s, Victor Horsley (Figure 1.3) would prefer Prunières concept involving fractures, adding a modern twist of his own, over Broca's demonic hypothesis as we shall now see.

Victor Horsley on Neolithic trepanation for epilepsy

Although Horsley never picked up a shovel to dig for prehistoric skulls, he took an avid interest in Broca's findings. He examined and photographed the Neolithic crania in the Broca Museum in Paris where some of them were stored after Broca's death in 1880. His new variation of Prunières' theory stemmed from his observation that the holes made during the

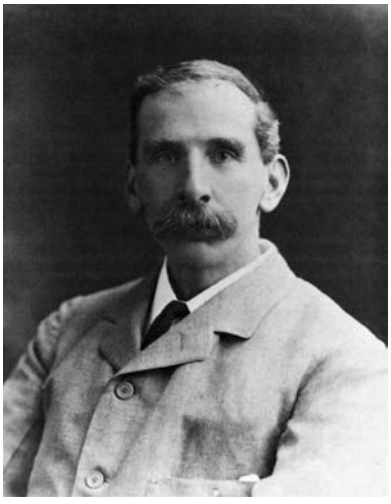

Figure 1.3 Victor Horsley (1857–1916).[40]

Neolithic period were not randomly placed but mostly over the vertex of the head, more or less above the motor cortex as it was then envisioned. In Horsley's mind, that was proof enough that surgical trepanations had been performed for epilepsy. In his own words:

> By means of this composite arrangement it was demonstrated beyond question, that in almost all known instances of this practice the opening of the skull was made over that portion of the surface of the brain which is known to be more especially the seat of representation of movement. This region of the brain, moreover, is the seat of origin of that special form of convulsions which is known as Jacksonian epilepsy, and which so frequently follows injuries to the skull and the brain.[12]

Horsley's enthusiasm for his hypothesis of medical trepanations in the late Stone Age must have received a boost by his recent success at the operating table. He had, at age 29, on 25 May 1886, operated on his first patient with epilepsy in the National Hospital for the Paralyzed and Epileptic. James B., a 20-year old Scotsman who was under the care of Jackson and Ferrier, had sustained a depressed skull fracture 15 years earlier. He then had intermittent Jacksonian seizures starting in his right leg. More recently, episodes of status epilepticus had developed. Horsley's skilful use of the trephane revealed a vascularized scar in the superior frontal sulcus, and removal of the scar and some surrounding cortex led to seizure freedom for one year.[13,14] Coming back from the operating table where he had cured epilepsy, Horsley felt that his experience with modern trepanation and cortical resection for epilepsy strongly supported his theory on the medical usefulness of Neolithic trepanation for epilepsy. He suggested that removing bone fragments and splinters will eliminate or severely diminish epilepsy. In his words: 'Consequently the operation would gain a certain reputation for the cure of convulsions generally, and as such might have been frequently practised among savages ....'[12]

Although being devoid of demonology, Horsley's surgical theory was met with considerable skepticisms from the anthropologists whose territory he had clearly entered. Sir William Osler, one of the most respected physicians of his time, clearly favored Broca's theory. According to Osler:[15] 'the operation was done in infantile convulsions, headache, and various cerebral diseases believed to be due to confined demons, to whom the hole gave a ready method of escape'. But to many people then and now, the weakest part of Broca's theory was that it confined trepanation to infantile children, he could not provide evidence for trepanation of skulls of infants. Also, others pointed out that a number of skulls showed several trepanation defects which seemed difficult to reconcile with a medical procedure.[16] In addition, Horsley's suggestion that the holes were made over the motor cortex was challenged. To others it seemed that the holes were indiscriminately placed over the vault of the skull. With all due respect for Horsley's enthusiasm, the enigma of Neolithic cranial trepanation baffles researchers to the present days.[1] We still have many firm views and few conclusive data on Stone Age surgical trepanation for epilepsy, if any. With that, let us continue our search for further, and perhaps better evidence of trepanation for epilepsy in Europe from ancient times to 1800.

Trepanation for epilepsy from Ancient Greece to the 18th century

The earliest mention of trepanation with a detailed description of different techniques and indications stem from the 5th to 4th century BC and are found in the Hippocratic writings as quoted above. In his aphorisms 'On Injuries of the Head', written in 400 BC he states:

> and if, when an indentation by weapon takes place in a bone, it be attended with fracture and contusion, and even if contusion alone, without fracture, be combined with the indentation, it requires trepanning.

The use of the crown trepan for drilling is mentioned. Two crown trepans have been found in the grave of a Roman army surgeon in Bingen, Germany (Figure 1.4).

Other procedures used for trepanation are scraping, or an incision resulting in a rectangle or round skull defect. The prevalence of trepanation in Europe is difficult to ascertain,

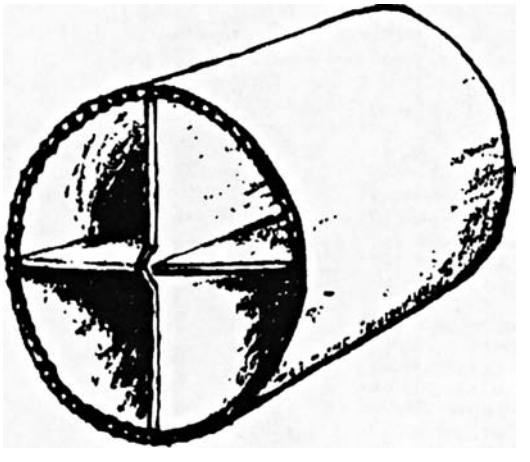

Figure 1.4 Cylindrical crown saw or trepan. This one was found in the grave of Roman military surgeon in Bingen, Germany.[41]

definitions of trepanation vary, and the pre-Roman and Roman custom of cremation may have destroyed evidence. Despite these obstacles, it has been estimated that 630 skulls showing at least one trepanation have been collected in 17 European countries.[17]

In Europe trepanned skulls became rare after the Neolithic era, partly because in the later Bronze Age the dead were mostly cremated. Nevertheless a few examples are available from France, Scandinavia, Germany, Czechoslovakia, Hungary, Rumania, Bulgaria, Russia and other countries.[18] In the European medical tradition, in addition to its use in treating head injury, particularly for depressed fractures and penetrating head wounds, trepanation for epilepsy was practised by ancient Greek and Roman surgeons.[2] According to Temkin,[1] Aretaeus the Cappadocian (ca. 150), one of the most famous Greek clinicians, began the tradition of trepanning as a treatment of epilepsy or convulsions. It lasted, with ups and downs in its acceptance, into the 18th century.[2] According to Caelius Aurelianus, the Methodist Themison employed the trephine as a therapeutic adjunct in cases of epilepsy and paralysis.[19] During the European Renaissance, craniotomies used to be performed for epilepsy, especially of traumatic origin, although the purpose of the operation was still to remove bone fragments or a build-up of fluid, or 'evil' air, – not to remove epileptogenic brain. In the Sloane manuscript, a collection of medical manuscripts at the end of the 12th century, a person with epilepsy ('epilepticus') is undergoing both trepanation and cauterization (Figure 1.5). The legend of the figure is 'epilepticus sic curabitur' (The way to cure an epileptic).

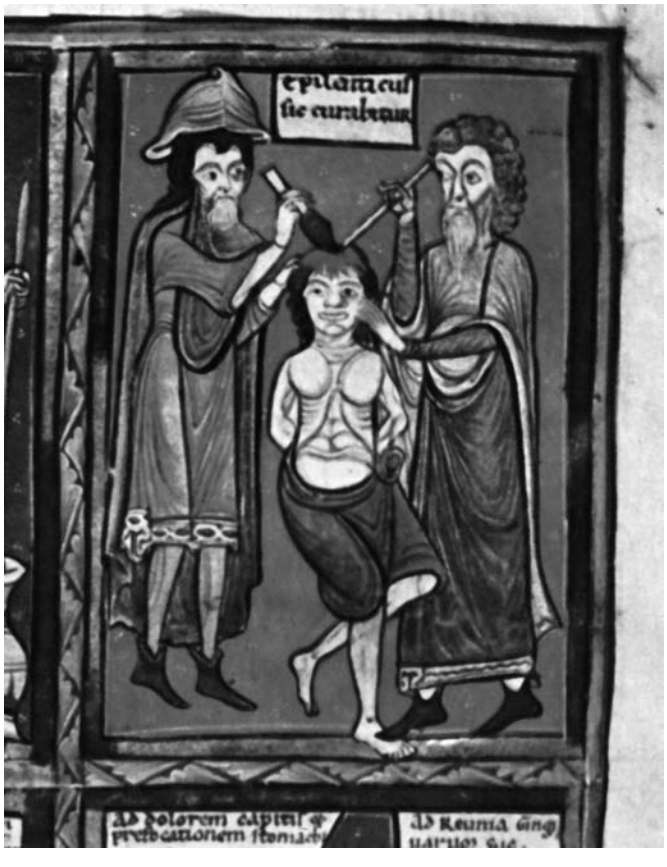

Figure 1.5 The way to cure an epileptic (Epilepticus sic curabitur) is the inscription of this picture showing a person with epilepsy undergoing trepanation and cauterization. The picture is from the Sloane manuscript, a collection of medical manuscripts from the end of the 12th century (with permission, British Library, London).

Cauterization was considered a form of treatment used in the Middle Ages and perhaps before when trepanation had failed to control the seizures.[20] The usual site of application was the back of the head or brow, sometimes the spine, chest or arm. It is unclear if cauterization was usually done before trepanation was considered, or performed in cases refractory to trepanation or together as suggested by Figure 1.5. In a 13th-century surgical text, *Quattor magistri* for example, opening the skulls of epileptic patients was recommended 'that the humours and air my go out and evaporate' (Temkin, p. 235).[2] Although we found no reports if trepanation and cauterization affected seizure control, it is not inconceivable that the drama of the operation may have led to a transient remission of seizures, at least in some patients. It seems that there was seldom a medical reason for the surgery, for example to raise a piece of the skullcap which had entered the inner part of the skull, as a result of an injury, perhaps in war, and which was thought to have caused epileptic seizures in the person. In such a case, the surgeon tried to raise a piece of the bone and thus remove the cause of the epilepsy. However, as will be shown in the next paragraph, medical charlatans, quack-doctors and barber /surgeons took advantage of the concept of medical trepanation for epilepsy, by pretending to remove brain stones 2 × 1′′ by incision of the scalp.

Stone cutting for epilepsy?

Hieronymus Bosch and other early Renaissance artists depicted 'stone operations' in which stones were supposedly surgically removed by quack doctors from the head as a treatment for mental illness including epilepsy. Although we found no reports on postsurgical seizure outcome, it is not inconceivable that the drama of the sham operation on the scalp may have led to a transient remission of seizures, at least in some patients. Probably the most famous depiction of trepanation for mental disease is Hieronymus Bosch's (1460–1516) 'The Cure for Madness or Folly', also known as *The Stone Operation* of around 1485 (Figure 1.6).

After Bosch there were a number of painters, usually Flemish, depicting the removal of stones as a cure for madness and folly. In the 'Stone Cutter' from Jan Sanders of Hemessen (ca. 1500–1555), exhibited in the Prado Museum of Madrid, a barber/surgeon enjoying his work pretends to remove a stone with a razor knife (Figure 1.7). Up to the 18th century 'stone cutters' would roam European countries pretending to be medical healer and making a living with their quackery.

In a miniature of the 'Book of properties' by Bartholomeus from the middle of the 15th century, taken from the section on epilepsy, Saint Lucas is shown to perform an incision of the scalp (Figure 1.8).

These works, shown in Figures 1.6–1.8, have usually been interpreted either as portraying a contemporary practice of medical charlatans or an allegory of human folly, rather than a real event (see Schupbach 1978).[21] However, as trepanation for head injury and mental disease including epilepsy was actually carried out in Europe at this time, another interpretation is that it is likely that Bosch, and the other artists, who produced the various pictures of stone operations, knew of the existence of the actual contemporary medical procedure of trepanation (Gross, 1999).[4] Indeed, the details of their portrayals of 'stone operations' were often very close to the

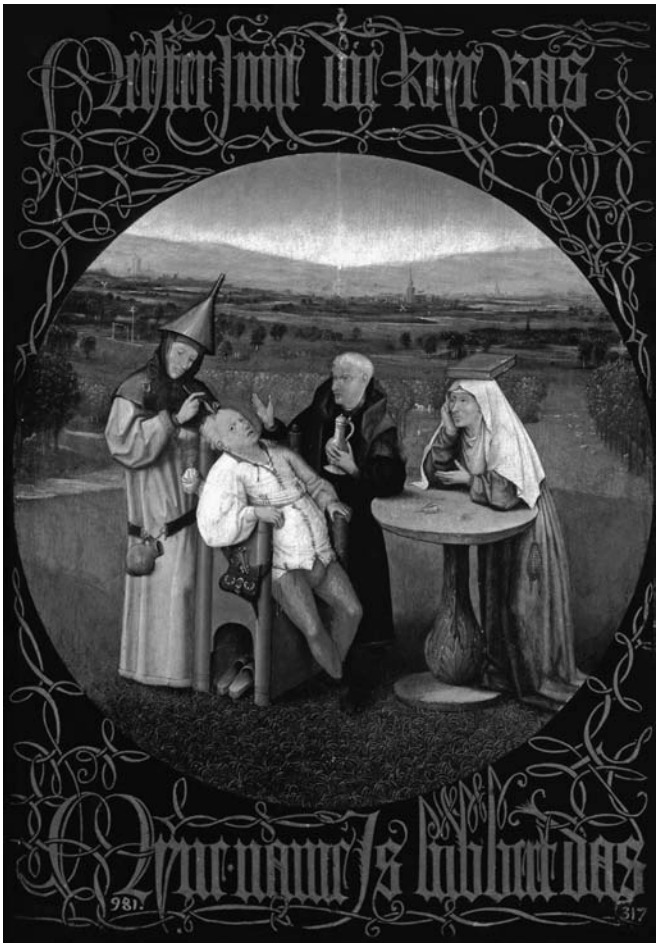

Figure 1.6 'Stone Cutting'. The painting by Hieronymus Bosch from approximately 1845 shows a patient who is undergoing 'stone cutting' by a quack. Stones were thought to be responsible for a number of brain diseases including epilepsy. However, Bosch has exchanged the traditional 'stone' as the object of sham extraction with a tulip. Another tulip is on the table. Two interpretations exist why a tulip has been chosen. One idea is to show that the doctor is a charlatan, as does the funnel hat. The other interpretation is that the flower is a pun on 'tulip head' – meaning mad in the Netherlands. The inscription reads: 'Meester snyt die Keye ras–myne name is Lubbert' (Master cut away the stone–my name is Lubbert Das). Lubbert Das was a comical/foolish character in Dutch literature. Barber/surgeons and quacks earned a lot of money by fraudulent claims that they could cut open the head and extract stones which they had hidden in their palm (with permission, Prado Mùseùm, Madrid).[42]

Figure 1.7 **'**Stone Cutting'. The painting by Jan Sander van Hemessen (around 1500–1555). shows a patient who is undergoing 'stone cutting' by a quack on a fair. The barber/surgeon with knife in hand seems to be pleased about the success of the mock surgery. Behind him one sees a number of stones on a string as a sign of his success as a stone cutter. The stone has already been planted by the quack in the surgical wound and will be removed from the incision any time soon. The next patient to be operated on can be seen on the right. He is desperately wringing his hands and turns his head to the sky, perhaps praying (with permission, Prado Mùseùm, Madrid).[42]

detailed instructional diagrams on trephining in surgical handbooks such as that of Johann Schultes or Joannis sculte-tus' *Armamentarium Chirurgicum of* 1655 as pointed out by Gross (1999).[4]

The first account of epilepsy surgery in the 16th century

The first account of surgery specifically for epilepsy was by Divetus (1527–1586), as described by Meador (1999):[22]

> A bone of the skull of a twelve-year-old youth had been broken and depressed by a fall and had by negligence not been restored. The brain was therefore hindered in its growth, since the injured bone itself could not grow so as to become able to hold a larger brain. Consequently in his eighteenth year the youth suffered from epilepsy because of the oppression of the brain. He was, however, cured by perforation of the depressed bone, for thus the oppression of the brain was removed.

Trepanation for epilepsy in the 17th and 18th centuries: a last resort

In cases with penetrating war injury trepanation was performed by Matthäus Gottfried Purmann (1648–1721), a military surgeon at the time of the Thirty Years' War. He operated on a soldier with an open penetrating frontal lobe injury who suffered from convulsions on the third day. The patient who was unconscious for two days was surgically treated on the third day with a trepanation and extraction of pieces of bone and the projectile (Purmann, 1693).[23] He regained consciousness and survived both the injury and the surgery. Although Purrmann was delighted about the surgical outcome, he cautioned that: 'It is certainly a rare and remarkable example, which occur in hardly one of thousand (cases)' (Purmann 1693).[23] Despite such individual success stories, the benefit of the procedure must have been less impressive for many, considering that by the 17th century trepanation for epilepsy was seen as a last resort. As noted by Riverus in the 'The Practice of Physick' (1655):

> If all means fail the last remedy is to open the fore part of the Skull with a trepan, at distance from the sutures, that the evil air may breath out. By this means any desperate epilepsies have been cured and it may safely done if the Chyrurgeon be skilful (Temkin, 1971, p. 235).[2]

Lorenz Heister (1683–1758), one of the most prominent trauma surgeons of the 18th century, warned however,

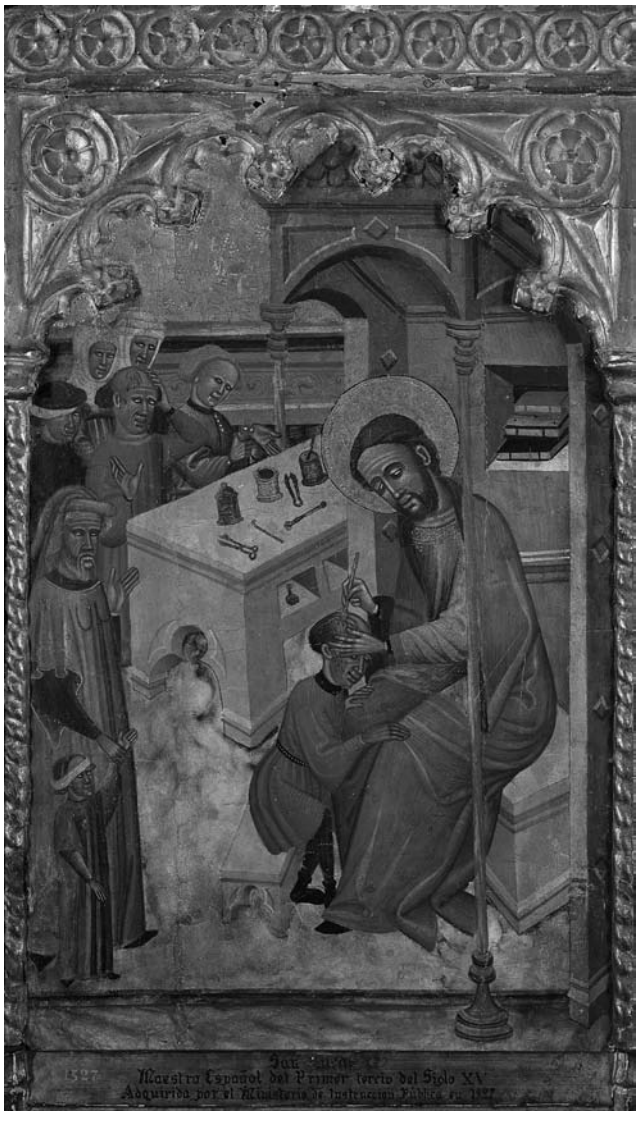

Figure 1.8 Saint Lucas performing an incision of the scalp. A miniature of the 'Book of properties' by Bartholomeus (Bibliotheque Nationale, Paris) from the middle of the 15th century. The adult patient with balding hair has child-like proportions, as has the next patient to be operated on shown on the left. In the background, an adult-sized patient can be seen with bleeding still showing from the earlier incision (with permission, Prado Mùseùm, Madrid).[42]

that trepanation is only clearly justified in fractures or depressions of the skull with clinical symptoms such as convulsions. The French 'Encyclopedie' by Diderot (1763) depicted a trepanation (Figure 1.9). For trepanation, two instruments were commonly used. One was a hand trepan (Figure 1.10a). The other a more sophisticated one for two hand use (Figure 1.10b). Twelve hours after the scalp incision to allow for clotting of blood in the wound, trepanation with the one hand trepan would begin with the so-called male crown with a little longer sharp central point to stabilize the trepan (see Figure 1.10a,b) followed by successive use of the other trepan instruments to be rotated with an hand turn.

By the 18th century, there was agreement that trepanation should never should be performed on epilepsy without trauma.[24]

Figure 1.9 The French 'encyclopedie' depicting a trepanation (Diderot, 1763, cited by Ruisinger, 2003).[24]

From skull surgery (trepanation) to brain surgery

The transition from skull surgery (trepanation) to the beginning of modern brain surgery took place between the mid 18th century up to the middle of the 19th century.[25-27] The 1881 Medical World Congress in London marked the beginning of modern brain surgery.[27] At the Congress established figures of the rapidly changing field of modern medicine – such as David Ferrier, Hughlings Jackson, Jean Marie Charcot, Louis Pasteur, Joseph Lister, Rudolf Virchow – met with the first representatives of the developing field of neurosurgery – William MacEwen from Glasgow, Richman Godlee and Victor Horsley from London, and William W. Keen from the USA. The transition from pre-modern skull surgery to modern brain surgery was prompted by an increasingly critical view of trepanation, by the emerging localization theories of the brain, and last, not least by the introduction of antisepsis and better pain treatment.

Growing concern about the risk of trepanation

The surgeons themselves were becoming increasingly criticial about the merits of trepanation. For example, Benjamin Bell (1749–1806), in his textbook on surgery, denounced extensive use of unproven and unnecessary trepanations.[28] He and others

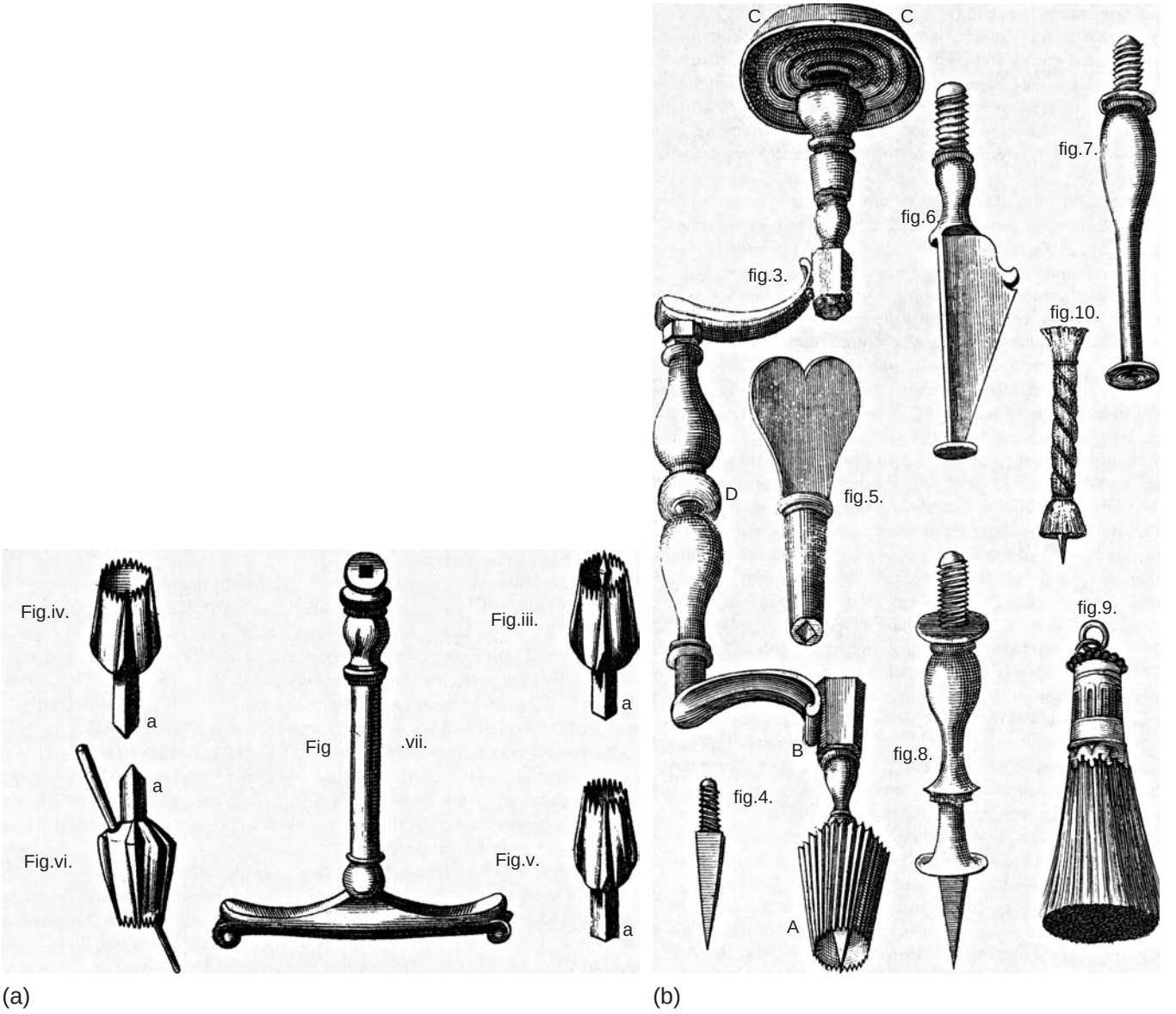

Figure 1.10 For trepanation, two instruments were commonly used. One was a hand trepan (a). The other, a more sophisticated two hand trepan as recommended by Lorenz Heister (b) (from Ruisinger 2003).[24]

pointed out the ill-defined indications for trepanations. Although some experts, for instance, August Gottlieb Richter, Professor of Surgery at the University of Göttingen, Germany since 1766, tried to maintain trepanation by delivering clear clinical indications for the procedure.[29] In his seven-volume handbook from 1780 about surgery ('Wundarzneikunst'), he defined three indications for the surgical intervention in head trauma: the open skull wound, the skull impression fracture, and interestingly, epileptic seizures ('Zufälle'). However, Richter was critical about the prophylactic use of trepanations as performed extensively by Percival Pott (1713–1788) in England. Henri Francois Le Dran from France (1730) noted that not the skull fracture itself but the following brain damage was the cause of drowsiness and loss of consciousness.[29]

Victor Bruns, Professor of Surgery at the University of Tübingen, Germany in 1850, pointed out that besides defined indications of trepanation as in epidural hematoma, subdural hematoma and brain abscess, the interventions in most of the cases were not successful because the intracranial localization of the disturbances was difficult due to limited knowledge of brain function.[30]

The work of Bruns indicated for the first time the transition from skull surgery *per se* to brain surgery. The interest on the functional relevance of the brain stimulated the research in the functional organization of the cortex. The localization theory had both pre-scientific and scientific roots that will be discussed now.

The development of localization theory

For centuries study of the human physiognomy was an accepted wide-spread and social method, method for judging disposition, affection, and character from the features of face and body. Phrenology, as a part of sub-profession physiognomics, tried to explain distinct cognitive and moral abilities of each individual by describing the surface relief of the skull.[31] Franz Joseph Gall (1758–1828) and J.C. Spurzheim were important founders of this theory.[32] Following the

hypothesis that the brain is the organ of the soul they started to project characteristics of the personality directly to distinct regions ('Organgrenzen') of the brain surface. The association between individual functions and distinct brain areas was however generated intuitively and was not scientifically verified. Although phrenology was scientifically untenable, nevertheless it stimulated research of the cortex. Thus phrenology was the first pre-scientific step to associate morphology and function.

Meanwhile Hermann Munk, a physiologist in Berlin, Germany, was the first in the middle of the 19th century who pointed out in his intensive studies of the cortex that the perception of sensoric stimuli is located within the Rolandic cortex.[33] Gustav Fritsch and Eduard Hitzig (1870)[34] from Berlin experimentally verified Munk's findings and extended them to the motor system. A few years later, David Ferrier (1876) delivered the first functional atlas of the cortex. Additionally, he associated the surface of the brain to external points of the skull thus providing important landmarks for surgeons. The motor speech area was described in 1863 by Pierre Paul Broca and the area of sensoric speech by Karl Wernicke (1848–1905). Even as phrenology was discredited, a scientifically verified roadmap of the brain functions was developing step by step. Based on this insight, Jackson initiated the first successful operations in patients with epilepsy by carefully analysing hemimotor seizures.[13,35]

From the morphological point of view,Theodore Meynert (1833–1892) was the first who correlated structurally different cortical areas with their functions. During the following years data were generated in zytoarchitecture (K. Brodmann, W. Campbell), in myeloarchitecture (C.u.O. Vogt), and in angioarchitecture (Pfeifer).

Antisepsis and treatment of pain

In addition to an improved knowledge of brain function and localization of brain function, the introduction of antisepsis and the treatment of pain during an operation was important for the development of brain/epilepsy surgery. Joseph Lister (1867)[36] and Robert Koch (1878)[37] were important pioneers in the introduction of antisepsis. Pain-free operations were performed in Boston by William Morten and John Collins Warren in 1846 for the first time with ether-aerosol and by James Simson in 1847 with chloroform (as) narcotics.

Now the pre-conditions for the development of modern brain / epilepsy surgery were in place.[38]

Conclusions and summary

Pre-modern surgery for epilepsy was undoubtedly performed, at least in some patients. However, surgery was limited to trepanation or cauterization of the bone. Trepanation was done for medical reasons such as to elevate bone fragments after trauma and for mystical reasons such as allow demons or the devil to escape from the ailing brain. However, nobody was thinking about epilepsy as a cortical disorder of the brain before John Hughlings Jackson's did in 1870, let alone that epilepsy could be treated by removing seizure-causing tissue on the surface of the brain by Horsley.[25,26]

Acknowledgments

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2 Epilepsy surgery in Asia before the 19th century

N-S Chu, T Hori, S-K Lee, Y Mayanagi, K Radhakrishnan, and H Shibasaki

For preparing this chapter, data were collected by Dr. N-S. Chu for China and Taiwan, by Dr. K. Radhakrishnan for India, by Drs. Y. Mayanagi and T. Hori for Japan, and by Dr. S-K. Lee for Korea. The collected data were integrated into a chapter by Dr. H. Shibasaki. In spite of extensive literature survey, at least in these countries, clearly documented evidence of epilepsy surgery has not been found until the end of the 19th century.

However, archeological excavation of a multi-trephined skull of a Neolithic woman from the pit-dwellers of Burzahom in the northwestern Himalayan region (Kashmir valley of the present day) suggests that trephination might have been practiced in prehistoric India (4000 to 4300 years ago) for acquired neurological ailments.[1] Multiple skulls from the same era have been found during different excavations, providing evidence that trephination or multiple craniotomy was carried out by the Harappan people of Indus Valley. One particular skull from Burzahom, first discovered in 1968, revealed 11 attempts at trephination, with six neatly completed circular or oval perforations, all in the left parietal bone (Figure 2.1). The left calvarium showed hypertrophy, which could have been related to long-standing atrophy of the underlying brain. It is likely that drills of various sizes were used; however, no instruments for such surgery were found at the site, raising the speculation that an Indus civilization 'surgeon' with personal instruments might have lived then. It was impossible to establish the precise symptoms that might have afflicted the individual, but the Burzahom woman might have been either 'insane, epileptic, or otherwise different'.[1] The carefully performed trephination, suggestive of a multistage procedure on a possibly anomalous skull, argues for a surgical approach for medical reasons on a living person who did not survive the procedure. It is also likely that this might have been part of a ritual in a primitive society that regarded epilepsy or other neurological disease that the Burzahom woman suffered from to be a result of possession by spirits.

About 2000 years ago in India, medicine practice was based on Āyurveda (knowledge and practice of wholesome healthy living), and *shalya chikitsa* (surgical treatment) was one of its major branches.[2] The sage Sushruta was a master surgeon of his time, and his surgical techniques have been documented in the treatise of *Sushruta Samhita* (Sushruta's surgical treatise). Although well versed in many aspects of surgery, no specific references to epilepsy surgery have been made in the treatise. In Ayurveda, epilepsy was referred to as *Apasmara*; the prefix *apa* meaning negation or loss and *smara* meaning consciousness or memory.[3] At that time, aura was already recognized, and epilepsy was classified into four types according to clinical manifestations.[3] Since then, a modern era of neurosurgery in India was not to commence for several millennia, until the arrival of the British. The first medical schools were established by the British in India in the 19th century (Calcutta in 1835, Madras in 1836, and Bombay in 1845).[4] The first department of neurosurgery was founded in 1949 at the Christian Medical College of Vellore, in southern India.[4] The first modern epilepsy surgery in India was performed in 1951 by Jacob Chandy of the Christian Medical College, Vellore.[5]

In China, skulls with holes that had evidence of healing were also found in prehistoric men on recent archeological excavations (personal communication with Professor Wu Xun of Beijing). Shortly after, Hippocrates wrote a monograph on the Sacred Diseases in around 435 BC and opposed the supernatural force as the cause of epilepsy.[6] The first description of a clinical picture of epilepsy in Asia appeared in the *Yellow Emperor's Nei Ching* (The Canon of Internal Medicine) in China which was compiled between 300–100 BC and is considered the earliest work of classic Chinese medicine.[7] It was in the section of *Dian Kuang* that the falling sickness was mentioned. Dian Kuang referred to madness or psychosis; *Kuang* to mania; but *Dian* either to falling or insanity. The ambiguity of *Dian* led to confusion between epilepsy and insanity in Chinese medical literature.[8,9]

In the Siu dynasty (589–618 AD) in China, the term *Xian* was introduced and referred to convulsion or seizure.[10,11] In the authoritative book *Principles and Practice of Medicine* by Wang Keng-tang (1549–1613), *Dian, Kuang,* and *Xian* were put together as the title for a chapter.[12] Chinese medicine was based on the concept of Ying (negative) and Yang (positive), the theory of Five Elements (wood, fire, earth, metal, water), and the idea of a correspondence between microcosm (body) and macrocosm (nature). Thus, the falling sickness was considered a disease of excessive negative force, wind, excessive heat, excessive fullness, or emotional shock. Classification of seizures in China was first attempted by Chao Yuan-feng (610 AD) who proposed three classifications; based on age of onset, *Xian* for seizures occurring before the age of 10 years and *Dian* for those occurring after 10; based on symptoms and causes, *Yang* (positive) epilepsy, *Ying* (negative) epilepsy, wind epilepsy, wet epilepsy, and labor epilepsy; based on causes, wind epilepsy, frightened epilepsy, and eating epilepsy.[10] Another classification by Sun

Figure 2.1 Photograph of the Burzahom skull showing trephination (white arrow) and attempted trephination (black arrow) on the left parietal bone. This trephination is estimated to have been done 4000 to 4300 years ago in the northwestern Himalayan region. (Cited from Sankhyan AR, Weber GHJ, Int J Osteoarcheol 2001[1] with permission).

Szu-mo, a contemporary of Chao, was based on the similarity of epileptic cry to animal cry; goat epilepsy, horse epilepsy, pig epilepsy, dog epilepsy, cow epilepsy, and chicken epilepsy.[11] He also classified epilepsy according to the organ involved; heart epilepsy, liver epilepsy, spleen epilepsy, lung epilepsy, and kidney epilepsy.[11] Many etiologies were proposed and usually based on *Ying–Yang* (negative–positive) imbalance, dysfunction of organs, climatic influence (particularly wind and heat), and disturbance of qi, phlegm, and blood. According to *Nei Ching*, infantile seizure was caused by emotional shock of the mother when she was pregnant,[7] and it was called 'fetal disease'. For later authors, the main cause of pediatric epilepsy was prenatal maldevelopment or postnatal malnutrition.[11] It is interesting to note that only the brain was left out. In the early 19th century, Wang Ching-jen proposed that epilepsy was due to insufficiency of vital energy and blood stagnation of 'brain marrow'.[13] Although he advocated brain as the seat of mind, he still considered the brain as bone marrow inside the skull.

In Chinese medicine, herbal drug has been the main method of treating epilepsy. Prior to the 19th century, there were over 100 prescriptions claimed to be effective for treating epilepsy. Particularly interesting were drugs of animal origin. Scorpion, centipede, earthworm, and stiff silkworm (*Bombyx batryticatus*) were often used to combat epilepsies from wind, phlegm, frightfulness, or stagnation.[14] Certain epilepsies were treated by inducing sweating, vomiting, and diarrhea. Non-medical treatments that may be considered as equivalent to minor surgery have included acupuncture, catgut implantation, and blood letting. Acupuncture was advocated to treat falling sickness in *Yellow Emperor's Nei Ching*.[7] The meridians that connect with the head or the 'brain marrow' were chosen. Acupuncture points on and around the head were also favored.[15] In *Mai Xien* (catgut implantation), a piece of goat (sheep) intestine was buried into the acupuncture points. The layman term for epilepsy was 'goat falling madness' either because epileptic cry was thought to resemble goat's cry,[8] or epileptic convulsions resembled goat's bucking-like movements. Another belief was that the onset of epilepsy was linked to the consumption of goat (sheep) meat while the mother was pregnant.[16] Blood letting by acupuncture needle at acupuncture points was also attempted to release evil phlegm, excessive heat, or other unfavorable conditions.[15] Epilepsy surgery was performed first by Omura[17] in Taiwan in 1942 during the Japanese colonial period and by Duan *et al.*[18] in 1955 in China.

In Japan, epilepsy was described as early as 984 in the first textbook of medicine 'Ishinpou' compiled by Yasuyori Tanba. This compilation was so extensive as to cite more than 200 Chinese and Korean medical books including Yellow Emperor's Nei Ching.[7,19] Since then, symptoms and signs of epileptic seizures have been discussed in details, though without mention of the relationship between epilepsy and brain.[20] The term 'Ten-Kan', meaning epilepsy, is composed of two Chinese characters; 'Ten' (the same word pronounced Dian in Chinese) meaning adult epilepsy and 'Kan' (the same word pronounced Kuang in Chinese) meaning childhood epilepsy. Today 'Ten-kan' is an official medical term for epilepsy in Japan. An impressive drawing of generalized epileptic seizure, compiled in a medical book 'Ihon Yamai no Soushi' (Illustrations of Diseases – a variant version) in the 12th century, surprisingly shows precise observation by the painter to express dreadful aspects of a generalized convulsion[21] (Figure 2.2). In the 16th century, the Portuguese came to Japan and introduced European medicine, later followed by the Dutch. Starting in 1639, Japan had been closed from the western world for 230 years due to the national isolation policy of the Tokugawa Shogunate, during which time only the Dutch traders were allowed to come to Dejima, a small island of Nagasaki. Through this narrow canal, Japanese scientists sought information about the progress in the world outside. For example, in 1699 Yeikyu Narabayashi translated the Dutch version of Ambroise Pare's textbook of surgery into Japanese. This book was published in 1706 as 'Geka Soden' and widely distributed.[22] Genpaku Sugita had a very rare occasion to watch dissection of a cadaver in 1771. Impressed by the exactness of the drawings of a book, Tafel Anatomia (a Dutch version of J. A. Kulmus' Anatomische Tabellen in 1647) that he had bought before, he in collaboration with Ryotaku

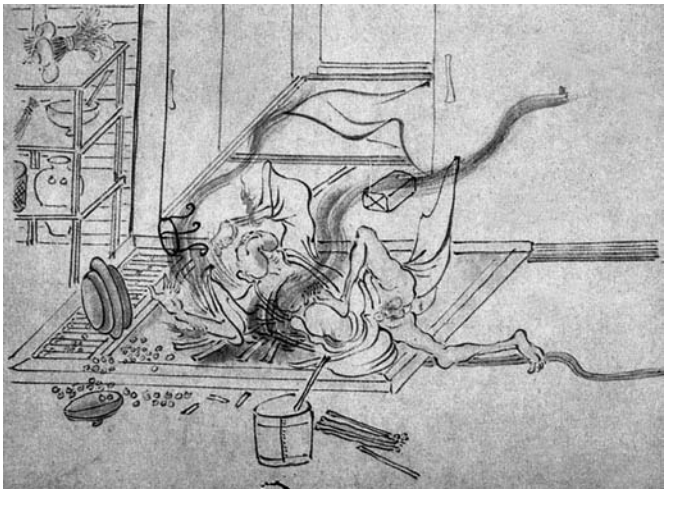

Figure 2.2 Drawing of generalized epileptic seizure from the medical book 'Ihon Yamai no Soushi' (Illustrations of Diseases – a variant version) compiled in the 12th century in Japan (from collections of National Kyoto Museum).[21]

Maeno translated this book into Japanese in 1774; 'Kaitai Shinsho' (New Text of Anatomy).[23] At the dawn of the 19th century, Seishuu Hanaoka accomplished total resection of breast cancer under general anesthesia for the first time in the world. However, nothing about surgical treatment of epilepsy was documented in Japan until the end of the 19th century.[24]

Epilepsy surgery in Japan developed in parallel with general neurosurgery. Susumu Sato made a trephination for a depressed fracture and drainage of a brain abscess during the Meiji civil war in 1877. This operation is admitted as the first craniotomy in Japan.[25,26] According to the monograph by Keiji Sano,[27] Hayari Miyake in 1893 precisely described an operation for an open depressed fracture performed by Julius Scriba, Professor of Surgery at Tokyo University. In his paper, Miyake also referred to Jacksonian seizure and cerebral functional localization.[27] Later, Miyake became Professor of Surgery at Kyusyu University and in 1905 removed a brain tumor successfully for the first time in Japan. Hayazo Ito was the first surgeon in Japan who took interest in epilepsy surgery[28,29] (Figure 2.3). During three years' stay in Bern, he learned cranial decompression for epilepsy from Theodore Kocher, and performed experimental studies on the treatment of epilepsy based on Dr. Kocher's idea that epilepsy occurs due to abnormal excitation of motor cortex following abrupt increase in intracranial pressure.[29] After returning home as Professor of Surgery at Kyoto University, he reported his own experience on 39 cases at the first meeting of the Japan Medical Association in 1902.[30] Chugei Yamagata of Sendai, impressed by Ito, also reported six cases of cranial decompression in the same year.[31] Ito kept his interest in epilepsy surgery throughout his professional career and later applied a more essential procedure to the treatment of epilepsy, such as the repair of depressed fracture or cortical resection by Horsley. Until his retirement in 1924, he operated upon 182 cases of epilepsy.[32] Further development of epilepsy surgery in Japan has been summarized by Seino and Mihara in the previous edition of this book.[33]

Figure 2.3 Profile of Dr. Hayazo Ito (1864–1929) who was the first surgeon in Japan who took interest in epilepsy surgery.

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3 Epilepsy surgery in Latin America before the 19th century

MG Campos

Introduction

Even though epilepsy and its treatment are as ancient as mankind, its historical background within the pre-Columbian South American peoples is hardly known since the Incas and their predecessors did not have a writing system. However, they had significant graphic representations in ceramics, such as the so-called *huacos*. These figures represent different diseases and medical procedures.

Such knowledge can be tracked back through the Paleopathology, a science devoted to study the diseases that are likely to be demonstrated in ancient human or animal remains. Therefore, little was known about epilepsy prior to the advent of written documents since the materials used by Paleopathology consist basically of bone remains from caves, deposits, or from a necropolis. The main pathologies that can be diagnosed are traumatic injuries (fractures) (Figure 3.1), infections (osteomyelitis, syphilis, tuberculosis, etc.), metabolic diseases (raquitism, scurvy), degenerative diseases (arthrosis, spondylosis, etc.), bone tumors, or meningeomas and dental conditions.[1,2]

Trepanations in pre-Columbian America

The word 'trepanation' means removal of a fragment of skull bone by means of an instrument called a trepan, which comes from the Greek word *tripanon* (puncher).[3] In the pre-Columbian America, trepanations were carried out only occasionally in North America, Central America (Mayas), and Mexico, where the Zapotec and then the Mixteca cultures established themselves in the huge city of Monte Alban, Oaxaca. They probably carried out trepanation just as a ritual, since the skulls found belong to young people of both genders.[4,5]

Nevertheless, trepanations became more frequently performed on the coast of the South America Pacific Ocean, within the arid climate zones that today belong to Peru and North of Chile (the Paraca, Nazca, and Mochica cultures) as well as in the central Andean highlands (Altiplano) of Peru and Bolivia (Huari or Wari, Tiahuanaco, or Tiwanaku, Chimu, and Inca cultures).[6] The dry climate of the Peruvian coast has allowed an excellent conservation of more than 15,000 mummies from the pre-Columbian period; most of them are stored in the National Museum of Anthropology and Archaeology in Lima, Peru.[7] The age of these mummies can date back to 2500 years and 5% of them show evidence of *in vivo* trepanation. Seventy percent of the skulls from the pre-Columbian Peru belong to men.

The Spanish chronicles of the conquest make no reference of trepanations, thus it is suspected that these practices were either abandoned or secretly practiced during this period. Furthermore, little or no attention was paid to the 'surgical instruments' that decorated the museums. In fact, most of the conquerors were not erudite men and just a few of the participants of the expeditions wrote the chronicles. Felipe Guaman Poma de Ayala[8] was an exception; he illustrated his observations in hundreds of drawings. That was the way we probably got the first description of epilepsy in the pre-Columbian Peru. It referred to Mrs. Chimbo Mama Cava, spouse of Capac Yupanqui, one of the last Inca emperors, who ruled until he died in 1525[9] (Figure 3.2). Other references of epilepsies in the Inca period come from Garcilazo de la Vega's writings in *Real Comments on the Incas*, which describe probable focal epilepsy events.

There was no specific term for 'epilepsy' in *Quechua* (a language used by the Inca people), which defines it as a special neurological condition. However, many Quechua expressions might have been used to refer to epilepsy, e.g. *Sonko-Nanay*. This is based on the fact that *Sonko* has different meanings: heart, mind, and in some cases, brain; i.e. the essential component of the human being, while the word *Nanay* means pain or illness.[9] Therefore, *Sonko Nanay* may have been used to refer to epilepsy cases, mental diseases, syncope, etc.

It has also been posed that the Quechua word *ayahuayra* may have been used to refer to epilepsy. This word derives from the expression *aya*, which means death, and *huayra*, wind or air. Consequently, the Quechua cultures may have associated epilepsy to death.[10]

The word *Perlesía* was used by the Spanish conquerors to denominate a series of 'neurological syndromes' such as stroke, hemiplegia, and possibly epilepsy or 'non-neurological diseases', e.g. heart diseases or syncope.

The first trepanned 'Incaic' skull was described by Samuel G. Morton in his book *Crania Americana* in 1839, though it was interpreted as a war injury. In the year 1865, Efraín G. Squier, explorer and USA Business Attaché in Peru, published his book 'Incidents from a trip to Peru, country of the Incas' and presented part of a trepanned skull in the Academy of Medicine in New York (Figure 3.3).[11] Squier showed this trepanned skull to Paul Broca (1824–1880), who had previously described the language localization and the hemispheric dominance. In addition to having been one of the

Figure 3.1 (a) Skull with a depressed frontal fracture (bone depression). (b) Skull with exophytic meningioma. National Museum of Anthropology and Archaeology, Lima, Peru.

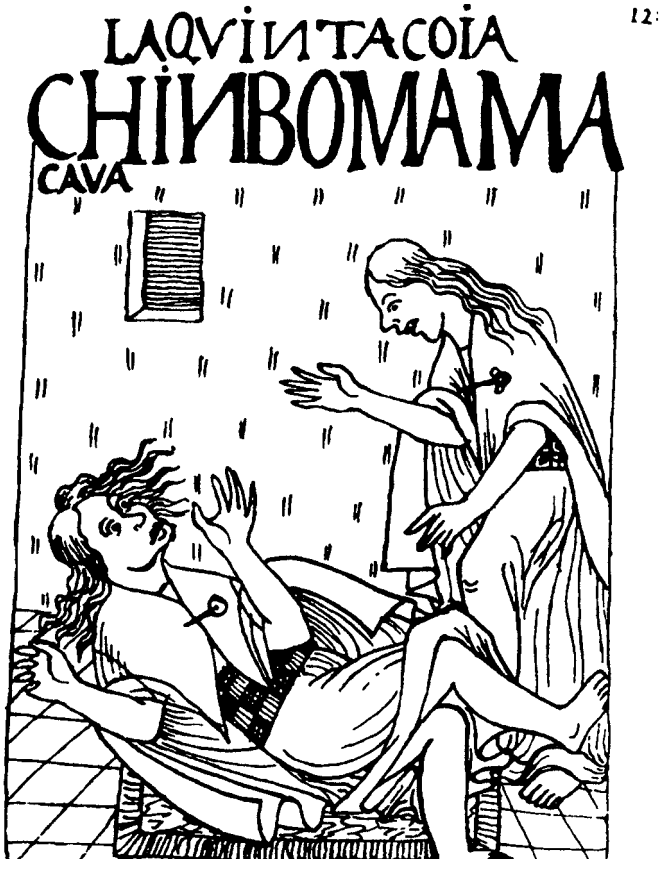


Figure 3.2 Drawing from Guaman Poma de Ayala, who describes: 'The lady was very beautiful, peaceful and modest. After her marriage she got epilepsy, which made her suffer three times a day. She cried and screamed, attacked others, and pulled her hair. She was left very ugly'.

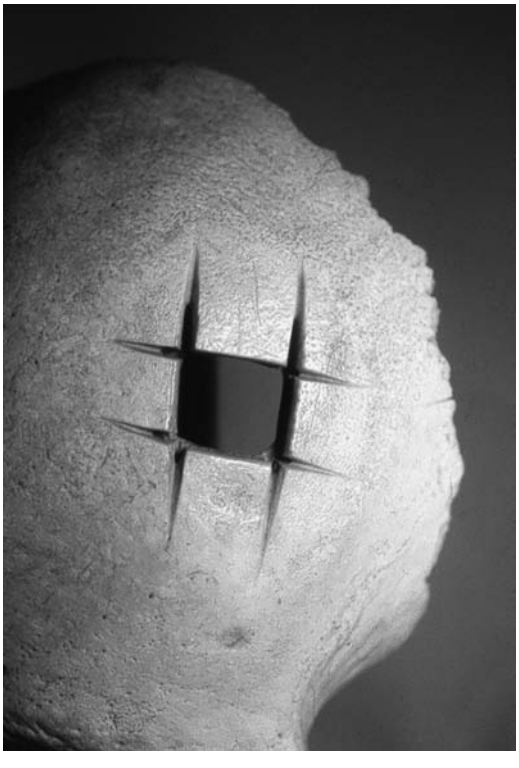


Figure 3.3 Skull from the Inca cemetery of the Yucay Valley, showing a left frontal quadrilateral trepanation and slight healing signs. It was obtained by EG Squier in the house of a lady from Cuzco. The skull is dated between 1400 and 1530. At present, it is found in the Natural History Museum of New York.

founders of the Anthropologic Society of Paris, Broca suggested that the Inca skull belonged to a person that had survived for 1 or 2 weeks.[12] This discovery preceded many trepanned skulls that were subsequently found in Europe (France, Germany, England, Check Republic, etc.). These skulls were also studied by Paul Broca, who was the first medical doctor in modern age to propose trepanation as a possible surgery for epilepsy (this had been previously mentioned by Hippocrates). It was also proposed later on by Victor Horsley (1857–1916) upon examining Broca's collection of trepanned skulls.[13]

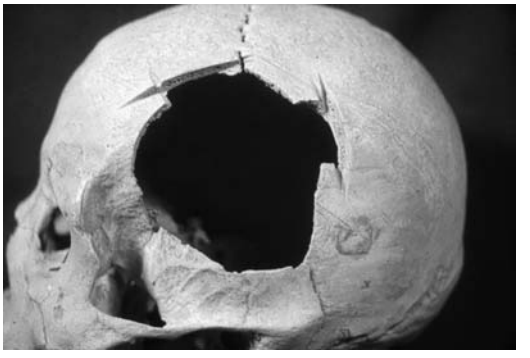


Figure 3.4 Operated fronto-temporal fracture, with no patient survival (no healing signs), which could belong to a soldier hurt during the battle.

Historical background

There is a mistaken tendency to refer to 'Inca trepanations', since the Inca Empire was rather new at that time. It is estimated that it was founded by *Manco Capac* by year 1200 AD, following unification of all the peoples of the region under only one Emperor. In other words, when the Spanish arrived, the Inca Empire was only 300 years old. In fact, most of the trepanations were carried out by pre-Incaic peoples (Paracas, Nazca, Mochica, Ica, Huari, Tiahuanaco, and Chimú cultures), who practiced them much more frequently and long before the Incas.[6] The oldest skulls come from the Paraca culture (1000–200 BC) located in the South-Central Coast of Peru, and also from the Tiahuanaco culture, around the Titicaca lake, which is today Bolivia, where they found trepanned and deformed skulls dating back to 1500 BC.

The Incas used to name their empire as *Tahuantinsuyu* or 'the land of the four corners'. In 1492, when Christopher Columbus (*Cristóbal Colon*) discovered America, the Inca Empire was already the largest in the world. This included the current countries of Peru, Ecuador, Bolivia, and some parts of Chile, Colombia, and Argentina. Unfortunately, the Inca empire fell in less than 100 years, soon after the arrival of the Spanish Francisco Pizarro, in Tumbes, together with 179 conquerors in 1532.[7]

Purposes of trepanations

Craniotomies seem to be a common cultural practice among many societies, independent of the period (since the Neolithic, 10,000 years to date) or geographical location (Europe, Latin America, Oceania, Northern Africa, etc.).[13–19] However, in no other place but the South American Pacific lands were such a significant number of procedures performed, with an estimated survival rate in 50–70% of 'patients'.[7]

The probable motivations of the pre-Incaic peoples to practice trepanation could have been as follows.

Treatment of cranial trauma

This is based on the fact that these were warrior peoples who used stone mallets; therefore, they were exposed to trauma and cranial fractures, including bone depression. Moreover, the fractures could have been associated to intracranial haematomas. There are multiple trepanned skulls associated to fractures supporting this hypothesis (Figure 3.4); many of them show injuries in the temporal or left fronto-parietal area, which indicates that the attacker was right-handed. Also, trepanned skulls have been found in the altiplanic Inca's military zones, the valley of Urubamba, near Cuzco (capital of the Inca Empire). It has been suggested that from 30% to 50% of the trepanations in the altiplan were due to battle injuries.[11,20]

Religious procedures

Many of the trepanned skulls show deformations provoked by pads and boards that were tied to the head since childhood (Figure 3.5). Some of these deformed skulls also show some trepanations. Even today there are some seaside tribes that carry out ritual trepanations in the occipital region, which is also seen in the pre-Columbian adult skulls of the Huara culture.[2,21]

Epilepsy surgery

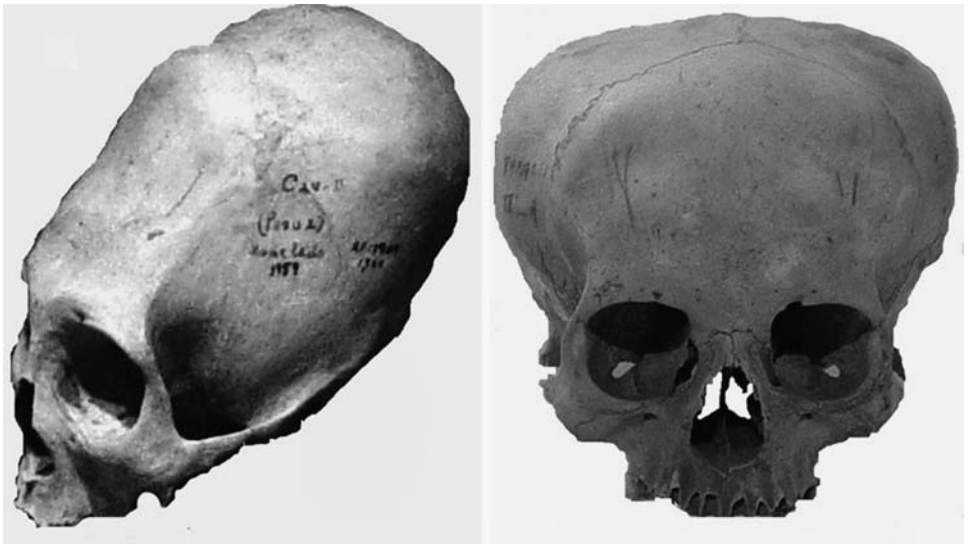
It has been proposed that trepanation may have been performed to remove the cause of the disease. This is based on the fact that most of the trepanned skulls have neither fractures, nor deformations; however, many of them show more than one trepanation, performed at different times. This is known because there are different healing levels in the various trepanations of the same skull (Figure 3.6). Therefore, these were individuals with chronic conditions (epilepsy, headache, etc.) or people predestined to multiple trepanations, due to unknown reasons.[19,20] Such hypothesis is contrary to the finding that trepanations in children were very few.

It is also worth noting that the Incas, unlike the Mayas, did not attribute the cause of epilepsy to 'a possession by the devil'.[22]

Pre-Incaic peoples as neurosurgeons

Surgery rooms

Craniotomies were practiced throughout the Inca Empire, except in the Amazonian area, corresponding mostly to the actual Peru, part of Bolivia, and North of Chile, though there were also necropolis that were real trepanation centers. The existence of neurosurgical centers or training schools in



(a) (b)

Figure 3.5 (a) Deformed skull in the shape of a tower. (b) Skull with bilobulated deformation.

Paracas and Cuzco has even been suggested, where possible ruins of hospitals have been found.[23]

The 'neurosurgeon'

Probably, there were two types of 'surgeons': the ones who had been trained, called *Hampicamayac* (Figure 3.7) and the others called *Soncoyoc* (Chamanes), who had neither knowledge nor technical skills.[6,11] The expression *Sirkak* is also known to refer to the surgeon or 'sangrador' (blood-letter). Most of the trepanned skulls show a 'surgery' performed with anatomical knowledge, e.g., outside the path of the venous sinuses. Besides, more than a half of the skulls found show signs of survival, either with healing evidence or osteomyelitis. The risks of infection were evidently present and multiple skulls with different degrees of osteomyelitis were found (Figure 3.8).

Sedation

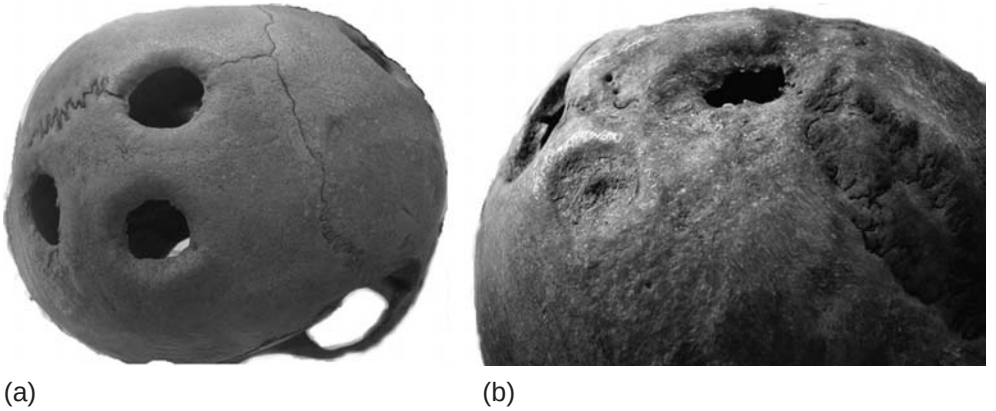
Sedation may have been applied to conscious patients, using fermented 'mandioca' or alcoholic beverage. It is also believed that they used Coca (*Erytroxylon coca*) in powder and chewable coca leaves. This plant has anesthetic properties and it is native to the Andes.[24] Thus, it helped to relieve the pain produced by the scalp incision, which was the only painful part of this surgery.

Surgical instruments

Both stone cutting instruments, like volcanic crystal (pedernal) and a volcanic rock called obsidian, as well as a knife-shaped piece of metal (copper or bronze) known as the classical 'Tumi' (Figure 3.9), which is a knife in the shape of a half circle, were used. The knife occasionally had a human or animal figure engraved in its handle. There were also pincers that may have been used to remove bone fragments or for depilation purposes (see Figure 3.13).[4,11,25,26]

Haemostasis

The bleeding may have been controlled with the use of extracts from the roots of *ratania* and the liana *pumacbuca*, both of which are rich in tannic acid and well known by the pre-Columbian peoples.[7,24]



(a) (b)

Figure 3.6 (a) Skull with multiple trepanations, at different times. (b) Skull close-up with multiple craniotomies and signs of regeneration at its edges, which indicates survival.

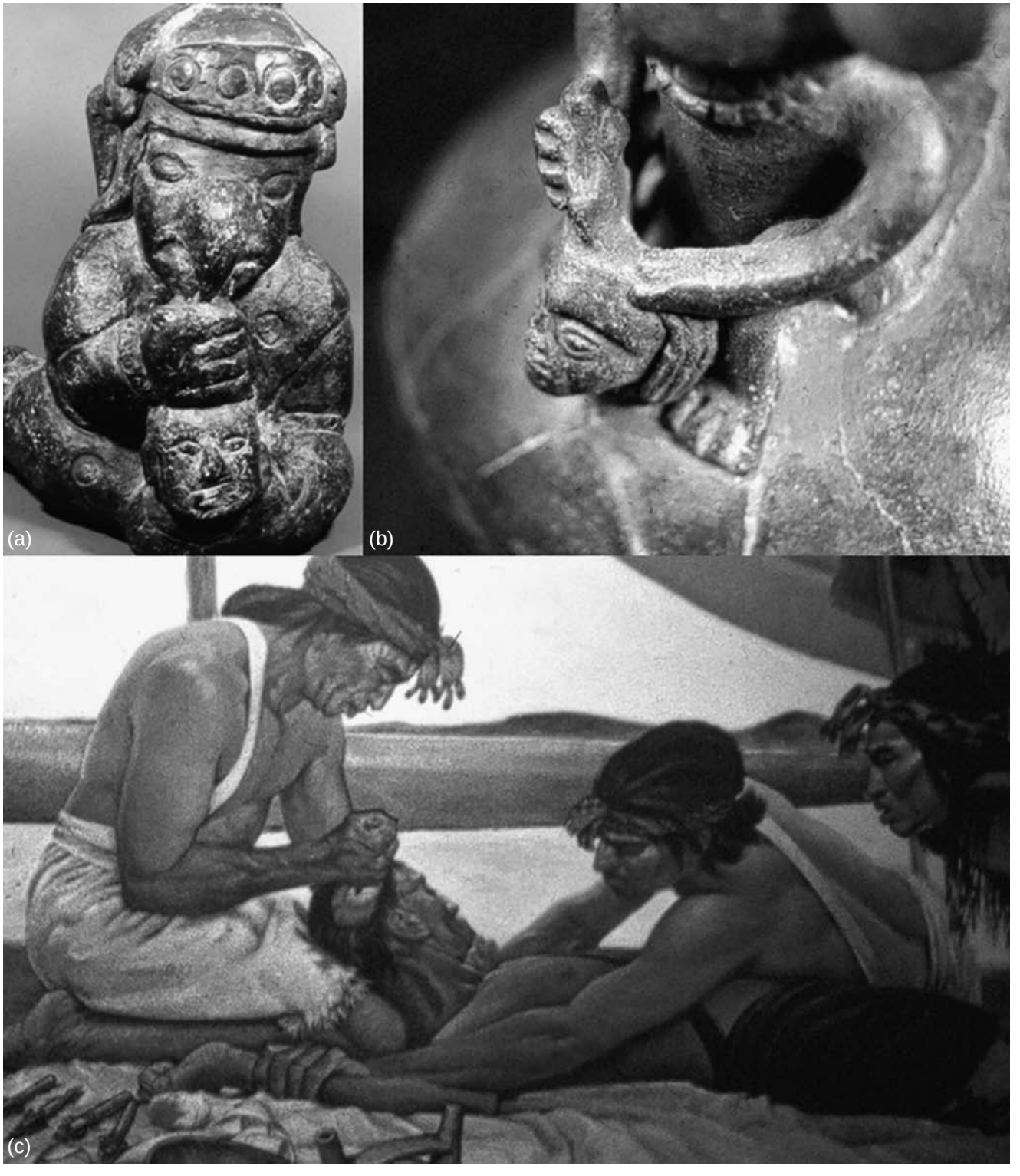


Figure 3.7 (a) Ceramics representing skull surgery performed by a man with a bird-mask. (b) This ceramics was found in the 'Casma' cemetery, on the Peruvian coast, near the Callejón de Huaylas. This *huaco* was made public in 1916 by Dr. Carlos Morales-Macedo. It shows a 'surgeon' working on a skull with a Tumi. (c) Artistic representation of an Incaic trepanation; the surgical instruments are underlined in the inferior left angle, together with the sedating beverage.

The surgical technique

Skulls with no significant signs of healing and cases that failed to survive the surgical procedure have allowed us to gain a wider knowledge of the techniques employed. There were basically three (Figure 3.10). The first corresponded to craniotomies with straight cuts limiting quadrilateral, polygonal, or circular edges in these procedures. They possibly used hard obsidian knives with strongly polished edges. The second type referred to scrapings, probably by means of an abrasive stone tool, which was rubbed over the surface of the skull until the internal skull board was pierced and it reached the meninges. Subsequently, the opening was widened to keep on fracturing the weakened borders of the bone. This technique was used by the Paraca culture, but these skulls usually did not show signs

(a) (b) (c)

Figure 3.8 (a) Bone regeneration, which would probably cause spontaneous healing or by means of healing herbs. (b) Extensive osteomyelitis with bone porosity. (c) Wide bone healing which might have taken many years of regeneration and survival. It is worth noting that these are probably accompanied by a significant suppuration of the wound after surgery or due to meningitis.

(a)

(b)

Figure 3.9 (a) Volcanic stone (Obsidian) with a pointed shape, used for trepanations, which was either mounted or not in a wooden handle. (b) Half-moon shaped knives called Tumi. It was originally an axe, which was used for multiple cutting activities. Therefore, this was not a specific surgical instrument and it was possibly used to open the skin of the patient, not the bone, unless it was a Tumi of the chisel type.

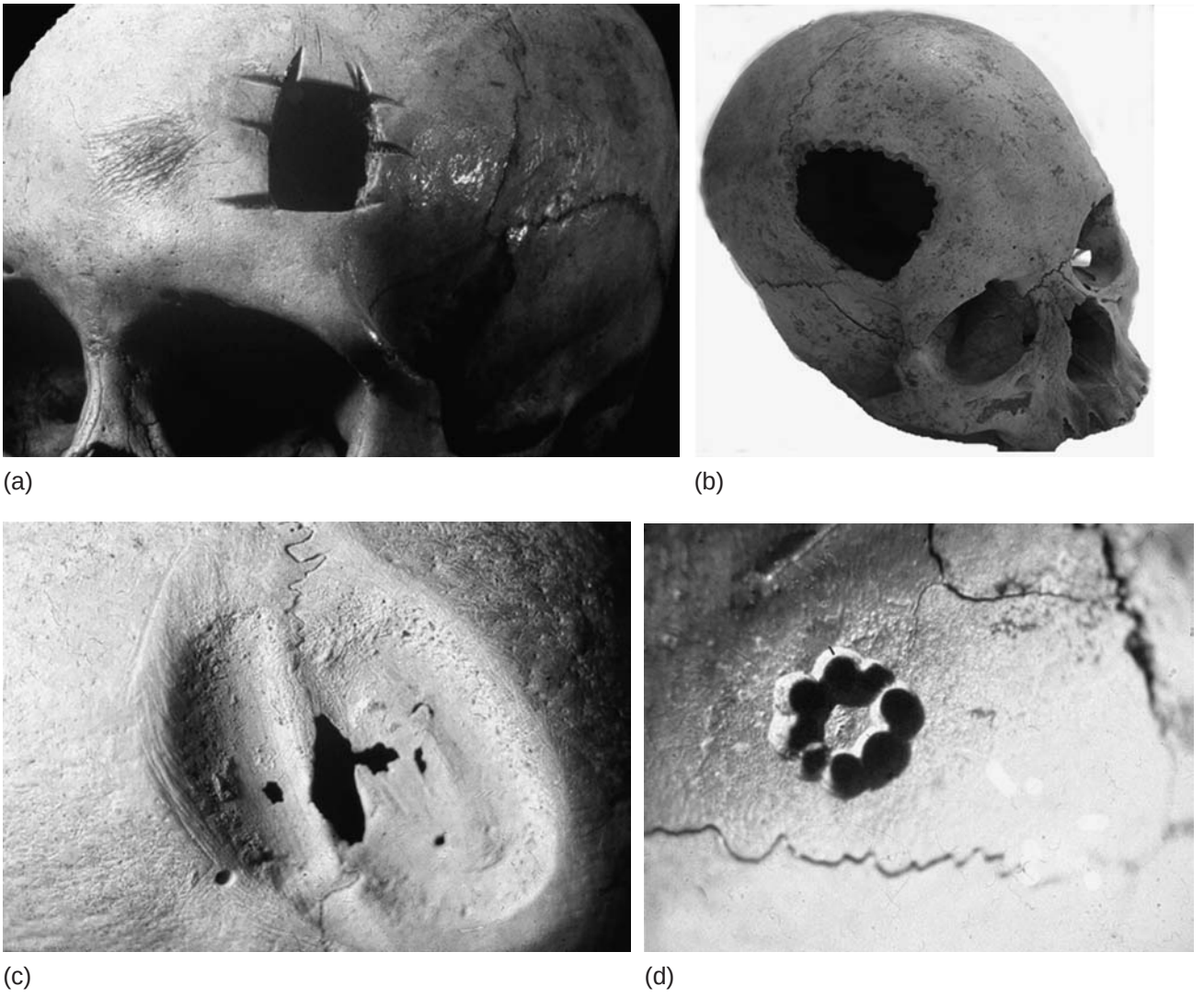


Figure 3.10 (a) Lineal trepanation; evidences of a cutting tool are seen in the borders, (b) Craniotomy with cutting tool of the punch type, which leaves marks on the borders. (c) Skull close-up, showing the external board, the spongy one, and the internal board. The diploe porosities indicate that there was no survival. (d) Trepanation by knife rotation over the skull.

of survival. The third technique corresponded to multiple drill holes bordering the bone area to be removed. Punchers with polygonal profiles were rotated and spinned until the skull was perforated.[6,7,11,27]

Suture

Metal needles and pieces of cotton thread have been found in burials, which suggest the method used to suture the skin. Another hypothesis is that they tied up the hair to the edges of the wound and then joined the borders.[24]

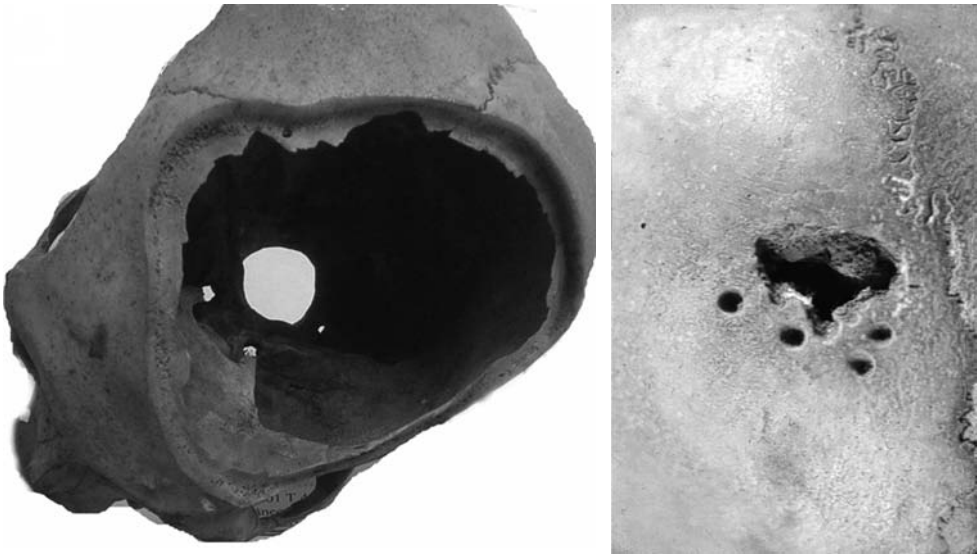
Surgery time

It is estimated that it took an expert neurosurgeon between 30 to 60 minutes to carry out a trepanation. The latter has been demonstrated on two occasions in Peru. The first case was in Cuzco in 1944, where two neurosurgeons operated with original pre-Incaic instruments on a 22-year old young man with cranial trauma after a tree fell down on his head. The instruments used were obtained from the Archaeological Museum of this city. They used a Tumi to make the incision in the skin and the separation of the periostium; and then they were able to open the bone with a sterilized obsidian chisel and were able to carry out a 6×3 cm. trepanation. They sutured the edges of the wound with a *champi* needle. The surgery procedure lasted one hour but the patient died 7 days later because of pneumonia. We must remember that antibiotics were not yet available.[28]

The second case was in 1953, where two Peruvian neurosurgeons (Graña and Rocca)[29] first carried out experimental surgery on a cadaver. They obtained Tumi and obsidian knives from the National Museum of Anthropology and Archaeology in Lima. They then practiced an *in vivo* surgery on a patient with cranial trauma, hemiplegia, and aphasia. The patient was intubated and sedated and then the sterilized pre-Inca instruments were used to perform an oval craniotomy with exposure of the meninges and drainage of a haematoma.

Complications

The first complication was death, which occurred in less than 50% of 'patients' (Figure 3.11). However, bone infections (osteomyelitis) were very frequent, presenting either as little porosities around the trepanation, or as severe infections



(a) (b)

Figure 3.11 (a) Extensive craniotomy, with no survival signs. (b) Some trepanations consisted of just some small holes, but they also show osteomyelitis at the borders.

including signs of regeneration. In such cases the original type of trepanation cannot be recognized, but they are indicative of survival for many years. We can even find mummies showing replacement of the normal skin by a fibrous tissue, which becomes adhered to the meninges. Some individuals died during surgery and then were mummified; this has allowed us to learn about the way the 'neurosurgeon' opened the skin of the skull with cross-like (cruciform) incisions.[11]

Figure 3.12 Skull with two trepanations, the one at the back shows a cranioplasty with a golden slice. The 'patient' does not present signs of survival. This skull repair method may have been applied to people belonging to aristocracy (Lima, Peru).

Cranioplasties

It was has been proposed that the treatment of bone that failed to heal may have been done with organic elements, such as mate or coca leaves or pumpkin skin, though it is biologically impossible. Likewise, small gold slices used to repair such bone defects have been found (Figure 3.12). They are believed to have been used in patients who were members of the nobility; however, these skulls do not present survival signs, which suggest a failed attempt to close the bone defect.[30]

Variant of a trepanation

A variant of a classical trepanation corresponds to a pseudo-trepanation (scraping or small trepanation) carried out over the inions of the occipital region, in the masto-occipital suture, over the so-called 'wormian bones' (Figure 3.13), which are small intercalated bones. Fifty-two percent of these skulls with wormian bones also show intentional deformations,[21] as compared to 33% of the skulls with no deformations. Some authors believe that these were not real trepanations but bone necrosis due to pressure.

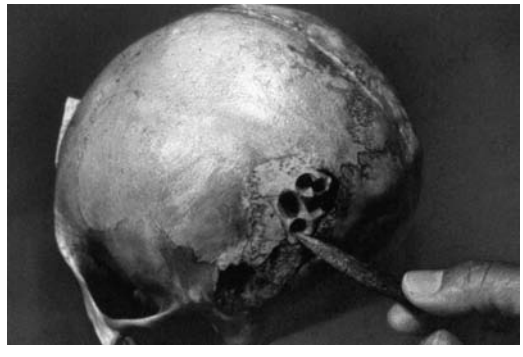


Figure 3.13 Trepanation with a punch in Wormian occipital bones (Lima, Peru).

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4a The history of epilepsy surgery in the United Kingdom

CE Polkey

Introduction

A historical survey of epilepsy surgery in any particular geographical location must be subject to two influences. The first is the need to recognize that only major players can be identified and considered to have an influence on the course and development of the topic. The second is that the course of epilepsy surgery has to be viewed in relation to developments in other geographical areas and also the ebbing and flowing of the subspeciality within the main body of neurosurgery. This review has been assembled on the premise that a number of periods can be identified. In some circumstances the pre-eminence of one group or individual may have been the major inspiration for a particular phase or development. It is convenient therefore to consider the following sequential periods:

1. The early years:	1890–1930
2. The doldrums	1930–1950
3. The perception of pathology	1950–1970
4. The influence of direct brain imaging	1970–2005
5. The present	2005

These divisions are of course artificial and merge into one another. The first two periods between 1890 and 1930 are no longer within the experience of any living individual and the material for these sections has been obtained from literature review and 'folklore'.

The early years

Trephining or trepanation was a well accepted method of operating on the head at the time when this review starts. There are some 56 papers in the literature from British authors describing the use of this procedure in epilepsy. The earliest, from Newcastle in 1877, describes a case of an acute seizure following a frontal wound. The patient was operated seven days after the injury and subdural pus was found. The patient unfortunately died seven days later and at autopsy there was extensive subdural pus.[1] Thereafter there are a number of accounts, some of which describe treatment in acute cases but others at some interval after injury, for example Bennett and Gould describe a patient operated six years after injury for focal seizures. The dura was opened but nothing abnormal was found. The fits are said to have been relieved for five months.[2] In the early part of this period the basis of surgery was based on the idea that thickening or distortion of the skull could, of itself, cause epilepsy and if this distortion or thickening were relieved the epilepsy would be cured. A clear distinction is made in the literature between 'Jacksonian' epilepsy and other kinds of epilepsy. It was recognized, especially with increasing knowledge of cerebral localization, that 'Jacksonian' epilepsy was connected with local brain injury and this was usually due to head injury. The procedure was still regarded seriously and much debated. The notion that such operations were undertaken lightly or thoughtlessly is not borne out by the literature. It must also be remembered that the medical treatment of epilepsy at that time was inefficient and as individual patients developed epilepsy the frequency and severity of the seizures would increase to a level seldom seen nowadays, causing the patient and their advisers to seek desperate remedies. In addition, as the 19th century drew to a close, the introduction of anesthesia and antisepsis made the procedure safer and to some extent more effective by allowing the surgeon time to work. Walsham describes a case operated at St Bartholomew's Hospital where trepanation was performed twice on a patient with post-traumatic epilepsy four years after a fall from scaffolding. These operations reduced the frequency of the patient's seizures although the dura does not appear to have been opened. He then reviews 82 cases of post-traumatic epilepsy described in the literature. Mortality was 20.2% but he also notes that at that time mortality from trephining in general was between 10.6% and 14.5% and infers that the increased mortality is due to late deaths not related to the surgery. His conclusion, which may be that of an enthusiast, is as follows.

> Where there is a clear history of injury, a well-marked cicatrix or sinus leading to dead bone and the epilepsy has as clearly followed the injury, there can, I think, be no doubt of the propriety of trephining, and there are few surgeons, I should imagine, who under such circumstances, would hesitate to do so.

However he goes on to say that if there is a history of head injury and some indication of localized trauma, even if only a persistent tender spot then trephining is justified. He supports this argument partly by stating that it is not a dangerous operation especially if 'the membranes are not wounded'.[3] One of the intriguing puzzles of this period, recognized by practitioners at the time, is how epilepsy could be cured without operating on or exposing the cerebral cortex. However the case reports in the late 1890s almost universally describe opening

of the dura with pathological lesions in many cases. After that a number of successful cases were described. On some occasions more than one trephining was performed. There is a particularly interesting case described by Bidwell and Sherrington in 1893. After head injury a patient developed focal motor seizures involving the foot and ankle. Two trephines with brain resection were carried out. At the first operation discolored brain possibly an old hemorrhage, was removed without improvement. At the second operation Sherrington stimulated the brain and part of the leg area was removed. There was an improvement in the fits affecting the leg but the focal motor seizures affecting the arm were unaffected, however, the patient's daily seizures were abolished.[4] Ransom also described stimulation of the cortex under similar circumstances in 1892.[5] Taylor, discussing the question of operation in the treatment of epilepsy observes that 'Again a history of epileptic fits extending over twenty five years or more is anything but an invitation to operation.' [6] The attitude of physicians towards the operative treatment of epilepsy is revealed in Osler's textbook of medicine published in 1892.[7]

> In Jacksonian epilepsy the propriety of surgical interference is universally granted. It is questionable, however, whether in the epilepsy following hemiplegia, considering the anatomical condition, it is likely to be of benefit. In idiopathic epilepsy, when the fit starts in a certain region – the thumb, for instance – and the signal symptom is invariable, the center controlling this part may be removed. This procedure has been practised by Macewen, Horsley, Keen and others, but time alone can determine its value. The traumatic epilepsy, in which the fit follows the fracture, is much more hopeful. The operation, *per se*, appears in some cases to have a curative effect. Thus of 50 cases for trephining in epilepsy, in which nothing abnormal was found to account for the symptoms, 25 were reported as cured and 18 as improved. The operations have not always been on the skull, and White has collected an interesting series in which various surgical procedures have been resorted to, often with curative effect, such as ligation of the carotid artery, castration, tracheotomy, excision of the superior cervical ganglia, incision of the scalp, circumcision etc. [8]

However, two surgeons who stand out in this era as founders of British neurosurgery, William Macewen and Sir Victor Horsley, adapted their surgery to the evolving knowledge of cerebral function and localization (Figures 4a.1 and 4a.2). Although contemporaneous, they were two very different men. Macewen, relatively isolated in Glasgow, was more of a pragmatic surgeon with no background of experimental work or apparent association with a group of like-minded individuals in the field which would now be described as neurosciences. Indeed, in his Presidential Address to the BMA, meeting in Glasgow in 1922, he plays tribute to the work of Ferrier, Horsley and Beevor in investigating cerebral function in animals and to Horsley Godlee and Balance in applying this knowledge to their operating practice.[9] When he was a student in Glasgow in 1873 he describes seeing a patient who had sustained a fracture of the right parietal bone and thereafter suffered from spasms of the left arm. Operation showed a spicule of bone which had penetrated the dura and lodged in the middle part of the ascending

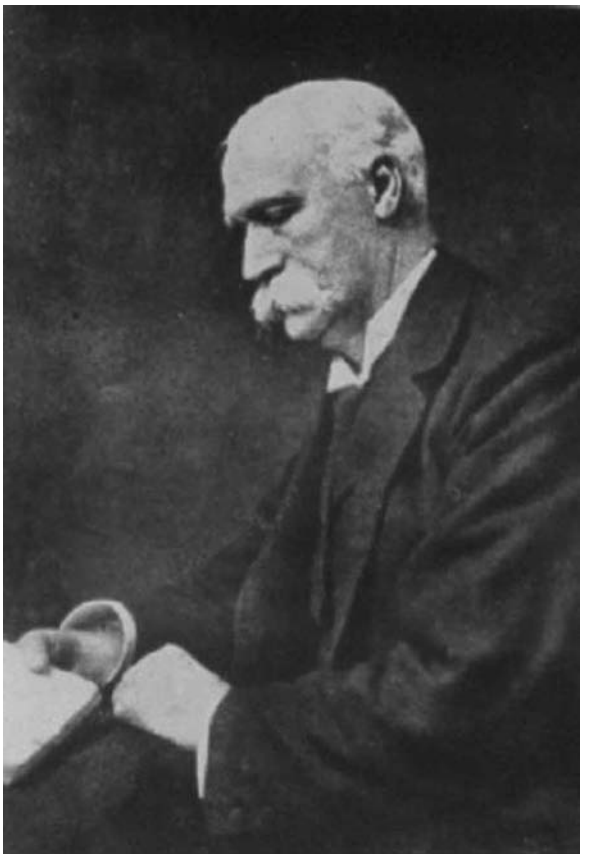


Figure 4a.1 Sir William Macewen (source unknown).

frontal convolution. It was removed, the spasms ceased and the weakness recovered over a few weeks, so he was clearly familiar with the possibility of relieving focal epilepsy by surgery. Horsley, who held appointments enabling him to undertake experimental work as well as clinical work, had also laid down principles for the safe practice of neurosurgery which he set out in his paper of 1886. It is in this paper that he also describes the three cases of chronic epilepsy treated by cortical resection and observes that in one case he and Dr. Beevor were able to stimulate the brain and produce movements.[10] It is not known whether there were any further operations. In 1906 Horsley notes that in 1890 and 1983 he had tried, without success, to persuade physicians to limit the period of medical treatment before referring the patient for surgery.[11]

In the early years of the 20th century skull X-rays began to be used to assist diagnosis. In the first case, described by Palmer in 1910, the patient was subjected to a second operation for focal sensory seizures in which an X-ray showed a dark shadow but exploration by Mr Balance was negative.[12] However, in two further cases where the patients had suffered from epilepsy for over 20 years an X-ray showed a middle fossa mass. Resection of the mass in both cases resulted in cure of the epilepsy.[13,14] By 1924 the position was still ambiguous. At a meeting of the BMA section of neurology Dr. Collier noted that he had never seen a case of traumatic epilepsy benefited by operation. Dr Worster-Drought disagreed, quoting two cases, which had benefited.[15] In a paper on epilepsy in 1926, Symonds, one of the influential neurologists of that time, does not mention surgical treatment directly but hints at it.[16] Davidoff, describing a visit to Prof. Foerster's clinic in Breslau notes that patients with Jacksonian epilepsy are investigated very carefully, including

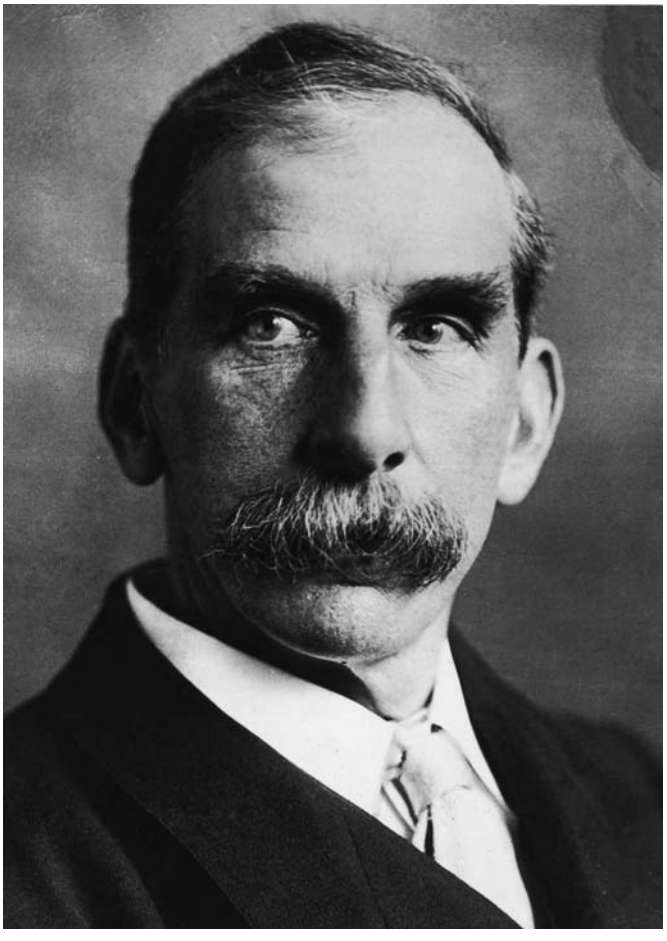


Figure 4a.2 Sir Victor Horsley in 1910 (by permission of the Getty Archive).

the latest imaging technique of air encephalography.[17] In a seminal paper, published in Brain in 1930, and therefore presumably read by appropriate specialists in the UK, Foerster and Penfield describe their experimental and clinical work on traumatic epilepsy.[18] At this stage the advice in Osler's textbook regarding surgical treatment of epilepsy, had been modified, but not changed.[19] The attitude of the British neurosurgical community is represented by two surgeons, Jefferson and Young. At the seventh Congress of La Internationale Societe de Chirugie both were asked to comment on a paper on Jacksonian epilepsy presented by Leriche. Jeffferson noted that Jacksonian epilepsy is rare in civilian practice, stated that he believed that epilepsy has a natural tendency to remit and called attention to the placebo effect of treatment. His own practice, he said, is conservative.[20]

The doldrums

With these uninspiring facts we enter the period of virtual inactivity for 20 years which included World War II. Towards the end of this period, and before the emergence of Murray Falconer and his group at the Maudsley Hospital, there is evidence of activity by two groups although the publications are small. Cairns described three cases of hemispherectomy in 1951, the emphasis being on the intellectual and behavioral benefits. All three became seizure free. Cairns also carried out some neurophysiological investigations co-operating with Adrian and Matthews in 1934 to enable them to record from the exposed occipital cortex before and after the removal of a glioma. (Figure 4a.3.).[21] He is also recorded as using intralesional electrodes to investigate a patient in 1944.[22] Mr. Wylie McKissock, working at the National Hospital, Queen Square, had carried out a substantial number of hemispherectomies following the description of this procedure by Krynauw.[23] In 1956 the British Medical Journal carried an editorial pointing out the benefits of hemispherectomy. The long-term results of McKissock's series were described in 1970.[24] McKissock also carried out other procedures since a patient who underwent a right temporal lobectomy by him in 1944 is described by Ettlinger *et al.*[25] The other active surgeon at this time, again with relatively few publications, was Northfield who was at the Royal London Hospital.

The perception of pathology

The next period between 1950 and 1970 is dominated by the group working at the Maudsley Hospital and closely identified with Murray Falconer. It must be made clear at the outset that although Murray Falconer ran what would in modern terms be recognized as an epilepsy surgery program it was operated at the time as part of a general neurosurgical service. Another player of note during this period was Mr. D.W. Northfield, who worked at what was then the London Hospital, now the Royal London Hospital. Their productivity, in terms of patients operated and academic publications was vastly different and Murray Falconer had the help of a team of fellow professionals, which does not seem to be the case with Mr. Northfield. There is an interesting discussion, recorded in the Proceedings of the Royal Society of Medicine in 1958 between Mr. Northfield and the Maudsley team, which will be referred to later. There were other surgeons doing some surgery, Eric Turner in Birmingham was using a form of temporal lobotomy in the treatment of temporal lobe epilepsy. He was as interested in the effects of his surgery on behavior as epilepsy.[26]

Murray Falconer was a New Zealander who had come to Europe and America in the late 1930s to further his neurosurgical education. He had remained in the UK during the Second World War working in the military services and he had met a number of neurologists and neurosurgeons who would become prominent in their field after the war. In 1942 or 1943 he returned to New Zealand to take up an appointment in the

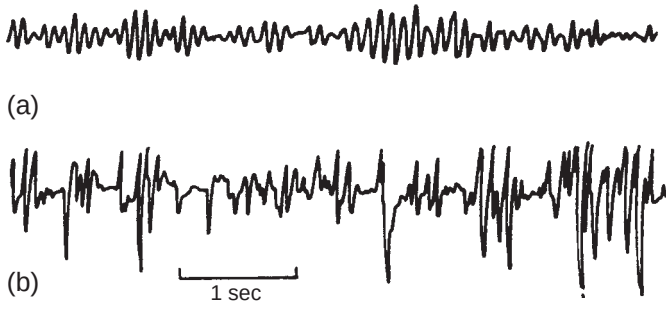


Figure 4a.3 Probably the earliest published electrocorticogram in the English literature. Recorded from a patient operated upon by H. Cairns. From Ref. 21 by kind permission of the Editors of *Brain*.

University of Otago with the express purpose of setting up a neurosurgical service. In the late 1940s Sir Charles Symonds wished to set up a neurosurgical unit in Guys Hospital and there were good reasons for associating this with the Maudsley Hospital. Murray Falconer was invited to become the director of this new unit which initially was located in Guys Hospital and then moved to purpose built accommodation in what had previously been the private patients building of the Maudsley Hospital in 1951 (Figures 4a.4 and 4a.5) From this base, where he continued to work until his retirement in 1975, about 300 patients were operated on in 25 years and a large number of publications were made. An unpublished analysis of his work during this period shows that the majority of the operations, more than 75%, were anterior temporal lobectomies, with the next commonest operation being anatomical hemispherectomy. All this was done with mainly interictal non-invasive EEG, although acute sphenoidal recording was used and in all cases, except hemispherectomy, acute electrocorticography was carried out. For brain imaging plain X-rays, carotid and vertebral angiography and air encephalography were used. Neuropsychological testing including carotid amytal tests was also available. In 25 years between 1950 and 1975 Murray Falconer published 93 papers 61% of which were concerned with epilepsy and its surgical treatment. During this time only seven papers on epilepsy surgery were read at the Society of British Neurological Surgeons, five of which were from Murray Falconer's unit. At various times during this period he had as co-authors or advisors a number of colleagues including: neuropathologists, Meyer, Corsellis, and Cavanagh; clinical neurophysiologists and epileptologists, Hill, Driver, and Engel; psychologists Ettlinger and Blakemore; and psychiatrists Pond, Hill, and Taylor.

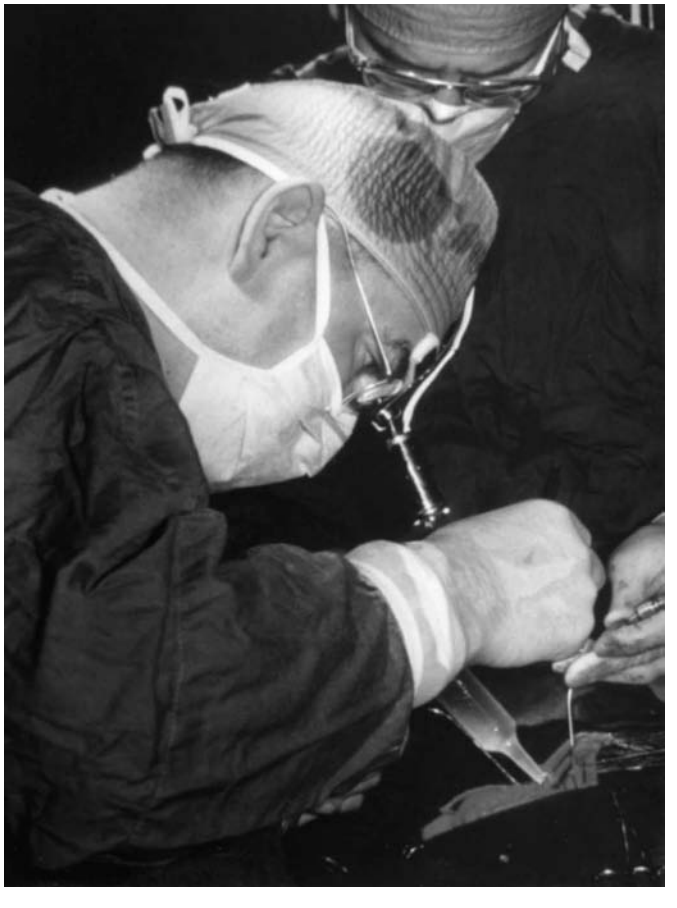


Figure 4a.4 Mr. Murray Falconer operating in the late 1960s. (private source).

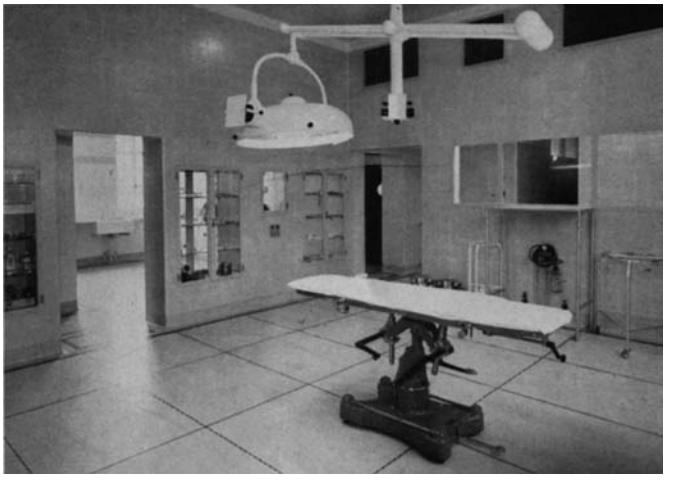


Figure 4a.5 The operating theater at the Neurosurgical Unit at the Maudsley Hospital as shown in the brochure produced at its opening in 1951.

Murray Falconer's other advantage was his proclivity for travel, and his ability to form and maintain a wide network of friends in neurosurgery and epileptology, especially in the USA and Canada. Many of these welcomed him in their departments and also visited the unit at the Maudsley Hospital as witnessed by the signatures in the theater's visitor's book. As a result of this he kept abreast of thinking in epileptology and epilepsy surgery and was able to evaluate developments. At an early stage in performing these operations he realized that if the role of pathology in epilepsy surgery was to be properly evaluated it was necessary to obtain appropriate tissue samples. As a result of this he modified the technique of temporal lobe resection so as to include the mesial structures, the hippocampus, and amygdala, within the specimen delivered to the pathology laboratory. Encouraged by Corsellis's work on mesial temporal sclerosis,[27] and confident that the specimens would be appropriately examined, he began to use him, ably assisted by Clive Bruton, at Runwell Hospital in Essex to do the neuropathology. They began to observe that the lesion of mesial temporal sclerosis was found in about half of the specimens submitted for examination and that this was often, but not invariably, connected with certain events in the patients previous history, notably atypical, prolonged febrile convulsions. He also had close informal links with the Park Hospital at Oxford where Ounsted had carried out his work on the origins and developmental consequences of temporal lobe epilepsy in children. When, at a later date together with David Taylor, they also described the lesion of focal cortical dysplasia, the group began to focus on the events in childhood which might determine subsequent chronic drug-resistant epilepsy. There had also been significant publications, involving David Taylor over many years, of the intellectual, developmental, and psychiatric consequences of epilepsy. Latterly David Taylor was appointed to the Park Hospital in Oxford. Therefore, towards the end of his career, Murray Falconer began to ponder the possibility that surgical treatment of epilepsy in childhood would result in less education and social damage.

In 1968 Northfield, the only other significant operator in the field, described the use of subdural and depth electrodes in the investigation of epilepsy at the London Hospital since 1952.[28] His final series of temporal lobe operations seems to have numbered 58, as quoted in his book, *The Surgery of the Central Nervous System*.[29] In 1958, in the Proceedings of the Royal Society of Medicine, there is an account of papers read at the meeting of the Section of Neurology. The first, by Mr Northfield, explores the notion of the epileptic focus and recounts the difficulties in obtaining appropriate neurophysiological data. There is an account of the 30 cases operated at the Royal London Hospital with results with regard to seizure control and quality of life. There is no account of the pathology from the specimens except to say that tumors have been excluded.[30] The next paper, given by the psychiatrist Denis Hill, describes the selection procedures applied to patients with epilepsy presenting at his psychiatric clinic at the Maudsley Hospital and the results from those who were treated by temporal lobectomy by Murray Falconer. The pathology in the specimens is described and its influence on the outcome is also recounted.[31] In the third paper Murray Falconer describes his experience of 50 patients with adequate follow-up of two to seven years. The rationale and advantages of the *en bloc* removal are explained and the results of pathological examination of the specimens are detailed.[32] Thus at the beginning of the 1970s the major center for epilepsy surgery in the UK was the Maudsley Hospital with the majority of the investigations and all of the surgery being carried out within the neurosurgical unit. The unit, with three consultants, also served as a general training unit in neurosurgery but it is remarkable that few of the trainees, who inevitably worked in their senior placements with Murray Falconer, subsequently set up epilepsy surgery program. In fact only two surgeons successfully continued to practise epilepsy surgery after Murray Falconer's retirement in 1975. Charles Polkey continued the program at the Maudsley Hospital and Chris Adams set up a service at Oxford initially working with the patients from the Park Hospital who had previously been referred to Murray Falconer at the Maudsley.

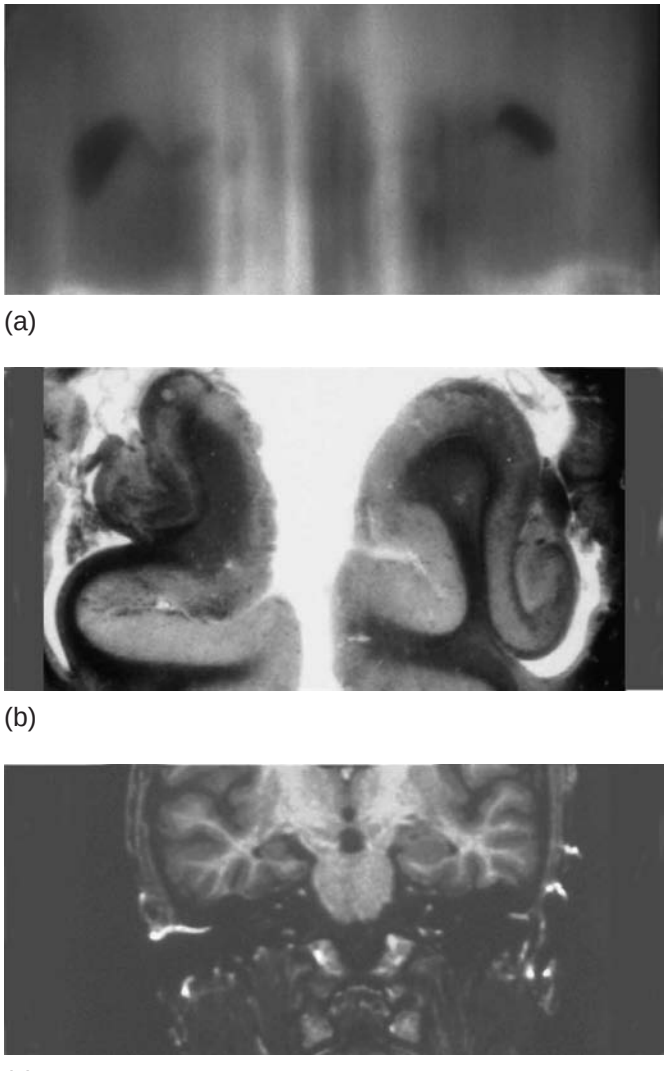
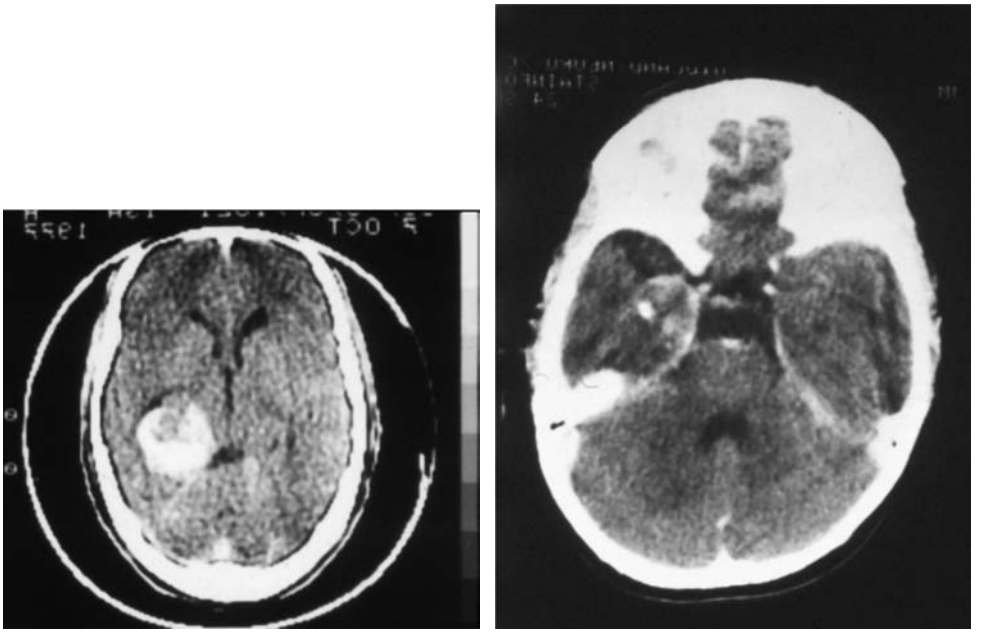


Figure 4a.6 Comparison between the radiological and pathological appearances of MTS. (a) Air encephalogram from 1978 showing dilated temporal horn. (b) Brain cut from Murray Falconer's slide collection comparing sclerosed and normal hippocampus supplied to him by Prof. N. Corsellis in the 1950s. (c) MRI scan showing the same pathology.

The influence of direct brain imaging

In the mid-1970s, because of the difficulty of structural diagnosis using indirect brain imaging, by which is meant air studies and cerebral angiography, and reliance upon neurophysiological studies of varying complexity, it seemed that epilepsy surgery would remain restricted to a few specialized units. However the invention first of CT scanning, and subsequently of MRI, both incidentally British inventions, changed the situation beyond recognition. (Figures 4a.6 and 4a.7) It had long been recognized, both in the UK and America, that due to processes such as secondary epileptogenesis, solitary lesions could give rise to bilateral EEG changes as reported by Falconer and Cavanagh.[33] This methodology enabled the diagnosis of structural lesions causing long-standing epilepsy to be made in any reasonably equipped neuroscience center. The hit rate was approximately 70% of patients having a structural lesion with CT and 95% with MRI, not all being operable. The second consequence was that patients and their relatives were now aware that in many cases epilepsy was secondary to a structural lesion and were asking about the possibilities of surgical treatment which was itself now regarded as safer than previously. Finally there was a greater awareness in general of epilepsy which must be credited to some degree to the influence of Dr. E.H. Reynolds and his pupils many of whom worked with him on his research projects at the Maudsley Hospital in the early 1970s. They subsequently completed their training and became consultant neurologists, working, as is the custom in the UK, as general neurologists with a special interest in epilepsy. This group would include Prof. David Chadwick in Liverpool, Prof. Simon Shorvon at the National Hospital and Dr. Robert Elwes at the Maudsley Hospital. By their influence they set up units which inevitably spawned surgical teams as part of their research and treatment options. Compared with the 1950s it was now clear the epilepsy surgery needed to be organized into multidisciplinary groups which are now known as epilepsy surgery programs. A number of disciplines were essential to these groups and included neuroradiologists, neuropathologists, neurophysiologists and neuropsychologists. There was



(a) (b)

Figure 4a.7 Two early CT scans taken in 1977 showing: (a) a posterior temporal tumor; (b) a temporal tumor. The technical limitations of the early scans can be seen.

little difficulty in recruiting neuroradiologists since most of the programs were attached to neurosciences centers and the same could be said of neuropathologists, although both of these disciplines were to some extent in short supply for other reasons. However, good neurophysiologists were more difficult to find and interest in these programs. In the case of the Denmark Hill site they were fortunate in attracting Prof. Colin Binnie to return to the UK and he soon established intracranial recording and videotelemetry on that site. When he moved to Queen Square the late David Marsden recognized epilepsy as a growing area of research interest and arranged for Dr. David Fish to spend a year at the Montreal Neurological Institute to study the neurophysiology of epilepsy. Dr. Fish then returned to the National Hospital where he organized telemetry services necessary to run an epilepsy surgery program. This program initially referred patients to the Maudsley Hospital for surgery and received some informal advice on aspects of electrocorticography. However the intention was clearly to develop an independent service and in early 1991 Mr. William Harkness was given a joint appointment between Queen Square and the adjacent Hospital for Sick Children (GOS) again to have a special interest in epilepsy surgery. At the time of taking up this appointment he spent six months as a fellow in UCLA. The development of pediatric epilepsy services followed a similar route. Murray Falconer had formed a link with an 'epileptic colony' for children, St Piers, at Lingfield in Sussex. This link with the Maudsley program continued for many years after his retirement. Referrals from GOS began to come to the Maudsley program after Murray's retirement. Again however it was clear that the Hospital for Sick children would want to set up an independent program. In 1989, Prof. Brian Neville was appointed Professor of Pediatric Neurology there and with Dr. Helen Cross a large program of assessment of children was established. Interestingly, David Taylor, who originally worked with Murray Falconer, joined this team producing the concept of a 'contract' for surgical treatment between the surgical team and the patient and their parents.[34] The link from Lingfield to the Maudsley was then broken with the establishment of the National Center for Young People with Epilepsy (NCYPE), which effectively linked it with GOS. This paralleled the adult situation where the 'epileptic colony' at Chalfont in Buckinghamshire, north of London had been used by the National Hospital as an assessment and long-term treatment center. In addition a charity was set up, the National Society for Epilepsy (NSE), which very successfully gathered funds which were used to buy diagnostic and research equipment. By this means the nucleus of what has become, quite rightly, a large and influential group, expert in the imaging of epilepsy, has emerged. The other problem was the development of neuropsychological services. The neuropsychological service at the Maudsley was continued by Dr. Graham Powell and is now organized by Prof. Robin Morris. Good services with research interests were established by Dr. Pamela Thompson at the National, Prof. Varga-Khardem at GOS, Dr. Susan Oxbury at Oxford, and Dr. Gus Baker in Liverpool.

As well as the London units major working units in epilepsy surgery are now active in Birmingham, Cardiff, Liverpool, Newcastle, and Oxford. In Oxford the supervising neurologist was Dr. John Oxbury, in Liverpool Prof. David Chadwick organized a service with Paul Eldridge as the surgeon. In Birmingham the service was organized by Dr. Tim Betts and the surgery is performed by Mr. Richard Walshe, appointed in 1991, and trained in Seattle by Prof. George Ojemann. In Cardiff Mr. R. Weeks had performed some epilepsy surgery for many years and the service was taken over by Mr. Richard Hatfield who received his general neurosurgical training in Cambridge but after appointment in Cardiff was seconded to the Maudsley for training. In Newcastle the surgery is performed by Mr. David Jenkins. There have been attempts to set up a service in Scotland currently supervised

by Dr. Rod Duncan and some surgery also in Edinburgh. There is an epilepsy surgery service in Eire, set up by Hugh Staunton and currently run by Prof. Jack Phillips, but this is dealt with in a separate chapter. The group at Queen Square asserts, probably correctly, that they now have the largest epilepsy surgery program in the UK and this is almost certainly true if they are considered together with GOS.

Technical advances in the last decade have also to be considered. The most important is probably the refinement in MRI, especially the development of the FLAIR sequence and of fMRI; the latter, especially when co-registered with the structural MRI, is useful in terms of speech determination and primary motor mapping. Such facilities are available both as a clinical and research resource in the larger centers.

The introduction in the operating theater, towards the end of the 1990s, of frameless stereotaxy, which is a general neurosurgical tool, enables the surgeon to reach the resection target or place intracranial electrodes accurately. Neuromodulation as a means of controlling epilepsy has been seen mainly in terms of vagus nerve stimulation. The first system was inserted at the Maudsley Hospital in 1995 and they are now used to varying degrees across the UK. Their deployment depends to some extent on the attitude of financial providers.

There have been a number of other influences on the development of epilepsy surgery during this 25-year period. Presentations about epilepsy surgery at the meetings of the Society of British Neurological Surgeons have increased and diversified but attempts to set up a special interest group have net with no success. In the last five years a British functional neurosurgery group has been set up, mainly concerned with the stereotactic treatment of movement disorder, but including epilepsy surgery. At the first Palm Desert symposium in 1986 there were only seven contributors from the UK, by the second Palm desert symposium in 1992 there were nine. With the setting up of epilepsy programs at the National Hospital and GOS the influence of North American views increased and for some 10 to 15 years there was an increased attendance and contribution from the UK at meetings of the American Epilepsy Society (AES). The main reason for this was because this was the only annual meeting available which had a high standard of basic research and clinical research content. Until recently the influence of our continental neighbors was minimal, there were a number of reasons for this. Epilepsy surgery had been a minority interest on the continent and had mainly developed under the influence of the French School of Talairach and Bancaud. There was both a language barrier, and probably more important, a conceptual barrier with their emphasis on neurophysiological findings especially SEEG, and stereotactic methodology being at odds with the British ideas regarding pathology and epilepsy. Until the late 1990s the training body responsible for neurosurgery in the UK did not think that trainees needed to learn stereotactic methodology. However, as direct imaging became more important the two viewpoints have merged, mainly due to the influence of the late Claudio Munari. There is now a well-organized European meeting on epilepsy every year, whose standard in recent years has approached that of the AES.

The development of pediatric neurosurgery has also influenced epilepsy surgery in the UK. Over the last decade or so pediatric surgery has become more regulated so that consultants must now have at least one year as a pediatric fellow in a recognized department before practising independently. In addition departments which practice this speciality must have a minimal number of pediatric procedures per year and appropriate personnel and facilities for dealing with this age group. These are sensible and much needed changes, but in effect make it difficult to practice pediatric epilepsy surgery outside of a department of pediatric neurosurgery.

The various reorganizations of the NHS in the UK have also played their part. This should be seen against the following background. The Department of Health has taken the view that certain specialized services could be set up in a few centers because they were sufficiently arcane for it to be unreasonable for a local hospital to provide that service. They have always insisted that epilepsy was a common disease whose diagnosis and treatment had to remain at a local level. When hospitals were organized into trusts it was realized that not all trusts could supply all services and therefore a mechanism, extracontractual referrals, was devised whereby a trust providing specialist treatment could reclaim the money from the referring trust, usually the patient's geographical hospital. The income from this kind of activity allowed a sort of expansion of the service which was as it were, self-sustaining. However, another reform handed financial control to local primary care trusts whose function was to contract with local services to treat any particular diagnostic group at the lowest possible cost. This made it more difficult to refer patients away from the local services for two reasons. The first was that understanding of the diagnostic and treatment options involved in epilepsy surgery were less at that level so more time and effort was involved in obtaining finance to treat the patient, and the second was that local services were pressed to treat these patients with the available facilities. This led to attempts at epilepsy surgery being made and then not sustained.

In 1991 the British branch of the International League Against Epilepsy (ILAE) commissioned a report, prepared after a workshop attended by the interested parties, into the surgical treatment of epilepsy.[35] There were 25 attendees of whom four were invited foreign speakers. The remaining 21 participants included only four neurosurgeons and the whole group represented only nine centers. Only four centers performed any particular operation more than five times and the number of operations performed in that year were 10, 13, 18 and 51. A similar exercise was repeated in 2003 and reported by Lhatoo *et al.*[36] The results of the two exercises are summarized in Table 4a.1.

These figures indicate that there has been an increase in the number of surgeons performing these operations over a decade or so although according to the authors this level of work just keeps pace with the new cases leaving a considerable backlog.

Summary

The progress of epilepsy surgery in the UK has been reviewed from its early beginning in 1870 to the most recent developments in the first decades of the 21st century. As might be expected progress has been determined in large part by changes in other fields. The general improvements in surgical and neurosurgical technique have fuelled advances and this was particularly evident towards the end of the 19th century. Improvements in safety made surgery feasible and the weakness of drug treatment made it necessary. The stasis and lack of interest in the early decades of the 20th century are hard to

Table 4a.1 Comparison of the results of two surveys of epilepsy surgery practice in the UK conducted in 1991 and 2003[35,36]

	1991	2003
Number of surgeons responding	58 (50.4%)	110 (76%)
Number of surgeons performing epilepsy surgery	23 (22%)	32 (22%)
Number of operations per year	150	422
Commonest operations		
Temporal lobe resection	Yes	318 (76%)
Extratemporal lesional resections	Not known	58 (14%)
Vagus nerve stimulators	Not applicable	156

explain, especially as considerable progress was being made elsewhere, for example in Europe and North America. Whereas the concepts which led to advances in the latter part of the 19th century were common to America, Europe, and the UK by the middle of the 20th century there was a clear divergence of philosophy between the functional and neurophysiological emphasis in Europe and America on the one hand and the pathological emphasis in the UK, although the practitioners in all three areas shared common interests in seizure semiology and cerebral localization. The explosion of direct brain imaging, especially MRI, directed attention momentarily towards the structural lesions although by the end of the 1990s groups in the UK, as elsewhere, were beginning to address the problem of MRI negative, focal epilepsy. Neuromodulation, almost exclusively in the form of vagus nerve stimulation, appeared in the mid-1990s and so far has been restricted to centers with epilepsy surgery programs. The peculiarly British methodology of disorganized organization has resulted in centers with varying strengths and workloads which are treating a significant number of patients but still with a probable reservoir of untreated patients.

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4b Epilepsy surgery in Ireland

P Widdess-Walsh, N Delanty, and JP Phillips

Introduction

The Republic of Ireland has a population of almost four million people, of whom up to 40,000 have epilepsy. Given that approximately 30% of patients will be refractory to medication, and half of these may be surgical candidates, there may be three to four thousand patients who might benefit from epilepsy surgery in Ireland.

Ireland's health system is based on a socialized medicine model, with public hospitals operated by the Irish Department of Health and Children. The total number of public neurology consultant physicians in Ireland is sixteen, one per 244,000 of the population, of whom three have a special interest in epilepsy. Politicized control of resources and manpower has made the development of the Irish Epilepsy Surgery Program challenging. The Irish history of epilepsy surgery demonstrates the achievement of a world-class surgical epilepsy program despite limited resources.

Irish neurosurgery: early origins

One of the earliest accounts of a 'surgical' treatment for epilepsy in Ireland, came from Dr. M. Tuohy of Dublin in 1810:[1]

> Where in consequence of the long continuance of the complaint, and of the violence and frequency of the convulsions, we have reason to fear effusion on the brain might ensue, it will be proper to shave the whole of the head, to cover it with a large blister, which must be left on perhaps for sixteen hours, certainly until a vesication takes place, and to keep up a discharge from it with savin ointment or vesicating ointment until all danger disappears

The origins of *modern* surgery in Ireland ran parallel with the UK, with Mr. John MacDonnell performing the first operation under anesthesia in Ireland at the Richmond Surgical Hospital on New Year's day 1847, 11 days after Lord Lister first used operative ether in London. Neurosurgery was pioneered in Ireland by Professor Adams McConnell in the Richmond Surgical Hospital from 1911. McConnell achieved considerable international reputation in vascular and traumatic neurosurgery, and was one of only a handful of neurosurgeons operating in the UK and Ireland at that time. No accounts exist of primary surgical resections for epilepsy during that time, despite documents showing correspondence between Professor McConnell and Olfrid Föerster on a number of other matters.[2–4]

The Richmond surgical hospital

The Richmond surgical hospital (Figure 4b.1) is intimately connected with Irish Neurosurgery and Epilepsy. The hospital was opened with 129 beds in a former nunnery on 4 June 1811, and was named after the Duke of Richmond, viceroy to Ireland (1807–1813) during the English occupation. The hospital served to provide surgical care to the House of Industry, a workhouse established by the government of the time for the 'relief and employment of unfortunates, deserted infants and children'. The hospital counted as honorary staff, physicians, and surgeons such as Robert Adams, Richard Carmichael, John Cheyne, and Sir Dominic Corrigan.[5] Neurosurgery in Ireland, and eventually epilepsy surgery evolved here until the closure of the hospital and transfer of neurological and neurosurgical services to Beaumont Hospital, Dublin, in 1987.[6,7]

Dublin neurology in the first half of the century

Frank Purser was the first neurologist at the Richmond, until the appointment of Harry Lee Parker in 1934. Harry Lee Parker was a senior staff physician at the Richmond Hospital and Professor of Neurology at Trinity College Dublin between 1934 and 1946, whereupon he returned to the Mayo Clinic to become chair of the Department of Neurology. While in the United States in the early 1930s he published a large series of intracerebral tumor related seizures. He documented cases where the surgical removal of tumors had a beneficial effect on the epilepsy. In one case description, a patient with complex partial and nocturnal convulsive seizures had a 9 cm meningioma removed from the left falx cerebri. There were no postoperative seizures. However, the patient died 11 days after the operation from septic meningitis.[8]

In later publications based on his time in Dublin, he reported a good surgical outcome of a patient with complex partial seizures and a right temporal lobe glioma: 'whatever convulsive attacks he had after surgery can be controlled by drugs'. Prior to the surgery he commented:

> should the tumor be intracerebral, this patient should have a resection of part or all of his right temporal lobe, with the tumor cleanly removed in the center. It is some consolation that the right temporal lobe is the one involved: the left is not so amenable to surgery because of the speechlessness which operation would be certain to cause in a right-handed man.

Figure 4b.1 The Richmond surgical hospital, Dublin, in 1811.

In another 56 year old patient with visual auras, convulsive seizures, and a left temporal 'abnormal focus' on EEG, he states 'direct surgical exploration of the brain in a patient of this age would be unwise, since even if a tumor is present, it is on the dominant side, and removal would be likely followed by hemiplegia and aphasia'.

Based on his work in Dublin, Dr. Parker made many insightful comments on surgical epilepsy, including the existence of drug resistance in epilepsy, Ammon's horn sclerosis, and non-lesional epilepsy; 'some patients under medication do well, but so often the drug used loses its power and attacks start up again', and 'psychomotor seizures ... produce an EEG that is different from that obtained in other forms of epilepsy, and the other safe drugs (*referring to phenobarbital and hydantoins*) do not control these fits'. He recognized at the time the importance of the Spielmeyer's pathological description of Ammon's horn sclerosis; 'pathologists are coming back to that in finding scars in that region'. He realized that many cases of 'idiopathic epilepsy' would become clear in time: 'with modern method of air encephalograms, arteriograms, and electro-encephalography, more and more of the so-called primary and idiopathic epilepsies are being explained and treated scientifically', and 'even after all causes apparently have been excluded, we grudgingly assume that this exclusion is only temporary, and that the final cause is unknown because of a lack of evidence to date'.[9]

The origin of the epilepsy surgery program

After Harry Lee Parker's departure, Neurological services were provided by Brendan McEntee, a self-professed general physician with an interest in neurology (E. Martin, personal communication). The Department of Neurosurgery was pre-eminent in this era, at least until the appointment of Hugh Staunton (Figure 4b.2), the driving force behind Irish epilepsy surgery, as consultant neurologist to the Richmond Hospital in 1971.

The building stones that were in place at the time were Mr. Patrick (Paddy) Carey, consultant neurosurgeon and the EEG services provided by Dr. John (Joe) Kirker. Paddy Carey was appointed in 1957, and performed the first temporal lobectomy in Ireland in 1975. Mr. Carey trained at the Karolinska Institute in Stockholm under Lars Leksell and in Zurich under M. Gazi Yasargil. One temporal lobectomy was performed by Mr. Carey's colleague, Mr. John Lanigan. Mr. Carey retired in 1987, and epilepsy surgeries were continued by Professor Jack Phillips until his retirement in 2006, and currently performed by Mr. Donncha O'Brien.

Figure 4b.2 Dr. Hugh Staunton (1937–).

Dr. Clem Dempsey introduced the first EEG machine to Ireland in the early 1950s (a four-channel Marconi machine), although shortly thereafter diverted to practise family medicine. Dr. John Kirker graduated from Trinity College Dublin, and was a medical student on Harry Lee Parkers rounds. After training with Lennox in Boston, he returned in 1953 to develop Irish electroencephalography.

Hugh Staunton's clinical training was at the National Hospital for Neurology and Neurosurgery at Queen Square, London, and he performed research at the Max Planck Institute for Brain Research, Frankfurt on Main, Germany, based on recruiting responses during direct electrical stimulation of the feline cerebral cortex. Following the reported successes of Bailey and Penfield in performing temporal lobectomy for TLE, the need for temporal lobe epilepsy surgery in Ireland was clearly apparent.[10,11] The first patient was a publican's son from County Louth, who is still working and driving a car today. Initial procedures were based on the Murray Falconer technique,[12] using suction to take 5–7 cm (5 cm in the case of the dominant hemisphere) of the anterior temporal lobe and mesial structures.[13]

Early protocols

The pre-surgical evaluation of the time was based on clinical semiology, interictal EEG, and a bilateral Wada test. Methohexitol-induced epileptiform activity on the interictal sphenoidal EEG, under the supervision of anesthesiology, was used as a supplement to the EEG evaluation, with good success.[14] Wada testing was performed initially by Dr. Staunton personally before the development of neuropsychology services at the hospital in the mid-1980s, as the importance of

pre- and post-operative neuropsychological testing was increasingly recognized. Top psychology graduates from University College Dublin trained and work as clinical epilepsy neuropsychologists. Among them, Teresa Burke and Deirdre McMackin received additional specialist training from Brenda Milner and Laughlin B. Taylor, at the Montreal Neurological Institute (MNI). After further post-doctoral training with Marilyn Jones-Gotman at the MNI in the early 1990s, Deirdre McMackin, went on to develop a comprehensive and mature Neuropsychology Department at Beaumont Hospital, which is now headed by Niall Pender. Computed tomography was not introduced until 1978, and Ireland's first video-EEG telemetry unit opened in 1988. Results demonstrate that despite limited resources of the day, a conservative surgical approach could provide an effective surgical relief of intractable epilepsy.[15] By 1988 over 70 cases had been performed with minimal morbidity, reported at 4%, and no mortality. One early case was associated with a postoperative hemiparesis, presumed to be due to a middle cerebral artery perforator injury before such complications were fully recognized. Postoperative psychiatric outcome was disappointing in some cases; over the course of the epilepsy surgery program 3-4 patients committed suicide in the months after surgery (H. Staunton, personal communication). If epilepsy surgery was performed before the age of 20 years, psychosocial and vocational outcomes were improved.[15] Follow-up was remarkable, and essentially 100%, as Ireland is a uniquely homogenous population served by one epilepsy surgery center.

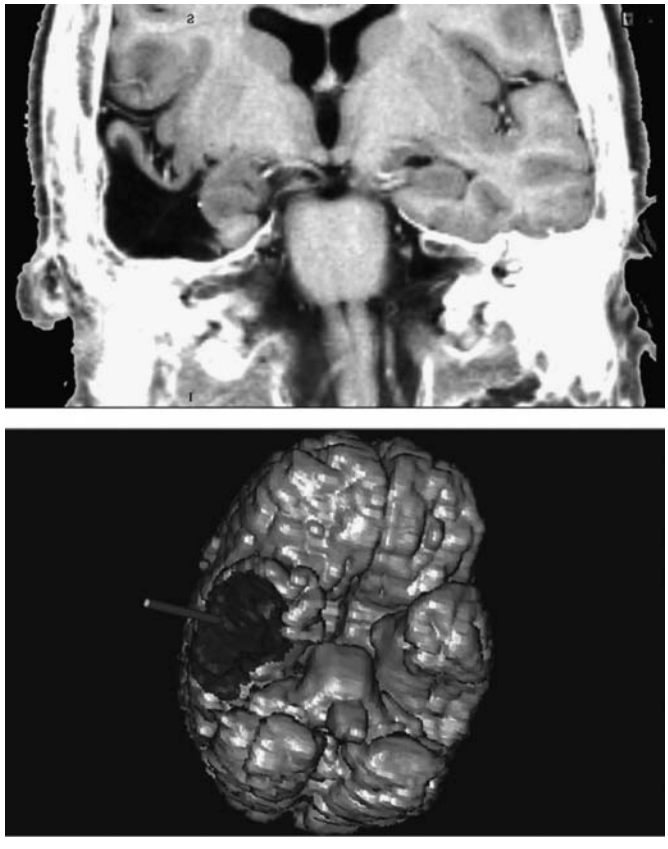

Figure 4b.3 Postoperative coronal T1-weighted MRI with 3D reconstruction demonstrates the extent of resection following a right temporal neocorticectomy.

Neocorticectomy for temporal lobe epilepsy

No formal neuropathologist was employed during the early days of the program, (being between the appointments of Dr. Paddy Bofin and Dr. Michael Farrell), the interim pathologist noted that there was no hippocampal tissue in the pathological sections. Hence, it was presumed that the operation was a temporal neocorticectomy without removal of the mesial structures. The patients undergoing neocorticectomy seemed to do well in terms of seizure freedom and memory outcomes so the procedure was continued in a more formal manner, under the pathophysiological assumption that disconnection of the neocortex from the mesial structures would limit the spread of clinical seizures, remove any cortical generators of epileptiform activity, and leave any hippocampal discharges confined to the hippocampus. Also, given the risk of memory impairment with removal of mesial structures and given the limited resources for pre-surgical localization,[16,17] a conservative approach such as neocorticectomy was favored from the late 1970s to approximately 1992, when the surgical outcomes for standard anterior temporal lobectomies[18] or selective amygdalohippocampectomies[19] were more established, and better services for pre-operative work-up were available. The surgical technique for neocorticectomy was described as (Figure 4b.3):[20]

> the area of resection extends posteriorly to a distance of 4.5–6 cm from the anterior temporal tip. The area of resection takes in the lower half of the superior temporal gyrus along with the middle and lower temporal gyri. The resection extends vertically down to the temporal horn, which is opened. The resection is continued, angulated anteroinferiorly, resulting in an *en bloc* removal. The amygdala and anterior hippocampus are exposed but not resected.

The outcomes for the neocorticectomy group have been published in detail,[15] and have been compared favorably as a group with selective hippocampectomies from Zurich, and anterior temporal lobectomies from Montreal.[21] Perhaps surprisingly, the memory deficits (at least on a range of non-spatial tasks) were similar in each group, which was seen as support for the temporal lobe disconnection theory. In another analysis of the Dublin group, only mild material specific memory deficits were seen after neocorticectomy, supporting the view at the time that neocorticectomy was safer in terms of postoperative memory dysfunction.[22–24] Later results questioned that assumption, at least to some extent, as postoperative MRI analysis of Dublin cases evaluated in the Jones–Gotman study showed that of 24 patients nominally undergoing neocorticecomy, there was some encroachment on mesial structures in 18 cases.

The most common procedure performed since the early 1990s has been a selective hippocampectomy preserving the amygdala and temporal neocortex, with outcomes similar to other series in the Western world (J. Phillips, personal communication).

Building on the foundation

The Richmond Institute of Neurology and Neurosurgery and its fund-raising partner, the Irish Brain Research Foundation (IBRF) were formed by Hugh Staunton, James Toland, and Jack Phillips in 1984 with the objectives of the promotion of postgraduate teaching and research in the neurological sciences, and continues today in the form of the Irish Institute of Clinical Neuroscience.

Funding for a formal epilepsy surgery program was obtained in 1987, after the publication of a report initiated by Dr. Staunton on the potential role of epilepsy surgery in Ireland. The positions of neuropsychologist, physicist, computer programmer, epilepsy nurse, psychiatrist and a research fellow were funded by private or charitable funds via the IBRF/Brain Research for a period of five years. The IBRF and the Department of Health entered into negotiations and the Department for Epilepsy Surgery was established in Beaumont Hospital in 1994. The Irish Department of Health took over the above salaries, and awarded a further grant of $209,000 per year, which was used for capital expenses.

A multidisciplinary approach was emphasized once the program had been established. Dr. Michael Farrell received epilepsy neuropathology training at UCLA with Dr. Harry Vinters. Epilepsy psychiatric evaluations were performed by Professor David Taylor, on a monthly consulting basis from the UK. The video-EEG telemetry unit operated from 1988, with a dedicated telemetry nurse and EEG technicians. Further training and mentorship was obtained by both Hugh Staunton and Jack Phillips. Hugh Staunton met with Peter Crandall at UCLA, and Theodore Rasmussen, Andre Olivier, and Frederick Andermann at Montreal. Jack Phillips undertook a traveling fellowship in 1994 to Montreal (Dr. Andre Olivier), Cleveland (Dr. Yousef Comair), and Seattle (Dr. George Ojeman and Dr. Alan Wyler).

Research

A multifaceted clinical and basic science program played an important role in the development of the Epilepsy Surgery Department, and was critical for maintaining its academic and scientific integrity. Early research focused on *neuropsychology* and *outcomes after epilepsy surgery.*[15,24,25] Eleanor Maguire and Teresa Burke described a novel method of evaluating topographical disorientation by using first-person video of a route in the Irish town of Blackrock and demonstrated abnormalities in both right and left temporal lobectomy patients (excisions typically involved encroachment on mesial structures), despite in some cases, normal standard neuropsychological testing.[26,27] After completing her PhD studies, Dr. Maguire went on to develop this work at The Wellcome Departments of Cognitive Neurology and Imaging Neuroscience, Queen Square, London, where she continues to employ ecologically valid or 'real life' paradigms to explore the role of left and right hippocampi in navigation and episodic memory.

The addition of a physicist, Mary Fitzsimons, facilitated research in neuroimaging, and continues in collaboration with Dr. Colin Doherty'.[27–29] *Basic science* research has contributed understanding to the pathology and biometabolism of temporal lobe epilepsy; Jack Phillips and his research colleagues in the Department of Neurosurgery have successfully performed intra operative microdialysis on patients undergoing temporal lobectomy. Elevated extra cellular levels of glutamate, aspartate, and gamma and aminoliulyric acid were detected in the spontaneously epileptiform hippocampus during the operative procedures.[30–32] An extensive *pregnancy* registry has been established. Genetic and surgical specimen sample banks for substantial numbers of patients will provide fruitful data for current projects including the promising field of *pharmacogenomics.*[33,34] The epilepsy pharmacogenomics project now has over one thousand samples collected.

Other surgeries

Vagus nerve stimulators have been placed in almost 90 patients. Corpus callosotomies for intractable generalized seizures have been performed since the early 1980s. In a series of twenty patients, 80% had a beneficial effect from callosotomy.[36] Subdural contact strips on the inferior and lateral surface of the temporal, or on the mesial and lateral frontal surface have been inserted through burr holes for intracranial EEG recordings. Intra-operative electrocorticography and microdialysis recordings have contributed to the clinical and research programs.[31] Functional hemispherectomies have been performed in three patients. Hemispheric devascularization by embolization of the anterior and middle cerebral arteries was performed in two children with a major reduction of seizure frequency in one patient, the other patient eventually requiring a functional hemispherectomy.[37]

Conclusion

The program initially played to its relative strengths: interictal EEG, neuropsychology, clinical assessment, and highly skilled individuals who sought out the best training and experience available, which, in a setting of lack of funding and resources, was still able to produce a successful surgical program, with one of the highest surgical volumes in the UK and Ireland, and with outcomes similar to other major groups.[21] In the current era, the Irish Epilepsy Surgery Program has embraced and incorporated advances in the field, including MRI technology, ictal SPECT, and pharmacogenomics.

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5 Epilepsy surgery in Germany

A Ebner, H Stefan, B Pohlmann-Eden, and PA Winkler

Introduction

The challenge of writing a historical overview of epilepsy surgery in Germany is honorable but also difficult because of the tremendous and radical political changes caused by the takeover of the fascist regime and World War II. Therefore we subdivide the history of epilepsy surgery in Germany into the period between the first attempts in epilepsy surgery and the year 1933, which meant a radical incision sending epilepsy surgery from a promising start in Berlin and Breslau into a state of hibernation, that lasted for almost thirty years. Awaking from this hibernation was slow, first diffident attempts in epilepsy research were made in the 1960s, but it took another fifty years for a serious and wide application of epilepsy surgery.

Nowadays, epilepsy surgery plays an important role in the armamentarium of modern medicine to treat devastating disease. Despite the economic restrictions medicine today is subject to, epilepsy surgery is still developing and promotable. This is due to the fact that the economic effects of epilepsy apply the lesser, the earlier epilepsy is under control. Still the fastest and least expensive way to control medically intractable epilepsy in many cases is epilepsy surgery, causing the steadily growing establishment of centers all across Germany, providing presurgical evaluation and surgical procedures for epilepsy patients within a fairly acceptable (and continuously improving) time-span for the individual patient.

History of epilepsy surgery in Germany before 1933

Over the centuries well-meaning approaches entering the cranial vault and a variety of other surgical procedures were carried out in an effort to treat epileptic seizures. In the modern history of epilepsy surgery good examples of complementary relationships between medical experimentation and praxis were stated, as enlisted hereby in chronological order.

For instance Wilhelm Griesinger[1] (Figure 5.1) carefully noted ictal symptoms and correlated them with the anatomic location of cerebral lesions identified post mortem. He was active in Tübingen and Zürich (Burghoelzli). On 1 May, 1866 he opened and headed the first autonomous Department of Neurology at the University of Berlin-Charité; in 1868/1869 he proposed the terms 'psychomotor' and 'epileptoid status'. Griesinger therefore provided a first basis for using the clinical features of an epileptic seizure to predict the precise localization of the pathologic substrate.

Gustav Theodor Fritsch and Eduard Hitzig[2] in 1870 published the results of their eminently important work even by today's standard by mapping the canine motor cortex using faradic stimulation – the same method we use nowadays to determine the function of the cortical areas and to narrow down on the epileptic focus.

Another success in 'narrowing down' on epileptogenic structures was proved by Karl Wilhelm Sommer[3] at the Wehlau-Institute in Eastern Prussia with his description of changes on the ammon's horn in the later called Sommer's Sector in 1880. Sommer noted that the CA1-Segment (Cornu Ammonis field 1) appears susceptible to anoxia particularly in epilepsy and ischemia.

Emil Bratz,[4] psychiatrist and director of the asylum Dalldorf, underlined Sommer's term ammon's horn sclerosis and forged in 1907 the term 'Affektepilepsie', affective epilepsy for eventual convulsions, triggered by fever convulsions and abuse of alcohol.

Otto Binswanger[5] was Director of the Department of Neurology and Psychiatry at the University of Jena and chairman of Hans Berger, the inventor of the EEG. He created the term 'surgical enthusiasm' and referred to the recent advances in localization. His own contributions were critical and he stressed the importance of follow-up investigations exceeding six months. Furthermore he pointed out the possible role of secondary scars. He suggested restricting the indication of surgery to patients of reflex epilepsy and of traumatic Jacksonian seizures. Considering the social consequences he concluded that surgical interventions were only justified if the disease was socially disabling, and tended to produce *status epilepticus*. The mortality of these procedures at that time was rather high (5–7%).

A.S.F. Grünbaum, a german physiologist, emigrated to Liverpool. Together with C.S. Sherrington they did a mapping of a chimpanzee's cortex and drew the first accurate cortical map, thus doing the spadework for the later published cortical mapping on human brains by Krause (see below).

Due to the efforts by colleagues to avoid formation of scars resulting from operations Trendelenburg discussed instead of resection the alternative of 'undercutting' the focus, which was applied by Kirschner in the hope of reducing the risk of secondary epileptogenesis from surgical scar. According to Krause the contemporary authors overestimated this risk, an appreciation we today know to be wrong.

Fedor Krause[6–8] (Figure 5.2) dedicated much of his life's work to epilepsy surgery. He seems to have been the first who stimulated the human motor cortex (Figure 5.3). He reported the earliest stimulation in his book '*Chirurgie des Gehirns und Rückenmarks nach eigenen Erfahrungen*', published by Urban and Schwarzenberg in 1911.[6] The patient was a 15-year-old girl with

Figure 5.1 Wilhelm Griesinger 1817–1868, with permission from C.H. Beck-Verlag-München.[109]

Figure 5.2 Fedor Krause 1857–1937.

Jacksonian seizures and Jacksonian status starting at the age of three years and caused by a postencephalitic cyst following meningitis at the age of two years. After the removal of the postencephalitic cyst the patient was followed for 17 years, she became seizure-free and improved considerably in her cognitive performance. Krause preferred the technique of monopolar faradic stimulation and described it meticulously. He felt that monopolar faradic stimulation was less irritating of severe seizures than galvanic stimulation that was preferred by Foerster.[9]

He restricted his resections to the motor-strip, of which he could present a detailed functional map based on electrical stimulation (Figure 5.4).

He reported more restricted resections to avoid loss of motor functions, whereas Foerster according to Krause advocated at the same time more extensive resections to achieve more and better control over epileptic seizures. In 1932 Krause, together with his co-worker Schum published a 900-page book on epilepsy.[8] This work was part of a series of surgical monographs concerned with surgical procedures. Interestingly, interventions like lumbar puncture, pneumoencephalography, transcallosal puncture ('Balkenstich'), sympathectomy, ligation or carotid artery, digital massage, alcohol injection into the focus, application of local anesthetics, adrenotomy, transplantations of endocrinous tissue, and peripheral operations in reflex epilepsy are discussed. Apart from a few specially defined situations these are all dismissed by the authors. Krause and Schum were also very skeptical about procedures that aim at reduction of intracranial pressure in cases of 'genuine' epilepsy. They point out, that this procedure mentioned above is based on unsubstantiated theories. Krause and Schum leave no doubt that the only worthwhile epilepsy surgery is the excision of the 'primary convulsing center' ('primäres krampfendes Zentrum'). The success of surgery in their opinion did not depend on a short history of seizures. They did not want to restrict surgical therapy but considered it in all patients with a definite focus of the seizures, even if no visible pathology was found.

Krause had a lifelong interest in the surgical treatment of intractable focal or Jacksonian epilepsy, accumulating an outstanding experience over 400 cases by the end of his career. Contemporaries described him as a modest and likeable human being. After his retirement he lived in Rome, where he spent his last years and devoted himself to a consuming interest in music.

In his work from 1926, Otfried Foerster (Figure 5.4) from Breslau reported an unknown number of operations in the precentral area and 54 other cortical areas.[10] Foerster became more involved with the surgical procedures of other areas, because there were smaller risks of functional deficits, which allowed more effective surgical interventions. His writings show a more detailed interest in the semiology of seizures and its localizing significance. To understand the entire message of these writings we have to remember that they are based exclusively on anatomical landmarks, detailed analysis of clinical phenomena, and the results of cortical electric stimulation at a time when EEG and electrocorticography (ECOG) were not yet available.[11]

In 1930, an article by Foerster and Penfield discussed the role of scar traction in epilepsy surgery.[12–14] In this article surgical interventions at many sites of the cerebral surface were reported, and case No. 5 described in this article comes close

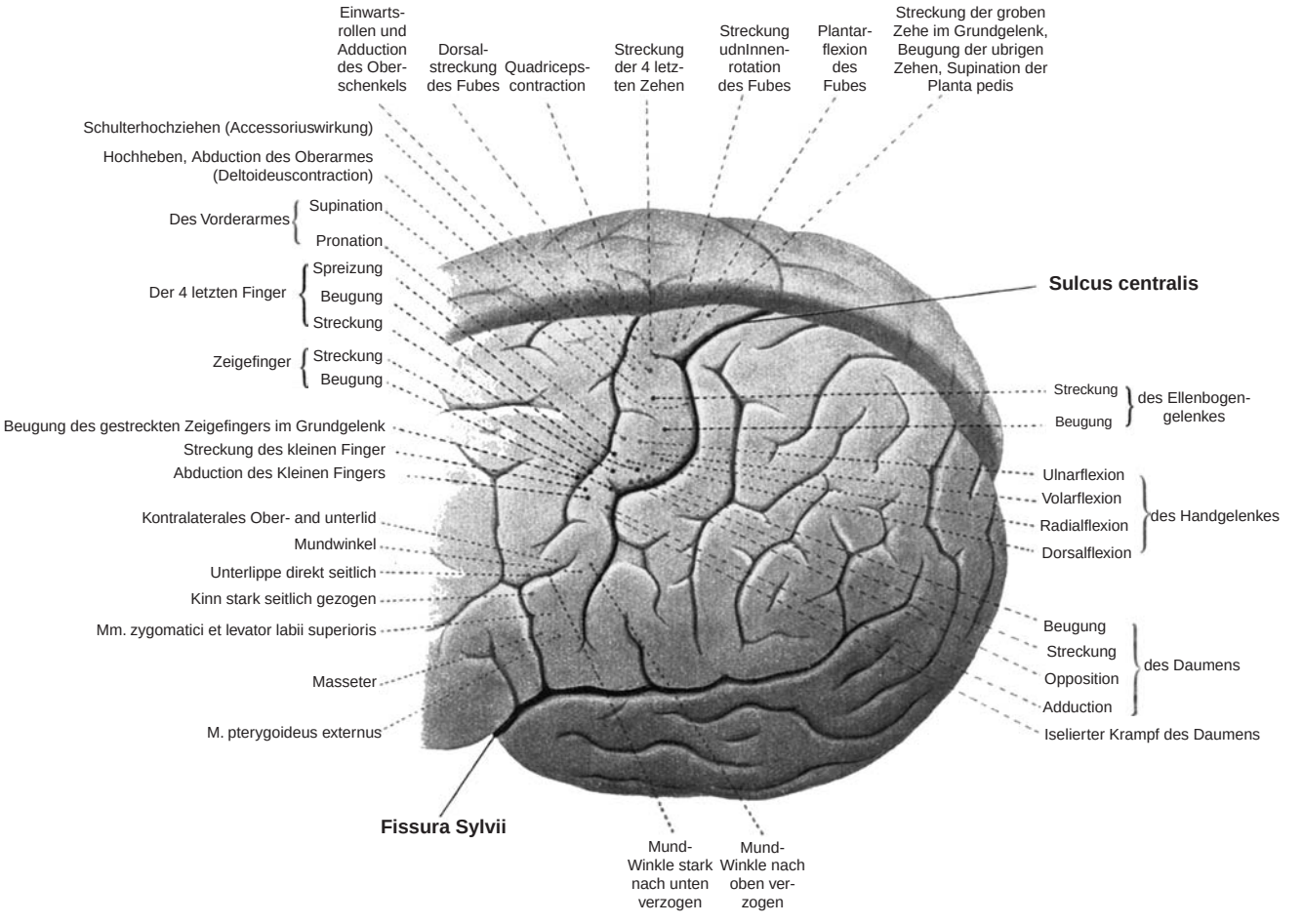

Figure 5.3 Krause's meticulous functional map of the motor cortex based on stimulation results from 142 operations.

to what today is considered a partial hemispherectomy. The article concludes with an account of Foerster's, Krause's, and Penfield's experiences with cortical stimulation in relation to Oskar Vogt's brain map. They concluded that the results of both approaches were convergent.

In the meantime Hans (Johannes) Berger in Jena followed Binswanger as Director of the Department of Neurology and Psychiatry at the University of Jena. In a 1929 publication he claims 6 July 1927 as the 'Day of the Invention' of the EEG, which he called 'Electroencephalogramm'.[15] Bergers publication referred only to the human cortex, the principle of the EEG had already been described in 1877 by the Liverpool physiologist Richard Caton in animal experiments. These results were known to Berger, as well as those published by the Polish physiologists N. Cybulsky and his pupil A. Beck and his Russian colleague V.V. Práwdicz-Neminski, who in 1925 published his 'Elektrocerebrogramm', as he called the photographic documentation of the electric activity of the brain. Ironically, Berger's findings, which are today's diagnostic basis of epileptic disorders, were for a long time not taken seriously especially in Germany. Berger was tolerated generally by his colleagues and especially by the acting chairman of the Department of Physiology of his own medical faculty. Contrary to his reception at home, in the UK and USA his invention was enthusiastically taken up and enhanced.

In recognition of his invention he was nominated for the Nobel Prize, but the Nazi regime pressurized him to renounce the acceptance of this honor. Furthermore it was suggested he retire early from his position as chairman by officials. Disappointed by the political developments in Germany he committed suicide on 1 June 1941.[16]

History of epilepsy surgery in Germany from 1933 to the 1980s

Cecile and Oskar Vogt were dismissed from office by the Nazi government in 1935 because of his protection of Jewish coworkers. Nevertheless by 1937 they had continued with their work in a privately funded institute in Neustadt, in the Black Forest on the identification of the precentral gyrus as the motor cortex brain stimulation in animals,[17] which they had begun on roughly two decades before. The Vogts' and Brodmann's monumental work on brain cytoarchitectonics, supplemented with electrical stimulation of the exposed cerebral cortex, demonstrated correlations between evoked functional responses and the topography of brain regions endowed with distinct cytoarchitectonic structure (topistic units). This opened the field of functional brain mapping, a subject hotly pursued at the present time.[18]

Walther Spielmeyer described ammon's horn-sclerosis as a consequence and not a possible cause of seizures.[19] He was Director of the Institute of Neuropathology, sponsored by the Rockefeller Foundation and named after the german emperor 'Kaiser-Wilhelm-Institut' in Munich, which was the preceding

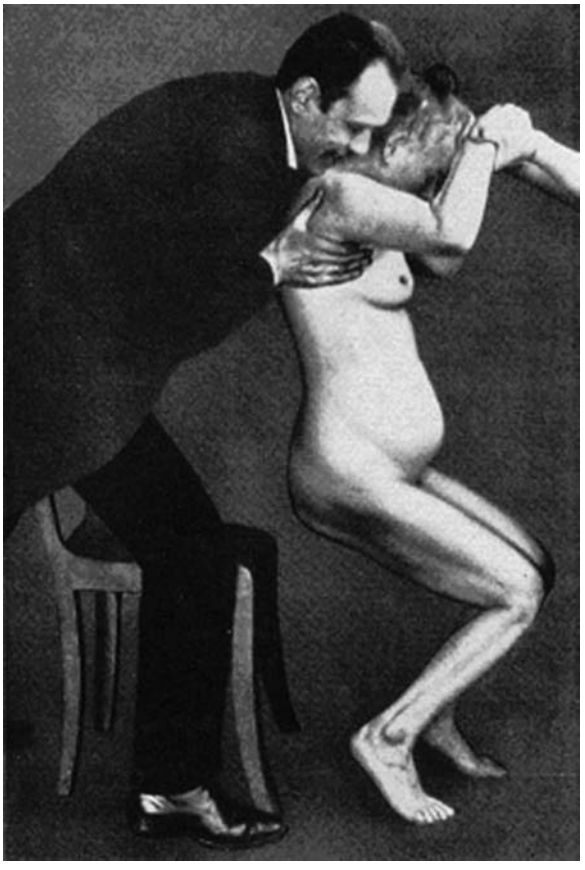

Figure 5.4 The young Ottfried Foerster (1873–1941) assisting a patient.

institute to today's Max Plank Research Institutes. Despite his exposed position he practiced an open resistance against the fascist regime by, for instance, helping many that were prosecuted by the regime, thus endangering his own life.

Stauder was probably the first author after Jackson to write, in 1935, a landmark paper on epilepsy and the temporal lobe.[20] He departed from the observation that convulsive seizures were particularly frequent in diseases of the temporal lobe, especially tumors. By that time, epigastric sensations, dreamy states, and other temporal auras had come, by a still unexplained process, to be considered as a diagnosis for genuine or hereditary epilepsy. Stauder was aware of the likeness of the symptoms of temporal lobe seizures and those of genuine epilepsy, but did not arrive at a critique of the latter concept of temporal lobe epilepsy. These new concepts were developed only under the influence of electroencephalography.

In the surgical field stereotactic procedures were developed initially for the treatment of movement disorders and were later applied to epilepsies with the aim of destroying an epileptogenic focus or to interrupt pathways of epileptic discharge.

Based upon the assumption that the fornix is the major efferent structure of the hippocampus, which regularly discharged on temporal lobe epilepsy, surgeons advocated its section for the relief of psychomotor epilepsy. In 1957 Hassler and Riechert placed lesions in the fornix at the posterior margin of anterior commissure.[21] Umbach reported on 29 patients with partial seizures in whom the fornix was destroyed unilaterally alone, or with lesions in the intralaminar nuclei amygdala, or laminar medialis. Another six patients had bilateral fornix lesions placed six to eight months apart without producing neurological or memory disturbances. Both partial and generalized seizures were eliminated in some patients.[22–24] In a later report of 50 cases, Bouchard[25] and Umbach noted a diminution of *grand mal* seizures by 65% and of lesser seizures by 62%.

Schaltenbrand *et al.*[26] reported on fornicotomies in five patients with psychomotor seizures indicating improvement in four cases. The addition of a lesion of the anterior commissure did not improve the results.

Mundinger[27] also performed stereotactic functional neurosurgery on patients with predominantly temporal epilepsy. He published his results of 45 patients with long term follow-up (up to 24 years) and found an improvement in more than two-thirds of the cases. The advances in the fascinating field of stereotactic neurosurgery were watched with great hope by all neurologists, neurosurgeons, and other specialists interested in the various aspects of causation, symptomatology, diagnosis, and treatment of epilepsy, but their hopes were only partly fulfilled. Other strategies had still to be found.

Despite the dedicated efforts of a few, epilepsy surgery did not exceed a mere beginning due to the break, the Third Reich and World War II had caused for this special field of neurosurgery. Efforts and results began to grow in Germany rather from the 1980s on. Also, it is remarkable that none of the Nuremberg accused physicians was explicitly an epileptologist or epilepsy surgeon.

Epilepsy surgery in recent years

The modern era of epilepsy surgery in Germany started in the mid-eighties. Several programs were initiated with the financial support of the states of Bavaria (Erlangen) and especially North-Rhine-Westphalia (Bonn, Bielefeld/Bethel). Since the development of epilepsy surgery was interrupted in Germany by the Nazi regime and World War II, knowledge of preoperative evaluation and epilepsy surgery had to be acquired from programs active outside Germany such as Switzerland, France, and North America. The numbers of epilepsy surgery programs as well as the numbers of epilepsy surgeries grew constantly over the following years. A survey done in 2004 revealed that 14 programs had been established accounting for ca. 500 cases of surgery a year. Two-thirds of those surgical cases were performed at the top five institutions. The exact numbers are shown in Figure 5.5.

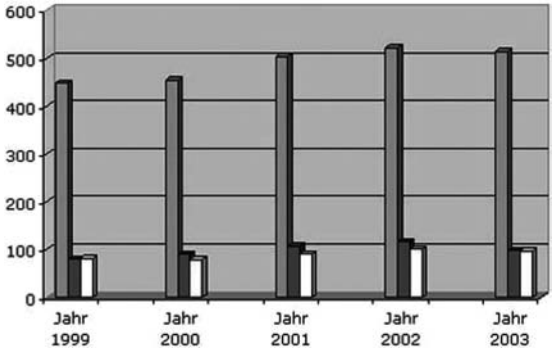

Figure 5.5 Number of epilepsy surgeries per year in Germany from 1999 to 2003. Light gray columns: all surgeries; dark gray: proportion of patients under 16 years; white: number of implanted vagal nerve stimulators.

The German epilepsy surgery program was supported by the German Ministry of Health. The financial support led to the build up of centers for epilepsy surgery and a working committee for preoperative diagnostics and epilepsy surgery including reports of a state of the art and minimal consensus for presurgical evaluation and indications for epilepsy surgery.[28]

In 1992 the Working Committee of Presurgical Epilepsy Evaluation and Surgical Epilepsy Therapy (Arbeitsgemeinschaft für prächirurgische Epilepsiediagnostik und operative Epilepsietherapie e.V.) was founded with the aim of promoting this form of epilepsy therapy in Germany. Scientific symposia and teaching courses are held on a yearly basis covering all aspects of diagnostic and therapeutic issues of this special field of epilepsy therapy.

Guidelines for manpower requirements and apparative equipment were established and published as well as guidelines for the education of all professional specialities working together in the multidisciplinary team.[29,30] The organ of notification of the working committee is the 'Zeitschrift für Epileptologie' (*Journal of Epileptology*), the official organ of the German chapter of the league against epilepsy.

In 2005 a catalogue of criteria which have to be fulfilled in order to get approval as an epilepsy surgery center was published.[31]

A further goal includes establishing and maintaining supportive relationships to other scientific societies on a national and international basis. Financial support of research projects and grants for educational purposes can also be provided. At present there are 170 people of various professions who are active members of this Working Committee. Altogether, the Working Committee can be regarded as a success having contributed to the rapid growth of epilepsy surgery programs of high standards in Germany.

Epilepsy register

A Neuropathological Reference Center for Epilepsy Surgery was established at the Department of Neuropathology, University of Erlangen-Nuremberg (http://www.epilepsie-register.de). Since May 2003, German epilepsy centers from Erlangen, Bielefeld-Bethel, Bonn, Freiburg, Berlin, Vogtareuth, Greifswald, Munich, Marburg, Augsburg, Hamburg, Göttingen, and Münster participated and contributed surgical specimens and/or diagnostic reports for a second opinion as well as collection of surgical specimens. A total of 2673 diagnoses have been reviewed so far. Major entities comprise hippocampal sclerosis ($n = 981$, including 135 cases presenting with dual pathologies), epilepsy-associated tumours ($n = 804$), cortical dysplasias ($n = 344$), vascular lesions ($n = 160$), ischemic lesions ($n = 130$), encephalitis ($n = 44$), traumatic injuries ($n = 10$), and 200 cases without significant neuropathological alterations (including reactive astrogliosis as a solitary finding). The purpose of this interdisciplinary project is to:

(1) standardize neuropathological classification systems of epilepsy-associated lesions;
(2) to establish a comprehensive tissue bank assisting and fostering scientific collaborations across Germany;
(3) to provide a review of surgical specimens (second opinion); and
(4) to support clinical therapy and outcome studies.

Annual meetings were organized to discuss specific topics, i.e., correlation between neuroradiological and neuropathological findings, and to microscopically review interesting cases.

Scientific research in German epilepsy surgery programs

Epilepsy surgery is performed in three different kinds of institutions. Several subdivisions of university departments of neurology subsequently developed highly sophisticated epilepsy programs including presurgical evaluation and epilepsy surgery listed in alphabetical order: Erlangen, Freiburg, Greifswald, Marburg and Munich. There is only one German university department with a specification to epileptology (Bonn) including basic neuroscience. Three additional non-university centers (all of them tertiary referral hospitals) such as Bethel, Kehl-Kork and Vogtareuth (only children) can be considered as comprehensive epilepsy programs in which epilepsy surgery is an integral part of a multidisciplinary approach aiming at a holistic medicine (intensive social counselling, long-term antiepileptic treatment, specialization in learning disabilities and handicapped people, rehabilitation units, education programs, and more). Most centers decided at an early time-point of their epilepsy surgery program to parallel this by more or less intensive and systematic research activities in order to guarantee a high clinical standard and to help establish an evidence-based new form of effective epilepsy therapy. The latter one was also crucial in the beginning of epilepsy surgery programs in Germany to convince health insurance companies to pay for this kind of 'new' treatment. According to the specific profile, logistics and resources of the individual center (some of them linked to basic neuroscience, eg., Berlin, Bonn, and Freiburg), different areas of research interests, and projects developed over time, are summarized in Table 5.1 (only when main focus of research and repeatedly published).

Specific research activities of the individual centers (alphabetical order)

Berlin

- Postoperative outcome in relation to neuropathological findings, psychiatric comorbidity and neuropsychological variables.
- Investigation of epileptogenic tissue in regard of glial function, neurotransmitters (GABA, glutamate), multiple drug transporter expression.[56,77,78,84]

Bielefeld-Bethel

- Extensive analysis of seizure semiology: role of lateralizing semiology for seizure outcome after epilepsy surgery,[32] hyperorality in seizures,[38] orgasmic auras,[37,55] 'alien limb phenomena'.[32] Seizure semiology in children.[5,34,35]
- Cortical dysplasia and pediatric epilepsy surgery.[54,76]

Table 5.1 Research activities of German epilepsy centers with main references relating to these fields

Research field	German epilepsy center	References (selection)
Seizure semiology	BI, KK, MR, M	32–40
Cognition/neuropsychology	BI, BN, E, F	41–46
Language	BI, BN, E, F, MR	47–51
Psychiatric comorbidity	BI, G	52,53
Clinical outcome	BI, BN, G, E	54,55
EEG as predictor for outcome	BI	43,56,57
Seizure prediction	BN, E, F, KK, MR	58,59
MRI – morphology (HS, FCD)	BI, E, F, M, V	49,55,60–62
Functional MRI	BI, BN, F, MR, E	50,51,63
Multimodal imaging-MEG-SPECT	E, M	20,47,64–67
Brain/neurostimulation	BI, BN, KK, MR	68,69
Radiotherapy	F, KK, E	70,71
Neuropathology	BI, BN, E, F,V	72–76
In-vitro- slice	B, BN, F	56,77–80
Molecular genetics	BN, F	81,82
Pharmacoresistance	B, BI, F, G, E	83–85

Abbreviations for epilepsy centers: Berlin (B), Bethel-Bielefeld (BI), Bonn (BN), Erlangen (E), Freiburg (F), Greifswald (G), Kehl-Kork (KK), Marburg (MR), Munich (M), Vogatreuth (V).

- Predictors for seizure outcome with special focus on pre- and postoperative EEG findings (spike-pattern distribution uni- vs. bilateral, -propagation[57]), clinical and MRI-Data.[48,57,86]
- Preoperative psychiatric comorbidity as predictor for postoperative incidence of psychosis.[52]
- Cognitive development of children after epilepsy surgery.[43]
- Brain plasticity and reorganisation with special focus on memory and language transfer using neuropsychological assessment and functional MRI.[44,48,51]
- Perioperative microdialysis of epileptogenic brain tissue as a model to understand pharmakoresistance.[72,83]

Bonn

- Neurophysiology of hippocampal slices of resected human epileptogenic tissue and in animal experiments.[72]
- Hippocampal slices in animal models.[80]
- Neurogenetics and channelopathies.[82]
- Psychophysiology of the mesial temporal lobe as accessed by subdural or hippocampal electrodes.[45]
- Seizure prediction by application of linear and non-linear algorithms to invasive and non-invasive EEG-data.[59]
- Neuropsychology of the epilepsies including studies on the long-term outcome of epilepsy surgeries.[42]
- Functional neuroimaging in patients and healthy subjects.[63]
- Development of modified functional hemispherectomy-technique.[87–89]

Erlangen

- Improvement of non-invasive presurgical evaluation by means of multimodal coregistrations of imaging and electrophysiology: multichannel MEG/EEG recordings in addition to high resolution MRI to define the correlation between structural findings, focal epileptic and functional important regions.[47,64,90]
- Non-invasive registration to preserve brain function by means of neuronavigation and intraoperative MRI and EcoG.[60,91]
- Seizure semiology in presurgical evaluation emotional-affective and autonomic ictal signs.[92,93]
- Pharmacoresistance and multiple drug transporter.[94]
- Radiotherapy.[95,96]
- Postoperative clinical outcome analysis after tailored resection and with regard to etiology.[97–99]

Freiburg (partly in co-operation with Epilepsy Center Kehl-Kork)

- Improving the sensitivity of structural imaging for the detection of subtle malformations of cortical developments using high-field MR scanning[61] and new postprocessing algorithms such as voxel-based morphometry.[63]
- Development of functional MR imaging algorithms for localization of language and memory functions.[50]
- Radiosurgical therapy including stereotactic interstitial radiosurgery and LINAC-radiosurgery in patients with hypothalamic hamartomas.[70,71]
- Epilepsies due to cortical dysplasia: mechanisms and treatment options.[73]
- Development and analysis of seizure prediction algorithms[41] and analysis of network oscillations as electrophysiological correlates of memory processes.[58,100]
- *In-vitro* studies of neuroprotection with special regard to the role of endocannaboids in both animal experiments and human epileptogenic and non-epileptogenic brain tissue.[79]
- Morphological and molecular mechanisms of ammonìs horn sclerosis.[81,101]

- Clinical, radilogical and histopathological correlation of temporal lobe epilepsies.[102,103]

Greifswald

- The role of ictal and interictal SPECT-imaging in the presurgical evaluation oftemporal lobe epilepsy.[104]
- Neuropsychological findings in temporal lobe epilepsy.[53]
- Multidrug transporters in dysembryoplastic tumors as cause for pharmakoresistance.[85]

Kehl-Kork (partly in co-operation with University of Freiburg)

- Correlation of neuropathology and electrocinical findings in cortical dysplasia.[75]
- Hemispheric dominance for language by means of functional MRI.[50]
- R-TMS – a predictor for successful vagal nerve stimulation.
- Predictive variables in presurgical evaluation.[105]
- Brain stimulation and seizure inhibition after automatic seizure detection (closed loop-system).
- Neuropsychology of temporal lobe epilepsies.[46]

Marburg

- Cortex physiology studied by TMS and direct stimulation of and recording from subdural electrodes.[68,69]
- Automated seizure detection and brain stimulation (co-operation Kehl-Kork).
- Language lateralization by means of transcranial Doppler-sonography and WADA testing.[49]
- High-resolution structural imaging by means of 3T and DTI-MR imaging for subtle focal brain abnormalities.[106]

Munich

- Extensive analysis of seizure semiology[36] including movements during epileptic seizures.[39,40]
- Localization of the epileptogenic zone in adults by SPECT and 3D image registration of [C-11]-flumazenil-PET and MRI.[65,107]
- Usefulness of 3-D reconstructed images of the human cerebral cortex for localization of subdural electrodes in epilepsy surgery.[66]
- Neurosurgical microanatomy-laboratory-investigations of deep seated brain areas and their significance for epilepsy surgery.[108]
- MR measurement of regional relative cerebral blood volume in epilepsy.[67]
- Reduction of benzodiazepine receptor binding is related to the seizure onset zone in extratemporal focal cortical dysplasia.[12]

Vogtareuth (children only)

- Cortical dysplasia classification and pediatric epilepsy surgery.[74]

Research networks

Several interdisciplinary research networks have been developed over time in Germany in order to: (1) create linkage to basic neuroscience programs such as, for example, molecular genetics, (2) to develop a neuropathology databasis, or (3) to increase statistical power of variables involved. All the above-mentioned epilepsy centers are part of national and international widespread research networks.

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6 Epilepsy surgery in France

P Kahane, A Arzimanoglou, A-L Benabid, and P Chauvel

The pioneer period (1950–1960)

Epilepsy surgery in France was probably born at the beginning of the 1950s, when H. Hécaen, who was already well known for his work on neuropsychology, went for 1 year (1952) to the Montreal Neurological Institute (MNI) to study post-surgical patients with W. Penfield. Although it was not the purpose of his visit, Hécaen was impressed by the results of surgery in terms of seizure relief, and he came back in Paris full of enthusiasm for such a treatment. He therefore encouraged G. Mazars to develop at Sainte-Anne Hospital an epilepsy surgery program based on the MNI method. Mazars was a neurosurgeon who was already interested in epilepsy surgery. He had started with J. Guillaume to operate epileptic patients using peroperative electrocorticography[1,2] and they published their first results in the early 1950s.[3–5] Interestingly, they were probably among the first to describe insular epileptic seizures, and the surgical technique for operating on them.[6,7] Also, Mazars contributed in the following years to the development of original therapeutic approaches such as refrigeration and freezing of the epileptic focus for seizure alleviation.[8]

During the same early period, J. Talairach, the founder of modern stereotactic surgery, was also working in the Neurosurgery Department of Sainte-Anne Hospital, under the supervision of his mentor, M. David. Since 1946, he had been developing stereotactic approaches to functional neurosurgery for chronic pain, movement disorders, pituitary diseases, and unoperable tumors. His interest was especially focused on the stereotactic definition of deep brain structures[9] and he built up a coordinate system based on the anterior commissure-posterior commissure axis, which allowed him to 'normalize' anatomical data from different brains. This led to the publication, in 1957, of his first stereotactic atlas on deep brain nuclei.[10] His second stereotactic atlas, devoted to telencephalic structures, would be published 10 years later while he was already working with J. Bancaud.[11]

J. Bancaud, a neurologist and electroencephalographer, was a student of H. Fishgold, a radiologist who was working at La Salpétrière Hospital in Paris. At the beginning of the 1950s, Fishgold's group joined David's group in Sainte-Anne Hospital, and this undoubtedly represented a turning point for both Talairach and Bancaud's careers. They were then evolving at the same institution, where epilepsy surgery had began, and they benefited from the high scientific experience of P. and M.D. Dell in neurophysiology, and of H. Hécaen and J. de Ajurriaguera in neuropsychology. Bancaud, largely influenced by Hécaen as well as by Penfield's work, understood very early the importance of clinical symptomatology for cerebral localization purposes, either in the presence of lesions or for the assesment of epileptic seizures. This appears in his medical thesis on the relationships between neuropsychological deficits and EEG alterations in patients with cerebral tumors. Bancaud was convinced by the fundamental interest of epilepsy surgery, but considered that current methods of investigation were not well adaptated for the precise localization of the brain regions involved in seizure generation. Since the seizure was the symptom to be cured, it was the cortical region generating epileptic seizures that had to be electrophysiologically defined, in correlation with its anatomical correspondence. In other words, the idea was to accurately record the electrical activity of different brain structures during the course of a seizure, rather than to use findings from the study of interictal spikes.

Bancaud saw the potential of Talairach's method to localize the sources of EEG discharges in three-dimensional space, and he began working with him to develop applications of stereotactic functional exploration for presurgical evaluation of medically intractable epilepsies. An operating room dedicated to stereotactic neurosurgery opened at Sainte-Anne Hospital in 1959, and the project to record epileptic seizures by means of stereotactically implanted intracerebral electrodes became a reality.[12–17] The term stereoelectroencephalography (SEEG) was coined in 1962 to account for this new method,[18] a method which, for many reasons, was revolutionary in the field of epilepsy surgery:

1. SEEG recordings allowed to study the spatiotemporal dynamics of seizure discharges with respect to their clinical features, and with a high degree of anatomical precision;
2. the technique of SEEG offered the possibility to dissociate the presurgical investigation phase from the surgical therapeutic act: SEEG recordings and electrical stimulations were carried out in the operative room under 'acute' conditions; after removal of the intracerebral electrodes, resection surgery was planned, and performed in a second step;
3. SEEG directly derived from a new conceptual approach for studying partial epileptic seizures, which was based on the assumption that the chronological occurrence of ictal clinical signs reflects the spatio-temporal organization of the epileptic discharge within the brain (Figure 6.1).

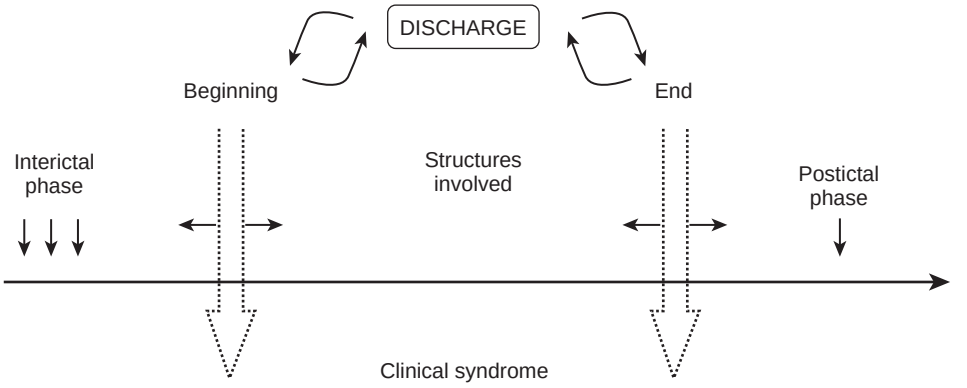

Figure 6.1 The model of a partial seizure, as proposed by Bancaud and Talairach (modified).[19]

This approach, popularized in France under the term of 'anatomo-electro-clinical correlations', has remained the principal guide of the whole presurgical process that Talairach and Bancaud would use all their career, and that they would transmit to their pupils.

The development of SEEG (1960–1970)

The development of SEEG ushered in a new area that coincided with a complete reorganization of the Sainte-Anne Department of Neurosurgery. In 1960, David and Fishgold moved to La Pitié-Salpétrière Hospital (Paris), and Talairach became the head of a new Department of Functional Neurosurgery. In 1964, A. Bonis, a neurologist and student of R. Garcin, joined the Sainte-Anne team and became the 'right arm' of Jean Bancaud. The same year, Talairach's team was completed by G. Szikla, an emigrant from Hungary who devoted his career to anatomy and stereotaxy, and played a major role in the development of stereotactic angiography. More particularly, carefully looking at the close relationships of cortical vessels to the convolutions and sulci, Szikla showed that a meticulous analysis of vascular trajectories allowed to extract gyral form and dimension,[20] and provided constant landmarks for interpretation of anatomical variablity.[21] Thus, stereotactic angiography was not only a routine procedure for safe implantation of intracerebral electrodes, but also a valuable tool for deducing the actual location of electrode contacts, particularly before the availability of modern imaging methods.

With time, the novel SEEG technique of Bancaud and Talairach became a comprehensive methodology, the aim of which was to study, in each individual case, the origin and spread of ictal discharges in order to precisely define the cortical area to be surgically removed (see Kahane and Francione, this book, Chapter 73). The selection of the structures to be explored was based on a very careful analysis of all the data – notably clinical – collected during the non-invasive presurgical investigations. Such an analysis led to one or several hypotheses concerning the site(s) of seizure onset and the pathways of preferential ictal spread.[22] Electrodes were then placed accordingly, in a way that enabled interpolation of intracerebral EEG activity within the interelectrode space. Proceeding this way, Bancaud and Talairach could precisely study how symptoms accumulated as the epileptic discharge propagated into different cortical structures and, in turn, could confirm or infirm their initial hypotheses (Figure 6.2).

The high spatial and temporal resolution coupled with a high power of localization that the SEEG procedures offered, rapidly provided a large amount of data that had immediate repercussions on the practice of epilepsy surgery. In particular, Bancaud and Talairach described the role of the amygdala and hippocampus in the clinical symptomatology of temporal lobe seizures,[23,24] as well as the role of (mesial) frontal anterior and intermediate areas in the occurrence of clinical manifestations usually attributed to generalized seizures and thought to be of centrencephalic origin.[25–28] Their dynamic view of focal epilepsies culminated in a key book published in 1965, *La Stéréoelectroencéphalographie dans l'Epilepsie*.[29] In this book, using detailed observations and discussions, they re-defined topographic diagnosis based on seizure patterns (under this term, Bancaud and Talairach considered that ictal clinical symptomatology must be viewed as a whole, and they regarded the order and sequence of semiological elements as crucial). Also, benefiting from Talairach's experience in the field of stereotaxic neurosurgery using radioisotopes, they translated such a therapeutic possibility in a few patients in whom seizure origin was relatively limited in space.[30]

During this same period, Talairach and Bancaud also developed SEEG criteria for detecting non-expansive brain lesions that could not be shown by the neuroradiological techniques available at the time. In this context, they used the term of 'lesional zone', which referred to the area occupied by electrical silence or various types of slow-wave activity, and which presumed a macroscopic alteration of neural tissue. The correlations were clearly superior to those given by the neuroradiological images available, allowing to map the extent and anatomical location of astrocytomas or oligodendrogliomas. This made more safe resective surgery and more accurate stereotactic interstitial radiotherapy. Their experience in this field is summarized in a second important book, *EEG et SEEG dans les tumeurs cérébrales et l'Épilepsie*,[31] in which they described the topographic transitions between electrical silence inside glial tumors, slow waves, spiking, subclinical paroxysms, and seizure activity. This book also collected important data on simultaneous recordings of scalp-EEG and SEEG. As such it still provides, more than 30 years later,

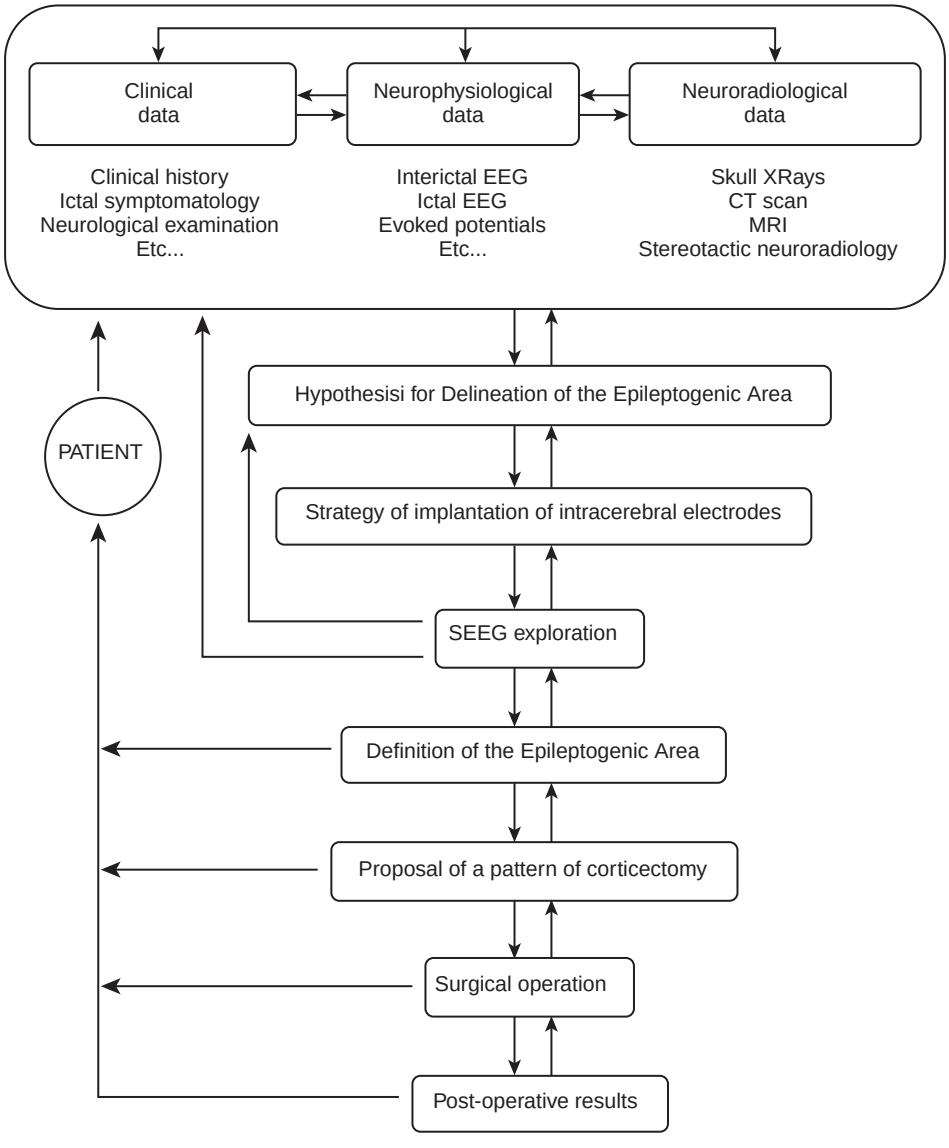

Figure 6.2 Schematic representation of the methodology used by Bancaud and Talairach for examining a patient for surgical treatment of epilepsy (modified)[19].

valuable information on what we record and what we miss using surface recordings.

From these early studies emerged the novel concept of the 'epileptogenic zone', a term which directly derived from the necessity to create a new definition – based on seizure recordings – of the brain area to be resected.[32] SEEG definitions of seizure onset were proposed, which could slightly vary from one structure to another (temporal limbic, neocortical …), but which all emphasized the existence of fast synchronizing discharges that might involve a single region, or distinct but interconnected regions. The epileptogenic zone was differentiated from the 'irritative zone' (the area occupied by interictal spikes) and from the 'lesional zone'. Indeed, Talairach and Bancaud[33] observed that the respective topography of these different zones were not fully overlapping. This led to a new type of surgery, based on a three-dimensional representation of the three zones on the basis of which, together with the results of electrical stimulation, the surgical plan could be carefully prepared and adapted to the individual patient's case.

Bancaud and Talairach rapidly understood that their method also represented a remarkable tool for studying 'normal' neurophysiology. Using intracerebral electrical stimulation, they brought new insights on the anatomo-functional organization of the supplementary motor area[18,34,35] and, with the help of P. Buser, worked on various aspects of motor systems. Buser was a neurophysiologist who was especially interested in the pyramidal system and sensory |polymodal afferents to the frontal cortex. One of the models he used was the startle reaction in the anesthetized cat. He began to work with Bancaud in 1964, and they developed together new concepts on the physiopathology of startle epilepsies,[36,37] Kojewnikow syndrome,[38–40] and post-anoxic myoclonus.[41] Also, using evoked potentials, they studied cortico-cortical connections and their facilitation inside the epileptogenic zone.[42–45]

The Sainte-Anne team becomes the Sainte-Anne school (1970–1990)

In 1970, the *Institut National de la Santé et de la Recherche Médicale* (INSERM) created the U97 research unit entitled

'Stereotaxic Functional Exploration and Surgical Treatment of the Epilepsies'. It was headed first by Talairach for 5 years, and then by Bancaud. Other people joined the Sainte-Anne group, among whom P. Chauvel from Rennes, and C. Munari from Bologna (Italy), who would both later have a major influence on the development of epilepsy surgery in France. The Sainte-Anne group was then composed of neurosurgeons (C. Munari, G. Szikla, J. Talairach), neurologists (A. Bonis, P. Chauvel, S. Geier, S. Trottier, C. Schaub) and researchers (P. Buser, J. Louvel, M. Lamarche, R. Pumain). During this period, the collaborative work of Talairach and Bancaud culminated in the general report presented in 1974 to *the Société de Neurochirurgie de Langue Française*, entitled '*Approche Nouvelle de la Chirurgie de L'Épilepsie*'. In this report, Talairach and Bancaud exhaustively specified the successive and multidisciplinary steps of their method, and described the surgical results obtained in 204 epileptic patients operated on during the 1957–1973 period, including 160 resections and 44 stereotactic destructions.[46]

During the 1970s, technical progress allowed to prolong the SEEG recordings. It was now possible not only to record seizures during the 'acute' phase in the operating theater but also in the laboratory. The advent of telemetry and video-recording were retrospectively matched with EEG signals, and this allowed a much better study of ictal clinical symptoms, such as 'automatisms'. Bancaud and coworkers were especially interested in gestural automatisms, and they identified correlations between particular gestural manifestations with anterior frontal lobe seizures,[87–89] as well as the characteristics that helped to distinguish them from gestural manifestations of temporal lobe origin.[90,91] In the search for mechanisms of automatisms, they also described the behavioural effects of anterior cingulate gyrus stimulation, which consisted in complex coordinated movements associated with mood alteration.[92] Some observations made at this time also suggested that an epileptogenic zone could be distributed between different lobes, thus leading to the concept of frontotemporal,[19] perisylvian,[93] and temporo-parieto-occipital epilepsies,[94] and therefore to a concomitant change in surgical strategy.[95] The continuous evaluation of the clinical features of partial epileptic seizures, thanks to SEEG results, progressively led to the refinement of seizure semiology and significant advances were achieved in the study of temporal and frontal lobe epilepsies.[46]

The method of Bancaud and Talairach generated considerable interest abroad and a number of physicians visited the Sainte-Anne group, coming from Argentina (Dr Betti), Austria (Dr Mempel), Belgium (Dr Petrov), Brasil (Dr Marino), Canada (Dr Saint-Hilaire), Chile (Dr Serrano), Germany (Dr Tomalske), Greece (Dr Prosalentis), Italy (Dr Signorelli), Japan (Drs Hori, Dr Takeda), Mexico (Dr Lopez-Gonzales, Dr Moises), Paraguay (Dr Bordas-Ferrer), Poland (Drs Sierpinsky, Dr Valencak), Romania (Dr Cinca, Dr Russu), Spain (Dr Manrique), Switzerland (Dr Bernouilly, Dr Wieser), Tchecoslovaquie (Dr Rektor), Turkey (Dr Oproic Ozdemir Aral), and the United States (Dr Zervas). In France, a number of neurosurgeons came at Sainte-Anne Hospital to learn stereotactic surgery. Some would play later a crucial role for the development of epilepsy surgery in Bordeaux (A. Rougier), Grenoble (A.L. Benabid), Marseille (J.C. Perragut), and Rennes (J.M. Scarabin).

Epilepsy surgery in France today (1990–)

During the last 20 years a number of epilepsy surgery centers were developed, first as an initiative of A. Rougier in Bordeaux (where P. Loiseau and P. Jallon had developed a comprehensive epilepsy program),[47] and then under the impulse of the most prominent pupils of Talairach and Bancaud: P. Chauvel (who started the centres of Rennes and Marseille in collaboration with J.M. Scarabin and J.C. Perragut, respectively), and the late C. Munari (who founded the centre of Grenoble with A.L. Benabid, and then moved to Milano).

Later, other centers were started, so that more than ten University Hospitals have specifically developed an epilepsy-surgery program (Figure 6.3). Most are using the SEEG method when necessary, mainly for adult patients. Both centres have developed not only clinical programs but also, in line with the spirit of Sainte-Anne School, research programs in which emphasis is placed on the value of clinical semiology and its integration through 'anatomo-electro-clinical correlations'. As a result, important contributions have emerged these last years from the French epilepsy surgery community including, among others: the SEEG investigation of hypothalamic hamartomas and focal cortical dysplasia;[48,49] the development of innovative methods for signal analysis to better understand how epileptogenic networks are organized;[50–53] the characterization of different subtypes of mesio-temporal lobe seizures and the identification of the role of the temporal pole and entorhinal cortex in a number of such seizures;[54–56] the recognition of the insular cortex as a potential key structure in seizure spread and seizure generation;[57–60] the delineation of the concept of 'temporal plus' epilepsies;[61,62] the development of new therapeutic approaches such as gamma-knife surgery,[63–65] sub-thalamic nucleus stimulation,[66,67] and SEEG-guided thermocoagulation.[68] In 1999 the first international epilepsy journal was started which was regularly published with an accompanying DVD to include video-EEG recordings; *Epileptic Disorders (www.epilepticdisorders.com)*, always in the search of refinement in the analysis of electro-clinical semiology.

In children, one of the first epilepsy groups to support epilepsy surgery was that of J. Aicardi (Hôpital Necker-Enfants Malades, Paris) in collaboration with the Sainte-Anne group (J. Bancaud, S. Trottier, and colleagues) for SEEG cases, and with the Neurosurgery Department (J.F. Hirsch and C. Sainte-Rose) of the Enfants-Malades Hospital. They contributed to the better individualization of surgical indications in Sturge-Weber syndrome,[69–72] as well as to a better evaluation of the effectiveness of 'lesionectomy' for different brain epileptogenic lesions.[73–75] The group of O. Dulac (Saint-Vincent-de Paul Hospital, Paris) also developed an epilepsy surgery program, in collaboration with the group of O. Delalande (Fondation Rothschild, Paris). They have a particular interest in large hemispheric lesions in young children with severe epileptic encephalopathies, and they were among the first to propose a modified technique for hemispherectomy, the vertical parasagittal hemispherectomy.[76,77] They contributed also to significant advances in the surgical treatment of hypothalamic hamartomas by extending the disconnection method for

Figure 6.3 Geographic distribution of epilepsy surgery centers in France. Four centers are located in Paris: *Sainte-Anne hospital* (F. Chassoux B. Devaux, E. Landré, B. Turak), *Hôpital de la Salpétrière* (C. Adam, M. Baulac, S. Clémenceau, S. Dupont), *Fondation Rothschild* (O. Delalande, M. Fohlen, C. Jallin), *and Hôpital Necker-Enfants Malades* (M. Bourgeois, C. Sainte-Rose). The remaining centers are located in *Bordeaux* (C. Marchal, A. Rougier), *Grenoble* (S. Chabardès, D. Hoffmann, P. Kahane, L. Minotti, E. Seigneuret), *Lille* (S. Blond, P. Derambure, N. Reyns, W. Szurhaj), *Lyon* (M. Guénot, J. Isnard, F. Mauguière, P. Ryvlin), *Marseille* (F. Bartolomei, D. Broglin, P. Chauvel, J.C. Perragut, J. Régis), *Montpellier* (P. Coubes, A. Crespel, P. Gélisse), *Rennes* (A. Biraben, D. Taussig), *Strasbourg* (S. Chassagnon, E. Hirsch, P. Kherli, M.P. Valenti), *Toulouse* (J.C. Sol, L. Valton).

this indication and by developing a stereoendoscopic approach.[77–80] They represent today in France one of the two major groups regularly dealing with epilepsy surgery in children.

Recently, surgery has been 'officially' recognized in France as being part of the treatment of drug-resistant partial epilepsies.[81] Also, following the results of a multicentric medico-economic study,[82] the French Ministry of Health accepted to re-evaluate the reimbursement cost for a SEEG evaluation (it was reimbursed less than 1500 Euros until early 2007 but was re-estimated to nearly 13 000 Euros). These are certainly important steps, and the available facilities now allow operation about 400 to 500 patients each year in French territory. However, as for other countries, a vast majority of epilepsy surgery centers mainly deal with adult patients, and epilepsy surgery in children remains one of the priorities in this field in the near future.

Such a priority was emphasized more than 10 years ago by C. Munari, when he organized in Paris a meeting specifically devoted to drug-resistant focal epilepsies in children.[83] Under his impulsion and in collaboration with C. Sainte-Rose, a multidisciplinary group, including adult and child neurologists, neurosurgeons, neuroradiologists, and neuropsychologists from various cities and French University Hospitals (Grenoble, Lyon, Paris-Robert Debré, Paris-Necker, Strasbourg, Rouen) started working together on a regular basis in order to better evaluate indications and surgical approaches for children with drug-resistant epilepsies. Meetings on a monthly basis facilitated the evaluation of an important number of children with focal epilepsies or epileptic encephalopathies. This 'multidisciplinary network' and regional collaboration undoubtedly accelerated access of children to various presurgical evaluations since it allowed to all participating medical groups to benefit from facilities available at the various centers, but not necessarily to all. Earlier access to surgery was also facilitated by the regular participation of the neurosurgeons in the analysis of the anatomo-electro-clinical data. The progressive development of a 'common language' between the various groups progressively diminished the number of children that needed SEEG recordings.

During the last 5 years, however, it became evident, following the expansion of epilepsy surgery indications, that the small number of centers dedicated to children could not cover the needs at a national level (60 million inhabitants). It is currently estimated that more than 500 children per year could benefit from epilepsy surgery while not more than 150 are effectively operated on. This remains true despite the fact that

the French social security system covers all medical expenses, including transport, a fact that enormously facilitated the way of working of the above-mentioned multidisciplinary group, since it allowed patients to move from one city to another for a more rapid access to various presurgical evaluation techniques. On the basis of this evidently difficult-to- accept situation, some of the members of the 'multidisciplinary network' (A. Arzimanoglou, E. Hirsch, P. Kahane, P. Ryvlin, and C. Sainte-Rose) elaborated in 2004 a project for starting a national reference center, now known under the acronym IDEE (Institute for Children and Adolescents with Epilepsy). IDEE was conceived as a university hospital-based institute that would combine four main characteristics:

1. a health service, with at least 14 monitoring beds (four of which dedicated to SEEG recordings), with a concentration of highly-qualified epileptologists (neurologists and child neurologists) and paramedics with a wide experience of video-EEG monitoring;
2. a clinical and fundamental research department, with the participation of all clinicians of the medical department and research units working on topics related to cognitive development and epilepsy;
3. a medico-social center, under the management of a major lay association, that will develop specific projects of global epilepsy care (neuropsychology, psychological support, speech therapy, education of parents and children on epilepsy management issues, epilepsy nurses);
4. a sector dedicated to industrial development of techniques and treatment approaches directly related to the missions of IDEE.

In 2006, the University of Lyon accepted to endorse the project for commissioning the institute and the agreement of the French health authorities was obtained. IDEE is expected to be functional early in 2010 and will have, among others, a mission of evaluation of medical practices and research production related to epilepsy surgery.

Concluding remarks

Epilepsy surgery in France has more than half a century of history. In 2007 almost all major university hospitals throughout the country comprise of units dedicated to adult epilepsy surgery. Despite this remarkable development, many of these centers still lack the necessary manpower to develop comprehensive epilepsy surgery programs and access to surgery may still take several months, even when clearly indicated. Epilepsy surgery for children is just terminating its neonatal period. The most important contribution of the 'French school' is undoubtedly the stereo-electroencephalography approach of depth recordings developed by Bancaud, Talairach, and their pupils.[85] This anatomo-electro-clinical approach largely enriched the international medical literature on issues related to seizure semiology and localization.

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7 Epilepsy surgery in Italy

G Avanzini and L Tassi

Introduction

Italy is a country of 57 million inhabitants, subdivided into 20 different areas (regions) (Figure 7.1). Each region manages the health and the hospitals in its area under the superintendence of the Health Ministry. The state provides public health covering all Italian citizens for any medical or surgical treatment independently from their social, economic, ethnic, or religious condition. Citizens have their first medical contact with a family doctor (general practitioner) who decides, on the basis of the diagnosis to treat the patient or to send it to a first, second or third level hospital.

It has been evaluated that approximately 570,000 patients in the country are suffering from epilepsy and about 20,000 with a focal drug-resistant epilepsy could be candidates to epilepsy surgery. Most epileptic patients are currently treated in third-level centers, but despite the high density of specialized centers, about half are in the charge of general neurologists, pediatricians or general practitioners.

At the present time drug-resistant patients with focal epilepsies are referred to one of the two centers dedicated specifically to epilepsy surgery, from one of the regional epilepsy centers, after a diagnostic and pharmacological work-up. These two epilepsy surgery centers are located in the northern and southern part of Italy.

Historical development

From 1955 to 1970

After early attempts dating back to the beginning of the 40s, two main groups led by Franco Marossero and Carlo Alberto Pagni in Milano and by Victor Aldo Fasano in Torino[1,2] continued the task to implement epilepsy surgery by developing specific programs including the refinement of invasive presurgical methodologies such as 'electrodurographic' and 'stereo-electroencephalographic' recordings.[3,4,6]

The lack of a strict co-operation between neurosurgeons and neurologists and neurophysiologists specifically devoted to epilepsy and properly trained, resulted in poor outcomes and frequency of surgical complications.

Several patients were submitted to temporal lobectomy.[1,2,5] However, the absence of accurate anatomo-electroclinical correlations led to discouraging results and therefore epilepsy surgery became quickly discredited. As a consequence, neurologists and epileptologists tended to stick to the pharmacological treatment, even if it could not control the seizures.

From 1970 to 1994

Although epilepsy surgery was considered among the possible options of epilepsy treatment, in practice it only had a 'marginal' role. Once again the multidisciplinary approach to a complex pathology failed, no dedicated centers were created, and the neurosurgeons managed epilepsy inside neurosurgery departments.

A pioneering work in sensitizing the Italian epileptologist had been carried out earlier in Genova and then in Roma by Gianfranco Rossi and his group tried to outline the general guidelines for epilepsy surgery.[7–9,12]

In addition palliative surgery,[10,14] and lesionectomies, particularly in epilepsies associated with tumoral lesions,[11] were carried out by Isacco Papo in Ancona and by Giovanni Broggi in Milano. Later on, disconnective techniques and hemispherectomies were carried out.[18,19]

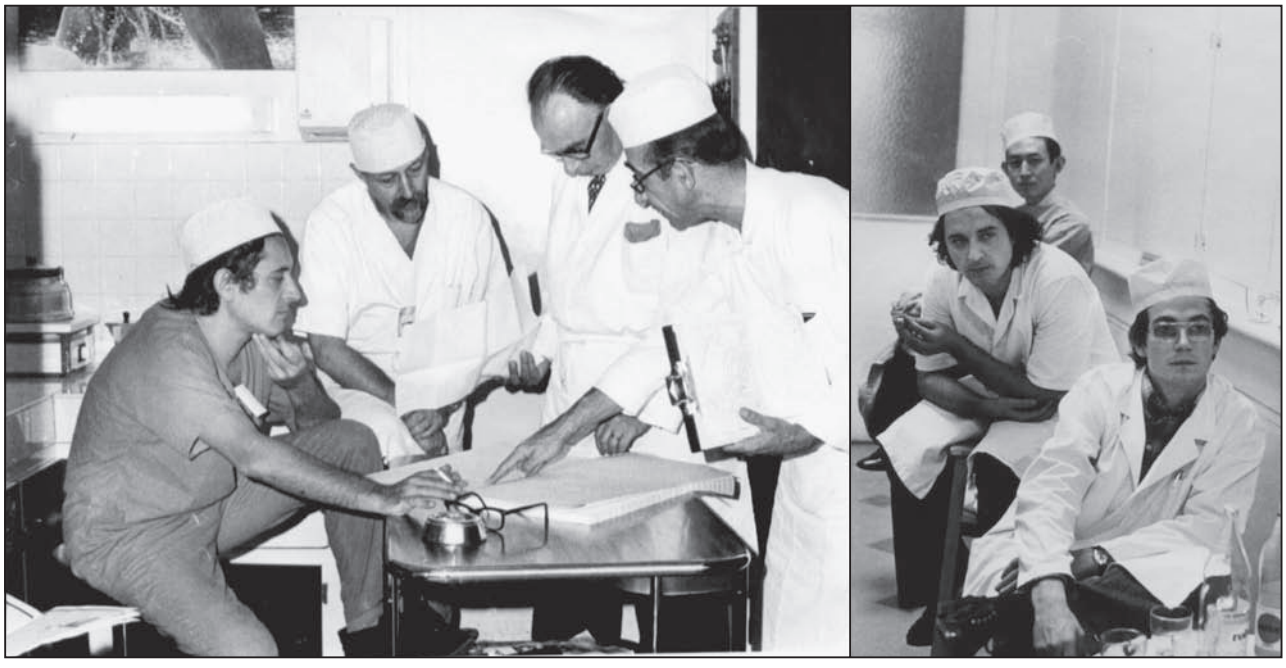
The Claudio Munari contributions to epilepsy surgery in Italy (1993–1999)

Claudio Munari, after a post-graduate certification in neurosurgery and in neurology in Bologna, and a period in Marseille, moved to Paris in 1977 and worked with Jean Bancaud and Jean Talairach at the Ste. Anne Hospital (Figure 7.2). In 1994, 17 years after his departure, he returned to Italy (Figure 7.3). His scientific and clinical training, both in neurology and neurosurgery, makes him a 'unique specimen' in epilepsy surgery: he could manage a patient from the first outpatient examination to the operating theater.

His entire life was devoted to his work addressed to the cure and to the care of patients; it was not infrequent to find him after 10 p.m, with his unfailing cigarette, at his desk reviewing EEGs, planning the *next* day (after) surgery or visiting patients. His entire professional career was aimed at contributing to the comprehension of epileptogenic mechanisms and to development and improvement of epilepsy surgery always with a great respect toward the patients and empathy for their problems.

The major contrast between the European (and particularly French) school and the US clinical approach, concerned the concept of uniqueness of each patient and of each epilepsy. The correlations between ictal symptomatology, anatomical data and the neurophysiological explorations permitted him to define, in a single patient, the so-called 'Epileptogenic Zone' and to carefully plan the surgical resection. His fluency not only in Italian but also in French and English languages had characterized many a discussion sometimes 'vigorous and excited' particularly on the relationships between the anatomical lesion and the epileptogenic zone.

Figure 7.1 Topographic map of Italy, subdivided into 20 different regions.



(a) (b)

Figure 7.2 Claudio Munari at the Ste. Anne Hospital. A: with Jean Bancaud, interpreting a EEG (the first from the left and the third from the left). B: in the operating theatre with Patrick Chauvel (the second from the bottom and the first from the bottom).

He transformed the Stereo-EEG investigation, inherited from Bancaud and Tailarach, in a methodological and systematic approach.[13,15]

In 1990 he left Paris to the Neurosurgery Service in Grenoble headed by Alim Louis Benabid, where, with his precious collaboration, he created an epilepsy surgery center.

When he moved to Milan in 1994, the first dedicated epilepsy surgery center was created in Italy. His strenuous activity was divided between Milano, Genova, Paris, and Grenoble, allowing the Center to rapidly attain international standard. He became, having been one of the founders, President of the Italian League Against Epilepsy (LICE) in 1996 (Figure 7.3), and he was with a number of commissions and task forces within the International League Against Epilepsy.

He was a magical and helpful 'maestro' to his numerous pupils teaching them how to learn and improve from their mistakes. He gave them the gift of a scientific methodology and the clinical, semiological, neurophysiological, and anatomical fundamentals to ensure the heritage of his work.[16,17,20]

Since his untimely death, on 2 October 1999, the epilepsy surgery center is dedicated to him.

Mechanisms of referral

Regional Centers of Epilepsy and the LICE (Lega Italiana Contro l'Epilessia)

The development of centers of excellence (second and third level) for the care of epileptic patients, adults and children, has occurred in almost all Italian regions. They are located in the hospitals or associated with University centers. The Italian League Against Epilepsy promotes and encourages the scientific

Figure 7.3 Claudio Munari in Italy, before and during his presidency of the Lega Italiana Contro l'Epilessia.

and professional training of the epileptologists, and supports the development of epilepsy surgery centers.

The degree of service offered at each center can vary from routine diagnostic, monitoring, and follow-up care to intensive monitoring.

Access of the epileptic patient to the epilepsy surgery centers is through referral by the neurologist, neurophysiologist, or neuropediatrician working in each center.

Although the existence of the epilepsy surgery centers is increasingly known, the benefits of surgical treatment are not yet sufficiently known and therefore too often the patients are referred too late to epilepsy surgery.

Epilepsy surgery: the present

'Claudio Munari' Center (Milan) and Neuromed (Pozzilli)

Nowadays two epilepsy surgery centers (Figure 7.4) are working in Italy. The first one in Milano, founded by Claudio Munari, with about 100 patients operated on per year. A multidisciplinary approach permits us to define the surgical strategy, and Stereo-EEG evaluation is available for more complicated epilepsies. A team of neurologists, neurophysiologists and neurosurgeons ensures the mandatory work-up in focal drug-resistant epilepsy.

The second center, located in Pozzilli (Isernia), is based on the same strategy and methodology, except that invasive investigations are carried out by subdural electrodes. About 100 patients per year undergo epilepsy surgery in Pozzilli.

The other centers

Other neurosurgery departments of the Istituto Nazionale Neurologico C. Besta of Milano and of the Universities of Siena, Bologna, Udine, Roma, in collaboration with the two main epilepsy surgery centers, include evaluation and surgical treatment of epileptic patients, mainly symptomatic. No invasive investigations are available, although long-term monitoring is frequently accessible.

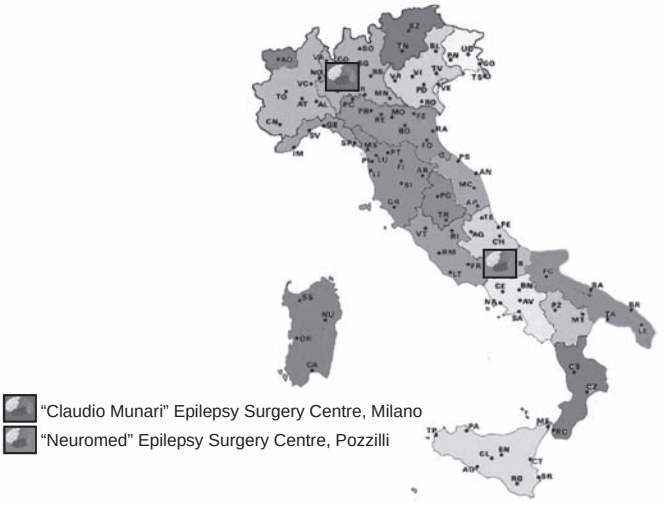


Figure 7.4 The location of the two dedicated epilepsy surgery Centers in Italy: the red one in the Northern part, and the green one in the South. (See Color plates.)

Conclusion

A dedicated epilepsy surgery center has only been operating in Italy since 1994, founded by Claudio Munari, and dedicated to him. A second center is functioning in Pozzilli, in the southern part of Italy. Unfortunately, the total number of patients does not exceed 200 persons per year, in comparison with thousands of patients needing surgical treatment.

A Commission of the Italian League Against Epilepsy is drafting a comprehensive guideline for epilepsy surgery and for pre-surgical evaluations.

From 1994, about 800 patients were operated on in Italy, and a network of epilepsy care centers is available to improve the medical, social, and surgical management of these patients.

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8a Epilepsy surgery in Switzerland

HG Wieser and K Schindler

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The surgical forerunners in Switzerland

Theodor Kocher (1841–1917), well known as a surgeon awarded the Nobel Prize (1909), Hayazo Ito (1864–1929) and Harvey Cushing (1869–1939) worked in Berne, Switzerland (Figure 8a.1).

Cushing arrived at Berne one year after Ito left Kochers clinic for Kyoto in 1899. Cushing stayed 5 months (November 1900–March 1901) in Berne. William Osler and William Halstead, at the Johns Hopkins Hospital, had persuaded Cushing to spend a year in Europe. Osler himself was in England at the beginning of Cushing's trip, thus assuring that Cushing received many professional and social invitations. Cushing met Victor Horsley in London and Charles S. Sherrington in Liverpool. Following his stay in Berne, Cushing left to Turin (Italy) where he spent 4 weeks at the laboratory of Angelo Mosso. On Kocher`s suggestion, during his stay in Berne, Cushing engaged in a research project in the laboratory of the physiology department under the guidance of Professor Hugo Kronecker. Cushing studied brain stem control of systemic blood pressure during raised intracranial pressure (Cushing response).[2,3]

Ito, *the* pioneer of epilepsy surgery in Japan, the first professor of the second surgical department of Kyoto University from 1900 to 1924, spent over three years as a volunteer research fellow to Kocher and engaged in experimental studies on the relationship between intracranial pressure and epileptic seizures.[4,5]

Theodor Kocher considered the necessity of a 'surgical neurology' ('chirurgische Neurologie') as a specialty. In relation to epilepsy surgery he stated in 1893 that all traumatic epilepsies have to be submitted to surgery.[5] However, Switzerland needed another 20 years until the founding of the first department of neurosurgery in 1939 by Hugo Krayenbühl took place in Zurich, although Rudolf Krönlein, the successor of Prof. Billroth (well known for his classic types of gastrectomy cited in every textbook of surgery), must be mentioned as a pioneer in this field around 1900.[6]

Otfrid Foerster (1873–1941; Figure 8a.1 right), the 'foremost teacher and most learned authority in the field of neurology and one of the strongest personalities of his time in medicine' (statement by John F. Fulton in 1942) has historical connections to Switzerland, and, of course, many famous visitors, among them John Fulton, Wilder Penfield, Percival Bailey, Paul Bucy, Maclean M. Kennard, and W. Mahoney. Post-traumatic epilepsy due to war wounds had stimulated Foerster`s interest, and led to the neurosurgical removal of cerebral scar tissue by excision in all accessible parts of the cerebral cortex. A pioneer in epilepsy surgery, Foerster performed cortical stimulation under local anesthesia before resecting epileptogenic areas.[7] Together with Altenberger, Foerster recorded the first electrocorticogram of a brain tumor; he introduced hyperventilation to provoke epileptic seizures and coined the term 'psychomotor epilepsy'. Although we know that the technique of Foerster, the neurosurgeon self-trained in surgery, was not elegant or meticulous, in his world-famous work on cortical representation which he reported at the 100th anniversary of Hughlings Jackson in the ninth memorial lecture ('Electrical excitability of the human cerebral cortex', delivered at University College, London, April 2–30, 1931) he documented his mastery in the anatomy and physiology of the human central nervous system. Harvey Cushing honored him as 'surgeon-in-chief pro tempore'. It was 1931 in Berne that Foerster wrote the resolution asking the governments of the participating nations to create an academic representation of neurology at their universities. The first who received the Otfrid Foerster Award, one of the most prestigious awards of the German Society of Neurosurgery, was Percival Bailey in 1953. Wilder Penfield was honored by it in 1966, and Hugo Krayenbühl in 1973.[8–11] It should be mentioned here, that Penfield, who spent 'an interlude in Germany' with Foerster in Breslau,[12] had close contact to Hugo Krayenbühl*.

*Penfield dedicated his book *Epilepsy and Cerebral Localization*[13] on 9 July 1946 'to Professor Krayenbühl – with best wishes from his colleague Wilder Penfield'. The senior author has a letter from Krayenbühl to Penfield, dated 25 February 1976, in which Krayenbühl 'thanks for (WPs) kind letter of February 12, 1976'. After having expressed his 'delight to see Priscilla again ...' Krayenbühl continues discussing Penfield's book *The Mystery of the Mind* [14] praising WPs 'outstanding clinical neurophysiological research on the function of the brain'. Krayenbühl then quotes Walter R. Hess and Hans Fischer and finally he confesses that he adheres to Hess' statement 'that we have to content ourselves with the recognition that much exists and evolves in this world which is not accessible to our comprehension, since our cerebral organization is primarily devised so that it secures secure survival of the individual in its natural surroundings'.

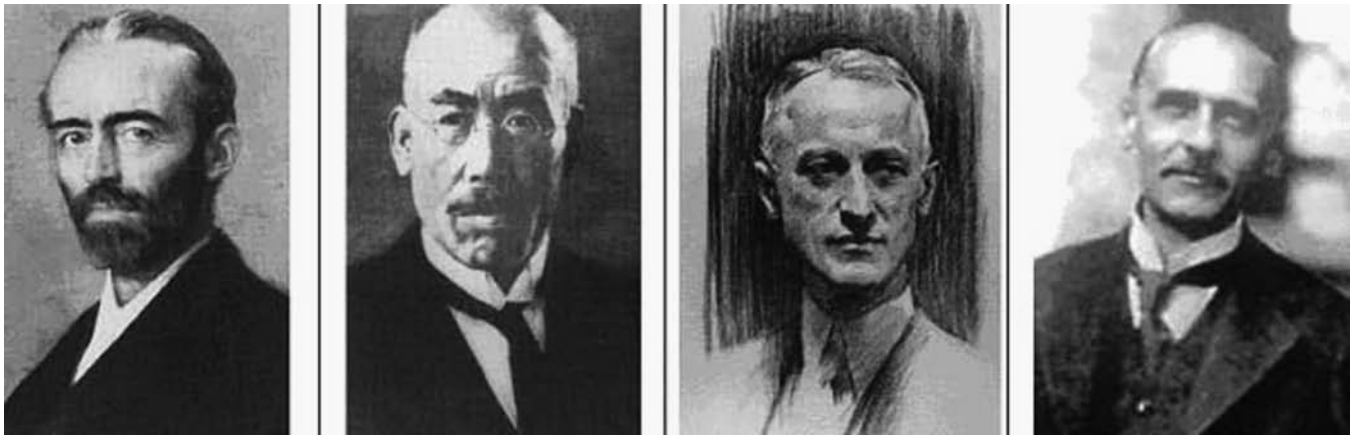

Figure 8a.1 From left to right: Portraits of Theodor Kocher (1841–1917), Hayazo Ito (1864–1929),[5] Harvey Cushing (1869–1939)[15] and Otfrid Foerster (1873–1941).[11]

Hugo Krayenbühl's legacy

The history and development of modern neurosurgery in Switzerland has been linked since the early beginning to the study and surgical management of epilepsy.

The idea of a ward for neurosurgical patients in Zurich became a reality when the old deaconess hospital located in the Heliostrasse called 'Krankenstation Hegibach' (Figure 8a.2 left) was given from the government to the surgical department of the 'Kantonsspital Zurich'. In 1936, in the uppermost floor of the building and under the far-sighted guidance of Krayenbühl, a ward specially dedicated to neurosurgical cases was opened. In 1939 Krayenbühl officially assumed the direction of the Division of Neurosurgery, still a part of the surgical department.

Krayenbühl was born on 3 December 1902 in Zihlschlacht, a small village located in Thurgau in Switzerland. He was the son of a well-known Swiss psychiatrist who was chief of the psychiatric hospital in Zihlschlacht. At home, during his childhood and adolescence, Krayenbühl was deeply influenced by discussions about the causes and treatment modalities of mental and neurological diseases. He started his medical training in Geneva in 1921, and continued his studies in Kiel (Germany) with the later renowned psychiatrist Manfred Bleuler. Krayenbühl returned home and graduated from the medical faculty of the University of Zurich in 1927. He began his nine-year postgraduate training in pathology, internal medicine, psychiatry, and general surgery in Zurich, and continued in neurology (Prof. K. Bonhoeffer) in Berlin, and in neurosurgery (1934–1935) in London with Sir Hugh Cairns.[16] After his return to Zurich in 1936 he worked as a 'Voluntärassistent' at the surgical department in Zurich under Paul Clairmont.

Krayenbühl's hard work during the following two years succeeded in convincing the faculty to establish a

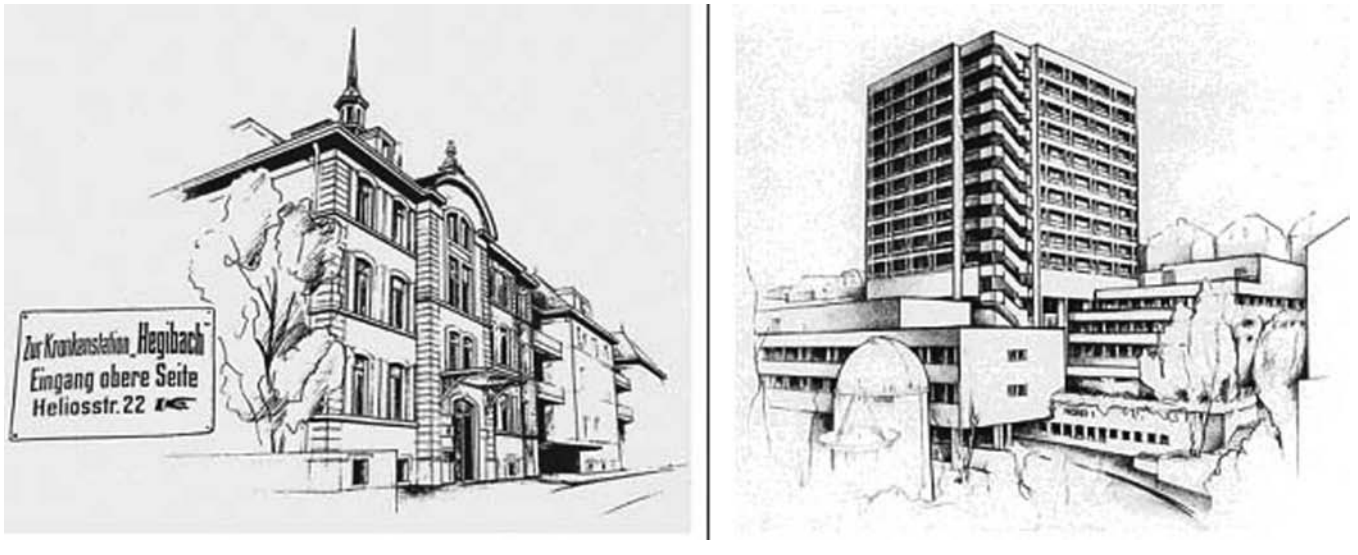

Figure 8a.2 Left: The neurosurgical ward at Hegibach started with a few beds during the year 1936. In 1939, it was recognized as a division of the Department of General Surgery under Professor Paul Clairmont (1875–1945). Later on, in 1945, an independent Department of Neurosurgery was created under the direction of Professor Hugo Krayenbühl. In 'Hegibach'the first installation took place of an EEG station during 1948 as a division of the neurosurgical department. During 1951 the Department of Neurosurgery moved to the new building of the Cantonal Hospital of Zurich (University Hospital) at the Rämistrasse where a new in-patient ward of the neurological clinic was opened. Right: In 1999 the neurosurgery moved to the new Nordtrakt II of the University Hospital Zurich, with theaters and the ICU on floor C, and wards on floors M and N. (Illustrations: P. Roth).

neurosurgical ward. Later, during the winter semester of 1944–1945, an independent Department of Neurosurgery was officially inaugurated. With this historical milestone, Krayenbühl became the first chief of a Department of Neurosurgery in Switzerland.

Krayenbühl's interest in epilepsy surgery was already apparent in his early career as a neurological surgeon. On 13 May 1941, he received the Venia legendi from the University of Zurich, based on ten original publications and the monograph 'Das Hirnaneurysma', an 84-page long manuscript published in the Swiss Archives of Neurology and Psychiatry. For his 'Probevortrag', an introducing lecture given to the members of the faculty, Krayenbühl chose the issue 'Epilepsie und ihre chirurgische Behandlung' (epilepsy and its surgical treatment). This reflected his interest in epilepsy and revealed the multidisciplinary nature of it. No other disease or human suffering could bring together so tightly different medical specialties as epilepsy. Influenced by his predecessors Victor Horsley (1857–1916) and Harvey Cushing (1869–1939) as well as Wilder Penfield (1891–1976), Krayenbühl succeeded in specifying a common path for neurologists, neurophysiologists, neuropsychologists, and neurosurgeons dedicated to the study and treatment of epileptic seizure disorders.

Krayenbühl was promoted to Professor Titularius on 30 April 1945, to Professor Extraordinarius ad personam on 23 September 1948, and to Professor Ordinarius on 16 April 1963.

His colleagues considered Krayenbühl, because of his huge and profound knowledge in neurology and his clinical skills, as a 'neurological surgeon'. Until 1952 all outpatients of the neurological clinic who required hospitalization for check-up or diagnostic reasons were admitted to the neurosurgical department. There were two reasons for this historical situation. First the new diagnostic techniques such as electroencephalography (EEG), pneumoencephalography (PEG), myelography, and angiography were locally introduced with great impetus by Krayenbühl. Second, an in-patient station at the neurological department was absent. Only eight years after the establishment of the neurosurgical department, the neurological department opened a ward for patients who required hospitalization for diagnostic purposes.

During the first 18 years, a total of 2336 patients with epilepsy were assessed and treated in the neurosurgical department under Krayenbühl. A brain tumor was causing the seizures in 343 patients (15%) and 608 patients suffered from a so-called 'Spätepilepsie', i.e., idiopathic epilepsy of the elderly. [17] This sample was described by several publications.[18, 19] Thereby, neurologists and neurophysiologists, founded a bank of knowledge at the neurosurgical department. Based on experimental studies on 'extrapyramidal epilepsy' and its pathophysiology, Krayenbühl defined its clinical features.[18]

With the introduction of an EEG-station in 1948 and the facilities in the new building of the 'Kantonsspital' (1951/2), surgery for epilepsy became routine in the daily activities of the department. The discovery and neurophysiological evaluation of many cases with 'psychomotor epilepsy' raised the interest of temporal lobe epilepsy and surgical management. Krayenbühl had been performing anterior temporal lobectomies with a standard technique since 1936, and started to use intraoperative electrocorticography (ECoG) in 1949. His surgical decisions were always based on the convergence of clinical features and EEG findings (Figure 8a.3). His meticulous technique did not differ much from that practiced since 1934 by Wilder Penfield at the Montreal Neurological Institute (MNI).[20, 21] The posterior line of resection of a nondominant anterior temporal lobectomy was the vein of Labbé, the temporal horn was punctured at the beginning of the operation via a small corticotomy in the middle temporal gyrus, and the uncinate gyrus was sucked away very carefully to remove the mesial structures of the temporal lobe.

In October 1951, Krayenbühl revealed his passionate interest in psychomotor epilepsy in a lecture he gave to the medical faculty of the University of Zurich. He presented his surgical series of patients with lesional and nonlesional epilepsy and increased his pupils' interest in temporal lobe epilepsy. Together with Hans Peter Weber, his intraoperative illustrator, Krayenbühl and his collaborators documented carefully each case with epilepsy (Figure 8a.4).

Krayenbühl developed his own concept of epilepsy surgery and he expressed his estimation of the work of his colleagues in London,[22] Paris,[23, 24] and Montreal.[20, 21]

Krayenbühl's absolute priority was to limit the exposure of the brain surface during surgery. The brain and its surrounding structures had to be carefully handled. Although together with Rudolf Hess he performed numerous electrical intraoperative stimulations, he was skeptical and showed distrust toward new invasive presurgical diagnostic methods, such as the SEEG, until he proved them and was convinced of their safety and efficacy. It is typical that he

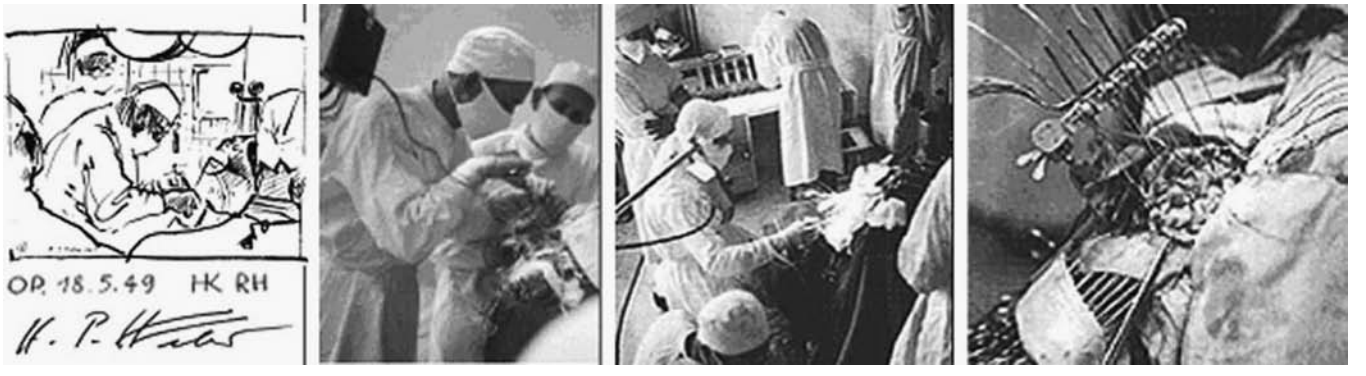

Figure 8a.3 Hugo Krayenbühl (HK) and Rudolf M. Hess (RH) at operation on May 18, 1949 – drawing by Hans Peter Weber. Photographs from left to right: RH places the cortical electrodes. HK performs cortical electrical stimulation whilst RH observes the ECoG recording. ECoG with Penfield holder.

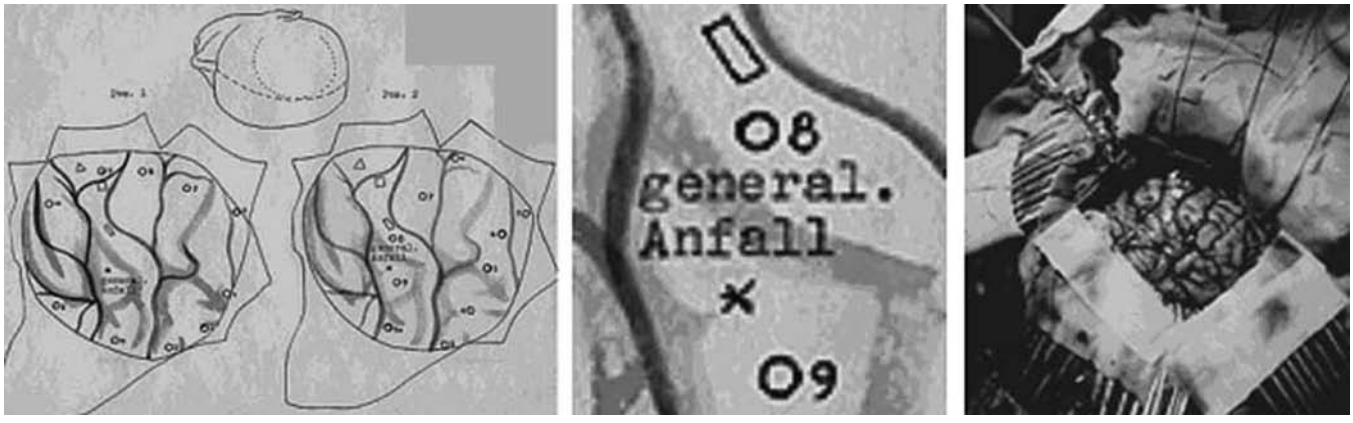

Figure 8a.4 Documentation of the intraoperative situs in an epilepsy surgery (25 years old male, surgery 8 December, 1950) with the brain area from where secondary generalized seizures were elicited by electrical stimulation (between ECoG electrodes 8 and 9).

wanted to see that depth electrodes had advantages over intraoperative recording (Figure 8a.5).

In association with distinguished neurosurgeons of Europe and the US, Krayenbühl engineered and founded the publication 'Advances and Technical Standards in Neurosurgery', its first issue appearing in 1972.

Krayenbühl was a gentle individual who stimulated his pupils and transmitted his philosophy to them. He left an indelible trace in all of them. His strictness and his demonstration of authority, sometimes led to outbursts of rage. According to Krayenbühl, 'One has to say to the people what they did wrong, what they did right is self-evident'. Many of his pupils and colleagues discovered a paternalism coming from their teacher. The strive for excellence in the daily work was his main occupation. His authoritative behavior was used only to serve.

In 1995 at the commemoration of Krayenbühl's death, Yasargil expressed, 'I still continue to learn from my teacher in my daily activities and decisions, and I am often involved in discussions with him, even in my dreams' (Figure 8a.6).

After 22 years as chairman of the Department of Neurosurgery, Krayenbühl retired in 1973, dedicating his last years to finishing ongoing projects and meditating about his life as a neurosurgeon, teacher, and philosopher. Professor Hugo Krayenbühl died on 1 January 1985, 83 years old.

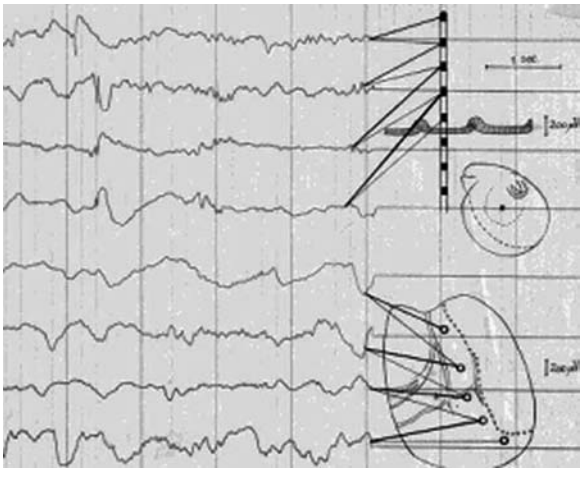

Figure 8a.5 Combined intraoperative ECoG and depth recording using a rigid 'electrode aigue' of the Saint Anne school, showing spikes in the intracortical, but not in the epicortical recordings.

The Zürich Neurology and Brain Research Institute

Twelve years after the first chair for neurology had been created for J.M. Charcot, (Paris 1882), Constantin von Monakow (1853–1930), who was seeing patients in a private praxis in Zurich since 1887, was elected as professor extraordinarius for 'hirnanatomische Fächer' (brain anatomy; 1 October 1894) (Figure 8a.7). In 1910 Monakow's private laboratory for brain research has been taken over by the Canton Zurich. From 1913 on there existed a 'Hirnanatomisches Institut' and a 'Neurologische Poliklinik',[25] but the first neurological ward was only available in 1952 under the successor of von Monakow, Miecyzyslav Minkowski (1928–1954). Monakow retired in 1927 and was succeeded by Minokowski in 1928 who was at the same time promoted to professor extraordinarius (with etat) and nominated director of the 'Neurologische Poliklinik' and the 'Hirnanatomisches Institut'.[26]

The 'Hirnanatomisches Institut', later called the Brain Research Institute, is also indebted to Krayenbühl. After the retirement of Minkowski as chief of the Neurological Clinic and director of the Institute in 1954, the prestigious Brain Anatomy Institute was almost shut down. Throughout the decade, with continuous negotiations with the University of Zurich and the Medical Faculty, Krayenbühl was successful in his efforts, and an additional academic position was created for the guidance of the Institute. Konrad Akert was appointed chairman in 1960, and the traditional research at the Institute was complemented with research in the pathogenesis of epilepsy (Figure 8a.8).[27]

The EEG Unit at the Neurosurgical Department

Krayenbühl, considering the new development of advanced neurosurgery, installed an EEG-station at Hegibach in 1948. Very soon Krayenbühl had recognized the importance of this

Figure 8a.6 Left: Portrait of Professor Hugo Krayenbühl (1902–1985), founder and chairman of the first neurosurgical department in Switzerland. Middle: Hugo Krayenbühl is congratulated on his 70th anniversary by HGW. Right: Hugo Krayenbühl during the celebration of his 80th birthday in Zurich accompanied by his pupils M. Gazi Yasargil and Konrad Akert, Director of the Brain Research Institute of the University of Zurich. Photo: P. Roth.

method for epilepsy and neurosurgery.[18,19] Intraoperative EEG recording from the brain (ECoG) was already considered an important tool for definition of the 'epileptic focus', according to the pioneer work of Penfield and Jasper in Montreal. At that time in Zurich, about one third of the patients admitted to the neurosurgical department presented with seizures. In 15% of the cases a tumor could be diagnosed as the cause of epilepsy.

The historical context at that time was optimal for the development of electrophysiology in Zurich. One decade of surgical experience in neurological surgery, the cumulated number of patients with epilepsy, an independent neurosurgical department, as well as the support of many brilliant colleagues, such as neurophysiologist and 1949 Nobel Prize winner Walter Rudolf Hess (Figure 8a.9, *left*), allowed Krayenbühl to initiate a very fruitful era of EEG in Switzerland. Krayenbühl assigned this task to Rudolf Hess (Figure 8a.9, *middle*), who was trained in 1947–1948 by Dr. W. A. Cobb at Queens Square National Hospital in London, Dr. Grey Walter, Bristol, and in 1957 by Dr. Herbert Jasper in Montreal. Rudolf Hess also engaged himself in experimental sleep studies (Figure 8a.9, *right*) and was responsible for the development of clinical electrophysiology in Zurich.

Hess recorded the first scalp EEG (in a 31-year-old patient K., in 1917) on 8 October 1948, and the first intraoperative ECoG on 18 May 1949, in patient Elisabeth. Krayenbühl performed this operation, while Rudolf Hess was fortunate to record a well-localized spontaneous ictal event (Figure 8a.10).

Hess himself pushed the only existing eight-channel EEG apparatus of that time from the ward to the operation room until the department moved to a modern building at the

Figure 8a.7 'Das Kränzchen' (13 February, 1902) pictured in the Heliostrasse 16, in Zurich showing Prof Constantin von Monakow (from left to right: Natalie Felix, Adolf Fick (Dr.med, opthalmologist and Privatdocent); Anne Martin, Walther Hermann Felix (1860–1926; Professor for Anatomy), Mathilde Monakow, Rudolf Martin (1864–1926; Professor for Anthropology); Constantin von Monakow and Marieli Fick.

Figure 8a.8 Left: Konrad Akert and Rudolf Hess at the EEG Congress 1953 in Cambridge, Boston. Right: Konrad Akert delivering words of appreciation to Rudolf Hess at occasion of the International Symposium on *Presurgical Evaluation of Epileptics,* Zurich (12–15, September 1985) dedicated to Prof. R. Hess.

Rämistrasse in 1952. The operation room at this hospital, later called University Hospital, was designed and built according to modern standards and well equipped for intraoperative EEG recording and electrical stimulation.[29,30] Epilepsy surgery became a routine procedure. More than 500 lesional, nonlesional, temporal, and extratemporal resections were performed throughout two decades.

The method of stereo-electroencephalography (SEEG), as pioneered in Paris by Bancaud and Talairach in 1965,[23,24] was introduced in Zurich with the cooperation of Christoph Bernoulli, epileptologist, and Jean Siegfried, functional neurosurgeon. Bernoulli had been trained with the Saint Anne's team in Paris, and Siegfried at the same time in Montreal. The first, at this time 'acute' SEEG exploration was done on 20 February, 1970 (patient M.S. in 1959) with the help of Gabor Szikla (from the Saint Anne team; Figure 8a.11) who did the so-called 'répèrage', i.e., the neuroradiological examination under stereotactic condition, consisting of pneumencephalography, angiography, and ventriculography, and performed with the patient's head fixed in the Talairach frame (Figure 8a.12). Up to 1984 depth EEG long-term recordings had to be done hard-wired in the laboratory (Figure 8a.13).

Seven years later, in 1977, Bernoulli *et al.* reported a person-to-person transmission of Creutzfeld–Jakob disease after SEEG exploration.[31] The popularity of this technique hid under the shadow of this fatal experience and less invasive and less risky presurgical evaluation methods were looked for, developed, and favored whenever possible. Nevertheless, SEEG had allowed for a deepened understanding of the phenomenology and electroclinical features of partial epilepsy syndromes and in particular temporal-limbic seizures.[32] These stereoelectroencephalographic studies inspired the development of new surgical techniques for the treatment of the so-called mesial temporal lobe epilepsy syndrome. The good results obtained in Zürich with the microsurgically performed selective temporal lobe resections stimulated and inspired the later development and introduction in Zurich of the foramen ovale (FO) electrode, a semi-invasive method for preoperative assessment of mesial temporal lobe epilepsy, in 1983.[33] Since 1984 FO electrodes were used in Zurich in 272 patients. Most of them were studied with radiotelemetry, which was

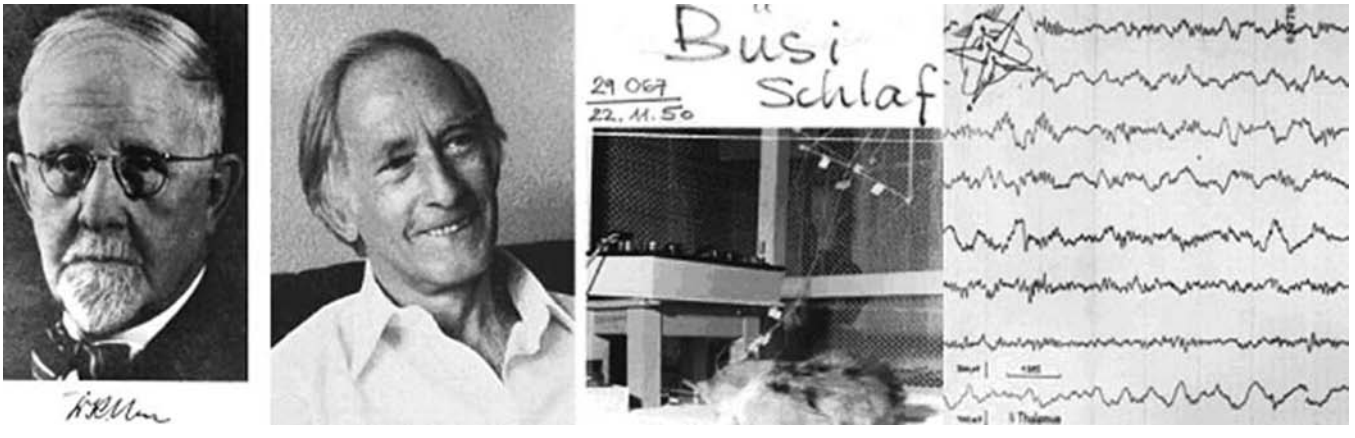

Figure 8a.9 Left: Walter Rudolf Hess, Nobel Prize winner 1949, father of Rudolf M. Hess. Middle: Rudolf M. Hess, Prof. emeritus, former director of the Institute for Electroencephalography, University Zurich. Right: Composite showing the sleep EEG recording in cat 'Büsi' 29 067; 22 November 1950, from the surface and the thalamus. This experimental work followed the tradition of W. R. Hess and seeked for research in spindle sleep.[28]

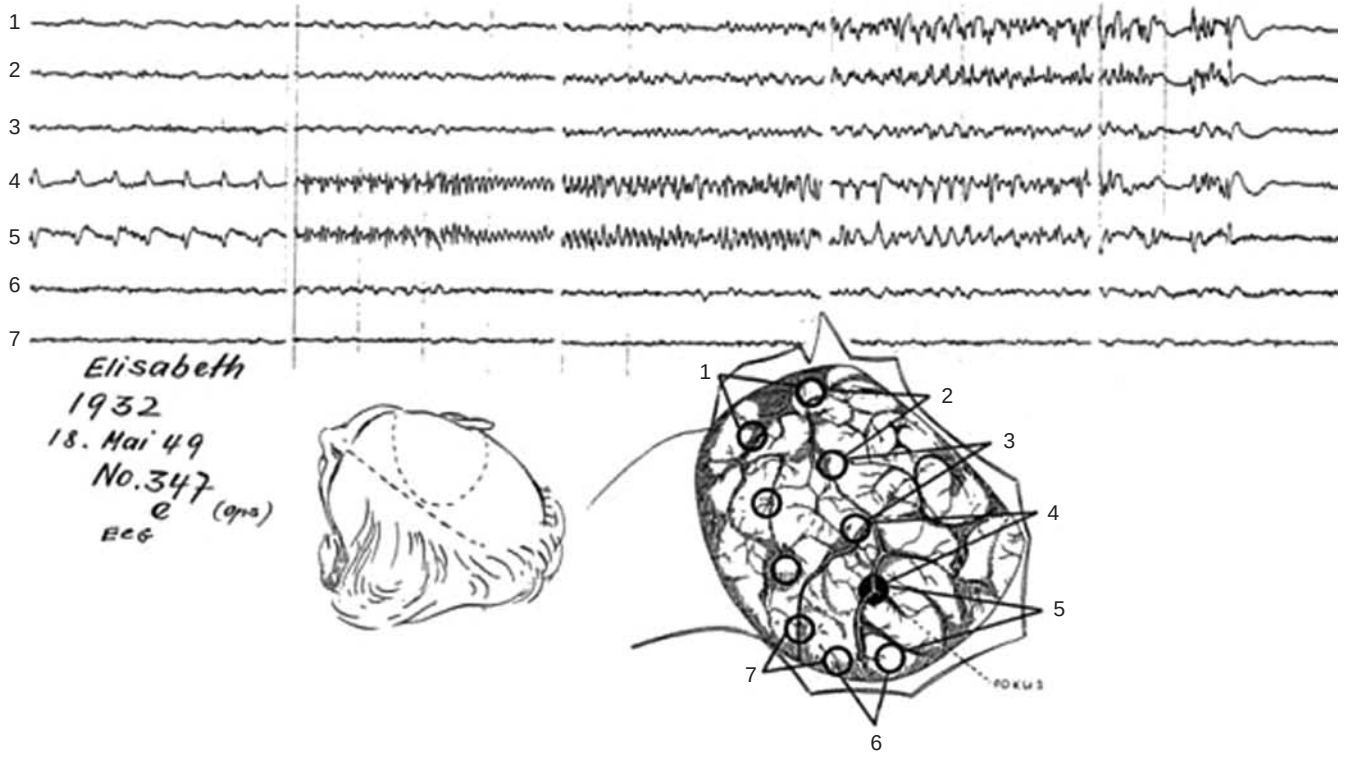

Figure 8a.10 First electrocorticogram in Zurich with a spontaneous focal seizure originating at the electrode marked in black.

introduced in 1986. The FO-electrode technique became popular worldwide.

Cerebral angiography and the study of cerebrovascular anatomy

Krayenbühl learned the angiographic technique from Cairns in Oxford (Cairns, who had worked at the London Hospital, returned to Oxford in 1937) and introduced it in Zurich in 1939. In 1941 he reported the first angiogram of a saccular aneurysm of the basilar artery and in 1952 he published his experiences in the monograph 'Cerebral angiography' together with Dr. H. Richter.[34]

On 4 January 1953, M. Gazi Yasargil began his training in neurosurgery with Hugo Krayenbühl and Gerhard Weber. Krayenbühl assigned Yasargil to develop the technique of percutaneous cerebral angiography. Until 1965 Yasargil performed percutaneous carotid, vertebral, and orbital angiography on several thousand patients. The analyses of these angiograms and injected arteries and veins on 200 cadaver brains concerning their variations and courses have been published in several books, among them: in 1957 'Vascular diseases of vertebral and basilar arteries'[35] and in 1964 'Cerebral angiography'.[36]

In this way, the pioneering work of Krayenbühl and Yasargil on cerebral angiography converged again with the study and surgical treatment of epilepsy. Fifty years after the

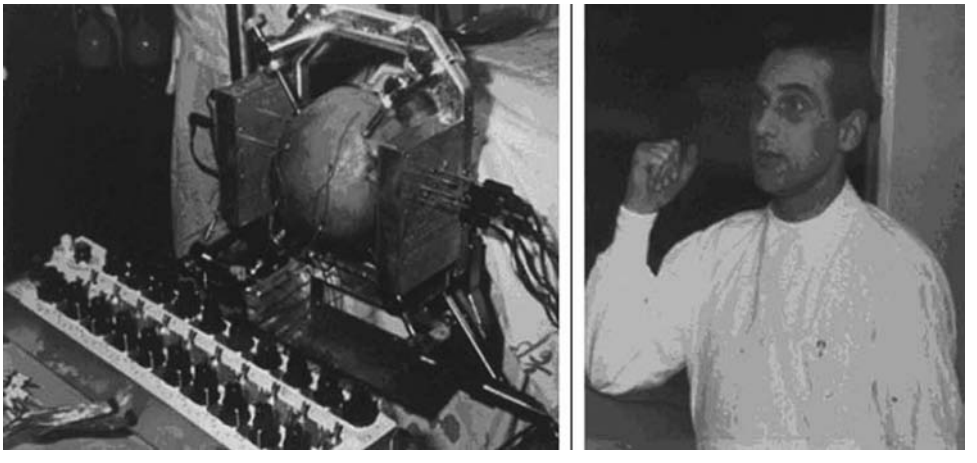

Figure 8a.11 Left: First 'acute' stereo-electroencephalography in Zurich 20 February 1970 (patient M.S. *1959) with the help of Gabor Szikla (right).

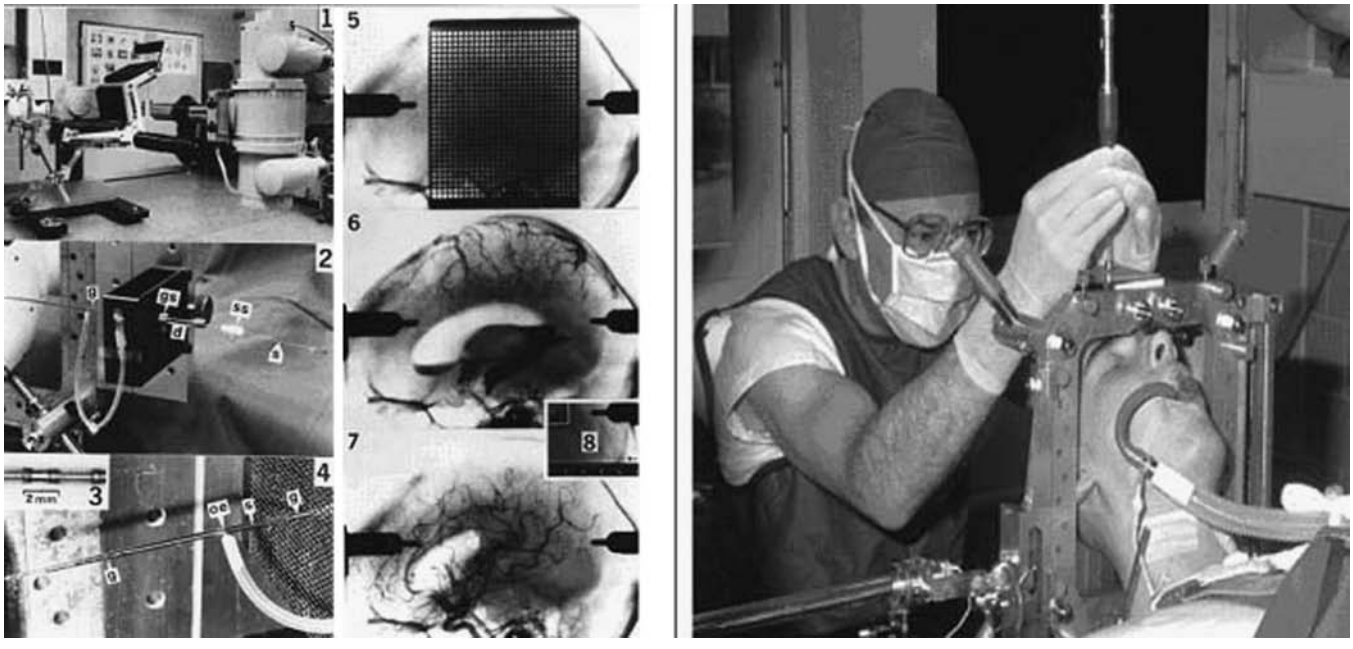

Figure 8a.12 Left: Illustration of the répèrage, i.e., neuroradiological examination under stereotactic conditions (1, 5–7) and insertion of the depth electrodes (2–4, 8). 1: Table of Alexander, 2 and 4: Electrode and insertion device mounted on the Talairach frame with the double grid. The guiding cannula (g) enters the bony orifice. Then the distance between the guide stopper (gs) and the end of the guide for the stylet was measured (d) and added to the calculated position of the stylet stopper (ss). To allow placement of the hollow-core electrode (see insert, 3) with mounted connector on the rigid stylet (s) between the grid and the patient's head, the double grid had to be removed by 6 cm. Photograph 4 shows how the guiding stylet was introduced into the lumen of the electrode (oe). Photographs 5, 6, and 7 show the lateral X-rays with the double grid in good centration (5), the veins (6), and arteries (7); the insert 8 shows the small burr hole for the depth electrode and one inserted depth electrode in the a–p view. Right: Trepanation for a depth electrode with the special drill.

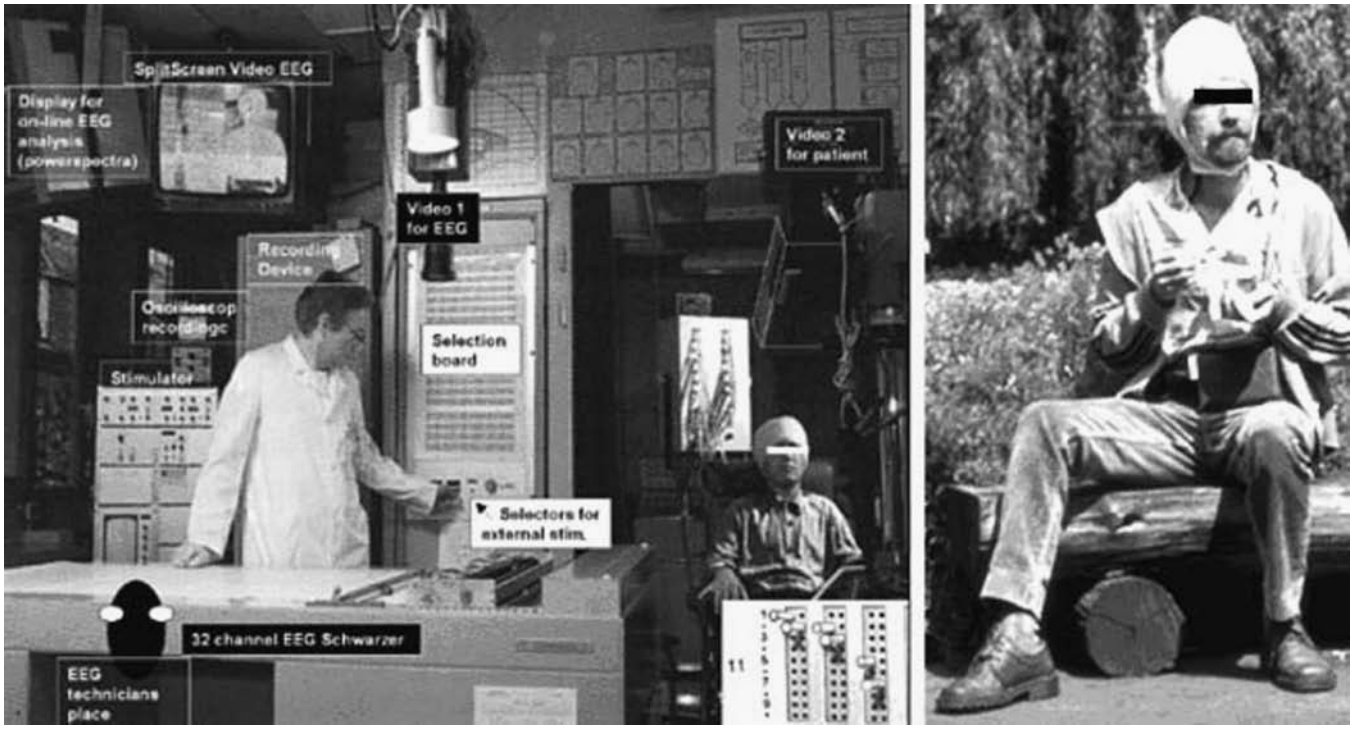

Figure 8a.13 Left: Photograph of the Zurich SEEG laboratory used in 1980 with a Faraday cage and the main parts of the recording and stimulation device. The selection board used the principle of a 'Kreuzschiene'(selection board), which allowed the composition of every conceivable combination of electrode contacts for recording and stimulation. There were 32 channels (horizontal) versus 17 × 10 signal entries (vertical). The insert (bottom, right) illustrates a detail of the selection board indicating that channel 1 records from contacts 1–2 of the depth electrode, channel 2 from contacts 2–3, etc. The lower part of the board hosts the selectors (two black rectangles) for external electrical stimulation. Right: First ambulatory depth EEG cassette recording 1984 (patient D.L.)

introduction of cerebral angiography in Zurich, another remarkable contribution of neuroradiology to epilepsy surgery was reported. In 1989 the introduction of the selective and superselective Amytal memory tests in Zurich allowed more exact presurgical language and memory investigations. The selective catheterization of the anterior choroidal artery in the so-called selective temporal lobe Amytal memory tests,[37] as well as branches of middle and posterior cerebral arteries supplying eloquent cortices in the so-called selective language Wada tests[38] was performed by Professor Anton Valavanis, chief of the Institute of Neuroradiology. Such selective co-injections of Amytal and a SPECT tracer became a routine procedure for selective Wada tests in Zurich. MRI replaced preoperative diagnostic and postoperative follow-up CT after epilepsy surgery in the Zurich series in 1983. The inclusion of new functional imaging methods, such as SPECT and PET in the presurgical evaluation of candidates for epilepsy surgery started in February 1988. More recently magnetic resonance spectroscopy (MRS) and functional MRI (fMRI) could be added.

Gazi M. Yasargil and the introduction of microneurosurgery

Krayenbühl highlighted 'the place of microsurgical technique in neurosurgical surgery' during the Fifth Sir Hugh Cairns Memorial Lecture of the British Society of Neurological Surgeons in London on 30 May 1969, 'I wish to emphasize, with Hugh Cairns, that surgery is and must be always an art, but its progress and thus its vitality depend on the maximum application to it of the methods and discoveries of science'.[39] This statement showed the immense and open foresight of a man who was already 67-years-old. In fact, it is easy to imagine how difficult it would be for a surgeon, after thirty years of surgical experience, to accept a better 'new way to do it'. In 1962 the Swedish cardiovascular surgeon Professor A. Senning, active in Zurich, was worried about thrombotic complications of leptomeningeal arteries after heart surgery using extracorporal circulation. He inquired whether a microvascular technique could be applied to solve the iatrogenic embolized arteries. Krayenbühl decided to send Yasargil to the United States to learn the microsurgical techniques, at that time mainly applied to peripheral neuro and vascular surgery. Theodor Rasmussen, Director of the MNI, recommended Professor R.M. Peardon Donaghy from Burlington, VT. Donaghy was already a pioneer in reconstructive vascular surgery, initiated at his clinic in 1960 by J. H. Jacobson. Yasargil went to the US in 1965 and spent a year in Donaghy laboratory. Here, he learned and developed microtechniques for the reconstruction of the brain arteries.[40]

The era Gazi M. Yasargil

Mahmut Gazi Yasargil (Figure 8a.14) was born in Lice, Turkey, on 6 July 1925. In order to study medicine, he left Turkey in 1943 and went first to Vienna and then to Jena where he studied in medical schools two semesters and then moved to Basle, Switzerland, where he graduated in Fall 1949. According to his intention to become a neurosurgeon he spent three months at the Basle Institute of Anatomy 'Vesalianum' and learned from Professor Josef Klingler the special dissection technique of the formaldehyde fixed cadaver brain. He continued these studies during his postgraduate training in the following three years.

His basic medical training was complemented with a year of psychiatry and neurology (Professor Max Müller, Münsingen), internal medicine (Professor W. Baumgartner), and general surgery (Professor W. Bandi) in Interlaken. In January 1953 he joined the Department of Neurosurgery at the University Hospital Zurich and started his training in Neurosurgery with Hugo Krayenbühl and Gerhard Weber. His first paper on neurosurgery titled 'Vertebralisangiographie' was published in 1955.[41] From 1958–1965 Yasargil was involved in stereotactic procedures for the treatment of movement disorders and of chronic pain using the Riechert–Mundinger stereotactic frame and the high frequency coagulation apparatus of O. Wyss and R.W. Hunsperger, developed at the Institute of Physiology, University of Zürich. In 1957 he spent some weeks in Freiburg/Breisgau (Germany) and 1960 four weeks in Paris with Prof. Jean Talairach. From 1965–1966 he spent 14 months in the laboratory of cardiovascular surgery at the University Vermont, Burlington, USA where amongst others R.M.P. Donaghy was pioneering microvascular surgical techniques. Before leaving Zurich he introduced Jean Siegfried to the field of functional neurosurgery.

Yasargil envisioned that the field of microneurosurgery developed for reconstructive neurovascular procedures (introduction of extracranial–intracranial anastomosis), would gradually encompass other vascular lesions, aneurysms, arteriovenous malformations, and brain tumors, and, eventually, involve the whole realm of neurosurgery. During difficult vascular procedures he expressed to Krayenbühl the necessity 'to see better'. Good illumination, unobstructed vision and a view of the whole operative field are essential to the surgeon. In the foreword of Yasargil's famous book '*Microsurgery Applied to Neurosurgery*'.[42] Krayenbühl points out, 'It is astonishing that the operating microscope came to be employed so late in the field of neurosurgery, since it has been an indispensable tool in the routine otologic surgery for four decades'. The historical invention and development of the bipolar coagulation done by Leonard I. Malis (chief of the Department of Neurosurgery, Mt. Sinai Medical Center, NY, from 1970–1991) accompanied by the introduction of a counterbalanced operating microscope stand and numerous microinstruments designed or re-designed by Yasargil (presented in a Zurich course in microsurgery, 14–20 November 1968), allowed the application of microtechniques in neurosurgery. Yasargil's contribution to neurosurgical literature culminates with his latest book in the series 'Microneurosurgery' in 1996.[43]

Gazi Yasargil introduced microtechniques to neurosurgery in 1967. The design and development of a counterbalance microscope stand (System Yasargil, SMED®); numerous microinstruments and new approaches became very fast the gold standard technique in vascular and tumoral neurosurgery and contributed to the development and technical improvement of epilepsy surgery. Over 3000 colleagues (neurosurgeons and other surgical specialists) from around the world were introduced to and trained in the techniques of

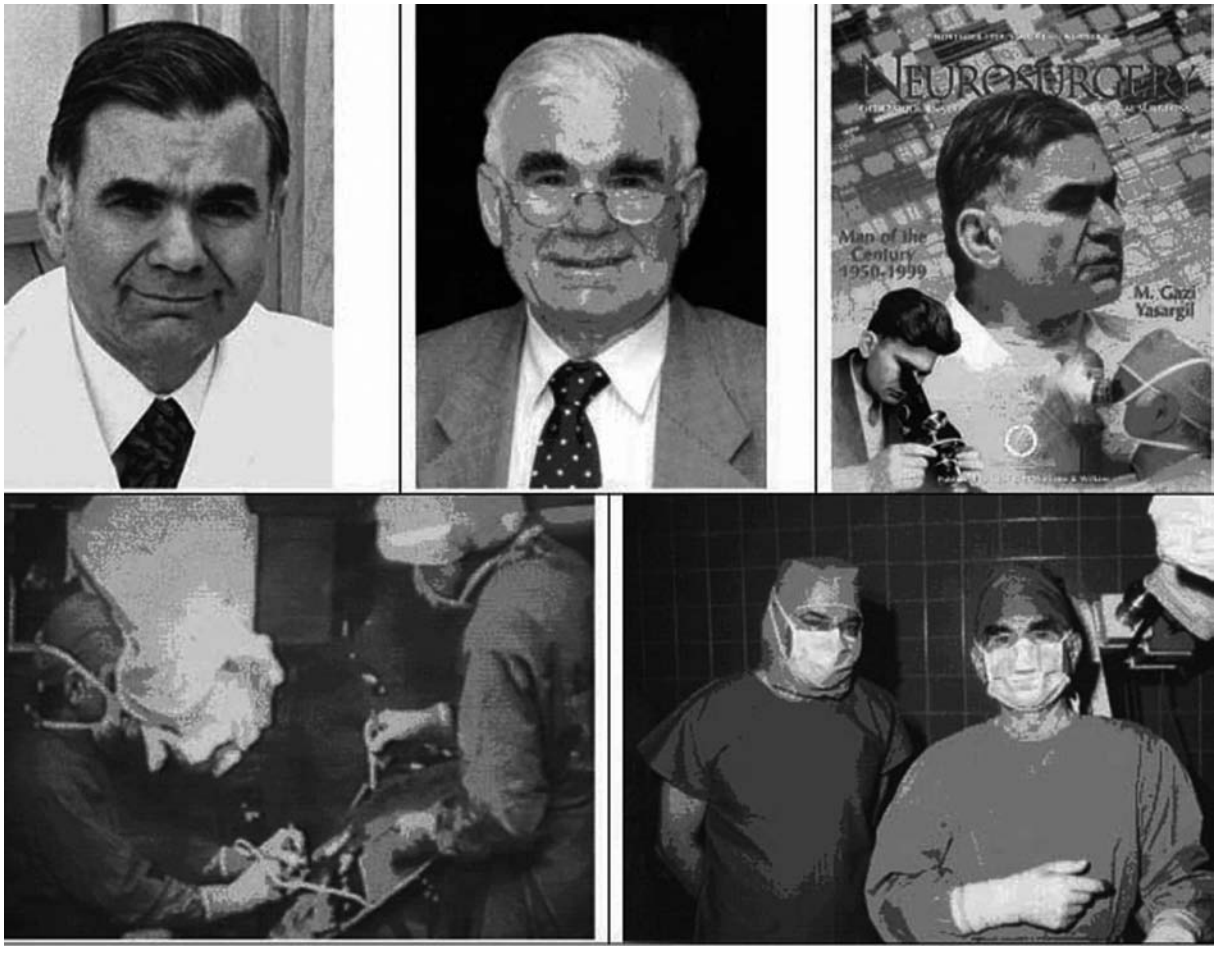

Figure 8a.14 Top: Gazi Yasargil at the beginning (left) and at the end (middle) of his career in Zurich. Right: Title page of the *Neurosurgery* 1999, vol.5, honoring M. Gazi Yasargil as Neurosurgery's Man of the Century. Bottom: Gazi Yasargil performing microneurosurgery and assisted by Diane Yasargil (left) and after his last selective amygdalohippocampectomy performed in Zurich (right).

microsurgery in Zurich. The development of the subarachnoid approaches allowed noninvasive explorations and complete elimination of extrinsic and intrinsic lesions of the CNS: 'the subarachnoid pathways are the route maps for microneurosurgery'. In more recent years, Yasargil's interest focused on 'autoregulated integral functional units' of the central nervous system. Observations and experiences in a large series of operated patients with vascular and neoplastic lesions led him to conceptualize the 'limbic–paralimbic' compartment.[44]

Yasargil retired in Zurich 1992 after completing 40 years of activities at the University Hospital of Zurich. He was appointed in 1994 at the University of Arkansas in Little Rock, AR (USA) as professor of neurosurgery (Department of Neurosurgery, chairman Prof. Ossama Al-Mefty), where he continues his academic and surgical activities. He received the Medal of Honor of the World Federation of Neurosurgical Societies during the XI International Congress of Neurological Surgery held in Amsterdam in 1997. Harvey Cushing (1869–1939) and M. Gazi Yasargil were selected as the Neurosurgery`s Men of the Century by the Editorial Board and the International Liasin ad Advisory Panel of Neurosurgery, the official Journal of the Congress of Neurological Surgeons.[45–49] Since then Yasargil has continued improving neurosurgical training[50] and to advice his pupils.[49]

The present

Yasuhiro Yonekawa, a graduate of Kyoto University, was sent by Prof. H. Handa (founder of the Department of Neurosurgery in Kyoto University) to Zurich (Figure 8a.15). To speak in Prof. Yonekawa's own words[51] he came to Zurich in 1970 as 'one of the many pilgrims' and trained with Prof. Yasargil from 1970–1976, at first as resident and later as a chief resident (Oberarzt). Yonekawa returned to Japan in 1976 and was nominated Director of the National Center for Vascular Surgery in Osaka. At the beginning 1993 he was called as Yasargil's successor to direct the Neurosurgery Department. In his most recent paper[52] Yonekawa speculates on the reasons for 'the final decision why and how a Japanese was elected' and came to the conclusion that one of the main reasons must be that he (Yonekawa) knows 'exactly how and what the Zurich school of neurosurgery is: style of working and tradition above all'. Indeed one of us (HGW) witnessed that the operative excellency was the decisive criterion for the succession of Yasargil in 1993. In his No Shinkei Geka article[52] Yonekawa gave a brief review of the history of the Zurich Neurosurgery department and devoted one paragraph to 'what is now going on?'. In this paragraph he lists 'epilepsy surgery' under number 4 [after # 1: Vascular neurosurgery, including Moyamoya angiopathy; # 2: Skull base tumors, deeply seated tumors, and # 3: Glioma-glioblastoma surgery. Under # 5 he mentions

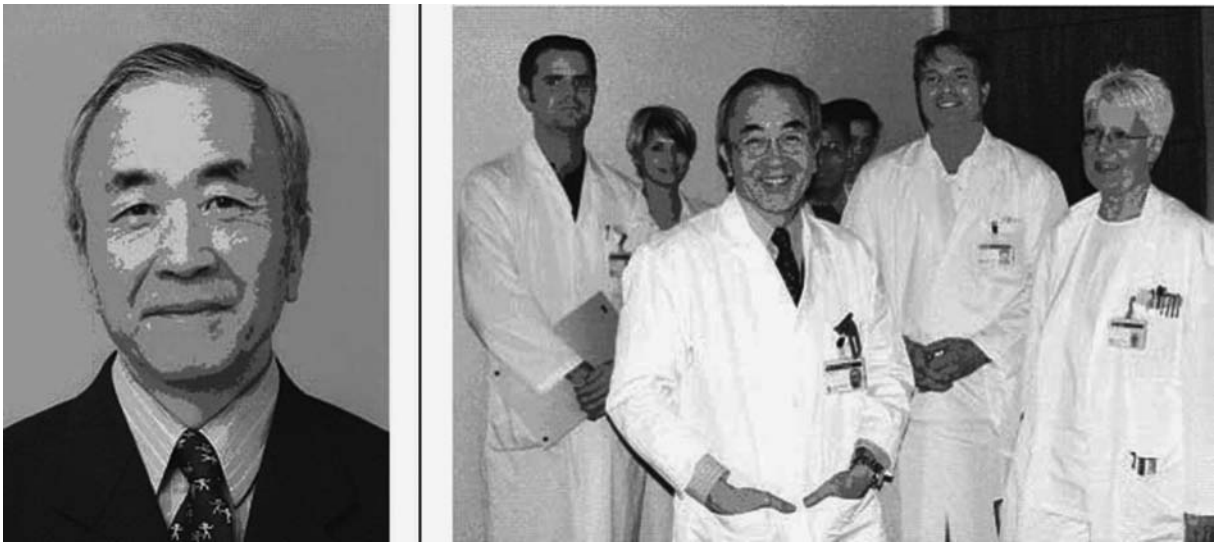

Figure 8a.15 Yasuhiro Yonekawa, chairman of the neurosurgical department of the University Hospital Zurich since 1993 with some of his collaborators in 2005 (right).

neuronavigation, open MRI, and neurophysiological monitoring, under # 6 neurosurgical intensive medicine. # 7 covers stereotactic surgery, # 8 postgraduate education and exchange of information and knowledge by international and regional meetings. In # 9 he mentions approaches of routine use developed recently besides selective extradural anterior clinoidectomy and SCTT (supracerebellar transtentorial) approaches. Under epilepsy surgery he addresses the selective amygdalohippocampectomy series[53] and his supracerebellar transtentorial approach[54] as well as the infratentorial supracerebellar approach for posterior hippocampectomy and intraoperative EEG monitoring[55] including ECoG and electrical cortex stimulation.[56] It should be mentioned that Prof Yonekawa re-introduced epilepsy surgery in the awake patient for cases with planned resections in highly eloquent brain areas[57] and by his en bloc resection of the hippocampus helped tremendously the experimental research.[58a,b]

Selective amygdalohippocampectomy

Prior to 1969, resective surgical therapy of temporal lobe epilepsies in Zurich was done by means of anterior two-third resections. Patients who underwent this operation met the following criteria: (a) drug-resistant complex partial seizures, and (b) spike foci well and consistently lateralized to one temporal lobe in surface EEG. Patients usually underwent PEG and ventriculography as well as carotid angiography; intraoperatively, ECoG confirmed the spike focus and the extent of resection was approximated according to it.[19] This approach had several shortcomings and the results did not entirely satisfy. Therefore, the method of SEEG, as mentioned before, was adopted and introduced in Zurich in 1970. From 1970 to 1974, the criteria, mode of exploration ('acute'), and stereotactic techniques, as well as the analysis methods of the depth EEG, were more or less identical to the Parisian approach,[23,24] i.e., a broad spectrum of patients with various types of focal epilepsies (temporal and extratemporal) were evaluated.

In patients with temporal lobe epilepsy, particularly in those cases in which a seizure origin had been identified within the mediobasal temporal lobe structures, the question arose in 1973 to perform a selective amygdalo-hippo-parahippocampectomy using a microsurgical technique. Gastaut had already stated in 1950 that the origin of temporal lobe epilepsy is in most cases rhinencephalic.[59] Paulo Niemeyer presented his experiences on 19 patients at the 2nd International Colloquium (Bethesda, Maryland, USA, 1958): he had successfully removed through a transventricular approach the mediobasal temporal lobe structures. In the subsequently appearing book based on this Colloquium (edited by M. Baldwin and P. Bailey), Niemeyer[60] gave credit to Riechert and Jung, who interrupted stereotactically the fornix, to J. Viana, who had removed the hippocampus in unselected epilepsy patients, and to Scoville and Milner.

A review of the history of epilepsy surgery documents that the surgical procedures for the treatment of epilepsy were dependent on, and related to the precise definition of the seizure focus.[61–64]

The microsurgical selective amygdalohippocampectomy introduced by Yasargil is the result of the experience gained since 1967 by microsurgical approaches in the treatment of aneurysms, AVMs and especially mesiobasal temporal tumors.[65–67] Yasargil was influenced by two main issues: first, he found that gangliogliomas, ganglioneuromas, astrocytomas, and AVMs confined to the mediobasal temporal lobe could radically be extirpated without recourse to lobectomy. Second, he noted that local removal of mediobasal temporal tumors and AVMs had been accompanied by fewer postoperative fits if the amygdala and parahippocampus were resected simultaneously.[66,67]

The development of the pterional craniotomy and its various refinements provided familiarity in exposing the proximal Sylvian fissure just above the limen insulae. The transsylvian route was readily adapted for exploration of the mediobasal superior lobe with approach to the amygdala and parahippocampal cortex. After gentle opening of the Sylvian fissure using sharp dissection, a 1–2 cm cortical incision in the sulcus insulae circularis pars inferior, lateral to M-1 and inferior trunc of M-2, is done to reach and remove the amygdala, to open the pia-arachnoideal layers, to explore the ambient and

crural cisterns, to identify the courses of the anterior choroidal and P1-segment of posterior cerebral artery, the optic tract, and the oculomotor nerve. The temporal horn is identified, dissected, and the hippocampus and parahippocampal gyrus are removed. This technique requires considerable microsurgical experience and, above all, familiarity with the regional anatomy, which can only be gained after 'meticulous cadaver microdissection'.[67] This technique has been somewhat underestimated by neurosurgeons who do not have enough experience in vascular microneurosurgery not realizing the great benefit of this selective technique considering its outcome with respect to seizures and neuropsychology. The manipulation and recognition of the vascularization of the amygdala, gyrus parahippocampalis, uncus, and hippocampus and regular variability has to be kept in mind during surgery.

In the last 10 years Yonekawa has steadily refined the posterior hippocampectomy for symptomatic posterior hippocampal epilepsies. Such lesions were difficult to approach with Yasargil's transsylvian technique. Today the posterior hippocampectomy (PHE) constitutes a remarkable large percentage of mesial TL resections at our hospital: 35 PHE versus 150 sAHE.

The criteria considered for the 'curative' selective amygdalohippocampectomy include (a) unequivocal unilateral medial temporal focal seizure onset at these structures associated with typical clinical symptoms and (b) contralateral hippocampal functions intact (special neuropsychological testing for learning and memory performance, selective temporal lobe Amytal testing, and presence of signs indicative of hippocampal atrophy and/or Ammon's horn sclerosis). A 'palliative' operation of this type might be indicated in cases where the primary seizure generating zone in the lateral posterior temporal neocortex cannot be removed without anticipated intolerable functional deficit, and where the ipsilateral hippocampal formation is rapidly involved by the ictal discharges acting as a 'secondary pacemaker'. In the time-period since 1975, 513 patients underwent selective amygdalohippocampectomy with satisfying results.[68–70]

Perspectives and final remarks

Professor Krayenbühl will be remembered as a teacher whose forethought and encouragement allowed the advances in neurosurgery and development of his pupils. Epilepsy, as the common meeting point of many medical disciplines has allowed neurosurgery to develop smoothly through the fields of EEG, neuroradiology and microtechniques throughout the last six decades.

New functional neuroimaging methods, such as SPECT, PET, magnetic resonance spectroscopy (MRS), fMRI, as well as less invasive surgical methods and techniques supported by real time imaging during surgery (like open MRI or frameless computer assisted stereotactic localization) have been introduced in Zurich in the last few years without ignoring the tradition and legacy of the predecessors.

Meanwhile epilepsy surgery and related research is done in several institutions in Switzerland. With the election of Professor Theodor Landis as chairman of the neurology in Geneva and his move from Zurich to Geneva the surgical program 'neurologie et neurochirurgie fonctionelle Vaud – Geneva' started in 1955. Margitta Seeck and Jean-Guy Villemure recently presented their first 150 patients consisting of pediatric (one third) and adult epilepsy surgery patients. This very active surgical program has at its disposal all modern presurgical evaluation methods, including 3T-MRI, PET, ictal SPECT including subtraction analysis SISCOM, fMRI and EEG-triggered fMRI, as well as high resolution EEG recordings with electric source imaging on the basis of up to 256 scalp EEG channels. They also use invasive and semi-invasive intracranial recording and perform all accepted curative and palliative surgical procedures, including functional hemispherectomy, selective amygdalohippocampectomy, tailored neocortical resections both temporal and extratemporal, and VNS.

Epilepsy surgery is also done in other university hospitals, such as Berne, and with a more limited approach in several other institutions and Cantonal hospitals. Today there is a very fruitful and close collaboration between the University Hospital Basle and the Swiss Epilepsy Center in Zürich on one hand and the epilepsy surgery program of the University Zurich on the other. Thus, as Wilder Penfield has masterly outlined in his biography 'No Man Alone'[12] epilepsy surgery in Switzerland has emerged to network collaboration. Reasons for this advantageous development of epilepsy surgery in Switzerland are:

(1) the availability of advanced non-invasive diagnostic tools to delineate epileptogenic lesions, epilepsy related functional deficits and to prove epileptogenicity;
(2) improved knowledge on surgically remediable epilepsy syndromes; and
(3) improved surgical techniques by means of microsurgery and the availability of intraoperative MRI and intraoperative monitoring, including recording and cortical electrical stimulation.

All these factors translate into better post-surgical outcome figures and a larger population of difficult-to-treat patients profiting from surgery. Although 'much has been reached at, more has to be done'! The Zurich team adheres to the principles of Hugo Krayenbühl to learn from failures ('one has to say to the people what they did wrong – what they did right is self-evident') and remains aware of Gazi Yasargil's statement 'each surgical action compromises not only science, experience, knowledge, and techniques, but also artistic, philosophical, and religious attitudes from a neurosurgeon'.

The Zurich team, in order to master neurosurgery, remains aware of Yasargil's statement: 'each surgical action comprises not only science, experience, knowledge, and techniques, but also artistic, philosophical, and religious attitudes from a neurosurgeon'.[41]

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8b Epilepsy surgery in Austria

C Baumgartner, T Czech, and O Schröttner

Development of epilepsy surgery in Vienna

Neurosurgery in Austria began at the turn of the 19th century when Anton von Eiselsberg (1860–1939) (Figure 8b.1a) removed a gliomatous brain tumor in the central region in 1904. The patient wasdischarged in excellent condition two months after surgery. After spending some time in Paris studying neurology under Charcot, von Eiselsberg began his surgical career under the famous Christian Theodor Billroth (1829–1885) in 1882 just one year after Billroth had performed the first successful gastric resection. Von Eiselsberg was appointed chairman of the First Department of Surgery of the University of Vienna at the Vienna General Hospital ('Allgemeines Krankenhaus der Stadt Wien') in 1901 (Figure 8b.1b). Subsequently, Vienna developed to one of the leading centers for neurosurgery at that time and even Harvey Cushing came to Vienna to learn from von Eiselsberg. In 1908, von Eiselsberg published a review of the first 23 brain tumors treated surgically in his department.

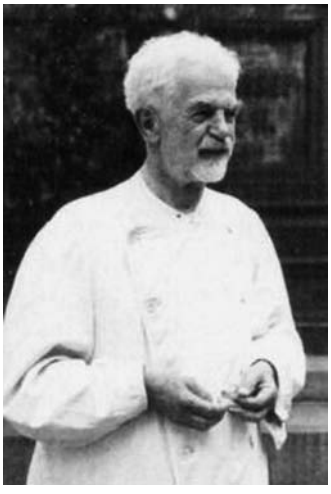
In 1910, when Harvey Cushing performed his first brain tumor surgery, von Eiselsberg already published his experience on 71 brain tumor resections [1]. Between 1901 and 1913 von Eiselsberg and his coworker Egon Ranzi (1875–1938) (Figure 8b.1c) operated on 168 brain and medullary tumors among them many patients suffering from focal epilepsy.[2] Von Eiselsberg's intense interest in neurosurgery is further reflected in 17 publications on neurological surgery out of his 95 major publications. In 1920, the anatomist Julius Tandler and Egon Ranzi published a book on the surgical anatomy and operative techniques of the central nervous system which was considered the international reference work at that time.[3]

Subsequently there developed an intense collaboration between Egon Ranzi from the Department of Surgery and Otto Marburg, Chairman of the Department of Neurology which culminated in a publication on 318 brain tumors treated surgically in Vienna (Figure 8b.1d).[4] In this seminal paper the authors mention epileptic seizures as one of the key symptoms for the diagnosis of brain tumors. They correctly disputed Victor Horsely's postulate that every patient with adult-onset epilepsy should be treated surgically. They presented a detailed table on 35 patients with epilepsy categorized according to epilepsy type, tumor type and tumor location. They pointed out the importance of an accurate history for the localization of the seizure-onset zone and the high reliability of Jacksonian seizures for localizing the seizure-onset zone to the central region. They reported on a patient with ictal aphasia with a tumor located in Broca's area. They also meticulously analyzed the temporal relationship between the onset of epilepsy and other symptoms and also reported on a subgroup of 8 patients suffering from long-lasting epilepsy without other symptoms. Concerning outcome they reported 20 patients with supratentorial tumors in whom the tumor could be identified during the operation and could be either totally or partially resected. While 10 patients died either early or late (within 6 months after surgery), 10 patients were considered as cured by the surgery, long-term results were available for 7 of them. The authors remarked that seizures stopped after surgery in some cases, while they were not influenced by the operation in others. They also reported that 8 out of 41 patients in whom a brain tumor was removed between 1901 and 1913 were still alive and fully functional after a follow-up for 7 to 15 years. Concerning epilepsy they already distinguished between two groups of patients, namely those whose seizures could be cured by surgery and those with persistent seizures due to some 'disposition to epilepsy'. [4]

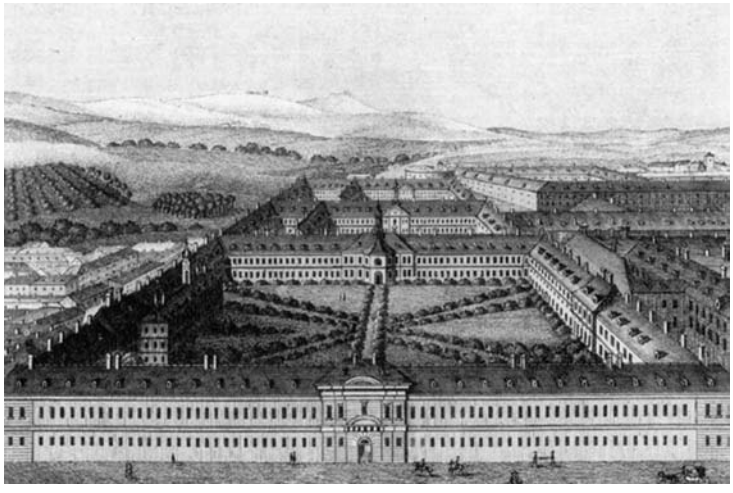
While the experience with brain tumors in the First Department of Surgery accumulated to 500 cases in the meanwhile, failures, complications and surgical mortality remained high, which deeply concerned von Eiselsberg. He gave a critical lecture during the 50th Congress of the German Society of Surgeons in 1926 where he said 'as Billroth taught me to look for the causes of failure at my own doorsteps, I spent many miserable hours doing so, wondering why my results, when compared with the success achieved by the American surgeons, particularly Cushing, were so poor'.[5]

In 1931, Eiselsberg stepped down as chairman of the First Surgical department. He was followed by Egon Ranzi who delivered his inaugural lecture on the development and advances of neurosurgery in 1932.[6] Ranzi believed that the ideal neurosurgeon was one who combined the skills of the surgeon with the knowledge of the neurologist, as Cushing and Otfried Förster had done. He stressed the necessity of intense collaboration between neurology and neurosurgery. In 1938 Ranzi had to step down as chairman for political reasons and died in the same year. In 1939, Eiselsberg died in a railroad accident. Two other pioneers of neurosurgery in Vienna, Marburg and Hirsch, had to leave the country and immigrated to the Unites States.

Leopold Schönbauer (1888–1963) (Figure 8b.1e) became chairman of the Department of Surgery in 1939. He was the last living representative of von Eiselsberg's legacy. Schönbauer joined von Eiselsberg' team in 1916 and became increasingly interested in neurosurgery. In 1924 Schönbauer visited Harvey Cushing in Boston and spent 4 months there. Schönbauer became deeply impressed by Cushing's approach to neurosurgery, his skills



(a)



(b)

(c)

Herrn Professor Dr. A. Eiselsberg zum sechzigsten Geburtstage.

Zur Klinik und Therapie der Hirntumoren mit besonderer Berücksichtigung der Endresultate.

Von

Prof. Dr. **Otto Marburg** und Prof. Dr. **Egon Ranzi.**

(Aus der I. chirurgischen Klinik in Wien [Vorstand: Prof. Eiselsberg].)

Mit 1 Textabbildung.

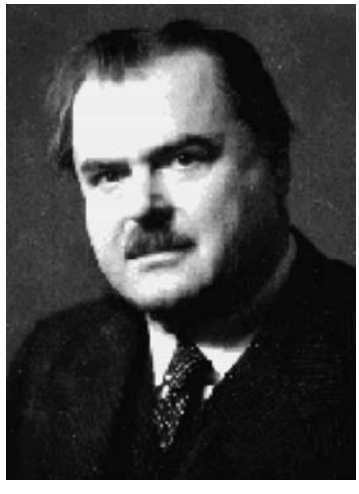
(*Eingegangen am 1. Oktober 1920.*)

(d)

Figure 8b.1 a, Anton von Eiselsberg (1860–1939), chairman of the First Surgical Department at the University of Vienna 1901 to 1931. b, Historical view of the Vienna General Hospital ('Allgemeines Krankenhaus'). c, Egon Ranzi (1875–1938), chairman of the First Surgical Department at the University of Vienna 1932 to 1938. d, Title of the seminal paper on 318 brain tumors treated surgically in Vienna by Otto Marburg and Egon Ranzi submitted in 1920 and published in 1921.

and achievements. Schönbauer realized that any surgeon who wanted to achieve Cushing's standards must devote his efforts to neurosurgery exclusively which was not possible at that time in Vienna. Between 1930 and 1939 Schönbauer was head of the department of surgery in the Hospital of Lainz in Vienna where he established the first center of neurosurgical practice together with the famous neurologist Hans Hoff. They published a monograph entitled 'Hirnchirurgie' ('brain surgery') and operated on 10 brain tumors a month. Despite the help of Hans Hoff for the localization of tumors, postoperative mortality remained high averaging around 30%.[1,5]

Herbert Kraus (1910–1975) who started as a resident under Ranzi in 1935 became Associate Professor under Schönbauer and focused his interest on neurosurgery. Only his first seven publications dealt with general surgical themes, the ensuing 100 publications were devoted to neurosurgical subjects. In 1949 he visited several major centers in the USA. In 1964 he was appointed Chairman of the newly founded Neurosurgical Department of the University of Vienna. Heinz Brenner (born in 1926, a disciple of Schönbauer), Wolfgang Koos (1930–2000), and Josef Ganglberger (born in 1921) (Figure 8b.1f), who was trained in stereotaxic neurosurgery in Freiburg, Germany under



(e)

(f)

Figure 8b.1, Cont'd e, Leopold Schönbauer (1888–1963), chairman of the First Surgical Department at the University of Vienna 1938 to 1961. f, Josef Ganglberger (born in 1921) introduced stereotaxic treatment of epilepsy in Vienna.

Traugott Riechert, joined his team.[1, 5] Gangelberger introduced stereotaxic treatment of epilepsy in Vienna. He performed several stereotaxic fornicotomies, anterior comissurotomies, and amygdalotomies. In addition he recognized the critical role of pathways from the basal-lateral amygdala and the anterior temporal cortex via the ansa peduncularis and the pedunculus thalami extracapsularis to the medial nucleus of the thalamus for seizure propagation. He therefore carried out stereotaxic interruptions of this pathway on the rostro-ventral margin of the medial thalamic nucleus and could successfully treat several patients who were still suffering from seizures after fornico-and anterior comissurotomies. Ganglberger and coworkers also performed meticulous invasive electrophysiological studies during stereotaxic procedures studying evoked potentials and event-related slow potentials.[7-10] Kraus died from lung cancer in 1975. He was followed by Wolfgang Koos (1930–2000) who developed the department to a modern neurosurgical clinic.

Development of epilepsy surgery in Graz

At the University of Graz (Figure 8b 2a), the first neurosurgical unit was established within the department of surgery under Fritz Heppner (1917–2002) in 1950 (Figure 8b.2b). Heppner started his surgical training in Vienna in 1940 and completed his neurosurgical training under Herbert Olivecrona in Stockholm and under Sir Wylie McKissock in London.[1] Stereotaxic and functional neurosurgery was introduced in Austria in 1962 by his coworker Hans Erich Diemath (born in 1931). Soon after the establishment of neurosurgery as a separate discipline at the University of Graz in 1950, the surgical treatment of epilepsy began. Heppner and colleagues published several papers on the surgical treatment of epilepsy.[11–18] In 1987 they summarized their extensive experience on epilepsy surgery performed in Graz since 1950.[19] The indication for the first 28 patients was still vague, surgical procedures consisted of sympathectomy in 7 patients, corticotomies in 18 patients, meningolysis (subdurography) in 5 patients, and a probatory exploration in 1 patient. In 1954 the indications for epilepsy surgery became more clearly defined and included 'proof of medical intractability, a constant EEG focus, localization of the epileptic focus within a dispensable area of the brain, undamaged contralateral brain areas, and a sufficient IQ for social rehabilitation'. One hundred and fifteen patients underwent epilepsy surgery following these criteria between 1954 and 1985 including 6 hemispherectomies, 50 hippocampectomies, 6 fornicotomies, 40 anterior cingulectomies and 13 stereotaxic amygdalotomies. Six children aged 3 to 13 years with spastic infantile hemiplegia underwent hemispherectomies. Long-term follow-up was available in 3 children all of whom

Figure 8b.2 (a) Historical view of the Landeskrankenhaus Graz.

remained seizure free. One child died postoperatively from meningitis. Hippocampectomy was performed in 50 patients suffering from psychomotor epilepsy (Figure 8b.2c and d). In the first 40 patients a partial anterior temporal lobe resection with removal of the hippocampus was performed. The resection was limited to the hippocampus in the last 10 patients. In order to limit the formation of scar tissue and minimize trauma, a CO_2 laser beam method was applied. Long-term results were available for 34 patients, 18 of whom became completely seizure free. In 9 patients seizures were markedly improved, in 2 patients somewhat improved and in 3 patients seizures remained unchanged. Moreover, mental status and employment situation were improved postoperatively in the majority of patients. Stereotaxic fornicotomy was successfully performed in 6 patients who did not benefit from hippocampectomy. This method consisted of stereotaxic interruption of the fornix close to the anterior commissure with the rationale 'to prevent the spread of epileptic discharges from the hippocampus to the rest of the brain'. While 3 patients became seizure-free, the other 3 became manageable by antiepileptic drugs. Bilateral anterior cingulectomies, which were first described by LeBeau in 1948, were performed in 40 patients. In 3 cases the stereotaxic method was applied, in 8 cases the CO_2 laser beam method was used with vaporization of the anterior cingulate gyrus. In 17 patients long-term follow-up was available. Seizure-freedom could be achieved in 4 patients who displayed focal epileptic activity on the electrocorticogram in the area of the cingulum. In 5 patients marked improvement could be observed, 3 patients improved somewhat, and 5 patients remained unchanged. Emotional behavior was markedly improved in 6 patients, somewhat improved in 4 patients, and remained unchanged in 5 patients. Finally, bilateral stereotaxic amygdalotomies were performed in 13 patients suffering from epilepsy with an aggressive form of debility and resulted in a considerable improvement of psychic control in all patients.[19]

After Heppner's retirement in 1987, the department was led for 3 years by Peter-Wolf Ascher (born in 1939). In 1990, Gerhard Pendl (born in 1934), a student of Kraus and an upholder of von Eiselsberg's tradition, was appointed chairman of the department in Graz. In addition to completely reorganizing the department to modern standards, he introduced radiosurgery with the gamma knife in Graz in 1992.[1] Under the leadership of Gerhard Pendl and Oskar Schröttner pioneering work in the radiosurgical treatment of epilepsy including treatment of patients with mesial temporal lobe epilepsy, vascular malformations, tumoral epilepsy, and hypothalamic hamartomas was performed in Graz.[20–22] Furthermore the Graz group was the first to successfully perform callosotomies with the gamma knife.[23]

The modern area

The modern area of epilepsy surgery in Austria was introduced by Christoph Baumgartner (Neurology) who was trained at the Cleveland Clinic Foundation under Hans Lüders and Thomas Czech (Neurosurgery) at the University of Vienna in the Vienna General Hospital ('Wiener Allgemeines Krankenhaus') in close collaboration with the Neurological Department of the Krankenhaus Rosenhügel in 1992. In the following years epilepsy surgery centers were established at the Wagner-Jauregg Krankenhaus in Linz, the University of Innsbruck and the University of Graz. These centers offer all possibilities of modern presurgical evaluation and surgical techniques. A review of the activities of these four Austrian centers was recently published.[24]

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9 Epilepsy surgery in the Nordic countries

K Källén, H Høgenhaven, KO Nakken, and R Kalviäinen

Four of the five Nordic countries have active epilepsy surgery teams, which are the Scandinavian countries (comprising Sweden, Denmark and Norway) and Finland. They are located in the northern part of Europe, partly surrounded by the North Sea and the Baltic Sea as illustrated in Figure 9.1. The four countries are in many aspects homogeneous with similar health care systems. The recruitment of patients for epilepsy surgery is exclusively dependent on the general social insurance system and is not influenced by the socioeconomic situation of the individual patient. Patients with severe and therapy-resistant epilepsy are referred to the centers with epilepsy surgery programs. Not only patients who are optimal surgical candidates are evaluated, but also mixed populations with diverse prognoses and chances for successful surgical outcome.

The four countries are small with a combined population of 24 million inhabitants; Sweden has nine million, Denmark and Finland more than five million each, and Norway four and a half million. Denmark and Norway have chosen to centralize their surgical programs to National Centers for Epilepsy Surgery while Sweden has a population-based regional referring system. The Swedish model is a decentralized model, with six centers at the regional university hospitals working in close collaboration, and with all centers participating in a national epilepsy surgery register for quality control. In Finland there are two centers with comprehensive epilepsy teams and epilepsy surgery programs. In Iceland, the fifth Nordic country, patients are sent abroad, mainly to the USA, for epilepsy surgery.

In this chapter the history of epilepsy surgery in the Nordic countries is described in detail for comparison of different ways of organizing epilepsy surgical programs in four developed countries with public health care systems.

Epilepsy surgery in Sweden

by Kristina Källén, Lund University Hospital

In Sweden, series of patients with difficult to treat epilepsy underwent epilepsy surgery during the 1950s, operated on by Olivecrona in Stockholm and by Jeppsson at the regional hospital in the southern part of Sweden, Lund University Hospital. A new phase of development was initiated by the neurosurgeon Herbert Silfvenius and collaborators at Umeå University Hospital in northern Sweden. Silfvenius, who had trained at Montreal Neurological Institute, initiated the modern era of comprehensive multiprofessional epilepsy surgery evaluation in Sweden and operated on 87 patients during 1980 to 1988. At this time epilepsy surgery was also revitalized in Lund, Göteborg, and Uppsala. From 1979 to 1994 a total of 430 epilepsy surgery procedures were performed.

During this period the future organization of epilepsy surgery in Sweden was extensively discussed. In contrast to the situation in Denmark and Norway, Sweden did not have a national epilepsy center and active epilepsy surgery teams were already developing at several university hospitals. Under the auspices of the Swedish National Board of Health and Welfare a group of experts produced background information concerning the national organization of epilepsy care in general as well as that of epilepsy surgery.[1] Criteria for a reference center for epilepsy surgery in Sweden were defined as: (1) a center with a multidisciplinary core team with a neurophysiologist, neurologist, and neurosurgeon; (2) access to a comprehensive epilepsy team with specialized personnel; and (3) access to other specialists such as neuroradiologists, neuropsychologists, neuropsychiatrists and a neurorehabilitation team. Furthermore, centers should have access to advanced techniques for video-EEG-monitoring and neuro-imaging and perform a sufficient number of diagnostic and therapeutic investigations yearly to keep and develop their competence. The importance of national and international collaboration was also emphasized.[1]

In order to evaluate the results of epilepsy surgery the Swedish National Board of Health and Welfare also requested an audit of the results from the operating centers from 1980 to 1990, which led to two scientific reports, one retrospective multicenter study focusing on surgical procedures and two-year seizure outcome, and one study of health-related quality of life two years after epilepsy surgery. These studies demonstrated that epilepsy surgery could be performed in Sweden with satisfactory results both concerning seizure outcome and quality of life.[2,3]

Based on these two reports, the Swedish National Board of Health and Welfare accepted the continuation of decentralized epilepsy surgery in Sweden but requested the construction of a national epilepsy surgery register, as one of the several Swedish quality control registers auditing health care. The experiences from the retrospective studies of epilepsy surgery in the 1980s were used in the creation of a prospective epilepsy surgery database. From the early 1990s and onwards, all six Swedish university hospitals (in Lund, Göteborg, Linköping, Stockholm, Uppsala, and Umeå) have provided specialized epilepsy care including epilepsy surgery, and there is a population-based regional referring system. Sweden has a population of nine million inhabitants and approximately 60,000 persons (0.7%), 50,000 adults, and 10,000 children, have active epilepsy.[4]

Figure 9.1 Map showing the Nordic countries and all centers with comprehensive epilepsy surgery teams. Denmark and Norway have chosen to centralize their surgical programs to National Centers, Sweden has a decentralized model with six centers at the regional university hospitals working in close collaboration, and in Finland there are two centers with epilepsy surgery programs.

All centers contribute to the Swedish National Epilepsy Surgery Register, which has a steering committee with participation from all centers. The register protocol includes data on medical history, investigational findings, side and site of the operation, histopathological diagnoses, complications during the pre-surgical evaluation or at surgery, and a two-year follow-up of seizure outcome, antiepileptic medication, and psychosocial data. It has recently been decided to prolong the prospective follow-up of all operated patients, and a five-year as well as a ten-year follow-up will be included in the register. The validity of the data collected from the centers is regularly checked by several systems. Intrinsic checkpoints within the database reject certain impossible combinations. An external revision is also performed: two epilepsy nurses visit all centers regularly and compare the data entered into the data base with the original data from the patient file for a random sample of the patients operated at that center. The items controlled in this external revision include side and site of operation, complications, neuropathological findings, and seizure outcome at the two year follow-up. So far, there have been no mismatches in the reporting on any of these central items.

The register is prospective since 1995 and has full coverage of every epilepsy surgery procedure in Sweden. Up to now it contains data on 924 patients, 668 have proceeded to surgery (418 adults and 250 children), while the remainder consists of suspended preoperative investigations and ongoing investigations. Temporal lobe resections dominate in the Swedish series (459 patients) as elsewhere, followed by extratemporal lobe resections (141 patients), and the remaining patients have undergone callosotomies, hemispherotomies, or multilobar resections. Intracranial recordings are performed in 20–40% of evaluations. During recent years the trend has been towards fewer invasive recordings.

There is a close network cooperation between the six centers, with regular workshops and case discussions. There are, however, differences between the centers both regarding number of operations and choice of and access to advanced investigational techniques. For example, PET is exclusively performed at Uppsala University PET-Centrum, while ictal SPECT is most extensively used in the program at Lund University Hospital. The register gives the possibility of a regular audit, with yearly reports sent to the Swedish National Board of Health and Welfare. The yearly reports are also distributed to all participating centers and discussed at the annual meetings.

The register is also the basis of scientific reports at a population-based national level. Two-year seizure outcomes are regularly analyzed in different patient populations and have been shown to compare well with results from international centers. As expected lesionectomies show the best results, with around 80% seizure freedom, followed by temporal lobe resections, where a relation with intellectual level has also been demonstrated.[5,6] In 325 patients who underwent temporal lobe resection 1990–99, 65% of the patients with IQ > 70 were seizure-free two years after surgery compared to 42% of the patients with IQ 50–69.[7,8] During the same time period 19 hemispherotomies were performed and 63% of these patients were seizure free at the two-year follow-up, while none of the five patients who underwent subtotal hemispherectomy obtained seizure freedom.[9]

One concern related to the decentralization of epilepsy surgery pertains to the risk for complications. An analysis of complications was therefore performed, based on data from the Swedish National Epilepsy Surgery register 1990–1995.[10] Complication rates were analyzed for 654 surgical procedures, 205 of which were invasive electrode procedures and 449 were therapeutic procedures. A complication was defined as minor if it resolved within three months and major if it affected activities of daily living and lasted longer than three months. The complication rates were shown to be low, minor complications were seen in 8.9% and major complications in 3.1%, which is quite comparable to the complication rates reported from big single centers.[11] It was also demonstrated that risk was related to age, patients younger than 35 years at surgery had a very low risk.

The Swedish National Epilepsy Surgery Register has also made it possible to study the referral trends over a ten-year period during the 1990s, a period when the epilepsy surgery programs were well established and had been very active.[12] At the beginning of this time period patients had often had their epilepsy for a very long time before being referred (median 20 years for adults). It was hoped that due to more information about the epilepsy surgery programs and better neuroimaging, patients would successively be referred earlier, but this was not the case during this ten year period. At the

end of the 1990s patients with temporal lobe epilepsy still had an epilepsy duration of around half of their lives before being referred for surgical evaluation. Even patients with lesions were treated 5–10 years for their medically resistant epilepsy before referral to the epilepsy surgery center. There has, however, been a tendency towards somewhat shorter mean epilepsy duration at referral since 2000. Regional differences are also apparent; there are four-fold variations in the regional utilization of epilepsy surgery between various Swedish counties, which cannot be accounted for by differences in number of referring neurologists or neuropediatricians. In total, the number of operations has diminished from a median of 78 epilepsy surgery procedures yearly during the 1990s (0.8–1.0 operations/100,000 inhabitants) to the present median of 50 during the 2000s (around 0.5/100,000 inhabitants yearly).

Epilepsy surgery in Denmark

by Hans Høgenhaven, Copenhagen University Hospital, Rigshospitalet

Surgery for temporal lobe epilepsy was introduced in Denmark at Copenhagen University Hospital, Rigshospitalet in 1960 by the neurosurgeon Kjeld Værnet. The criteria for selecting the patients for surgery were long-standing drug-resistant epilepsy and a preoperative unilateral temporal focus found on EEG, in accordance with the principles of Penfield (Montreal) and Falconer (London). The operation consisted of an *en bloc* anterior temporal lobectomy, usually going back to the vein of Labbé. Neurologist Inge Jensen followed up extensively all 74 patients operated upon in the first 10 years with special reference to neuropathology, social conditions and surgical outcome.[13] Interestingly, many of the observations and conclusions still hold true today. In her thesis 'Temporal Lobe Epilepsy' from 1977, she found that 64% were seizure-free at the time of follow up. If the group of patients with at least 75% reduction in seizure frequency was included, 83% of the patients derived benefit from surgery. The final conclusion of the thesis was that 'patients should be operated on as early as possible, and in all events as soon as their epilepsy had proven resistant to medication'. Despite the excellent results, the number of operations for epilepsy declined slowly through the 1970s and 1980s, partly because epilepsy surgery was confused with psychosurgery by the public.

Improved results and new enthusiasm from the major centers in North America convinced neurologist Mogens Dam to revitalize epilepsy surgery in Denmark in 1987. 'The National Epilepsy Surgery Group' was formed as a multidisciplinary team from several institutions, primarily involving Copenhagen University Hospitals and Dianalund Epilepsy Hospital. However, in 1993 Danish National Health authorities felt the need to regulate the activity, mainly due to epidemiological considerations. Denmark, with a population of 5.3 million people, was thought to be too small a country to generate enough patients to justify the implementation of highly specialized diagnostic and epilepsy surgical procedures. Also, at the time there was a lack of uniform internationally recognized and evidence-based standards for selection of patients, diagnostic and treatment procedures, safety and results. It was decided that intracranial diagnostic procedures should not be performed, leaving the Danish program for some years with a non-invasive protocol and the option of temporal lobe surgery only. Patients who met the borders of the protocol or had extra-temporal epilepsy were referred to international epilepsy surgery centers abroad, mainly in the USA (MINCEP, Mayo and Cleveland Clinics) and in Germany (Bethel, Bielefeld), and the costs were covered by the national health services. Although it was not the intention, one of the consequences of this regulation was that fewer Danish patients had epilepsy surgery than in the other Nordic countries.

Today, epilepsy surgery in Denmark is centralized at one center, 'The National Epilepsy Surgery Group' at Rigshospitalet, in close cooperation with Dianalund Epilepsy Hospital. The program now meets the recommended standards of a referral center outlined by the Commission on Neurosurgery of the International League Against Epilepsy (ILAE)[14] and has at its disposal all the necessary diagnostic modalities, i.e., long term video EEG monitoring, PET, SPECT, ECoG, Wada-test, highly specialized neuropsychological and psychiatric services, and dedicated MRI, including fMRI, as well as intracranial recordings and stimulations. The capacity of the program has been set at 40 operations (resective surgery) per year, i.e., 0.8 operations per 100,000, both children and adults.

For this program, the working definition of epilepsy surgery is 'an operation performed on the background of medically resistant epilepsy with incapacitating seizures, not caused by an etiology (ex: a tumor) which by itself sets the indication for operation.' This implies that some types of lesionectomies in epilepsy patients, as well as initial presurgical work-up, may be performed at other university clinics if they are in accordance with the epilepsy surgery protocol. However, if the epileptogenic zone has to be characterized preoperatively, the patients are referred to the National Epilepsy Surgery Group. In the presurgical evaluation all candidates have to follow a protocol that includes a neurological examination, ictal video scalp-EEG monitoring, and a cerebral MRI. PET, interictal and ictal SPECT, Wada-test, and fMRI are employed when necessary, followed by neuropsychological testing and an optional neuropsychiatric evaluation. If necessary, ictal video-EEG monitoring utilizing intracranial electrodes, is performed, with stimulation if indicated. Approximately one third of the patients referred to the program proceed to surgery. In the last decade 25% of patients have been children under the age of 18 years.

All patients who undergo epilepsy surgery will have postoperative evaluations by the National Epilepsy Surgery Group after 3, 6, and 12 months. One year postoperatively, all patients have a comprehensive evaluation, including a full neuropsychological examination and a quality of life assessment, and the need for rehabilitation is addressed. The postoperative outcome is documented using the classification of Engel. (An additional comprehensive evaluation after 24 months is under consideration.) At this time the adult patients are referred to the care of their local doctors, while the children stay in the program for several years.

The results of epilepsy surgery in the Danish patients, many of whom until recently have been operated on abroad, are comparable to international reports. Approximately 2/3 of patients with temporal lobe resections are seizure-free.

The complication rate in terms of permanent neurological or cognitive deficits is low.

The number of candidates referred has been slowly rising during the last 10 years. Currently, Danish patients have had epilepsy for an average of 17 years at the time of surgery, so the recommendation from Inge Jensen's thesis based on the operations performed in the 1960s that 'patients should be operated as early as possible' has not yet come true.

Epilepsy surgery in Norway

by Karl Otto Nakken, National Centre for Epilepsy in Sandvika

In 1949, Kristian Kristiansen at Ullevaal Hospital in Oslo introduced epilepsy surgery in Norway. He had been trained by Wilder Penfield at Montreal Neurological Institute, and for many years he was the only Norwegian surgeon who performed epilepsy surgery. When he retired in 1976, this activity was transferred to the National Hospital in Oslo (now Rikshospitalet University Hospital).

While lesionectomies in epilepsy patients are performed at all regional hospitals (Oslo, Bergen, Trondheim, Tromsø), 'pure' epilepsy surgery, i.e., removal of the epileptogenic zone, has for the last ~30 years been centralized to the Rikshospitalet University Hospital, in close collaboration with the National Center for Epilepsy in Sandvika. From a modest start, the number of patients undergoing epilepsy surgery has been fairly constant over recent years, approximately 30–40 operations per year.

With a population of 4.5 million inhabitants, about 32,000 persons are estimated to have epilepsy in Norway. About 30% of these have difficult-to-control seizures, and a considerable number of these patients are potential candidates for epilepsy surgery. After primary epileptological assessment at the local/regional hospital, those patients who have drug-resistant and disabling seizures are referred to the National Centre for Epilepsy. Here they undergo a comprehensive presurgical evaluation, including a clinical, neurophysiological, neuropsychological, and neuroradiological assessment. All candidates for surgery have a neurological examination, an ictal video scalp-EEG monitoring, and a cerebral MRI investigation according to an epilepsy protocol. Currently, all PET investigations are performed in Sweden (Uppsala University PET-Centrum). Only about 25% of these patients actually proceed to surgery. The approximate yearly number of presurgical investigations are shown in Table 9.1.

Table 9.1 Presurgical investigations in Norway

Type of procedures	Numbers per year
Neuropsychological assessments	40
Intracranial recordings	20
PET investigations	50
Ictal SPECT investigations	10
Wada-tests	40
fMRI investigations	10

While clinical, neurophysiological, and neuropsychological assessments are performed at the epilepsy center, the neuroradiological investigations, the Wada-tests, and the diagnostic and therapeutic surgery take place at Rikshospitalet University Hospital. Hence, the Wada-test is included in the presurgical diagnostic work-up, and for the time being fMRI cannot, in our opinion, fully replace this test. Specimens of resected brain tissue are examined histopathologically.

All patients who have had epilepsy surgery are followed up at the National Centre for Epilepsy 3, 6, 12, and 24 months postoperatively. Two years following surgery all patients have a comprehensive evaluation, including a clinical, neurophysiological, and neuropsychological assessment, and the postoperative results are classified *ad modum* Engel.[15] The need for further rehabilitation is assessed, and later on the patients are followed up by their local pediatricians /neurologists.

The results of epilepsy surgery in Norway compare well with what is reported from other epilepsy centers. Seizure freedom is achieved in ~70% of patients with temporal lobe resections, while ~50% of those with extratemporal resections become seizure free. The complication rate in terms of permanent neurological or cognitive deficits is low.

In our opinion, the psychosocial outcome of epilepsy surgery is a largely neglected field of research. Guldvog *et al.*[16] compared surgically and conservatively treated patients and found no evidence of significant psychosocial improvement after surgery, even in seizure-free patients or in patients with a marked reduction of seizures.

In our experience, focal surgery may be a good treatment option also in epilepsy patients with low IQ, provided the resections are performed relatively early after seizure onset.[17] Furthermore, among adult patients with speech localized to the left hemisphere, we have found indications of a gender difference in vulnerability to epilepsy surgery, exhibiting greater reduction in long-delay verbal memory in men operated in the left hemisphere compared to women.[18]

A few patients have had epilepsy surgery outside Norway. Some selected children with catastrophic epilepsy have undergone hemispherotomy in Germany (Bonn), and some few complicated cases have been operated in the US (Dartmouth Hitchcock Medical Center, New Hampshire).

Despite increased attention the recent years, epilepsy surgery is assumed to be under-utilized in Norway. We believe that at least 50 patients should be operated yearly in Norway, and it will be a great challenge in the years to come to further market this very effective treatment option.

Epilepsy surgery in Finland

by Reetta Kälviäinen, Kuopio Epilepsy Center

In Finland, the first 37 patients with difficult to treat epilepsy underwent epilepsy surgery between 1979–88 at Oulu University Hospital in a program led by the neurosurgeons Stig Nyström and Esa Heikkinen. Before initiating the first modern comprehensive multidisciplinary epilepsy surgery evaluation team in Kuopio in 1988, Neurosurgeon Matti Vapalahti and his team members (neurologists, neurophysiologists, and a neuropsychologist) were trained at the Montreal Neurological Institute. The second comprehensive epilepsy center was initiated in Helsinki in 1991, after Dr. Marja-Liisa Granström had been trained at the Cleveland Clinic, Dr. Eija

Gaily at the University of California in Los Angeles, and neurosurgeon Göran Blomstedt at Umeå University Hospital in Sweden. Currently the Finnish Ministry of Social Affairs and Health has recognized Kuopio and Helsinki as the two highly specialized centers in Finland for invasive diagnostics and surgery for patients with therapy resistant epilepsy. Finland has a population of 5.2 million inhabitants. Altogether 36,000 patients use current medication for epilepsy and about 9,000 patients use more than one antiepileptic drug indicating intractable epilepsy.

Between 1988 and 2005, altogether 333 therapeutic epilepsy surgery interventions have been performed in the Center in Kuopio University Hospital. Kuopio has concentrated in temporal lobe epilepsy and has performed the majority of temporal resections in the country (n = 248). The program has also included extratemporal resections (n = 33), callosotomies (n = 28), lesionectomies with corticography (n = 22), and hemisphereotomies (n = 2), 80% are adults and 20% children, about half of the patients referred for evaluation proceed to surgery. In the majority of adult patients with temporal lobe epilepsy, MRI and extracranial EEG-videotelemetry provides sufficient localization of seizure origin for making the decision about surgery. However in Kuopio altogether 40% of those temporal lobe epilepsy patients who have undergone resective surgery have needed preoperative invasive intracranial recordings (i.e. subdural and/or intracerebral depth electrodes). Indication for invasive EEG-investigations has been: suspected bitemporal epilepsy (52%); extratemporal (36%) onset of seizures; or remote structural lesion (12%).[19] Functional imaging methods (ictal-SPECT, PET, fMRI, MEG)[20] are also used to provide additional evidence, when needed. A special strength in Kuopio has been the intensive co-operation with the Department of Neurobiology of Kuopio University on research on epileptogenesis and molecular biology of epilepsy with direct clinical correlations and applications in surgical treatment.[21]

Kuopio Epilepsy Center has published long-term outcome results from a consecutive series of 140 adults with TLE operated on between 1988 and 1999.[22] The aim of surgery was defined preoperatively as: 'curative' for 74% (n = 103) of patients with unilateral TLE; or as 'palliative' for 26% (n = 37) of the patients. The palliative category included patients with bitemporal seizure onset (49%), multifocal epilepsy, dual pathology, or patients in whom the epileptic focus could not be completely resected. Outcome of surgery was assessed independently in unilateral TLE and in palliative patients due to the significant difference in expected outcome. The study demonstrated that patients without restricted unilateral seizure focus also may benefit from surgery and that the outcome of surgery improved significantly after introduction of the standardised MRI protocol (Table 9.2). Eighty-six percent of all seizure relapses occurred within one year after surgery, and late seizure relapse (>2 years after surgery) was observed in only 5% of all patients and was often preceded by a specific explanatory factor such as withdrawal of antiepileptic medication. In a multivariate analysis, unitemporal MRI abnormalities, early onset of epilepsy, or the predominance of focal seizures with impaired consciousness with focal ictal EEG, were identified as predictors for successful postoperative outcome.

The epilepsy unit in Helsinki University Hospital (Hospital for Children and Adolescents and Department of Neurosurgery) started in 1991 with pediatric epilepsy surgery, and since 1998 the team has also offered epilepsy surgery to adult patients in collaboration with the Department of Neurology. Between 1991 and 2005 a total of 187 therapeutic epilepsy surgery interventions had been performed in Helsinki. The program has included temporal resections (n = 72), extratemporal resections (n = 49), callosotomies (n = 34), hemispherotomies (n = 29), multiple subpial transections (n = 1), and radiotherapy of hamartomas (n = 2). During preoperative evaluation all patients were studied with video-EEG, 1.5 T MRI, and neuropsychology. When necessary ictal-SPECT, MEG (localization of interictal spikes and functional areas), FDG-PET, magnetic resonance spectroscopy, and/or invasive monitoring with subdural grids (n = 22) and strips (n = 3) is used during the presurgical work-up. Nearly all patients undergo psychiatric evaluation. The majority of the patients are children or adolescents (76%) and due to the heterogeneous population regarding syndromes and etiologies (including catastrophic epilepsies of

Table 9.2 Long-term postsurgical seizure outcome in 140 adult temporal lobe epilepsy (TLE) patients in Kuopio Epilepsy Center[22]

	Curative group with unilateral TLE (n=103)		Palliative TLE epilepsy group (n=37)
	Entire group (%)	Standardized MRI protocol (%) (n=59)	(%)
Seizure free	45	61	27
Persisting auras	12	11	3
Worthwhile outcome (Engel I-II)	68	74	62

early childhood) general outcome figures are difficult to evaluate. The team has, however, recently evaluated the two-year follow-up of cognitive outcome after pediatric epilepsy surgery.[23] Altogether 38 patients, between 3–17 years of age, were evaluated before surgery and six months and 2 years postoperatively. No significant change in verbal or performance IQ was demonstrated at group level. Lateralization, type of surgery, age, sex, and presurgical IQ did not affect outcome. In conclusion, epilepsy surgery in children and adolescents did not in general have a significant impact on cognitive development in a two-year perspective.

Medical intractability is defined as persistent seizures despite 2–3 maximally tolerated AED trials. In older children and adults medical intractability can be diagnosed in two years in most cases. However, the median duration of epilepsy in patients referred to presurgical evaluation at Kuopio Epilepsy Center has been 19 years.[22] In the future, emphasis should be put on early prediction of medically intractable temporal lobe epilepsy in children and adolescents, since early surgery probably improves the overall outcome, especially in younger patients. Further evaluation for long-term cognitive outcome is also warranted. The epilepsy unit in Helsinki continues to focus on pediatric epilepsy surgery, accepting pediatric patients from all parts of Finland and adults within their own catchment area. Kuopio Epilepsy Center continues to treat patients with medically refractory temporal or extra-temporal focal epilepsy of all ages from the whole country, especially focusing on getting patients referred earlier.

The future of epilepsy surgery in the Nordic countries?

Despite increased attention in recent years, epilepsy surgery is assumed to be under-utilized in the Nordic countries. Approximate yearly numbers of procedures in Sweden, Norway and Finland are shown in Table 9.3. Too few patients, especially children in the Scandinavian three countries, with severe, drug-resistant epilepsy, are referred to the centers for surgical evaluation, and many are referred too late, i.e., long after psychosocial problems have become irreversible. This situation is most probably not at all unique since there is a general concern that epilepsy surgery is underused. One reason for this underutilization of the resource of epilepsy surgery might be lack of knowledge about epilepsy within the medical profession[24] or lack of knowledge about the favorable results of surgical treatment of epilepsy within the neurological community. In a survey concerning the provision of epilepsy services in Europe which was undertaken by the ILAE Commission on European Affairs a few years ago, all countries but six stated that they had epilepsy surgery programs.[24] Lack of epilepsy surgery was more commonly reported from Eastern and Southern Europe, whereas several western ILAE chapters mentioned as a problem that epilepsy surgery was present but underused.

The epilepsy surgery groups in the Scandinavian countries together with Finland recently decided to organize a meeting for collaboration and the first Nordic epilepsy surgery meeting was held in Sweden in 2004. The second will be held in Norway 2006. In the future the epilepsy surgery groups in the Nordic countries plan to meet at regular intervals to learn from each other and expand their network cooperation for the benefit of the patients.

Acknowledgment

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Table 9.3 Yearly epilepsy surgery procedures in the Nordic Countries based on an average over a 10–15 year period

	Sweden (9 million inhab.)	Denmark (5.3 million inhab.)	Norway (4.5 million inhab.)	Finland (5.2 million inhab.)
Temporal lobe resections (selective AHE included)	41	14	25	19
Extra-temporal lobe resections	14	2	7	5
Mixed group Multilobar resections, hemispherotomies, MST, callosotomies, hamartomas (pure lesionectomies are also included in the mixed group in Finland)	14	4	3	7

Inhab. = inhabitants.

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10 The development of epilepsy surgery in the Netherlands and Belgium

W van Emde Boas and PAJM Boon

The Netherlands[1]

In the Netherlands, initial development of brain surgery came relatively late. In his jubilee speech on the development of surgery during the last 30 years, at the occasion of the 25th anniversary of the Nederlands Tijdschrift voor Geneeskunde (NTvG) in 1882, J.W.R. Tilanus (1829–1914), professor of surgery in Amsterdam, does not yet even mention surgery of the nervous system[2] and, apart from the usual descriptions of trepanation in early general medical or surgical texts, up to 1890 no papers on surgical intervention on either the central or the peripheral nervous system had been published in the NTvG, then as now the main Dutch medical journal, nor by Dutch authors, in other medical journals or books.[3,4] This changed at the initiative of Cornelis Winkler (1855–1941), the first professor in psychiatry and neurology in the Netherlands and generally considered the founding father of modern Dutch Neurology (Figure 10.1).

First steps: the neurologist and the surgeon

Winkler studied medicine in Utrecht where he was greatly influenced by the strict scientific approach of ophthalmologist and physiologist F.C. Donders (1818–1889). Following graduation and obtaining a PhD degree on a thesis on Virus Tuberculosum 1879; and a brief period as clinical resident in The Hague, Winkler expressed to his former teacher the desire for a more research oriented position in Utrecht. Offered the position of reader in psychiatry, Winkler initially declined, considering psychiatry too philosophical and unscientific to his liking. After some clinical work with neurological patients in the clinic for internal medicine of S. Talma (1847–1918) and following visits to T. Meynert (1833–1892) and J. Wagner von Jauregg (1857–1940) in Vienna and to numerous German protagonists of the neuropathological oriented school of psychiatry and neurology, he became convinced of the advantages of teaching both neurology and psychiatry as a whole and accepted in 1885 the lectureship of psychiatry in Utrecht, followed in 1893 by the appointment to professor in psychiatry and neurology, the first such chair to be officially created in the Netherlands.'[5]

Winkler was well aware of the current clinical and experimental literature on the localization of brain functions and the application of these findings to clinical neurology and early on expressed his intention to follow the example of V. Horsley (1857–1916) and others and to focus attention also on brain surgery as a possible treatment for neurological disorders, notably in epilepsy patients with seizures comparable to those, induced by electrical stimulation of the cortex in animals by E. Hitzig (1838–1907) or described in humans by J. Hughlings Jackson (1835–1911).[5] As luck would have it, Winkler's appointment coincided with that of his friend and fellow student J.A. Guldenarm (1852–1905) as general surgeon in the Deaconess Hospital in Utrecht. According to Winkler, Guldenarm was a gifted and inventive surgeon, who made his own instruments, operated very neatly and with whom he felt sufficiently confident to try to remove brain tumours, '*a great endeavour, considering that we hardly knew what we were going to do*'.[5]

On 11 November 1889 they performed their first published surgery on a 54-year-old ex-soldier with a two year history of Jackson type seizures, beginning in the right leg and with fast neurological and mental deterioration during the last few weeks. Exploring the left frontocentral area, they partially resected an angiosarcoma from the left gyrus frontalis superior, lobus paracentralis, and gyrus centralis anterior. The patient survived the procedure and remained without seizures but with hemiplegia, aphasia, progressive loss of consciousness and increasing prolapsus cerebri before dying, three weeks after surgery.[6]

Between 1891 and 1893 Winkler and Guldenarm, together with A. Huysman, ENT surgeon, and H. Buringh Boekhoudt, resident to Winkler, published a series of five 'contributions to surgery of the brain' in the NTvG in which they provided meticulous detailed clinical histories of 15 patients (3 not operated) and discuss the value, possibilities and – often – impossibilities of surgical intervention in various neuropathological conditions.[6–10] Although epilepsy was not mentioned in the title of any of these five papers it was a major symptom in five and the primary indication for surgery in a further two of the twelve operated patients. The first of the latter was a 22-year-old man with an 11 year history of Jacksonian seizures in the left hand and arm who had a right frontocentral angioma removed by Guldenarm on 4 April 1890[6] and changed from >40 seizures a day to multiple days without seizures with a follow up of 7 years.[11] This patient was also published in a thesis 1891; by a Dutch physician, P.C. Th. Lens, defended however in Giessen and thus not really to be considered the first Dutch thesis on epilepsy surgery.[12] The second patient was a 19-year-old boy with an epilepsy history of 6 years, following a skull trauma at the age of 8 years. He became free of seizures, following extirpation of a calcified lesion from the left hand area[9] but died from

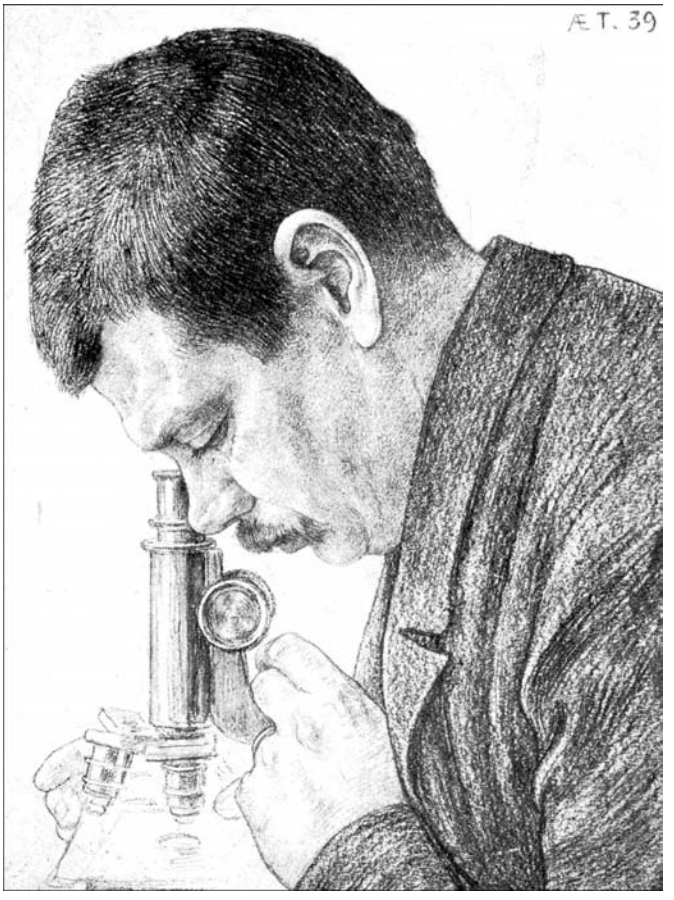

Figure 10.1 Cornelis Winkler (1855–1941). Pencil drawing by Jan Veth, 1896. The portrait was made just after Winkler resigned in Utrecht and before he moved to Amsterdam. While making this portrait Veth (1864–1925) proposed to Winkler to give art lessons to medical doctors, in order to improve the quality of the illustrations in their publications. The idea however was never realized.[5]

an occupational accident a few years later.[11] Some of the early tumor cases, including one patient with Jacksonian seizures, were collected and described in the really first Dutch PhD thesis on brain surgery, defended by Winkler's pupil R. S. Hermanides[13] and again in the NTvG.[14]

Surgical techniques are not dealt with in detail in these papers although there is some discussion about the relative advances of a bony versus a soft tissue closing of the trepanation area in certain circumstances. Some procedures were only performed '*after we had ascertained ourselves on the cadaver that the surgery was possible*'.[6] Major emphasis is given on the other hand to the problem of correct localization, prior to surgical intervention. The papers include some patients where Winkler failed to make a proper preoperative localizing diagnosis and he frankly admits that in at least one patient, in whom surgery failed, the obduction showed a right tentorium meningioma that, on correct diagnosis, could have been successfully removed.[6] Winkler strongly believed that, unless surgeons had extensive knowledge of brain anatomy and physiology, brain surgery should be guided by the neurologist as the one both to make the exact diagnosis and to decide about the indication for surgical exploration and the place and extent of the necessary trepanation. For the latter he developed a new method to enable the neurologist and the surgeon to estimate the position of the central and Sylvian sulci and of the targeted cortical gyri, using just two external reference points (the glabella and the protuberantia occipitalis externa) to create a grid of triangles, projecting over skin of the skull.[15] Since this system was based on comparative rather than absolute measurements it was considered to be more reliable than that of Horsley or others and the 'triangulation according to Winkler' (Figure 10.2) became the standard procedure for guiding the trepanation in the Netherlands for the next few decades.

Such was Winkler's enthusiasm for brain surgery that in 1895 he even published a long popular paper on the subject in *De Gids*, the most important cultural monthly magazine in the Netherlands. Despite the overall poor results (only 4 out of 18 operated cases still alive at the time of publication and only

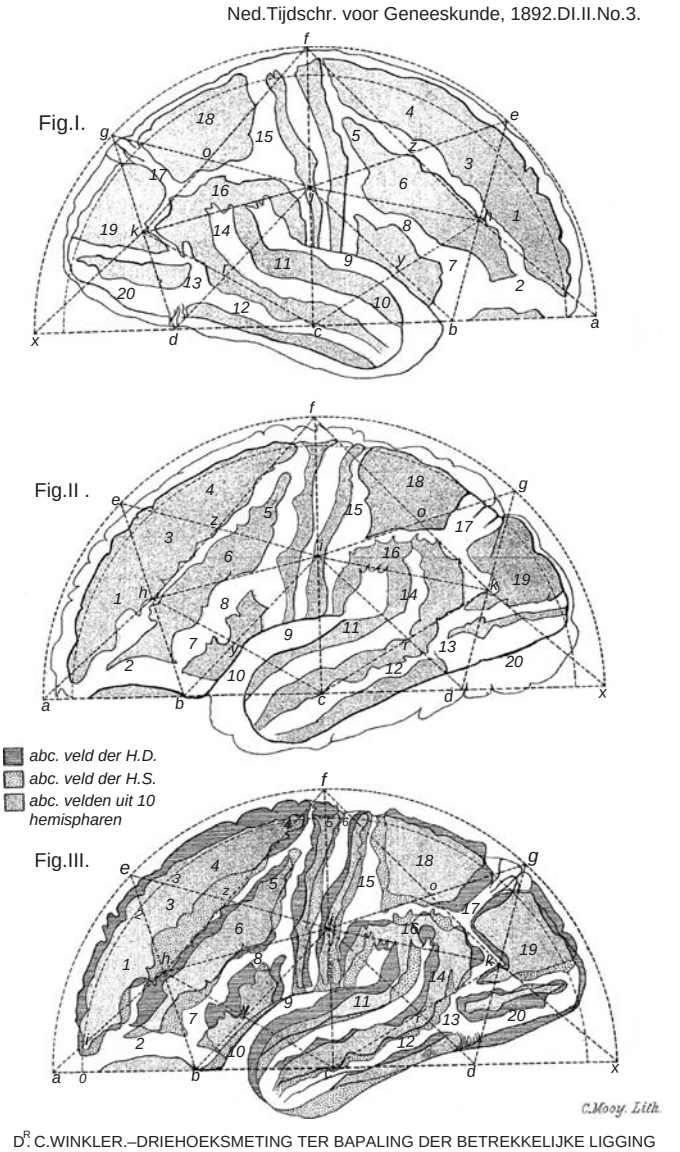

Figure 10.2 Winklers method of triangulation. By constructing a series of triangles, based on the line between the glabella and the protuberantia occipitalis and the perpendicular dissecting line at midpoint he obtained a reasonable estimate of the position of the underlying cortical structures. The drawing is based on studies on 10 adult subjects; the darkened areas and numbers indicate cortical areas or sulci that reliably will be found within that specific triangle (lithograph illustration of Winkler's paper[15] in the NTvG, Bohn: Haarlem, 1892).

two really cured) he argues for an aggressive approach since the patients, mostly tumor cases, have little to lose. For patients with epilepsy he considers the loss of some function to be preferred to the constant irritation of the cortex and the risks of the recurrent seizures. He discussed the use of electrical stimulation to identify the epileptic focus and the different surgical options. He preferred resection of the cortex, notably when abnormal on inspection, and did not think highly of the practice of just cutting around the suspected area in order to prevent seizure propagation. In an interesting last paragraph he commented on some early efforts on psychosurgery by Burckhart in Switzerland, which he rejected since he was of the opinion that one should treat the underlying disease in mental patients and not just the symptoms.[16]

In 1896, being refused a new clinic that was initially promised to him, Winkler resigned his position in Utrecht and within months accepted the newly created chair of Neurology and Psychiatry in Amsterdam where he would have ample access to clinical beds both for neurology and psychiatry and would be able to work together with J.K.A. Wertheim Salomonson (1864–1922), who already ran a clinic for neurology and electrotherapy, and in 1899 would be appointed to the first chair in neurology, electrotherapy, and radiography in the Netherlands. In Amsterdam Winkler continued his neurosurgical activities, together with the surgeons J.A. Korteweg (1851–1930) and J.A. Rotgans (1859–1948) and the professor in Internal medicine P.K. Pel (1851–1919), who also was actively interested in neurological diseases. Epilepsy initially remained a major indication. In 1897 Winkler's pupil H.H. van Eyk (1869–1930) obtained his Ph.D. on the first (and until Brekelmans[17] the last) Dutch dissertation to deal specifically with the surgical treatment of partial epilepsy[18] and in that same year Winkler, in recognition of his expertise in the field, was invited to lecture on 'Surgical intervention in the epilepsies' at the International Congress of Psychiatry, Neurology and Hypnology In Brussels.[11]

In his dissertation Van Eyk described 10 cases of predominantly posttraumatic epilepsy, nine of them operated and with clear improvement in five. In addition he summarized the data from the literature, 13 cases of epilepsy due to subdural haematoma and 100 cases of posttraumatic epilepsy, including 7 of his own, and showed that the best results were obtained in patients in whom a recognizable lesion could be removed. His case #9 concerns a 20-year-old man with a 2 year history of focal seizures, beginning in the left hand. A first exploration by Rotgans and Buringh Boekhoudt showed local thickening of the dura over the hand area, identified by electrostimulation by Wertheim Salomonson. Nothing was excised and there was no improvement. Following two further surgeries with temporary improvement the patient was operated upon a fourth time on 18 June 1897, this time with Winkler performing the electrostimulation. A seizure was provoked by stimulating the finger area '*which was photographically documented and found to be identical to the spontaneously observed seizures*', the first case of intracranial and intraoperative seizure monitoring? Following a local cortectomy the patient became paretic but also free of seizures for at least the next two months.[18]

At the congress in Brussels Winkler discussed 20 patients who had surgery, including two patients, successfully operated for 'reflex-epilepsy', due to peripheral nerve injury (one a cornea corpus alienum, the other a bullet injury of a branch of the trigeminal nerve), a clinical entity which certainly was not epilepsy but was generally accepted at the time and considered a good indication for surgical intervention.[19] In 13 patients partial epilepsy was the primary indication for surgery, in 5 the seizures were but a symptom of more serious neurological disease. According to Winkler posttraumatic cases had the best prognosis, tumor cases a varying outcome and infectious cases (Lues, TBC, otogenic abcesses) or alcoholic cases a poor prognosis. In cases without an external or internal scar and with a normal aspect of the cortex, cortectomy should only be performed if a typical seizure could be elicited from that area by electrical stimulation. For toxic epilepsies, even if manifesting with partial seizures, surgery was not indicated.[11]

Even at the time of the congress, however, the initial enthusiasm for epilepsy surgery (or even brain surgery in general) appeared to be lessening. In a comprehensive review of all neurosurgical interventions performed in the Netherlands between 1889 and 1900, published in the famous 3 volume series of A. Chipault (1866–1920) on the current state of neurosurgery in 1902, Winkler and Rotgans briefly refer to the earlier work but epilepsy is not mentioned anymore as a specific indication.[3] This appears to be in line with developments elsewhere. In a long letter from London where he was visiting a number of hospitals, Wertheim Salomonson describes his admiration for the surgical skills of Horsley but also mentioned that at that time, in 1898, Horsley had not operated for epilepsy in the last 18 months because of disappointing results.[20] Two conference reports and a review in the NTvG from the same period but citing predominantly German and Swiss sources also emphasized overall poor results of surgery for epilepsy[21–23] and W.J.M Indemans (1868–1932), a general practitioner in Maastricht, reporting one patient, operated with moderate success for posttraumatic partial epilepsy, actually complained that he could not find a surgeon willing to operate on a second case.[24] Winkler himself apparently lost interest and did not publish anything on epilepsy surgery afterwards although he remained involved in some cases later published by others.

Also the attitude of the surgeons to surgery on the nervous system was changing. While most of the surgeons with whom Winkler had collaborated in Utrecht and, after 1896, in Amsterdam, apparently had little problems with his approach by which they had to rely completely on the diagnostic and localizing acumen of the neurologist, J.E. van Iterson (1842–1901), with whom Winkler performed some surgeries in Utrecht, was the first to challenge this approach. In a 1899 paper on the present state of surgery effectively citing Winkler himself, he stated that:

> *The recognition and localisation of the pathology [in the brain] still is wanting and I am pleased to report that according to the first Dutch authority in this field [Winkler] this situation will not improve unless the surgeons themselves take up the diagnosis of brain disorders and stop acting only on guidance by specialists.*[25]

With this, van Iterson started a controversy that was to continue for the next three decades and would clearly influence the further development of neurosurgery, and thus epilepsy surgery, in the Netherlands. At the time, however,

his word was hardly heeded and for some time to come the neurologist remained either the active guide of the surgeon or, by reversing the situation sketched by Winkler, actually took over the scalpel and the trephine.

Intermezzo: the neurologist–neurosurgeon

Louis Jacob Joseph Muskens (1872–1937)[26] studied medicine in Utrecht and, significantly influenced by Donders and Winkler, early on decided for a career in physiology and neurology. After obtaining his PhD in 1896 on a thesis on the reflex mechanisms of the frog heart, supervised by T. Engelmann (1843–1909), successor [and son in law] of Donders, Muskens, on a travel grant provided by the Donders Society, spent two years in the USA where he visited and worked with C.L. Dana (1853–1935) in New York and H.P. Bowditch (1840–1911) in Boston. Stimulated by Winkler to further specialize himself he spent a next period in London in the National Hospital for the Paralysed and the Epileptic, working under W. Gowers (1845–1911) and notably, for 20 months, under Horsley in order to master the surgical skills necessary to render him independent from the general surgeon.[27,28]

In the USA and in London Muskens appeared to have developed his interest in epilepsy which to a large extent would mark his further career. Back in the Netherlands he instigated the founding, in 1902 in the Hague, of the 'Dutch Society Against Falling Sickness', which, contrary to the older 1882; 'Christian Society for the Care of Sufferers from the Falling Sickness', aimed to promote treatment rather than care of epilepsy. In the same year Muskens moved to Amsterdam in 1902 and took up a practice as specialist for nervous disorders, including the position (from its inception until 1918) of medical supervisor of the clinical and outpatient departments of the 'Amsterdamse Gasthuis Tegen Vallende Ziekte' (Amsterdam Hospital for Epilepsy), an initiative by the Amsterdam Branch of the Dutch Society and, in 1903, the first non-university-associated neurological clinic in the country. Together with the Hungarian J. Donath, Muskens, in 1908, founded the *Journal Epilepsia* and, in 1909, the International League Against Epilepsy (ILAE) of which he would remain active as general secretary for many years and which he helped to revive in 1937, after a long interruption of the ILAE activities following the turmoil of World War I.[29]

A prolific writer, Muskens published extensively about epilepsy, both from an experimental and a clinical view and with major emphasis on the social aspects and needs of persons with epilepsy. His vast clinical and experimental experience culminated in a major monograph on epilepsy, published in 1924 and translated both in German and in English.[30] Other subjects included the segmental distribution of the sensory input of the cerebral cortex, the anatomo-physio-pathology of upper brain-stem connections, subject of a second major monograph on the supra-vestibular system,[31] technical and clinical aspects of neurosurgery and a series of papers on the relation between neurology, neurosurgery, and psychiatry and the way those specialties should be taught to students and be practiced.

In 1906 Muskens was admitted as private lecturer on nervous diseases at the municipal university of Amsterdam and in his official public lecture advocated the further development of organ oriented (sub) specialties in medicine, a subject highly controversial at the time[32] (Muskens, 1906). In Muskens's view specialties should focus on the anatomy, physiology, pathology, conservative treatment options and surgery of specific organs, the central nervous system representing one of the most ideal organ systems for such an approach. Psychiatry was to be separated from neurology [in the Netherlands it was not until 1974 that this separation finally was realized] and the surgical approach to the nervous system was best left to the neurologist with specific surgical training (i.e., Muskens himself). Like Winkler had done before him Muskens published a series of 'contributions to the surgical treatment of the central nervous system' in the NTvG, the third including a number of patients with seizures and the last dealing specifically with posttraumatic epilepsy,[33–36] in addition to a large number of other papers or reports of clinical demonstrations of neurosurgical cases in Dutch or foreign journals. Unfortunately and contrary to the papers of his predecessor and teacher Muskens's patient descriptions are often rather short and, when repeated, as is often the case, factual data (dates, type of trauma, patient initials, patient age) differ in successive publications, in part probably due to the then current poor quality of proofreading and correction in association with very fast publication, but in part apparently due to either shoddy writing or – worse – 'massaging' the data. Moreover Muskens had a highly contentious style of writing and presenting, emphasizing presumed diagnostic errors or failed procedures by others and exaggerating his own activities and results. Repeatedly and usually with good arguments and in terms which in today's perspective would be considered too offensive for public discussion in print, his claims are refuted, his results doubted, his qualifications as a neurologist-surgeon denied, and his references identified as incorrect, not only by the general surgeons but notably also by his fellow neurologists and by the chief editor of the NTvG.[37–44] Although Muskens apparently was considered as sufficiently an expert to be invited by the Belgian Red Cross to assist in setting up a unit for war casualties with brain or spinal injuries in Antwerp[45] the chiefs of the university clinics in Amsterdam repeatedly refused to have Muskens operate in their clinics.[44] Significantly, the well-known Amsterdam neurologist C. T. van Valkenburg (1872–1962), who for a number of years was the medical director of Muskens's hospital, relied on other surgeons for his work on the sensory neuroanatomy of the human cortex, based on electrical stimulation during surgery.[46–48]

As far as epilepsy is concerned only few successful surgery cases eventually are listed in the chapter on posttraumatic and focal epilepsy and the surgical treatment of epilepsy in Muskens's 1924 monograph.[30] These include three of his favorite cases which he published and presented at many occasions, the first a patient with probably posttraumatic serous meningitis, operated in 1907 because of fast neurological deterioration, in whom the seizures were but a secondary symptom, and the second, a girl of 18 (cranial trauma at age 3 years) in whom Muskens, guided by sensory loss in the ulnar region of the left arm, ligated some 'abnormal pial veins' and claimed successful treatment of 'seizures' that by all his peers of the Amsterdam Neurological community, many of which previously had observed this patient, were consistently interpreted

as psychogenic events. Only the third represents a true epilepsy surgery success story: a female patient who following trauma at age 4 and two earlier surgical interventions by Winkler and Rotgans at the age of 4 and 16, finally was rendered seizure free by Muskens by removal of two tiny bone fragments, found under the previous bone flap and, when the seizures still persisted, in a second session a small cortisectomy from the area where habitual seizures could be elicited by electrical stimulation. The remaining 7 patients in the chapter, which purports to present 'a comprehensive report' of a lifetime experience include one non-traumatic tumor patient (presented to illustrate the limited value of surgery in those cases), one patient operated in 1910 but without clinical information ('all files lost') or follow up, other than that the patient was successfully employed as a marine officer, 1 patient, operated by others with poor results, 2 patients with less than a year of follow up at the time of writing, leaving only two more reasonably well-documented cases, successfully operated for posttraumatic epilepsy in 1913 and 1918.[30]

In the same period that Muskens was active, occasional reports indicated that, as before, some surgical procedures for posttraumatic or other symptomatic forms of epilepsy were performed by a general surgeons, assisted by a neurologist, generally with acceptable results for posttraumatic epilepsy and poor results for all other cases. These were not part of any organized program but in number and results appear equal or even superior to Muskens's activities. Not surprisingly Muskens academic career never progressed beyond his private readership and even as a neurosurgeon his real activities appear to have remained limited.

Looking back, Muskens remains a major figure in the development of epileptology and epilepsy care, both in the Netherlands and internationally.[26] For the actual development of either neurosurgery in general or epilepsy surgery in particular, however, this self proclaimed 'self operating neurologist' did relatively little and achieved even less.

A second start: the neurosurgeon and the neuro(physio)logist

Since otherwise the field remained in the hands of general surgeons with neither specific training nor interest in neurological disorders, the overall practice of neurosurgery in the Netherlands remained limited and of relatively poor quality for well into the first three decades of the 20th century. Yet increasingly the need for surgical treatment of some neurological disorders was felt and again it was a neurologist who took the initiative.

In 1923 Bernard Brouwer (1881–1949), who studied medicine in Amsterdam and then trained with Winkler, was appointed to the chair of neurology, now for the first time divided from psychiatry, in the city of his Alma Mater. For his surgical cases he worked with the general surgeons O. Lanz (1865–1935) and W. Noordenbos Sr. (1875–1954) but he was well aware of the gap between their results and those reported by others. Contacts with H. Cushing (1869–1939) and W. Dandy (1886–1946) during a lecture tour in the USA in 1926 convinced him that good quality neurosurgery was only possible in a special setting and by dedicated and undivided neurosurgeons with specific and adequate training. In Amsterdam he managed to convince the municipal authorities to have a new 100 bed clinic to be built, exclusively for neurological patients and including a fully equipped neurosurgical unit that could function independent of the general surgical clinic. While the clinic was being built Brouwer selected Ignaz Oljenick (1888–1981), a young resident surgeon, and sent him to Boston for training with Harvey Cushing. In 1929 Oljenick returned to Amsterdam and in September of that year the neurosurgical unit in the newly opened clinic started its activities.[1] As far as can be ascertained from his publications Oljenick did not perform any procedures specifically for epilepsy. His first trainee, however, would.

Arnaud Cornelis de Vet (1904–2001), studied medicine in Amsterdam and in 1929 applied for and obtained the position, offered by Brouwer, of resident in neurosurgery. De Vet thus became the first physician to be trained formally as a neurosurgeon in the Netherlands. After finishing his years of training with Brouwer and Oljenick and a study trip of several months to neurosurgical clinics in numerous European cities, De Vet in 1936 obtained his PhD, supported by Brouwer, on a thesis on the diagnosis of cerebral meningioma.[49] His material concerns a series of 36 operated and (with one exception, histologically verified) and two unoperated cases, including 17 patients in whom seizures were the major ($n = 13$) or a contributing symptom. Fifteen of these had their meningeoma removed, two died within a few days following surgery, and of the remaining 13 no follow up is provided. He points to the potential value but also the risks of ventriculography for the diagnosis of these (and other) intracranial processes but also emphasizes the need for a meticulous anamnesis and clinical work up and devotes a special chapter on the epileptic symptoms, found predominantly in patients with meningeoma over the convexity or the parasaggittal areas of the brain, and their localizing significance.

In the summer of 1936 De Vet left Amsterdam and moved to Wassenaar, a suburban village near The Hague where a former psychiatric clinic had been rebuild as the second non university associated hospital for psychiatric and neurological disorders, including the first non-university neurosurgical unit in the country. In the St. Ursula Clinic De Vet continued to pursue his interest in epilepsy as a possible target for surgical intervention and in 1938 he was appointed consultant neurosurgeon in the epilepsy clinic 'Meer and Bosch' in Heemstede.

'Meer and Bosch' was named after the stately mansion and the surrounding grounds, acquired in 1885 by the Christian Foundation for the care of Sufferers from the Falling Disease, founded in 1882, as living quarters for the clergyman-director. The institute, modeled after the Bodelschwing Institutions in Bielefeld, Germany, started in a small garden building at the premises of the founder, Lady A. J. M. Teding van Berkhout (1833–1909), in Haarlem but by 1938 had grown into a conglomerate of many buildings for housing, care, occupation or education, of adults and children with chronic epilepsy. Whereas care, provided by deaconess brothers and sisters, had been the original task of the foundation, the second quarter of the 20th century brought a shift towards a more medical oriented approach. In 1930 B. Ch. Ledeboer (1897–1959) was appointed as the first medical director, working together and not any more under the still prevailing clergyman director. Within a few years he managed to have a modern clinic built on the premises, with observation wards for adults and children, laboratories and even surgical facilities. In 1934 the

Queen Emma Clinic was officially opened and it was there that De Vet, starting 22 November 1938, practiced part time, in addition to his work in the St. Ursula Clinic. De Vet strongly believed in the value of ventriculography and designed a movable and translucent model of the ventricular system for better understanding of the movement of air through the ventricles and for illustrating and teaching puposes.[50,51] He advocated that every patient with epilepsy should have at least one diagnostic encephalogram and from the register of surgical procedures of the Queen Emma Clinic[52] it is clear that he practiced what he preached.

From the 377 procedures performed between November 1938 and February 1942, less than 40 appear to have involved real neurosurgical interventions, including five resections of cortical scars or areas from which seizures could be elicited. Others concerned lesiectomies (glioma, angioma, meningioma, etc.) which De Vet himself did not consider 'epilepsy surgery'.[53] The vast majority of the procedures were suboccipital ventriculgraphies, usually performed by A. Verjaal (1910–1973), the later Professor of Neurology in Leiden but then first assistant to Ledeboer, the remainder some 20–30 bi-occipital trepanations for direct puncture of the ventricles, performed by De Vet, Verjaal assisting. In 1942 the clinics in Heemstede closed and all patients returned home in order to prevent the German occupation forces and their Dutch collaborators to take over the management of the clinics. The St. Ursula clinic remained active. Occasional surgeries for epilepsy, either as the main symptom or as a secondary phenomenon, were also performed elsewhere since neurosurgical departments by this time also had been established in other university clinics in the Netherlands. In the Valerius Clinic, associated with the Free University of Amsterdam, general surgeon C. van Gelderen actually performed some interventions, including a tumor case with seizures, guided by some of the earliest electroencephalographic (EEG) recordings performed in the Netherlands.[54] These early Dutch endeavors in the field of EEG by physicist L.J. Koopman, psychiatrist L.J. Franke, and physiologist J. ten Cate were discontinued, due to war conditions (Jonkman[1]).

After the war the neurosurgical activities in Heemstede were resumed but according to the register it was not until 1949 that some real surgical intervention, other than diagnostic procedures was performed. In that year de Vet was joined by Otto Magnus, who, due to the vicissitudes of war had worked in Zurich with W.R. Hess (1881–1973), and then trained in Neurology in London. In 1947 De Vet had suggested that Magnus, rather than starting a residency in neurosurgery, should pursue his earlier neurophysiologic interest and acquaint himself with electroencephalography (EEG). Following two more years of training in Montreal with H. Jasper (1906–1999) and W. Penfield (1891–1976), Magnus returned and introduced EEG both in Wassenaar and in Heemstede. Magnus also introduced acute electrocorticography (ACoG) as a regular procedure for epilepsy surgery and according to the register, from June 1949 to September 1954 17 cortical excisions, guided by ACoG were performed, either by P. Hanraets, pupil and later associate of De Vet or by De Vet himself, who has his last entry on 23 September 1954. After that time no neurosurgical procedures were performed in Heemstede and on arrival of A.M. Lorentz de Haas (1911–1967) as successor to Ledeboer the operating room, which had remained in use for minor surgeries, was closed. All epilepsy surgery activities thus were moved to Wassenaar but Magnus remained head of the EEG department, both in Wassenaar and in Heemstede, acting as a liaison between the two clinics until 1968.

In an early report, specifically mentioning epilepsy, De Vet reported 80 cases of epilepsy admitted to the clinic in Wassenaar between 1936 and 1938, 63 of them being symptomatic cases. No mention was made concerning number of surgeries or outcome.[55] In 1949 he reported on 105 operated patients with a good outcome (comparable to Engel I and II) in 50%. Most patients had lesions. In 15 patients he removed small areas of normal looking cortex where seizures could be elicited and from those 15 only 4 had a satisfactory outcome.[53] In 1962 Magnus compared the results of the first 45 procedures with ACoG with those of the earlier series and found them to be more or less equal[56]. In his last paper on the subject[57] De Vet however emphasised the value of ACoG in cases of non-lesional temporal lobe epilepsy. From a total series of 213 patients, operated for epilepsy in the period 1936–1969, 78 could be identified with psychomotor epilepsy, where 33 of these turned out to have a lesion. From the remaining 45, all operated with the help of ACoG by Magnus, 18 became seizure free and another 13 showed major improvement, an outcome far superior to the 1949 results.[53]

In 1969 De Vet retired from the St. Ursula Clinic and after his departure the interest in epilepsy surgery quickly diminished. Only a few procedures were performed in the following years and in the new Westeinde Hospital in The Hague to which the neurological and neurosurgical departments were moved in 1979 no epilepsy surgery was performed any more. By this time however the torch had already been taken over by another team, already evident in De Vet's 1972 paper[57] where he discussed the options of stereotactic intracranial EEG investigations, advocated its application in cases of bitemporal lobe EEG foci and illustrated his point by an X-ray picture of a skull with multiple intracerebral and subdural electrodes, 'Courtesy Prof. Dr. W. Storm van Leeuwen'.

Consolidation: The Dutch Collaborative Epilepsy Surgery Programme

Reference to stereotactic procedures had already been made by De Vet before. Like other neurosurgeons of the period he had been actively involved in psychosurgery and, well aware of the major drawbacks of both open or closed leucotomy techniques, he recognized the potential advances of multiple and successive microcoagulations, performed through chronic indwelling micro-electrodes, but considered the technique as yet insufficiently developed.[58] By the time of his retirement this had changed.

Willem Storm van Leeuwen (1912–2005) studied medicine in Leiden and specialized in physiology and neurophysiology with G. J. J. Rademaker (1887–1957). In 1945 he obtained his PhD on a thesis on cardiac arrhythmia, elicited by experimental injury of the central nervous system. Supported by a Rockefeller Fellowship he then spent some years in the UK with Lord Adrian in London and with W. Gray Walter in Bristol, where he obtained his training in EEG.[59] On returning to the Netherlands Storm van Leeuwen was one of the driving forces behind the further development of clinical

neurophysiology in the Netherlands. Following alternating appointments in Leiden and Utrecht he finally settled in Utrecht in 1959 as director of the department of clinical neurophysiology and of the department of brain research of the Medical Physical Institute (MFI) of the National Dutch organization for applied physical research (TNO). The fortuitous situation of clinical neurophysiologists such as Storm van Leeuwen, Magnus, and Portugese born Fernando Lopes da Silva, whom Storm van Leeuwen had brought to Holland from the UK, collaborating with physicists as Anton Kamp in Utrecht and Henk van der Tweel (1915–1997) in Amsterdam, resulted in major advances in recording techniques and equipment, innovative early methods of computer analysis, and the development of miniaturized radiotelemetry with depth electrodes which was to be decisive for the further development of psychosurgery and, in its wake, also of epilepsy surgery in the Netherlands.

Following some pioneer stereotactic coagulation procedures by a group of Dutch and Belgian neurologists and neurosurgeons, including Arthur Sonnen (1932–2000) and Jan van Manen [60] in 1971, largely through an initiative of Harry Meinardi and the Dutch National Commission for Epilepsy Research (CLEO) a working group for neuro-physio-surgery was constituted to discuss all Dutch patients for whom psychosurgical interventions were considered.[61] Medical, social and ethical impact of such interventions were considered to exceed the individual responsibility of individual doctors and requiring peer review and as such the working group, although initiated by some of the core members, soon obtained formal recognition by the Dutch health authorities. Storm van Leeuwen held the chair. Members were neurologists, psychiatrists, clinical neurophysiologists, and neurosurgeons actively involved in psychosurgery and came from different clinics in the Netherlands as well as from the Dutch speaking part of Belgium. Since gross leucotomy by that time was totally discredited the method of choice was chronic stereotaxic microcogulation as originally advocated by Crow *et al.*[62] but employing the electrodes developed originally for animal experimentation by Kamp and Lopes da Silva. Since at the onset it was clear that evaluation of epileptic patients for possible surgery would require comparable electrode types and stereotactic techniques it was decided that the activities of the working group should also include epilepsy and that epileptologists should participate.[61] Special multistranded depth electrodes and subdural wire and reed multi-electrodes were developed at MFI and a method was developed for the stereotactic implantation of two to six intracerebral electrodes, aimed at the hippocampus, amygdala and mesio-frontobasal cortex, combined with 8–16 narrow subdural reeds, guided by hand and fluoroscopy over wide areas of the lateral and basal frontal, temporal and centroparietal cortex of both hemispheres, all electrodes introduced through just two small bifrontal trephine holes[63] (Figure 10.3).

Although reaching fewer intracerebral sites than the orthogonal stereotactic approach, developed by Taillairach and Bancaud,[63] the Dutch approach performed excellently[64] and had the advantage of better access to the surface cortex bilaterally with less risk for intracerebral hemorrhage and with relatively minor surgical trauma, compared to the subdural strip and grid methods, developed shortly afterwards in the USA. All procedures, including those on patients from Belgium, were performed in Utrecht by neurosurgeon C.W.M van Veelen.

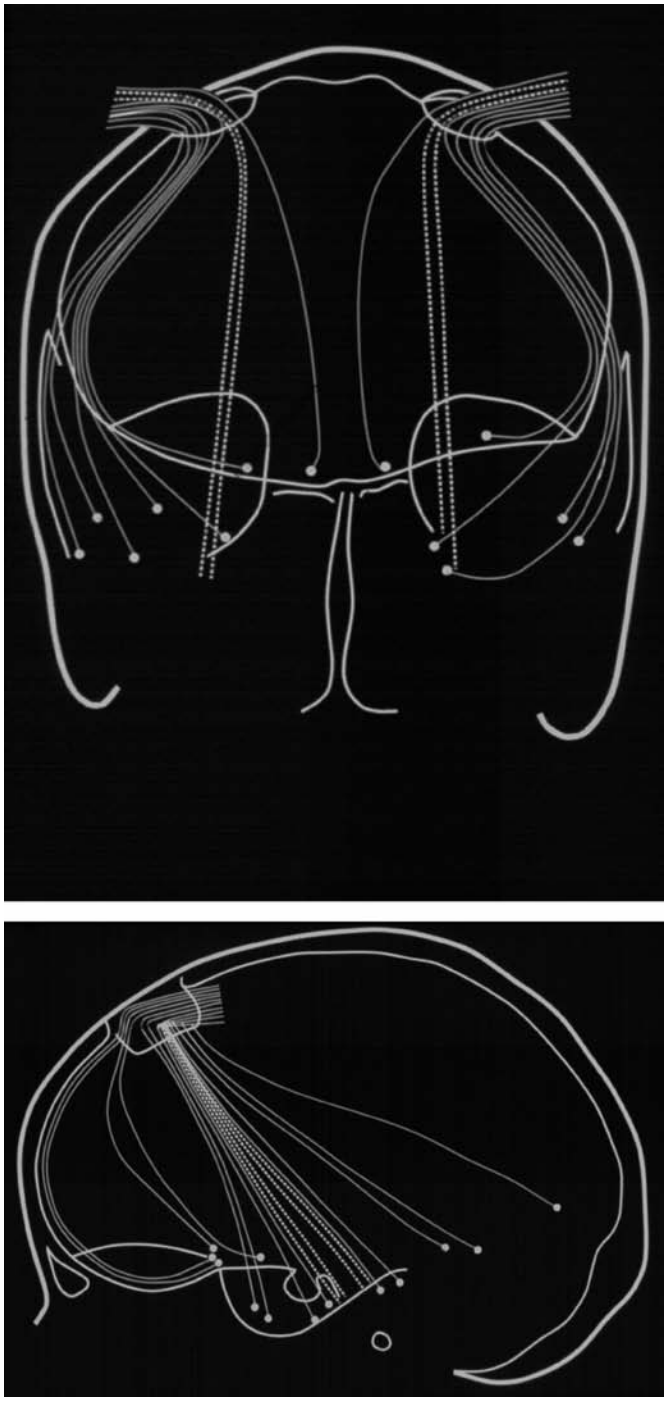

Figure 10.3 (a, b) Frontal and lateral scheme, drawn after postimplantation X-ray of a patient with bilateral subdural wire and reed electrodes (continuous lines) and four depth electrodes (dotted lines) in the mesilimbic structures, all electrodes implanted through small bifrontal trephine holes according to the method, developed by the group of Storm van Leeuwen, Lopes da Silva, and Van Veelen.[62]

Initially psychosurgery constituted the brunt of the working group's activities. Although at the time of Storm van Leeuwen's retirement in 1979 the number of such cases, was dwindling, the workgroup activities continued, stimulated by the arrival of C. D. Binnie, London and Cambridge trained clinical neurophysiologist, who in 1976 had taken up the position of director of the department of clinical neurophysiology at 'Meer and Bosch'. There he had created the first telemetric long term EEG and video monitoring unit in the country

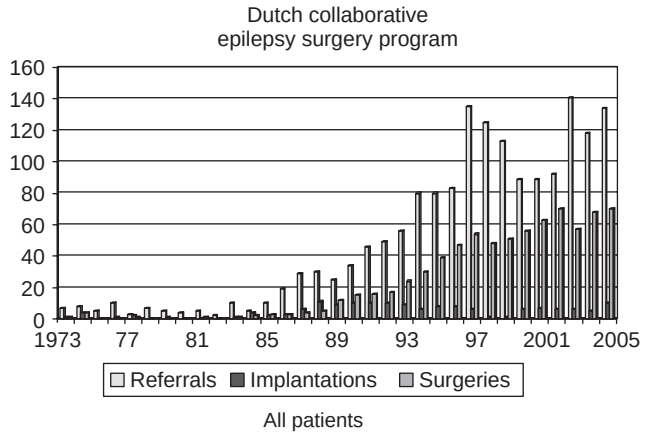

Figure 10.4 Dutch Collaborative Epilepsy Surgery Program activities 1973–2005: all patients A total of 1656 patients has been referred and evaluated resulting in 775 resections. 160 patients had intracranial recordings (135 bilateral or unilateral depth and subdural electrodes, 25 subdural grids).

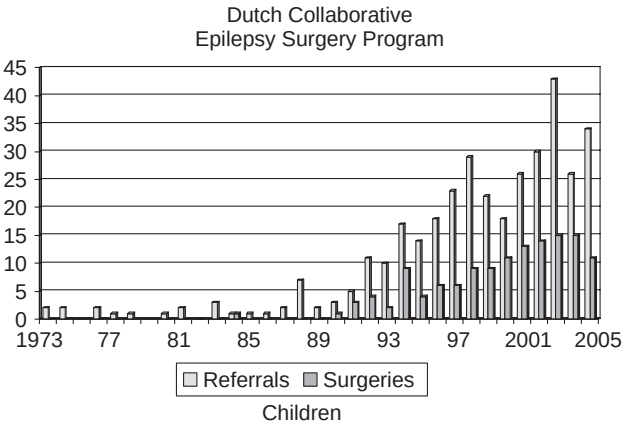

Figure 10.5 Dutch Collaborative Epilepsy Surgery Program activities 1973–2005: children, up to the age of 16 years. 357 children were referred of which 133 had surgery, with one exception all since 1990. Surgical procedures range from limited lesionectomies or partial resections to structural or functional hemispherectomies and a small number of anterior callosotomies.

where he could accommodate even depth implanted patients, who at that time could not be monitored in Utrecht.[66]

The emphasis now changed from psychiatry to epilepsy, at first still at a very low pace but, following the appointments, in 1985, of A. C. van Huffelen as successor of Storm van Leeuwen and of W. van Emde Boas on the position of Binnie, who returned to the UK, the program quickly expanded (Figure 10.4).

In 1989–1990 Van Emde Boas spent 5 months for additional training with F. Andermann and P. Gloor (1923–2003) in Montreal and on his return in Heemstede expanded the capacity for presurgical evaluation by creating a new 'non-hospital but home-like' three bed epilepsy monitoring unit, where, weather permitting, patients, including those with implanted electrodes, could be recorded, even while sitting outside in the garden. Van Huffelen, at the same time, prepared a medical technology assessment project and obtained government funding for the period 1990–1992.

The final report of this project, supervised by Van Huffelen, Van Veelen, and Van Emde Boas, was offered to the Dutch health authorities in 1993 and resulted in formal acceptance – and thus formal albeit hardly sufficient third-party payment – of epilepsy surgery, including the necessary presurgical evaluation for up to an initially 50 patient maximum per year, Utrecht Academic Hospital being the only recognized hospital allowed to perform these operations in close collaboration with the three specialized Dutch epilepsy centers.

By that time the constitution and procedures of the working group had drastically changed. With monitoring facilities now also available in the Epilepsy Centers Kempenhaeghe in Heeze and the Dr. Hans Berger Clinic in Breda, more clinical neurophysiologists and neurologists attended the meetings in Utrecht together with the neuropsychologists, responsible for pre- and post-surgical assessment and the Intracarotid Sodium Amytal test.[67] A second monthly meeting was organized in Heemstede for the clinical neurophysiologists only for a collective review of all the seizures, video and EEG, of the patients to be discussed in the next plenary session in Utrecht, where a brief summary would be presented. Other neurosurgeons joined van Veelen and pediatric epilepsy surgery, already practiced on a limited scale, got a major impetus when O. van Nieuwenhuizen, shortly afterwards to be appointed professor of child neurology in Utrecht, joined the group in 1991 (Figure 10.5).

Special MRI protocols were developed[68] and PET and occasional SPECT studies[69] were performed in selected patients, the former first in collaboration with the University clinic in Liege (Belgium)' and later in the Free University in Amsterdam, where in 1997 Magneto Encephalography (MEG) also became available. After lifting of the earlier imposed restrictions the university hospitals of Maastricht and of the Free University in Amsterdam joined the workgroup activities in 1997 and 2002.

While the number of referrals and surgeries steadily increased, until levelling off around 2002 (Figure 10.5) the number of intracranial investigations sharply dropped, then started to rise again following the introduction of Grids recordings in Utrecht under the supervision of Heemstede trained F. Leijten. Initially some Belgian patients continued to be referred to the Dutch program but this came to an end following the development of epilepsy surgery in Gent and elsewhere in Belgium.

Collaboration between programs on both sides of the border continued however, notably in the field of research in addition to multiple contacts between the Dutch program (since renamed 'National Working Group for Epilepsy Surgery' [LWEC] within the Netherlands and 'Dutch Collaborative Epilepsy Surgery Program' [DCESP] for international purposes) and international circles. Members of the group actively participated in many international meetings and van Emde Boas and van Nieuwenhuizen acted as commission members for the commission on epilepsy surgery and the subcommission for pediatric epilepsy surgery of the International League Against Epilepsy. Between 1973 and 2005 775 patients had been operated, the last overall results (on 338 patients operated up to 1998) published by van Veelen in 2001.[70] An overview of the papers published by participating workgroup members and associated research programs (Appendix) can be obtained through Pub Med.

Vagal nerve stimulation never was part of the activities of the LWEC although some of the member epileptologists and surgeons were or are involved in early pilot studies and in the current multicenter program for a limited number of VNS implants per year, accepted by the health authorities and coordinated by G. Hageman (Enschede) for adults and M. Majoie (Heeze) for children.

Growth of patient numbers and the increased complexity of presurgical work up of individual patients and of traffic in the densely populated Netherlands have made the process of regular, now two per month, general meetings in Heemstede and Utrecht an increasing burden on the participants and some members of the LWEC have advocated the creation of local teams, leaving only the most difficult cases for broad discussion in the central group. A team consisting of neurologists, neurophysiologists, neuropsychologists, and neurosurgeons from the University of Maastricht and Epilepsy Center Kempenhaeghe has started its activities in 2005, reviewing cases from the southern part of the Netherlands; the first resective procedures have recently been performed in Maastricht. However, it takes expertise also to recognize 'easy cases' inasmuch as these exist and the LWEC intends, with the development of teleconferencing techniques, to continue to monitor, coordinate, and guide all epilepsy surgery activities in the Netherlands.

Belgium

At the end of the 16th century Jean Baptiste van Helmont (1577–1644), the founder of the Iatrochemical School, which looked to chemical explanations of vital phenomena, from Leuven, was the first to write about the underlying mechanism of epilepsy in the Low Countries. He attributed epilepsy to a dysfunction of the orifice of the stomach where a duumvirate of stomach and spleen was thought to regulate functions of life. However, he also acknowledged that seizures could be provoked by strong emotions affecting the sensitive soul.[71] In modern times, it was only after 70 years of its independence from the Netherlands in 1830 that Belgium saw some early efforts in surgical treatment of patients with epilepsy. Crocq[72] mentioned 13 mostly posttraumatic cases from nine authors in his 1902 review and in that same year Lowie from Eecloo reported another patient at a major Flemish meeting.[73] Yet these activities, and comparable ones in the years to follow, remained isolated cases, performed by general surgeons and not incorporated in a structured program. The interest in neurosurgery and epilepsy in Belgium dates from immediately before the World War I. In 1905, Van Gehuchten began to film neurological and psychiatric patients, among some with epileptic fits; the original nitrate movies have survived and represent in fact the first Belgian films. The Great War, with 90% of the country under German occupation, represented a period of scientific stagnation. Only in Flanders Fields did some surgeons acquire great experience in traumatology. Noteworthy is the contribution by De Page who designed a special electromagnetic device used for removing deep seated shrapnel and bullets from the brain.[74] As the capacity of (neuro)surgical care on the battlefield was very limited, the Belgian Red Cross called upon the services of Muskens from The Netherlands to help setting up a unit for central nervous system war injuries in 1914. Immediately after the World War I, Paul Martin was the first Belgian surgeon who went to the USA for training in neurosurgery with Harvey Cushing and became head of the surgical laboratory at Harvard University. He later returned to Belgium to become the first professor of neurosurgery at the University of Brussels.[74] In the meantime, Van Gehuchten had joined forces with Jean Morelle, a neurosurgeon who had also trained in the USA and set up a nucleus of neurosurgery within the general surgery department at Leuven. A similar attempt was made at the University of Liège, where Christophe, who had worked with Frazier, Adson and Cushing, became lecturer in neurosurgery in 1933, probably the first of his kind in Europe.[74] However, the first independent neurosurgical departments were founded only after the World War II but initially there was no special interest for epilepsy surgery.

In fact, specialized epilepsy care in Belgium as such did not start until in the fifties of the 20th century. In 1955 academical neuropsychiatrists from the Universities of Gent, Brussels, Leuven, and Liège and other interested professionals founded the Belgian National League against Epilepsy. The league has survived to date but currently serves as an umbrella organization of two active regional leagues (one Flemish-speaking and one French-speaking) reflecting the federal nature of the Belgian state. According to a review by Sorel, by the end of the fifties in-patient facilities for epilepsy patients were available in neurological departments of 59 hospitals throughout the country.[75] In about 10 neurosurgical units nationwide occasional epilepsy surgery procedures were performed. In the late sixties and early seventies two institutions for residential care of refractory epilepsy patients were founded in Pulderbos and in Ottignies. Pulderbos, located in the Flemish-speaking part of the country, emerged from collaboration between the University Hospital of Leuven and a major health care provider. The 'Centre Neurologique William Lennox' was founded in 1972 and is associated with the French-speaking 'Université Catholique de Louvain'.

The first reports in the international peer-reviewed literature of epilepsy surgery in Belgium originate from Liège where in the mid-sixties A. Waltregny, a neurosurgeon and clinical neurophysiologist, performed experimental and human studies using invasive EEG recording based on the teachings of Gastaut and Bancaud in France.[64,76] Relatively few resective procedures were performed, however, without further contributions to the international epilepsy surgery literature. Many patients eligible for surgery were referred to epilepsy surgery centers in France, The Netherlands, and Western Germany.

In the beginning of the eighties P. Tugendhaft and J. Brotchi at Hôpital Erasme, an academical hospital associated with the French-speaking 'Université Libre de Bruxelles', performed a series of invasive EEG recordings using the methodology of Wyler from the USA. and initiated the first epilepsy surgery series in Belgium.[77] Neuropsychological assessment and intracarotid amytal procedures were routinely performed.

In 1990, the first comprehensive epilepsy surgery center in Belgium was established at Ghent University by P. Boon, and L. Calliauw, chair of neurosurgery at Ghent University Hospital. P. Boon, a neurologist and clinical neurophysiologist, trained at Winston-Salem, NC with Penry and at

Yale University with Williamson and Spencer. Soon E. Thiery, professor of neuropsychology at Ghent University and E. Achten, neuroradiologist at Ghent University Hospital, joined the team. Their collaboration resulted in the first multidisciplinary epilepsy surgery team in Belgium, evaluating and operating increasing numbers of patients and performing clinical research.[78,79] The first combined placement of depth and subdural electrodes in patients requiring invasive EEG recording, the first implantation of a vagus nerve stimulator in Belgium, and the first long-term treatment with amygdalohippocampal deep brain stimulation for temporal lobe epilepsy in Europe were all performed by their team. Over time the group in Gent came to include K. Vonck, a neurologist with special expertise in neuromodulation and D. Van Roost, a functional neurosurgeon with long-standing experience in epilepsy surgery, who trained with the neurosurgical team of Schramm at Bonn University Hospital.[80,81]

At about the same time, the team from the 'Université de Liège' headed by G. Franck and B. Sadzot, who had trained in Baltimore, USA, established a positron emission tomography unit in which patients with refractory epilepsy were systematically investigated. Most of these patients were referred from the Dutch Collaborative Epilepsy Surgery Programme in Utrecht.[69,82]

In the late nineties W. Van Paesschen, a neurologist who trained with Duncan and his group in London and J. Van Loon, a neurosurgeon, started with presurgical evaluation and epilepsy surgery at the 'Katholieke Universiteit Leuven'. Their group has a strong focus on non-invasive diagnostic tools such as ictal SPECT.[83] This was quickly followed by similar initiatives to establish epilepsy surgery programs at the 'Université de Liege' (headed by B. Sadzot and T. Grisar), the 'Cliniques Universitaires St-Luc' in Brussels (headed by K. Van Rijckevorsel and C. Raftopoulos), and in the 'Centrum voor Epilepsie en Psycho-organische Stoornissen', a private initiative in Duffel (headed by R. Hauman). The already active programme at 'Hôpital Erasme', Bruxelles, now directed by B. Legros and P. Van Bogaert, during the same period expanded its activities.

A major breakthrough in terms of acceptance by the health authorities and funding by the national reimbursement agency was the establishment of 'Reference Centers for Refractory Epilepsy' in 2000. Strict criteria were defined with regard to the necessary availability of technical infrastructure, human resources and neurological and neurosurgical expertise for academical centers to be recognized as a referral center for epilepsy surgery. The main purpose was to concentrate know-how in a limited number of centers, guarantee high quality standards and limit the costs. Only patients treated in such centers got reimbursement for presurgical evaluation and surgical procedures for refractory epilepsy.

After an initial phase during which six centers were recognized in 2000, presently four Reference Centers for Refractory Epilepsy are active in Belgium: in Gent (Universitair Ziekenhuis Gent), Leuven (Universitair Ziekenhuis Gasthuisberg), and two in Brussels (Hôpital Erasme, Cliniques Universitaires St-Luc). All have dedicated epilepsy surgery teams and follow a similar presugical evaluation protocol. In each center, video-EEG monitoring, 1.5T or 3T optimum MRI facilities, PET, SPECT, and neuropsychological assessment are available. Biannually, in each center quality and performance parameters are assessed by the national reimbursement agency. In 2003–2004, 300 patients annually underwent presurgical evaluation (including invasive video-EEG monitoring in 20 patients) resulting in 70 resective procedures and 60 implantations of a vagus nerve stimulator in patients who were not eligible for resective surgery.

Presurgical evaluation and epilepsy surgery are a strong impetus for performing clinical and experimental research. Epilepsy research in Belgium has basically followed the same timelines as the clinical development of epilepsy care described above. While scientific reports on epilepsy surgery related work were scarce until the 1980s, clinical researchers from Gent, Leuven, Bruxelles, Louvain and Liège have been increasingly active. Among the most published topics in the past 15 years are EEG source localization (Gent), optimal structural magnetic resonance imaging (Gent, Leuven), functional magnetic resonance imaging (Gent), PET (Liège), ictal SPECT (Leuven), magnetoencephalography (Gent), seizure anticipation (Gent, Leuven), antiepileptic drug research (all centers), vagus nerve stimulation (Gent), and deep brain stimulation (Gent, Bruxelles).[80–89] The groups from Gent and Liège have experimental animal facilities providing many relevant epilepsy animal models and they are active in the field of basic neurophysiology, neurostimulation and stem cell applications in epilepsy.[90–93]

Appendix: Core members[a] of the Dutch Collaborative Epilepsy Surgery Program workgroup 1980–2005

Secretariat and logistic coordination

E. van Wijk-Leenaars[5]

Clinical Neurophysiology / Epileptology

C.D. Binnie,[1*] M. Bourez-Swart,[5] G.J.F. Brekelmans,[1*] S. Claus[1], A. Colon,[3] W. van Emde Boas[1] (Chair 2003–present), J. Parra Gomez[1], A.C. van Huffelen[5], J. Jonkman*, V. van Kranen-Mastenbroek[7], F. Leijten[5], W. v.d. Meij[5*], J. Overweg[1*] (Chair 1990–1998), L. Reebok[4], H.E. Ronner[6], A.E.H. Sonnen[4†], W. ter Spill[4*], C.J. Stam[6], D.N. Velis[1], E. Veltman[3] (Chair 1999–2002), P.H.A. Voskuil[4*], L. Wagner[4], A.W. de Weerd[2], A. van Wieringen[1*]

Neurology / Epileptology

J. Bruens,[4†] R.M.C. Debets,[1] A. Elderson[5*], M.C.T.F.M de Krom[7], H. van Lambalgen[2], J. van Manen* (Chair 1980–1989), H. Meinardi[1*], Th. Rentmeester[3*], F.B.J. Scholtes[4*], R.T.M. Starrenburg[3*]

[a] Many persons have occasionally attended the meetings as guest or as short term participants. In this list only those that have been actively involved for the whole period or major lengths of time are listed. The members of the still existing subgroup for psychosurgery are not mentioned. For a list of members of the original group 1971–1979 see reference 61.

* Past member.

Paediatric Neurology

O. van Nieuwenhuizen,[5] W.O. Renier*

Neurosurgery

H. Baaijen,[6] J. Dings,[7] P. Gosselaar[5], G. van Overbeke[5*], P. van Rijen[5], C.W.M. van Veelen[5*], V. Visser-Vandewalle[7]

Neuropsychology

W.C. Alpherts,[1] M.L. Franken[3*], M.P. Hendriks[3], A. Jennekens-Schinkel[5*], M. Klein[6], J. Vermeulen[1]

Neuroradiology

L.C. Meiners,[5*] G.A.de Kort[5], L.M. Ramos[5*], T.D. Witkamp[5*]

Psychiatry

W.P. Haaijman*

Research associates

A.P. Aldenkamp,[2] J.Arends,[2] E. Arronica[9], P.A.J.M. Boon[2], A.van Dieren[5], B.W. van Dijk[6], W.H. Gispen[8], J.A. Gorter[9], P.N. de Graan[8], M. v.d. Heide[1], G. Hoogland[8], G.J. Huiskamp[8], F. Jansen[5], S. Kalitzin[1], F. H. Lopes da Silva[9], H. Meeren[6], J. C. de Munck[6], P. Ossenblok[2], E.A. Proper[8], J.P. Pijn[1 †], N. Ramsey[5], G.J. Rutten[5], P. Suffczinski[1], D. Troost[9], M. Vreugdenhil[9], W. J. Wadman[9]

Participating Hospitals

[1]Epilepsy Centre Meer and Bosch; SEIN, Heemstede, [2]Epilepsy Centre Heemstaete; SEIN, Zwolle, [3]Epilepsy Centre Kempenhaeghe, Heeze, [4]Epilepsy Centre Dr. H. Berger kliniek, Breda, [5]University Medical Centre Utrecht, [6]Free University Medical Centre Amsterdam, [7]Academic Hospital Maastricht

Main Associated research groups

[8]Rudolf Magnus Institute of Neuroscience, Utrecht, [9]Swammerdam Inst. of Life Science, Amsterdam

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11 History of epilepsy surgery in the Middle- and East-European countries and Russia

P Halász

Epilepsy surgery in the Middle- and East-European region and in Russia developed under the influence of the USA and of the French schools. In the majority of countries a strong neurosurgical school developed at the beginning of the 20th century, and epilepsy surgery was built up with a more or less delay on a double basis: on classical neurosurgery and on independently developing clinical neurophysiology. The two disciplines have been amalgamated by the emerging clinical epileptological knowledge throughout the world in the multidisciplinatory assessment of epilepsy surgery. In these countries the development of epilepsy surgery was severely hindered by the information blockade due to the realm of the antidemocratic political power and to the delayed application of the contemporary neuroimaging techniques due to economical reasons. Presently the development of epilepsy surgery practice reached the international standards of leading centers in the world in Poland, Czech Republic and Hungary.

Poland

In the second half of the 19th century surgical treatment was directed to vascular surgery, mainly on the sympathetic system, according to the theory that the disturbance in blood supply, especially vasospasm, was the direct cause of the epileptic seizure. R. Baracz in 1888 and 1893 published papers 'On the ligation and resection of the vertebral arteries and the resection of sympathetic nerve for treatment of spontaneous epilepsy'. In the same year (1893) J. Bogdanik published a similar paper 'On the resection of sympathetic nerve in treatment of spontaneous epilepsy' and found improvement after such operations. Later on this procedure was applied by Raum and others as well.

Later it was held that epilepsy is the consequence of the collection of cerebrospinal fluid on the surface of the brain in various kinds of cysts and can be treated by trephination and decompression. Decompressive trephinations were used by Baracz in 1890, Krajewski in 1894 and 1899, Schramm in 1899, and Raum in 1900. A. Domaszewicz and J. Zaczek published the paper (1922): 'On the surgical treatment of epilepsy with personal experience' describing the operative findings and the results of the decompressive craniotomy.

Founder of the modern Polish neurosurgery was Jerzy Choróbski (1903–1986), head of the Department of Neurosurgery in Warsawa. He was Penfield's pupil spending several years working with him and started neurosurgery in Poland in 1935. At the beginning, during World War II and directly after, he performed several procedures for removing brain scars in cases of posttraumatic epilepsy, so important at that time. As soon as conditions after the war allowed and necessary equipment was obtained, among others EEG apparatus, he carried out the first surgery of focal, cryptogenic epilepsy on 27 November 1957 by temporal lobectomy. Diagnosis was derived from the clinical picture, PEG, EEG, and was proved intraoperatively by electrocorticography and brain electrostimulation. Later Choróbski was doing mostly temporal resections or, in special cases, hemispherectomy.

The epilepsy surgery team included L. Stępień and J. Bidziński (neurosurgery), T. Bacia (electrophysiology), all trained at the Montreal Neurological Institute and J. Wislawski (neuropathology). After Choróbski's retirement, the next head of the Department, Lucjan Stępień, continued this work with the above mentioned co-workers. Anatomical hemispherectomy was replaced by functional hemispherectomy. Extensive electrophysiological non-invasive investigations included various pharmacological activations and whole night physiological sleep. New diagnostic methods were consequently introduced: the Wada test (1960), psychological examination, invasive diagnosis as stereotactically implanted chronic electrodes, chronic epi- and subdural electrodes (Bidziński and Bacia in 1974). PEG was replaced by CT and NMR, and isotope studies were introduced. The results of their work were published in several publications with very long follow-up of several hundred patients and presented at international meetings.

Beyond resective surgery, other methods, such as stereotactic lesions (amygdala, Forel's field, Bidziński in 1981) and cerebellar electrostimulation (Bidzinski and Bacia in 1981) were tried with questionable results.

The Next head of the Department, J. Bidzinski, continued epilepsy surgery and introduced anterior callosotomy and vagal nerve stimulation in Poland (1990). The present head of the Department, Prof. A Marchel with co-worker A. Rysz, are continuing the tradition of epilepsy surgery in this department with electrophysiology.

As the surgical treatment of epilepsy became more popular, new neurosurgical centers started to offer surgical treatment. E. Mempel in Warsawa for many years did stereotactic

amygdalotomy in patients with emotional disturbances in epilepsy and introduced acute stereoEEG in 1968. Since 1961, Z. Huber in Poznań has performed several temporal lobectomies in adults and recently in children. Specially important was the establishment of an epilepsy surgery center for children at the Children's Hospital, Mother Health Center in Warsawa, in 1995 (head, M. Roszkowski.), and at the Children's Hospital in Lodz, in 2001 (head, L. Polis). In these centers children are treated up to 16 years of age. Recently two more neurosurgical departments joined the centers doing epilepsy surgery: in 2002 the Department of Neurosurgery in the Ministry of Administration Hospital in Warsawa (head W. Maksymowicz) and in 2004 the Department of Children's Neurosurgery Medical University in Katowice (head M. Mandela).

Russia

Epilepsy surgery in Russia and the former Soviet Union dates back to the end of the 19th and the beginning of the 20th centuries. In his 'clinical lectures' published in St Petersburg in 1898, A. Tauberg described cases of surgical treatment of 'cortical epilepsy' after brain trauma. F. Rein (1897) published a paper 'Results and indications for the surgical tratment of Jacksonian epilepsy'. V. A. Muratov considered Jacksonian type seizures to be the indication to surgery. S. Timopheev (1913) and L. Pusepp (1919) reported long-term follow up of patients operated because of 'Jacksonian epilepsy'.

There were also several attempts to treat non-focal epilepsies surgically at that time. Various types of operations has been suggested, including operations on the autonomic nervous system. Later the idea of surgical treatment of focal epilepsies was supported by the famous Russian neurosurgeon N. Burdenko.

Since the middle of 20th century epilepsy surgery has been developed in several regions of the Soviet Union: in St Petersburg Bechterewa, in Tbilis, Georgia (P. Saragishvily and P Chencheli), in Kiev, Ukraine (A. Romodanovĺ), in Sverdlovsk (now Ekaterinburg) (D. Shefer), and in Omsk (Yu. Savchenko). Stereotactic methodology of the Paris school was the basis of surgical interventions in these centers. Several papers and books dedicated to epilepsy surgery have been published in the Russian language by the above-mentioned authors.

Presently in Russia, epilepsy surgery is being performed in St Petersburg (V. Bernsev), Ekaterinburg (A. Shershever), Viatka (B. Bein), and Omsk (A. Savchenko) on a considerable number of patients. The basic diagnostic disciplines, the diagnostic system used, the participation of neuroimaging methods in the presurgical procedure are deviating in several aspects from the contemporary European and USA epileptological standards. Evidence based evaluation of the results have so far not been published.

Five years ago a joint surgery program was established in Moscow between the Department of Neurology and Neurosurgery of the Russian State Medical University and the Institute of Neurosurgery, based on a multidisciplinary team. This team decided to join to the contemporary epilepsy surgery programs in Europe using the same standards, evaluation and surgical methods. More than 400 patients have been evaluated and from them 58 patients selected for presurgical evaluation, 30 patients were operated, mainly on the temporal lobe, with good results.

Romania

The founder of Romanian neurosurgery was Prof. Dimitrie Bagdasar, trained in Prof. Cushing's Department in Boston, and the first dedicated neurosurgical department in Bucharest was founded by him in 1935. His follower Prof C. Arseni was the next determining leader in neurosurgery until 1989.

The modern era of Romanian neurosurgery was introduced by Prof. Al. Constantinovici and later by Prof. A.V. Ciurea. In 1993, a large neurosurgical hospital was established in Bucharest, named 'Bagdasar-Arseni', having departments for general neurosurgery, pediatric nerosurgery, spine neurosurgery, and adult neurosurgery. In March 2005 a neuroimaging department was added.

Epilepsy surgery is still restricted to resective procedures of standard temporal lobectomies (3–4 yearly), a few tailored temporal surgical procedures (5–7 yearly) and 3–4 extratemporal resections yearly, in the last three years.

Within this hospital a multidisciplinary team is starting to perform epilepsy surgery together with the Romanian National Reference Center of ILAE ruled by Dr. R. Rogozea. They are equipped with video-EEG, SPECT, and 1.5 Tesla MRI, using special 'epilepsy protocols', they recently introduced cortical mapping by subdural electrodes, and transcranial magnetic stimulation. They do not have as yet PET, fMRI, or MEG.

Czech Republic

Epilepsy surgery in the Czech Republic (at that time part of Czechoslovakia) started in departments of neurosurgery of Medical Faculties of Charles University in Prague and Hradec Králové. Since 1956 patients with epilepsy were operated in the Department of Neurosurgery of Faculty of General Medicine of Charles University and the Military Hospital in Prague. There were two young associate professors (Šourek and Vladyka) deeply interested in epilepsy. At first they performed excisions of cortical foci and temporal lobe resections. Stereotaxic operations were introduced later.

At the beginning surgery was performed only in patients with intractable epilepsy lasting for tens of years. Therefore the number of successful outcomes was relatively low but it increased with the shift to patients with a shorter history of therapy resistant epilepsy. Šourek and Vladyka introduced a method of local cooling of the temporal lobe with the aim to open the blood–brain barrier and then apply intravenously a bolus of an antiepileptic drug. Until 1974 they used this method on 71 patients and approximately 25% of them remained seizure free, unsuccessful operations also represented 27% of patients and the remaining patients exhibited different degrees of improvement.

The number of neurosurgery departments interested in epilepsy progressively increased so that there are at present at least seven departments performing more or less frequent

epileptosurgical operations (Prague, Brno, Hradec Králové, Plzeň, and Olomouc).

Modern techniques, including video-EEG studies and intracranial explorations, were introduced during the 1990s. The Homolka Center in Prague had been educated primarily in English-speaking countries, and subdural recordings were the dominant method of invasive explorations (62%). The Epilepsy Center Brno was based on the model of a French school using the stereo-EEG method when invasive intracranial detection was necessary (92%). A recent analysis of the surgical results of the two centers in 248 adult patients with post-surgical follow-up of at least two years displayed Engel I in 58.9%, Engel II in 15.5%, Engel III in 13.3%, and Engel IV and V in 11.3%.

Turkey[2–6]

Epilepsy surgery has a relatively long history in Turkey although a modern teamwork approach was started during 1990s. Prof. Kenan Tukel (Figure 11.1) who was a pupil of Penfield and Jasper in the Montreal Neurological Institute established the first EEG lab in the early 1950s in Istanbul University. However, the first case report related to epilepsy surgery was published from Hacettepe University Medical Faculty, Ankara in 1960 by V. Turkmen and A. Erbengi. It was about a patient with infantile hemiplegia operated by hemispherectomy. The first electrocorticography (ECoG) during surgery was applied again in the same hospital in 1965 where epilepsy surgery gained speed with the efforts of O. Kalabay and V. Bertan from the departments of neurology and neurosurgery. In 1986, A. Erdem performed extratemporal cortical resections guided by ECoG in Ankara University. After being trained by G. Yasargil in Zurich, A. Erdem in Ankara and later E. Ozyurt in Istanbul introduced selective amygdalohippocampectomy in the early 1990s. Epilepsy surgery teams working in a multidiciplinary fashion were established in 1993 in Hacettepe and 1995 in Cerrahpasa Medical faculties and have continued since then with addition of different centers including Gazi University, Istanbul Medical Faculty, Marmara University and others.

Estonia[7–11]

The founder of the national school of neurosurgery in Estonia was Professor Ludvig Puusepp (1875–1942) who operated 318 epileptic patients during 1901–1920. Thereafter, the summary of operations in 1921–1930 (1–5 cases per year) were published.

During the following years the number of operations have fallen dramatically, primarily due to effective medical treatment. In Tartu, EEG has been available since 1961, intraoperative electrocorticography (ECoG) since 1967, computerized tomography scanning since 1983, and magnetic resonance imaging since 1992. In 1996, the measurement of AED concentration just became available for routine use.

Long-term video-EEG has been available in Tartu since 2003. In recent years all patients for epilepsy surgery were investigated in long-term video-EEG (only scalp-electrodes). An average of two patients per year has been operated, all typical MRI-positive hippocampal temporal lobe epilepsies. ECoG was performed in 50% of the cases.

Figure 11.1 Dr. Kenan Tükel as a member of the Montreal team in 1952.

Latvia[12–17]

Episodical epilepsy surgery in the case of symptomatic disease (mainly tumors) in the territory of Latvia was performed at the beginning of the 20th century (A. von Bergmann, P. Klemm, L. Bornhoupt, E. von Schwartz in Riga's 1st Hospital). During the 1920s and 1930s neurosurgical operations in 3 hospitals in Riga were performed by general surgeons (V. Minz, J. Jankovsky, P. Mucenieks, A. Udre, P. Stradins, K. Dolietis *et al.*), and in rare cases neurosurgical operations were made for cerebral disease with epilepsy.

In the year 1939, K. Dolietis became the first certified neurosurgeon in Latvia and operated several patients with symptomatic epilepsy. At the end of the World War II, K. Dolietis emigrated to Sweden.

Development of neurosurgery continued in Riga's 1st Hospital; in 1946, the Clinic of Neurology and Neurosurgery was opened (A. Liepukalns and K. Arajs).

In 1969 I. Purins organized the Neurosurgical Center on the basis of P. Stradin's Clinical Hospital in Riga. Soon after that T. Apinis and Z. Grinbergs, doctors of this hospital, made the first steps to specialized epilepsy surgery after practices in the clinics of Moscow and Leningrad. The main method for epilepsy surgery was temporal lobectomy. Sometimes intraoperative cerebral surface electrodes were used for more precise diagnosis of the lesion locus.

Other types of operations were frontal lobotomies, gyrotomies, callosotomies; some hemispherectomies were also performed. Fifteen operations of intracranial superficial hypothermia in patients with epilepsy did not give any influence to the disease course.

A total of 145 operations for epilepsy were registered in this hospital during the period from 1974 to 1988. Epilepsy surgery in other hospitals of Latvia at this time was not very significant. Recently epileptic patients were selected for surgery in two neurosurgical departments of Riga: in the Clinical Hospital 'Gailezers' and in the P. Stradin's University Hospital. The surgery for symptomatic epilepsy due to cerebral tumors, dysplasias, heterotopias, mesial sclerosis etc. is accentuated; the number of operations of such type is approximately 20–30 per year. The new technologies (neuronavigation and invasive electrode techniques) are also used in the epilepsy surgery.

Lithuania

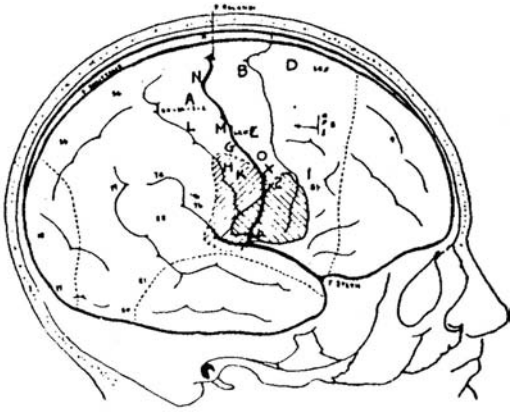
The first specialized neurosurgery unit in Lithuania was established in 1951 at Kaunas Clinical Hospital (Kaunas University Hospital at present). The start of epilepsy surgery took place in 1974 when the first temporal lobe resection was performed by doctors Henrikas Juozakas and Vytautas Paškauskas. Since 1976 subpial cortical suction, and since 1978 stereotactic hippocampo-amygdalotomy have been introduced, the latter also being performed nowadays. The stereotactic method for epilepsy surgery has been introduced and is still being developed by docent Juozas Šidiškis. In 1980 the Neurosurgery Clinic was established in Kaunas, with six specialized neurosurgery units. The Unit of Functional Surgery was a specialized unit for epilepsy surgery and microneurosurgery, with Professor Egidijus Jarûemskas as the Head until 1998, and Dr. Jonas Gelūnas until 2001. Professor E. Jaržemskas was the one who developed epilepsy surgery in Lithuania. Also, he was the founder and the president of the Society for Epileptology of Lithuania, which joined ILAE as a chapter in 1995. In 2001 the Neurosurgery Clinic was reorganized, and a specialized unit for cerebral surgery was established, with the Sector for Epilepsy Surgery included and headed by Dr. Arūnas Žobakas.

The diagnostic method implanted depth electrodes was introduced in 1982, and the use of subdural electrodes for the localization of the epileptogenic focus in 1989. Sleep EEG and video-EEG for presurgical diagnostics have been introduced at Kaunas University Hospital since 2000. The development of comprehensive presurgical multidisciplinary evaluation is one of the strategic plans at Kaunas University Hospital for the near future.

Hungary[18–21]

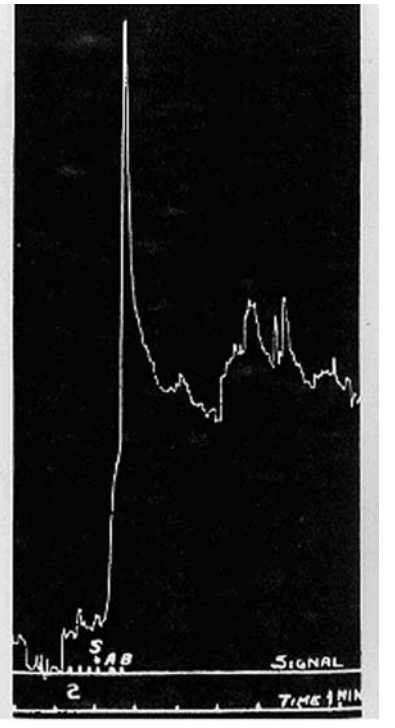
Kálmán Sántha and István Környey, friends and legendary personalities in the Hungarian history of neurology contributed equally to establish neurosurgery in the 1930s in Szeged and later in the 1940s in Pécs and Debrecen. István Környei was educated in Boston and Ann Arbor, Kálmán Sántha (Figure 11.2) in Montreal by W. Penfield, supported by the Rockefeller fellowship. Sántha, together with Cipriani, was the first to provided evidence that during an epileptic seizure it was not vasoconstriction (as was stated in the theory of Mayer) but just the opposite procedure, an important elevation in blood flow, that occured (Sántha, Cipriani, and Penfield 1938) (Figure 11.3). This work should be held as a first move toward the contemporary development of the ictal SPECT method. The first decisive steps of Hungarian epilepsy surgery were taken by J. Hullay in Debrecen, a pupil of Sántha, who reported on 50 temporal lobectomies as early as 1958.[18,19] Later in the 1970s in the same institution (Department of Neurology, Medical University of

Figure 11.2 Prof. Dr. Kálmán Sántha.



(Case 1.) Thermocouple positions are represented by points 1 and 2. Letters refer to stimulation points. The shaded area is the approximate location of the epileptogenic lesion.

(a)



(Case 1.) Attack III. Blood flow record with the thermocouple in position 2. Stimulation was at point X (Fig. 4) indicated by S on the signal line. The attack was recognized by the operator at A on signal line and was over at B.

(b)

Figure 11.3 Registration of blood flow changes during experimental and human epileptic seizures. Sántha and Cipriani MNI, 1938.

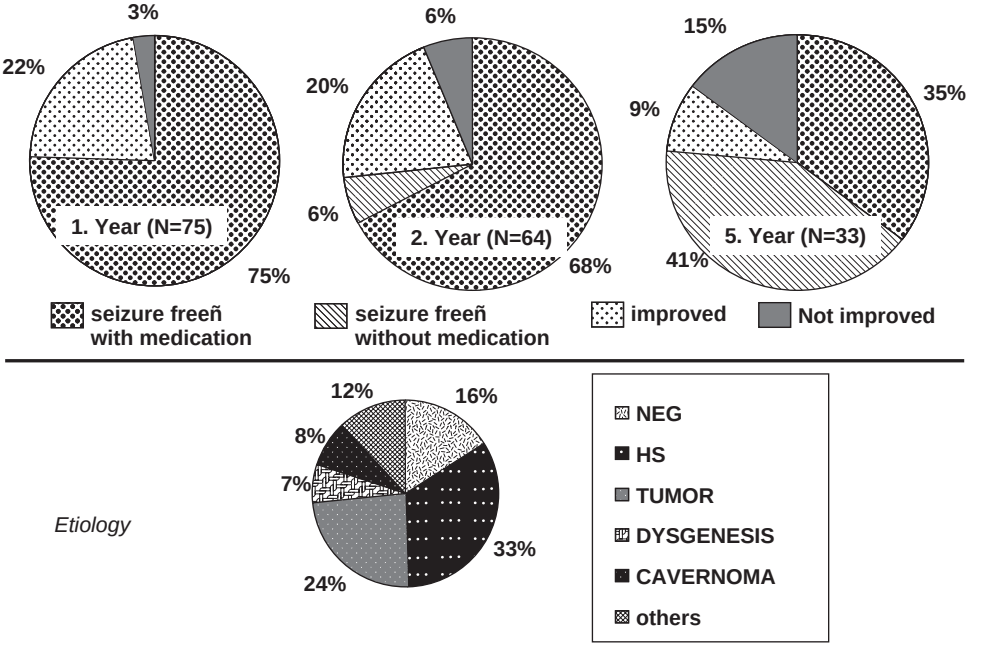


Figure 11.4 Surgical results, TS, TLE (1989-2001) National Institute of Psychiatry and Neurology.

Debrecen) within the framework of the epilepsy surgery program, invasive presurgical monitoring with the Bancaud–Tailerach stereotactic methods was carried out on several patients.[20]

The new wave of modern epilepsy surgery was started in the 1990s with the foundation of a 'Co-operative epilepsy surgery program' in which under the leadership of the National Institute of Psychiatry and Neurology, Epilepsy Center, several neurological institutions, and the National Institution of Neurosurgery participated including the Bethesda Children Hospital where a video-EEG monitoring unit has been working since 1997.[21] The number of patients involved and operated using the presurgical protocol is 20–30 yearly. The overwhelming majority of surgical interventions are partial temporal lobectomies in therapy resistant MTLE syndrome, but a few extratemporal surgeries are done yearly with invasive presurgical evaluation by subdural strips and grids. Results of temporal lobe surgery are illustrated in the Figure 11.4. In 2005 a new epilepsy surgery program was started in Pécs in the Neurological Clinic of the Medical University.

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12 Epilepsy surgery in Canada

W Feindel

The Montreal School

From 1934, Wilder Penfield with his surgical partner William Cone, their associates and many successors, developed at the Montreal Neurological Institute a center that became known world-wide for its systematic surgical treatment, research and teaching related to epilepsy (Figure 12.1).[1–6] Following Victor Horsley's pioneer efforts,[7] many surgeons in North America ventured to operate on patients suffering from seizures related mostly to cerebral trauma or tumors.[8,9] But their reports were often a litany of failures. Harvey Cushing had treated patients with seizures by surgery under local anesthesia and was the first to report mapping by electrical stimulation of the sensory cortex.[10] But Cushing centered his main interest on brain tumors, noting in 1932 to Wilder Penfield his former student,

> at all events, you can see that I, too, just thirty years ago was extirpating a cortex for epilepsy. If I had the industry and ability that you and Foerster combine, I might have gone ahead with it and made something of it. But I soon dropped it for things I thought I could do better.[11]

While at Columbia-Presbyterian Hospital in New York, in the 1920s, Penfield had taken a special interest in the problem of how a wounded brain heals, hoping that a better understanding would lead to improvement in excision of brain lesions, such as the post-traumatic scars associated with epilepsy.[5,11] He pursued this interest by going to Madrid in 1924, where he studied with Ramon y Cajàl's brilliant student Pio del Rìo-Hortega the role of neuroglia and microglia in brain healing, tumors and inflammation.[12]

As the first English speaking pupil of the Cajal school of neurohistology, Penfield returned to New York and applied his unique expertise to neurosurgical problems, and especially to epilepsy. Then in 1928 during his transition between New York and taking up neurosurgical practice in Montreal, he spent six months with Otfrid Foerster in Breslau. Here he learned the technique of electrical stimulation of the cortex with the patient awake under local anesthesia. He also took advantage of his familiarity with the Spanish methods to study the histology of the meningo-cerebral cicatrix in a dozen patients, mostly with head injuries, upon whom Foerster had operated for seizures.[13]

In September 1928, Penfield arrived in Montreal on the invitation of Edward Archibald to take over his neurosurgical practice at the Royal Victoria Hospital associated with McGill University. Archibald had been a student in 1906 of Sir Victor Horsley and Sir William Gowers at the National Hospital, Queen Square, and thus became the first surgeon in Canada to focus on neurosurgery. In 1908, he published the 375-page monograph on 'Surgical Affections and Wounds of the Head' in Bryant and Buck's *American Practice of Surgery*.[90] It was the same year that Harvey Cushing's extensive review of 259 pages on neurosurgery appeared in Keen's *Surgery: Its Principles and Practice*.[91] But Archibald began to take greater interest in thoracic surgery, in which he would become one of the American leaders. He also turned to the problem of post-graduate surgical education and directed his influence to establishing the American Board of Surgery.

Earlier at McGill University, William Osler was a keen protagonist for the emerging specialty of neurosurgery. From 1869 to 1884 he performed a thousand autopsies at the Montreal General Hospital. Among these, he reported many examples of neurological disorders, including epilepsy.[14,15] In commenting on the first operation for a brain tumor performed by Rickman Godlee in 1884 at London, Osler compared his own case where a post-mortem examination in 1883 disclosed a small glioma in the leg center of the cortex. This had caused Jacksonian seizures for twelve years, eventually ending in a fatal bout of status epilepticus: 'an instance', Osler wrote, 'in which operation would have been justifiable and possibly have been the means of saving life'.[16] Osler's spirited humanism and his positive attitude toward brain surgery influenced the field of neurosurgery through his friendships with both Harvey Cushing and Wilder Penfield.[17,18]

The Royal Victoria Hospital, Montreal (1928–1934)

In November 1928, two months after Penfield moved with his surgical partner William Cone from New York to Montreal, he performed his first operation at the Royal Victoria Hospital for focal epilepsy. (Figure 12.1) The young patient (RM) had fallen from a horse ten years earlier when he required surgery for a right-sided subdural hematoma and brain contusion. He developed seizures with increasing frequency, from 5 to 20 a day.

Eventually, this complex post-traumatic epileptogenic lesion required three operations to control these intractable seizures. At the first procedure, a small area of cortex was

Figure 12.1 Wilder Penfield (left) and William Cone, the neurosurgical partners, at the Royal Victoria Hospital, 1932.

excised near the motor strip that was defined by stimulation. The attacks continued. A second exploratory craniotomy followed a few months later to expose the frontal lobe on the opposite side; no abnormalities were found so no removal of any sort was made. For the third and final operation, three years later, Stanley Cobb and William Lennox came from Boston as consultants. Cobb's sketch and Penfield's comments (in bold letters) show the sites of the stimulation responses and delineates the thin scarred cortex of the temporal area that was widely resected (Figure 12.2).

Penfield referred to this as his first temporal lobectomy for seizures. He had applied stimulation and excision techniques learned in Foerster's clinic at Breslau (Foerster and Penfield, 1930b) In the first few years after operation, the patient had a greatly reduced number of seizures. After starting dilantin in 1939, his attacks numbered four in the next 13 years.[20]

In 1930, Penfield listed the neurosurgical cases for the preceding two years at the Royal Victoria Hospital. Among the 325 operations carried out by him and William Cone, there were fourteen examples of surgery for focal epilepsy. The successful transfer to Montreal of the laboratory of neurocytology, which they had started in New York, was already attracting students from the United States and abroad. During this period Penfield edited for publication a three volume multi-authored work destined to become a neurological classic, *Cytology and Cellular Pathology of the Nervous System*.[21]

The Montreal Neurological Institute

After a refusal and several delays, the Rockefeller Foundation responded in 1932 to the proposal of Wilder Penfield and McGill University for a Neurological Institute 'to provide,' Penfield hoped, 'a center for neurological thought that would serve the whole continent.' He envisaged clinical neurology and neurosurgery carried on in the same building that contained laboratories for research in neuropathology, neurophysiology and the anatomy and psychology relating to the nervous system.[22]

The Montreal Neurological Institute (MNI) opened its doors in 1934. An interesting hybrid, it was unique in its time, a 50-bed hospital for patients with neurological disorders, combined with a research center for the scientific study of the nervous system and a teaching Department of Neurology and Neurosurgery for McGill University.

With the provision of endowment by the Rockefeller Foundation of $1,000,000, further support garnered from generous citizens in Montreal as well as ongoing pledges by the City and Provincial governments for hospital support, the stage was set and the actors were in place to carry out Penfield's master plan.[5,20,23] Penfield and his surgical partner, William Cone, expanded their studies on the histopathology of brain scars and brain tumors with an enthusiastic and ever growing team of young assistants. They made persistent efforts to treat intractable epilepsy caused by trauma or tumors, applying the Foerster technique to score some brilliant successes. At multidisciplinarian weekly conferences, seizure patterns of patients were scrutinized in great detail, catalogued, and matched with the type and location of the lesions predicted by X-ray and EEG and as revealed and photographed at operation. Meticulous analysis of hundreds of stimulation points were plotted out to constitute brain maps of the sensory and motor areas that gave more detail than the earlier maps published by Horsley, Foerster, Krause, and Cushing.[24,25] These findings extended eventually to the definition of speech areas[26] and to the complex problem of how the brain remembers.[27,28,29]

Maximal removals of frontal tumors and scars causing epilepsy resulted in surprising retention of intellectual functioning in the patients as determined by.[29,30] Hebb's studies on Penfield's patients also activated the field of clinical neuropsychology which at the MNI over many years has been of critical importance for the pre- and post-operative evaluation of patients.[31]

Cortical stimulation: the homunculus

In 1937, Penfield with Edwin Boldrey reviewed 163 patients, who were operated upon under local anesthesia and in whom the motor-sensory responses to cortical stimulation were carefully plotted. These composite stimulation maps became familiar in the numerous publications from Penfield and his team over the years. Their report marked also the first appearance of the 'homunculus' (Figure 12.3) who would later appear in several guises (Figure 12.4) to highlight the cortical localization subserving anatomical regions of the body (Penfield and Rasmussen, 1950; Penfield and Jasper, 1954).

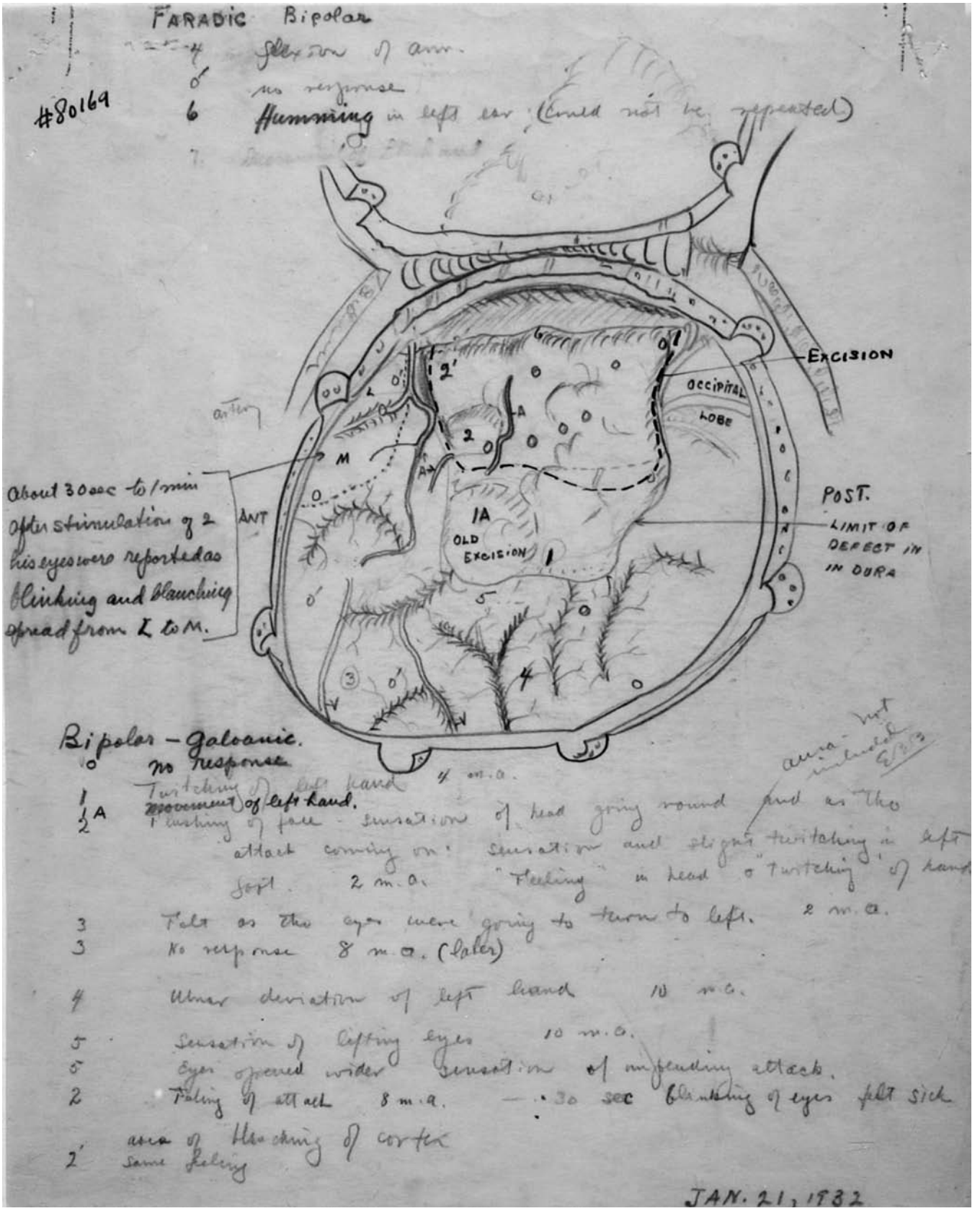


Figure 12.2 Penfield's sketch and notes during the operation on patient R.M. The brain is upside down as viewed by the surgeon, with the frontal lobe to the left. Two excisions, outlined by dashed lines, include a small area in front of the motor cortex (1A) and a much larger resection of the temporal lobe shown in the upper part of the sketch. Penfield's notes are in bold script; the notes in finer lettering and possibly some of the details of the sketch are in Stanley Cobb's hand.

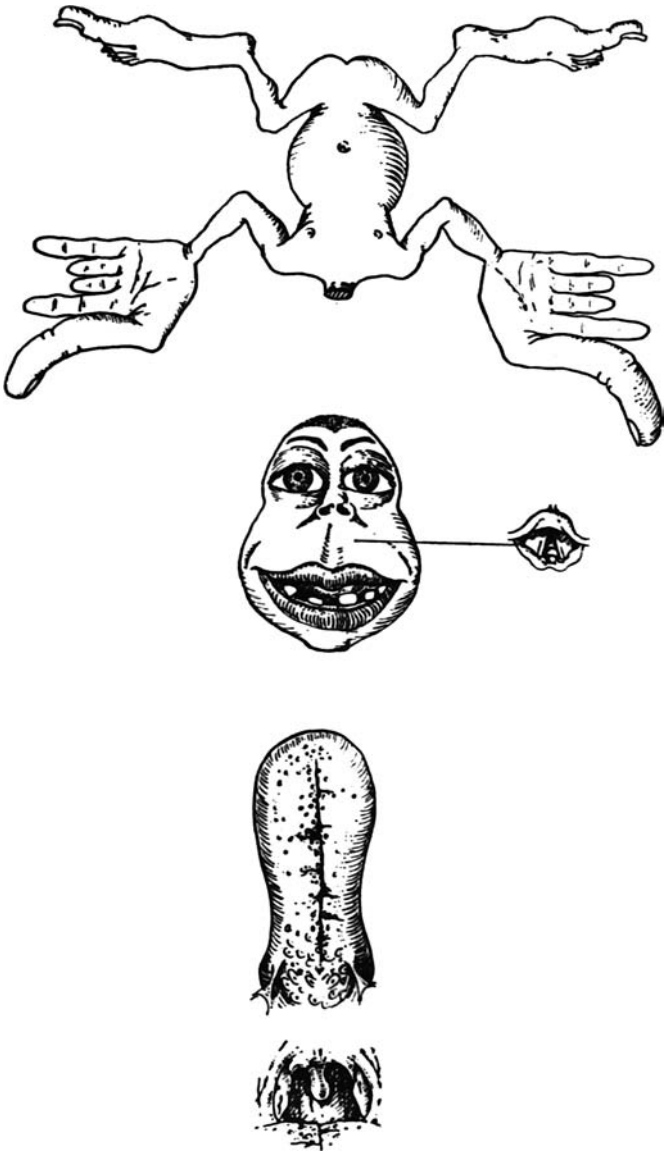


Figure 12.3 Homunculus appearing first in the article by Penfield and Boldrey in 1937, to illustrate the relative size of body parts represented on the motor cortex as defined by electrical stimulation at operation.

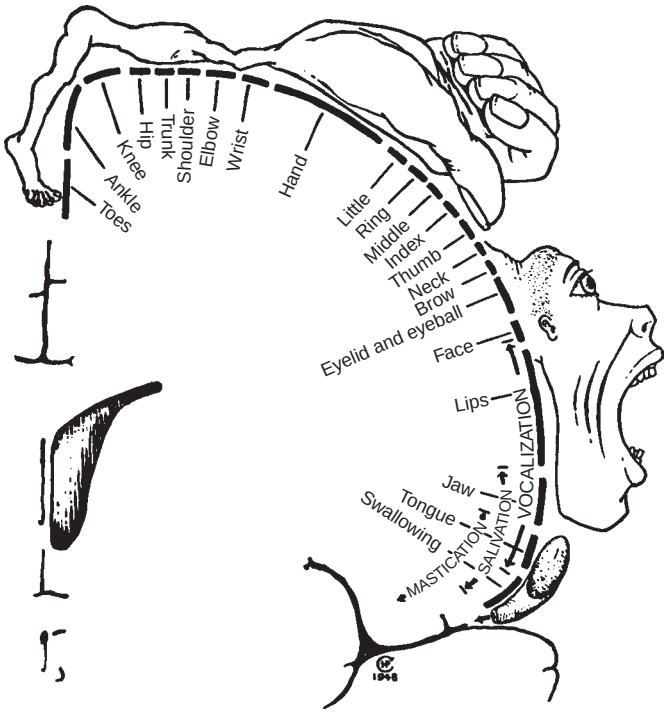


Figure 12.4 A later version of the homunculus, with reference to the representation in the motor cortex, from the studies of Penfield and Rasmussen in 1948.

Herbert Jasper and the advent of electroencephalography

A chance encounter at Brown University in 1937 led Penfield to bring Herbert Jasper to Montreal to apply the new techniques of electroencephalography (EEG) and electrocorticography (ECG). Jasper with Carmichael in 1935[93] had reported on the application of Berger's new technique of EEG, in the same year that the Boston group led by Gibbs had noted its value in epilepsy.[32] EEG refined the task of localizing the site of origin of seizure discharge by recording spikes and sharp waves that were pathognomonic for epilepsy.[33] This greatly improved the selection of patients with focal seizures for surgical treatment. ECG mapped the localization of seizure activity during surgery by recording directly from the cortex and by monitoring stimulation responses. The application of the new technology to epilepsy resulted in a long series of clinical studies by Penfield, Jasper and their associates. Jasper's background in psychology and electrophysiology also generated at the MNI an expansion in neurophysiological research which over the years elucidated the complex mechanism of epilepsy and sharpened the criteria for surgical treatment.[34] Jasper's chapter in the monograph by Penfield and Erickson of 1941 on *Epilepsy and Cerebral Localization* provided the first comprehensive review of the use of EEG and corticography in the diagnosis and surgical treatment of epilepsy.[94]

Numerous monographs and publications by Penfield with his associates, Jasper, Kristiansen, Rasmussen and a long list of neurosurgical Fellows, continued to document from 1934 to 1950 much detailed evidence for the successful surgical treatment of focal epilepsy at the MNI.[20]

Surgery for temporal lobe seizures

The anterior and lateral temporal cortex

The emergence at the MNI in the early 1950s of surgery for seizures related to the temporal lobe opened a new era for what has now become the most frequent surgical approach for the surgical treatment of epilepsy. There were several phases in the development of such surgery, each distinguished by a substantial increase in knowledge about the pathophysiology of seizures arising from the temporal lobe. Penfield and Flanigin[35] reviewed 68 temporal lobe operations carried out over the decade from 1939 to 1949, which had arrested or controlled seizures in over one-half of the patients. The resections in this series were limited mainly to the anterolateral temporal cortex; in only 10 cases was the uncus removed and in only two was a part of the hippocampus also removed. Bailey and Gibbs[36] in the meantime performed antero-lateral cortical removal in a series of patients, with no encroachment on

mesial temporal structures because Bailey was aware of the severe behavioral deficits in monkeys after bilateral mesial temporal ablations as reported by Klüver and Bucy[92] beginning in 1939.[37] This limited anterolateral approach was also supported by the pre-operative localization offered by EEG, either antero-lateral temporal, anterior Sylvian, or fronto-temporal.[38] Related experimental studies at the MNI were thus directed to clarify the connections of the temporal pole.[39,40] This is also well illustrated by similar antero-lateral temporal localization of ECG foci registered by Jasper and two young neurosurgeons[41] in 39 of the same series of patients reported by Penfield and Flanigin in 1950. In only a few patients was ECG abnormality detected in the inferior and mesial part of the temporal lobe. (Figure 12.5).

The mesial temporal region

The success rate of just over 50% in the two major surgical series, reported from Montreal by Penfield and Flanigin[35] and from Chicago by Bailey and Gibbs[36] indicated that resection limited to the antero-lateral temporal cortex did not eliminate all the epileptogenic tissue in many patients. Indeed in some cases persistent seizures led Penfield to persevere and carry out a second operation. In these, he extended the resection, under electrocorticographic control, sometimes posteriorly along the lateral temporal cortex (if on the nondominant side for speech) and also included more of the uncus and hippocampus.[20]

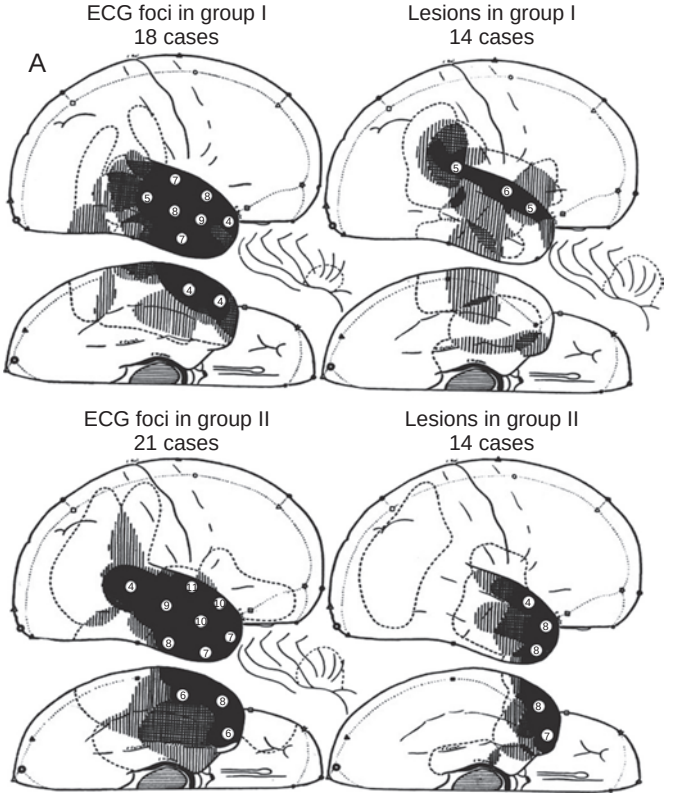


Figure 12.5 Localization of ECG foci and lesions reported by Jasper, Pertuiset, and Flanigan in 39 patients operated upon for temporal lobe seizures by Penfield. The maximum changes, areas indicated in black, involve mainly the antero-lateral cortex of the temporal lobe.

A second phase in the surgical approach to temporal lobe seizures unfolded rapidly in the early 1950s. Clues from experimental animal studies by Gastaut *et al.*[42] and Kaada[43] and from stimulation at operation[44,45] pointed to the mesial and inferior surfaces of the temporal lobe for the origin of the epileptic attack. Penfield noted instances where stimulation in the uncinate region produced auras of the patients' attacks. In one such instance, a seizure with automatism was recorded consisting of low voltage fast activity followed by 3 per second waves to spread from the stimulation point to involve a wide region of the temporal cortex. (Figure 12.6). These findings led Penfield in this case to extend his resection to include the mesial temporal region.

Stimulation responses from the claustro-amygdaloid complex

The most convincing evidence that the mesial temporal region was a crucial zone for the generation of temporal lobe seizures came in a third phase of surgical studies. This was the reproduction of the patient's habitual auras and other typical features of these attacks by anatomically directed depth stimulation or stimulation under direct vision at operation within and around the amygdala involving also the ventral claustrum and the anterior insula.[46] The resulting seizure discharges on corticography were seen to spread rapidly to encompass not only the temporal cortex but the exposed frontal parietal cortex.

In 1951, the surgical findings in the first patient in this series, initiated convincing evidence for the role of the amygdaloid region in temporal lobe seizures.[27]

Case report

Patient P.S., Age 26

He had a difficult birth and, from the age of 12, attacks which began with a vision of colored lights, a 'shock in the head', after which he became unresponsive, fumbled with his clothes and would later have no memory of his actions during this period. Pre-operative EEG study showed abnormal spike activity over the lateral and inferior temporal regions on the right side. At operation, a depth electrode was directed through the second temporal convolution 3.5 cm from the tip of the temporal lobe toward the region of the amygdala. One of his typical small attacks was produced with the electrode tip deep in temporal-insular sulcus, with electrodes recording from the lateral and inferior surface of the temporal lobe (Figure 12.7). Epileptic spikes were suddenly replaced by low voltage rapid activity, the patient was seen to stare and become unresponsive to questioning, while he plucked at the anaesthesist's coat and made chewing movements. His appearance was much like that seen in his habitual attacks. The electrographic changes lasted a minute and a half, at which time the patient appeared to have recovered, but seemed unaware of the attack (Figure 14.7). There was smallness and toughness of the first temporal convolution and mesial temporal region, as well as a zone of gelatinoid tissue about the size of a small walnut deep in the temporal lobe, lateral and inferior to the ventricle and encroaching on the amygdala. Microscopically, this showed dense astrocytic gliosis. On later review, the neuropathologist interpreted this as a grade I astrocytoma. Resection included

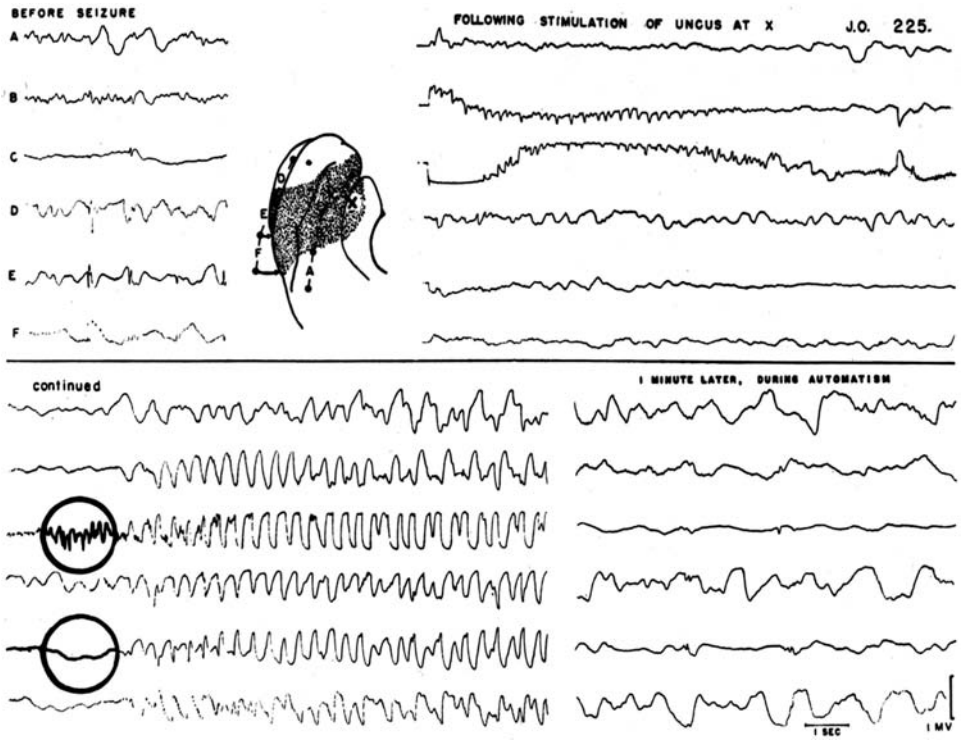


Figure 12.6 ECG recording at operation by Penfield. After stimulation of the uncinate region, a seizure discharge was recorded from a wide area of the inferior temporal cortex.[4,41]

6 cm. of antero-lateral cortex, as well as the mesial temporal region (amygdala; hippocampus) harboring the lesion. The patient continued free of attacks for 37 years later, with no reappearance of the tumor.

The role of the claustro-amygdaloid complex

In 15 other patients from that same study, similar features of automatism and amnesia were reproduced by stimulation in the peri-amygdaloid region (Figure 12.8). This first examination of stimulation and electrographic responses from the human amygdala demonstrated its role in visceral responses such as fear and its critical relation to recent memory.[46] It was noted that these findings corresponded to the localization for 'a particular variety of epilepsy' that had been proposed by Hughlings Jackson and others, just before the turn of the century:

> the discharge-lesions in these cases are made up of some cells, not of the uncinate gyrus alone, but of some cells of different parts of a region of which this gyrus is part – a very vague circumscription, I admit – the uncinate region.[47]

The rich network of connectivity subtended by the amygdala offered a valid explanation for many of the characteristic clinical features of 'uncinate' attacks described by Jackson.[27] Thus, the patient's epigastric aura, sometimes associated with a sense of fear, was reproduced from stimulation either of the amygdala itself or of the adjacent anterior insular cortex, which would later be shown to be physiologically associated with gastric movement.[48] The various emotional, autonomic, and visceral responses likewise seemed explicable because of the robust anatomical pathways then known from the amygdala to the septal and hypothalamic regions. The initial feature of brief tonic movement with some temporal lobe attacks could be effected by the amygdaline efferent pathways to the striatum; chewing and swallowing movements could be explained by connections with the brain stem. The interference of the epileptic discharge with memory recording, characterized by the profound postictal amnesia, could reasonably be related, it was proposed, to the amygdala–hippocampal connection as well as the projection of the amygdala to the reticular system of the brain stem.[49] Curiously, stimulation of the hippocampus directly at operation in the Montreal experience rarely produced such responses, even though epileptic abnormality might sometimes be recorded from the anterior part of the structure.[50]

Thus, this evidence indicated that the amygdala and the juxtaposed gray matter, including the ventral claustrum and the anterior insular cortex, could generate temporal lobe seizures; this provided a physiological hypothesis that explained for the first time many of the clinical aspects of these attacks (Figure 12.9a, b). It also indicated that the peri-amygdaloid zone should be removed in the surgical resection in order to produce the most beneficial outcome. This critical role of the peri-amygdaloid region in mesial temporal seizures became confirmed in many later studies, as summarized for example in the monograph by Gloor in 1997.[51]

Incisural sclerosis

The pathological counterpart of this physiological hypothesis was offered in a concurrent study by Earle, Baldwin, and Penfield in 1953.[52] They introduced the concept of incisural

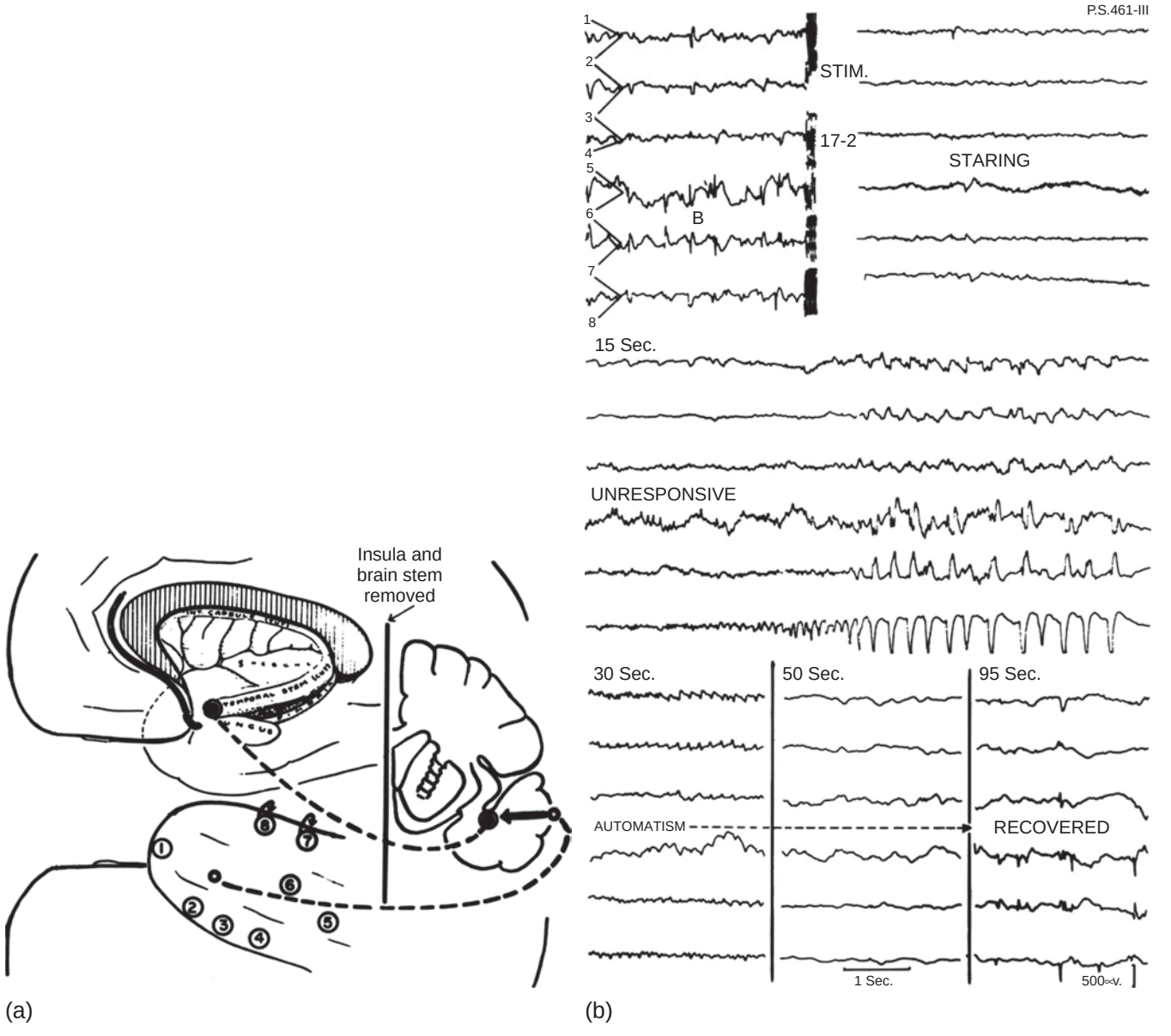


Figure 12.7 (a) Brain drawing to show electrode positions (in numbered circles) and depth stimulation in the amygdaloid region (black circles) from patient P.S.[27] (b) ECG showing rapid low-voltage activity from the temporal lobe and then return of the prestimulation spike activity. The patient had automatism and amnesia for the episode. Compare with Figure 14.6.[27]

sclerosis, which they postulated was due to herniation of the mesial part of the temporal lobe over the tentorial edge associated with increased intracranial pressure during a difficult birth (Figure 12.10). They considered this to cause injury to the hippocampal region, both by direct compression of the tissue and by arterial and venous vascular compression with resulting ischemia. Although they did not emphasize this, the uncus with the contiguous amygdala and entorhinal cortex are even more likely to herniate into the prepeduncular space and to be subject to compressive damage.

Application of the Montreal procedure

Based on these new findings from stimulation results and pathological studies, a radically different surgical approach was developed, with excision not only of the anterolateral cortex, but also removal under direct vision of the mesial part of the temporal lobe to include the amygdala, hippocampus and entorhinal cortex. Details of this operative technique were first described by Penfield and Baldwin in 1952[53] (Figure 12.11) and revised in 1961 by Penfield *et al.*[54] With the application of this approach, successful surgical outcome improved from 50% to 65%.

From 1953 onward, many neurosurgical centers, often involving surgeons and scientists who had studied at The Montreal Neurological Institute, took up the procedure of temporal lobe resection for the treatment of seizures. A colloquium on advances in the surgical treatment of temporal lobe epilepsy, organized by Gastaut and his associates in Marseilles in 1954, gave an opportunity for Penfield to provide an overview of the early experimental and surgical results of his team, which firmly established the important role of the mesial temporal region in the pathogenesis and surgical treatment.[55] The extensive monograph of 1954 by Penfield

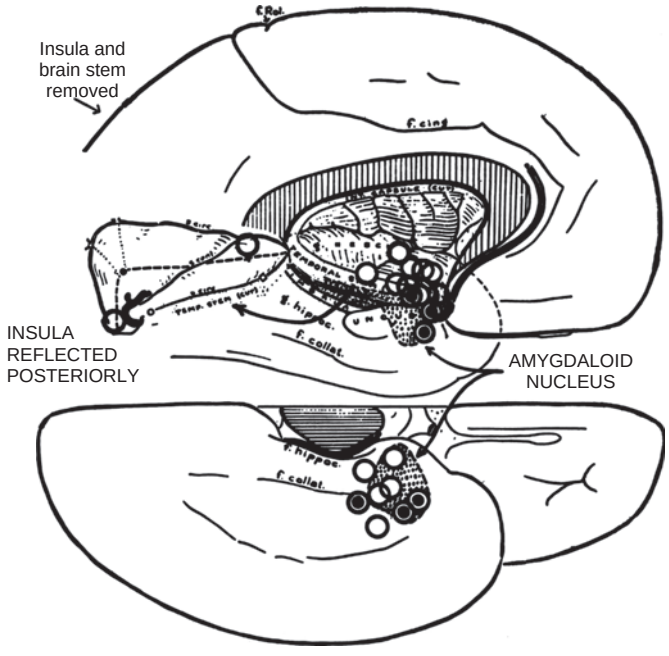


Figure 12.8 Sites of stimulation from 16 operations that produced features of temporal lobe seizures such as epigastric area, fear, memory disturbance, automatism and amnesia.

and Jasper reviewed this Montreal experience.(Figure 12.12) A second colloquium sponsored by Maitland Baldwin and Pearce Bailey[56] in 1958 at the National Institutes of Health, USA, extended and confirmed the significance of subtotal temporal lobectomy, including particularly the mesial temporal structures, for treating temporal lobe seizures.[57]

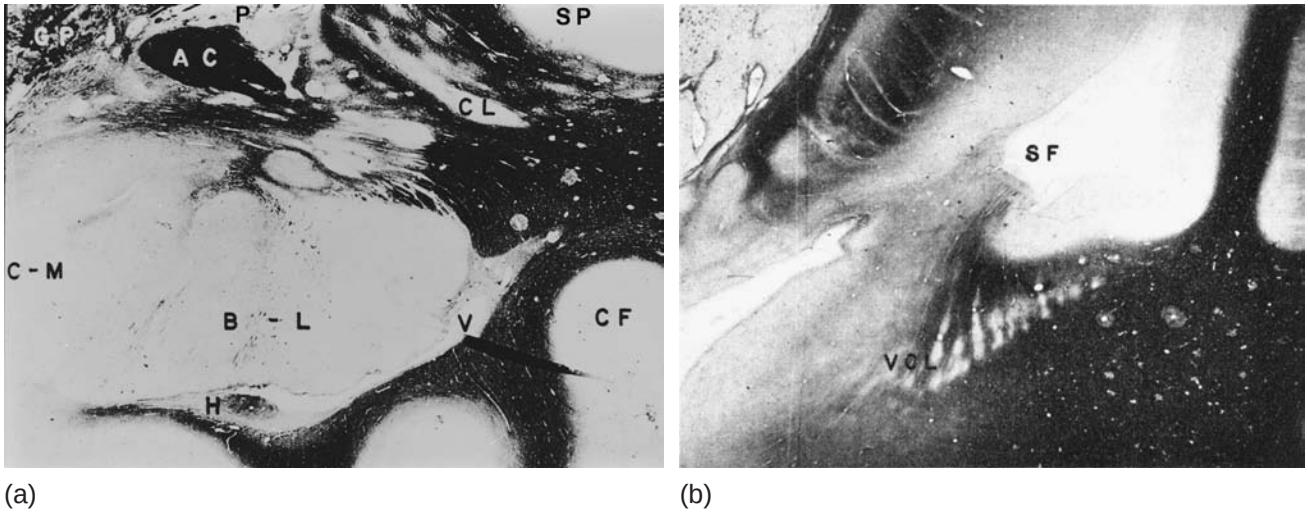
Memory deficit with bilateral temporal lesions

Scoville and his group at Hartford[44] had also produced stimulation responses from the uncus which resembled some features of temporal lobe seizures. This induced him to carry out bilateral resection of the mesial temporal region by a subfrontal approach in a few patients with epilepsy. One of these patients, H.M., who has since become noteworthy in the annals of neuropsychology, developed a severe deficit in recent memory.[58] This was similar to the syndrome that had been reported earlier by Milner and Penfield[28] from the MNI series, in three patients after unilateral temporal excision in the presence of what later became recognized as bitemporal mesial temporal pathology, especially involving the hippocampus.[59,60] These findings, together with the initial observation by Feindel and Penfield[27] that stimulation of the amygdala evoked ictal amnesia, directed attention to the important role of the mesial temporal structures in memory mechanisms.[28]

Toward a surgical cure

The surgery of focal temporal seizures, augmented by many contributions, has become one of the most successful therapeutic measures in modern neurosurgery.[61,62] Many thousands of patients have had the benefit of such surgery. The patterning of the surgical resection in order to obtain the most satisfactory surgical outcome and at the same time to minimize neurological deficit continues to be examined currently in over 100 neurosurgical centers.[23,62] A vast literature has now become available on the anatomy, physiology, pathology, and cognitive aspects of the temporal lobe.[63–68] Gloor summarized this field in 1997 in his masterly monograph on the temporal lobe and limbic system.[51]

The developments in EEG such as sphenoidal recordings and computerized-video monitoring greatly enhanced the pre-operative localization of the epileptogenic region.[69] The increasing use of detailed neuropsychological evaluation by Milner and her associates and the application of the intracarotid amytal test developed by Wada and Rasmussen for defining lateralization of speech and memory function proved to be invaluable adjuncts.[28,69,70]



(a) (b)

Figure 12.9 (a) Enlarged view of the claustro-amygdaloid complex which shows the Sylvian fissure (SF), claustrum (CL), anterior commissure (AC), globus pallidum (GP), centro-medial and baso-lateral nuclei of the amygdala (C-M, B-L) hippocampus (H), ventricle (V), and collateral fissure (C-F).[27] (b) A more anterior coronal section shows the Sylvian fissure (SF) and grey matter of the ventral claustrum (VCL). This section relates to the site of the depth stimulation.[27]

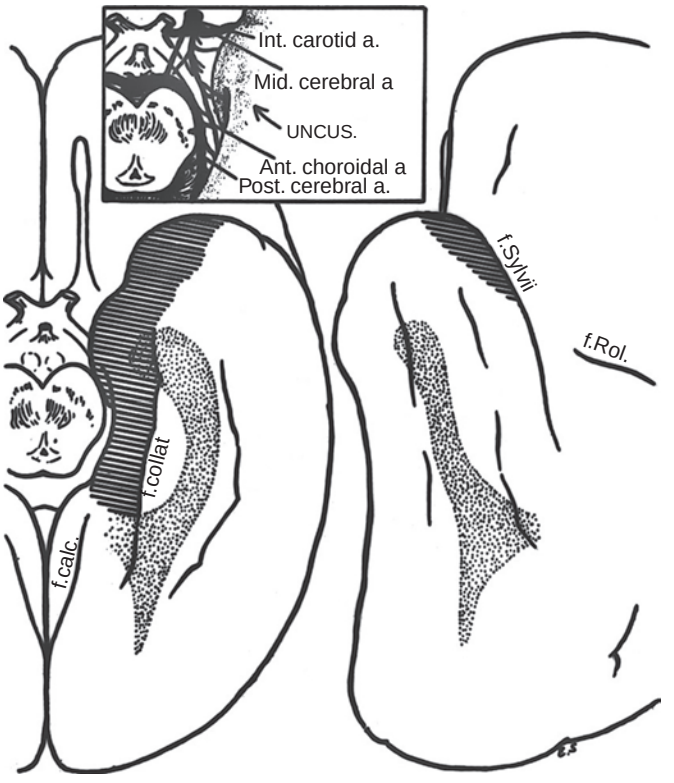


Figure 12.10 Drawing to show the region of sclerosis and the mesial blood vessels involved in tentorial herniation of the uncinate region, for example, during abnormal birth.[52]

Surgical techniques have become refined and selection of patients for the surgical procedure has grown far more enlightened.[71–73] Amygdalo-hippocampectomy introduced by Niemeyer in 1958[74] and adopted enthusiastically by Wieser and Yasargil in 1982,[75] has yielded an excellent surgical outcome and may well prove on evidence to become the resection of choice in selected patients.[72]

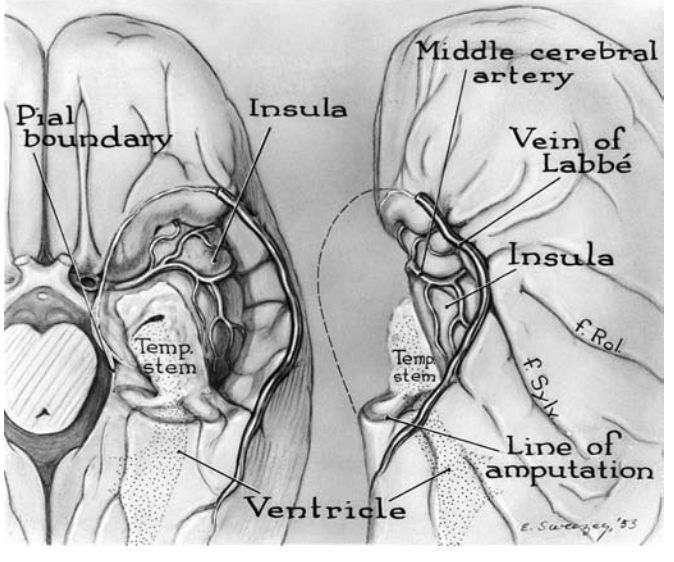


Figure 12.11 Drawing to show subtotal temporal lobectomy that includes the amygdala and up to 4 cm of the hippocampus as well as the antero-lateral temporal cortex, as described by Penfield and Baldwin in 1952.[53] This operation became widely adopted.

Figure 12.12 Wilder Penfield (seated), and Herbert Jasper photographed in 1954 on the publication of their monograph, *Epilepsy and the Functional Anatomy of the Human Brain*.

Further surgical evidence from the MNI[76] indicates that temporal corticectomy with radical resection of the amygdala and uncus but with minimal removal of the hippocampus can achieve an excellent surgical outcome in 65% of patients (Figure 12.13a) At the same time the relative sparing of the hippocampus reduces the possibility of deficit in memory function which had been assigned by Milner and others[31,69] to varying degrees of damage to the hippocampal regions.

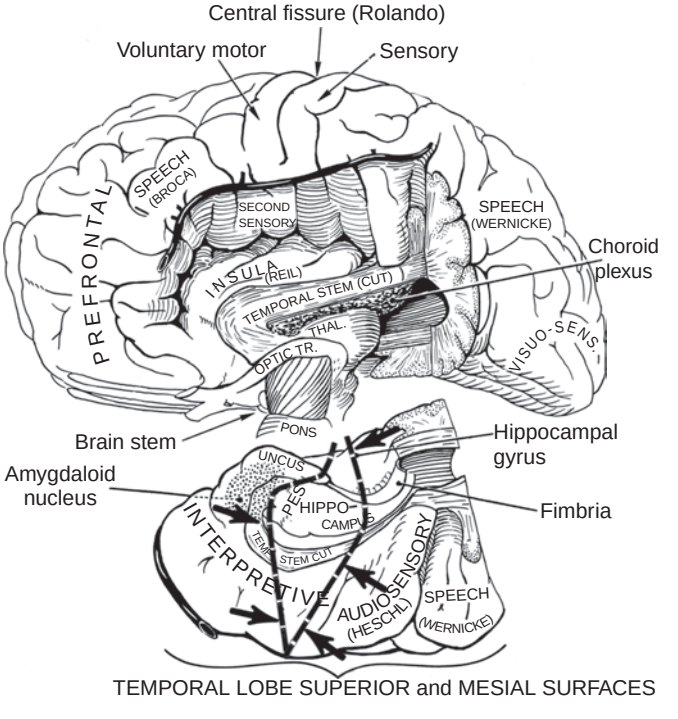


Figure 12.13 (a) Anatomical dissection of the temporal lobe to show cortico-amygdalectomy (hatched line on the left) compared to cortico-amygdalo-hippocampectomy (hatched line on the right).[76] (b) Post-operative MRI to show radical excision of the amygdala and minimal removal of the hippocampus.[9]

The acquisition at the MNI of magnetic resonance imaging (MRI) in 1985 gave a significant new dimension to the selection of patients for operation by identifying small structural lesions in the temporal lobe in more than 25% of patient and also the presence in another 30% of patients of mesial temporal sclerosis involving the hippocampus and later demonstrated also to include the amygdala and entorhinal cortex.[73,77,78] MRI also provided the *sine qua non* for monitoring the exact anatomical extent of the surgical resection to compare with the type of surgical outcome reported from different centers.[20] In the span of fifty years covered by this review, the effective control of temporal lobe seizures by surgical treatment has thus improved from 50% to almost 90%, with minimal morbidity and mortality.[71,79] The role of mesial temporal sclerosis in the pathogenesis of temporal lobe seizures is now widely recognized.[68] The significance of the amygdalo-hippocampal region in the physiopathology has been well substantiated from many stimulation studies,[80,81] and by greater detail available on the anatomy and pathology of these structures.[82–84] Marked improvement based on limited excision of the hippocampus but radical resection of the amygdala and minimal cortical ablation has been achieved in the surgical cure of temporal lobe seizures.[76]

Contributions from the Toronto school

Kenneth McKenzie trained with Harvey Cushing at Boston in 1923 and returned to establish the first neurosurgical unit in Toronto in 1924.[15,85] He performed the first hemispherectomy for seizures in 1936. He reported the case in 1938 at a meeting of the American Medical Association. The patient, a 16-year-old woman, had seizures from infancy and progressive hemiplegia. After operation she was seizure-free and lived with her family for another 23 years. McKenzie's experience antedated by 14 years the series of 12 patients with seizures treated by hemispherectomy by R.A. Krynau and published in 1950. McKenzie never published his case but the patient was studied and reported by Williams and Scott[86] in 1939 in relation to autonomic responses following hemidecortication.

At the Sick Children's Hospital in Toronto, Stobo Pritchard established a comprehensive neurological clinic for childhood epilepsy. On his foundation the pediatric neurosurgeons of the Toronto school, especially Harold Hoffman, developed an active center for surgical treatment of epilepsy in the 1970s.

Epilepsy program at London, Ontario

In 1977 Warren Blume, a neurologist and epileptologist, and John Girvin, a neurosurgeon and neurophysiologist, both trained at the MNI and McGill, established an Epilepsy Unit, coordinating a multidisciplinary team of health care professionals. Although somewhat in the shadow of the illustrious team led by Drake, Barnett, Ferguson, and Peerless, who were world-leaders in the cerebrovascular field, the Epilepsy Unit developed successfully over the next two decades. A convincing milestone in the long record of evidence for the effectiveness of surgery for temporal lobe epilepsy was reported by the London group from an ingen-ious randomized trial comparing medical treatment with surgical treatment at this unit from July 1996 to August 2000.[87] From a study of 80 patients divided into two groups, they found that 64% of the 36 patients operated upon by temporal lobe resection were free of seizures compared to 8% in the group assigned to medical treatment, an eight-fold benefit.

The pre-operative investigation and selection for surgery in this London project evidently followed the same lines as those practiced for many years at the Montreal Neurological Institute. The pattern of surgical excision, based on the procedure introduced by the Montreal group in the 1950s,[53] included the antero-lateral temporal cortex and the mesial structures, especially the amygdala and hippocampus.[88] Thus the London study was another vindication of the successful results of surgery reported from the MNI over a period of 50 years and documented in extensive long-term follow-up studies by Rasmussen and many colleagues. These demonstrated a post-operative outcome of 65% of patients seizure-free and over 85% showing significant improvement in regard to seizure control.[89]

Other Canadian centers

Neurological and neurosurgical trainees from the Montreal Neurological Institute and McGill introduced neurosurgical treament for epilepsy in many other Canadian cities, including Edmonton, Saskatoon, Vancouver, Calgary, Winnipeg, and Halifax.

Returning to Montreal, the major neurosurgical unit at Notre-Dame Hospital affiliated with the University of Montreal and first established in 1947 by Claude Bertrand, who had trained with Penfield and Cone at the MNI, became a world center for functional neurosurgery. This included the operative treatment of epilepsy.

Although many children with focal epilepsy had been treated over the years at the MNI by Penfield and his team, in the 1970s an active group dealing with childhood epilepsy was established through the efforts of Preston Robb, head of neurology, and Kathleen Metrakos in charge of EEG. José Montes after completing his training at the MNI developed one of the most active centers at the Montreal Children's Hospital (MCH) for the surgical treatment of epilepsy in children.

Conclusion

This historical outline highlights the contributions in Canada that enhanced our basic understanding of the surgical treatment of epilepsy. From 1934 to 1984 the MNI was headed by three successive Directors who were neurosurgeons with a persisting interest in epilepsy surgery (Figure 12.14). Trainees in neurosurgery, neurology, EEG, neurophysiology, neuropsychology and neuroimaging from the MNI have translated the benefits of surgical treatment throughout Canada and to many other countries around the world. In particular, many of the major centers for epilepsy surgery in the United States were established by MNI graduates.

Since the early 1970s, the revolutionary advances in brain imaging have elucidated the pathological and neurochemical changes in epilepsy and also provided elegant three-dimensional visualization to the surgeon for pre-operative diagnosis, precise anatomical navigation during operation and exact monitoring of the surgical resection to correlate with clinical outcome.

Figure 12.14 Successive neurosurgical directors of the MNI, from the left, Theodore Rasmussen, William Feindel, and Wilder Penfield who promoted research, teaching, and surgical treatment of epilepsy. Photograph taken in 1974 at the celebration of the 40th Anniversary of the MNI.

Acknowledgments

This review reflects contributions over the past 60 years of my teachers and colleagues at the MNI as credited in the selected list of references. I appreciate the help of Helmut Bernhard, Department of Neurophotography for formatting the illustrations and thank Ann Watson and Linda Zegarelli for editorial assistance. The illustrations are reproduced from the Wilder Penfield Archive and the Neuro Archives of the Montreal Neurological Institute. Research for this review was supported by the Class of Medicine McGill 1945 Wilder Penfield Archive Fund, the Thomas Willis Fund of the Montreal Neurological Institute, and by grants from the Donner Medical Foundation and Associated Medical Services, Inc. (through the Jason Hannah Institute for the History of Medicine), for the Neuro-History Project, Montreal Neurological Institute.

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13 A brief history of epilepsy surgery in the United States

PJ Connolly, DD Spencer, and AA Cohen-Gadol

If I wished to show a student the difficulties of getting at the truth from clinical experience, I would give him The History of Epilepsy to read.

Oliver Wendell Holmes[1]

The history of epilepsy treatment revolves around individuals who through their ingenuity and innovation have elucidated the understanding of epilepsy pathophysiology. In the following chapter, we will review some of the contributions of these key individuals from the United States of America.

Benjamin Winslow Dudley

Dudley who had earned his MD from University of Pennsylvania, traveled to England and France to learn the art of surgery and trephining. When he returned to Kentucky in 1818, he became the first American to perform surgery for epilepsy and the first surgeon to ever publish a series (five) of epilepsy surgery patients. He conducted surgery for post-traumatic epilepsy. All five patients in his series survived, three were seizure free and the other two had decreased seizure frequency.[2] Dudley attributed his success to the 'good clean air' of the Kentucky frontier.

Harvey W Cushing

The history of modern epilepsy surgery in many ways reflects the history of neurosurgery in the late 19th and early 20th centuries. During his training, Cushing (considered to be the father of modern neurosurgery) went abroad in 1901, where he visited Horsley but he was not impressed by Horsley's speedy surgical techniques. Upon his return to the United States and expansion of his practice at Peter Bent Brigham Hospital in Boston, Cushing established the safety of intracranial surgery and neurosurgery training programs. He had a particular interest in surgical treatment of brain tumors. He demonstrated the localizing value of epileptic syndromes although he had no special interest in electrophysiology. He trained many future leaders in epilepsy surgery including Percival Bailey and Wilder Penfield.

Bailey and Gibbs

As early as 1938, Frederic and Erna Gibbs along with Lennox had suggested the idea of operating on an electrical focus responsible for epilepsy in the absence of a structural lesion. In 1948, the Gibbs studied 300 patients' EEG findings associated with psychomotor seizures localized to the anterior temporal lobe.[3] They convinced Percival Bailey (who was trained by Cushing) to perform anterior temporal resections for psychomotor epilepsy. By 1954, Bailey had operated on 72 patients with a five year follow-up and concluded that 'major convulsions are abolished or greatly reduced in half of the cases.' The hippocampus and hippocampal gyrus were spared in these operations.[4] The Gibbs' and Bailey's efforts were one of the earlier attempts at surgical treatment of non-lesional epilepsy.

More recent generation of epilepsy surgeons in the United States

Earl Walker's[5] physiological studies on the brain and more specifically thalamus provided further data regarding electrophysiological mechanisms underlying epilepsy. Arthur Ward[6,7] was the first to perform intracellular recordings from human epileptic neurons. His demonstration of temporal lobe electrophysiology responsible for epilepsy further complemented Crandall's[8] pioneering work in chronic depth electrode recordings. An amalgam of Falconer's demonstration of anatomic abnormalities and Crandall's analysis of corresponding electrophysiological characteristics has founded our current comprehension of temporal lobe epilepsy. The more complex electrophysiology responsible for extra-temporal epilepsy has partly delayed our more detailed understanding of mechanisms involved in extra-temporal epilepsy syndromes.

Other surgical procedures for epilepsy

Hemispherectomy was initially described by Dandy in 1928 for gliomas, and used by Krynauw[9] in 1950 for children with epilepsy and infantile hemiplegia. As was mentioned previously, Rasmussen described 'functional hemispherectomy' which further minimized the complications associated with an anatomic hemispherectomy. Based on Horsley's and Erickson's observations regarding the importance of corpus callosum in transferring epileptic discharges between hemispheres, Van Wagenen and Herron performed the first corpus callosotomy in 1940.

As the first part of the 20th century demonstrated the efficacy of epilepsy surgery; the second part of century defined who would be likely to benefit most from surgery and also expanded the repertoire of surgical technique: callosotomy,[10] focal cortical resection,[11] multiple subpial transactions.[12] Multiple subpial transaction was first described in 1989.[12] The technique has been applied successfully to epilepsy foci in eloquent cortex by severing the 'horizontal' or traversing fibers while preserving the descending fibers, therefore; isolating the route of seizure spread. In addition, application of intracranial monitoring strategies has made epilepsy surgery available for patients with focal epilepsy and non-structural abnormalities.

Other procedures such as vagus nerve stimulation (VNS) (approved in 1997) has been used for patients with generalized seizures who have typically bilateral or non focal epileptiform activity on EEG and are not candidates for resective surgery. The mechanism of action of VNS is not known, but it may reduce seizure frequency with a similar efficacy as those of new generation of anticonvulsant drugs. Another new procedure for intractable generalized seizures is deep brain stimulation in the anterior nucleus of thalamus.[13] The anterior thalamus is known to play a role in seizure propagation. This is a novel treatment for patients with generalized seizures, who are not typically candidates for resective surgery. The future treatments in epilepsy will depend on a better understanding of the cellular phenomenon and networks involved in seizure generation.

Neuroimaging and epilepsy

The evolution of imaging modalities has significantly expanded the application of surgery through improved localization of seizure foci. In 1930s, Penfield used ventriculography, pneumoencephalography and angiography to evaluate epileptogenic mass lesions. MRI scanning was a significant advance due to its high resolution of soft tissues revealing anatomic details and pathologic signal changes with striking clarity. Multiplanar imaging allowed visualization of medial temporal and neocortical structures in anatomically useful cross sections.[14] With the advent of MRI, there was a preoperative correlate to EEG. Hippocampal sclerosis and atrophy on the side of seizure origin was found to effectively predict seizure remission.[15] Furthermore, the degree of hippocampal resection was found to affect seizure outcomes.[16]

Further evolution of imaging modalities including functional MRI, positron emission tomography and single photon emission computed tomography have further facilitated delineation of more subtle areas of structural and metabolic abnormality. Regions of electrographic abnormality have become correlated with areas of radiographic abnormality as disclosed by magnetic resonance imaging. Localization of a 'seizure generator' by two independent methods has improved the likelihood of obtaining a surgical cure. Functional imaging coregistered with structural and electrographic data has become an important tool in epilepsy surgery.[17]

Conclusions

In the present chapter, we reviewed an abbreviated history of epilepsy surgery in the United States. We highlighted the milestones in the development of epilepsy surgery which began with an understanding of cortical electrical activity and its role in epilepsy. Advances in electrical localization, beginning with scalp EEG recordings and shortly followed by cortical and depth recordings, have enhances our preoperative localizing power, significantly increasing the effectiveness of epilepsy surgery. Further improvement in our treatment paradigms is possible with multicenter trials and understanding the networks and molecular basis of epilepsy.

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14 Epilepsy surgery in Latin America

J Godoy, AC Sakamoto, and ALF Palmini

Although waxing and waning, interest in epilepsy surgery appeared in Latin America shortly after this therapy was introduced by Penfield's pioneering work at the Montreal Neurological Institute. The first systematic resective surgeries for epilepsy were performed in the region in the 1940s.[1] For decades, this treatment was used mainly in isolated, anecdotal cases or performed in very small series, having included almost all its modalities: temporal and extratemporal resections, hemispherectomies, callosotomies, lesionectomies, stereotaxia, and amigdalo-hippocampectomies.[2–4] During the last 15 years several systematic epilepsy surgery programs have been established in the region, including some centers that use advanced techniques. However many Latin-American countries still have not performed any epilepsy surgery and some even lack the facilities for a complete patient presurgical evaluation. As in the rest of the world, the actual number of epilepsy surgeries represents a very small fraction of the total number of patients that need this type of therapy. Certainly one of the main challenges on this regard is to make this treatment available to the whole region.

Three are two major difficulties for the development of epilepsy surgery in Latin America. The first is economical limitations and the second the unawareness of the usefulness of surgical treatment and its proper timing within the neurological and neurosurgical community. Although unified by a common language and socio-cultural roots, Latin America is a continent where healthcare systems coexist with major differences not only between countries but also within a same country. According to World Bank data,[5] per capita income in Latin America ranges from US$400 in Haiti to US$6,230 in Mexico, while health expenditure per capita ranges from as low as US$29 per year in Haiti up to US$361 per year in Uruguay, compared to US$5,274 in the USA. This latter figure is higher than the total per capita income of almost all countries in the region. The impact of the economical development on epilepsy care is shown by the fact that the five countries with the highest income in the region have established epilepsy surgery programs while none of the five poorest countries have them. In this context of economical constraints it is easy to understand that there are quite a number of priorities that compete for health resources and explains why epilepsy surgeries are virtually nonexistent in public health systems in the region, with very few exceptions. On this regard, a major political step in favor of the development of epilepsy surgery in Latin America was made on September 9, 2005, in Santiago, Chile, where the 'Latin-American Declaration on Epilepsy' was read on behalf of several international organizations, including ILAE, IBE, WHO, and UNICEF, as part of the 'Epilepsy out of the Shadows' global campaign. This declaration included a statement calling to warrant availability and access to 'surgery and all forms of effective treatments'.[6]

Even more critical than the economical restrictions is the need for well-trained medical professionals who not only make epilepsy surgery programs technically feasible but also inform and teach local and regional neurological communities about this modality of therapy, and promote changes in healthcare systems for setting up the epilepsy surgery programs. Indeed all current epilepsy surgery centers in the region are led by epileptologists and neurosurgeons trained at top world-class epilepsy centers, mainly the Montreal Neurological Institute and the Cleveland Clinic. Probably the best contribution first-world epileptologists can do for the further development of epilepsy surgery in Latin America is to train physicians and other professionals in the different disciplines needed in this field.

Precursors

Before the development of modern neurophysiological techniques, surgery was performed in Latin America mainly for post-traumatic epilepsy.[2,7] Usually, the site of an obvious structural lesion or simply the site of a head injury was selected for resection. Preoperative investigations were very limited because no EEGs were performed. Some patients were operated on based only on clinical history and plain skull X-ray findings (fractures, depressions, etc.).

It is surprising to know that this approach was occasionally used in Latin America as early as the end of the 19th century. Razetti *et al.*, in Venezuela, and Maldonado *et al.*, in Colombia, operated on patients with jacksonian post-traumatic epilepsy, in 1893 and 1897, respectively;[8] in 1894 Navarro,[9] in Montevideo, Uruguay, operated on a patient who developed frequent seizures after a head injury with a skull depression. He used a silver plate as a craneoplasty; the patient developed a right hemiplegia and remained with seizures for a few days, improving afterwards and being able to return to work 6 weeks later.

Argentina

The first systematic epilepsy surgery attempts were made almost 50 years ago in this country. In 1957, Ghersi *et al.*[10] reported a series of 25 patients with no demonstrable structural lesion who underwent temporal lobectomies or gyrectomies based on clinical history, surface EEG, and intraoperative corticograms (performed before and after the

initial resections in all cases). Although all patients improved significantly (40–80% seizure reduction), none was completely cured; their series also included some hemispherectomies which had good outcomes. Pardal *et al.*[11] performed stereotaxic surgery on six epileptic patients in 1960 and reported good outcome in all of them. A few years later the group of Basso and Betti,[3] from the University of Buenos Aires, using Bancaud and Talairach's technique, implanted electrodes for acute or chronic recordings in 61 patients, 36 of whom had temporal lobe epilepsy. They explored the amygdala, hippocampus, temporal cortex, thalamus, and other structures; in some patients they produced thalamic injuries and in others they destroyed epileptogenic areas with yttrium (Y-90) or performed amygdalo-hippocampotomy. Unfortunately, detailed preoperative and follow-up protocols were not provided. These authors also used combined surgical approaches, which included stereotaxic treatment for temporal lobe epilepsies and, in case of failure, topectomy of the affected cortex or temporal lobectomy.[3] In 1977 Chescotta *et al.*[12] reported a group of 62 epileptic patients on whom amygdalotomies and fornicotomies were performed; a significant improvement was obtained in 66% of the patients. Costales and Ferrarese[13] from Bahía Blanca, Argentina, presented a case report on a patient with a refractory status epilepticus successfully treated with temporal lobectomy.

Nowadays, there are four groups performing epilepsy surgery in Argentina. The group of Pomata, working in Buenos Aires at Juan P. Garrahan National Pediatric Hospital and at the FLENI Institute, started epilepsy surgery in 1995 (Pomata H, personal communication). Up to 2005 their series included 158 temporal and 139 extratemporal lobe surgeries, 34 hemispherectomies (2 of them anatomical), 35 callosotomies, and 13 vagal nerve stimulators. These authors reported part of their experience in 2001,[14] describing 60 children with extratemporal epilepsies, treated with resections, disconnections, and in one case, hemispherectomy; 10 of these patients underwent invasive evaluations; the one year follow-up showed that 38 patients were on Engel's class I. They also presented a small group of patients with Rasmussen encephalitis who underwent hemispherectomy,[15] and additionally described a 6 year-old child with refractory status epilepticus successfully treated with multiple subpial transection.[16]

Another epilepsy surgery program in Buenos Aires is located at the Hospital Italiano where Rabadan *et al.* have performed epilepsy surgery since 1999. They reported part of their series in 2000.[17] As of 2005 they have operated on 35 adult patients, including temporal and extratemporal resections as well as callosotomies (Rabadan A, personal communication). Also in Buenos Aires, at the Ramos Mejia Hospital, Kochen, Silva, Seoane, and Consalvo continued the work of Basso and Betti.[18] They introduced Video-EEG monitoring in 1996, invasive studies in 2001, and started extratemporal resections in 2003. They have also performed some callosotomies and vagal nerve stimulation since 2001 (Kochen S, personal communication).

Outside the capital city, epilepsy surgery has been performed in two provinces. One in the northern city of Cordoba, where Bulacio, Sfaello, and Muñoz started an epilepsy surgery program at The Santisima Trinidad Children's hospital and at the Center for the Study and Treatment of Epilepsy and Sleep Disorders (Bulacio J, personal communication); they have practiced temporal and extratemporal resections in a small group of patients since 2004. In Mendoza city, the above-mentioned neurosurgeon Pomata has also performed temporal and extratemporal resections in children (Pomata H, personal communication).

Bolivia

In this country, cortical resections were reported in post-traumatic epilepsies by Enriquez in 1959.[7] In his series, no EEG recordings were practiced and therefore patients were operated on based only on clinical history and plain skull X-ray findings, mainly guided by fractures and depressions. This same author also described the use of suboccipital pneumoencephalography for treating epilepsies after central nervous system infections, but no controlled results were reported.[7] There are currently no established epilepsy surgery programs in Bolivia not are these known surgical treatment attempts in the past.

Brazil

In the largest Latin-American country interest in epilepsy surgery goes back to the 1950s, and the most important and original contribution from the Brazilians to this field was made by the neurosurgeon Paulo Niemeyer Soares, one of the founders of the Brazilian League against Epilepsy, who also made contributions in several other neurosurgical pathologies, including Parkinson's disease surgery (Figure 14.1).[19] Niemeyer, who started to work at the Santa Casa de Misericordia Hospital, in Rio de Janeiro, initially as a general surgeon, was the first to propose and to perform amygdalohippocampectomies for the treatment of temporal lobe epilepsy. He used a transventricular approach, a technique that he presented for the first time in Washington in 1957, and later described in more detail in a book chapter.[20] In 1973 his group presented a

Figure 14.1 Dr Paulo Niemeyer Soares, brazilian neurosurgeon who first described amygdalohippocampectomy in 1957 (courtesy of Americo Sakamoto, MD).

series of 42 patients who underwent amygdalohippocampectomies,[4] reporting satisfactory results in 74% of the patients, after a follow-up period ranging from 6 months to 10 years; this figure was similar to the one the same group had obtained in 35 temporal lobectomies with resections tailored according to post-ablation electrocorticographic recordings.

In order to better understand the meaning of post resection epileptiform discharges he eventually left in place tiny copper electrodes over the operated cortex and performed post-surgical recordings.[19] These electrodes were externalized through small trepanation holes and after finishing the recordings were simply pulled out. With this technique, he soon realized that there was an immediate post-operative worsening of the frequency of epileptiform discharges, an effect that vanished in hours or a few days. Many years later this finding was replicated in a prospective study by Cendes *et al.*,[21] in a group of amygdalohippocampectomy patients; these authors coined the term 'Niemeyer effect' to describe this phenomenon. Niemeyer and his group also performed the first electrocortical recordings in Brazil in the early 1950s, using a single channel Garcier electroencephalograph.[19]

While Niemeyer's pioneering work in the field of epilepsy surgery was developed as part of his extensive practice as a general neurosurgeon, more recent initiatives in Brazil already embraced the idea of a comprehensive epilepsy surgery program, involving a multidisciplinary team including neurologists, neurosurgeons, psychologists, technologists, and more recently, neuroradiologists, psychiatrists, social workers, and physicists.

According to this principle the first Brazilian epilepsy surgery center was established in the 1970s, at the Hospital das Clinicas da Universidade de São Paulo, in the city of São Paulo, led by neurosurgeon Raul Marino Jr., who started a program mainly focused on treating diffuse epileptic encephalopathies through corpus callosotomy.[22] In the 1980s the second epilepsy surgery center was implemented at the Instituto Neurologico de Goiânia, led by neurologist Paulo C. Ragazzo, who was trained at the MNI and had previously participated in the team from the Hospital das Clinicas da Universidade de São Paulo.

It was really in the 1990s that the field of epilepsy surgery experienced major developments in Brazil. Two major reasons were of paramount importance in this move to provide the country with epilepsy surgery centers at the level of first-class centers of the developed world, not only in terms of infrastructure and methodologies, but also in terms of results for both adult and pediatric patients.[23,24] The first reason was the return to Brazil of well-trained physicians who established new epilepsy surgery centers and introduced state-of-the-art methodologies for the presurgical evaluation and selection of surgical candidates, as well as for the surgical treatment itself. Two new centers were implemented in that decade, one at the Pontificia Universidade Católica, in Porto Alegre, in the early 1990s, under the leadership of the neurologists André L.F. Palmini (trained at the MNI) and Jaderson C. da Costa (trained in pediatric neurology at Boston Children's Hospital), and the second at Hospital das Clinicas de Ribeirão Preto, Universidade de São Paulo, in Ribeirão Preto, State of São Paulo, in the mid 1990s, under the leaderships of the neurologist Américo C. Sakamoto (trained at The Cleveland Clinic Foundation, Cleveland, USA, and Epilepsy Center Bethel, Bielefeld, Germany) and neurosurgeon João A. Assirati Jr. (extensive neurosurgical training in various centers in the USA). The second and more important reason was the establishment of a national epilepsy surgery program in 1994, within the public health system, sponsored and coordinated by the Health Department. This program was created after joint effort from the Brazilian League of Epilepsy, the Brazilian Society of Clinical Neurophysiology, and the Brazilian Society of Neurosurgery, all of them active participants of a committee named directly by the Minister of Health. The main objectives of this committee were three-fold: (a) to establish a nationwide epilepsy surgery program, (b) to implement internationally accepted medical standards, and (c) to compromise maximal resources and minimal costs. In order to achieve these goals a two-steps strategy was implemented, which included strict criteria for accreditation of epilepsy surgery centers based on minimal requirements and clearly defined guidelines for indication of epilepsy surgery (temporal and extratemporal resective surgery, hemispherectomy and callosotomy).

After completion of the first 10 years of experience (1994–2004), the program was shown to be highly successful in many different aspects. It started out in 1994 with three initially accredited centers (Hospital das Clinicas da Universidade de São Paulo – São Paulo, Instituto Neurologico de Goiânia – Goiânia, and Hospital São Lucas da Pontifícia Universidade Católica – Porto Alegre), and progressively expanded to the current eight centers distributed in different geographical regions, seven of them connected to academic institutions dedicated not only to medical assistance but also to education and research. In recent years many other epilepsy surgery centers were established and reached accreditation status: at the Hospital das Clinicas da Universidade Estadual de Campinas, in Campinas, under the leadership of the neurologist Fernando Cendes who was trained at the MNI, at the Hospital da Universidade Federal de São Paulo, in São Paulo, under the leadership of neurologists Américo C. Sakamoto and Elza M. T. Yacubian (trained at the National Institutes of Health, Bethesda, USA), at the Hospital das Clinicas da Universidade Federal do Paraná, in Curitiba, under the leadership of the neurologists Luciano de Paola (trained at the University of Minneapolis) and Carlos S. Silvado; and at Hospital Regional, in São José do Rio Preto, under the leadership of neurologist Lucia H. Marques (trained at Universidade Estadual de Campinas). Other emerging centers are currently applying for accreditation as epilepsy surgery centers, in an organized process led by the Health Department.

The nationwide implementation of this program was able to assure universal access to epilepsy surgery in Brazil, to increase 13 times the total number of epilepsy surgery per year, to increase 2.7 times the number of epilepsy surgery accredited (or in final stages to be accredited) centers, to increase 5 times the number of surgeries per center per year, to boost the scientific development in the field of epileptology, and equally important, to create a network of centers with full capacity of training young Brazilian professionals in the area of epilepsy surgery, warranting the expansion and continuity of the program in the country, and consequently, the future of epilepsy surgery in Brazil.

Chile

In this country there is also a lengthy history on epilepsy surgery. Alfonso Asenjo, who is recognized as one of the founders

of Latin American neurosurgery, was actively involved in promoting this therapy more than 50 years ago. He established in 1950 the Instituto de Neurocirugía e Investigaciones Cerebrales de Chile (currently The Asenjo Institute), one of the first teaching and investigation centers in neurosurgery in Latina America, where hundreds of neurosurgeons have been trained, from Chile and other South and Central American countries. Asenjo worked with Carlos Villavicencio, a neurophysiologist trained in Montreal between 1939 and 1941 under Wielder Penfield[25] and who started electroencephalography in Chile in 1944, in a room called 'Hans Berger', at the Instituto de Neurocirugía, in Santiago. In 1951 they published,[2] a series of 221 epilepsy surgery patients, although only 96 of their patients had lesions without surgical indication *per se*, most of them frontal and mainly post-traumatic. Preoperative investigations included repeated surface electroencephalograms (EEGs), plain skull X-rays, cerebral angiograms, pneumoencephalograms, and ventriculograms; intraoperative corticograms and electrical stimulation were performed for tailoring the resections. The authors reported significant improvement or complete control in up to 69% of the patients. Other surgical procedures were also practiced at that time, such as hemispherectomies, performed in 1954 at the same institution;[25] The group continued to perform epilepsy surgery for some years but with a progressive decay in interest. A new impulse came at this center in 1990 when a pediatric epilepsy surgery program started, under the leadership of Lilian Cuadra. Up to 2004, they have operated on more than 100 children, mainly using temporal lobectomies and callosotomies (Cuadra, personal communication), entirely supported by public funds.

Another center with a long history in epilepsy surgery in Chile is the Hospital de la Universidad Catolica, where epilepsy surgery was initiated in 1962 led by Cristian Vera, a neurosurgeon trained at the Montreal Neurological Institute from 1956 to 1961; anecdotically, he had the opportunity to assist in the last epilepsy surgery that Penfield performed at the MNI. In Chile, Vera himself not only performed the surgery but also the electrocorticograms, using a portable eight-channel Hofner equipment, going back and forth from the operation table to the EEG machine. His group, that included Luis F. Quesney as a novel student, who later became a distinguished epileptologist, performed both temporal and frontal resections as well as hemispherectomies. Patients were also evaluated with surface EEG, skull X-rays, pneumoencephalography and an amytal test (Vera, personal communication). They also operated at the Hospital Psiquiatrico in Santiago, to where they eventually moved the only EEG machine they had. In some patients, before the resections, they made recordings from the amygdala, using implanted gold electrodes while at the same time tested memory.

Again, interest decayed and no epilepsy surgeries were performed for almost 20 years, until 1990, when a new program was started by the neurophysiologist Godoy, trained at the Cleveland Clinic, and the neurosurgeon Torrealba;[26] this program had an additional impulse in 1996, when Campos, neurosurgeon trained in Bonn, joined the group. At this center temporal and extratemporal resections are performed and patients undergo prolonged Video EEG monitoring, and when needed, evaluation with subdural grids or foramen ovale electrodes.[27,28] In addition to high resolution MRI, SPECT (ictal and interictal) are performed and more recently PET scanning.

Several stereotaxic techniques were used in the past both at the Asenjo Institute and at the Santiago's Psychiatric Hospital.[29] In this latter center this epilepsy surgery was performed in the 1960s and 1970s, led by Mario Poblete (L. Aranda, personal communication).

Colombia

In Colombia, Sierra *et al.*[30] reported in 1960 a Sturge–Weber–Dimitri patient with intractable epilepsy, successfully treated with hemispherectomy; he had no seizure recurrence, even after complete anti-convulsant withdrawal. Gutierrez-Lara *et al.*[31] performed stereotaxic surgery in 15 children between 1973 and 1976. Patients underwent Forel campotomy, amygdalotomy and, in those with associated hyperkinetic syndrome (probably meant attention deficit disorder), hypothalamotomy; they described good results in 8 patients, with a 6–18 month follow up.

One of the largest, oldest and most significant epilepsy surgery program in Latin America has been developed in Cartagena de Indias, Colombia by Jaime Fandiño-Franky.[32,33] It is worth mentioning that a huge personnel effort has been put by Fandiño-Franky, who has been able to overcome all kind of difficulties and established a comprehensive epilepsy program supported by non-governmental entities for more than 20 years. In 1996, an international workshop on specific aspects of epilepsy in the developing world was organized by ILAE Commission of Epilepsy in Developing Countries, during which it was stated that 'Fandino-Franky inspired the entire Workshop when he described his experiences'.[34] He was trained in Sweden and shortly after his return to Colombia got actively involved in epilepsy. Fandiño-Franky performed the first anatomical hemispherectomy in Colombia in 1981 and in 1989 founded an epilepsy hospital (Hospital Neurologico) that belongs to the Colombian League Against Epilepsy; the same year his group performed the first callosotomy and the first anterior temporal lobectomy. As of 2005 they have performed 680 epilepsy surgery procedures, including temporal and extratemporal resective surgeries, callosotomies, hemispherectomies (anatomical and functional), multiple subpial transections etc. This comprehensive program also includes a nicely developed rehabilitation program (Fandiño-Franky, personal communication).

Other efforts have also been made in Colombia. In Bogotá, Nariño *et al.* developed an epilepsy surgery at the Hospital Central de la Policía and at the Palermo Clinic. They have already operated on 45 patients, including some with invasive studies (Nariño, personal communication).

Costa Rica

Epilepsy surgery has been performed only recently in Costa Rica. Sittenfeld and his group at the Hospital Doctor Carlos Saenz, have operated on 45 children since 200l. the group includes callosotomies, temporal lobectomies and extratemporal resections; some patients required invasive studies. At 2-year follow-up the authors report Engel's class I outcome

in 2/3 of their patients, both temporal and extratemporal groups as well as significant seizure reduction in 8/17 callosotomies practiced on children (Sittenfeld, unpublished work).

Cuba

An epilepsy surgery program was created in 2000, at the International Center for Restorative Neurology (CIREN) in Havana,[35] where they have started to perform video-EEG monitorings in 2000; the first surgical procedures, temporal resections, began in 2002 and later a few callosotomies have been performed. The medical team, which includes neurophysiologists, epileptologists, neuropsychologist, and neurosurgeon, was trained at the MNI. Patients are evaluated with surface video-EEG monitoring, neuroimaging, and SPECT; Wada tests are not performed (Bender, personal communication).

Dominican Republic

In this country there were no known epilepsy surgery treatments in the past. Since 2003 Video-EEG monitoring has been practiced at the Corazones Unidos Clinic, in Santo Domingo City where anecdotical extratemporal resections have been performed recently (Santos-Viloria, personal communication).

Ecuador

There has been no known epilepsy surgeries performed in Ecuador. Just recently Video-EEG monitoring was started at the 'Hospital Metropolitano', in Quito, the capital city, by the epileptologists Abad and Pesantes and the neurosurgeon Varsallo, trained in epilepsy surgery in Freiburg, Germany (Pesantes J, personal communication).

Mexico

The first communications about epilepsy surgery in Mexico date back to the early 1950s and were performed by Manuel Velasco Suarez, one of the most distinguished Mexican neurosurgeons. In 1951 he founded the Mexican League Against Epilepsy and later, in 1964, the National Institute of Neurology and Neurosurgery (Mexico City).[36]

Later, a pioneering work on deep brain stimulation has been developed since the mid-1980s by two other neurosurgeons, Francisco and Marcos Velasco, from the Instituto Mejicano de Seguridad Social Medical Center. They proposed centromedian median thalamic nuclei stimulation for the treatment of patients with intractable generalized tonic-clonic seizures,[37–39] using this therapy for up to 2 years, through a special device they had developed; they described good outcomes in generalized seizures but not in generalized tonic nor complex partial seizures. These same authors also reported the use of subacute electrical hippocampal stimulation, with either depth or subdural electrodes, in 10 patients who had withdrawn anticonvulsants for 48–72 hours; after a stimulation period of 2–3 weeks the patients underwent anterior temporal resections. With this method seizures were abolished in seven of these patients and even the interictal spiking was reduced significantly.[40] The Velascos have also reported on the use of bilateral cerebellar stimulation in a group of five refractory epilepsy patients, in a double-blind controlled study which used the same patients as controls, and obtained a statistically significant seizure reduction.[41]

An epilepsy surgery program that uses a more conventional approach was established in Mexico City, at the National Institute of Neurology and Neurosurgery, where temporal and extratemporal resections are performed, using intraoperative electrocorticography and cortical stimulation whenever appropriate. A 2-year follow-up report of 100 resective surgeries in temporal lobe epilepsy was presented in 2004, showing seizure free outcome in 84% of the patients.[42] At this center, vagal nerve stimulation was also implemented for refractory epilepsy in 2001.[43] Pella *et al.*, also in Mexico City, established an epilepsy surgery program at the Angeles del Pedregal Hospital in 1995. They have performed more than 100 surgeries, in both children and adults, including temporal and extratemporal lobectomies, callosotomies, and radiosurgical procedures (Pella *et al.*, personal communication).

Recently epilepsy surgery has been developed at the Instituto Potosino de Neurociencias, in San Luis de Potosí. Villalobos *et al.*[44] reported their experience in a group of 40 patients, children and adults, who underwent resective surgery.

Peru

Esteban Rocca, a neurosurgeon trained under the Chilean Alfonso Asenjo in the 1940s, founded the Neurosurgery Unit at the Hospital Obrero in Lima in 1947.[45] Working with Juan Franco, a neurosurgeon trained in Chile and the USA, he performed resective surgeries in 1955, using corticograms as guidance.[46] However, details of the surgical procedures and results were not presented. In Arequipa, a southern Peruvian city, Ortega and Gamero[47] in 1973 reported on 30 intractable patients with generalized seizure disorders that were treated with surgical section of the genu of the corpus callosum and anterior white commissure; significant improvement or complete control was achieved in 90% of these patients. No epilepsy surgery programs are currently established in Peru.

Uruguay

Alejandro Schroeder, the founder of Uruguayan neurosurgery, introduced the EEG and initiated epilepsy surgery at the Instituto Neurologico in Montevideo. He was initially trained in central nervous system histology in Hamburg, Germany and later he had the chance to work with Ostrid Fester in Breslau; after this latter experience he became interested in neurosurgery, starting his practice in 1930.[9] In 1949 he reported the first Latin-American series on lesionectomies at the Third South American Neurosurgery Congress held in Buenos Aires, Argentina.[1] It included ten patients studied preoperatively with surface EEG and cerebral angiograms; intraoperative electrocorticography was also performed and used as the main criterion for guiding surgery, since resections were done only when corticograms showed spikes, which was the case in the seven patients. The authors stated

that, after clinical and EEG studies, 'we mark on the skin the epileptic focus as exactly as possible'. Also in Montevideo, Arana Iñiguez, a neurosurgeon trained in Santiago, Chile, and Boston, USA performed one of the earliest hemispherectomies in Latin-America.[9] In 1961, Bogacz *et al.*[48] studied 62 patients with unilateral temporal lobe foci, using nasopharyngeal and sphenoidal electrodes. Seven of these patients underwent invasive studies with deep electrode threads for 24 hours, followed by temporal lobectomy.

As has happened in many other countries, no further epilepsy surgeries were performed for decades and only recently has an epilepsy surgery program been started in Montevideo at the Instituto de Neurologia del Hospital de Clínicas, led by Alejandro Scaramelli. Up to date they have performed 17 temporal lobectomies using non-invasive techniques (Scaramelli, personal communication).

Venezuela

Arminio Martinez *et al.*[49] working at the José María Vargas Hospital, in Caracas, the capital city, started temporal lobectomies in 1955, following the Montreal Neurological Institute approach, including the use of intraoperative electrocorticography and electrical stimulation; up to 1972 they had operated on 13 patients, reporting complete control in 9 and improvement in 2 patients. The same group performed the first hemispherectomy in Venezuela in 1959. After several decades Scholtz and Ponce, at the same Vargas Hospital, performed some other epilepsy surgery procedures. In 2000, Soto, *et al.* established a new epilepsy surgery program, working at the Domingo Luciani University Hospital and the Floresta Medical Institute where they have performed temporal and extratemporal resections, callosotomies, and vagal nerve stimulations (Soto, personal communication).

Concluding remarks

The history of epilepsy surgery in Latin America parallels the rest of the world. Very early attempts to develop this therapy following the Montreal Neurological Institute's approach can be found in several countries of the region. The pioneering work of the Brazilian neurosurgeon Paulo Niemeyer Soares, who proposed almost 50 years ago the selective amygdalohippocampectomy, a technique still used nowadays, is a good example of the interest Latin America has historically shown in epilepsy surgery.

More recently in the region, epilepsy surgery has followed the extraordinary development in first-world countries, including the area of neuroimaging. Unfortunately, Latin America has also great diversity in the organization of the health system and the breach between the number of patients needing epilepsy surgery and the actual amount of surgeries performed is certainly much larger than in developed countries. Only Brazil has a nationwide epilepsy surgery program and this experience, in this respect, probably has unique features, due to its universality (available to every citizen independent of socioeconomic status), high medical standards at minimal costs (strict definitions of human and technical requirements, and surgical protocols), and a controlled and organized accreditation system (supervised by Health Department and medical societies) which could be seen as an example not only for developing but also to developed countries.

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15 Epilepsy surgery in Africa

MF Moodley and EL Khamlichi

Introduction

Epilepsy is the most common chronic neurological disorder estimated to affect at least 50 million people worldwide; 80% of whom reside in developing countries.[1] In Africa where 50% of the population is under 16 years of age, the prevalence is even higher making epilepsy a significant health and socio-economic burden.

Africa is the second largest continent with 35 million square kilometers and more than 800 million people distributed in 52 different countries.[2] Seventy-five percent of people with epilepsy in Africa receive inadequate or no treatment at all. Paralleling the enormous geographic, cultural and economic differences in this continent the neurological and neurosurgical services are equally diverse. Limited financial resources, illiteracy, social instability, war, lack of prioritization, poor health system infrastructure, and inadequate supplies of antiepileptic drugs in concert hinder the delivery of appropriate treatment. Furthermore, the vast majority of Africans still live in villages and there is a significant rural/urban divide in epilepsy services, with the vast majority of neurologists and neurosurgeons being concentrated in the major cities. Belief in supernatural causes and traditional treatment of epilepsy in Africa further contribute to the under-utilization of available medical services, to discrimination and social isolation.

Epidemiology and etiology of epilepsy

In Africa preventable causes of epilepsy (central nervous system infections, head trauma, poor antenatal and perinatal care) are more frequent resulting in greater disability and mortality in Africa than elsewhere.[3] The high incidence figures for epilepsy in developing countries is significantly attributable to symptomatic epilepsies caused by a host of parasitic and infectious diseases that are largely absent in industrialized countries.[4–6] Neurocysticercosis, for example is frequently found in people with epilepsy in developing countries and in South Africa it is a major cause of seizures in both children and adults.[4,7] Furthermore, in South Africa, 50% of children with recurrent seizures had had their first seizure before the age of 2 years, and 32% and 11% of the patients studied had a history of perinatal complications and meningitis respectively.[6]

Epidemiologic studies from North Africa are scarce, but in general, prevalence and incidence of epilepsy are much lower, perhaps because of a lower rate of infection than in Sub-Saharan Africa, better medical infrastructures, and more trained medical personnel in the North than in Sub-Saharan Africa.[8]

Despite the advent of modern anti-epileptic drugs in the last three decades, 30–40% of patients with epilepsy have intractable seizures. Almost half of these patients are potential surgical candidates and of these carefully selected patients, chance of freedom from seizures after surgery is in the range of 60–75%. If we consider the high number of African patients with refractory epilepsy, the cost of the anti-epileptic drugs, hospitalization, and the economic conditions of the majority of patients, it becomes clear that surgical treatment is more cost effective than sustained pharmacotherapy.

Epilepsy surgery has thus become readily adapted in many developing countries with limited resources like Brazil, China, India, and Turkey.[9,10] These all argue in favor of the development of epilepsy surgery programs in Africa, and African neurologists and neurosurgeons should develop epilepsy surgery programs with the knowledge that the success of epilepsy surgery depends more on well-trained clinical teams, than on high-level technology.

Contribution of Africa to the history of epilepsy and epilepsy surgery

Epilepsy is an ancient disorder, well described in many early civilizations with remarkable descriptions of epileptic attacks in early Babylonian texts of medicine (1000 BC)[11] Despite this very ancient description, the concept of epilepsy etiology has remained for centuries dominated by supernatural views, considering seizure attacks as a divine visitation (religious concept), or with an invasion of the body by evil spirits (superstitious concept). Consequently the treatment was not medical but spiritual with religious and/or various social approaches. The contributions of Africa, particularly the Northern part, to the history of epilepsy had been significant in the Middle Ages, between the 9th and 13th centuries, the golden age of the Arab–Islamic civilization, which extended at the time around the Mediterranean Sea. Among some outstanding individuals with medical knowledge, two individuals stand out: Abu-Bakr Al Razi, 'Rhazes' (830–923) and Hussein Ibn Sina, 'Avicenna' (980–1037), who left us the best descriptions of epilepsy.[12]

In his huge monograph ('Alkanun FiTib', Rules of Medicine), Avicenna described different types of epilepsy syndromes: tonic-clonic seizures, absence and focal seizures including focal-motor seizures, with its typical extension from the toes to the proximal lower limbs and from the fingers to the proximal upper limbs, and known today under the name

of Jackson, who described it 800 years later.[13] In Avicenna's monograph he also described many symptoms which can occur before or after a seizure which we now recognize as auras and postictal phenomena.

The interesting point in this historical manuscript is that Avicenna, referring to Hippocrates, mentions the concept that epilepsy is a brain disease and that seizures result from an invasion of the frontal lobes by a noxious substance which then propagates towards the posterior part of the brain and later to the spinal cord and the peripheral nerves. This propagation engenders generalized seizures. He considered these seizures of the body as resulting from a contraction of the brain which is necessary for the expulsion of noxious substances, and comparing also these contractions of the brain to the contractions of the stomach during hiccup or vomiting in order to 'chase noxious food'.[13] This medical knowledge about epilepsy and many other brain diseases that excelled between the 9th and the 13th centuries in Fez and Marrakech (Morocco), in Kairouan (Tunisia), and in Cairo (Egypt), was later transmitted to Europe in the 14th and 15th centuries, where it would be improved to prepare the Renaissance movement of neurology in the 18th and 19th centuries and the modern era of epilepsy.

As far as African neurosurgery is concerned it is well known that during the pharaonic era, neurosurgical procedures like trephinations were widely used in the whole continent, practiced and taught by healers in African tribes.[14] The technical concepts of this trephination are based, to a great extent, on the descriptions of Arab physicians of the Middle Ages.[14]

Of the many outstanding Arab physicians it was mainly Abulkassim Al Zahraoui (Abulkassis) who was the pioneer of neurosurgery. He is credited with devoting a volume of his treatise (made up of 30 volumes) to neurosurgery, a precise description of many aspects of neurosurgical pathology, its treatment, instruments and neurosurgical techniques.[14] In Kenya, the traditional art of skull trephination, passed down from generation to generation, and is still practiced by the Kisii tribesmen in the highlands of the South Nyanza District of Kenya.[15] As recently as 1982 a local daily newspaper featured an article entitled 'Skull Surgeon Who Never Went to Medical School'. This story focused on one of the well-known practitioners of trephination since 1955 having learned it from his grandfather. He claimed that he had performed hundreds of these procedures and that most of his patients had already been treated at hospitals without success.[15]

He added, 'Doctors in Kenya are not able to open the skull the way I do, and when a patient goes to them full of broken bones in the head, the treatment is often incomplete.' Neurosurgeons in Kenya encounter patients who have undergone this procedure. The openings in the skull vary from a few centimeters to removal of the entire vault. Trephinations were made for ritual or therapeutic purposes. It is speculated that they were intended to free the body from devils and spirits. It is thus easy to imagine that epileptics, in many African cultures viewed as possessed, underwent these trephinations.[15]

It is interesting to note that despite these significant contributions and the fact that this land was the birth place of our early human ancestors the vast majority of its population has not yet been part of the great technological/industrial revolutions that has occurred in many other parts of the world. Thus, the challenges facing Africa in the domain of medicine remain immense.[16]

Neurosurgical practice developed in many African countries only during colonization, together with the development of the health system as soon as the European colonizers came to these countries. Initially, neurosurgery was practiced in the departments of general surgery either by general surgeons or rarely by neurosurgeons themselves.[14]

Modern neurosurgery was introduced and started to develop in most African countries in the early 1960s, and the teaching of this subspecialty in many African universities began between 1960 and 1970, soon after their independence. However, in South Africa neurosurgery as an independent discipline commenced much earlier at the Groote Schuur Hospital in Cape Town with the return of Hermann de Villiers Hammann from Munich, Germany in 1946.[17]

Neurosurgery for intractable epilepsy, on the other hand, was practiced even earlier as the late 1940s. Roland A. Krynauw, a neurosurgeon from the Department of Neurosurgery, Johannesburg Hospital in South Africa pioneered hemispherectomy for children, adolescents and young adults with intractable seizures accompanying infantile hemiplegia.[18] Over a 5-year period he performed hemispherectomies on 12 patients with intractable seizures accompanying infantile hemiplegia with remarkable success. Epilepsy, either focal or generalized, was present in 10 of the 12 patients and in all these patients epileptic manifestations ceased in the post-operative period without any sedative medication. Furthermore, marked improvement in personality, behavior, and mental function was noted in all cases. His success with hemispherectomy soon attracted world wide attention to this neurosurgical procedure for intractable seizures.[18]

Management of epilepsy in Africa

While remarkable progress has been made worldwide in the second half of the 20th century in the diagnostic evaluation of neurological diseases, including epilepsy, in Africa this development was mainly-in the more affluent North and South Africa and remains restrained in the rest of the continent by the poor socio-economic conditions. In many countries in Sub Saharan Africa neurological and neurosurgical services are nonexistent creating a broad divide – 'From excellence to total absence'.

Fortunately, EEG is available in the majority of countries in Africa (82.4%), however, the availability of other investigations are limited in the majority of African countries.[19] Video EEG monitoring is available in 25.7% of African countries, 18 African countries have no CT scanners, 13 countries have only 1 CT scanner for each country and only 13 other countries have more than 2 CT scanners. Only North African countries and South Africa have an adequate number of CT and MRI scanners.[19–21] In addition, even in those countries with neuroimaging equipment, the majority of the population who live in rural areas do not have access to this equipment, because of limited economic resources and a lack of medical insurance. In the absence of these advanced technologies, most of the common causes of symptomatic epilepsy cannot be diagnosed in many countries in Africa.

The management of epilepsy in Africa is highly influenced by the socio-cultural misrepresentation of epilepsy. Consequently,

less than 20% of patients will seek medical attention after their first seizure, the other 20–30% will seek a healer or marabout (holy temple) for traditional treatment.[22] The remaining 50–60% will not seek any treatment. This delays diagnosis and treatment, with more than 50% of patients seeking medical help one year after their first seizure, and 30% 5 years after their first seizure.[23,24]

The mainstay of pharmacological treatment throughout Africa is phenobarbital, which has two main advantages: reliability of supplies and affordability with 50–80% of treated patients being on phenobarbital.[25] Most of the other older anticonvulsants like phenytoin, carbamazepine, valproic acid, and benzodiazepine are available in secondary and tertiary hospitals. The 'new' anticonvulsants discovered in the last 15 years are generally not available in the vast majority of countries in Africa. In South Africa on the other hand, it is available in most tertiary and quartenary hospitals and also in private clinics but cost is again a prohibitive factor for its widespread use.

Epilepsy surgery in Africa

Epilepsy surgery is a well accepted, safe and effective alternative treatment for patients with medically intractable epilepsy in developed countries.[26,27] However, in addition to appropriate technologies for pre-surgical evaluation, the success of epilepsy surgery depends on availability of well-trained clinical teams made up of neurologists, neurosurgeons, clinical neurophysiologists, neuropsychologists, and neuroradiologists, components not easily available in developing countries.

In the 1990s, 10 of 142 developing countries conducted epilepsy surgery and by 2000, 26 such countries have reported results of epilepsy surgery in carefully selected patients and this number is gradually increasing.[10] In Africa most of these reports emanate from the two extremes of the continent, the more affluent North and South Africa with almost the entire rest of the continent still experiencing a significant delay in the development of neurosurgery. The challenge is resource allocation in competition with other demands, in particular primary healthcare. A survey conducted in 1998 under the hospices of WHO, found only 565 neurosurgeons for a population of over 800 million (ratio of 1 neurosurgeon to 1,352,000 people).[20] The world wide ratio is 1 neurosurgeon to 230,000 people with 1 neurosurgeon to 121,000 people in Europe and 1 Neurosurgeon to 81,000 people in North America.[2] The distribution of neurosurgeons in the African continent shows that the majority are located in North Africa (Egypt 165, Algeria 130, Morocco 80, Tunisia 25) and South Africa (86). Consequently the total number of neurosurgeons in these countries is 486 for a total population of 174 million, with a ratio of 1 neurosurgeon to 358,000 people. Between North and South there are three countries that have between 8 and 15 neurosurgeons (Nigeria, Senegal, and Kenya), and the majority of other countries have between 1 and 5 neurosurgeons, with no neurosurgeons at all in 11 countries. Therefore, the ratio in Sub-Saharan Africa is 1 neurosurgeon to 7 million people. The biomedical equipment available has almost the same distribution.[2]

A local training program in neurosurgery is currently available only in North African countries and in South Africa. Most young neurosurgeons in the rest of Africa are trained outside the continent, mainly in Europe. Currently in South Africa there are a few centers in Cape Town, Johannesburg and Durban that have impressive pre-surgical technology and clinical teams who perform epilepsy surgery in carefully selected patients. (personal communication Roger Melville and James Butler). Subdural electrode placements, temporal lobectomies, and cortical resections account for the bulk of the surgery performed. Multiple subpial resections and functional hemisperectomies are also performed occasionally (personal communication Roger Melville).

In Morocco it took many years to find motivated people to create a multidisciplinary team and to commence epilepsy surgery which only began in February 2005. Surgical procedures so far have included temporal lobectomies and simple structural lesion surgery.

Faced with the reality of a scarcity of human and technological resources, is there room for epilepsy surgery in developing countries like those in Africa? Because of the high prevalence of epilepsy in Africa, the high cost of sustained pharmacotherapy, its medical intractability, and the high frequency of symptomatic epilepsy, epilepsy surgery offers a potential treatment to rescue a large number of patients with epilepsy in Africa.

Moreover, these are the reasons behind the development of many epilepsy surgery programs in countries with limited resources, like Brazil, China, and Turkey and these programs have demonstrated that surgery is more cost effective than sustained pharmacotherapy.[9] In addition, surgery will have a positive impact on the mental capacity of epileptic patients and of society in Africa, allowing patients to conceive of epilepsy as an organic disease originating from the brain, which can be cured with surgery. Even with limited technological and human resources carefully selected patients from an abundance of surgical candidates, the teams achieve outcomes comparable to those in the developed world with direct epilepsy surgery costs at a fraction of those in the developed world.

Future of neurosurgery and epilepsy in Africa

More than 80% of the 50 million people suffering from epilepsy around the world live in developing countries like those of Sub-Saharan Africa where the vast majority do not receive any modern treatment or are not even identified.[28] The main reasons behind this treatment gap are poor health care systems, illiteracy and cultural beliefs especially in Sub-Saharan Africa. Some other potential causes of this treatment gap are a lack of prioritization of epilepsy as a public health issue, inadequate preventative programs and a high prevalence of epilepsy in Africa.

Regarding the 'surgical treatment gap' in epilepsy there is a great divide – well catered for in North African countries (Egypt and Morocco) and South Africa and almost non-existent in the rest of the continent.[10,29] If we consider the proposed ratio by H. G. Wieser of 1 epilepsy center for 7 million people as estimated in developed countries, Africa with more than 800 million people, needs more than 100 epilepsy surgery centers making the bridging of the surgical treatment gap in

epilepsy in Africa an impossible dream.[10] The main problem to overcome is the scarcity of neurosurgeons and neurologists in the majority of African countries. Without their expertise it becomes difficult to organize any multidisciplinary team to solve the huge challenge of reducing the treatment gap in epilepsy between Africa and the developed world. Pioneering African neurosurgeons should develop neurosurgery in their countries by encouraging local training programs which remain the major pillar in the development and quicker promotion of neurosurgery in their countries as exemplified by North African countries and South Africa. African trainees in developed countries generally are not keen to return, and when they return do not have the resources which they have trained with rendering them ineffective or demoralized and thus paving the way for the growing 'brain drain' from Africa to Europe and North America.

The second main problem is to convince the political authorities and health planners that epilepsy is a public health issue, despite other high priority health demands, as in most African countries epilepsy and neurosurgery in general seem to have a very small place on public health priority programs.

Neurologists and neurosurgeons as advocates for patients with epilepsy should sensitize other individuals including non-medical professionals, patients and community Non-Governmental Organization (NGOs) to apply pressure on governments, health planners, and decision makers so that proposals for building sustainable training programs are put in place.

Epilepsy care development in Africa can also benefit from international cooperation and the help of international institutions like the WHO, the ILAE, and the International Bureau for Epilepsy (IBE). These three institutions make a major collaborative effort through the global campaign against epilepsy 'Out of the Shadows', which was launched in 1997 'to improve acceptability, treatment, services and prevention of epilepsy worldwide in order to address discrimination against people with epilepsy and to diminish the treatment gap in the developing regions of the world.'[1]

Three other institutions can efficiently help epilepsy programs in Africa: The World Federation of Neurosurgical Societies (WFNS), the World Federation of Neurology (WFN), and the Pan-African Association of Neurological Sciences (PAANS).[30] These institutions can help at different levels: at the information level by sending reports on the epilepsy care situation in Africa to governments and universities in African countries; at the training and research levels by organizing courses, seminars, and granting fellowships to young African doctors to be trained in neurology and neurosurgery. In 1998 the WFNS initiated the creation of the 'WHO Africa Sub-Committee in Neurosurgery,' which prepared a report on the state of neurosurgery in Africa, which was presented to the WFNS and the WHO working group in Neurosurgery in 1999,[20] resulting in the creation of the 'WFNS Foundation For Training Young Neurosurgeons from developing countries' in 2002. It also created the first reference center in the Department of Neurosurgery at the University Hospital in Rabat to train young African doctors, and the Mohamed V University of Rabat arranges and insures their training.

Conclusion

Epilepsy remains an important public health problem in Africa. With its high prevalence and the lack of appropriate diagnostic and therapeutic facilities it represents an important economic and social burden in the majority of African countries. The main constraints widening the treatment gap in epilepsy include lack of knowledge about epilepsy, cultural attitudes especially in rural people, poor advocacy for neurosurgery at governmental level, and the limited human and material resources in the majority of African countries.

The optimistic element, however, is the existence of neurosurgical centers of excellence at the two extreme parts of the continent, namely North and South Africa. Neurosurgeons in these areas can integrate epilepsy surgery in a fairly rapid way in their centers, using non-invasive pre-surgical investigations to successfully select the patients with intractable epilepsy. With the combined effort of North Africa and South Africa and substantial support for African neurosurgery from the international community, the development of neurology and neurosurgery in Sub-Saharan Africa can be improved and the treatment gap in epilepsy can be filled.

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16a History of epilepsy surgery in Southeast Asia

S-H Lim

Overview of epilepsy surgery in Southeast Asia

Southeast Asia (SEA) covers an area of about 4 100 000 square kilometers containing the following countries: Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. As of 2007, there are more than 580 million people living in this region. If the epilepsy prevalence rate is 5 per 1000 population, SEA would have around 2.9 million people with epilepsy (PWE). If a quarter of these PWE are medically refractory, more than 700 000 of them could be evaluated for epilepsy surgery. However the epilepsy surgery treatment gap is huge in SEA.

An informal survey conducted by the author in 2003 (unpublished data) showed that <150 epilepsy surgeries were performed for adult and pediatric patients in SEA in the 1990s and early 2000s, mainly in Thailand, Singapore, Malaysia, and Indonesia, with fewer cases in the Philippines. 80–90% of these surgeries, were temporal lobectomy (standard anterior temporal lobectomy > selective amygdalo-hippocampectomy) while the rest were lesionectomy, neocortical resection, corpus callosotomy, hemispherectomy, and implantation of vagus nerve stimulator (VNS). Similar to the results in countries belonging with developing economies, 60–70% of temporal lobectomy patients achieved Engel Class I seizure outcome, while another 10–15% had rare seizures or worthwhile improvement.

These surgeries were performed at tertiary referral centers, established in the late 1980s in Thailand, early 1990s in Singapore, and in the second half of the 1990s in Malaysia, Philippines, and Indonesia. There are currently 1–4 centers per country, located in capital cities. Each centre has 1–5 epileptologists and 1–2 neurosurgeons with special interest and/or trained in epilepsy surgery. Many centers perform long-term video-EEG monitoring and structural MRI routinely. The usage of SPECT, Wada Test, MRS, neuropsychological testing, and psychiatric assessment is variable. Intracranial EEG recordings are rarely performed and PET study is only available in two countries. To date, there is no epilepsy surgery program in Brunei, Cambodia, Laos, Myanmar, or Vietnam.

There are common issues in SEA that continue to retard the development of epilepsy surgery in this region. Costs of evaluations and surgery are relatively high in most countries. Socially and culturally, many patients were reluctant to undergo cranial surgery for a condition not considered immediately life-threatening by these patients and their family. This tied in with the perception by the lay that cranial surgery is oftentimes morbid and considered an extreme intervention. Family support in SEA was relatively strong, thereby obviating the need for independence and self-support. Many patients in the rural areas are still probably undiagnosed and not informed of the epilepsy services available in the country. Public transport services in big cities are fairly prevalent and convenient. The need to be seizure free to drive was not as pressing as in other countries like the United States.

The following sections describe the development of epilepsy surgery in Indonesia, Malaysia, Philippines, and Singapore. The epilepsy surgery programe in Thailand is briefly mentioned here as the details are described in Chapter 19.

History of epilepsy surgery in Indonesia

Indonesia is the largest country in Southeast Asia with a population of 224 millions and has the largest pool of epilepsy patients who require epilepsy surgery. However, there was no epilepsy surgery program till the end of the 1990s. Unlike other SEA countries where epilepsy surgeries are driven by trained epileptologists, surgery for epilepsy in Indonesia was initiated by a neurosurgeon, Dr Zainal Muttaqin from Semarang, Indonesia.

Dr Muttaqin, influenced by the blooming of epilepsy surgeries in other parts of the world, developed an increasing interest in epilepsy surgery in the middle of the 1990s. To increase the awareness of clinicians and lay-public in epilepsy surgeries, he organized an epilepsy surgery symposia at national and regional neurology scientific meetings, at which Prof T Hori from Japan was a keynote speaker. He also started writing review articles on surgery for epilepsy in Indonesian language medical journals. He then decided to acquire the skills of epilepsy surgery and traveled to Hiroshima, Japan many times between 1996 and 2001 to learn epilepsy surgery from Dr Kazunori Arita and Prof Kaoru Kurisu, at the Hiroshima University. With their help, the first case of left temporal lobectomy was performed in 1999. Surgery was performed based on clinical information suggestive of temporal lobe seizures and MRI evidence of left temporal sclerosis. Another 10 cases were operated in 2000–2001, all based on clinical history suggestive of TLE semiology and unilateral hippocampal structural abnormality on MRI.

Due to the limitation of financial resourses, most of the MRI machines were of 0.5 Tesla in strength, including the only centre (Diponegoro University Hospital) that performed epilepsy surgery. Only a few hospitals affiliated to universities had acquired 1.5 Tesla machines which are not used for presurgical evaluation. Prolonged EEG recording with video monitoring facility is still lacking, thus it is not part of presurgical evaluation protocol. Even for routine EEG recording, most of the machines were 10 channels, though a few of the nonepilepsy surgery centers have acquired 20–32-channel EEG machines with video recording capability. There is also a lack of trained electroencephalographers (EEGers) in Indonesia. Between 2000 and 2006, there were three adult neurologists who received 6–12 months of training, mainly in routine and noninvasive long-term EEG monitoring and clinical epileptology. Other issues included inconsistent presurgical evaluation protocols, postoperative follow-up mainly by neurosurgeon, no other trained neurosurgeon, as well as late identification and referral of intractable cases. As such, decision for surgery was made mainly by Dr Muttaqin, very often based mainly on the findings obtained from low-resolution MRI imaging.

Despite the above-mentioned limitations, more than 100 patients had epilepsy surgery between 1999 and 2006. Over 90% had temporal lobectomy with removal of mesial structures, mainly for patients with mesial temporal sclerosis. A few patients had a Wada test and subdural grid recording (in those with normal MRI). One patient had intraoperative ECoG. For those with temporal lobectomy that had 12–82 months of follow-up, about 75% had Engel's class I seizure outcome and two-thirds of these patients could have their AEDs withdrawn. A few patients had lesionectomy, multiple subpial transaction, functional hemispherectomy and corpus callosotomy.

History of epilepsy surgery in Malaysia

Malaysia has a population of 28 million people but only had one 'one-stop' epilepsy surgery center in the 1990s and early 2000s. The adult epileptologist who pioneered the epilepsy surgery programme in Malaysia was Professor Raymond Azman Ali. He was trained by Prof David Fish in video-EEG monitoring, presurgical evaluation, and neuroimaging at the Institute of Neurology, Queen Square, London, from 1992 to 1994. At the same time, a neurosurgeon, Prof Benedict Selladurai, was also trained at the institute by Prof David Thomas and Mr. William Harkness in epilepsy surgery.

Upon returning to Malaysia in 1994, they together started the epilepsy surgery programme in 1995 at the Universiti Kebangsann Malaysia Hospital. The first operation was performed on an 11-year-old boy with a dysembryoplastic neuroepithelial tumor in the mesial temporal region, who became seizure free. When they announced the successful operation in one of the national newspapers, interest in epilepsy surgery amongst PWE increased tremendously. Not all surgical patients were from the same hospital, as many were referred from other major hospitals, including Kuala Lumpur Hospital and University Malaya Medical Centre. The hospital was supportive in upgrading the neurophysiology laboratory and neuroimaging service. However, they did not have a stand-alone epilepsy surgery centre, in-patient ward or epilepsy nursing staff. They also employed neuropsychologists interested in epilepsy. One of the psychiatrists went on to subspecialize in neuropsychiatry. In 2000, Prof Lai-Choo Ong, a pediatric neurologist, received training in Royal Melbourne Children's Hospital under the supervision of Dr Simon Harvey. Another adult neurologist, Dr Hui-Jin Tan, is currently being trained in clinical epilepsy.

EEG facilities included a video-EEG monitoring unit using scalp and sphenoidal electrodes. A few patients had intraoperative ECoG. They have not developed intracranial EEG capability. As for neuro-imaging capability, they have 1.5 T MRI machine and are able to add MRS to their evaluation protocol. Ictal SPECT was rarely performed. Neuropsychological evaluation was routine, but there was no expertise in performing WADA tests.

Standard anterior temporal lobectomy was started in 1996, followed by selective amygdalohippocampectomy and lesionectomy in 1999. Hemispherectomy, corpus callosotomy, and implantation of vagus nerve stimulator were started in 2001. Between 1996 and 2006 around 75 cases of anterior temporal lobectomy and 15 cases of selective amygdalohippocampectomy were performed with 70% of these patients achieving Engel's Class I seizure outcome. Two patients had hemispherectomy and both became seizure free. Twelve patients had lesionectomy and 55% achieved Class I seizure outcome. There were three cases of corpus callosotomy and one VNS and all had Class IV seizure outcome.

The main challenges encountered in developing the epilepsy surgery programme were lack of full-time staff (epileptologists, epilepsy neurosurgeons, neuroradiologists, neuropsychologists, nurses, and neuroanaesthesiologists). Currently only one centre performs a consistent number of epilepsy surgeries. Even then, the infrastructure for this 'one-stop' centre is underdeveloped.

History of epilepsy surgery in the Philippines

The Philippines have a population of 87 millions. There are 3–4 hospitals offering epilepsy surgery since the late 1990s. With the continued return of clinicians trained in epileptology and subsequently in epilepsy surgery, the comprehensive epilepsy program was established in 1997 at the St. Luke's Medical center. This center is one of the premier private hospitals in the country with the necessary resources to support the epilepsy surgery program. The center had a 'multidisciplinary team' composed of the following members: epileptologists, an epilepsy surgeon (Dr Annabelle Chua), neurophysiologists, psychiatrist, nurses, EEG technicians, and dieticians. The objective of the program was not only to evaluate patients and their suitability for epilepsy surgery, but also to offer overall better management and control of patients with difficult to control seizures.

The Epilepsy Monitoring Unit at the St. Luke's Medical Center is a three-bed unit capable of offering 2-hour and prolonged video-EEG monitoring. In addition, there are three other one-bed units in other hospitals with in-house epileptologists trained in video-EEG monitoring, namely the University of the Philippines-Philippine General Hospital, the Philippine Children's Medical Center, and the Makati Medical

Center. Epilepsy clinics were established in two training hospitals: the University of the Philippines-Philippine General Hospital and the University of the East-Ramon Magsaysay Medical Center.

Presurgical evaluation included CT scan, MRI, PET scan, video-EEG, neuropsychological evaluation and WADA test. For the latter, this is being done only at St. Luke's Medical Center, with its performance being limited by the difficulty in procuring amobarbital from the United States. There was also intracranial electrode placement, extraoperative monitoring, intraoperative ECoG, and mapping of eloquent cortex.

Most patients who had resective surgery had either hippocampal sclerosis or lesion such as tumors and vascular malformations. Detailed information on the number and types of surgery, as well as seizure outcome were not available.

History of epilepsy surgery in Singapore

Singapore is the smallest country that provides epilepsy surgery in SEA. It has a population of 3.6 million, and thus the number of potential surgical candidates is considered relatively low.

An epilepsy surgery programme was established in Singapore in 1992 after the return of an adult neurologist, Dr Shih-Hui Lim, from the Cleveland Clinic Foundation (CCF). With the sponsorship of the Ministry of Health, Singapore, Dr Lim completed a formal clinical fellowship in epilepsy and clinical neurophysiology under the supervision of Prof Hans O Lüders from 1989 to 1991. He also obtained board certification by the American Board of Clinical Neurophysiology. A year later, another adult neurologist, Dr Michael WL Chee, also sponsored by the Ministry, completed similar training at CCF from 1990 to 1992. In addition, Dr Prem Kumar Pillay, a Singaporean doctor receiving his neurosurgery residency training at CCF in the late 1980s and early 1990s, was trained in epilepsy surgery by Dr Isam Awad. In the early 1990s, a pediatric neurologist, Dr Wei-Ling Lee received pediatric epilepsy training at Toronto Children's Hospital in Canada as well as at the CCF. In the mid-1990s, Dr Ngai-Kun Loh, an adult neurologist spent a year and Dr Kheng-Kooi Tan, a neurosurgeon, spent a few months at CCF. Dr Andrew Pan, an adult neurologist, was sent by Ministry of Health to CCF from 1999 to 2001 to be trained in Epileptology and Sleep Disorders. Thus the epilepsy surgery programe in Singapore in the first 10 years was considerably influenced by the philosophy of Dr Lüders. In 2003, Dr Nigel Tan received his epilepsy training with Prof Sam Berkovic at the Comprehensive Epilepsy Program at Austin Health. His return added value to the existing epilepsy surgery programme.

One-Bed video-EEG monitoring unit was first set up at Tan Tock Seng Hospital in 1992 and at Singapore General Hospital in 1993. Scalp and sphenoidal electrodes were used routinely. Most patients were monitored for 4–5 days after stopping medication, with an aim of recording at least three seizures. Due to administrative and logistic reasons, early postictal SPECT was carried out during office hours at the Singapore General Hospital. For those who had postictal SPECT had interictal SPECT during the monitoring period. All patients had structural MRI (1.5 T) which included oblique coronal images with flash/gradient echo, T2-weighted, and FLAIR sequences. Volumetric study was performed as part of the research. MRS was introduced towards the end of the 1990s. FMRI for language lateralization was started in the early 2000s, mainly for research purposes. From 2005, structural MRI using a 3.0 T MRI machine became more common. WADA tests were performed routinely in the 1990s and infrequently in the 2000s. Neuropsychological and psychiatric assessments were routine. Decision for surgery was made mainly based on structural MRI findings, scalp EEG data, and analysis of semiology of recorded seizures. As long as there was no discordant information, good candidates would proceed with resective surgery. Depth electrodes implantation was performed only once in 1994 to lateralize seizure onset. Chronically implanted subdural grid electrodes and extraoperative cortical mapping were carried out in four patients with nonlesional extratemporal lobe epilepsy in 1994 and 1995. Due to the poor seizure outcome from these cases, better MRI imaging facilities, avoidance of performing resective surgery in patients with no lesion on MRI, as well as constraint of doctors' time, invasive intracranial EEG recordings were rarely performed in the 2000s.

As expected from a center conducting mainly noninvasive presurgical evaluation, temporal lobe surgeries (standard anterior temporal lobectomy cases were more than selective amygdalohippocampectomy) and to a lesser extent, lesionectomy, were the most commonly performed surgeries. Corpus callosotomy, extratemporal resective surgery, hemispherectomy and implantation of vagus nerve stimulator were much less frequently performed.

Between 1992 and 2002, more than 110 patients had temporal lobectomy, 12 had lesionectomy, four had corpus callosotomy, three had extratemporal resection, two had hemispherectomy and seven had VNS implanted. They have been followed-up for an average of 8.5 years (range 5–15 years). There was no death or irreversible complications from surgery or intracranial EEG recording. Of those who had temporal lobe surgeries, about 66% had Class I seizure outcome (including 2 patients who had re-operation), 20% had worthwhile improvement (>90% seizure reduction) and the rest had no significant change (<90% improvement). Seizure outcomes from other surgeries were less than satisfactory (Class III and IV) and this had led to further reduction in these surgical procedures in the last 5 years.

History of epilepsy surgery in Thailand

Thailand has a population of 67 million people and has the oldest epilepsy surgery programme in SEA. It also had the largest number of epilepsy surgery cases performed (>300) in the last 10 years. As described in Chapter __, the were two eras of epilepsy surgery in Thailand: the era of general neurosurgery before the 1990s and the era of epilepsy surgery as a specialty after the 1990s. For the latter, detailed neuroimaging and clinical neurophysiology information became an integral part of the presurgical evaluation process. Professor Sira Bunyaratavej and Professor Pongsakdi Visudhipan from Ramathibodi Hospital played an important role in the development of the new epilepsy surgery era in the 1990s.

The major epilepsy surgery center in Thailand is the Chulalongkorn Comprehensive Epilepsy Program (CCEP) at Chulalongkorn University Hospital, Bangkok, Thailand, led by Dr Chaichon Locharernkul, an adult epileptologist and Dr Teeradej Srikijvilaikul, an adult and pediatric neurosurgeon. Dr Chaichon was trained in presurgical evaluation by Prof GA Ojemann and Prof GE Chatrain at University of Washington at Seattle, USA and by Dr A Ebner at the Bethel Epilepsy Center in Germany. Dr Srikijvilaikul was trained by Dr WE Bingaman at CCF. Other team members included Drs Tayard Desudchit, Krishnapundha Bunyaratavej, Chusak Limotai, and Jakrin Loplumlert, all had formal training in USA (three at CCF). Together, they offered the most comprehensive presurgical evaluation, including the routine use of SISCOM and 3.0 T MRI.

Other centers providing epilepsy surgery programme were located at Pramongkutklao Hospital and Bangkok General Hospital. Both centers were established by Dr Yotin Chinvarun in 2001 and 2002, respectively. Dr Chinvarun was an adult epileptologist trained by Prof Sam Berkovic in Australia. Members in his team included Dr Siraruj Sakoolnamarka and Dr Dittapong Boonnampol (both were adult and pediatric neurosurgeons), as well as Dr Chachrine Nabangchang (a pediatric epileptologist). This is the only center in SEA that provided gamma knife surgery for epilepsy.

Acknowledgments

The author greatly appreciates the following persons who have given the above information: Dr Zainal Muttaqin from Indonesia, Dr Raymond Azman Ali from Malaysia, Dr Annabelle Chua from the Philippines, Drs Pongsakdi Visudhipan, Chaichon Locharernkul, and Yotin Chinvarun from Thailand.

16b Epilepsy surgery in India

DK Lachhwani and K Radhakrishnan

Although trephination as a treatment for epilepsy might have been practiced in ancient India more than 4000 years ago,[1] the first modern epilepsy surgery in India was undertaken in the year 1952.[2] As has happened elsewhere in the world,[3] surgical treatment of epilepsy in India went through three phases: an initial enthusiasm (1951–1970), followed by a period of decline and a recent resurgence (from 1995). In this chapter, we intend to trace the evolution of epilepsy surgery in India along with a brief biographical sketch of the pioneers who contributed to its early development, and discuss in detail its present state and future perspectives.

The beginning

The modern era of neurosurgery in India commenced with the establishment of the first department of neurosurgery by Dr. Jacob Chandy (Figure 16b.1a) in 1949 at the Christian Medical College, Vellore, in the erstwhile state of Madras (present Tamil Nadu) in southern India.[4] After completing his medical education at Madras Medical College, Madras and Masters in Surgery at the University of Pennsylvania, Philadelphia, Chandy underwent neurosurgical training at the Montreal Neurological Institute during 1945–1948 under Dr. Wilder Penfield. After a brief assignment with Dr. Theodore Rasmussen, who was then setting up a neurosurgery department at Chicago, Chandy returned to India and joined the Christian Medical College, Vellore in 1949. One year later, Dr. Baldev Singh (Figure 16b.1b) joined Chandy as a neurologist. After completing his medical graduation, Singh joined King Edward Medical College, Lahore in 1922, where his initial interest in neuroanatomy developed. During his training in neurology at the National Hospital, Queen Square, London, Singh was fortunate to work with Kinnear Wilson, Lord Brain and McDonald Critchley. Reading about Berger's rhythm, stimulated Singh to undergo a training course in electronics and construct an indigenous apparatus in the 1940s to record the electrical activity of the brain of experimental animals. Singh went over to Gibbs's laboratory at Chicago in 1950 and spent the year, where he met Dr. Percival Bailey and participated in EEG recording on epilepsy patients on whom Bailey operated. This training proved useful to Singh to develop an epilepsy surgery program at Christian Medical College, Vellore. Coinciding with Penfield's visit to Christian Medical College, Vellore, the first epilepsy surgery in India was performed on Aug 25, 1952 by Chandy on a 19-year old male patient with infantile right hemiplegia. Singh was in the operation theater supervising the EEG recording.

At that time, 150 km north of Vellore, in the city of Madras, the second department of neurosurgery in India was being developed by Dr. B. Ramamurthi (Figure. 16b.1c). After a brilliant undergraduate education, he secured Master of Surgery and Fellowship of the Royal College of Surgeons of Edinburgh in 1947. Ramamurthi received his initial training in neurosurgery at Newcastle, UK. He subsequently visited various neurosurgical centers in Europe and spent four months with Penfield at the Montreal Neurological Institute. In October 1950, Ramamurthi joined the Madras General Hospital and Madras Medical College and started the department of neurosurgery, which he later developed into the Institute of Neurology, Madras.[5] Ramamurthi was helped with the EEG recording by Dr. T. S. Narasimhan (Figure 16b.1d), a neurosurgeon and electroencephalographer practicing in the city of Madras, who also held an honorary attachment in the Madras General Hospital. The first epilepsy surgery at the Madras General Hospital was done by Ramamurthi in 1954.

Incidentally, the four pioneers who were involved with the early development of epilepsy surgery in India – Chandy, Singh, Ramamurthi, and Narasimhan – started the Neurological Society of India in 1951 at Madras.[5] While three of them passed away, (Narasimhan in 1959, Singh in 1998, and Ramamurthi in 2003), Chandy expired on June 23, 2007.

Initial enthusiasm

During the 1950s, 1960s, and the first half of the 1970s, several patients with uncontrolled epilepsies were operated at Christian Medical College, Vellore,[2,6,7] and Institute of Neurology, Madras.[8–10] The localization of the epileptogenic focus was based on seizure semiology as obtained by history, and data from scalp interictal EEG and radiological investigations available then such as skull radiograph, pneumoencephalogram, and carotid angiogram. At the Christian Medical College, Vellore, while local anesthesia was favored during the first decade and half, most of the subsequent surgeries were performed under general anesthesia.[6,7] Pre- and post-resection electrocorticogram (ECoG) was routinely done using surface and depth electrodes. Cortical stimulation to map motor and language areas and induction of seizures intraoperatively were practiced when indicated. In a recent retrospective analysis of the clinical profile and outcome of 141 patients operated for intractable epilepsy at Christian Medical College, Vellore (a majority of them during 1950s, 1960s, and first half of the 1970s), 102 (73%) had temporal

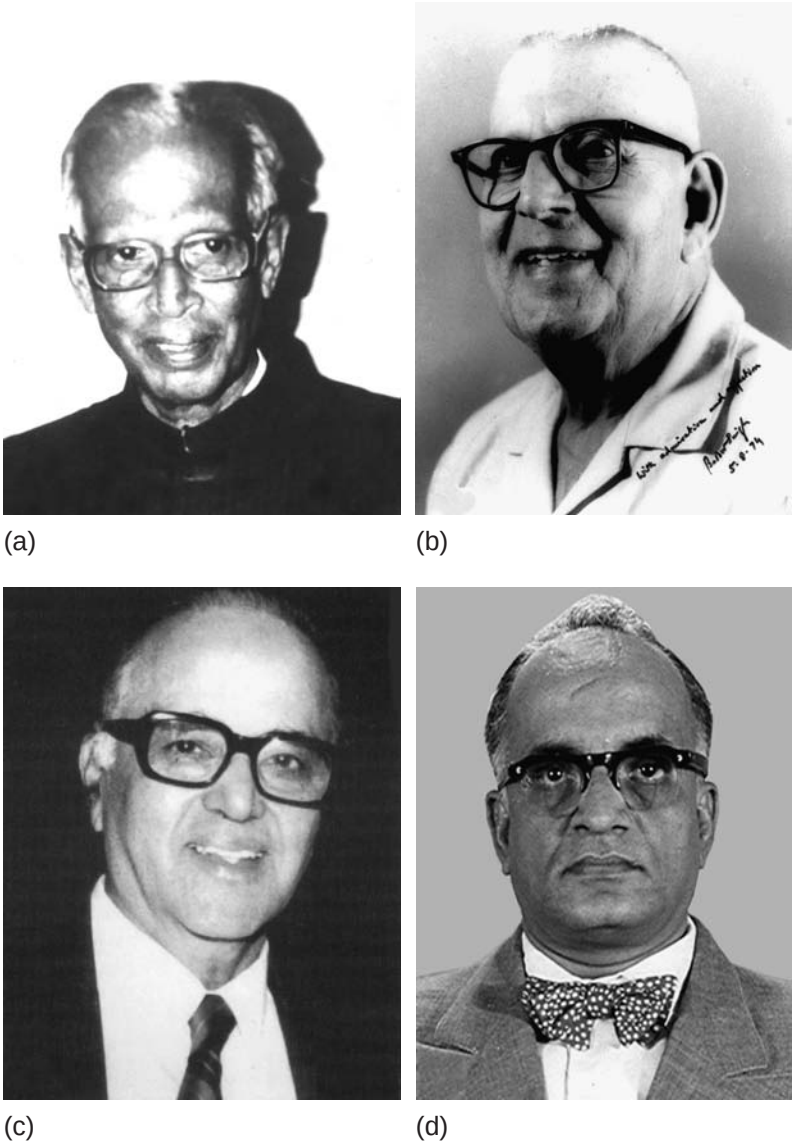


Figure 16b.1 The pioneers who contributed to early development of epilepsy surgery in India. (a) Professor Jacob Chandy (1910–2007). (b) Professor Baldev Singh (1904–1998). (c) Professor B. Ramamurthi (1922–2003). (d) Dr. T. S. Narasimhan (1913–1959).

lobe, 23 (16%) had extratemporal, and 16 (11%) had multifocal seizures.[11] The surgical procedures undertaken for TLE were lesionectomy (28 patients), temporal lobectomy with amygdalotomy (25 patients), temporal lobectomy with amygdalotomy and hippocampectomy (10 patients), amygdalotomy alone (15 patients), and lesionectomy with amygdalotomy in one case. For extratemporal epilepsies, lesionectomy was done in 24 patients and lobectomy for 2 patients. For multififocal epilepsy, 12 hemispherectomies and 4 stereotactic anosotomies were performed. The overall outcome was assessed as total or near total seizure control in 53% of patients and a worthwhile improvement in 20% of patients.[11]

In the mid-sixties, functional neurosurgery was established in the Institute of Neurology, Madras and stereotactic procedures for focal and generalized seizures were practiced.[5] Stereotactic lesions were made in the amygdalohippocampal region for TLE and in the central medial nucleus of the thalamus, the field of Forel, and in the internal capsule for generalized seizures and infantile spasms.[8–10]

The decline

In the mid-seventies, epilepsy surgery took a dramatic downward trend in the country. Thus, 100 out of the 102 patients with intractable TLE operated on at Christian Medical College, Vellore, until 1990,[11] were performed before 1980.[7] The retirement from active service of Chandy and Ramamurthi from the centers they almost single-handedly developed, less than expected post-operative seizure outcome, availability of more effective antiepileptic drugs, and stigma associated with epilepsy surgery due to its mistaken identity with psychosurgery collectively contributed to this decline.

The resurgence

The recognition in the 1990s that a majority of patients with medically refractory partial seizures have surgically remediable lesions that can be identified by relatively simple non-invasive studies such as magnetic resonance imaging (MRI) and scalp recorded interictal and ictal EEG has resulted in the evolution

of epilepsy surgery programs in developing countries with results comparable to that of developed countries.[12,13] A recent survey revealed that, in 26 of 142 (18.3%) developing nations, at least one center regularly conducted epilepsy surgery.[14] One of the authors (KR) returned to India in 1994 after having had training at the Epilepsy Program, Mayo Clinic, Rochester, MN and developed the R. Madhavan Nayar Center for Comprehensive Epilepsy Care at the Sree Chitra Tirunal Institute for Medical Sciences and Technology, a tertiary referral center, situated at Trivandrum, the capital city of the South Indian state of Kerala.[15] Since mid-1995, this center has undertaken, on average, 66 epilepsy surgeries per year. Almost simultaneously, epilepsy surgery programs were started at the All India Institute of Medical Sciences, New Delhi, and National Institute of Mental Health and Neurosciences, Bangalore. During the last decade, these three centers together have undertaken nearly 1000 epilepsy surgeries, which is five times more than the epilepsy surgeries performed in India during the previous four and half decades.

Present state

The success of epilepsy surgery is dependent upon the early identification of potential surgical candidates, and selecting from them, ideal candidates destined to have a postoperative seizure-free outcome.[16] Two basic requirements must be fulfilled before an epilepsy surgery program can be introduced in any geographical region: existence of a level of medical infrastructure to identify epilepsy patients with medical refractoriness, and a comprehensive epilepsy care organization where such patients can be subjected to a multidisciplinary evaluation to decide about surgical candidacy.

There are only about 800 neurologists for the 5–10 million persons with epilepsy in India. While 70% of the people with epilepsy in India reside in rural areas, almost all the neurologists practice in urban areas.[17] A majority of patients with epilepsy in India and other developing countries are therefore treated and followed-up by primary- and secondary-care physicians, who have little knowledge about the recent trends in the management of epilepsies. To many of them, epilepsy is still an incurable chronic disorder. Epilepsy clinics in a developing country set-up have to cater to a large number of patients with very limited skilled personnel. Overcrowding with patients and the consequent overburdening of the service providers, make time available for clinical assessment of individual patients very limited.[18] A frequent difficulty encountered in identifying medical refractoriness among patients with chronic epilepsy in developing countries is that, although many drugs have been used, none were given for sufficiently long periods and in adequate dosages, either alone or in proper combinations.[19] These factors contribute to considerable delay in the identification of prospective surgical candidates.

Epilepsy surgery centers in developing countries will lack the full range of state-of-the-art technologies such as single photon emission tomography (SPECT), positron emission tomography (PET), and magnetoencephalography usually available in centers in the developed world to perform non-invasive presurgical evaluation.[20] In India, patients or their families will have to bear the cost of epilepsy care. Although the total direct cost of presurgical evaluation and surgery in developing countries amounts to a small fraction of the cost incurred in the Industrialized World, this expenditure is beyond the reach of the majority.[21] Very few patients in India can afford the cost of intracranial electrodes used for invasive evaluation. In order to become cost-effective, epilepsy surgery centers in developing countries will have to achieve excellent results by selecting candidates destined to have a seizure-free outcome using locally available limited technology and expertise, without compromising on patient safety.[21] Because of these reasons, the process of selection of patients for epilepsy surgery in India to some extent differs from that of developed countries.

Patients with medical refractory epilepsy belong to different categories depending upon the degree of complexity involved in presurgical evaluation and the post-operative seizure outcome.[22] The prototype of a surgically remediable syndrome is mesial TLE with hippocampal sclerosis (MTLE-HS), which constitutes more than half of those patients with medically refractory epilepsy worldwide.[23] Non-invasive evaluation utilizing history, high resolution MRI, scalp video-EEG, and neuropsychological findings can identify patients with mesial temporal lobe epilepsy and those with other circumscribed, potentially epileptogenic lesions, 70–90% of whom become seizure-free following resective surgery.[16,24] Selected mesial temporal lobe epilepsy patients with consistent unilateral temporal interictal epileptiform abnormalities may not even require ictal video-EEG recordings.[25] Patients with large epileptogenic lesions involving primarily one hemisphere, and those with diffuse epileptic encephalopathies and multifocal disease can be selected for functional hemispherectomy or hemispherotomy and corpus callosotomy, respectively, based on non-invasive data.[22] Patients with extratemporal partial seizures, disorders of cortical development, and those with normal MRI will require extensive, sometimes repetitive studies with PET, SPECT, and intracranial electrode placement, which escalate enormously the cost of presurgical evaluation.[20] Even with these expensive evaluations, in this group of patients, the postoperative outcome is often not favorable.[26,27] A stepwise approach by initially operating on best outcome patients and reserving more difficult to treat patients to a later date as experience develops will help each center to understand its capabilities and limitations and to move forward.[21]

As detailed below, in evolving the most productive epilepsy surgery program in India today, the R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Trivandum, has given due emphasis to address the above special issues relevant to epilepsy care in developing countries.

R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Trivandum

The center is named after the late R. Madhavan Nayar, a pioneering industrialist of Kerala, who donated a generous sum of money to start a comprehensive epilepsy care program.[15] Three neurologists, two neurosurgeons, two neuroradiologists, a psychologist, a psychiatrist, and a medical social worker spend 25–50% of their working time with the epilepsy program. A three-patient video-EEG monitoring facility performs on an average 300 long-term monitoring studies

annually. A facility to do functional studies, spectroscopy, and T2 relaxometry was added recently to the 1.5 Tesla MRI already available.

Patients are classified according to their income into four categories; while the poorest group (~15% of patients) receives totally free treatment, the richest group (~30%) will have to bear the total hospital charges, and the intermediate groups pays 50–75% of the incurred actual cost. The center is sustained by the income generated through patient charges and by the financial support received from the Government of India for caring for the underprivileged. In addition, a local patient organization, Epilepsy Self Help Group, chips in with financial assistance for the needy through the donations it receives.[15]

The first epilepsy surgery (anterior temporal lobectomy with amygdalohippocampectomy) at the R. Madhavan Nayar Center for Comprehensive Epilepsy Care was undertaken on March 20, 1995. The patient was a 25-year-old gentleman with left mesial temporal sclerosis and medically refractory complex partial seizures. The important milestones of the surgical program and the break up of 706 epilepsy surgeries performed upto December 31, 2005 are provided in Tables 16b.1 and 16b.2, respectively. prior to September 2001, all the candidates were selected by non-invasive protocol utilizing history, clinical examination, interictal and ictal scalp EEG, high resolution MRI, and neuropsychological evaluation data, and all surgeries were done under general anesthesia. Nearly 90% of the patients operated during this period had MTLE-HS or MRI identified other focal lesions not adjacent to eloquent areas. Sphenoidal electrodes were inserted during long-term video-EEG monitoring of patients with suspected TLE only when initial scalp recorded ictal EEG pattern is poorly visualized or contaminated by movement artifacts.[28] Wada test was undertaken only in those patients in whom dominant extended temporal lobe resection is planned and in whom neuropsychological testing has revealed bilateral or discordant memory dysfunction. Even in patients with apparent TLE and normal MRI, careful analysis of the non-invasive data could identify favorable surgical candidates.[29] Such strategies prevented unnecessary escalation of the cost of temporal lobe epilepsy surgery. The non-invasive presurgical evaluation data of every patient is thoroughly discussed in the weekly patient management conference to collectively decide about surgical candidacy and to decide about further evaluation strategy in those with discordant features (Figure 16b.2).

Table 16b.1 Major milestones of the R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Trivandrum

1st epilepsy surgery	March 20, 1995
100th epilepsy surgery	October 28, 1997
200th epilepsy surgery	April 22, 1999
300th epilepsy surgery	October 5, 2000
400th epilepsy surgery	March 25, 2002
500th epilepsy surgery	August 1, 2003
600th epilepsy surgery	September 24, 2004
700th epilepsy surgery	November 24, 2005

Table 16b.2 Epilepsy surgeries undertaken at the R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Trivandrum from March 1995 through December 2005

Procedure	No.
Temporal lobe resections	588
Extratemporal resections	70
Corpus callosotomy	18
Hemispherectomy/hemispherotomy	30
Total	706

With the experience gained through the initial five years, intraoperative ECoG, subdural and depth electrode placements, and intraoperative and extraoperative cortical stimulation and mapping was started in 2001. These procedures have helped us to select patients whose epileptogenic zone could not be localized by non-invasive means and those with lesions such as malformations of cortical development close to eloquent areas. The R. Madhavan Nayar Center for Comprehensive Epilepsy Care is presently the only center in the country performing invasive presurgical evaluation. Upto December 31, 2005, 18 patients underwent long-term monitoring with bilateral temporal depth electrodes and 25 patients with subdural grid and strip electrodes placements. The Wada test is being replaced by functional MRI. During the last year, more restricted resective procedures such as selective amygdalohippocampectomy through subtemporal approach were being increasingly undertaken. Functional hemispherotomy is preferred to hemispherectomy for extensive unihemispherical lesions.

The step-wise evolution of the epilepsy surgery program at the R. Madhavan Nayar Center for Comprehensive Epilepsy Care as outlined above is illustrated through some case scenarios in Figure 16b.3.

Out of 351 patients with MTLE-HS operated on between March 1995 and March 2002 and have completed 2 years or more of post-operative follow-up, 286 (81.5%) are seizure-free, and 132 (37.7%) of them have been completely weaned off the antiepileptic drugs. During the median follow-up period of 4 years following surgery, out of 34 patients with tumoral TLE, 27 (79%) achieved a completely seizure-free state. Out of 46 patients with lesional extratemporal lobe epilepsies, 25 (55.6%) were seizure free during a median post-surgery follow-up of 4 years. Of the 6 patients operated for hypothalamic hamartoma through a transcallosal interforniceal approach, two were completely seizure free and three had more than 75% reduction of the seizures. Out of the 21 patients who completed ≥1 year of follow up following hemispherectomy/hemispherotomy, 18 patients (90%) became seizure free and 2 patients had more than 75% seizure freedom.

One patient died a few hours following an uneventful anterior temporal lobectomy, the cause of which remained obscure. Three patients, following anterior temporal lobectomy, developed disabling hemiplegia due to vascular injury. An abscess at the site of an intracranial grid electrode occurred in one patient, who made a recovery without sequel following

(a)

(b)

Figure 16b.2 Discussion on (a) clinical, (b) radiological and

(c)

Figure 16b.2 cont'd (c) video-EEG data in progress during the weekly patient management conference at the R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Trivandrum.

surgical drainage and antibiotic therapy. The rest of the complications were either minor or transient.

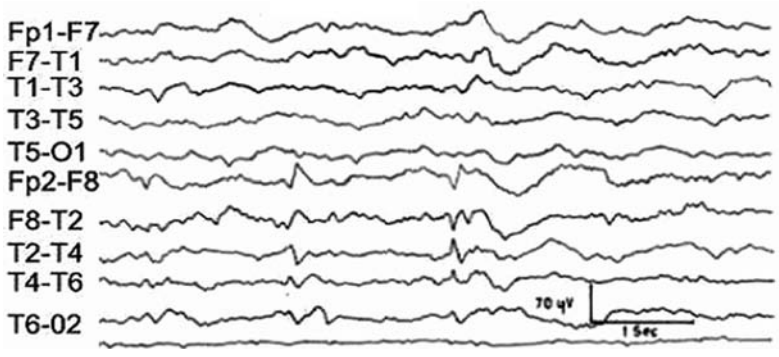
Other epilepsy surgery centers

The All India Institute of Medical Sciences, New Delhi has undertaken 273 epilepsy surgeries from April 1995 through December 2005, the break-up of which is given in Table 16b.3. Among the 121 patients operated for refractory epilepsy at the National Institute of Mental Health and Neurosciences, Bangalore, between 1998 and December 2005, 90 had anterior temporal lobectomy, 30 had lesionectomy, and 1 had corpus callosotomy. Detailed post-operative outcome data from these centers are not yet available, although preliminary results are comparable to those from the R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Trivandrum.[30,31] The following centers in India have performed less than 50 epilepsy surgeries, during the last five years, Nizam's Institute of Medical Sciences, Hyderabad, CARE Hospital, Hyderabad, KEM Hospital, Mumbai, Jaslok Hospital, Mumbai, Poona Neurological Institute, Poona, Jahanghir Hospital, Poona, Postgraduate Institute of Medical Education and Research, Chandigarh, and Lourdes Hospital, Kochi. The National Hospital, Colombo, Sri Lanka has a very successful epilepsy surgery program and has offered surgery to nearly 60 patients in the last 3 years. The R Madhavan Nayar Center for Comprehensive Epilepsy Care, Trivandrum has actively participated in the development of the Sri Lankan program.

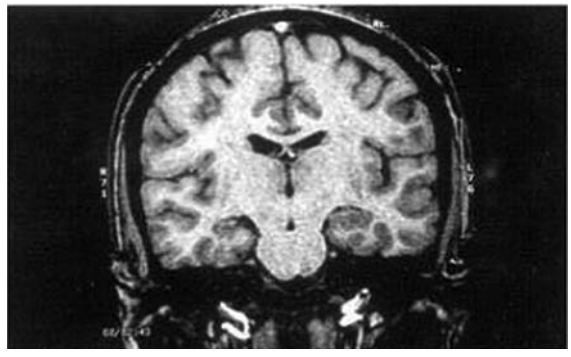
Future perspectives

In India, with over one billion inhabitants, there are approximately one million persons with medically refractory epilepsy; among them as many as one-quarter to one-half are potential surgical candidates. However, no more than 150 epilepsy surgeries are currently being performed per year in India. Thus, only a minuscule of potential surgical candidates in India and other developing countries ever get a chance to undergo presurgical evaluation. The lack of availability and affordability has resulted in an enormous gap in developing countries between number of patients who could be benefited from epilepsy surgery and those who actually receive this treatment, which can only be minimized by developing more centers in the country, where epilepsy surgery can be undertaken.

The out-of-pocket payment for epilepsy surgery (including non-invasive presurgical evaluation) at the R. Madhavan Nayar Center for Comprehensive Epilepsy Care is Rs. 50,000 (US$1200).[21] With invasive evaluation the cost would escalate to two to threefold of this amount. The computed direct total cost for caring a patient with refractory temporal lobe epilepsy from age 26 to 60 years works out to be Rs. 200,000 (US$5000).[21] The results from R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Trivandrum and other epilepsy surgery centers in India show that over 70% of patients will be seizure-free following surgery for temporal lobe epilepsy, and there is a 30% chance that they will be

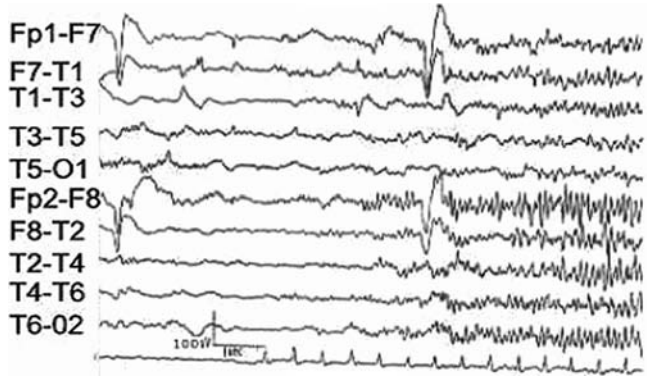


(a)



(b)

(c)



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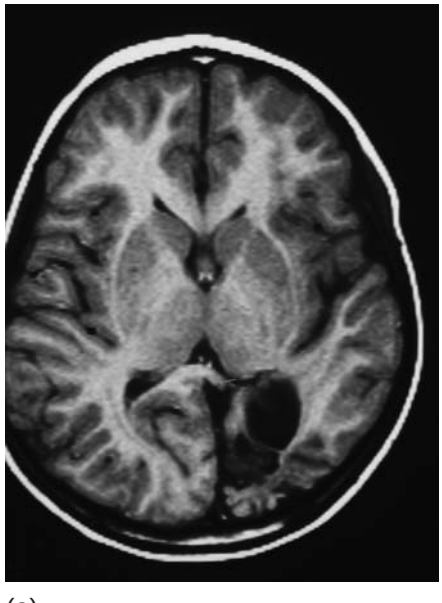

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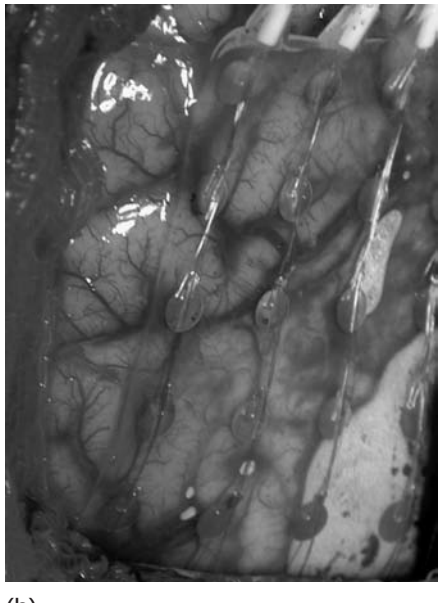
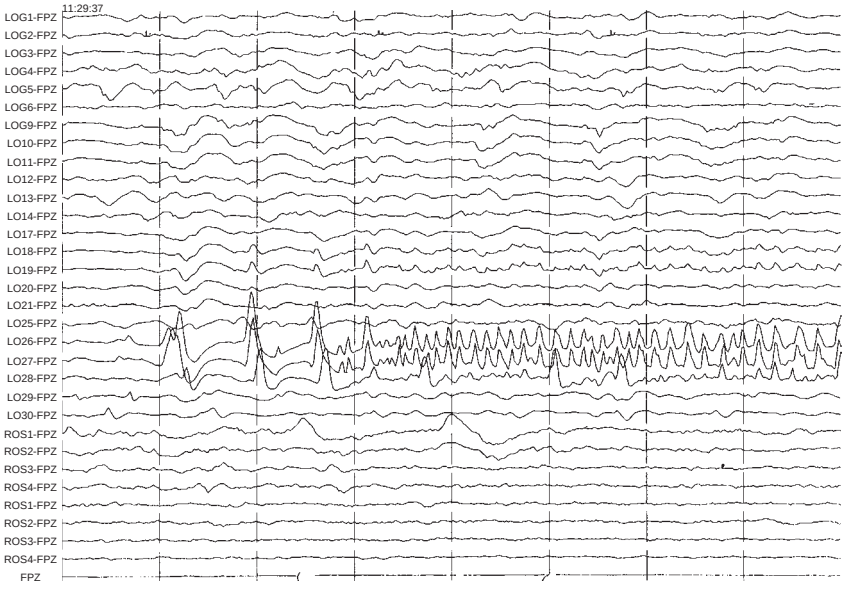


(b)

Figure 16b.3 Case scenarios from R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Trivandrum, to illustrate step-wise progress with time from straightforward to more complicated and advanced presurgical evaluation and surgical strategy. (i) Selection for epilepsy surgery by noninvasive evaluation: (a) right temporal spike discharges on scalp EEG, (b) right hippocampal atrophy on T1 weighted coronal MRI, (c) left upper extremity dystonic posturing during a complex partial seizure, and (d) rhythmic EEG activity during the seizure. Patient is seizure-free since right anterior temporal lobectomy with amygdalohippocampectomy on May 1997. (ii) A 14-year-old boy with refractory partial seizures with inconclusive scalp EEG data: (a) left occipital gliotic lesion in T1 weighted MRI, (b) left occipital-parietal grid electrode, and



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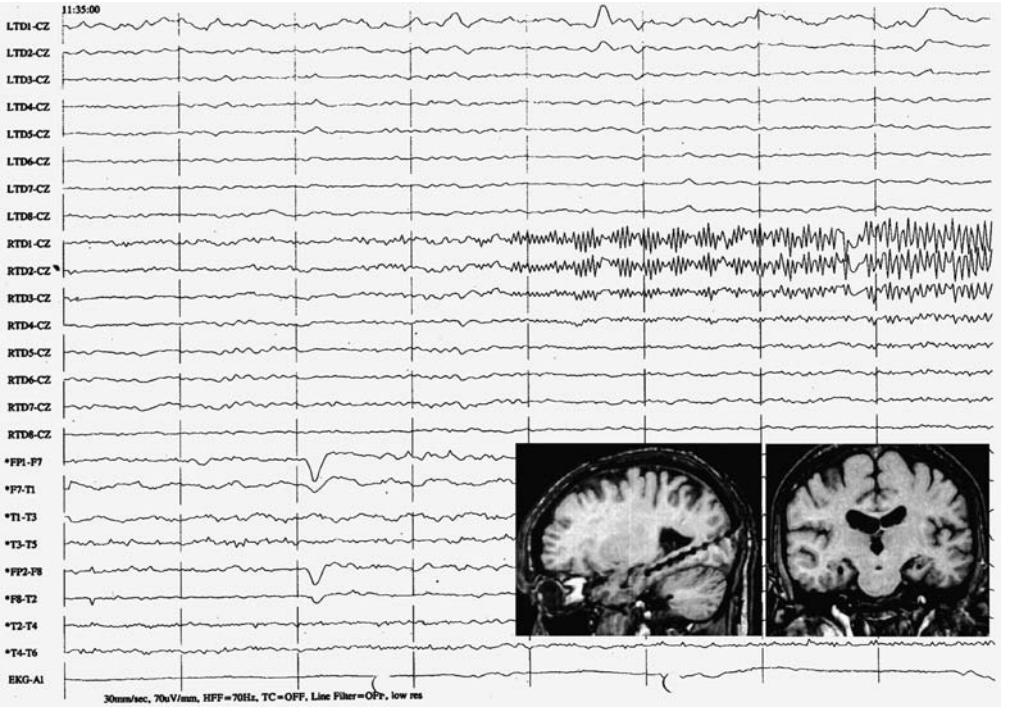

Figure 16b.3, cont'd (c) seizure origin from left occipital region. Seizure free since left occipital lobectomy on January 2002. (iii) A 42-year old male with inconclusive scalp EEG data. Inset shows stereotactically placed bilateral temporal depth electrodes. Seizure origin from anterior contacts of right hippocampal depth electrode. Seizure-free since right anterior temporal lobectomy with amygdalohippocampectomy on April 2003.

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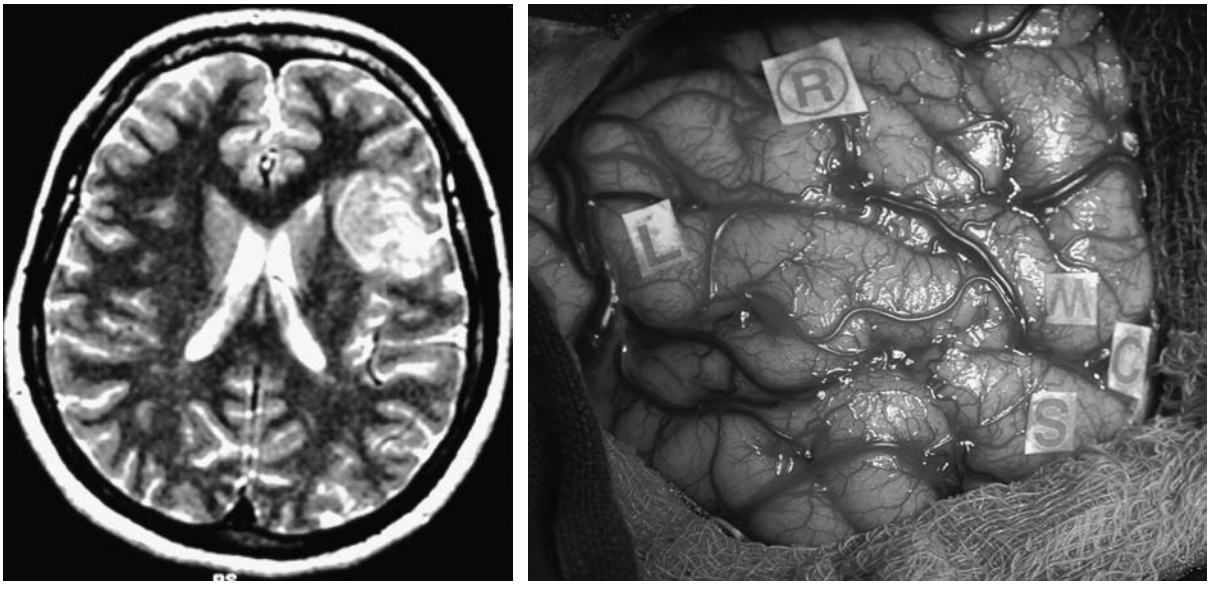
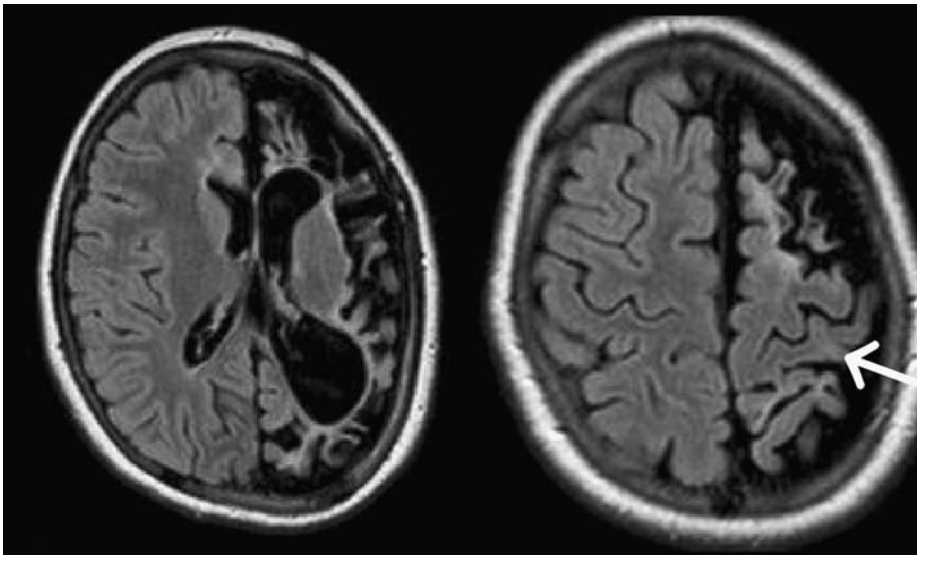


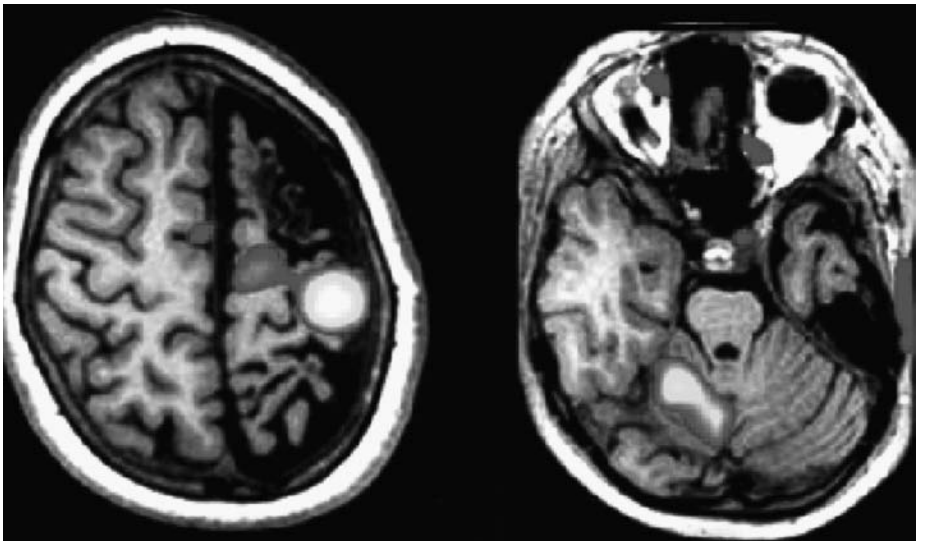
(a) (b)

Figure 16b.3, cont'd (iv) A 20-year-old female with (a) left frontal cortical dysplasia close to motor and speech areas in T2 weighted MRI, (b) awake craniotomy and cortical stimulation mapped motor cortex (m), sensory cortex (s), Broca's area (l), and central sulcus (c). Area R was resected without any neurological deficit on June 2004. After a complete seizure freedom during first post-operative year, she had had recurrence with few non-disabling seizures.



(a)

Figure 16b.3, cont'd (v) A 13-year-old left handed boy with refractory focal seizures and mild right hemiparesis due to hemorrahagic disease of new born. (a) axial MRI FLAIR sequences shows marked gliosis and atrophy of the left hemisphere with relative preservation of the primary sensory-motor cortex (arrow).



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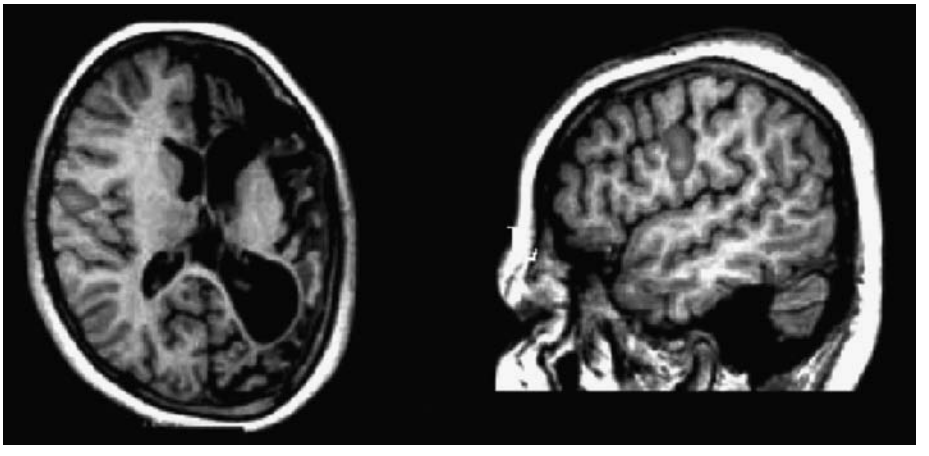

Figure 16b.3, cont'd (b) inline BOLD MRI right finger tapping versus rest shows left motor cortex activation, and (c) inline BOLD MRI verbal fluency versus silence shows strongly right hemisphrere lateralized language distribution. Based on the information, left motor strip was spared during hemispherotomy performed on July 2005 with little post-operative weakness of right-sided extremities. No seizure recurrence during six months' follow-up.

Table 16.3 Epilepsy surgeries undertaken at the All India Institute of Medical Sciences, New Delhi, from April 1995 through December 2005

Procedure	No.
Temporal lobe resctions	204
Extratemporal resections	51
Corpus callosotomy	12
Hemispherectomy/hemispherotomy	6
Total	273

completely off antiepileptic drugs within 2 years following surgery.[12,30] Even with new antiepileptic drugs, complete seizure freedom occurs in only less than 10% of temporal lobe epilepsy patients.[32] A seizure-free person could be better employed, achieve an improved quality of life, and often becomes a productive member of society. Therefore, surgical treatment of refractory temporal lobe epilepsy is definitely a better cost-effective option than continued medical treatment even in developing countries. Epilepsy centers in developing countries could effectively use these statistics to obtain governmental subsidies and non-governmental financial supports for implementing and sustaining epilepsy surgery programs.

Conclusions

In order to become cost-effective, epilepsy surgery centers in India will have to achieve excellent results by selecting candidates destined to have a seizure-free outcome using locally available limited technology and expertise, without compromising on patient safety. The recent experience from epilepsy

surgery centers in India illustrates that this goal can be accomplished by selecting patients whose epileptogenic zone can be unquestionably established, based on history, high resolution MRI, and interictal and ictal scalp EEG findings such as those with MTLE-HS, and those with circumscribed potentially epileptogenic lesions. A stepwise approach by reserving more difficult to treat patients at a later date as experience develops, or by referring them to a better-equipped center, will help each center to understand its capabilities and limitations and to move forward. It is encouraging to note that, despite major challenges, in the last decade, several epilepsy centers in India have not only successfully implemented epilepsy surgery programs, but have also produced results comparable to that from developed countries at a fractional cost.

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17 Treatment of epilepsy in Australia

A Mohamed

Introduction

Despite a relatively small population, Australia is the sixth largest nation in area following Russia, Canada, China, the United States of America, and Brazil. It is a very dry continent with most of the population living in its coastal margins. It is a federation of six states and two territories. The largest state, Western Australia, is about the same size as Western Europe.

Over 60,000 years before the arrival of European settlers in 1788, Aboriginal and Torres Strait Islander peoples inhabited most areas of the Australian continent. There were an estimated 300,000 Indigenous Australians living on the continent. Today, the population of Australia is slightly over 20 million and concentrated in large cities around the coast (Table 17.1).

Epilepsy and illness in the indigenous population

Aboriginal groups prior to European settlement were traditional hunter and gatherer communities and had enviable health in terms of nutrition and leisure. They lived in small closed groups of kin. The population numbers depended on availability of water and other essential resources. These groups followed up a more or less nomadic lifestyle. Most aboriginal groups were spread sparsely over the continent that mitigated against the spread of disease. These small groups followed a seasonal pattern of movement within a defined territory to which they had spiritual ties. Periodically, they would congregate in large numbers for ceremonial purposes or seasonal abundance of some food store at a particular site.[1]

In aboriginal culture prior to European settlement, sorcery or black magic provided an explanation of illness, pain, or death where the cause was not known or obvious. The explanations were always personal or spiritual. Someone or some spiritual powers performed black magic on the victim because of animosity or because the victim had broken a taboo. Aboriginal healers were able either to restore health or at least the group, via sorcery, could retain equilibrium. Not to know the cause of the illness or death was a disturbing factor in the psychological and social life of the group – therefore an acceptable explanation was necessary to enable the community to readjust itself to the events and go about its business.[2] The sick were kept tranquil in a familiar environment with their own people about them hearing familiar voices and passed away in peace with their own kind when death was upon them.[1]

The aboriginal healer symbolically extracted a bone, quartz, or other stone from the patient's body or would bring back the wandering soul through rituals, and all was well. If the patient could not be healed, both the patient and group would prepare for death. The patient was also in a condition of high suggestibility and was ready to realize the idea suggested by the aboriginal healer. If told that he was healed, he would be reassured and prepare for improvement. Likewise, if a doctor suggested that death was inevitable, the patient would think of the spirits of the departed, turn his face to the wall, and prepare for death.[2]

There is no evidence that aboriginal culture placed a premium on abnormality or the epileptic. There was no reverence for epileptic patients as found in other cultures.[2]

Aboriginal medicine men, far from being charlatans, were men of high degree and had degrees in the secret of life beyond that taken by most adults. This required discipline, mental training, courage and confidence. Their positions commanded respect, and they were men of outstanding personality. In addition, the psychological health of the group largely depended on their powers, and they specialized in the working of the human mind.[2]

Despite some notable improvements in the past 20 years, the health status of aboriginal people remains of great concern. They carry a double burden of disease – not only disease of poverty but increasingly disease characteristic of a Western lifestyle. Leading causes of death includes cardiorespiratory diseases, accidents and to moving trauma, suicide, violence, and cancer.[1] Incidence of epilepsy existing in the Aboriginal community is at least of the same proportion as the rest of Australia (1–2%). However this is probably an underestimate due to lifestyle factors such as alcoholism, substance abuse, and injury.

History of epilepsy in Australia after European settlement

The early history of the treatment of epilepsy in Australia closely followed the path paved in the UK because of the close relationship between the two countries. Australia's geographical isolation and low population density were compensated for by a tradition of overseas travel by doctors to undertake postgraduate studies in Europe.

As with many European countries, during the 19th century, it was customary for epileptics to be institutionalized as they were thought as unfit to be at large. Epilepsy was thought to be a precursor of insanity. Many with brain disorders were institutionalized in prisons side-by-side with felons. In early Australian European settlements, the incidence of epilepsy in the prison population varied from 7 to 13%.[3] The conditions in the prisons were grim and poor and it was not until later in

Table 17.1 Population and area of Australian state and territories

State or territory	Area (square km)	Population	Capital city
Queensland	1,723,936	3.64 m	Brisbane (1.65 m)
New South Wales	800,628	6.61 m	Sydney (4.15 m)
Australian Capital Territory	2,358	0.32 m	Canverra (0.32 m)
Victoria	227,010	4.82 m	Melbourne (3.49 m)
Tasmania	64,519	0.47 m	Hobart (0.20 m)
South Australia	978,810	1.51 m	Adelaide (1.11 m)
Western Australia	2,526,786	1.9 m	Perth (1.38 m)
Northern Territory	1,335,742	0.2 m	Darwin (0.11 m)
Australia	7,659,861	19.47 m	12.41 m

Source: Australian Bureau of Statistics Census 2001. Estimated June 30 2001.

the 19th century where most people with epilepsy were managed in asylums for the mentally ill.[3]

Towards the end of the 19th century, in the two large colonies of the time, New South Wales and Victoria, the decision was made to manage epileptics in institutions for the mentally ill.[3,4] The very first asylum was created in 1811 in Castle Hill in the outskirts of Sydney. The second asylum outside New South Wales opened in 1848 at Yarra Bend in Victoria, although many sufferers were still managed at home by family and local doctors.[5] Poverty, strained family relationships, and unemployment often played in large part in incarceration of these patients. Conditions in these asylums were very poor. Many of these patients suffered from a large number of physical illnesses including tuberculosis.[6] In Sydney, patients in one institution (Galdesville Hospital) were dying from typhoid and infectious diseases due to inadequate sewerage.[4]

Early in the 20th century, there was a shift of attitudes that allowed the liberation of epileptics to asylums. This change in attitude together with campaigns by medical practitioners and activists led to a number of government inquiries[4] that in turn led to the development of epileptic colonies in Sydney and Melbourne. In Sydney, moral therapists spearheaded these reforms. Work was created for epileptics and seen as a therapeutic instrument.[3] Attendance of church was encouraged and libraries and newspapers were furnished for the patients.

Prior to Hughlings Jackson's postulate that epilepsy was disease of the cortex, a variety of causes were hypothesized for seizures. These included alcohol, worms, anxiety, and masturbation.[3] In the late 18th century, medical treatments of epilepsy in Australia included:[3]

- Quiet rest, the feet placed in hot water and mustard bath
- Shaving of the scalp
- Mustard plaster to the back of the head
- Cooling of the head by a mixture of spirit of vinegar and water
- Bleeding in letting five fluid ounces of blood at a time
- Leeches to the temples
- Blister to the nape of the neck
- Use of prolonged chloroform anaesthesia
- Morphia
- Bromides introduced by Dr. Smith in 1873
- Blistering where local limb auras occurred.

At this time the treatment for epilepsy in the USA included bromides, arsenic, quinine, cod liver oil, iron, and hysterectomies.[7]

The concept of epilepsy as a disease of the cortex was introduced to Australia in a paper in 1886 by John Springthorpe.[8] He also recommended a systematic approach to treatment. This included removal of any irritants: bromides, zinc oxide, belladonna, atropine, cannabis, digitalis, and a Seton tie at the back of the neck. The Seton tie was a silk or cotton twine that was inserted through a large flap of skin and left there until a chronic running sore was created with drainage of pus from around the seton.[9]

The surgical treatment of epilepsy was first detailed by Dr. John Maund[10] in 1856 and later by Dr. Poulton in 1890.[11] In 1856 a patient with post-traumatic epilepsy who had an old depressed skull fracture and had failed medical therapy was treated successfully with trephining and removal of the bone at the side of the fracture – this occurred prior to the introduction of antiseptic techniques in cranial surgery by Horsely in 1880s.[3]

The beginnings of epilepsy surgery in Australia

Peter Bladin created the first epilepsy center in 1969 at the Austin Hospital in Melbourne. This was a nationwide service that provided the first comprehensive epilepsy program in Australia. Between 1969 and 1991 this program performed over 200 temporal lobectomies for refractory epilepsy.[12] In the late 1970s and early 1980s epilepsy centers were also established in three other Melbourne hospitals.

In the early 1970s in Sydney, a lavishly equipped and staffed Brain Research Institute at Rozelle Hospital was established, where psychiatrists, neurologists, and neurosurgeons worked together to select patients for psychosurgery. Part of the work-up involved the insertion, under stereotactic guidance, of recording electrodes into the hippocampus and amygdala. They were particularly interested in rage attacks, and whether these were due to epileptic activity in the amygdala. In the late 1970s there was public disquiet over such surgery (Figure 17.1). A royal commission was called that led to the shut down of this unit. The first comprehensive epilepsy center in Sydney was established in 1977 in Royal Prince Alfred Hospital[13] (Figure 17.2) with centers at Prince Henry


LATE FINAL EXTRA

Daily Mirror

10c

BIGGEST WEEKDAY SALES IN NSW

Cats spared brain surgery

HUMAN GUINEA PIGS STORM

EXPERIMENTS BANNED

Figure 17.1 A Sydney tabloid reports on psychosurgery in 1977 (copyright permission).

and Westmead Hospitals being established soon after. Between the years 1990 and 1997, 226 temporal lobectomies and 40 extra temporal lobe surgeries were performed at the three adult epilepsy centers in Sydney (personal communication).

Epilepsy surgery for refractory epilepsy in children were first performed at The Royal Children's Hospital in Melbourne in 1979 and in Sydney in 1988. An epilepsy surgery center was established in Western Australia in 1989 and by 2002, 122 patients were assessed for surgery.

Conclusion

There is little known of the treatment of epilepsy by the aboriginal population prior to European settlement.

(a)

(b)

Figure 17.2 Epilepsy monitoring unit at Royal Prince Alfred Hospital in 1990.

However, various sources suggest that the aboriginal had good health and a spiritualistic approach to illness. The treatment of epilepsy in Australia after 1788 paralleled that seen in Europe and in particular in the UK due to the close ties between the two countries. Epilepsy surgery, first pioneered in Melbourne, has become available at a number of epilepsy centers in a country with a large geographical area, and its population concentrated in large coastal cities.

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18 Epilepsy surgery in Korea

BI Lee

Traditional oriental medicine

Historically, Korean traditional medicine largely adopted the Chinese medicine since its beginning about 5,000 years ago. 'Fifty-two Diseases', the earliest Chinese medical record written 3,000 years ago, described symptoms of epilepsy and its treatment consisting of 'repeat bathing with fluid containing a brain pill' called '腦 丸藥(腦: brain, 丸: tablet, 藥: drug)'. This indicated that ancient Chinese doctors had already known that epilepsy was originating from the brain. Despite their clear insight on the origin of epilepsy there has been no record describing any surgical treatment of epilepsy throughout the prolonged history of Chinese medicine. The major treatment modality of epilepsy in Chinese medicine consisted of various prescriptions using herbs, minerals, and materials from animals, and various procedures such as acupunctures, massages, and moxacautery. In the early 16th century, Dr. Joon Huh, the father of Korean traditional medicine, wrote a book called '東醫 寶鑑 (東: east, 醫: medicine, 寶: gems, 鑑: book)', which had summarized his clinical experiences as well as previous medical knowledge available in Korean and Chinese medical literature. He classified epilepsy into eight types based on charateristic symptoms, age of onset, and the traditional concept of etiopathogenesis. The book, which is still regarded as the textbook of Korean traditional doctors, has described more than 300 prescriptions and various procedures applicable to different types of seizures but none for the surgical treatment of epilepsies.[1]

Era of Western medicine

Western medicine was first introduced by Dr. H.N. Allen (Figure 18.1) in 1884, who was the medical missionary from the North Presbyterian Denomination. He built a Royal Hospital called '濟衆院' (House of Universal Helpfulness, Figure 18.2) in 1885 by the sponsorship of King Kojong of Lee Dynasty. which was the first hospital practicing western medicine in Korea. In 1886, Dr. Allen started his medical education which was succeeded by Dr. Avison. He was the first principal of 濟衆院醫學校 (Chejungwon Medical School) and trained several assistant students. Among these, seven students had graduated in 1908 who were the first Korean medical doctors. In 1900, Mr. Severance in Cleveland, Ohio, donated $15,000 for the construction of a modern medical school and hospital which was opened in 1904 (Figure 18.3). The new medical complex was named the Severance Hospital and Medical School in memory of his generous contribution. In 1959, Severance Medical School was united with Yonhee University to form Yonsei University.[2] Korea was colonized by Japan from 1910 to 1945 and the Korean War occurred from 1950 to 1953. During the period, Korean society was seriously abandoned and most post-war medical activities were heavily dependent upon US aid. The modern medical management of epilepsy was initiated by Dr. L. Robinson (Figure 18.4) who was also an American medical missionary. She treated a girl suffering from epilepsy with phenytoin in 1963 and organized a mobile epilepsy clinic in association with Korean neurosurgeons and psychiatrists in 1964. These activities generated great hope among many patients and their families to organize the 'Rose Club', which did take initiatives of social movement as well as medical care for epilepsy. The rising phase of the Rose Club reached its peak during the 1970s and the first International Bureau Workshop for Epilepsy was held in the Severance Hospital on December, 1974. The Rose Club had grown to a huge social organization holding approximately 100,000 patients and their families and became a local chapter of IBE in 1979. Starting from 1980, the Korean economy had risen rapidly and most antiepileptic drugs became widely available in community hospitals. During this transitional period, the epilepsy care in Korea has gradually shifted from the Rose Club to community hospitals and the activities of the Rose club had gradually transformed into that of a lay

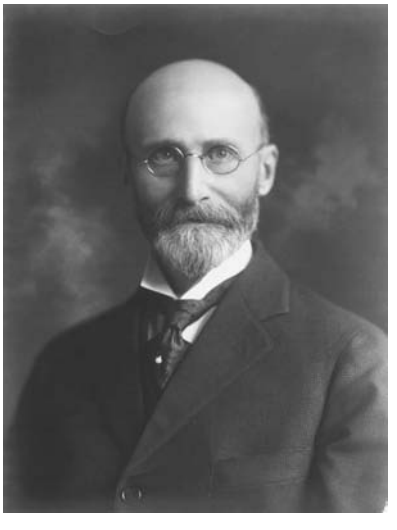

Figure 18.1 Dr. Horace Newton Allen (1858–1932). He founded the first hospital practicing western medicine (Chejungwon) in 1885 with the support of King Kojong of Lee dynasty.

Figure 18.2 濟衆院 (House of Universal Helpfulness). The first hospital practicing western medicine, which was established by Dr. H.N. Allen in 1885. The hospital was located in Che-dong, Seoul.

Figure 18.4 Dr. Lennabelle Robinson (1904–) in the center, who is discussing with Korean doctors (Dr. M.H. Kim in the left and Dr. W.S. Kang on the right) about the activities of the Rose Club.

people's organization. In 1982, the Korean Neurology Association was established to start a nationwide training program of neurology residents. In 1988, an epilepsy clinic was opened at Yonsei University Medical Center (Severance Hospital), which was the beginning of a specialized program for the care of epilepsy in Korea. In 1996, the Korean Epilepsy Society was organized and the major part of the Rose Club became the Korean Epilepsy Association, which has greatly promoted the quality of epilepsy care in Korea.

Era of epilepsy surgery

Dr. C.K. Lee (Figure 18.5), a neurosurgeon who had a postdoctoral training at the Montreal Neurological Institute in Canada, started epilepsy surgery from 1966 and published his surgical experiences of 51 cases suffering from intractable epilepsies in 1972.[3] His surgical technique was the electrocoagulation of the preoccipital cortex. He considered that the preoccipital cortex was the main pathway of spreading ictal discharges and its interruption by electrocoagulation should be beneficial for the amelioration of seizures. He recorded electrocorticography (ECoG) before the electrocoagulation and observed its change after intracortical injection of procainamide to predict surgical outcome (Figure 18.6). Among 51 patients, 3 patients became seizure free and 26 patients achieved a significant improvement after the procedure. In 1980, Dr. D.S. Chung and his colleagues at Catholic University started epilepsy surgery and published their surgical experience consisting of seven cases of corpus callosotomy and eight cases of selective amygdalohippocampectomy in 1989.[4] Nine patients showed significant improvement and none got worse. In this series, they did not perform any dedicated presurgical evaluations but their surgery was undertaken on the basis of clinical judgment, routine scalp EEG, and CT scan. The modern epilepsy surgery program employing the protocol of advanced presurgical evaluation was initiated at the Severance Hospital of Yonsei University Medical

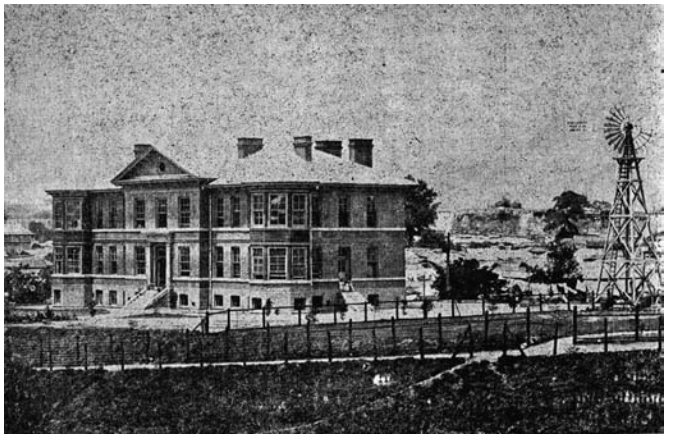

Figure 18.3 Severance Hospital and Medical School in 1904, which was built with the generous donation of Mr. Severance in Cleveland, Ohio. This building was located in Do-dong, Seoul. In 1995, this building was replaced by a 20-storey office building (Yonsei Severance Building) for the purpose of finacially supporting Yonsei University.

Figure 18.5 Dr. Chu Kul Lee (1914–) is the first neurosurgeon to perform epilepsy surgery in Korea.

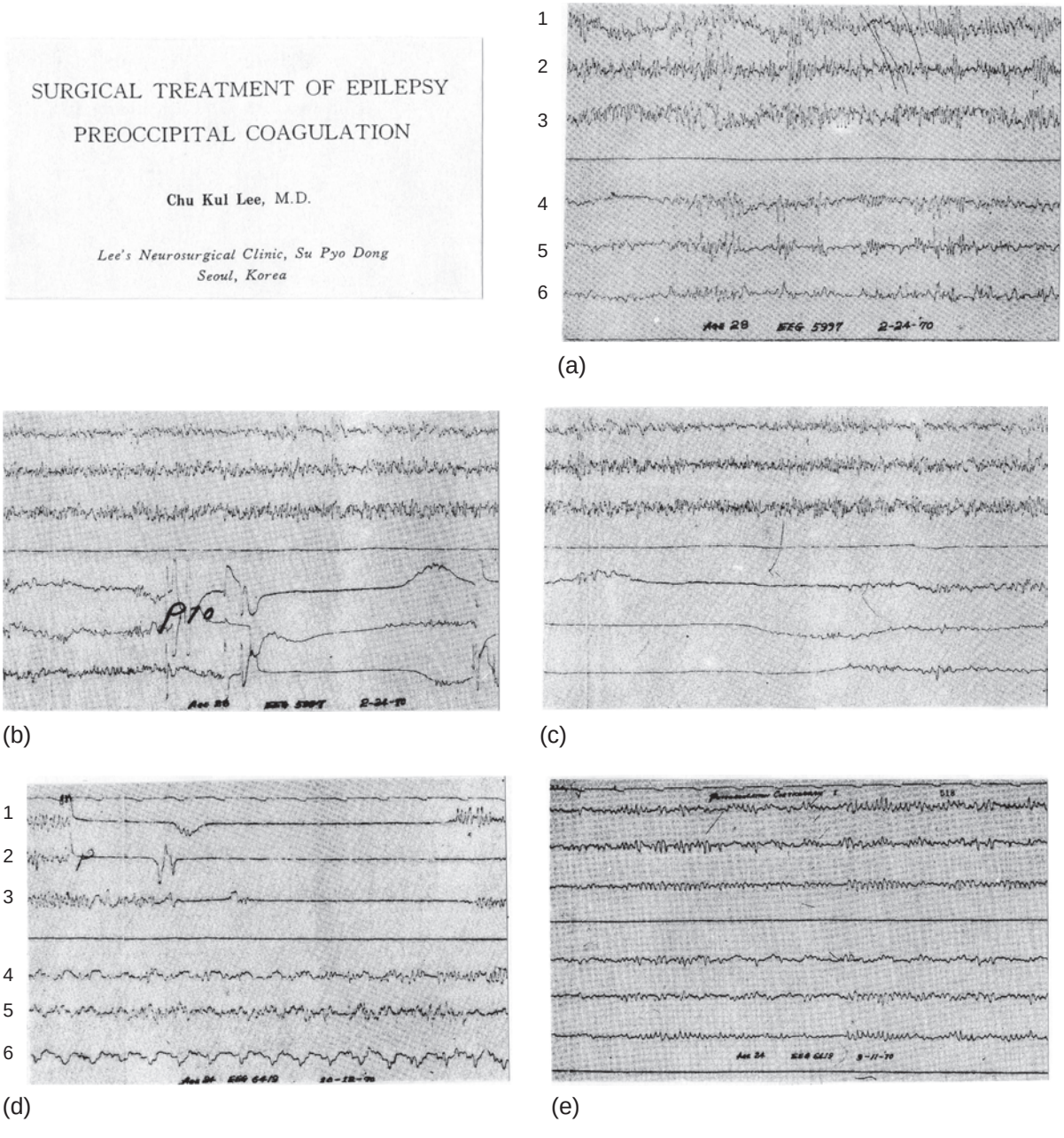

Figure 18.6 The first publication of epilepsy surgery in Korea (1972). Baseline electocorticogram of a patient showing multiple spikes at both preoccipital (leads 1, 2 and 3) and motor (leads 4, 5 and 6) areas (a) electrocorticograms showed no suppression of epileptiform discharges from the preoccipital region during (b) and after (c) procainization of the motor cortex. Electrocorticograms from the motor cortex showed the clear response during (d) and after (e) the procainization of the preoccipital cortex.

Center in 1988 by Dr. B.I. Lee and K. Huh who had returned to Korea after their completion of training in neurology (University of Minnesota) and epileptology (Cleveland Clinic and University of Georgia) in the USA. In the early 1990s many young neurologists and neurosurgeons with an interest in epilepsy surgery started to have fellowship trainings abroad and established surgery programs in major university hospitals upon their return to Korea.

Current status of epilepsy surgery

With the opening of a specialized epilepsy care program at Yonsei University Medical Center in 1988, epilepsy sugery has become rapidly recognized as an effective therapeutic measure for patients suffering from medically intractable epilepsies. In addition, the wide availability of MRI and EEG telemetry systems encouraged the organization of surgery programs in major university hospitals in Korea. During the late 1990s, 12 centers performed about 500 cases of epilepsy surgery annually and their surgical experiences started to appear in international epilepsy journals. However, the flourishing activities of many surgical centers had gradually declined from the year 2000, largely relating to the emergence of failure cases, shortage of patients requiring only basic presurgical evaluations, tough competitions among centers, and financial restrictions of presurgical evaluations imposed by National Health Insurance. As PET, SYSCOM, and advanced MR

Table 18.1 Surgical cases performed by epilepsy surgery centers during 2005 in Korea

	Epilepsy surgery centers						
Procedures	**AMC**	**CBUH**	**DSMC**	**PHIU**	**SNUH**	**SMC**	**YUMC**
ATL/SAH	24	16	12	1	29	26	35
CS: lesional	6	3	5	2	56	18	15
Non-lesional	1	2	3	3	14	6	2
HS/MLR	1	–	–	4	1	4	3
Corpus callosotomy	3	6	–	4	2	2	16
MST only	4	–	–	–	–	–	–
VNS	1	–	5	5	6	6	24
DBS	2	–	–	–	–	2	1
r-Knife surgery	4	–	–	–	2	3	–
Total	46	27	25	19	111	67	96

ATL/SAH, anterior temporal lobectomy/selective amygdalohippocampectomy; CS, cortisectomy; HS/MLR, hemisperectomy/multilobar resection, MST, multiple subpial transection; VNS, vagus nerve stimulation; DBS, deep brain stimulation; AMC, Asan Medical Center of Ulsan University (Seoul); CBUH, Chonbuk University Hospital (Cheonju); DSMC, Dongsan Medical Center of Kyemyung University (Daegu); PHIU, Paik's Hospital of Inje University (Seoul); SNUH, Seoul National University Hospital (Seoul); SMC, Samsung Medical Center of Sungyunkwan University (Seoul); YUMC, Yonsei University Medical Center (Seoul).

technologies became available in the late 1990s, advanced imaging technologies became the forerunner of interhospital competitions and centers not equipped with these facilities faced great restrictions in their activities to close their surgical programs. At present, seven centers are mantaining their surgical activities and the number of surgical cases has diminished to around 350 cases per year (Table 18.1). Compared to the gradual decrease in the number of resective surgeries, there has been a trend to increase implant of vagus nerve stimulation (VNS) for its simplicity, safety, and broad indications as well as its coverage by National Health Insurance. Deep brain stimulations (DBS) is also applied in a few centers despite its experimental stage of develop-ment. Magnetoencephalography (MEG) has become available recently.

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19 Epilepsy surgery in Thailand

T Srikijvilaikul, C Locharernkul, and A Boongird

The history of epilepsy surgery in Thailand can be divided into the era before and after 1990. Before 1990 was the time of modern neurosurgery establishment by Thai pioneer neurosurgeons. After 1990, advanced epilepsy surgery has been established in Thailand in parallel with the development of a comprehensive epilepsy program with standard and state-of-the-art clinical practice.

History of epilepsy surgery in Thailand before 1990s

Modern neurosurgery in Thailand began after a number of neurosurgeons returned from formal training in the USA in the late 1960s and established neurosurgical services at Siriraj and Chulalongkorn hospitals, the first two medical schools in Thailand. Pioneers on epilepsy surgery in the country were distinguished neurosurgeons, namely Professor Sira Bunyaratavej and Professor Charas Suwanwela.

Due to the lack of computer technology and advanced imaging at that time, localization mainly relied upon clinical information, namely detailed history taking, highly precise neurological examination (Figure 19.1) and surface electroencephalogram (EEG) (Figure 19.2). Early imaging included skull series, scintigraphy or isotope brain scan, cerebral angiography, pneumoencephalograhy, and after the mid-1970s, computerized tomography (CT). The surgical outcomes varied among patients. Surgical treatment of epilepsy was mainly resection of structural lesions causing seizures such as tumors, abscesses, vascular malformations, and depressed skull fracture scars. However, a few operations for intractable epilepsy were also performed. Hemispherectomy for a Sturge–Weber patient was first done by Professor Sira Bunyaratavej in 1966 (Bunyaratavej S, personal communication). Stereotactic amygdalotomy was performed in a case of temporal lobe epilepsy by Professor Charas Suwanwela in 1977 (Suwanwela C, operative record).

At King Chulalongkorn Memorial Hospital, modern surgery of the brain was first established in 1963 by Professor Charas Suwanwela. Granted by the prestigious Anandamahidol Foundation under His Majesty King Bhumibol Adulyadej of Thailand, he finished his neurosurgical residency training from North Carolina and certified American Board of Neurological Surgery in 1961. He began modern neurosurgical therapy for Thai people at the Bangkok Bank Building (Figure 19.3). Early brain surgeries regarding epilepsy were mainly surgical removal of intracranial space occupying lesions producing seizures as well as other neurological symptoms. However, the number of brain operations directed toward the correction of epileptic seizures was modestly reported.

There were at least three patients who received cicatrectomy for their long-standing epilepsy. Two cases had refractory seizures from undiagnosed depressed skull fractures long after their head injuries. One of the two was a hospital worker who had become seizure free after the cortical scar was completely removed and with antiepileptic drugs maintained. Another patient suffered from a brain abscess close to the motor area. Intractable epilepsy developed one year after the abscess was drained.[1] After the fibrous wall of the healed abscess was removed, his seizures were abolished without any post-operative neurological deficit.

One hemispherectomy was performed on 13 November, 1989 by Professor Charas Suwanwela on a patient with cerebral hemiatrophy (Davidoff–Dyke syndrome) (Suwanwela C, personal communication). A 9-year-old boy suffered from very frequent desperate seizures and mental deterioration. Left hemiatrophic limbs with good motor powers were noted on examination. His CT scan revealed small right hemicranium with dilated ventricles. After one year of unsuccessful antiepileptic drug therapy, modified anatomical hemispherectomy was performed on the right cerebral hemisphere. Post-operatively, his seizures decreased significantly to 1–2 attacks per month resulting in much relief of his caregivers. Although left-sided hemiparesis was acquired from surgery and a wheelchair was

Figure 19.1 Professor Charas Suwanwela, a distinguished physician of early modern neurosurgery in Thailand, performing a highly precise neurological examination on a Thai patient in the 1970s.

Figure 19.2 Professor Tongchan Hongsaladarom, a pioneer neurologist and electroencephalographer of Thailand, with the first 'Grass' paper EEG machine at EEG laboratory, Chulalongkorn University Hospital in the early 1960s.

needed, his postoperative reduction in seizures was greatly appreciated by his family. His condition has remained the same during the regular follow-up period of over 10 years.

There was a study on focal convulsions from small cortical lesions by Suwanwela C *et al.* (unpublished data). Twenty-two patients who had epileptic attacks from lesions within the cerebral cortex were analyzed. Lesions larger than 2 cm in diameter were surgically removed. Among these cases, brain abscess were found in two patients and cysticercosis in one patient. However, conservative treatment was found to be the option in most patients since periodic brain CT disclosed spontaneous resolution in many cases and cysticercosis was postulated to be the cause of these vanishing granulomas. The authors recommended observation and follow-up instead of doing resective surgery in these epileptogenic infectious lesions.

Figure 19.3 The Bangkok Bank Building, ideally designed for neurology, neurosurgery, and psychiatry services on each floor in its three-storied structure was opened in 1960. Early neurosurgery, of the 1960s to modern epilepsy surgery of the 21st century took place here in its long evolutionary history. Now the location of the Chulalongkorn Comprehensive Epilepsy Program.

Development of epilepsy surgery after the 1990s

The era of comprehensive epilepsy surgery program starts from early 1990, after a few young Thai neurologists and neurosurgeons returned from their full epilepsy trainings in distinguished western epilepsy centers. Brought back were the technical know-how in modern epilepsy presurgical evaluation, state-of-the-art in surgical techniques and their enthusiasm in relieving epilepsy burden in Thai epileptics. A group of clinicians established the first comprehensive epilepsy program under a university hospital environment in 1994 known as Chulalongkorn Comprehensive Epilepsy Program, or CCEP (Table 19.1) with the second author being the founder and the director of the program.

During this period, surgical treatment for epilepsy relied upon neurophysiologic data and advanced imagings. The first temporal lobectomy series for intractable epilepsy was introduced by Professor Sira Bunyaratavej and Professor Pongsakdi Visudhipan in July 1993.[2]

The epilepsy society of Thailand has been established by Professor Pongsakdi Visudhiphan and committee since 1996. The aim of the organization has focused on identification of surgical candidates for intractable epilepsy and educated both clinician and non-clinician workers to understand the options of epilepsy surgery and other medical aspects of epileptic patients care. This organization has consistently maintained policy and enrolled as a member of the International League Against Epilepsy (ILAE) in 1997 and the International Bureau for Epilepsy in 2004. The organization was honored to host the 5th Asian and Oceanean Epilepsy Congress in 2004.

Other than CCEP and Ramathibodi hospital, there have been other epilepsy surgery services established in Bangkok, namely the Phramongkutklao Hospital and the Prasat Neurological Institute. However, CCEP has been considered the only advanced comprehensive epilepsy surgery center in Thailand since 1994.[3,4] The details of CCEP development will be described in this chapter.

The strategies

Thailand, as a developing country, has adapted its own pattern of epilepsy surgery development. Due to its 64 millions population in 2004, with accordingly high numbers of epilepsy cases, low average income per capita, and limited resources (Human Development Index rank 74 by United Nations Development Programme's *Human Development Report 2006*), the surgical program development has aimed to serve most patients under cost-effective, sustainable, and self-sufficient economic strategies.

In order to utilize resources as effective as possible, CCEP has been developed in four progressing phases, starting from the *optimizing medical treatment phase* (phase I, 1994–1996), the *presurgical evaluation development phase* (phase II, 1997–2000), the *basic epilepsy surgery phase* (phase III, 2001–2003) to the phase of *surgery using advanced techniques* (phase IV, 2004–present). The presurgical work-up using minimal standard procedures was developed step-by-step as necessary, to reach the target of rationale and economic practices.

Table 19.1 Milestones of epilepsy surgery development at CCEP, Bangkok, Thailand

	The medical-technology arm		The public arm and the Royal patronage
	Phase I (1994–1996) – Optimizing medical treatment		
1994	Epilepsy Clinic*	1996	Home visit program to improve patients' compliance by CCEP and Thai Red Cross Society volunteers
1996	New AED trial		
	Phase II (1997–2000) – Developing epilepsy presurgical evaluations		
1997	24-hour video EEG telemetry* Epilepsy presurgical conference* First lesionectomy (temporal ganglioglioma)	1997	Media and magazine campaigns on epilepsy and epilepsy surgery
1998	MRI using epilepsy protocol* Ictal SPECT*	1998	Epilepsy patients working as volunteers and employees in the epilepsy program
1999	Sphenoidal electrodes* Wada test –Thai language version* First anterior temporal resection for HS	1999	*'Light for Life Foundation for Epilepsy'* established under HRH's patronage for financial support of low-income patients for epilepsy treatment
2000	MRS fMRI for motor area Intraoperative ECoG*	2000	CCEP website, www.thaiepilepsy.org for patient and public information as well as medical consultation
	Phase III (2001–2003) – Surgery for high-yield remediable syndromes		
2001	Short course in epileptology for Thai physicians Textbook of Comprehensive Epileptology (Thai) Neuropathology of epilepsy	2001	The *'New Life'* social events performed by seizure-free patients under Royal attendance Mobile epilepsy training for rural doctors in the 4 main parts of Thailand in cooperation with Thailand Ministry of Public Health (MOPH) Seizure free patients worked as volunteers and CCEP staffs
2002	Clinical practice guideline (CPG) for epilepsy & epilepsy surgery (Thai) First Surgery of hypothalamic hamartoma	2002	Financial support for referred epilepsy surgery to the program by Thailand MOPH
2003	First Corpus callosotomy CCEP-Bethel epilepsy management conference Subtraction-coregistration SPECT to MRI (SISCOM) * NPT, WPSI-Thai language version*	2003	The '*Nom Klao*' vocational rehabilitation program under HRH's patronage A Thai novel based on a story of a seizure free surgical case by a renounced author Personnel training and development in invasive EEG and advanced epilepsy surgery in Germany and U.S.A.
	Phase IV (2004–) – Epilepsy Surgery using Advanced Techniques		
2004	Stereotactic frameless guidance Awake operation and intraoperative cortical stimulation First Functional hemispherectomy* First VNS implantation* First invasive EEG (SDE) monitoring and cortical stimulation mapping* First propofol Wada test* Multilobar resection	2004	Government financial support for VNS devices
2005	Re-evaluation and re-operation for relapse after surgery Expanding video/EEG monitoring facilities; using of digital video/EEG Epilepsy fellowship training,* approved by The Royal College of Medicine, Thailand First frameless DBS (for PD and movement disorders)† First multiple subpial transection (MST)*	2005	*'Princess Epilepsy Congress 2005'* – Scientific and Public Congress on advanced epilepsy surgery on the auspicious occasion of HRH's 48th Birthday Anniversary Issues on epilepsy and the law, literatures, and arts liberated to public and media The '*New Life Project* 'under Thai government's support – providing 300 epilepsy surgeries free of charges from 2005 to 2008, to cerebrate HRH's 48–50th Birthday Anniversary

Table 19.1 cont'd

	The medical-technology arm		The public arm and the Royal patronage
2006	First FDG-PET for epilepsy presurgical evaluation* First depth electrode implantation* Textbook of Comprehensive Epileptology vol. II (Thai) Genetic studies in Thai epileptic patients with AED allergy	2006	CCEP, King Chulalongkorn Memorial Hospital, MOPH and National Health Security Office signed MOU on development of epilepsy clinics in main hospitals throughout Thailand using CCEP as a training model, establishing online epilepsy registration and referral system for epilepsy surgery Implementation of the issue 'Epilepsy and the Law' in Thailand

* First time developed in Thailand.
† First time performed in Asia.

Only international standard presurgical and surgical techniques have been used at the CCEP. Experimental therapeutic procedures and those unproven efficacy by evidence-based reviews were not used during the program development.

The optimization of medical treatment at the initial phase has reflected pictures of inappropriate medical treatment of epilepsy long being practiced among Thai general practitioners. Among the most common examples were inadequate adjustment of antiepileptic drug (AED) types and doses to reach the maximal effectiveness (40.9%), inappropriate choice of AEDs due to unclassified seizure types (17.4%), and early AED polytherapy (10.8%). Continuing use of failed drugs was found in a small proportion (2.4%) since sub-therapeutic dosing has been acquainted in most clinical practices.[5]

After phase I, the burden of truly medically intractable epilepsy was able to be determined. At phase II when needs have been clearly realized, standard presurgical diagnostic facilities have been successively developed. The introduction of surgery for high-yield remediable syndromes at phase III has eliminated fear and doubt of this new approach among Thai epileptics. The good surgical outcomes have gained dramatic acceptance and subsequent yearning for surgery from patients all over the country. The success of surgery has also brought public attention and continuing donation to the program. When discordant cases from basic evaluations have accumulated, advanced techniques have been developed at phase IV. Epilepsy surgery dealing with incongruent cases then began using relevant high cost, invasive diagnostic or intraoperative techniques. Many epilepsy presurgical and surgical techniques developed at CCEP have been considered for the first time ever in the medical history of Thailand.

The structure

CCEP, located at Bangkok Bank Building, King Chulalongkorn Memorial Hospital, Thai Red Cross Society is run as a charitable organization under the university hospital environment. CCEP comprises multidisciplinary medical staff of the Faculty of Medicine, Chulalongkorn University. CCEP has a structure of two arms developed in parallel, namely the medical technology arm and the community arm, with one heart, i.e. the program has been privileged to be under Royal patronage.

The medical technology arm development

A specialized epilepsy clinic was first established in September 1994. The clinic provided evidence-based medical treatment for epilepsy out-patients to achieve the best seizure control and to define medically intractable cases. Subsequently, standard presurgical evaluation facilities have been developed. A well-equipped two-bed epilepsy monitoring unit (EMU) comprised of 24-hour video EEG telemetry was first established in 1997 (Figure 19.4). Special electrode placement over true anterior temporal regions according to the international 10–10 system (T9T10, FT9FT10, F9F10)[6] has been routinely used in adults since late 1997. Sphenoidal electrode placement was first performed in January 1999.

The first epilepsy case management conference for surgical selection was conducted in June 1997 followed shortly by the first CCEP epilepsy surgery. Lesionectomy for right temporal ganglioglioma was performed on 16 June, 1997 by Professor Charas Suwanwela, rendering the patient seizure free for more than 9 years and AED totally discontinued for more than 7 years.

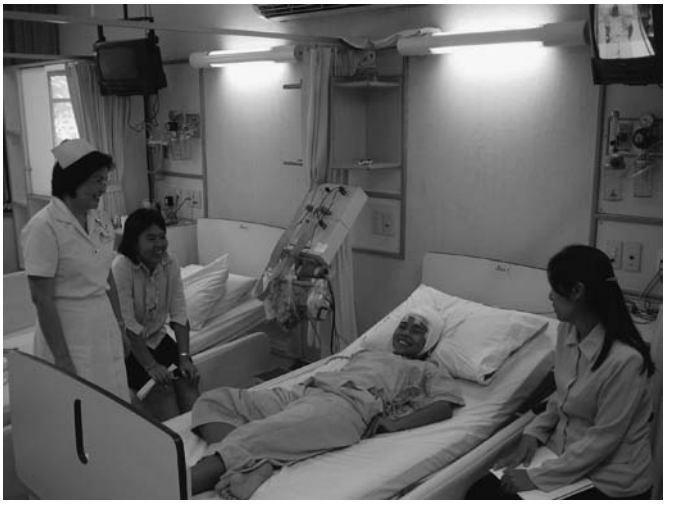

Figure 19.4 Epilepsy monitoring unit (EMU) equipped with long-term video/EEG telemetry was established in 1997. A 128-channel digital video/EEG analogue for cortical stimulation mapping and the four-bed facility were completed in 2004.

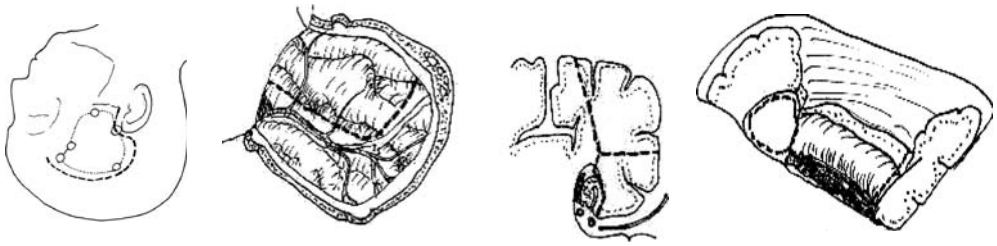

Figure 19.5 The first anterior temporal resection with amygdalo-hippocampectomy in a Thai MTLE patient (drawing by Professor Charas Suwanwela, the CCEP senior neurosurgeon, October 1999).

A 1.5 tesla high resolution MRI was first used for epilepsy in 1998.[7] Epilepsy protocol (thin cut on temporal lobes with planes parallel and perpendicular to hippocampal long axis) has been used. Fluid attenuation inversion recovery (FLAIR) technique has been added to routine epilepsy protocol since January 1999. Three-dimensional and reformatted software was developed in 2000 for detection of subtle cortical dysplasia. Magnetic resonance spectroscopy (MRS) and functional MRI (fMRI) for hand motor function were also developed in 2000.

Single photon emission tomography (SPECT) began in May 1998.[8] ^{99m}Tc-Ethyl Cysteinate Dimer (ECD) has been used for ictal and interictal injections. Ictal SPECT was limited only to official hours when ECD and scanner were available. A 3-head gamma camera scanner was first used in January 1999 which produced satisfactory high resolution images.

Thai language Wada test was invented by Tayard Desudchit *et al.*[9] Intracarotid amytal injection was, for the first time, performed to lateralize memory and speech functions in a Thai TLE patient in September 1999.

All epilepsy presurgical evaluations were completed and the first temporal lobectomy on intractable epilepsy from hippocampal sclerosis (HS) was performed at CCEP on 14 October 1999 by Professor Charas Suwanwela (Figure 19.5) which rendered the patient seizure free for over 7 years.

Surgical series that followed were the most prevalent and the most beneficial surgically remediable syndromes. These mainly included concordant temporal lobe epilepsy (TLE) with unilateral HS and localization related (focal) epilepsies from circumscribed tumors. Almost every candidate underwent the multidisciplinary presurgical evaluation and epilepsy conference. Mesial temporal lobe epilepsy (MTLE) is the most common adult epileptic syndrome operated, comprised of up to two-thirds of medically intractable cases, from which good surgical candidates can be found in 68% of cases.[10] The yield of excellent surgical outcome (>90% seizure freedom) in early surgical series had gained wide public acceptance. Subsequently, patients came to CCEP for surgical evaluation by information from others rather than by public information or referral system. The success in surgery obviously improved post-operative quality of life and relieved psychosocial stigmas of seizure-free patients. Many have become helpful volunteers of the program or even CCEP staffs in the expanding epilepsy service. Unfortunately, in early 2000, such success was acknowledged among the patient themselves rather than among medical personnel.

In 2001, a short course on epileptology was held by CCEP in Bangkok for education and training of general practitioners and physicians in related fields. The first book on epileptology was published in Thai to distribute recent advances and CCEP experiences in intractable epilepsy management to medical professions. A mobile epilepsy training module on epilepsy for rural doctors was conducted in 2001 in four main regions of Thailand, with partial funding from the Thai Ministry of Public Health (MOPH). In 2002, the first Clinical Practice Guideline (CPG) in Epilepsy and Manual on Epilepsy Surgery were published for Thai medical personnel for awareness and early referral to an epilepsy surgical center.

Surgeries were later performed in highly concordant TLE by using fewer resources as well as in less concordant cases. MRI and 24-hour video/EEG monitoring remains the minimal standard for presurgical evaluation of concordant right mesial TLE. The duration of hospital stay for monitoring was shortened significantly as skills in video/EEG recording and interpretation increased. Unnecessary SPECT and Wada tests were limited. The average scalp video/EEG monitoring period of 9 days in 1999 was reduced to 7.7 days in 2003 and 5.5 days in 2005.

Personnel training as well as technology development for advanced surgery have been conducted according to the CCEP plan. The Cleveland Clinic Foundation (CCF) Cleveland, Ohio, the University of Washington Regional Epilepsy Center, Seattle, USA, and the Bethel Epilepsy Center (BEZ), Bielefeld, Germany have contributed greatly to CCEP in such objectives and have created strong collaboration between the centers until now. The Chulabhorn Foundation under Professor Doctor Her Royal Highness Princess Chulabhorn's patronage has, for the first time, granted a qualified neurosurgeon (the first author) for 2-year epilepsy surgery fellowship training at CCF in 2001 to 2003. Invasive monitoring, cortical functional mapping as well as some aspects on neuropsychological tests, are among the transferred technology from BEZ to an adult epileptologist and two technicians from CCEP in late 2003.

Since then, expansion of advanced techniques has taken place at CCEP, most of which is the first time in Thailand. The first transcallosal resection of hypothalamic hamartoma was successfully done in September 2002.[11] Vagal nerve stimulation (VNS) was first implanted on 12 May, 2004 in a patient with Lennox–Gastaut syndrome. The first invasive EEG monitoring (IEM) and cortical stimulation mapping using subdural grid and strip electrodes was performed on 15 November, 2004, in a refractory TLE patient who had failed gamma knife radiosurgery at a private hospital, resulting in seizure freedom for more than 2 years.[12]

The worldwide shortage of sodium amytal in 2003 urged CCEP to study the use of propofol for the Wada test. The first intracarotid propofol procedure was performed on 22 October, 2004 with good results.[13] Digital video/EEG

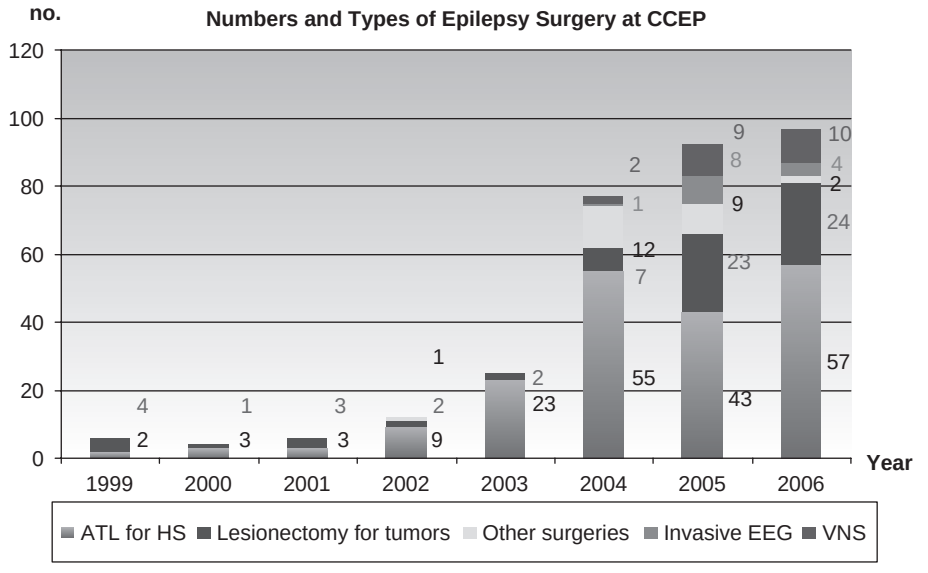

Figure 19.6 Numbers and types of epilepsy surgery at CCEP from 1999 to 15 December, 2006. The total numbers have reached 325 cases. The surgeries have been greatly increased since 2004, including cases receiving invasive EEG implantation.

telemetry, subtraction of ictal and interictal SPECT co-registered to MRI (SISCOM) and neuropsychological testing in Thai language are among other diagnostic facilities developed in parallel to the above advanced surgical techniques.

First multiple subpial transection (MST) was performed on 26 December, 2005 in a case of left insular cortical dysplasia with diffuse ictal onsets over eloquent frontotemporal regions. [18]FDG-PET was first used as a part of presurgical evaluations in July 2006. First depth electrode implantation was done on 21 August 2006 in a discordant unilateral MTLE patient.

Neurosurgical pathology also revealed many interesting epilepsy substrates from CCEP series. Many cases such as Rasmussen's encephalitis and desmoplastic infantile ganglioglioma (DIG tumor) were first reported in Thailand.[14] A case of low-grade hypothalamic neuronal tumor with gelastic/dacrystic seizure found at CCEP has never been reported in the world medical literature.

The number of surgical cases has tripled in 2004 (Figure 19.6). Anterior temporal lobectomy for HS is the most performed operation until now. Surgery on difficult cases with poorly defined epileptogenic zones such as cortical dysplasia (CD), bitemporal disease, and non-lesional epilepsy have increased in 2005. Moreover, the time after video/EEG monitoring to surgery, as well as the duration of hospital stay after surgery, has been reduced significantly in the last 3 years.

The community arm

Public activities have developed in parallel to medical technology. Serial public campaigns via media and magazines along with initial excellent surgical outcomes have dramatically converted initial fear and doubt in epilepsy surgery among the Thai population into the voluntary seeking of surgical therapy at the CCEP. The number of patients registered to the center has been increasing continuously to reach 3000 patients in 2006.

The 'Light for Life Foundation for Epilepsy' was founded in August 1999 as a charitable organization giving continuous financial support to low-income epilepsy patients. The foundation provides expenses for new AEDs, transportation, presurgical and surgical interventions including VNS supplies. Additional support was provided by the Thai MOPH with CCEP negotiation, i.e. funding for some anterior temporal lobectomy individuals from 2002 to 2004 and for VNS from 2004 to the present time.

A study from CCEP has shown that epilepsy surgery has magnificent impacts on the patients' QOL after surgery, when evaluated by occupational achievement and income acquisition.[15] Of the 111 adult epileptic patients operated between January 2002 and December 2004, an overall seizure free rate of 83% was obtained. There were 62% reduction of the unemployment rate, 43% increase of the postoperative professional achievement, and 48% increase of the average annual income per capita, when compared to the preoperative period ($p<0.001$), especially among seizure-free patients. The study proclaimed the worth of epilepsy surgery in terms of cost-effectiveness and the individual's dignity as well as emphasized the need of expansion of the surgery in Thailand, especially in those who have surgically remediable syndromes.

The CCEP website, www.thaiepilepsy.org, and 24-hour phone lines were open for consultation from patients as well as from the medical professions in 2000. A Thai novel written by a nation-renounced novelist in 2003 based on experience of a seizure free lady has subsequently brought better understanding toward epilepsy and its surgical aspects.

The Royal support

Thai monarchy is the center of merit for all Thai's hearts. The CCEP has had the privilege of Professor Doctor Her Royal Highness Princess Chulabhorn's patronage since August 1999. HRH Princess Chulabhorn, the youngest daughter of Their

Majesties King Bhumibol Adulyadej and Queen Sirikit of Thailand, received her Ph.D. degrees in biochemistry and toxicology, as well as her M.D, and Ph.D. in oncology.

HRH has followed Their Majesties' footsteps in promoting education, health, and sustainable development for the country. She also expressed her compassion on epileptic patients and her interest in expanding epilepsy surgery opportunity for them. HRH's concern at the tremendous suffering of epilepsy patients is echoed in Her speech:

> 'I have seen people under epileptic attacks and I feel much sympathy for them. When they came out of their seizures, they often felt embarrassed, as they were surrounded by gazing people. Although people would try to help them, they were unable to communicate. Afterwards, they would live with fear of unpredictable attacks. Many have lost their jobs. My heart goes out to these epilepsy patients. I deeply wish that they could become free of seizures.'

The special Thai ceremony of gratitude was performed under HRH's attendance in July, 2001 by persons who have become seizure free. The occasion signaled their good QOL and their willingness to become helpful social members after successful epilepsy surgery.

The 'Nom Klao Vocational Rehabilitation Project', another program under HRH's supervision to provide epileptics with handicraft skills to augment their income and dignity, was organized in 2003.

Education and training also play a major role in epilepsy surgery development in Thailand. On the Auspicious Occasion of HRH's 48th Birthday Anniversary, the CCEP organized the national Princess Epilepsy Congress (PEC2005) for audiences of all levels in the country. A scientific program on advanced epilepsy surgery, including lectures from invited world epilepsy experts, and workshops were opened for MD as well as for nurses and EEG technicians. A public program including psychosocial aspects of epilepsy, issues related to law, literatures, and arts have successfully extended the dimension of epilepsy interest into public and media.

Surgical series in Thailand and outcomes

There were few reports of epilepsy surgery in Thailand. In 1999, P. Visudhiphan *et al.* reported 70% seizure-free outcome following temporal lobectomy in 14 pediatric patients during 1993–1998. There were various kinds of pathologies in the report including hippocampal sclerosis, gliosis, tumor, and cavernoma.[2]

CCEP surgical series began with highly concordant temporal lobectomy and later developed to include all kinds of epilepsy surgeries, i.e. resection, palliative surgery, invasive EEG implantation, and vagal nerve stimulation (VNS).[16] Since 1997, CCEP has had a series of more than 300 epilepsy surgery patients.

Various epilepsy operations have been performed both in adults and children at CCEP. Up to December 2006, surgical substrates of temporal lobe resection have included hippocampal slerosis (HS) ($n = 172$), benign tumors ($n = 36$), cortical dysplasia (CD) ($n = 4$), cavernoma and arteriovenous malformation (AVM) ($n = 10$), hamartoma ($n = 1$) and gliosis ($n = 4$). Extratemporal resection was done on tumors ($n = 3$) and CD ($n = 5$). The rest were multilobar resection for CD ($n = 3$), corpus callosotomy ($n = 6$), functional hemispherectomy ($n = 10$), and removal of hypothalamic hamartoma ($n = 6$).

Twenty-one VNS had been implanted by December 2006. Some patients show modest reduction of seizures but have moderate improvement of emotional control, learning ability, awareness and communication. So far, subdural grid electrodes have been implanted in 12 patients, depth electrodes in 1 and bitemporal subdural strips in 4 with satisfactory results.

The outcome of 72 temporal lobectomy patients for hippocampal sclerosis who have at least 1 year follow-up are seizure free (Engel I) 60 cases (83.4%), almost seizure free (Engel II) 6 cases (8.3%), and worthwhile improved (Engel III) 6 cases (8.3%).[17,18] The results are comparable to an internationally published series. Epilepsy surgeries are increasing as more surgical candidates are identified by advanced diagnostic techniques and awareness of epilepsy surgery is expanding among patients and medical personnel.

Current situation of epilepsy surgery in Thailand

Epilepsy surgery has gained acceptance and expectation among patients with epilepsy in Thailand up until now. Nevertheless, drawbacks regarding inadequate knowledge in epilepsy surgery among personnel in local hospitals have affected proper timing and process of referral to a surgical center. The government has supported the CCEP 'New Life Project' by providing a budget for 300 upcoming epilepsy surgical cases from October 2005 to 2008 with a plan to expand more than 30 epilepsy clinics nationwide using CCEP as a prototype. As a result, more patients are expected to get access to standard presurgical evaluation and effective surgery by overcoming obstacles of limited referral to an epilepsy tertiary center.

Epilepsy surgery is gradually expanding in other medical institutes and private hospitals in Bangkok as well. However, up to now CCEP has been accepted as the only advanced comprehensive epilepsy surgery center serving patients from all parts of the country with routine highly standard protocol. Apart from the public communication and campaigns through the media in the early days, patients are now gaining their awareness of epilepsy surgery service among themselves. Its expansion has been supported mainly by charity funding under HRH's patronage and partly by the government sectors. Nevertheless, there are still large numbers of surgical candidates waiting to be evaluated and operated nationwide.

The epilepsy fellowship in Thailand has recently been established and approved by the Royal College of Physicians of Thailand (RCPT). CCEP is the first and only institution approved as an epilepsy fellow training center in 2005. The first fellowship started on June 1, having two fellows per year on a 2-year program. In the near future, as there are more trained epilepsy focusing physicians, suitable surgical candidates are anticipated to be better recognized and properly referred to the tertiary epilepsy center.

Projections into the future

CCEP is the pioneer in the development of epilepsy surgery in Thailand and has become an advanced epilepsy center at this stage. For sustainable development, education and training in epilepsy need to be distributed widely and continuously throughout the country. Basic epilepsy surgery needs to be developed as satellite regional centers in remote parts of Thailand to include more surgical remediable patients. Early and appropriate referral for surgery should be a promise.

Patient selection for surgery using minimal diagnostic facilities is another future expectation. As experience and confidence grow, epileptologists in a tertiary center can improvise presurgical evaluation to reduced cost and process but yet achieve good surgical outcome. Researches and development on this issue will be needed. On the other hand, some advanced investigations may substitute invasive and expensive work-up in a tertiary center, for example, fMRI for Wada test or PET scan for invasive EEG monitoring.

A national cyclotron and positron emission tomography (PET) center has been established at Chulabhorn Research Institute (CRI) Cancer Hospital in 2006 as a powerful diagnostic facility for cancer, epilepsy, and other diseases. The concept of sharing cyclotron and PET/CT scanners among surrounding medical schools and hospitals has been appraised by the International Atomic Energy Agency (IAEA). After its opening in July 2006, PET has improved localization of epileptogenic zone and identified more surgical candidates in certain epileptic syndromes, such as discordant TLE, non-lesional TLE and bitemporal disease.

Frameless deep brain stimulation (DBS) was first operated at King Chulalongkorn Memorial hospital in August 2005 for Parkinson's disease and dystonia. Although DBS for epilepsy is still an experimental approach, CCEP is ready for epilepsy application if this new modality proves effective in the future. However, upcoming advanced technologies should be wisely considered to fit the need and economical status of Thailand.

Parts of this chapter have been delivered as the Keynote Lecture by C. Locharernkul under the attendance of HRH Princess Chulabhorn and as a core lecture by T. Srikijvilaikul, at the Princess Epilepsy Congress 2005, Bangkok, 22–24 October, 2005.

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20 History of epilepsy and seizure classification

T Loddenkemper and HO Lüders

Terminology and definitions

Epilepsy

In ancient medical science the word 'epilepsy' was used to depict both the disease and its attacks. The presentation of the attacks defined the condition: 'Epilepsy is a convulsion of the whole body together with an impairment of the leading functions'.[1] Frequently, the Greek term 'epilepsie' initially did not refer to the disease itself, but only to the actual attack or the epileptic patient. The term epilepsy derives from the Greek term 'epilambanein' which means to seize. The disease itself was called 'the sacred disease'.[2] Interestingly, John of Gaddesdon provides a different translation, suggesting that the word derives from 'epi', above and 'ledo', injure; that is injury to the upper parts, that is, the head.[3] Concepts and terminology of epilepsy have been changing throughout the centuries. With the advent of additional technologies and knowledge, previous terms required either redefining or introduction of new terms became necessary. Based on a recent ILAE publication:

> epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. Elements in the definition of epilepsy include history of at least one seizure, enduring alteration in the brain that increases the likelihood of future seizures, and associated neurobiologic, cognitive, psychological, and social disturbances.[4]

Epileptic seizure

Seizures have been documented for more than 3000 years.[5] Since then abundant descriptions and explanation models can be found in the literature. The separation of both the actual attacks and epilepsy as a disease dates back to John Hughlings Jackson. Jackson's definition of a seizure still provides the basis for the understanding of seizures to the present day. According to Jackson:

> A convulsion is but a symptom, and implies only that there is an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles. This discharge occurs in all degrees; it occurs with all conditions of ill health, at all ages, and under innumerable circumstances.[6]

This definition has not changed much in the last 130 years. According to the International League Against Epilepsy (ILAE) an epileptic seizure 'is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain'.[4] Elements defining an epileptic seizure include 'mode of onset and termination, clinical manifestations, and abnormal enhanced synchrony'.[4]

Epileptic syndrome

The concept of epilepsy syndromes is relatively young. Although several authors in the literature attempted to delineate epilepsia proper from epilepsy related to other medical condtions, the terms epilepsy and epilepsy syndrome have frequently been used synonymously. Epilepsy syndromes based on presumed etiology have all been described within the last 150 years, including West syndrome, Rasmussen encephalitis, or Lennox–Gastaut syndrome. The first definition of epilepsy syndromes can be found in the 1985 epilepsy classification proposal.[7] This is the first proposal that officially differentiates between epilepsy and epilepsy syndrome. Here epilepsy syndromes have been defined as:

> an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together. The signs and symptoms may be clinical (e.g., case history, seizure type, modes of seizure recurrence, and neurological and psychological findings) or findings detected by ancillary studies (e.g., EEG, X-ray, CT, and NMR). In contradistinction to a disease, a syndrome does not necessarily have a common etiology and prognosis.[7]

In a revised proposal in 2001, the definition has been shifted to: 'A complex of signs and symptoms that define a unique epilepsy condition. This must involve more than just the seizure type: thus frontal lobe seizures *per se*, for instance, do not constitute a syndrome'.[8] Idiopathic, symptomatic, and probably symptomatic epilepsy syndromes are differentiated. A syndrome is perceived as a different entity than genuine epilepsy as a disease. This is 'a pathological condition with a single specific, well-defined etiology. Thus, progressive myoclonic epilepsy is a syndrome, but Unverricht–Lundborg is a disease'.[8]

Understanding of epilepsy through the ages

Mythical approach: from ancient times to Hippocrates and Galen

Hippocrates book on the 'sacred disease' localized epilepsy in the brain and fought mysticism and superstition, that epilepsy is not a sacred but a medical condition. Ancient definitions included the one by Aretaeus defining epilepsy as an 'illness of various shapes and horrible'.[1] One of the earliest definitions of epilepsy in antiquity was ascribed to Erasistratus:[1] 'Epilepsy is a convulsion of the whole body together with an impairment of the leading functions'. Galen adapted this most influential definition of epilepsy and defined epilepsy 'not only as convulsion of the whole body, but also interruption of the leading functions':[1] According to Galen, epilepsy was either related to congestion of humors in the ventricles of the brain or due to humors arising from other parts of the body. This was the prevailing concept of epilepsy until early Renaissance.

From Antiquity to Renaissance

In medieval times, the Galenic definition of epilepsy continued to prevail and was rarely questioned. The major advance during this period may be the influence of Paracelsus, who now interpreted epilepsy as a physical and chemical condition, with a possible chemical treatment. During Renaissance, the definition of epilepsy was broadened, and Marcus Marci (1595–1667) remarked that epilepsy could present as 'any affection of the body where the victims are disordered in their minds, while the members [of the body], be it all, or some, or only one, are moved against their will'.[9] This was mainly related to the increasing amount of single case reports and the resumption of autopsies that now allowed pathological correlation of clinical conditions, facilitating a better etiological understanding of epilepsy.

The 19th century and John Hughlings Jackson

Due to increasing clinical evidence, the humoral concept by Galen was slowly abandoned in the 19th century, and all epilepsies were thought to arise from the brain. Possible etiologies for epilepsy were either a structural lesion or a functional disturbance of the brain. Epilepsies due to structural lesions were named symptomatic, structural or lesional, or with an underlying pathophysiological approach, partial. Epilepsies without a cerebral lesion were called functional, idiopathic, true, or centrencephalic. In addition to these etiological concepts, John Hughlings Jackson is considered to be the first who introduced a localizing dimension to the understanding of epilepsy by differentiating between generalized and focal epilepsies.[10] Besides an anatomical and pathological subdivision, he also anticipated physiological findings that were later confirmed on EEG. According to Jackson 'Epilepsy is the name for occasional, sudden excessive, rapid and local discharges of grey matter'.[10] This rapid gain of knowledge in epilepsy at the end of the 19th century and the beginning of the 20th century changed our view on epilepsy so profoundly adding multiple facettes to epilepsy, that classifications after Jackson are outlined in a separate paragraph combining multiple classification angles such as localization, seizure type, etiology, age, and other circumstances (see later).

Invention of the EEG

The invention of the EEG by Hans Berger and pioneering work by Gibbs and Gibbs allowed further characterization of EEG patterns in patients with epilepsies. Initial attempts to recognize epilepsies included matching of semiological seizure patterns with typical EEG patterns. One of the major drawbacks of Jackson's theory was the lack of explanation for loss of consciousness during seizures. In 1954, Wilder Penfield and Herbert Jasper at the Neurological Institute in Montreal explained loss of consciousness by interaction of epileptiform discharges between the reticular-thalamic system and the cortex.[11] In the same year, Henry Gastaut published a monograph with an almost similar theory of epileptogenesis.[12] From that point on, epilepsies that were thought to interact with deeper brain structures were called generalized.

ILAE classifications and revisions

Henry Gastaut was also the first to lead the ILEA to a uniform classification of epilepsies.[13,14] This was characterized by an etiological (primary versus secondary) dimension and characterization of the localization (partial versus generalized). Description of benign focal epilepsy of childhood, the first 'partial primary' epilepsy necessitated a revision of this initial proposal, and revised versions in 1985[7] and 1989[15] attempted to classify epilepsies in syndromes according to a strict one-to-one relationship of EEG and clinical seizures. Since then a revised epilepsy scheme and a revised syndromic classification have been discussed.[8,16] Part of the current difficulties may be that there is no such disease as idiopathic epilepsy and generalized epilepsy anymore and this is particularly highlighted by research progress in epilepsy genetics and EEG. Borderlines between focal and generalized epilepsies become less reliable as ultrafast EEG recordings also suggest focal onset even in some generalized forms of epilepsy. Additionally, research in genetics more and more reveals underlying causes for so-called idiopathic epilepsies.

Classification according to clinical epileptic seizure types

The Sakikku ('all diseases') (1067 BC) is believed to be the oldest available written documentation of seizures and seizure semiology. This Babylonian plate deals almost exclusively with the clinical presentation of epilepsy. The translators of this document comment that 'it was evidently the discipline of the times to write down only what was seen.'[5] The main goal of this table appears to be the documentation of observation. In 55 separate entries, this text distinguishes meticulously different clinical features and presentations of seizures. Semiological features described include eye reddening, a warning (the patient that is possessed by a demon recognizes the onset and cries 'it is he again'), eye blinking, cheek twitching, limb extension, laughing, continuous flexion and extension of the limbs, body deviation to one side, paralysis

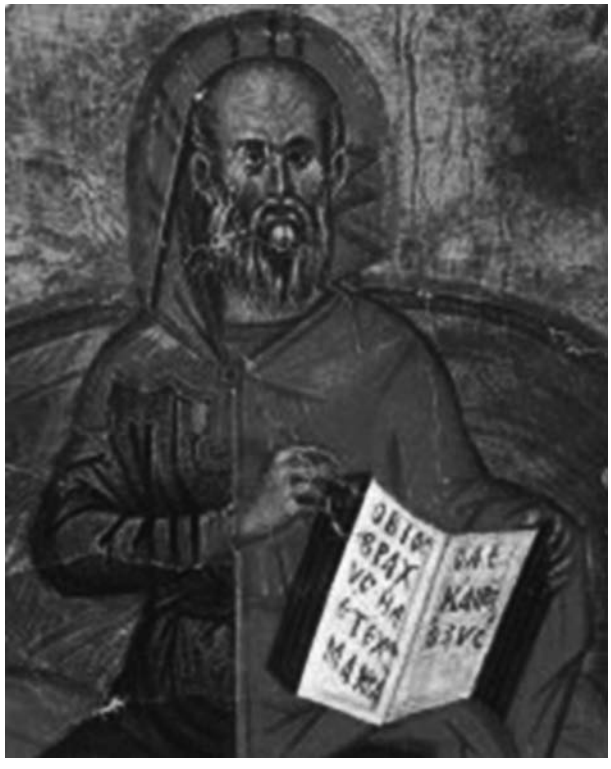

Figure 20.1 Hippocrates, from Nuremberg Chronicle. Courtesy of Beloit College, with permission.

Figure 20.2 Galen, with permission; Image courtesy of the Blocker History of Medicine Collections, Moody Medical Library, The University of Texas Medical Branch, Galveston, Texas, USA.

after a seizure, unilateral body heaviness and prickly feeling, headaches prior to seizures, emotional upset prior to seizures, eye deviation, a feeling of distention in the epigastrium, cloudiness in front of the eyes, hissing in the ears, and constant wiping clean of hands and face and other features. Seizures with and without loss of consciousness are distinguished.[5] Although one might argue that this is not a 'clear-cut' seizure classification, its organization in 55 different entries reveals an underlying structure of information.

The first differentiation of semiological seizure events is found in Hippocrates of Kos' Sacred Disease (400 BC) (Figure 20.1), which also documents the views of 'the others', the magicians, that do not believe that the cause of epilepsy is located in the brain.[17] This magical concept contains an interesting distinction between semiological elements, which are ascribed to different gods. The mother of gods was involved when teeth gnashing movements and right-sided motor seizures occurred. Poseidon induced cries, Ares was associated with salivation and kicking leg movements, and nocturnal events with fear and disorientation were ascribed to Hekate.[17] However, it is not clear whether only epilepsy is included in this classification. Other non-epileptic events and psychiatric conditions may also have been classified according to this scheme.[2]

Aretaeus of Cappadocia (1st century AD) separates premonitory symptoms into symptoms occurring longer before the onset of the event and immediately at the beginning of the seizure. Symptoms occurring longer before the event 'included stupor, vertigo, tension of the members, fullness and swelling of the neck, aversion to food, much vomiting of phlegm, flatulence, high diaphragm.' Symptoms occurring at the onset of the event include 'red or black lights or both together appear in arcs before the eyes, similar to the rainbow. The patients feel their ears ringing, they smell bad odors, are irritable, become angry without reason'.[1]

Although Claudius Galen's (circa 130–210 AD) (Figure 20.2) classification was embedded in Galen's medical theory of humors, it was also based on observation of seizure semiology overlapping with localization. The first type of epilepsy that originated in the brain was related to accumulation of phlegmatic humor in the ventricles causing obstruction.[1] The second type, epilepsy starting from the stomach, was brought on by accumulation of bile in the stomach, leading to evaporations that then also affect the brain.[1] The third type of epilepsy that starts in any other body part was explained by spread of a 'pneumatic substance' throughout the body.[1]

Three other clinical features were highlighted by Caelius Aurelianus (5th century AD) who also distinguished three types of epilepsy: the first type mimicked sleep, the second type presented with convulsion, and the third type manifested convulsion followed by deep sleep.[1] He separated seizures with and without warning.[18] His account of warning symptoms included:

> heaviness and giddiness in the head, an inner noise, which is felt in the occiput, too, tension in the eyes, ringing in the ears … or difficulty in hearing; and together with the vertigo, dimness of the eyesight or something hanging down before the eyes, as it were, either similar to the spots of marble which the Greeks call 'armarygmata' or 'marmary-gas', or similar to spider webs or very thin clouds or to very small flying animals like gnats. The patients also perceive tiny sparks, so to speak, or fiery circles borne around before their eyes. The tongue is not flexible, and at the same time muscles twitch, and they have pains in the back and between the shoulders. There also follow rigor in the throat and a concomitant precordial distention together with yawning, sneezing,

> flow of saliva, and aversion to food or immoderate appetite. … The mind is anxious and troubled, and they are readily roused to anger for no major reason. There is forgetfulness for what has been done shortly beforehand and a ready disposition for things causing gloom.[1]

With or without warning, the epileptic then falls to the ground. At this point, Caelius Aurelianus differs between three semiological seizure parts:

1. manifestation (unresponsiveness and generalized motor features with suffocation)
2. abatement (unconscious discharge of urine, feces, semen, saliva, then end of suffocation)
3. cessation (patient arises with ongoing postictal discomfort).[1]

Cassius Felix (5th century AD), similar to other ancient authors and close to Caelius Aurelianus, distinguishes two types of seizures, presenting either as motor seizure or as sleep.[19]

Theodorus Priscianus (5th century AD) was the first to describe the complete sequence of what today is considered a secondary generalized tonic–clonic seizure with different preceding symptoms, followed by stretching of the body, then by clonic activity, and finally by sleepiness.[1]

Sun Si Miao (682 AD) proposed one of the first seizure classifications in the traditional Chinese literature. This author differentiates between six different semiological seizure types based on the resemblance of the epileptic cry with animal sounds. He differentiated 'goat epilepsy', 'horse epilepsy', 'pig epilepsy', 'cow epilepsy', 'chicken epilepsy', and 'dog epilepsy'.[20]

In the Persian literature, Ibn Sina (Avicenna, 973–1037 AD) semiological seizures based on Galen's humoral pathology were separated into four types: The phlegm type was characterized by paleness, anxiety, fear, unconsciousness, and amnesia. The black-bile type presented with palpitations and chest pressure, obsession, and unrealistic thoughts. The blood type manifested with blood-shot eyes, enlarged neck veins, and cyanosis, and the yellow-bile type became apparent with a yellow face, short attacks, and depression.[21]

St. Hildegard of Bingen (1098–1179 AD) recognized two types of epileptic seizure closely tied to the character of the patient.[22] The first is characterized by 'demoniacal agitation of the irascible' and the second presents with 'pitiful helplessness of the moral weakling'.[22]

Matthaeus Platearius Salernitanus (circa 1150 AD) elaborated on 'major' and 'minor' epileptic seizures based on the galenic epilepsy model. Major seizures presented with distortion of the face, shaking of the neck and body, teeth clenching, and passing of urine, stool, or sperm. Patients with major seizures also continued to froth repeatedly, even if the froth is wiped off. During minor seizures the patient lost consciousness and may or may not fall. Froth did not appear after it has been wiped off the mouth.[19]

Samuel Tissot (1728–1797) is credited with the first semiological description of seizures with loss of consciousness, but nearly no motor features. His description of a 14-year-old girl illustrates his differentiation between grand accés and petits accés.

> … the young patient, in intervals between the great attacks (grands accés), frequently had very short, little (petits) attacks, which were merely marked by an instantaneous loss of consciousness, interrupting her speech, together with a very slight movement of the eyes.[23]

James Cowles Prichard (1786–1848) divided seizures into convulsive epilepsy, tetanic epilepsy, and leipothymia. Convulsive epilepsy presents with loss of consciousness and convulsions. Tetanic epilepsy is characterized by loss of consciousness without convulsions, but tonic activity. Leipothymia presented with sudden onset of loss of consciousness and no motor activity 'sometimes preceded by vertigo, but in other instances without any premonitory symptoms'.[24] Prichard also coined the term 'partial' seizures describing patients with focal motor features or an epigastic aura and no loss of consciousness.[25]

Louis Florentin Calmeil (1798–1895) based his classification in 1824 on severity of seizure semiology and differentiated between three seizure types:[26]

1. 'Grand mal' (generalized tonic–clonic seizure)
2. 'Petit mal, vertiges, étourdissemens parmi les malades'. This type may or may not occur prior to grand mal attacks, and can present with dizziness, head turning, arm extension, or unresponsiveness.
3. 'Absences' are described as short interruptions of consciousness. The patient interrupts his current activity, and even though the senses are aroused, 'ils sont mementanonément fermés aux impressions' – they are for a moment closed off from impressions.[26]

In 1854, Louis Jean Francois Delasiauve's (1804–1893) classified seizures according to severity in four categories: absences, vertiges, accès intermediares, and accès complete. He considered absences with its characteristic symptom loss of consciousness as the most severe form of seizures. This was followed by 'vertige', involving head deviation, ictal speech, and automatisms. Accés intermédiaries involve a variety of clonic, tonic, and myoclonic presentations, and accés complet represent a generalized tonic clonic seizure.[27]

Sir John Russell Reynolds (1828–1896) seizure classification (1861) is also based on the severity of clinical seizure presentation. This concept differentiates between four degrees: loss of consciousness, loss of consciousness with focal motor movements, loss of consciousness with generalized motor features, and focal or generalized motor features without loss of consciousness.[28]

In 1890, Sir John Hughlings Jackson (1834–1911) introduced the anatomical concept of partial versus generalized seizures. Until the 1870s Hughlings Jackson's research was dominated by a physiological research approach to epilepsy. According to this definition of epilepsy as 'occasional, sudden, excessive, rapid and local discharges of grey matter', many epilepsies existed.[6] However, this was not practical for everyday use and therefore he added an empirical semiological classification to his scientific model of epilepsy. He used a comparison between a gardner and a botanist and concluded that both classifications, a utilitarian and a taxonomic, are necessary. Therefore, his 'empirical arrangement of epilepsies and epileptiform convulsions' included: (I) Epilepsy

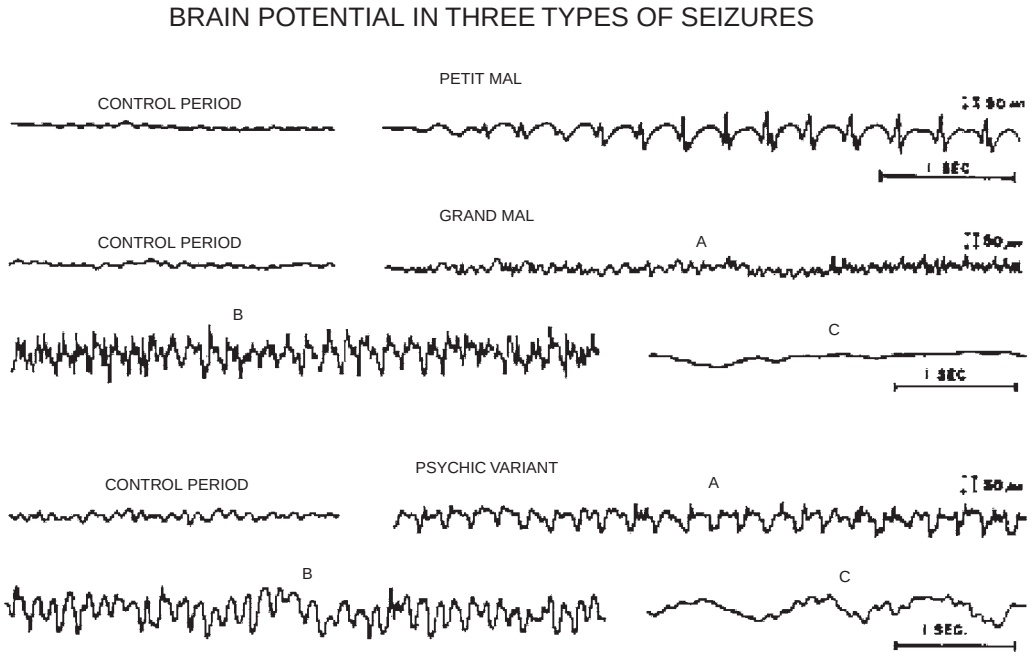

Figure 20.3 EEG classification according to Gibbs and Gibbs (1937), reprinted with permission from ref. 29.

proper: vertigo, petit mal, grand mal and (II) epileptiform and epileptoid convulsions beginning unilaterally, unilateral dysaesthesia (migraine), and epileptiform amaurosis.[25]

The invention of the EEG allowed Frederic Andrews Gibbs and Erna Leonhardt Gibbs (1937) to classify seizures based on their electroclinical presentation.[29] They distinguished three clinical seizure types associated with different EEG patterns (Figure 20.3). Their clinical seizure classification included grand mal as generalized tonic–clonic seizure, psychomotor attacks associated with small motor movements, and petit mal characterized by loss of consciousness.

> The normal frequency of the brain potentials is around 8–20 a second. In grand mal, these waves speed up to 25–30 a second, and appear in our records as sharp spikes. In psychomotor attacks (psychic variants) the rate slows to 3 or 4 a second with a square, flat-top wave predominant. In petit mal quick sharp spikes and slow, round waves at the rate of 3 a second alternate. We can explicitly say, that in grand mal the cortical activity is abnormally fast; in a psychomotor attack, it is abnormally slow; and in petit mal, it alternates between fast and slow.[29]

In 1943, this classification was further elaborated and psychomotor attacks and psychomotor variant were separated recognizing that different EEG features could present with similar clinical features.[30] The prediction of the clinical seizure type based on the EEG pattern was further questioned by Jasper and Kershmann, who only found a correlation between clinical presentation of absence seizures and 3 Hz spike and wave complexes. They subsequently published an EEG classification separate from clinical semiology.[31]

Based on his work with Gibbs and Gibbs, William G. Lennox (1960) outlined a clinical seizure classification in his book *Epilepsy and Related Disorders*.[32] This classification consisted of the petit mal triad including pure petit mal of pyknolepsy, myoclonic and atonic seizures, the convulsive triad including generalized, focal, and Jacksonian (or rolandic) seizures, and the temporal lobe triad including automatic, subjective, and tonic focal seizures.

The first ILAE classification of epileptic seizures was published by Henry Gastaut (1969).[33,34] The major breakthrough of this classification was that it set a common communication standard. The main feature of this classification is the distinction between generalized seizures from the onset and seizures that are focal at the onset and then become secondary generalized. It lists clinical seizure types closely connected with EEG seizure types, interictal EEG, anatomic correlation, etiology, and age. Seizure types include partial seizures with elementary symptomatology (with motor symptoms, with special sensory or somatosensory symptoms, autonomic symptoms, and compound forms), partial seizures with complex symptomatology (such as impaired consciousness only, cognitive symptomatology, affective symptomatology, psychosensory symptoms, psychomotor symptoms or automatisms and compound forms), partial seizures with secondary generalization, and generalized seizures (absences divided into simple and complex absences), myoclonic jerks, infantile spasms, clonic seizures, tonic seizures, tonic–clonic seizures (or 'grand mal'), atonic seizures, and akinetic seizures.[33,34]

In 1981, only 12 years later, an ILAE committee led by Fritz E. Dreifuss revised its clinical and electroencephalographic classification of epileptic seizures.[35] Rapid development and refinement of diagnostic and therapeutic methods, including the advent of simultaneous Video-EEG, and additional antiepileptic drugs and surgical techniques, increased the urge to develop a more precise classification tool for everyday use and research means in order to measure and predict treatment responses.

One of the major changes and most likely its greatest achievement is the inclusion of a glossary of terms to ensure universality of terminology. However, it broke with the previous convention of describing clinical seizure, EEG seizure, interictal EEG, anatomic correlation, etiology and age. Instead it lists clinical seizure type, EEG seizure type, and interictal manifestations. Again, the classification differentiates between partial (or focal, local) seizures, generalized seizures and unclassified epileptic seizures, and describes clinical seizure types in association with their one-to-one EEG presentation. Furthermore simple and complex partial seizures are separated by loss of consciousness. It is also the first classification that accounts for longitudinal seizure evolution of simple partial seizures into complex partial seizures and for evolution from partial into generalized seizures. Partial seizures were divided into simple partial seizures, complex partial seizures (with impairment of consciousness at onset or simple partial onset followed by impairment of consciousness), and partial seizure evolving to generalized tonic–clonic convulsions (preceded either by a simple or complex partial seizure). Generalized seizures were further divided into absence seizures (presenting with a generalized 3 Hz spike and wave pattern), myoclonic seizures, clonic seizures, tonic seizures, tonic–clonic seizures, and atonic seizures. Interestingly, infantile spasms were removed from this part. Unclassified seizure category 'includes all seizures that cannot be classified because of inadequate or incomplete data and some that defy classification …'.[36]

The strict one-to-one relationship of clinical ictal seizure semiology and ictal/interictal EEG manifestations in this classification insufficiently characterized many seizures, and the seizure classification has major limitiations in particular in pediatric patients. Hans O. Lüders and others at Cleveland Clinic pioneered a semiological seizure classification based exclusively on ictal semiology which was published in its preliminary form in 1993[37] and then presented in its finalized form in 1998.[38,39] Rekindled by the advances in video-EEG, this classification reintroduces the easiest and oldest classification of epileptic seizures exclusively based on their clinical presentation. Additionally, it also allows for specification of seizure progression and provides additional lateralizing and somatotopic information. Details of the main categories of this classification including auras, autonomic seizures, dialeptic seizures, motor seizures, and special seizures, are explained elsewhere in this book.

Based on the semiological seizure classification Warren T. Blume, Hans O. Lüders, and others published the *Glossary of Descriptive Terminology for Ictal Semiology* in the name of the ILAE in 2001.[40] This glossary was also included in a recent proposal of a diagnostic scheme by Jerome Engel in 2001.[8]

Classification according to localization in the brain

Trephining of the skull is the oldest known surgical procedure, and has been described in skulls from the Neolithic age around 5000 BC.[41,42] Although the indications for trepanation at that time are unknown due to lack of documentation, epilepsy may have been one of them (Figure 20.4). Perforation of the skull for treatment of epilepsy has later been documented by the founder of the Greek Methodist school of medicine Themison of Laodicea (around 50 BC).[1]

Hippocrates was the first who placed the origin of seizures in the brain. The main pathophysiological mechanism was phlegm located in the brain that has not been purified during the fetal period. The phlegm melts, rushes into the body vessels, obstructs these and produces symptoms (such as leg movements, eye deviation, and others) if it cannot be excreted, e.g. through the bowel by diarrhea or as excretion through the lungs.[1] One of the greatest advances of this pathophysiological theory is the localization in the brain. However, it also acknowledges the fetal development as a crucial and potentially vulnerable period.

The discovery of nerves has been ascribed to Herophilus and Erasistratus (3rd century AD) and this paved the way for Aretaeus, who also localized epilepsy in the brain (or rarely in the stomach) and suggested stimulation of peripheral nerves to explain the spread of symptoms.[1]

Asclepiades of Bithynia (about 124–40 BC) opposed the humoral principles of Hippocrates and explained epilepsy – based on his atomistic view of medicine – as an injury of the meninges, or alternatively due to fear. Soranus of Ephesus (2nd century AD) expanded this concept and added contusion to causes of epilepsy, elaborating on the Hippocratic description that seizures may occur in patients with fractures of the skull.[1,19]

The Roman author Apuleius (125–180 AD), together with Aristotle, is the first who describes further lateralization. Both mention that the disease is more difficult to cure if it affects

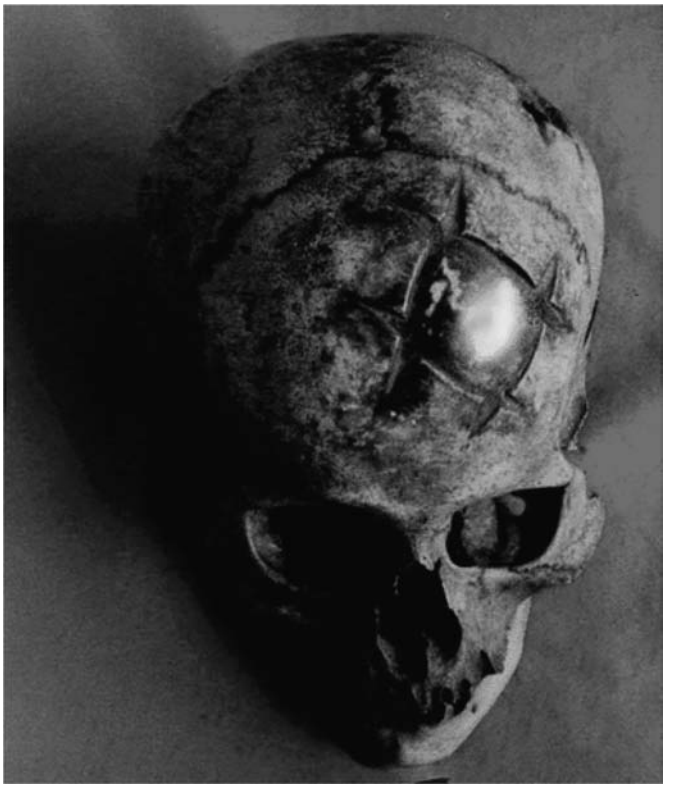

Figure 20.4 Skull demonstrating frontal cranioplasty with a gold plate and evidence of healing. Also note the left parietal craniectomy. Reprinted with permission from ref. 42.

the right side, referring to semiological features affecting the right side of the body.[1]

Claudius Galen (circa 130–210 AD) also localized epilepsy in the ventricles of the brain, in the stomach, or in any other body part.[1] Galen specifically mentions the third and fourth ventricle.[19] Avicenna localizes the origin of epilepsy to the 'anterior ventricle'.[19] This localization to the ventricular system is found throughout medieval times and was only markedly changed in the early 16th century at the beginning of the Renaissance when scientists started to debate and either opposed traditional views or tried to reinterpret authors from antiquity.

In medieval times, each of the three Galenic presentations of the disease was named differently. 'Epilepsy' then referred only to the type that initiated in the brain, whereas the type occurring from the stomach was called 'analepsy', and the type from any other part of the body was referred to as 'catalepsy'.[19]

Another modification of Galen's theory in the medieval times was the distinction between 'true' and 'not true' epilepsy, as documented in writings of Arnold of Villanova (circa 1234–1311 AD) and Gilbertus Anglicus (circa 1180–1250 AD). True or idiopathic epilepsies in their understanding meant epilepsy arising from the brain, whereas not true or sympathetic epilepsies arose from other body parts. This classification is still preserved in Boerhaave's textbook on neurological conditions (Praelectiones de morbis nervorum, 1761), that differentiates 'epilepsia ideopathica' arising from the brain and 'epilepsia deuteropathica' arising from the stomach or other body parts.[43]

However, based on wider clinical experience, the rebirth of case reports and increasing numbers of pathological and anatomical observations, Charles Le Pois (Carolus Piso, 1563–1633)[9] challenged the Galenic concept of origin of sympathetic epilepsies in the respective body parts.[9] Based on observations and rationale, he concluded that epilepsy (and hysterical symptoms) are caused in the brain. These observations of other research necessitated a revision of Galen's distinction between idiopathic and sympathetic epilepsies and paved the way for additional etiological theories.

Antoine Portal (Le Baron Portal, 1772–1832) came to similar conclusions stating that epilepsy was always located in the brain, in particular the medulla. Although he also distinguished idiopathic and sympathetic epilepsy, he concluded that sympathetic epilepsy was caused by irritation of nerves and this was conducted to the brain producing symptoms in respective areas of the body.[44] This was further elaborated by Marshall Hall (1790–1857) who localized centric epilepsy in the medulla oblongata and eccentric epilepsy as part of a reflex arch triggered by a peripheral stimulus.[45,46]

Sir John Hughlings Jackson (1834–1911) (Figure 20.5) distinguished between 'genuine epilepsy of authorities' and 'unilaterally beginning convulsions' in 1863. The genuine epilepsy of authorities presented without warning, consciousness is lost early, and onset of motor manifestations was often bilateral and equal, and the 'march of the spasm' was rapid. The unilaterally beginning convulsions were characterized by warning, consciousness is lost late, motor manifestations are frequently limited, unilateral, unequal and the 'march of the spasm' is slow.[25] This distinction is now considered the first division between generalized and focal epilepsies. In addition to that he added an etiological dimension to his classification by attempting to define the lesion better. This classification and his definition of epilepsy as 'occasional, sudden, excessive, rapid and local discharges of grey matter'[6] set new standards for future classifications.

Later publications also implied a classification of three levels in the nervous system combining clinical seizure types and localization in the brain. The lowest level, including the spinal cord, the medulla, and the pons represent simple movements. The rolandic area and the striatum represent more complex movements and represent the second level. The third level is represented by the prefrontal motor cortex, the highest level of evolution and center of the most complex movements and 'organ of the mind'.[10] Later, he also included 'uncinate fits' in his classification, to include seizures with olfactory and gustatory auras, automatisms, and 'the dreamy state'.[10] Classifications after John Huglings Jackson tend to include combinations of seizure types, localization, etiology, and other levels of classification (see later).

Classification according to etiology

The Sakikku ('all diseases') (1067 BC) is the oldest available documentation of epilepsy. Its 55 entries not always focused merely on semiology, but also provide information on the causing demon or ghost, the prognosis, the diurnal pattern, frequency, and on status epilepticus. According to the translators, these entries have been somewhat grouped and have been retrospectively sorted, considering seizure frequency patterns, single symptom entries, symptoms with prognosis, diurnal features, nocturnal features, features of chronic epilepsy,

Figure 20.5 Sir John Hughlings Jackson (1834), Image courtesy of the American Association of Neurological Surgeons' Cyber Museum of Neurorsurgery.

features preceding seizures, and features following seizures. Additionally, many entries have been ascribed to certain demons and ghosts. Accordingly, different types of epilepsies are differentiated including seizures ascribed to 'miqtu' and 'lilu', ghosts or the hand of ghosts. Additionally causative demons from the river, the 'bennu' demon, the 'e elu' demon and others are differentiated.[5]

In the Gospel according to Mark (9:14–29), we find indications that seizures were related to evil spirits and the devil. In this passage Jesus casts a devil from a young man:

> Teacher, I brought unto thee my son, who hath a dumb spirit; and wheresoever it taketh him, it dasheth him down: and he foameth, and grindeth his teeth, and pineth away: and I spake to thy disciples that they should cast it out; and they were not able (Mark 9;17–18[47]).

Another casting out of an unclean spirit was described in Mark (1; 23) (Figure 20.6).[47] Until the 16th century, many authors considered causes such as demoniac influence, witchcraft, and the devil[48] in addition to other underlying pathologies.

Hippocrates in 'On the sacred disease' indicated a hereditary etiology.[1] This, however, may have been more an argument against magic beliefs than the actual recognition of genetic factors in epilepsy.[1]

Cao Yuan Fang (610 AD) suggests five types of epilepsy based on etiology (and related semiology):[20]

1. Yang epilepsy presents with incontinence. The patient appears 'dead' and subsequently recovers after a short period of time.
2. Yin epilepsy is caused by bathing a child before the umbilical cord wound has healed.
3. Wind epilepsy presents with fixed gaze, limb stiffness, and goat-like crying. This can be caused by exposure to wind or by alcohol or sexual excess.
4. Wet epilepsy presents with frontal headaches and a heavy body feeling, caused by lack of hair drying.
5. Labor epilepsy manifests with upward deviation of the eyes, teeth clenching, and tonic body stiffening.[20]

Sun Si Miao (682 AD), who also provided us with a classification of seizures based on resemblance of the epileptic cry with animal sounds as outlined above, classifies epilepsies according to visceral organs. The diagnosis and classification of epilepsies according to this scheme was embedded in concepts of traditional Chinese medicine, that understands disease as an imbalance of Yin and Yang and an imbalance between five elements that have an organ correlation. Therefore this classification differentiates between heart, liver, spleen, lung, kidney, and intestine epilepsy.[20]

Claudius Galen (circa 130–210 AD) (Figure 20.2) classification was embedded in Galen's medical theory of humors. The first type of epilepsy that originated in the brain was related to accumulation of phlegmatic humor in the ventricles causing obstruction.[1] The second type, epilepsy starting from the stomach, was brought on by accumulation of bile in the stomach, leading to evaporations that then also affect the brain.[1] The third type of epilepsy that starts in any other body part was explained by spread of a 'pneumatic substance'

Figure 20.6 Jesus casts out an unclean spirit (Mark 1; 23). Image courtesy of History of Science Collections, University of Oklahoma Libraries; copyright the Board of Regents of the University of Oklahoma.

throughout the body.[1] Based on humoral pathology, he also lists and explains external factors causing seizures including frost, heat, strong winds, baths, repulsive foods, the sight of whirling wheels, sleeplessness, and indigestion among others.[1]

This etiological classification is found throughout medieval times and was only markedly changed in the early 16th century at the beginning of the Renaissance when scientists started to debate and either opposed traditional views or tried to reinterpret authors from antiquity.

Matthaeus Platearius Salernitanus (circa 1150 AD) elaborated on 'major' and 'minor' epileptic seizures based on the galenic epilepsy model. Major epileptic seizures are caused by complete obstruction of the ventricles, whereas minor epileptic seizures represent partial obstruction.[19]

Based on Galen's physiology and Arabic influences John of Gaddesdon (circa 1280–1361 AD) proposed three types of epilepsy: true, truer, and truest epilepsy. The truest epilepsy was induced by obstruction of the ventricles, the truer epilepsy was related to obstruction of the nerves, and true epilepsy was due to obstruction of the arteries.[19]

Paracelsus (Philip Theophrastus Bombastus von Hohenheim, 1493–1541) interpreted all events (and diseases) as reflections of the macrocosm (the world) in the microcosm (the patient). Interpretations were based on the chemical knowledge of his time. He believed in a living spirit in every creature and in a chemical cure for all disease.[45] Epilepsy was thought to be a boiling up of spirits in the patients brain. Based on observations in the macrocosm Paracelsus' distinguished four types of epilepsies deriving from the four elements fire, earth, water, and air and their impression comparing to epilepsy: the thunderstorm (fire), the earthquake (earth), the storm (water), and a milder thunderstorm (air).[49]

Besides Paracelsus' approach, the concept of sympathetic (epilepsies with symptoms that arise in body parts or in the stomach) and idiopathic epilepsies (that arise from the brain itself) continued to prevail until early Renaissance, when more and more case descriptions of multiple diseases causing epilepsy, such as syphilis and ergotism became available.[9]

Charles Le Pois (1563–1636) questioned the concept of sympathetic epilepsy and Galen's humoral pathology attributing all symptoms preceding seizures to a cause in the brain. Additionally, Georg Ernst Stahl (1660–1734 AD) was one of the first who moved the classification of epilepsies away from the severity of its symptoms, the seizures, and distinguished the condition epilepsy from symptomatic convulsive movements related to other medical conditions. This anticipated a change in classifications merely based on the severity or clinical manifestations towards possible etiologies and related conditions.[43] These contributions and additional information from multiple case reports led to several advances in the area of anatomy and pathology that paved the way towards a more etiologically oriented epilepsy classification.

The iatrochemist Franciscus Sylvius (Franz de le Boë) (1614–1672 AD) explained epilepsy by the mixing of a volatile acid spirit with a defective animal spirit that is responsible for movement and sensation. Step by step he lists five causes starting with bile and pancreatic juice as the antecedent cause, followed by an irritative cause (e.g. air or wrong diet), leading to a remote cause (evaporization of the juices). This in turn is the proximate cause (producing the symptoms in the brain) and the conjoint cause (because the symptoms last for the duration of the presence of the vapors).[43]

Samuel Tissot (1728–1797) published his 'Traité de l'épilepsie' in 1770 and distinguished between sympathetic and idiopathic epilepsies (Figure 20.7). Idiopathic epilepsies had its cause in the brain, whereas sympathetic epilepsy was caused by another part of the body. Although this classification reflects the antique epilepsy classification, it now was supported by case reports with some evidence of pathological changes of the brain. For the description of cases in which no definite anatomical cause could be found, Tissot chose the term essential epilepsy.[23] Additionally, Tissot separated between moral and physical provoking factors of epilepsy.[23]

William Cullen (1710–1790) also differentiated symptomatic and idiopathic epilepsies, and divided idiopathic epilepsy further into Epilepsia cerebralis (sudden onset of seizures without known cause), Epilepsia sympathica (preceded by an aura and with known cause), and Epilepsia occasionalis ('arising from manifest irritation, and ceasing when the irritation is removed').[23]

Figure 20.7 Samuel Tissot (1728–1797). Lithography by Jules Hébert (1812–1897) based on a portrait by Angelica Kauffmann (1741–1807). From the 'Album de la Suisse Romande', Vol. 1, Gruaz, Genève, 1843.

James Cowles Prichard (1786–1848) divided epilepsy in 1822 based on its etiology. He related seizures to certain internal organs and differentiated uterine epilepsy, epilepsy related to metastases, epilepsy related to diseases of the intestinal canal and the liver, and last but not least related to cerebral disease.[25]

In 1838, Jean Etienne Dominique Esquirol (1772–1840) separated epilepsy, similar to Galen, into idiopathic (located in the brain), sympathetic (due to a problem at any other place in the body), and sympathetic epilepsy. Idiopathic or essential epilepsy was subdivided into epilepsy caused by an external compression of the brain or skull, into epilepsy related to a structural brain lesion, cranium or meninges, or epilepsy caused by moral causes such as fear or anger. Sympathetic epilepsy could arise from the intestines, from the blood vessels and blood, from the lymphatic system, or from the organs of reproduction. Symptomatic epilepsy was related to the eruption or disappearance of cutaneous rashes, e.g. rubeola or scarlet fever.[25]

Louis Jean Francois Delasiauve's (1804–1893) classification of epilepsy from 1854 is also based on etiology. He distinguishes idiopathic, symptomatic and sympathetic epilepsies. In this classification 'Idiopathic' means absence of anatomical lesion, 'symptomatic' involves a brain lesion, and 'sympathetic' describes epilepsy caused by a condition involving any other part of the body.[25,27]

In 1825, Bouchet and Cazauvieilh classified their experience in a first statistical description of causes of epilepsy.[50] Among 69 patients with epilepsy, they identified fright (21), sorrow (10), masturbation (3), difficult menstruation (3), consequences of childbed (1), critical age (2), dentition (1), vexation (1), head injury (1), artificial insolation (1), and unknown causes (26). Temkin noted that the statistics do not sum up, since the total of these figures would be 70.[51] Similar statistics have later been published by Beau[52] and Leuret.[53]

Sir John Russell Reynolds (1828–1896)[28] developed this concept further and classified four different types of convulsions.

Idiopathic convulsions included epilepsy without a known cause. Secondary (or eccentric or sympathetic) convulsions were caused by diseases in other body parts than the brain leading to seizures. Diathetic (or cachectic convulsions) were related to nutritional causes, intoxications, retained excretions, and others. Symptomatic convulsions arose from diseases of the meninges and the nervous system.[28]

In addition to differentiating between generalized and focal epilepsies Sir John Hughlings Jackson (1834–1911) separated four causes of (unilateral) seizures, including the anatomical 'seat of the internal lesion', the 'functional nature' of the lesion implying the physiological impact of the lesion on the function of the nervous tissue, the 'pathological process' which caused the change in function, and finally 'circumstances which determine the paroxysm' indicating exacerbating factors. Additional etiological classification attempts after Jackson were frequently connected with other features such as localization, etiology, semiology, and age (see later).

Classification according to age

Classifications according to age are rare. In the ancient medical literature, it was recognized that epilepsy was a disease of children and adolescents, as recognized by Caelius Aurelianus.[1] He mentions that seizures occur most frequently during the period of teething.

Hippocrates also mentions that first appearance after the age of twenty years was exceptional.[1] He also related provoking causes such as temperature, season, and wind to the age of the patient and differentiated between children, adults, and elderly.[1]Puberty was considered crucial for the course of epilepsy: epilepsy may stop spontaneously if it occurs prior to puberty. If it occurs after the age of 25 it will last until death. If the disease is not improved by puberty, it will persist and will be difficult to control.[1]

According to Galen, the most frequent form of epilepsy was idiopathic epilepsy arising from the ventricles of the brain, and this form was a disease of early childhood. Rarely, two other forms of sympathetic epilepsy could be seen in older patients.[1]

In the literature on traditional Chinese medicine, Cao Yuan Fang (610 AD) proposes a classification based on age of onset. Patients with seizures under the age of 10 years old suffer from 'Jian' and patients above the age of 10 years old suffer from 'Dian'.

Abu bakr Mohamad ibn Zakariya Razi (Rhazes, 865–925 AD), a Persian physician, classified epilepsies according to the age of onset and distinguishes four types: infants, young children (<7 years), teenagers, and adults.[21]

Berthold of Regensburg (13th century AD) notes that patients suffering from epilepsy for more than 24 years will not be cured.[22] Although several seizure types in children have been described over the following centuries, age as part of epilepsy classifications gained additional importance in the 20th century (see later).

Epilepsy syndrome

The 'lumping' of various semiological and clinical features with possible etiologies is as old as the documentation of epilepsy and seizures itself (as reflected in 3000-year-old Babylonian scriptures).[5] Temkin states that:

> The distinction between symptomatic epilepsy, i.e., a syndrome which might be associated with various diseases, and the possible existence of an 'essential' or 'genuine' disease, epilepsy, is, however, of relatively modern origin and was of little importance in antiquity. The word epilepsy was used to connote both the disease and the single attack.[1]

According to Panayiotopoulos:

> The most important milestone in modern epileptology has been the recognition of epileptic syndromes and diseases, most of which are well-defined and easy to diagnose. The concept of epilepsies as specific syndromes is old (see for example pyknolepsy equals childhood absence epilepsy) [here the author quotes a paper by Adie from 1924][54] and the first attempt to formalize them in an international classification was published in 1970.[55]

Here the author refers to the first ILAE classification in 1970.[14]

Some specific syndromes can be traced back to the middle of the 18th and 19th centuries. One of the earliest publications on syndromes was by West on 26 January 1841 who reported 'on a peculiar form of infantile convulsions' including the case of his own son and several other infants he heard about.[56] Single case reports and clinical descriptions of other conditions similar to Lennox–Gastaut syndrome may also date back to the early 18th century. The invention of the EEG by Hans Berger in 1929 can be marked as the start of further delineation of electroclinical syndromes. Since the late 1930s, pioneers in the field such as Frederic A. Gibbs, Erna L. Gibbs and William G. Lennox supported the view of a one-to-one relationship of clinical presentation and EEG. This view was criticized and questioned by the Montreal School in the early 1950s.

The first attempt to systematically characterize and list epilepsies by the ILAE was published by Gastaut and Merlis in 1970.[14] In this attempt to classify epilepsies, similar criteria were applied to each form of epilepsy, meaning primary generalized, secondary generalized, partial (focal, local), and unclassifiable epilepsies. Subdivisions consisted of four clinical points (seizures, neurological status, age of onset, and etiology) and two electroencephalographic criteria (interical and ictal EEG) in each category. This proposal is very closely oriented on Henry Gastaut's proposal.[13,57] Although this proposal lumps certain types of epilepsies according to different criteria, the concept of epilepsy syndromes has not been mentioned in this proposal nor the actual classification proposal.

Syndromes have been officially introduced in the ILAE epilepsy classification during its revision in 1985.[7] In this classification a syndrome is defined as:

> an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together. The signs and symptoms may be clinical (e.g. case history, seizure type, modes of seizure recurrence, and neurological and psychological findings) or findings detected by ancillary studies (e.g., EEG, X-ray, CT, and NMR).

> In contradistinction to a disease, a syndrome does not necessarily have a common etiology and prognosis.[7]

The initial strict structure from 1970 that required information on each of these dimensions was abandoned in this revision.

The revision by the ILAE in 1989[15] again defines an epilepsy syndrome as:

> an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together; these include such items as type of seizure, etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and sometimes prognosis. However, in contradistinction to a disease, a syndrome does not necessarily have a common etiology and prognosis.[15]

A definite distinction between clinical seizure semiology and epilepsy syndrome was only introduced in a recent multiaxial ILAE proposal after publication of the semiological seizure classification. This classification lead to the publication of an ILEA glossary and was one of the decisive publications that lead to a new multi-axial epilepsy classification proposal by Engel in 2001.[8] This ILAE proposal differentiated between epilepsy syndrome, semiological seizure description, pathophysiological seizure type, etiology and impairment in different axes and is described in detail below. A more recent report on the progress of the ILAE core group in 2006 is moving again towards a syndromic classification approach, structuring epilepsy syndromes by age of onset.[16]

Recent concepts and attempts to combine seizures, localization, etiology, age of presentation, and syndrome

In 1954, the Montreal Epilepsy Center led by Penfield and Jasper with its focus on epilepsy surgery is anatomy oriented to identify the seizure onset focus and advanced the classification of different patterns of seizure types, EEG patterns, and imaging findings. They separated three epilepsy types including focal epilepsy, centrencephalic epilepsy, and cerebral seizures associated with different electroclinical presentations. 'Focal epilepsy' presents with psychic, autonomic, sensory features, loss of consciousness or automatisms and has an identifiable cerebral pathological correlate, e.g a tumor or a stroke. 'Centrencephalic' epilepsy is presumed focal, presents with grand mal, petit mal or psychomotor automatism seizures and has no identifiable pathological correlate. 'Petit mal' can either present as petit mal with myoclonus or petit mal with automatisms. 'Cerebral seizures' were not related to an anatomical lesion and not localized, but frequently associated with systemic conditions, such as fever or hypoglycemia.[11] A similar predominantly anatomical concept has also been proposed by McNaughton in 1952.[58]

Symonds (1955) pointed out that clinically similar seizures can present with different EEG patterns. He proposed a separate classification based on clinical, anatomical, physiological (EEG), pathological and therapeutic categories.[59] Masland (1960) also recommended a classification based on etiology, anatomy, physiology and functional impairment.[60] A similar approach has been suggested by Goldensohn (1965) who suggests a classification based on clinical presentation, etiology, and seizure localization. Clinical seizure presentations include generalized major, absence, focal motor, somatosensory, special sensory, automatisms, psychomotor, aphasia, myoclonic, akinetic, spasms, and autonomic. Etiological categories consist of congenital infections, intoxications, trauma, neoplasm, vascular, metabolic, hereditary, and unknown causes. Localizations include frontal, medial and lateral temporal, parietal, occipital and diencephalons. The localization can be more detailed if the affected gyrus is known.[61]

Gastaut's epilepsy classification in 1954 included clinical, EEG, and etiological factors, and it also considered the influence of related medical factors.[12] Gastaut suggested that epilepsy could be divided into partial and generalized epilepsies and then assigned each epilepsy type with different seizure types, EEG findings, etiological factors and related factors. Gastaut used the term partial because the so-called focal seizures not only involve the cortex but – based on EEG – represent an interaction between central gray matter and cortex.

In order to facilitate communication and standardization, the WHO set up a glossary (1967) based on four categories. Terms in this glossary should serve as common building stones in future classifications. The glossary is structured according to: etiology, physiology (clinical and EEG seizure), anatomy, and modifying conditions or circumstance of occurrence including age. This WHO classification was meant to be a framework that allows precise classification of every patient. Etiology includes organic, metabolic, genetic, and unknown causes. EEG and seizure patterns are generalized from the start, partial, erratic with a shifting focus and unilateral seizures. Seizures that are generalized from the start can be divided into typical and atypical seizures with subcategories including absences, generalized tonic clonic seizures, and myoclonic seizures. The anatomical classification is made up of centrencephalic, diffuse and partial epilepsy.[25]

Janz differentiated epilepsy syndromes with age-related petit mal seizures, epilepsies with non-age related petit mal seizures, and epilepsies with grand mal seizures in 'Die Epilepsien'[62] (1969). In the age-related section of his book he separated infantile petit-mal epilepsy, petit-mal epilepsy in school age children, and juvenile petit mal epilepsy. Additionally, he recognized epilepsies not age related including epilepsy with psychomotor seizures, epilepsy with neocortical seizures, and grand mal epilepsy.[62] Each of the three age-related epilepsy types is further described by semiological seizure types, EEG, clinical presentation (including course and prognosis, possible triggers, and etiology), pathological anatomy, pathogenesis, and therapy.

Gastaut revised a classification between 1963 and 1969 based on this glossary and with similarities to the classifications suggested by the Montreal School and McNaughton. In order to gain broader acceptance the glossary was simplified. Main categories include primary generalized epilepsies, secondary generalized epilepsies, undetermined generalized epilepsies, partial epilepsy, and unclassifiable epilepsy. Within these categories, each seizure type was sorted and related

interictal and ictal EEG features, etiology, pathology, and age of manifestation were noted. He differentiated between seizure types that occur in infancy, childhood, or all patients.[34]

This classification provided the basic concept for the first ILAE classification that was shortly thereafter published by Merlis in 1970. Dichotomization of localization of the epilepsies (generalized or partial), etiology (primary without a clear cause) and secondary (related to an organic cause) was also used.

Research advances, such as the wider recognition of benign focal epilepsy of childhood (BFEC) necessitated a revision of this initial classification. Until the description of BFEC, all focal epilepsies were thought to be associated with a certain etiology. Gastaut suggested implementation of primary partial epilepsies, including benign epilepsy with centro-temporal spikes and benign epilepsy with occipital spike-and-wave complexes, into the system. Interestingly, in 1985 Gastaut suggested the characterization of each of these four subcategories (primary versus secondary and generalized versus partial) by age of onset, clinical seizure semiology, ictal EEG, interictal EEG findings, exam, neuroimaging, history of brain injury, family history of epilepsy, response to antiepileptic medications, and prognosis.[63] This proposal was not considered.

In the same year the revised ILAE classification (1985)[7] introduced the concept of epilepsy syndromes. Syndromes were defined as:

> an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together. The signs and symptoms may be clinical (e.g., case history, seizure type, modes of seizure recurrence, and neurological and psychological findings) or as a result of findings detected by ancillary studies (e.g., EEG, X-ray, CT, and NMR).

Epilepsy syndromes were again dichotomized between the major divisions generalized and 'localization-related' epilepsies. The term 'secondary' was abandoned to avoid confusion with seizure classification ('secondary generalized seizure'). The etiological terminology was changed into idiopathic and symptomatic.

In the 1989 revision of the ILAE classification,[15] the term cryptogenic was added in order to characterize epilepsy syndromes with a presumed but unknown cause.

In 2001, an incomplete revised ILAE classification proposal by Engel[8] including classification axes was published. The huge advance in this proposal was again the differentiation of ictal semiology, etiology and suspected epileptic syndrome. However, this revision again relied heavily on epilepsy syndromes as 'complex of signs and symptoms that define a unique epilepsy condition'. Different axes consist of seizure description (axis 1), seizure type (axis 2), epilepsy syndrome (axis 3), etiology (axis 4), and impairment (axis 5). The first axis relied on seizure characterization according to the ILAE glossary published in the same year and is intended as descriptive seizure characterization.[40] The second axis classified seizure types based on underlying etiology, mechanism, pathophysiology or prognosis. In the third axis, the epilepsy syndrome is characterized. Here syndromes in development and completely characterized syndromes are differentiated. The fourth axis included an incomplete list of possible etiologies and diseases associated with epilepsy. And finally, the fifth axis was incomplete and was intended to outline the degree of impairment due to epilepsy based on a modified scale of the International Classification of Functioning, Disability and Health.

This revised ILAE proposal from 2001 reignited the ongoing debate about a more utilitarian or taxonomic classification of epilepsies, that was first brought up by Reynolds[28] and later by John Hughlings Jackson.[25] In several editorials in the official organ of the ILAE, *Epilepsia*, a taxonomic versus a utilitarian approach to classification was discussed in 2001. In particular, lack of definition criteria and clinical relevance of accepted ILAE syndromes has been questioned.[64] Limitations and shortcomings of this 2001 proposal and redundancy among classification axes have also been demonstrated in several attempts to apply this proposal of a diagnostic scheme to epilepsy patients.[65,66]

A 'report of the ILAE classification core group' in 2006 by Engel returned to a classification of electroclinical seizure types mingling clinical seizure semiology and EEG patterns and to an exclusively syndromic classification of epilepsy. Both the 2001 proposal[8] and the 2006 report[16] by the ILAE neglect that epilepsy syndromes may be less frequent than actually suspected.[65,66] New aspect of the 2006 report – in addition to additional description of syndromes – is the consideration of age of onset in the classification:[16] syndromes during the neonatal period, infancy, childhood, and adolescence from syndromes with less specific age relationship, special epilepsy conditions and conditions with epileptic seizures that do not require a diagnosis of epilepsy were defined.[16]

A possible solution of this dilemma of syndrome arrangements has been suggested by applying a general neurological approach to epilepsy classification rekindling the triple neurological concept of clinical presentation, localization and etiology using an anatomical-dimensional approach.[67] This approach classifies epilepsy according to a general neurological approach into three major categories and adds additional information on seizure frequency and related medical conditions in two more dimensions. The first three dimensions answer the basic neurological questions, namely localization of the lesion, symptomatic presentation and etiology. This is supplemented by dimension four (seizure frequency) and dimension five (related medical conditions). Whereas previous classifications frequently relied on complete information on each case, this diagnostic approach allows progressively detailed classification of each patient as further investigations become available. This classification represents a more practical and patient-oriented approach to each patient.[65] Its orientation towards focal epilepsy is backed by recent studies suggesting underlying focal structural cortical abnormalities in patients with so-called 'generalized' epilepsy[68,69] questioning our current separation of focal and generalized epilepsies.

Future outlook

Our incomplete and limited overview of selected historical and recent classifications of epileptic seizures, etiologies, localizations, age-related categorizations, and epilepsy syndromes revealed a broad spectrum of ways to sort epilepsies through the ages.

Currently, the final revision of the 1989 ILAE epilepsy classification is still pending. It is questionable if the controversy of different classifications for gardeners and botanists can be resolved in one single classification, or if the problem can only be solved by the solution proposed by Jackson – with two classification systems, at least until all details of the disease process are better understood.

Multi-layer and multi-facetted characters of the etiological dimension of epilepsies and further advances in genetics and other clinical and diagnostic techniques may make any classification attempt difficult and always adherent to its time and current knowledge.

This problem has already been recognized by Reynolds in 1861 and will continue to necessitate revisions of epilepsy classifications in the future:

> Perhaps no disease has been treated with more perfect empiricism on the one hand, or more rigid rationalism on the other than has epilepsy. Unfortunately both methods have often and completely failed; the former, as it must do, in a certain proportion of cases; the latter, in a still larger number because the theories upon which it has rested, have often been abundantly wrong.[28]

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21 History of electroencephalography as a pre-surgical evaluation tool: the pre-Berger years

WT Blume

Introduction

Inspired by notable advances in peripheral neurophysiology such as the first demonstration of the action potential of nerve by duBois-Reymond in 1984,[1] and first measurement of its velocity by Von Helmholtz in 1950;[2] Richard Caton sought similar activity in the central nervous system of animals but instead discovered persistent fluctuating potentials that he termed 'feeble currents of the brain'.[3] Finding large current oscillations upon exposure to light, Caton speculated that such phenomena would have localizing value within the cortex.

Hans Berger and the Gibbs

Familiar with the pioneering works of Caton and others in animals, Hans Berger in 1924–1929 ultimately succeeded in recording current oscillations from the scalp of humans.[4] Through a series of carefully designed experiments he demonstrated that such currents emanated from cerebral activity and not from the electrocardiogram, blood flow to the scalp, or other artifact.[5]

Berger first demonstrated the lateralizing value of EEG by recording slower waves and 'sudden rises and falls occurring repeatedly over the left central region associated with right-hand myoclonic jerks in a 45-year-old woman'.[6] Berger's Figures 7 and 9 of his seventh report display what now would be termed periodic lateralising epileptiform discharges (PLEDs) and delta activity over the left hemisphere in a patient with epilepsia partialis continua.[7] Subsequently, Gibbs *et al.*[8] also recorded such motor seizures.

By accurately describing several normal and abnormal awake and sleep EEG patterns and their clinical significances, the Gibbs with Davis and Lennox[9] were among those whose works set the stage for a clinical-electroencephalographic partnership in assessing human epilepsies.

Herbert Jasper

As had Wilder Penfield, Herbert Jasper grounded himself thoroughly in those basic sciences relative to his extraordinary accomplishments in electroencephalography and epilepsy. Both Penfield and Jasper trained extensively in Europe as well as in America, enabling each to view their sciences from multiple vantage points. Having confirmed Berger's findings with Leonard Carmichael at Brown University and having found Berger on a 1935 visit to Jena to be 'inspired and inspiring, humble, honest, friendly, distinguished and courageous', Jasper embarked upon a 'whole new field of research' that culminated in many landmark works in electrophysiology relating to epilepsy.[10,11]

Initially Penfield determined the area of cortical excision for epilepsy through scrutiny of the patient's seizure pattern whose features were matched with lesion location and that area whose electrical stimulation reproduced the ictal semiology. A background of many previous cases where seizure semiology and lesion location were related aided each deliberation. When Herbert Jasper brought EEG, then a novel technique of recording brain electrophysiology, to the Montreal Neurological Institute, the scene for Penfield altered significantly in two ways: 1) EEG delineated more precisely the epileptogenic area, and 2) epilepsies not suitable for surgical resective treatment could be identified.[12]

Jasper[12] described normal distinct EEG background patterns of five cerebral regions: 1) temporal-parietal occipital, 2) sensory motor, 3) intermediate frontal, 4) anterior frontal, and 5) hippocampal, insula, and limbic.

He also described aspects of scalp and cortical EEG which aided in localizing epileptogenesis: principally epileptiform discharges (spikes and sharp waves), and abnormal background activity for that region. Jasper found the interictal EEG to 'point to a focus or local area of onset' in over 80% of patients with focal seizures. Thus, he emphasised that the area identified by EEG spikes should also contain abnormal background activity to distinguish a primary spike source from one propagated to normal cortex.[13] These and other EEG and electrocorticographic localising data motivated Penfield to include among his three criteria for epilepsy surgery: 1) an objective abnormality of the brain, 2) clinical and electrophysiological identification of a zone of epileptic discharge within the cortex, and 3) that the identified area is dispensable.[14]

Jasper and Dr. Jack Kershman formed a fruitful electrographic-clinical collaboration culminating in their 1941 article correlating clinical seizure manifestation with interictal EEG abnormalities.[15] These correlations and the clinical associations described by Gibbs and colleagues[8,9] helped to identify those patients whose epilepsies would and would *not* be appropriately treated by resective surgery.

Subdural EEG

Hans Berger, through silver-chlorided needle electrodes placed on human cortex and subjacent white matter, obtained electrical activity only from the cortical gray matter and not from the subjacent white matter.[16] The more precise data so recorded likely instigated development of subdural recordings shortly thereafter. Jasper described a technique for their performance in 1941.[17] However credit is given by Bates[18] to Delgado for development of a technique for chronic implantation, first in monkeys and then in humans.[19,20] Early depth explorations aimed to investigate movement disorders and mental condition. Of some relevance to epilepsy, Gastaut[21] by depth recordings found an occipital response to light in humans that did not appear on surface leads.

From the early 1950s the use of depth recordings focused on the epilepsies.[22] The Mayo Clinic[23] held a symposium on 'intracerebral electrography' that discussed technique, normal rhythms, properties of epileptic foci, stimulation studies, and planning of surgical treatment of focal seizures. Initial advances and applications were made by Bickford[24] among others.

The fabrication and application of stereotactic instruments for precise electrode insertion allowed measurement of cerebral electrical activity in a three-dimensional way, thereby enhancing its accuracy. Initiated by the 'Paris school',[25,26] the Los Angeles group also made substantial gains using this method.[27]

Video-EEG and long-term monitoring

Because seizures occur suddenly, unpredictably, and briefly and because diagnostic and therapeutic decisions may hinge on recording their electrographic correlates (if any); epileptologists have long sought methods to facilitate ictal electrographic recording.

Before technical advances permitted prolonged monitoring, provoking a hopefully representative seizure was the favoured attempt at achieving this correlation. Although hyperventilation, originally used by Berger[28] has long been employed as an activating agent, Pentylenetetrazol (PTZ) (Metrazol) was commonly employed to reliably provoke focal and often secondarily generalised seizures in the 1940s to 1960s.[29] Ajmone Marsan and Ralston recorded PTZ-induced focally-originating seizures using standard scalp EEG, a microphone, and a camera. The resulting clinical-EEG correlations constitute a volume of high value to any epileptologist.[30] Unfortunately, several unwanted PTZ effects led to its abandonment: unpleasant not seizure-related sensations, the 'telescoping' of any focal phase to a few seconds, and the commonly ultimate generalised tonic-clonic seizure. Stepwise antiepileptic drug reduction, hyperventilation and sleep deprivation have replaced PTZ as 'activating agents'.

During the era of analog recording, the technique of long-term monitoring was simply an extension of routine EEG with methods to assure hours-long electrode stability. This led to stacks of paper EEG facing the EEGer every morning. Introduction of FM tape reduced the paper output as limited epochs could be selected, usually ones containing clinical seizures or other attacks.[31]

The advent of digital recording permitted simultaneous EEG and audiovisual recording providing accurate, sequential analysis of clinical-electrographic correlations. Methods of data reduction have enabled the extraction of certain features of interest which would have heretofore been eclipsed among irrelevant or redundant data. However, a knowledgeable decision has to be made concerning data to be jettisoned and in discerning cerebral data from artifact.[32]

In addition to epoch selection, automated detection and analysis of interictal and ictal events have strived to reduce total data and even to assist visual analysis. While distinct progress has been made, the threshold for some commercial systems remains sufficiently low that many 'false positives' are detected.

Nevertheless, digital-based extended monitoring has helped to distinguish seizures of different origins or distributions with common semiologies, e.g., temporal lobe seizures from absence. Such recordings also help to identify pseudoseizures.

Telemetric recordings, developed by Storm van Leeuwen and Kamp[33] and Stevens,[34] would seemingly have provided long-term monitoring while allowing greater freedom of movement. Their value has been limited by artifact and by a limited audiovisual component.[35] Ultimately, their use preceding inpatient epilepsy evaluation may shorten hospital stay and cost.

Integration of data

Principal among the several considerations involved in possible surgical management of the epilepsies are: 1) medical intractability, 2) seizure origin, and 3) dispensability of an epileptogenic area. Initially ictal semiology and obvious lesion location were Penfield's only guides and antiepileptic drug options were few.[10] Since then several other modalities, including electroencephalography, have emerged to assist in decision making. However, these additional components increase the likelihood of incongruent data appearing. Pierre Gloor[36] emerged as one of several wise marshals of such data, particularly the electroencephalographer's role in providing reliable and significant input in decisions such as the utilisation of invasive recordings and taking the option of surgery. Two qualities are requisite for an electroencephalographer to advise on these crucial matters: 1) a thorough knowledge of EEG and, 2) appreciation of EEG's place in the broader fields of basic and clinical neurosciences. Gloor and others like him possess(ed) both attributes.

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22 History of neuroimaging in the pre-surgical evaluation

B Diehl and P Ruggieri

The history of modern presurgical evaluation for epilepsy surgery has been shaped by several main influences and approaches in localizing the seizure focus and infer a lesion site: first, clinical observation and seizure semiology; second, the advances in EEG diagnostics; and last, the advances in our ability to image the brain. This chapter aims at illustrating seminal points in the history of brain imaging and highlights its relevance to the presurgical evaluation for patients with intractable focal epilepsy.

Arguably, there is no other technology that compares to modern structural and functional brain imaging in revolutionizing our way of thinking about epilepsy and the presurgical evaluation throughout the last decade of the last century, the decade of the brain. Therefore, reflecting upon the history of neuroimaging in the context of epilepsy surgery and how it shaped the thinking of generations of epileptologists and epilepsy surgeons will likely make us appreciate the huge opportunity we have in the new millennium.

For the longest time in the history of epilepsy surgery, there was no direct way of imaging the brain. In 1896, Sir William Gowers wrote in his famous textbook:

> The nervous system is almost entirely inaccessible to direct examination. The exceptions to this are trifling. The termination of one nerve, the optic, can be seen within the eye. Some of the nerve trunks in the limbs can be felt, as the ulnar, in the normal state; others only when enlarged by disease.[1,2]

Therefore, in the closing decades of the 19th century, evidence about the presence of pathology could only be gained indirectly, and was mainly based on the careful examination and clinical correlation of the deficit and the pathology later analyzed either after surgery or after postmortem pathological examination. Only in 1895, when Roentgen discovered X-rays, were we able to start to look inside the human body *in vivo*, even though with respect to the brain it remained an indirect window by careful analysis of bony changes secondary to intracerebral pathology.

The beginnings of imagery of the brain

For many centuries, the role of the brain was unknown. In ancient Egypt, for example, the heart was considered the essence of life and the brain discarded in the embalming process. Some valuable observations however concerning the brain were documented. In the famous Edwin Smith Surgical Papyrus, tracing its origins back to the third dynasty, approximately 3000 BC, mention is made of various head and brain injuries and how to approach them.[3] Concepts of the use of the brain and its structure and functioning emerging over the following centuries laid the groundwork for a modern understanding of the brain and its diseases.[4]

The brain as the seat of the mind was clearly recognized by an early Greek writer and philosopher-scientist, Alcmaeon of Croton. He detailed in his book around 500 BC the idea that the brain was the organ responsible for sensation and thought. He described that sensory organs were connected to the brain and he excised the eyeball of an animal and observed *poroi* (channels, i.e., the optic nerve) leading from the eye in the direction of the brain. In the years to come this very advanced concept was abandoned and other Greek philosopher physicians such as Hippocrates reverted to more primitive hydraulic theories, postulating that the 'essence' of life, a mysterious substance, was supposed to be carried by the blood. In the book 'on the sacred disease', which is ascribed to Hippocrates' authorship, he recognized however that the brain serves as the controlling center of the body. He also criticized the popular belief that epilepsy was a divine malediction. There is no doubt that Hippocrates recognized that seizures were arising in the head.[5] However, for many centuries to come, people, including Aristotele, ancient Greek's greatest natural philosopher, would continue to believe in the supremacy of the heart compared to the brain.

The history of imagery of the brain dates from antiquity. However, there is no evidence suggesting that these concepts were used to guide treatment.[6] Surgical interventions for the treatment of seizures were often guided by supernatural concepts about the cause of epilepsy. In the hellenistic world trephination was a well established remedy for epilepsy. The procedure was performed to serve as an outlet for pathogenic humors and vapors.[7] For many centuries the concept was that the brain was an organ that functioned as a whole.

Reviewing the history for cerebral localization and the search of the seat of the soul will help to understand the evolution of concepts for imagery and cerebral localization, which are prerequisites for epilepsy surgery.

Around 300 BC, the first human dissections were performed by Herophilus and later Erasistratus in Alexandria (Egypt); they wrote the first detailed account of the structure

of the brain and heart. Herophilus is generally considered the father of anatomy.

The nervous system is discovered and classified into different types of nerves (motor and sensory nerves).

Galen in the 2nd century AD divided the nerves into sensory and motor according to Herophilus and believed they originate in the anterior and posterior brain. He thought that the mental faculties resided in the brain substance. Three primary brain functions were described: sensus communis (the gathering together of all forms of sensory perception to produce imagination), reasoning, and memory. However, he also stated that injury to the ventricles could cause mental damage; this was often interpreted to mean that he placed the locus of cerebral activity in the cerebral ventricles.[8] Nerves as hollow channels were thought to convey the information from the ventricles through the body. Galen made great strides to understand biology and anatomy. His greatest work is considered De usu partium or on the usefulness of the parts of the body. Some time after Galen's death the sensus communis and imagination, reasoning and memory became located in the lateral, third, and fourth ventricles.

During the medieval ages, efforts to understand the human body in health and disease come to a standstill. The pictorial representation of illness in medieval art seen in book paintings in the biblical context offers insights in the symbolism and concepts of a disease characterized by events of sudden alteration of consciousness and unusual behaviors.[9]

Modern medicine began in 1543 with the publication of the first complete textbook of human anatomy, De Humanis Corporis Fabrica by Andreas Vesalius (1514–1564). It includes sections on the brain, and he disputes the prevailing doctrine that higher functions of the brain are situated in the ventricles. Anatomy illustrations became increasingly available for educational purposes, and many illustrate beautifully the new realism in Renaissance. Italian Renaissance artists became anatomists by necessity, as they attempted to refine a more lifelike, sculptural portrayal of the human figure.

Thomas Willis disputed the idea that higher functions were located in the ventricles and wrote in his book 'Cerebri anatome' (1664) that the cerebral hemispheres determine thought and action. He felt though that this was completely separate from the parts of the brain that control motor functions.

In 1791, Franz Josef Gall of Vienna may have been the first to propose that different mental faculties and behavioral functions occupied different anatomical locations in the brain.[6] Gall believed that mental function was localized in discrete areas of the brain and called those organs. He located the organs subserving intellectual function in the cerebral cortex. Although he published these seminal observations, his contributions were overshadowed by his introduction of phrenology, the practice of diagnosis based on palpation of the skull, which evolved increasingly in a pseudoscience. On the other hand, Gall and his disciple Spurzheimer developed a unique system of dissection using alcohol and significantly advanced the knowledge of neuroanatomy.[10]

Not until the mid-19th century did neuroscientists begin to use clinical pathological correlation and faradic stimulation to prove that cerebral gray matter indeed comprised functionally discreet regions.[6] In 1861, Broca published his landmark case, M. Leborgne, who suffered from epilepsy since childhood and had lost his ability to speak. After the patients's death from an unrelated cause, an autopsy showed a chronic progressive softening of the cortex in the third convolution of the frontal lobe. It is considered the turning point that persuaded many learned men to believe in cortical localization of function.[11]

Sir Hughlings Jackson, by many called the father of contemporary epileptology, was a brilliant observer and used the information obtained through analyzing the clinical manifestations of seizures to localize the ictal onset. In 1861 and 1863 he wrote about the unilateral seizures in cerebral syphilis and commented that:

> As autopsies of patients who have died after syphilitic epilepsy appear to show, the cause is obvious organic disease on the side of the brain opposite to the side of the body convulsed, frequently on the surface of the hemisphere.[12]

In 1870, Fritsch and Hitzig finally provided unequivocal experimental confirmation of a 'motor cortex' in the frontal lobes of dogs.[13]

Epilepsy surgery in the strict sense of a neurosurgical intervention at an anatomical site that is defined by the seizure semiology was introduced in the second half of the 20th century and developed from the analytical approach that is closely related to the observations by Jackson. The first epilepsy surgery was performed on 25 May, 1886, by Victor Horsley on a 22-year-old patient with focal motor seizures, due to a scar that had been caused 15 years earlier by a depressed skull fracture.[14] The surgery was planned purely based on clinical semiology, and performed taking into account the *in situ* appearance of the brain tissue. Krause appeared to be the first to utilize intraoperative cortical stimulation to guide surgery[15] particularly to identify central sulcus in cases of Jacksonian epilepsy. However, until the end of the 19th century, it remained impossible to directly or indirectly image the brain before surgery. This changed drastically in 1895.

Radiography and the application of X-rays to skull and brain pathology

The history of neuroimaging arguably starts with a great discovery: On 8 November, 1895, Wilhelm Konrad Roentgen, Professor of Physics at the University of Würzburg, discovered X-rays. Roentgen, an experimental physicist of the old school, had the custom to repeat experiments previously made by others at the beginning of a new experiment. Roentgen was interested in cathode rays and in assessing their range outside of charged tubes. He was repeating Hertz' and Lenard's experiments with cathode rays and used the same experimental armamentarium, then extended his experiments to include a Hittorf-Crookes' vacuum tube. On a Friday evening, 8 November 1895, 'at a late hour when assistants were no longer to be found in the laboratory', he made his groundbreaking observation.[16] Interviews with Roentgen on the discovery revealed the circumstances. One appeared in McClure's

magazine early 1896 written by a reporter, H. J. W. Dam.[17] When asked about the discovery, Roentgen told him:

> I was working with a Crookes' tube covered with a shield of black cardboard. A piece of barium platinocyanide paper lay on the bench there. I had been passing a current through the tube and I noticed a peculiar black line across the paper ... The effect was one which could only be produced, in ordinary parlance, by the passage of light. And when asked: "What did you think?" the answer was: I did not think, I investigated. I assumed that the effect must have come from the tube, since its character indicated that it could come from nowhere else. I tested it. Rays were coming from the tube which had a luminescent effect upon the paper. I tried it successfully at greater and greater distances, even at two metres. It seemed at first a new kind of invisible light.

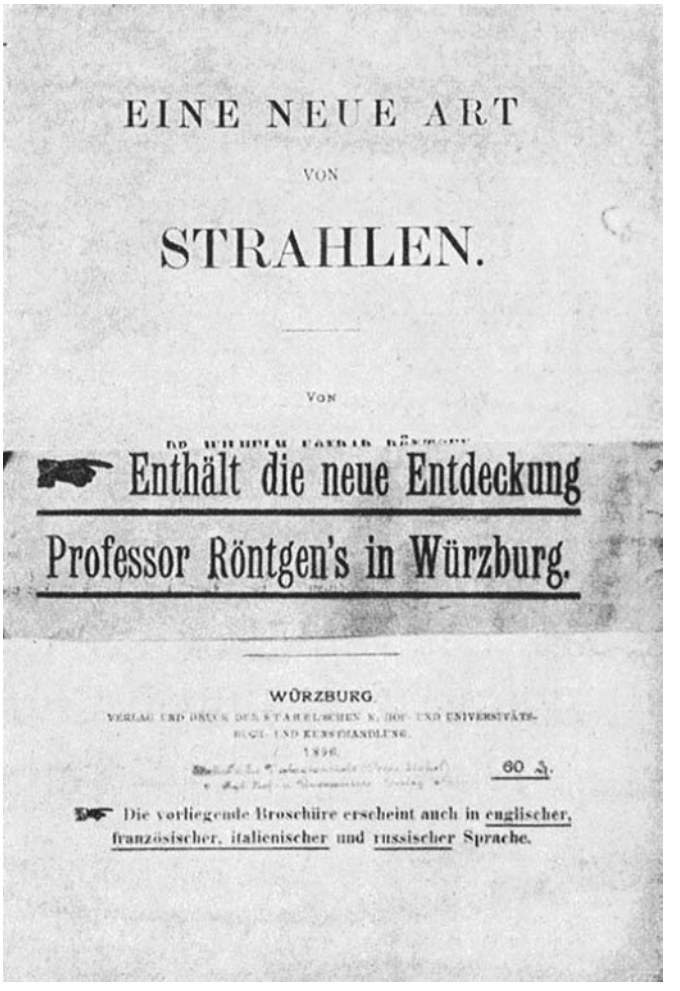
He plunged into seven weeks of meticulously planned and executed experiments to determine the nature of the rays. He worked in isolation, telling his close friend Boveri simply, 'I have discovered something interesting, but I do not know whether or not my observations are correct'. At the end of December, a brief communication 'on a new kind of rays' was published, the result of seven weeks of systematic studies and well-designed experiments.[18] Roentgen, the great and humble scientist himself gave the newly-discovered phenomenon the name X-rays on account of their unknown character and to distinguish them from other rays. For this discovery he was awarded the first Nobel Price in Physics in 1901 (Figures 22.1–22.3).

With this discovery, the era of radiology was born. Soon after Roentgen's breakthrough, X-rays were applied to examine the neurological system. Arthur Schueller, who graduated in Vienna and was introduced to the study of radiology, performed systematic studies of the skull and is generally considered the father of neuroradiology. He introduced the term Neuro-Roentgenologie.[20] His works on the X-ray examination of the skull are still considered classic,[21] carefully correlating autopsy and clinical findings with bony deformations. In his work on 'Roentgen diagnosis of diseases of the head' published in 1912 he describes a variety of skull X-ray findings in patients with epilepsy: bony defects and signs of underlying encephalomalacia, foreign bodies within the brain, depressed skull fractures, enostosis, and calcifications.[21]

The use of skull X-rays in the diagnosis of epilepsy has been advocated by a German Neurosurgeon, Fedor Krause. In his 'Surgery of the brain and Spinal Cord'[22,23] published in 1910 he remarks:

> Above all other means of diagnosis it furnishes the most useful in tumors with calcareous or bony deposits, as for instance in exostosis and any injury of the skull may bring on epileptic seizures .... whenever possible X-ray examination should be made; it is frequently a great aid in clearing up the diagnosis. Even in other forms of epilepsy, roentgenography is of urgent need.

Up to the 1960s and even the seventies, plain X-rays were recognized as having a place in the evaluation of patients with epilepsy. Bony changes and abnormal calcifications were the main findings in patients with epilepsy. Bony changes are found in a variety of conditions and may occur as a sign of the following conditions (from ref. 24):


EINE NEUE ART

VON

STRAHLEN.

VON

Enthält die neue Entdeckung

Professor Röntgen's in Würzburg.

WÜRZBURG.

Die vorliegende Broschüre erscheint auch in englischer, französischer, italienischer und russischer Sprache.

Figure 22.1 On a new kind of rays, cover of the first edition reprint and first page of the original manuscript (reprint from ref. 19 with premission from Elsevier).

1. Chronically elevated intracranial pressure with erosive changes of the pituitary fossa, thinning of the inner table of the skull, and if present in childhood widening of the skull sutures from hydrocephalus.
2. Dystrophic calcifictions may possibly occur in the setting of a menigeoma. The differential diagnosis includes calcium deposits from metastasis of prostate or breast cancer.
3. Bony erosions rarely are seen in the setting of epilepsy but could indicate primary hyperparathyroidism, some infectious diseases or pressure from adjacent masses.
4. Cranial hemiatrophy can be seen with there is less development of one hemisphere in the first year of life.
5. Pathological vascular markings can be seen in menigeomas.
6. Congenital cranial abnormalities such as meningoceles or encephaloceles can be detected.

How this information was utilized for the purpose of localizing the epilepsy will be shown in the case presentations below.

Throughout the first half of the last century, roentgenography was explored as a tool to help localize lesions causing

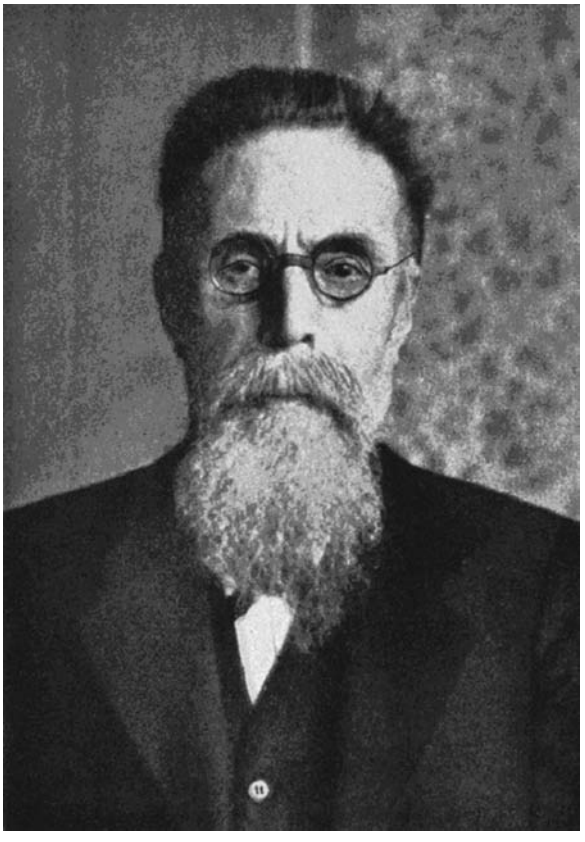


Figure 22.2 Roentgen a few weeks before he died (reprint from ref. 19 with premission from Elsevier).

seizures. In conjunction with pneumencephalography, it remained the main imaging technology for more than 50 years.

The history of pneumencephalography

In 1918, ventriculography using X-rays to explore that contrast between air and fluid was introduced by Walter Dandy.[20,25,26] One or more of the cerebral ventricles can be outlined in the skull X-ray if the ventricular fluid was withdrawn and replaced by an equal amount of air.[26] Dandy attributed the idea of using air as a contrast medium to observations made in roentgenograms of the abdomen and chest, as stomach and intestines were often seen outlined by the contained air.[27] However, earlier reports on spontaneous pneumencephalograms had already appeared and may have also influenced his thinking. In one case, air had entered as a result of head trauma. In another patient, a pneumatocele arose in association with surgery for an orbitoethmoidal osteoma.[28,29] For the first time, effects of intracranial pathology could be visualized without bony changes. The procedure as described by Dandy was mainly performed in the recumbent position, with the head at least 20 degrees higher than the body. 'With each injection, the air will then rush to the brain and a new supply of fluid will fall to the point of the needle.' The cisternae, subarrachnoid space, and sulci become visible. The initial publication included eight patients, five had normal pneumencephalograms, three had pathologies. Patient one showed

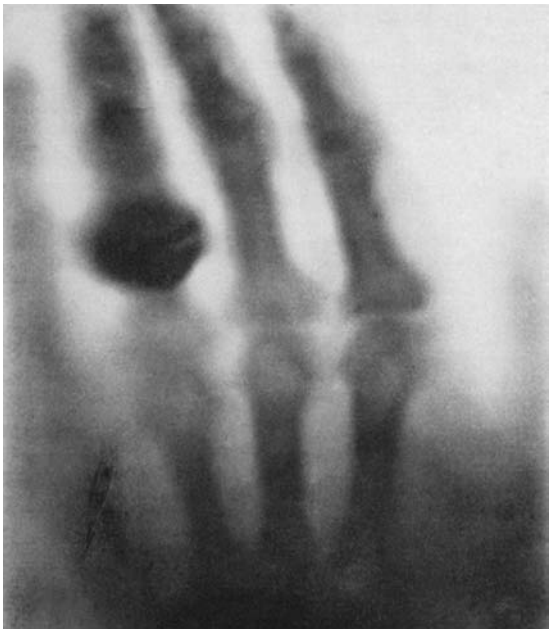


Figure 22.3 First Roentgen photograph of Ms. Roentgen's hand (reprint from ref. 19 with premission from Elsevier).

obstructive hydrocephalus at the level of the cisterna pontis due to meningitis, another patient showed a more localized finding of hydrocephalus, and the third patient was diagnosed with a presumed cerebellar tumor based on the pattern of the pneumencephalogram.

From then on pneumencephalography was used to get indirect evidence of brain lesions affecting the subarachnoid space. For example, tumors sitting near the surface of the brain and obliterating the subarachnoid space. Defects in the brain substance, filled with spinal fluid became visible when air was injected.

Brain imaging in the first half of the last century evaluated patients with epilepsy using X-rays and air contrast. The extensive documentation of cases undergoing surgery for intractable epilepsy particularly from the Montreal Neurological Institute illustrates how the new technologies were used to guide the presurgical diagnosis.

The use of skull X-rays and pneumencephalogram in the diagnosis of epilepsy in earlier part of the 20th century

The history of epilepsy surgery in the first half of the last century and in this context also of using imaging techniques to guide epilepsy surgery was dominated by the Montreal Neurological Institute, which opened its doors in 1934. Its founder, Wilder Penfield, had a background shaped by extensive travel and work in various places in Europe and North America. From Foerster, an experienced neurologist who became his own neurosurgeon, Penfield had learned the technique of mapping out the sensory and motor cortical areas by cortical stimulation in order to resect 'menigocerebral scars' safely.[30] Many cases resulted in failure as there were inadequate means to localize the epileptogenic zone.

The number of surgical epilepsy cases continued to increase every year. The thrust came from Penfield's determination to cure seizures by excision of the 'meningocerebral cicatrix'. Through careful catalogization and analysis of seizure type matched with the type of lesion found during surgery, a wealth of well-documented case histories is available from that era.

Etiologies for epilepsies was inferred from lesions visible from X-ray and pneumencephalography. In Wilder Penfield's famous book 'Epilepsy and the Functional Anatomy of the Brain'[31] and a wealth of other books and articles, cases were presented illustrating how indirect roentgenographic evidence was used to infer underlying brain lesions and to guide epilepsy surgery. From the standpoint of diagnosis and treatment, the epilepsies were divided into symptomatic epilepsies and in cryptogenic in the first half of the last century. The etiologies were readily recognized or reasonably assumed in the symptomatic cases and the unknown were classified as cryptogenic ('of obscure origin'). Common etiologies of epilepsies thought to be amenable to epilepsy surgery were grouped into 'expanding lesions' and 'atrophic lesions'.[32] The spectrum of the known etiologies also was remarkably complete for the time.[32,33]

McRae[32] summarized the radiological findings of patients with atrophic lesions operated on by Dr. Penfield and Eriksson between 1937 and 1946. The diagnosis was made based on history, physical signs, electroencephalographic methods, and radiological examination using plain skull films and pneumoencephalography. Often, the presurgical diagnosis was confirmed by the production of a typical seizure on electrical stimulation of an abnormal gyrus during surgery.

For the analysis of the X-rays, 'stereoscopic anteroposterior films', stereoscopic lateral films of the abnormal side and a single postero-anterior film were taken.

Great care was taken that no rotation was present for the frontal films. In order to judge for asymmetry, frontal films were traced on tracing paper and the skull was folded along the mid-sagittal plane and held against the light.[32] Electroencephalograpic studies consisted of six stereoscopic pairs of films.

Atrophy was considered to be secondary to traumatic brain injury and vascular etiologies. The following radiological findings were highlighted in atrophic lesions.[32,34] The most common finding was reduction in volume of the lateral cranial chamber. Other more variable findings were enlargement of the frontal or ethmoidal sinus on the small side, asymmetrical development of the mastoid cells, elevation and smoothness of one petrous ridge. Indirect evidence could be gathered on the timing of the injury. If atrophic lesions were acquired within the first two years of life, a large difference in brain volume between the two hemispheres could be seen; injury between age 2 and puberty may still result in an asymmetry in skull size. Displacement of the calcified pineal gland, calcified choroids plexus or falx these structures towards the side of the lesion is another indirect sign.

Roentgenological abnormalities in the surgical treatment of temporal lobe epilepsy were used as following: small size of the cranial chamber of one side was taken as evidence for an ischemic birth lesion at that side. Pneumencephalography may show enlargement of the inferior horn of the side of the lesion of the temporal lobe. In their series of surgical therapy of temporal lobe seizures, 27 patients were considered to be in the 'success' group and the pneumencephalogram was considered to indicate an abnormality of the temporal lobe, later shown to contain an epileptogenic lesion in 18 cases. In three cases, it pointed to the opposite side and in 6 cases no lateralizing evidence was concluded.[35] The following cases illustrate how indirect evidence form X ray and pneumencephalogram was used for localization to guide surgical intervention in patients with epilepsy.

Case examples

Figure 22.4 (from ref. 31) illustrates the skull X-ray of a 15-year-old boy who at the age of 5 years suffered an accident resulting in unconsciousness for 9 days. Seizures started at the age of 14 years.

The fracture is visible in the 'right frontal bone'. 'Above and posterior fracture line the undersurface of the skull presented such an area of cerebrocranial erosion with evidence of bone absortion and new bone formation'.

The epileptogenic focus was felt to be adjacent to this area delineated on the skull X-ray, the patient underwent surgery and bony erosions were demonstrated.

Another case after head trauma is illustrated in Figure 22.5 (from ref. 36). In 1914 the patient received a shell wound in the right frontal lobe. He suffered no loss of consciousness and immediately had surgery. He started to have seizures four years later characterized by turning of the eyes and head to the left, followed by movements of both the left extremities. Pneumencephalogram shows enlargement of the right lateral ventricle with upward and lateral displacement.

Figure 22.6 illustrates a case with small right hemicranium: 'Brain injury and subdural hematoma at birth, focal seizures from 6 months of age. The case illustrates marked atrophy of

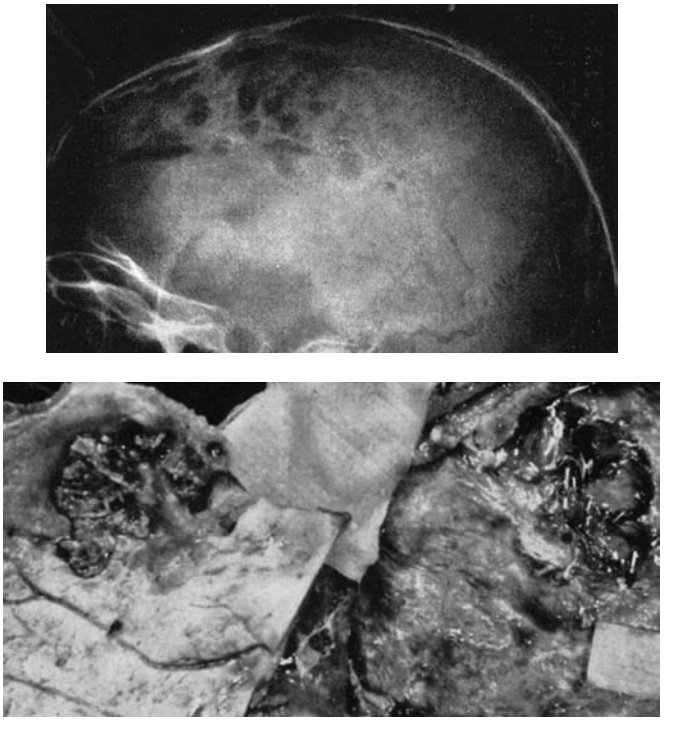


Figure 22.4 Fracture of the right frontal bone 10 years earlier in a 15-year-old boy with epilepsy since the head trauma. Above and posterior to the fracture, craniocerebral erosion is indicated by mottling. The frontoparietal bone flap was turned to show the eroded skull area and the bare brain in its corresponding area (case R.St., from ref. 31).

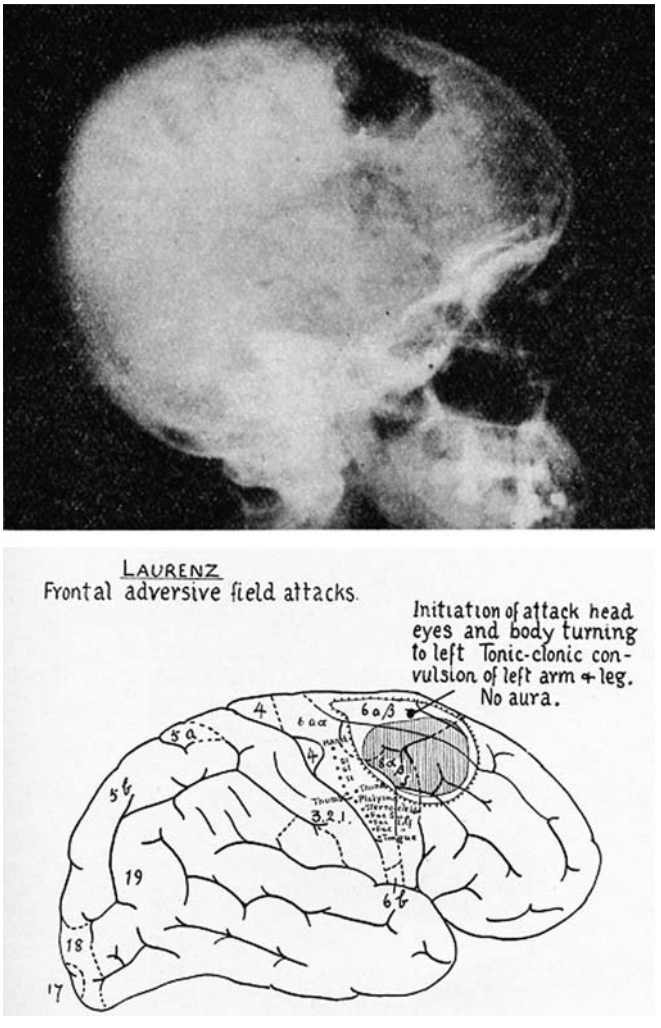


Figure 22.5 Top: Pneumencephalogram (right side of the head) showing cranial defect with enlargement of the anterior horn of the right lateral ventricle and deflection upwards of parts of both anterior horns. Bottom: Lesion as seen at the operation. Motor response to galvanic stimulation is indicated by small dots; the large dot indicates the area a seizure was induced using stimulation. From ref. 36.

the right posterior hemisphere and normal cortex anteriorly' (from ref. 31).

Another case (Figure 22.7) illustrates the use of pneumencephalogram in a patient with 'enlargement of the posterior end of the right lateral ventricle', replacing destroyed brain tissue. Natal or prenatal arterial occlusion produced 'ventricular enlargement without cranial hemiatrophy'.[31]

Figure 22.8 illustrates a case of temporal lobe seizures due to 'birth compression'.

Case J.Mc.[31,37], a 13-year-old girl, was referred for seizures at the age of 9 years, six days after she had the measles. She had a generalized convulsion which was followed by a 6-hour episode of unconsciousness. Seizures are described as 'aura of sensation in abomen and thorax, salivation, swallowing and automatic behavior'. Electrographic localization pointed to the left temporal region. Ventricles were slightly enlarged but symmetrical in size. Simple X-ray films showed the left middle fossa to be smaller than that on the right with an elevated petrous pyramid on the right. EEG showed left temporal sharp waves.

The patient was operated and Penfield comments that 'the first convolution was small and tough. The abnormality extended down into the uncus and hippocampus. Electrical stimulation of this issue reproduced the patient's habitual thoracic aura.' Interestingly, the cause of this abnormality was felt to be 'birth compression'. Histology revealed gliosis.

Penfield and Flanigan presented their results with epilepsy surgery in cases with temporal lobe epilepsy.[38] The epileptogenic zone was determined using the above-described means. Interestingly, the long-term seizure outcomes were not so different from the post MRI era: 52.9% were considered 'cured' with no seizures or only one or more attacks before cessation. 29% were felt to have worth while improvement, and 14% were surgical failures.

In 1991, Rasmussen presented another series on outcomes after temporal lobe surgery for epilepsy: 63% of 100 patients had complete or marked reduction of seizures after 'major hippocampectomy' with medial removal of the amygdala, the pes and half of the hippocampus.[39]

Radionuclide brain scanning

In February 1896, 3 months after Roentgen's discovery, Becquerel described natural radioactivity. The rays were being used for medical treatment. However, another 50 years had to pass before spontaneously emitted rays were used for diagnosis. The discovery was made by George Moore, a young surgeon from Minneapolis. He knew that fluorescein was taken up selectively by tumors of the eye. Prior to surgery for suspected gliomas, he injected a small dose intravenously and was able to detect it in the tissue using ultraviolet light. When the brain was exposed during surgery, he would shine the UV light on the brain and be able to identify the glioma and the edges well. The next step was to tag a radioactive substance to fluorescein; Dr. Moore chose radioactive iodine and used a Geiger counter to detect the radioactive emissions. He was immediately successful and localized 12 of 15 brain tumors.[40,41]

Over the next years this technique was refined and successfully evaluated in the diagnosis of a variety of neurological diseases. The conclusion from a larger study evaluating the utility of the radionuclide brain scan was that it is particularly useful in patients who develop localizing signs, in patents with 'focal fits' (eight of 11 such patients had abnormal scans), in patients with vascular disease and gradual onset of localizing signs and in patients with inflammatory conditions of the central nervous system.[42]

When brain scans were compared to EEG in a patient population with tumors, it was felt that successful localiza-tion using both methods was attained in 90% of all cases. Only in one case was there no congruence between the two methods.[43]

Up until the introduction of CT and later MRI into clinical practice in the late 1970s and 1980s, X-ray, pneumencephalography, and radionuclide brain scanning remained the only means of indirectly localizing a structural lesion in patients with epilepsy.

Carotid arteriography

By the middle of the 1920s, the Portuguese neurologist Egas Moniz investigated to inject radio-opaque material in the arteries. After some animal experiments using sodium iodide

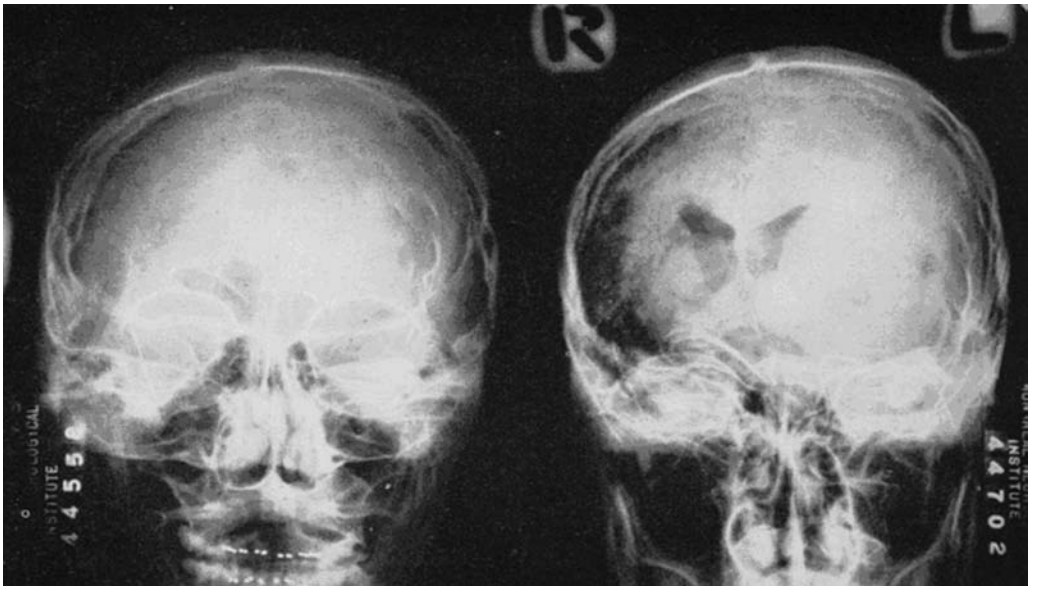


Figure 22.6 X-ray and pneumencephalogram illustrates a case with a small right hemicranium. Frontal sinuses are large on the right (case NP, from ref. 31).

as a contrast agent, he decided to experiment on human cadavers to learn anatomy. After an initial unsuccessful patient experiment when no contrast medium became visible, he concluded it was not injected, and the technique was changed. The next case was done after a surgical cutdown, so that the internal carotid artery was exposed, and the experiment was a success. In 1931, Moniz published his first 90 cases. There were only two deaths in that group, both in patients with artherosclerosis.[27,44]

It remained a valuable tool for epilepsy related to vascular malformations, to determine vascularity, supply extent and site of tumors, obtain indirect evidence to determine the pathology of a mass lesion based on the vascular characteristics.[24] It furthermore gained particular importance to date in pre-surgical investigation, as the development of angiography is a prerequisite for the injection of amobarbital or another barbiturate in order to accomplish language lateralization and assess memory function (intracarotid amobarbital test).

Computerized tomography (CT)

In the late 1960s, efforts were directed to perform measurements of X-ray transmissions from all possible directions through the body. The attenuation of the X-ray is measured from hundreds of different angles and the information is decoded and subdivided in a series of 'slices'. In 1972, Sir Godfrey Hounsfield introduced CT (see Figure 22.9).[45] In Hounsfield's initial experiments using a gamma ray source, it took nine days to acquire the data and 2.5 hours to reconstruct the image on a computer.[46] The second generation of scanners were much faster already: one slice could be acquired in 18 seconds.

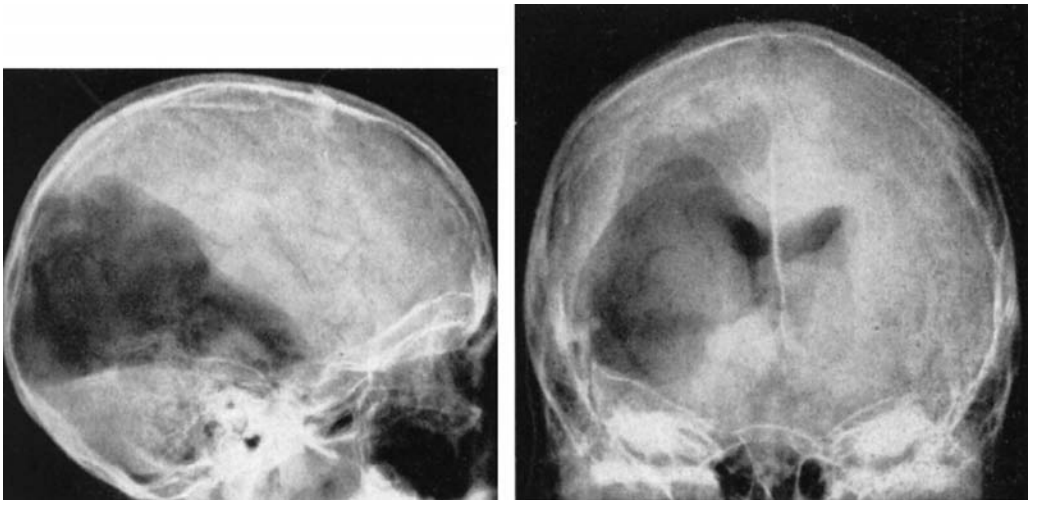


Figure 22.7 Natal or perinatal arterial occlusion producing ventricular enlargement without cranial hemiatrophy. The enlarged ventricle takes the place of the destroyed brain (case HG, from ref. 31).

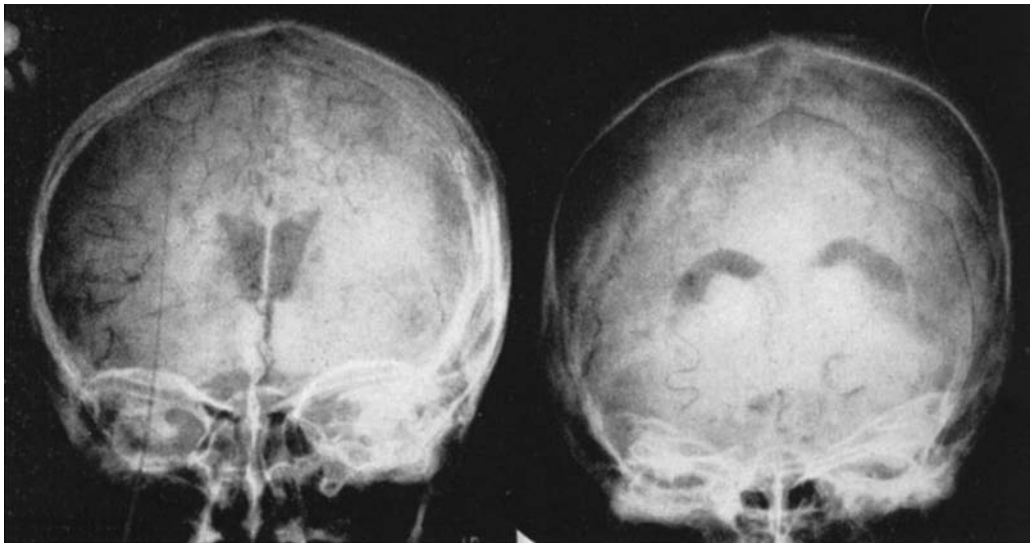


Figure 22.8 Temporal lobe seizures since age 9. Smallness of the middle fossa on the right is indicated by the greater height of the petrous pyramid and floor of middle fossa on that side (case JMc, from ref. 31).

In the 1970s, CT was introduced in clinical practice. Direct imaging of intraparenchymal abnormalities became possible for the first time. In epilepsy, the scanner was used to detect structural lesions and to determine cerebral atrophy. It was quickly shown that CT was superior to radionuclide scanning.[47]

In 1975, at the 21st European Congress of Electroencephalography and Epilepsy, the results of a total of 1702 patients from seven research groups were published. CT abnormalities were found in 46%. The most common abnormality was atrophy. Tumors were found in 10% of cases. It was well recognized that CT is quite sensitive to detect cerebral tumors and lesions like gliomas or various developmental tumors. Other pathologies including cerebrovascular disease, both ischemic and hemorrhagic, vascular malformations, post-traumatic changes and infectious disease could be visualized directly for the first time. It was also possible to demonstrate the structural lesions underlying the epilepsy in epilepsy syndromes such as temporal lobe epilepsy.

The CT scanner therefore replaced plain skull X-rays and pneumencephalography very fast in the 1970s. MRI would soon replace CT in its role to evaluate chronic epilepsy, especially as the sensitivity of CT in patients with epilepsy is no higher than 30% in unselected populations.

Today CT is readily available at all times and remains a valuable tool in many emergency situations and may have added value for the evaluation of intracranial calcifications.[48] If clinical presentation suggests a serious structural lesion, such as an acute intracranial hemorrhage or larger lesions that require immediate surgical intervention, emergent neuroimaging needs to be performed.[49] For the evaluation of a first seizure, CT is still performed if the patient's history and/or focal neurological signs make an acute symptomatic cause likely.

Magnetic resonance imaging (MRI)

In 1946, the first reports on nuclear magnetic resonance were published by Bloch, Hansen and Packard[50] at Stanford and by Purcell, Torrey and Pound[51] at Harvard. The importance of that discovery was recognized and, in 1952, the Nobel Prize for Physics was awarded to Bloch and Purcell.

In the 1980s, MRI was introduced in clinical practice. Since, it has revolutionized the practice of medicine in many areas. The ability to visualize anatomical details and pathologies underlying the focal epilepsy dramatically surpasses previous technologies. The first publications for its usefulness to detect lesions underlying focal epilepsy date to the mid 1980s.[51–54] It was soon demonstrated that MRI was more sensitive than CT to detect structural lesions underlying epilepsy.[54]

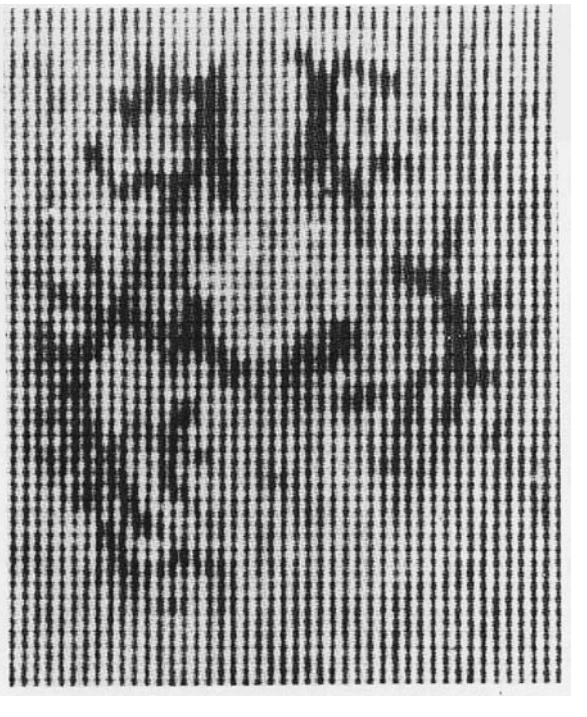


Figure 22.9 Picture of the first brain scanned on the laboratory CT machine. From ref. 46.

Nowadays, approximately 70% of all patients with focal epilepsy referred to a tertiary epilepsy center show structural pathology on MR.[48,55] It became possible to image the temporal lobe and detect hippocampal pathology in a non-invasive way (Figure 22.10). Several groups have found conventional MRI studies to be about 90% sensitive and 85% specific in the diagnosis of hippocampal sclerosis in a series of epilepsy patients undergoing temporal lobectomy.[56–59]

Over the past two decades, significant strides were made to improve the quality of MR-imaging. The introduction of fluid-attenuated inversion recovery sequences (FLAIR)[61] for the diagnosis of hippocampal sclerosis has significantly increased the accuracy of the detection of signal abnormalities in the mesial structures, as CSF is completely suppressed. Assessment of atrophy of the hippocampus can be improved by measuring hippocampal volumes. Visual analysis can detect 85–90% of atrophic hippocampi versus 90–97% detection rate with quantitative volumetry.[62–64] Post-processing methods such as voxel based morphometry and texture analysis have been used to improve the detection rate for cortical dysplasias.[55]

With higher field strength and improved imaging technique, MR images can now provide an unsurpassed anatomical detail[65] (see Figure 22.11).

Positron emission tomography (PET) and other nuclear medicine applications in the definition of the epileptogenic zone

In addition to the structural imaging, functional imaging including PET is an important imaging modality. The evolution of PET began in the early 1960s. Its initial importance as a diagnostic tool to evaluate the brain for structural abnormalities in the 1960s paralleled the widespread use of technetium scanning for the evaluation of brain tumors.[66] This method was fast replaced first by CT, then by MRI. Since then the role of PET has shifted to an evaluation of brain function. The first medical cyclotron installation was at Washington University in St. Louis and methods were developed to produce carbon 11 labeled glucose to evaluate glucose metabolism. Subsequently it was shown that fluorodioxyglucose (FDG) had biological properties similar to C11 labeled glucose and the longer lived fluorine 18 labelling procedure could be used.

PET was soon explored in patients with epilepsy undergoing presurgical evaluation.[67] The first reports of interictal hypometabolism in patients with epilepsy using PET were in the

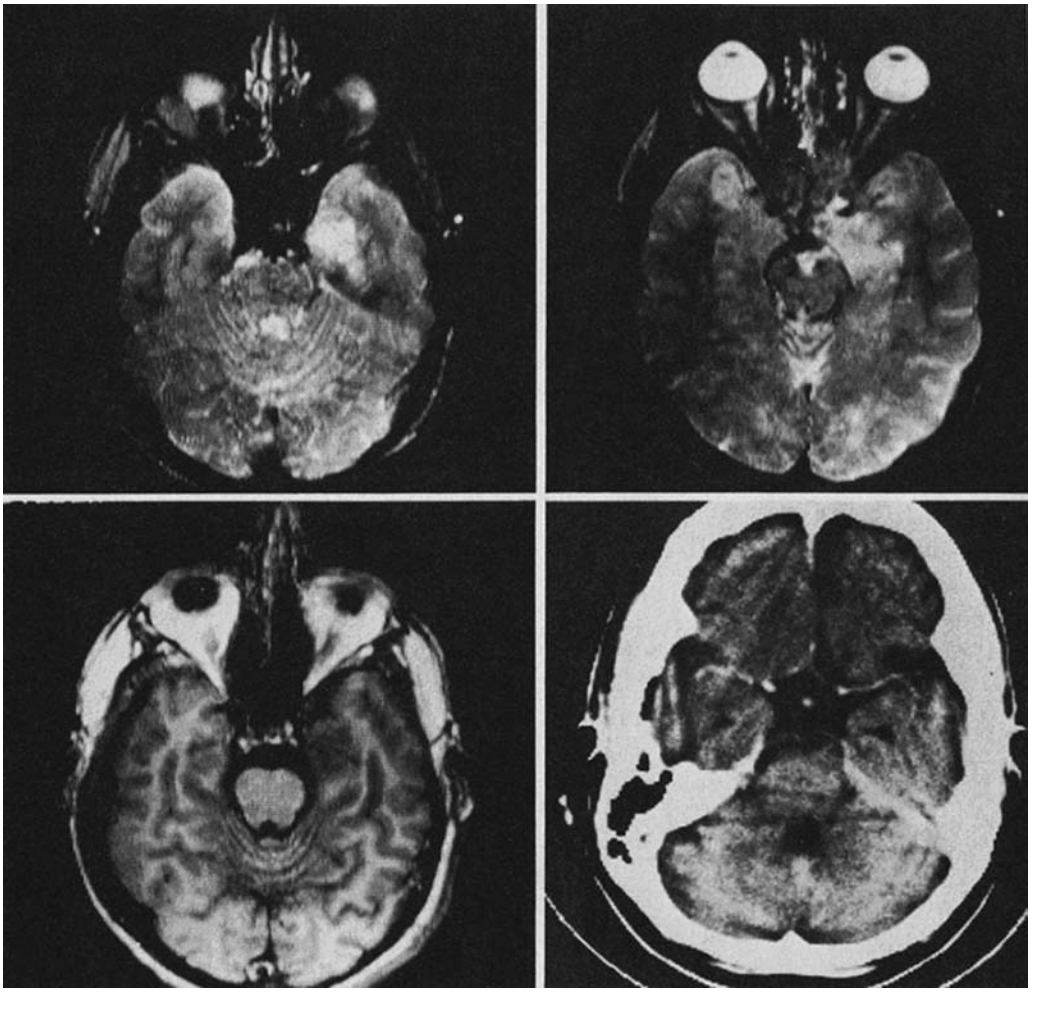


Figure 22.10 Early illustration of left hippocampal sclerosis. Top row: T2 spin echo image showing an rea of signal increase without mass effect in the mesial aspect of the temporal lobe. Bottom left: Inversion recovery image shows area of decreased signal in the same area (from ref. 60, with permission).

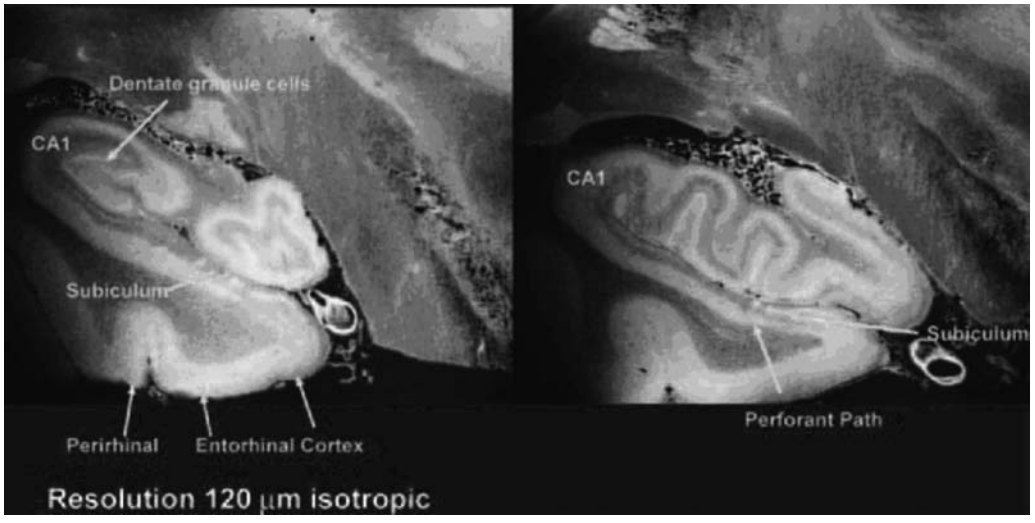


Figure 22.11 High-resolution image of the hippocampus of a human specimen at 7T. Image provided from Larry Wald, Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA (from ref. 65, with permission).

early 1980s,[68] ictal hypermetabolism was first reported in 1978.[69,70]

In temporal lobe epilepsy, interictal hypometabolism was described in the mesial temporal structures and has been implemented in the presurgical evaluation in patients with temporal lobe epilepsy.[71]

In 1995, the relative contributions of MRI, SPECT, and PET were summarized in a metaanlysis.[72] PET had the highest diagnostic sensitivity in temporal lobe epilepsy (84%) and also has a rather good sensitivity (95%) in mesial temporal sclerosis. In extratemporal lobe epilepsy, the sensitivity for PET is only considered around 33%. In recent years, receptor imaging using PET including imaging of benzodiazepine, glutamate, opiate, serotonine, and acetylcholine receptors has become feasible and will likely allow further insights in the mechanisms of epileptogenicity.[55]

The decade of the brain – what is next

The 1990s, the decade of the brain, saw the introduction of functional MRI. fMRI explores the BOLD (blood oxygenation-level dependent) effect: the magnetic properties of blood are dependent on the oxygenation state of the blood; deoxygenated hemoglobin is paramagnetic, oxyhemoglobin is diamagnetic. In activated brain areas, the relative percentage of deoxygenated hemoglobin is reduced compared to the non-active state, leading to an increase in T2-weighted and T2* weighted signal.

In 1990, the BOLD effect was first described by Sergej Ogawa.[73] In 1992, within one month of each other, S. Ogawa[74] and K. Kwong[75] described the BOLD signal change during visual stimulation in humans. Since, mapping of the cortex

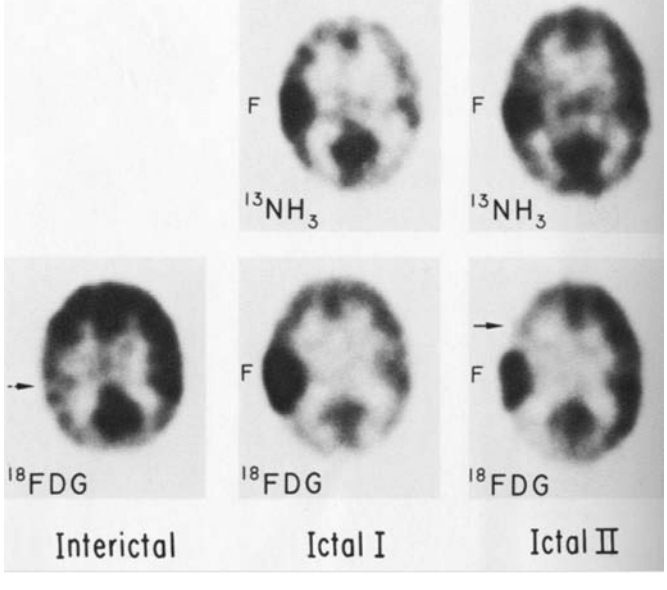


Figure 22.12 Interictal and ictal PET scan of a 5-year-old boy with a 10-month history of right focal motor seizures. The interictal PET (left) shows hypometabolism in the left temporoparietal cortex. At the same site, two ictal studies showed marked focal hypermetabolism (from ref. 70, with permission).

using fMRI has led to numerous publications within the neurosciences. fMRI of memory, language are important applications in intractable epilepsy patients evaluated for epilepsy surgery.[76] Imaging of the interictal activity using combined EEG and fMRI has become possible.

Imaging white matter pathways and connectivity became possible with the introduction of diffusion tensor imaging (DTI). All these new technologies will likely contribute to improving our definition of the epileptogenic zone, its connectivity and the relationship to functional cortex.

Outlook

Over the past century, imaging of the brain has evolved from the indirect window using X-rays and careful analysis of bony changes secondary to intracerebral pathology to the ability to directly visualize the brain structure and function with great anatomical detail.

The next decade will likely see further improvement in our ability to interrogate the brain tissue using new MRI sequences, acquisition and postprocessing techniques with better scanner hardware, higher field strength, and improvements in the signal to noise ratio. The hope is that we will find a structural substrate we can image non-invasively, thus reducing the number of cryptogenic patients with focal epilepsies. As we increase our sensitivity to detect subtle lesions, the number of these lesions will increase and we will need to understand the relation between these imaging abnormalities and the actual epileptogenic process.

The breakthrough may come from a close collaboration between basic science advancing our understanding of the cellular and molecular markers of epileptogenicity and our ability to image these in the future at a cellular level.

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23 Epilepsy surgery in literature and film

P Wolf and S Baxendale

Epilepsy surgery is a highly advanced and sophisticated field of modern medicine but, like all medicine, it does not take place in an ideal or abstract world but in the context of real societies. We should therefore be interested in the ways how it is perceived by the general public. Arts are both a reflection of societal perceptions and a vehicle of influencing them. Epilepsy has become a frequent subject of fiction[1–3] and film,[4] and both these artistic genres have also taken sufficient notice of its surgical treatment to make it worth while to consider how it is depicted.

Literature

Since the 19th century, literary accounts of epilepsy are frequent,[1,2] and can be analyzed under many aspects.[3] One aspect is the authors' factual knowledge of the medical aspects, and it has been noted that awareness of the aim of pharmacotherapy being seizure control, and that it can be obtained in many cases is very little spread amongst literary writers.[3] On the other hand, neurosurgical treatment, although it is a relatively young part of our therapeutic armamentarium, has rapidly caught the public's attention. It is therefore not surprising that surgical interventions already have become a subject of literature.

The first example, and related to the first wave of epilepsy surgery which began in the late 19th century[5] is a non-fiction book, *Travel Around My Skull* (1937) by Hungarian journalist and writer Frigyes Kárinthy (1887–1938), an autobiographic account of the author's cerebellar tumor, its symptomatology, diagnosis and operation by Dr. Olivecrona in Stockholm. The writer was married to a neurologist, and in the course of the diagnostic work-up he learns that in contemporary neurology a differentiated view of epilepsy has developed, and that Jacksonian seizures which are correctly defined, are now sometimes treated surgically. He sees a film which shows Dr. Harvey Cushing performing such an operation.

In *The Piano Man's Daughter* (1995) by Timothy Findley (1930–2002) the main character Lily's epilepsy is a central feature of the novel, which is considered under a multitude of aspects.[2] One side character is a Toronto neurosurgeon, Omar Warren, who in a dramatic scene in a small Canadian provincial town in 1907 performs on a kitchen table an emergency operation of a brain tumor. Dr. Warren had 'studied in England with the famous Victor Horsley' whose 'daring experiments and expertise in neurosurgery were legendary'. Horsley's role in epilepsy surgery is not mentioned here, but eleven years later in the story Dr. Warren has become still more renowned and is now 'even claiming he could perform operations in which he could solve the problem of seizures. In time, these came to be called *lobotomies*'. This completes the picture of epilepsy at the time which the author has been careful to depict correctly, but surgery is not discussed as a possible treatment for Lily.

A specific surgical intervention, callosotomy, *is* proposed at a certain stage to Désirée, the leading character in Swedish writer Majgull Axelsson's much praised novel *The April Witch* (1997). Highly intelligent Désirée lives in a nursery home because of severe tetraspasticity caused by a perinatal hemorrhage. She also has intractable epilepsy with a tendency to develop status epilepticus in response to strong emotions. The callosotomy is never seriously considered and seems to fulfil a similar purpose as with Findley's book. Axelsson's interest in epilepsy and related neurosurgery was created by the disturbing experience of her own sister's falling ill with epilepsy caused by a brain tumor.[6]

A similarly distressing autobiographic experience is at the base of another work, belonging to a genre on the fringe of literature, the impressive comic book *Epileptic* (1996–2004) by French cartoonist Daniel B. It is the history of his growing up with an older brother who develops epilepsy at the age of seven. All regular and more alternative cures are tried in vain. Amongst others, the family is:

> referred to Professor T. at the Sainte Anne hospital. Professor T. is a neurosurgeon who specializes in diseases of the brain. His operations are said to be marvels of precision. In 1969, Jean-Christophe is admitted to his care. He is 13 years old. He finds himself in a room with a boy who's been operated on by Professor T. It's his third operation. He got a 105-degree fever and his right side is paralyzed. Professor T. has claimed that the paralysis is temporary. But he's been like this for fifteen days. They examine Jean-Christophe. They perform gaseous encephalograms on him. They shoot gas into his brain to inflate it so they can take photos, in which they hope to find traces of a lesion or a tumor. When my parents tell me about it, I visualize my brother in the clutches of mad scientists. The doctors believe they've found a circumvolution in the brain that's causing my brother's seizures. 'Did it hurt him when he had the encephalograms?' Professor T. never answers. It's always a brusque doctor who answers for him. 'They injected gas into his brain. Of course it hurts!' ... Professor T. sees my parents in his office. He's decided to operate on Jean-Christophe. With the help of slides, he shows us how

he's going to open his skull and take away the 'thing' that, according to him, is causing the epileptic seizures. He goes into a big medical show-and-tell. He explains that this is a very delicate operation, that if his scalpel is off by so much as half a millimetre, my brother will be blind. He lists all the possible outcomes if his knife slips. If he cuts here, my brother loses the use of all his limbs. There, he loses the use of his right arm, there, he will be deaf. My mother faints. Professor T. reassures her: None of this will happen because he is a man of such exceptional skill. The damage will be limited. He'll lose his peripheral vision. 'So he won't be able to see out of the corners of his eyes?' 'Then if he wants to see something off the side he can just turn his head!' And he will be paralyzed for two days after the operation. My parents are shaken by the risks entailed by the operation. The doctor's morgue chills them. Jean-Christophe is the 'case'. He will allow Professor T. to perform a brilliant operation. What do the results matter so long as the surgeon cuts with elegance and precision under the admiring gaze of his assistants?' At this stage, the family reads about George Oshawa, the founder of Zen macrobiotics, and goes to see a Japanese healer, 'Master N.', who uses macrobiotic principles. According to him, the boy's 'root of life is withering. I can treat him. I must see him on a regular basis, and he must not be operated upon'. My parents return to the Sainte-Anne hospital to tell Professor T. and his court that they're refusing the operation. They're not at all happy to see their nice experiment vanish just like that. Jean-Christophe's operation becomes Professor T.'s operation. 'WHAT? You're refusing Professor T.'s operation? Get the hell out! There's nothing for you here! Your son is doomed! It's criminal of you to refuse this operation!' Only the doctor who is in charge of the electroencephalograms approves of my parent's choice, but with many reservations. 'Ultimately, I think that in some way you're not wrong not to want your son to be operated on'.

In fairness it must be said, that with the Japanese healer's treatment the boy becomes seizure free – for some months, then the seizures return.

American author Thom Jones draws much from his own experiences when he writes hard realistic stories from Vietnam and amateur boxing. In the title story of his first collection *The Pugilist at Rest* (1993) the narrator's, a Vietnam veteran's worries express a mixture of the guilt he feels about certain episodes of the war, and increasing numbers of fits of a left temporal lobe epilepsy which is the result of a boxing trauma. When, 'loaded on Depakene, phenobarbital, Tegretol, Dilantin – the whole shit load', he still gets seizures, his sister brings 'a neurosurgeon over to my place around Christmas – not some V.A. butcher but a guy from the university hospital. He was a slick dude in a nine-hundred-dollar suit. He came down on me hard, like a used-car salesman. He wants to cauterize a small spot in a nerve bundle in my brain. "It's not a lobotomy, it's a *cingulotomy*," he said. Reckless, desperate, last-ditch psychosurgery is still pretty much unthinkable in the conservative medical establishment. That's why he made a personal visit to my place. A house call. Drumming up some action to make himself a name. "See that bottle of Thorazine?" he said. "You can throw that poison away," he said. "All that amitriptyline. That's garbage, you can toss that, too." He said, "Tell me something. How can you take all of that shit and still walk?" He said, "You take enough drugs to drop an elephant."

He wants to cut me. He said that the feelings of guilt and worthlessness, and the heaviness of a heart blackened by sin, will go away. "It is *not* a lobotomy," he said. "I don't like the guy. I don't trust him. I'm not convinced, but I can't go on like this." At the end, he is inclined to accept but worries what would happen "if they fuck up the operation"'.

Again, not a flattering image of a neurosurgeon and his ethics, and an unfortunate confusion about epilepsy surgery and psychosurgery.

Concern about the full consequences of a brain operation to treat epilepsy is the subject of *Lying Awake* (2000) by Mark Salzmann. Sister John of the Cross, a Carmelite nun in Los Angeles in 1997 has a great gift for writing about contemplative life. Her collection of essays and poems 'Sparrow on a Roof' is very successful, and this is not only a spiritual joy but also an important contribution to her monastery's economy. The words come to her in a kind of 'ecstasies', accompanied by headaches, which are by a sleep EEG and a CT scan found out to be temporal-lobe seizures. 'Now the good news. The CT scan found what's causing the seizures, and we can do something about it. You have a small menangioma (sic!) – about the size of a raisin – just above your right ear. It's in an excellent position for removal, just under the skull. I've consulted with a surgeon about it, and he said they should be able to peel it right off. It'll be a very clean procedure, very straightforward. If we take care of it now, while the seizures are still localized, your prognosis for complete recovery is excellent.'

But Sister John is very troubled by the diagnosis epilepsy which she has learnt to perceive as a disorder of the soul. Someone applying to be a nun would be automatically rejected if she had to answer yes to the question 'have you ever been treated for mental illness or epilepsy?' 'Epilepsy was particularly feared because of its reputation for producing compelling – but false – visions. Doctors and clergy alike had referred to the disease as "holy madness"' The dilemma she finds herself in is twofold: the tumor should be removed, not the least in view of the future health hazards it carries, but if she loses her seizures, she loses her cherished spiritual experiences. On the other hand, if her ecstasies are not genuine spiritual experiences but spurious, a mere symptom of illness, is it right for her to want to keep them? What is the real worth of her poetry which she was so proud of? What finally decides her is the prioress's describing to her a seizure she had during service, where she wandered around the chapel, staring at the ceiling, humming to herself and threatening at any moment to do some disgrace. The thought of giving offence to her fellow nuns is clearly unacceptable for her.

Like in Daniel B.'s comic, full information about the potential hazards of the operation is given together with an assurance that these are very unlikely to happen because of the surgeon's experience. But Sister John is thoroughly prepared and takes the information calmly without anything like the terror that is provoked in the French family who was completely taken by surprise.

After the operation, she feels empty and depressed and learns from her doctor that this is rather common. 'When they


On lui fait des encéphalographies gazeuses. On envoie du gaz dans son cerveau pour le faire gonfler afin de prendre des photos sur lesquelles on pourra déceler les traces d'une lésion ou d'une tumeur. Quand mes parents m'en parlent, j'imagine mon frère aux prises avec des savants fous.


Les médecins pensent avoir trouvé dans une circonvolution du cerveau la cause des crises de mon frère.


Il explique que c'est une opération très délicate, que si son bistouri taille un demi-millimètre à côté, mon frère sera aveugle.


Il énumère tout ce qui risque d'arriver s'il loupe son coup.
S'il taille là, mon frère perd l'usage de tous ses membres, là il perd l'usage de son bras droit, là de ses jambes, là il sera sourd...
Ma mère s'évanouit.

took this out,' she says, pointing to her bandage, 'my muse went with it.' Her senior tells her that 'God must think you did enough with that gift. Now he wants you to do something else', and the story ends with her being appointed to take care of a novice with a difficult background. 'She'll need a novice mistress with a special understanding of the difficulties we face trying to do God's will.'

In his much-discussed[1] science fiction thriller of 1972, *The Terminal Man*, US writer Michael Crichton foresees a therapeutic intervention which 33 years later is about to become a reality,[7] i.e., treatment by interruption of beginning seizure activity by electric stimulation which is automatically delivered by an electronic device that can detect the activity. The literary connection did not escape a recent commentator.[8] In the novel, the results are dreadful.

The procedure has been developed in the Neuropsychiatric Research Unit of a Los Angeles university hospital. It is called the Stage Three Procedure and after 154 trials in rhesus monkeys used for the first time, on Wednesday 10, March 1971, for the treatment of a human being with temporal lobe or psychomotor epilepsy (both terms are used interchangeably). At neurosurgical grand rounds, surgeon Dr. Ellis explains:

> We know from the work of many researchers that it is possible to abort a seizure by delivering an electrical shock to the correct portion of the brain substance. These seizures begin slowly. There are a few seconds – sometimes as much as half a minute – before the seizure takes effect. A shock at that moment prevents the seizure. We face two problems. First, what is the correct part of the brain to shock? Well, we know roughly that it's in the amygdala, an anterior area of the so-called limbic system. We don't know *exactly* where, but we solve that problem by implanting a number of electrodes in the brain. Mr. Benson will have forty electrodes implanted tomorrow morning. Our second problem is how do we know when an attack is starting? We must know when to deliver our aborting shock. Well, fortunately the same electrodes that we use to deliver the shock can also be used to 'read' the electrical activity of the brain. And there is a characteristic electrical pattern that precedes a seizure. So we have a feedback system – the same electrodes are used to detect a new attack, and to deliver the aborting shock. A computer controls the feedback mechanism. The NPS staff has developed a computer that will monitor electrical activity of the brain, and when it sees an attack starting, will transmit a shock to the correct brain area. This computer is about the size of a postage stamp and weighs a tenth of an ounce. It will be implanted beneath the skin of the patient's neck. We will power the computer with a Handler PP-J plutonium power pack, which will be implanted beneath the skin of the shoulder. This makes the patient completely self-sufficient. The power pack supplies energy continuously and reliably for twenty years.

It is impressive to see all these details imagined by the author who calls them 'a limbic pacing procedure', even as we know that he has graduated from Harvard Medical School and worked briefly in medical research.

A 34-year-old computer scientist Harold Benson has, 2 years earlier, had a car accident with prolonged loss of consciousness. Six months later he developed 'blackouts' which could be provoked by intake of alcohol. They started with the sensation of peculiar, unpleasant odours which lasted several minutes and occurred about once a month. One year after the accident, the blackouts became more frequent and lasted longer; Benson often regained consciousness in unfamiliar surroundings, sometimes with bruises and cuts, suggesting he had been fighting. Again 6 months later, having been arrested with a suspicion he had severely beaten another person, his condition was diagnosed as right temporal lobe epilepsy, and he was started on 'a series of drug trials'. Within three months it was concluded that he showed no improvement to any of three drugs alone or in combination – here the author does not explain how this is possible with a seizure frequency that doesn't very much exceed one per month.

The story is complicated by two features which make it somewhat unfocussed. Benson in his seizures commits rather complex acts of violence for which he has no recall. The writer needs this for his plot to work but describes it as a typical feature of temporal lobe epilepsy: 'Unless you had seen a psychomotor seizure, you could not comprehend the unreasonable, brutal violence of an attack. It was completely beyond any normal life experience. Nothing else was like it, analogous to it, similar to it.'

'We don't know much about the causes of violence,' the chief of the Research Unit explains. 'And there's a lot of crap theory floating around, written by sociologists and paid for by perfectly good taxpayer money. But we do know that one particular illness, psychomotor epilepsy, may lead to violence. ... At the NPS, we think that psychomotor epilepsy may be extremely common among those people who engage in repetitive violent acts – like certain policemen, gangsters, rioters, Hell's Angels. ... We have no exact idea exactly how common psychomotor epilepsy is. But our guess is that as much as one or two percent of the population may suffer from it. That's two to four million Americans.'

Crichton was heavily criticized in the public and media for this denigration of people with TLE, and added a revocation and excuse in the paperback edition of the book.[1]

The other anomaly in the case history is that the patient, a specialist in artificial intelligence, at the time of the operation has developed a paranoid conviction that computers are conspiring against mankind, and actually are about to take over the world. That the operation turns himself into a kind of human-computer hybrid, a living computer terminal (this is what the title refers to) fits well with his delusion, but the author never gets the two disorders, epilepsy and psychosis, and their possible relation neatly sorted out, so that the concepts of seizure control and mind control get rather mixed up – not dissimilar to Thom Jones' *Pugilist*.

After the control unit is in place, stimulations are given to each of the 40 implanted electrodes. Then the author is carried away by his desire to create a sensational plot. As contacts for stimulation he lets the doctors not use ones which can abort a beginning seizure but ones which give the patient pleasant sensations including one which leads to erotic arousal. From here, the tragedy takes its course. The stimulations result in a reinforcing rather than the expected downgrading feedback, and seizure activity and interruptive stimuli increase in frequency to end up in a seizure during which he first has sexual intercourse with a girl friend and then kills her. The following rather conventional man-hunt of a cunning criminal ends with Benson being shot dead in self-defence by his lady psychiatrist who to the last moment wanted to save his life and re-circuit his stimulation device to produce non-dangerous behavior.

The author touches briefly on the important philosophical and ethical implications an intervention of this kind has, but the possible debate this could have initiated did not take place because all attention became focused on his ill-representation of violence as a typical symptom of psychomotor epilepsy.

Although the cinematic adaptation of Michael Crichton's *The Terminal Man* (1974) is generally faithful to the novel, the film rather suffers from the 1970s zeitgeist. The spare, white sets further dehumanize the medics who are cold and aloof whilst operating on Benson who is clearly conscious. Rather bizarrely, traditional surgical greens are dispensed with, in favour of space-age operating suits, with the result that the surgeons resemble an Apollo mission crew. Although clearly capable of monstrous acts, Benson is the only character with whom the audience is invited to connect with. The clinical cinematography and sparse dialogue discourages the audience to make any real connection with the victims. Thus the film strikes a discordant note. It is interesting to note that Crichton produced nine drafts of his book *The Terminal Man* and that it remains his least favorite book. Of the film he says '*I loathed 'The Terminal Man' and make no bones about it. I thought it was wretched and a lost opportunity*'.

Film

Whilst both epilepsy and neurosurgery frequently play a pivotal role in movie plots, epilepsy surgery is a relatively rare feature. Although fast growing, malignant brain tumors are hugely over-represented in the neurological movie population, seizures are very rarely seen in these characters. Other neurological signs (particularly loss of vision and paralysis) generally precipitate the neurosurgical interventions in these movies. The lack of seizures in these characters is curious, since film-makers haven't shied away from depicting seizures in other storylines.[8] Films with characters who experience epileptic seizures can be found in almost every genre, ranging from the classic Disney animation *Snow White* (1937), where Dopey, one of the seven dwarfs appears to experience a nocturnal seizure, when he returns home from a hard day's work in the diamond mine to find Snow White in his house,[9] to obscure cult horror films such as *Vampire Trailer Park* (1991), where the heroine receives helpful advice from her dead grandmother during her complex partial seizures, enabling her to track down a vampire who is running amok in an American trailer park.

Despite the highly imaginative and widespread use of seizures as plot devices, we generally do not see seizures in the very characters in whom they might be expected. One reason may be the continued stigma attached to epilepsy. Movie characters with brain tumors are frequently dignified and heroic and can remain so following the onset of gradual blindness or peripheral numbness. A seizure may well throw the audience off-balance and lead to unpredictable feelings towards the character, upsetting the director's narrative flow. It is interesting to note that the few films that do cover epilepsy surgery can on the whole be divided into two broad categories where this will not be an issue: true life stories and science fiction.

A notable exception is one of the very earliest films to tackle epilepsy surgery. Dr Kildare, the archetypal 'good' young American doctor was created by Frederick Schiller Faust (aka Max Brand) and first appeared in a fiction magazine in 1938. The character rapidly made the transition to the silver screen and appeared in a series of ten very popular feature films between 1939 and 1942. The fifth film in the series, *Dr Kildare's Crisis* (1940), provides a fascinating insight into the medical understanding of epilepsy and public attitudes towards seizures that were prevalent in the 1940s. The dashing young Dr Kildare is engaged to marry one of his pretty nurses, but soon discovers, to his horror, that her brother has epilepsy. This puts the impending marriage in doubt as she is obviously from damaged genetic stock, and his children may inherit epilepsy and as a result become insane. Dr Gillespie, an older and wiser doctor, establishes that the man's seizures are the result of a head injury, dissipating all hereditary concerns. What's more, the seizures can be cured by a simple operation. It is heartening to note that The Medical Society of New York lodged a formal complaint against the film, protesting against

the way that epilepsy was presented. They objected to the claims that epilepsy was automatically inherited, that it led to insanity and, ironically, and that it was curable by surgery.

The Dr Kildare film series ended in 1942, when the lead actor Lew Ayres announced his conscientious objection to the war, and was dropped by the studio. However, the character was revived in the 1960s for a hugely popular TV series with over 190 episodes produced, and is widely thought to have paved the way for Michael Crichton's current medical series *ER*. Although patients with epilepsy did feature, the original epilepsy story line was not repeated in the TV series.

Films based on a true story

The real experiences of epilepsy surgery patients have been the focus of a number of 'made for TV' movies. When Meryl Streep, the star of one of these films (*First Do No Harm,* 1997), was asked why the film was made for TV, she replied:

> There was a lot of talk about making *First Do No Harm* a feature (film), but we all thought that it would be better if it was seen by a lot of people; and you can't count on that in this movie climate. So we took it to TV. It's the populist medium, where we get out what we're trying to say to the most people.

This reply implies that these films are made not just for entertainment, but also have a message to impart. Certainly many of the directors of these films have been attracted to epilepsy surgery as a subject matter as a direct result of their own experiences with loved ones who have epilepsy. However, the messages these films impart regarding epilepsy surgery appear to be very mixed indeed.

In *First Do No Harm* (1997), Meryl Streep plays a mother who discovers the possibilities of the ketogenic diet at the eleventh hour, when neurosurgery appears to be the only option left for her son. Despite meeting considerable resistance and hostility from the medical profession, her son achieves complete seizure freedom by strictly adhering to the diet. The very title of the film implies that surgery equates to harm. The boy is presented as having a narrow escape from a horrific fate, inflicted by medics with closed minds. Many of the events and dialogues within the film were based on the actual experience of the director Jim Abrahams, who apparently withdrew his own child from epilepsy surgery the night before it was scheduled after reading about the possibilities of the ketogenic diet.

Although this boy is presented as having a narrow escape from a horrific fate, the dangers of surgery are largely implicit in *First Do No Harm*, since surgery doesn't actually occur. The harmful effects of epilepsy surgery are far more explicit in *Seizure: The Story of Kathy Morris* (1980); a true story based on the book *Seizure* (1978). Kathy Morris was a young music student who ignored memory difficulties and headaches until she woke up in the emergency department of a hospital having suffered a generalized convulsion. In a departure from his more famous *Star Trek* incarnation as Mr Spock, Leonard Nimoy plays the surgeon who attempts to remove a benign meningioma. Unfortunately, the surgery (which is being filmed for teaching purposes) goes horribly wrong, and the surgeon is forced to cut away normal tissue. Kathy undergoes two further procedures before the tumor is fully resected. Although she is left with profound language difficulties, the film charts her remarkable recovery and ends with Kathy singing again. Cameo performances from actual patients appear in both *First Do No Harm* and *Seizure: The Story of Kathy Morris*, emphasizing the 'real' nature of the portrayals in each film.

The uncertain outcomes associated with epilepsy surgery are also examined in *The Other Half of Me* (2001), which was based on the director/writers real life experience of dating a woman who had undergone a hemispherectomy as a child. Ostensibly a love story, the hero Mikey is on the rebound from a difficult relationship when is set up on a blind date with Morgan who 'only has half of a brain'. Mikey is undaunted by her surgical history and falls for her, despite the reservations of his friends. However, although she is open about her neurosurgical history, Morgan attempts to conceal her ongoing seizures, causing significant difficulties in the relationship. The writer/director Michael Mustizer explained the inspiration for the script.

> Mainly, I wrote of complications that may or may not arise in a girl with half a brain. Seizures. ... one night it happened. Meighan (his girlfriend) had a seizure while sleeping. She was choking. She was screaming. She was scared. When she came out of it, she was in a world all of her own. She was frightened of the cat. She had forgotten the name of her childhood teddy bear. She couldn't count, nor recite the alphabet. I was genuinely scared for the first time in my life ... When I began to film 'The Other Half of Me', I took all of this in. I memorized every aspect of that night. I put it into the script. I put it on screen. Those moments of the film are genuinely scary. And I am proud of that. I truly captured the fear I was going through.

This film is interesting in that the focus is not on the horrors of neurosurgery; the hemisphectomy in the plot is a curiosity, but is accepted, but rather the filmmaker uses the movie to portray the anguish and fear associated with ongoing seizures.

The rare but serious complications associated with early epilepsy surgical practices from the 1950s inspired the celebrated film *Memento* (2000). In *Memento*, the hero Leonard suffers from a dense anterograde amnesia following a severe head injury sustained during an assault during which his wife is killed. Despite his dense amnesia, he attempts to track down the killer and keeps abreast with his investigations with the extensive use of polaroid photographs and even tattoos. The fragmented style of the film echos Leonard's own fragmented memory processes. The film won an Oscar nomination for screenplay, which was directly inspired by the story of H.M., one of the most studied epilepsy surgery patients in the world. H.M., a 28-year-old motor winder underwent a bilateral temporal lobectomy in 1953 and suffered a dense anterograde amnesic syndrome as a result. His case had a significant impact on the history of epilepsy surgery practice and was pivotal in the development of the role of clinical neuropsychology in the presurgical evaluation of epilepsy surgery patients.

These negative and ambivalent attitudes to epilepsy surgery couldn't be further from those portrayed by Patrick Dempsey in *A Fighting Choice* (1986), another made-for-TV movie. Rather than a crude medical intervention, epilepsy surgery is presented as the ultimate goal in this film, as a teenager tormented by frequent generalized convulsions takes his parents to court to allow him to undergo 'split brain' surgery. Although a surgical option is presented in a much more positive light in this film than those reviewed thus far, the uncertain outcomes associated with surgery are again highlighted, with a firm focus on the 'experimental' nature of the treatment sought and the very considerable risks feared by the boy's parents.

Science fiction

Although neurosurgical procedures and devices frequently feature in films from the science fiction genre, most of these attempts at mind/behavior control do not involve seizures, with the notable exceptions of *The Terminal Man* (1974) and *Megaville* (1990). In the latter film, a cop living in the aptly named 'Hemisphere' is sent to neighboring Megaville to investigate the illegal viewing of television and movies. He suffers a series of seizure-like events, and it eventually becomes clear that these have been caused by the malfunctioning of a device implanted in his brain to alter his memories and personality. Although futuristic, these plots have much in common with ancient beliefs that external agents cause seizures. Here 'mad-science' and high tech devices have replaced demonic evocations. However, Megaville is unique in that it is the only film reviewed, where 'seizures' are portrayed as a window into 'real' life and therefore a good thing, rather than the customary temporary opt out from true experience.

Summary

Although epilepsy and neurosurgery frequently appear in movie plots, films featuring epilepsy surgery are relatively rare and generally fall into the 'true life – made for TV' or science fiction genres. The majority of films are characterized by a mistrust of a cavalier and incompetent medical profession. Even when it is presented as a desirable objective, epilepsy surgery is almost always presented as a high-risk, experimental procedure with unpredictable results in the movies. It is particularly interesting to note that the 'new' and 'experimental' qualities of surgery continue to prevail in the movies despite over 50 years of successful epilepsy surgery practise worldwide. As with the literature, sci-fi films that feature epilepsy surgery tend to confuse seizure control with mind control.

It is unrealistic to expect that epilepsy surgery will be treated objectively on the silver screen. Movies are made to entertain and make money, and a story of successful, uncomplicated epilepsy surgery is unlikely to draw big crowds at the box office. It seems probable that the perennially favourite movie themes of the mysteries of the human mind, a fascination with the medical profession and the triumph of the human spirit, will continue to provide ample material for future movie scripts. Whilst this remains the case, epilepsy surgery will remain a prominent target for misrepresentation and distortion but also, and more positively, discussion.

For literature, the situation seems to be slightly different, although there are similarities, and one of the more problematic films is based on an equally problematic book. However, stories and novels written to be read at leisure, some with a clear objective to stimulate the reader's thoughts and reflections, are more likely to present a differentiated view. The question thoughtfully raised in one book, of creativity connected with disease and its possible destruction by successful therapy is an example. But it is unfortunate to see epilepsy surgery in several books getting confounded with psychosurgery. At least three of the seven works discussed here, one novel, one comic book and one autobiography, are based on personal experiences, and the emotions which these experiences created are palpaple in the books. To conclude, like in film, epilepsy surgery does not yet appear in literature as the hopeful therapy which can make a big difference in a life, the way we perceive it in the professional world.

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NOTE

In Norwegian writer Edvard Hoem's non-fiction book Mors og Fars Historie (Mother's and Father's Story) of 2005, the father develops epidural hematoma with status epilepticus after a blunt head trauma. The surgeons save his life, and the event becomes a turning point in the parents' relation.

The leading character's post-traumatic epilepsy is a prominent and multifaceted feature in Garth Stein's very recommendable novel of 2005, How Evan Broke His Head and Other Secrets. At one point, epilepsy surgery is proposed to Evan but he rejects it because he fears it will damage his creativity as a musician. The background in real life is Stein's sister's surgically treated epilepsy (see the author's website www.garthstein.com).

24 The future of epilepsy surgery

F Andermann and W Harkness

The ability to generate electrical potentials is a fundamental property of the brain. Vitiation of these potentials can lead to the appearance of epileptic seizures. Long before these properties and mechanisms were recognized, clinical observations showed that brain injuries or lesions could lead to scars and seizures. This prompted attempts to remove these lesions. The work of pioneers like Victor Horsley and Fedor Krause is well recognized. A prolonged hiatus then ensued, until Otfried Foerster in Breslau (now Wroclaw in Poland) began to further advance this approach to treatment. Wilder Penfield, looking for new horizons, spent some months with Foerster and, as one may describe in present terms, was the first epilepsy fellow.

At the Montreal Neurological Institute, which Penfield founded in 1934, he learned of Hans Berger's work in electroencephalography, which promised the ability to recognize epileptic potentials and discharges and to help in localization of epileptic activity. He attracted Herbert Jasper, then working as a psychologist at Brown University in Rhode Island, and their fruitful collaboration provided great impetus to the field of surgical treatment of epilepsy. One of their main advances was the recognition of temporal lobe epilepsy, which later was shown to be the most important cause of intractable epilepsy. The school of Penfield and Jasper attracted numerous disciples from many parts of the world and, after World War II, there was considerable and widespread flowering of interest in the surgical treatment of epilepsy. This enthusiasm however was short lasting, and surgical treatment was widely deemphasized. In some countries, such as Germany or Japan, it was virtually proscribed. When I asked Dr. Theodore Rasmussen why this enthusiasm had waned at that time, he replied, 'It was the wrong surgeons, operating on the wrong patients'.

For years, surgical treatment of epilepsy was confined to very few centers, notably the Montreal Neurological Institute with Theodore Rasmussen, Bill Feindel and their disciples, King's Maudsley in London with Murray Falconer and his school, and the Hopital Ste. Anne in Paris with Jean Bancaud and Jean Talairach. Careful keeping of the score, as Dr. Rasmussen put it, led to recognition of optimal candidates for surgical treatment and the ability to formulate more informed prognosis in the different forms of epilepsy. Interestingly, during that period, the role of structural lesions, such as indolent tumors, was not accepted or well understood. The emphasis was on electrographic localization of the epileptogenic area.

The advent of modern imaging with computed tomography, and even more after the development of magnetic resonance, provided a second and very powerful impetus to surgical treatment of intractable epilepsy. It allowed recognition of the significance of the lesions, and their epileptogenic potential was increasingly emphasized. In the same period in the 1980s and early 1990s, the ability to identify a plethora of lesions previously invisible during life provided an additional stimulus to surgical treatment. A major step was the recognition during life of cortical dysplasia. This had been described by David Taylor from Falconer's group, based on pathological studies of material resected, and of course in those patients the lesion was not visible preoperatively. There was a tremendous explosion of interest in this topic, resulting in an enormous literature, with hundreds of contributions since, addressing the different modalities of investigation and of treatment.

The financial rewards of video telemetry stimulated hospital administrators and neurologists to introduce this investigative approach, which promised to generate important economic benefits. This was not necessarily combined with the development of the required team approach. Many centers had planned to develop surgical treatment without being adequately prepared or willing to provide support for the required multidisciplinary team. They soon dropped out of the field. We have however witnessed the development of a number of centers of excellence in the United States, and in Canada, where this was spearheaded by Penfield's disciples across the country. Comprehensive epilepsy centers with expert investigation and surgical expertise also developed in many parts of Europe, Germany, Italy, France, United Kingdom, and elsewhere.

The recognition of ideal candidates for surgical treatment was further refined and also enabled the development of centers for surgical treatment in the developing world, geared to the treatment of patients with identifiable lesions or unilateral mesial temporal sclerosis. There always remained a temptation to tackle difficult problems, such as for example operating on patients with frontal epilepsy without a lesion that can be demonstrated by imaging, and where the results are considerably inferior to those in well-selected cases.

Surgical treatment of epilepsy has always been complicated by prejudice on the part of neurologists and other physicians, and the amount of prejudice was inversely proportional to the knowledge and expertise of these doctors.

It was recognized early that the search for surgical treatment by patients and families was driving the referrals, much more than the initiative of the treating neurologists and other physicians. Though this type of prejudice seems to be diminishing, it continues to exist. There are also obvious financial incentives in not referring patients for surgical treatment.

There were numerous examples during the recent flowering of trials of new antiepileptic agents of patients going through trial after trial, even though the chances of success were minimal. These patients may have had a much better chance for a more normal life with surgical treatment.

The lack of awareness of the possibilities and advantages of surgical therapy however was probably an even greater factor, and this was coupled in many instances by inadequate interpretation to the patients and their families and of course by their inadequate understanding of the process.

After this lengthy preamble, we turn to the future of surgical treatment. That surgery has been underutilized has been stressed repeatedly by the Commission on Surgical Treatment of the International League Against Epilepsy. Calculated estimates of surgical candidates in the population yielded high figures, but it is not entirely clear whether these figures were always based on discrimination between patients with a very good chance of successful outcome compared to those who, though quite intractable, presented much more difficult problems and a lesser promise of a good result. Furthermore, there are important geographic considerations. In regions or countries where surgical treatment becomes available for the first time, there are a large numbers of patients with eminently treatable forms of epilepsy, such as for instance, people with temporal lobe epilepsy associated with unilateral mesial temporal sclerosis. Initial reports from such areas or centers are able to describe large series with good results obtained in a relatively short period of time. In areas where surgical treatment has been available for some time, and where there is much better awareness of what surgery can accomplish, such patients with optimal prognosis are becoming increasingly rare. I asked the senior surgeon at a major epilepsy center in the Eastern United States how many such ideal surgical candidates he would see in a year and he replied: 'six or seven'. He then proceeded to mention also that since imaging findings are more readily recognized now, such patients are often referred and operated by general neurosurgeons without an abiding interest in the treatment of epilepsy and without the benefit of more complete preoperative investigation. Such a comprehensive study would be likely to lead to even better results in the long run. Similar situations prevail, no doubt, in countries where surgical treatment is introduced for the first time. For example, impressive results were obtained in centers such as the one at Sri Chitra Tirunal in Trivandrum, State of Kerala in South India.

Because of the severity of the epilepsy, and the gradual deterioration of many patients, there is continuing temptation to address problems which are not as likely to lead to very good outcomes. Patients and their families however are generally very grateful even for improvement rather than complete control of their attacks, an often unexpected and gratifying attitude.

There is the hope that increasingly sophisticated technology and refining of functional imaging as well as of electrographic localization may lead to improved understanding of the epileptogenic process and thus to improved outcome. The use of innovative PET ligands, PET activation techniques, various forms of morphometry, magnetoencephalography, spike-driven FMRI, and recording from dense arrays of electrodes are amongst the techniques being developed that hold promise of increasing clinical usefulness.

An example of how new insights develop is provided by gelastic epilepsy related to hypothalamic hamartoma. First the clinical pattern was recognized to be associated with the hypothalamic lesions, and the advent of MRI greatly facilitated identification of these. Attempts of resecting the lesion were initially not encouraging. Identifying epileptogenic areas based on electrographic localization, even with depth electrode studies, led to a number of temporal and at times frontal resections. These were also fruitless. That the lesions themselves could generate epileptic potentials, was then found by Munari and his group using depth electrodes placed in the lesions. This led to a multiplicity of approaches designed to resect or destroy the hypothalamic hamartoma itself. It became clear that some approaches were preferable to others and at the moment a transcallosal approach appears to be optimal, particularly in lesions which are within the lumen of the third ventricle or not very extensive. The completeness of the resection, in so far as it can be determined by imaging and by direct visualization, appears to correlate with the outcome. The role of other approaches such as gamma knife surgery is yet to be confirmed. Despite the proven benefits of resective surgery, there continues to exist considerable reluctance on the part of many neurosurgeons to approach these lesions for fear of disastrous complications. Though some endocrine and other complications may occur with surgical treatment, the benefit, particularly in patients with gelastic seizures and catastrophic secondary generalization, far outweighs these risks.

How do other approaches to the treatment of intractable epilepsy impact on surgical treatment? The new generation of antiepileptic drugs are comparable in their effect to that of the previous generation of agents. It is generally recognized that their main benefit lies in reduction of side effects and that only less than 10% of patients who have intractable epilepsies are fully controllable by any of the new agents. To wait for new agents to be developed is to deprive patients of the benefit of a much better outcome obtainable by surgical treatment. Devices such as vagal nerve stimulation are strongly driven by industrial support and do not require complicated and technically difficult and prolonged investigations. There is also strong support for the utilization of this apparatus by industry sponsored specialized nurses working with the patients. Whether some forms of epilepsy are more likely to respond than others to vagal stimulation is not currently clear. The results appear to be better in children compared to adults. Cerebral stimulation and prostheses designed to arrest seizures at their onset are currently studied and remain experimental.

In reviewing a series of reports on postoperative psychosis arising de novo from Denmark, Finland, and the United Kingdom, it becomes clear that the risk of postoperative psychosis is present mainly in individuals whose seizures have not ceased following surgery. Only a very small number of patients whose seizures have been fully controlled by surgery develop psychosis, probably related more to the preexistent terrain and pathology than to the surgery itself.

One of the criticisms leveled at surgical treatment was that no controlled studies were present. This type of criticism could be leveled also at operations such as appendectomy. However, since some objective evidence seemed required, studies such as the one by Wiebe et al., have confirmed the benefit of surgical treatment in patients with temporal lobe epilepsy compared to

continued medical treatment. Further attempts based on multicenter trials are also planned or underway.

New and as yet unplanned developments in neuroscience may open new perspectives in our understanding of intractable epilepsy and may lead to new approaches, which cannot at present be foreseen.

The possibility that surgery may provide resolution of a person's epileptic problem as far as recurrent seizures are concerned must be kept in mind when seeing or reviewing a patient with epilepsy. It is important not to make value judgments about the severity and dangers of the epilepsy itself. Rather, one should be guided by the person's perception of his or her problem, within reason. Wanting to avoid antiepileptic medication completely is not necessarily a frivolous request. Though this usually cannot be promised, such requests need to be weighed against the possible side effects of a lifetime of possibly heavy antiepileptic medication. Often, the medication can be reduced postoperatively for a period of time and in some patients, eventually discontinued.

The available information at the time of the patient's first review is most often inadequate, and further investigation is required before the options can be presented to the patient and the family. Obsessive trials of every conceivable antiepileptic are not a very fruitful exercise. Above all, the pros and cons, risks, and benefits of surgery need to be explained to the patient's satisfaction, and it is essential to have some idea whether this has actually been understood and carefully considered.

Surgical treatment offers a resolution of the problem of recurrent attacks to many people with epilepsies both in developed and in the developing world, and these patients should not be deprived of this option. Even politicians and governmental agencies have a role to play in enabling patients to benefit from surgical treatment. The situation in Brazil, where this approach is given some priority by the government, is a good example of what can be accomplished in the developing world.

One may conclude that surgical treatment, despite its invasive nature, and often uncertain outcome, will continue to provide a valuable option unless it is surpassed in the unforeseeable future by different, less invasive, but equally effective, approaches.

SECTION 2

Overview

25 Medical intractability in epilepsy

DV Lardizabal

Anticonvulsant drug failure

The mainstay of epilepsy management is drug therapy with anticonvulsant drugs. The appropriate choice of anticonvulsant drugs is mainly determined by the type of epilepsy (generalized or partial) and the seizure type. The clinical goal of anticonvulsant therapy is to make patients seizure-free with minimal or no side effects. The anticonvulsant dose in controlling seizures is also very individualized. It is very important that during the anticonvulsant drug titration, the *lowest dose* that controls seizures should be first achieved. During the titration phase, there are three possible outcomes. First, the patient's seizures are controlled with no undesirable side effects – the therapeutic end point. Second, the patient may develop intolerable side effects or idiosyncratic drug reactions and the drug is discontinued during the first few days of drug titration. Third, the patient continues to have seizures when the drug is within the recommended dosage. At this point, the compliance of the patient should be investigated. Serum drug levels and pill counts are important in determining compliance. Assuming good drug compliance, the clinician's next step is to determine the maximum tolerable dose (MTD). The maximum tolerable dose is individualized and is determined by the patient's clinical side effects. The anticonvulsant should be titrated up slowly. If the patient has undesirable side effects at a specific dose, the clinician should *lower the dose* that will produce the least side effects (subtoxic). The maximum tolerable dose is the highest dose *before* reaching clinical toxicity. Hence, it is impossible to know that maximum tolerable dose until the patient reports significant neurotoxicity. It is important to note that the maximum tolerable dose is *not* based on the drug levels.[1] Sometimes, the patient may not experience clinical toxicity despite being above the 'therapeutic range'. Moreover, clinical toxicity may even develop within the 'therapeutic range'. The maximum tolerable dose may or may not control the seizures. An adequate anticonvulsant drug trial also takes into consideration the duration of therapy.[1] The appropriate length of time during which a drug should be tried will vary mainly as a function of the baseline seizure frequency. Reasonable drug trial duration for a given drug would be about 5 to 10 times the average seizure interval at baseline before the drug was introduced. This time frame may not apply to very high and very low seizure frequencies, such as more than two seizures per week or less than one seizure per month.[1] *Therefore, a drug failure is usually considered if the patient has uncontrolled seizures despite reaching the maximum tolerable dose and after an adequate treatment duration.* When there is a drug failure, there are usually two options: switch to another anticonvulsant or add another anticonvulsant with the first. In both situations, the lowest dose that can control seizures without side effects should be determined again. When necessary, the maximum tolerable dose must be sought if the seizures persist.

Definition and epidemiology of medical intractability

The usual criterion for drug remission is at least *one year* of the intake of anticonvulsant medication. The initial response to anticonvulsant drug therapy is highly predictive of long-term outcome. Almost two-thirds of patients respond to anticonvulsant therapy. Approximately 47% respond on one drug alone; about 13% respond to two drugs and 4% respond to three drugs or more.[2] Generally, it has been observed that the chance of achieving seizure control beyond three drugs is 5 to 10%.[3–5] Medical intractability is also known as *multidrug resistant* (MDR) *or pharmacoresistant* epilepsy. There is no general consensus on the definition of medical intractability. In recently published studies, the *minimum* number of anticonvulsant drug failures to qualify for medical intractability is two or three.[6–10] There are also other components in medical intractability. The seizure frequency and duration of drug refractoriness are important components in medical intractability.[6] The *stringent criteria*[6] for medical intractability as defined by Berg *et al.* are: (a) failure of two appropriate anticonvulsants, (b) the occurrence of an average of one seizure per month for at least 18 months, and (c) no more than 3 months of seizure-free hiatus during those 18 months. However, patients having very frequent seizures, multiple times per day or per week, have a greater impact than those patients with seizures occurring once a month. Hence, catastrophic epilepsy patients will require a shorter duration of observation in qualifying for medical intractability. The observation of drug refractoriness ranges from 6 months to 2 years. Another consideration in the defining medical intractability is the presence of a structural brain abnormality.[2] In patients with a known epileptogenic structural abnormality that is surgically accessible, a failure of at least two drugs may be all that is needed to classify pharmacoresistant epilepsy.

If the minimum two-drug criteria is use to classify medical intractability, the percentage meeting this criteria ranges from 31 to 37.5%.[7] Following the stringent criteria by Berg *et al.*, only 10% fulfilled medically intractability.[9] In a prospective study,[11] 13.8% and 23.2% of epilepsy children fulfilled the stringent criteria and two-drug failure criteria, respectively.

Hence, the two-drug failure criterion is sensitive for identifying refractory epilepsy. However, for surgical purposes, stringent criteria may be useful in identifying surgical candidates. Poor prognostic factors associated with medical intractability are early age at seizure onset, multiple seizure types, structural brain abnormalities (cortical dysplasia, hippocampal sclerosis), and high frequency of seizures before drug therapy, and persistence of seizures despite multiple drug trials.[2] The highest risks for medical intractability are the catastrophic epilepsy syndromes that occur frequently in children. Idiopathic (genetic) epilepsy has the least risk of drug resistance. Partial epilepsy has moderate risk of developing intractability. Using the two-drug failure criteria, the percentage of medical intractability are: focal epilepsy, 24%; idiopathic epilepsy, 9.3%; and catastrophic epilepsy, 66.7%. Using Berg's stringent criteria, 13.3% of focal epilepsy, 3.9% of idiopathic epilepsy, and 52.2% of catastrophic epilepsy are pharmacoresistant.[11]

In partial epilepsy, the duration of the epilepsy before becoming intractable is an average of 9 years (12). Younger patients (< 5 years old at onset of epilepsy) had a longer median latency time (15 years) before becoming intractable. In contrast, older patients (> 30 years old at onset of epilepsy) had a shorter *median* latency time of 1 to 2 years and an *average* of 3.2 to 3.6 years to become intractable. Among patients whose epilepsy onset was between 10 and 19 years old, the median latency and average duration to become intractable was 3 to 5.5 years and 7.2 to 8.6 years, respectively. In patients with partial epilepsy with *no* history of febrile seizures, the median latency was 5 years (9 years median latency with febrile seizure). Patients with hippocampal atrophy also had a longer median latency (8 years versus 3 years). Interestingly, about 47.5% of epilepsy patients whose seizure onset was at less than 5 years old reported a period of at least 1 year remission before they became medically intractable. There is a trend that epilepsy onset above 5 years or older had a smaller percentage of having a history of 1 year remission during drug therapy (7–28%).

Hypothesis of medical intractability

The factors leading to multidrug resistance are unknown. Drug resistance can be seen early in the course of the disease or up to several years after good drug response. There are two main hypotheses probably responsible for multidrug resistance. The first is the *Drug Transporter* hypothesis and the second, the *Drug Target* hypothesis.

Drug transporter hypothesis

Multidrug resistance transporter protein-1

There are a multiple drug transporters in the central nervous system that may be responsible for multidrug resistance.[13–16] The most studied efflux drug transporter is MDR1 or P-glycoprotein. It is commonly expressed in the brain, liver, intestine, and kidneys.[13] In the brain, MDR1 is found in astrocytes and in the endothelial lining of the blood brain barrier. It is a transmembrane 170 kD drug efflux transporter protein that belongs to the ATP-binding cassette (ABC) family (chromosome 7q21.1). Interest in MDR1 began with the discovery of MDR1 in cancer tissue resistant to chemotherapeutic medications. Drug resistance in cancer cells is secondary to the subtherapeutic *in situ* concentration of chemotherapy drugs. MDR1 has a broad substrate for the efflux transport of medications. These include antibiotics, steroids, lipid lowering drugs, calcium channel blockers, cardiac medications, HIV protease inhibitors, immunosuppresants, antiemetics, and antihistamines.[17–19]

Tishler *et al.* in 1995[20] were the first to report MDR1 protein expression in brain tissue of drug-resistant epilepsy patients. Out of the 19 cases studied, 10 had more than a tenfold increased expression of the MDR1 protein. Thirteen of the specimens were from patients with temporal lobe epilepsy secondary to hippocampal sclerosis. Five of these 13 also showed increased expression of MDR1. Similar results were obtained in studies on five patients with temporal lobe epilepsy,[21] and eight cases of cortical malformation.[22] Sisodiya *et al.*[21,22,23,24] reported evidence of MDR1 expression in the capillaries and perivascular glial tissue in 30 patients with cortical malformations and drug resistant epilepsy. Lazarowski *et al.*[25] reported one case of MDR1 expression in an epilepsy patient with tuberous sclerosis. Other epileptogenic brain tissue with increased MDR1 expression were found in eight patients with dysembryoplastic neuroepithelial tumor,[22] five patients with Rasmussen encephalitis,[26] and one case of fatal human status epilepticus.[27]

It is possible that frequent seizures can induce the overexpression of MDR1. This hypothesis is supported by animal studies that show that seizures can influence the expression of MDR1.[28–34] Rizzi *et al.*[28] studied the mRNA expression of MDR1 in the mouse after kainic acid-induced seizures and showed that MDR1 is increased by 85% 3–24 hours after seizure induction. Moreover, status epilepticus induction caused a 180% increase of MDR1 expression in the mouse hippocampus and a 500% increase in the entorihinal cortex. Seegers *et al.*[30] reported that amygdala-kindled rats showed an overexpression of MDR1 1–2 weeks after kindling. In rats genetically prone to epilepsy,[31] a single audiogenic-induced seizure caused a gradual increase of MDR1 in 4 hours to 7 days.

Functionally, the presence of MDR1 transporter proteins may lead to an efflux of antiepileptic drugs from epileptogenic brain parenchyma to blood vessel lumens. The effect of MDR1 on antiepileptic drugs has been shown in animal studies. Rizzi *et al.*[28] showed that extracelluar fluid (ECF) levels of phenytoin decreased by 30% after seizure induction. Potschka *et al.*[35,36] studied the effect of MDR1 and multidrug-related protein (MRP) inhibition of carbamazepine and phenytoin in the rat brain. Using microdialysis methods, inhibition of MDR1 and MRP caused a 40% increase of carbamazepine in the rat brain extracellular fluid. In 2002,[37] the study was extended to see the effect of MDR1 inhibition on the brain ECF concentrations of felbamate, phenobarbital, and lamotrigine. Using verapamil as an MDR1 inhibitor, AED concentrations increased in ECF by 52%, 95%, and 107%, respectively. In another experiement, chronic epileptic rats showed an increased responsiveness with phenytoin when treated with a selective MDR1 inhibitor, Tariquidar.[38] Only one study has demonstrated brain anticonvulsant levels in epilepsy patients using microdialysis techniques. Twenty-two pharmacoresistant epilepsy patients had intraoperative microdialysis measurements of brain anticonvulsants levels (extracelluar space) compared with cerebrospinal fluid (CSF). Brain concentration of anticonvulsants was significantly lower than CSF. However, there was no concomitant measurement from nonepileptogenic region.[39]

Aside from the over-expression of MDR1, it has been shown that the gene polymorphisms encoding for MDR1 protein also confer anticonvulsant drug resistance.[40–42] It has been found that patients with drug-resistant epilepsy were more likely to have the CC genotype at ABCB1 3435 than the TT genotype.[40] However, other studies have found no association of MDR1 polymorphisms with anticonvulsant drug resistance.[43,44]

Other drug transporters

The other efflux drug transporters are multidrug-resistance-related proteins (MRP1, MRP2, MRP5), Major Vault Proteins, and RLIP76.[15,21,45,46] The RLIP76 is not related to MDR1 or MRP. This transporter is expressed in the luminal surface of endothelial cell membranes of the blood brain barrier of excised pharmacoresistant epileptic brain tissue. Saturable, energy-dependent, antigradient transport of both phenytoin and carbamazepine were demonstrated using recombinant RLIP76 reconstituted into artificial membrane liposomes. Immunotitration studies showed that RLIP76 is dominant transporter for carbamazepine and phenytoin using crude membrane vesicles prepared from whole-brain tissue endothelium. In the RLIP76-/- knockout mice study, it exhibited dramatic toxicity upon phenytoin administration due to decreased drug extrusion mechanisms at the blood brain barrier.[46]

Drug resistance may also be related to a dysfunction of glutamate transporters of glial and neuronal cells of epileptogenic tissue.[47,48] Pharamacoresistant epilepsy brain slices showed that glutamate transporters in the glia (EAAT1 and EAAT2) and neurons (EAAT3) are downregulated in specific areas of the hippocampus.[47] It is probable that poor reuptake of glutamate cause increase levels of glutamate and worsen the epileptogenicity of the brain.

Drug target hypothesis

The hypothesis is that there is an intrinsic or acquired loss of brain target sensitivity to anticonvulsants.[14] The drug target hypothesis was recently described by Remy *et al.* in 2003. This study was based on studies with carbamazepine on voltage-gated sodium channels in hippocampal neurons. The primary mechanism of carbamazepine (CBZ) is well established, and it is thought to be related to its action on voltage-gated sodium channels that are integral to the generation of seizure discharges. Vreughdenhil *et al.*[49] first reported that the modulation of sodium current inactivation by CBZ in hippocampal CA1 neuron from patients with temporal lobe epilepsy (TLE) and mesial temporal lobe sclerosis was only half of that measured in neocortical neurons from the same patients and in CA1 neurons from patients without mesial temporal lobe sclerosis. These data was substantiated by Remy *et al.*[50] It showed that use-dependent block of voltage-dependent sodium channels of dentate granule cells by CBZ is completely lost in patients with CBZ-resistant temporal lobe epilepsy. A loss of drug–target sensitivity was also noted in rat models of TLE.[51] The study showed that use-dependent block of sodium channels of dentate granule cells by CBZ is absent in the pilocarpine rat model of TLE. It also demonstrated that the effect of phenytoin on the fast recovery from inactivation in hippocampal granule neurons was significantly reduced in the pilocarpine model, though not as much with the carbamazepine.[51]

Summary

In published literature, the consensus of medical intractability is usually a two to three anticonvulsant drug failure. Catastrophic epilepsy and partial epilepsy syndromes have the tendency to develop pharmacoresistance early. The mechanisms of multidrug resistance may be multifactorial. The current hypothesis of drug intractability is probably due to low drug penetration in the blood brain barrier, drug target insensitivity, or impaired reuptake of glutamate in epileptogenic brain tissue.

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26 Epidemiology of the intractable generalized epilepsies

AT Berg

Introduction

Gowers is often quoted as having said about epilepsy that, 'The tendency of the disease is toward self-perpetuation; each attack facilitates the occurrence of another by increasing the instability of the nerve elements... The spontaneous cessation of the disease is an event too rare to be reasonably anticipated'.[1] The first population-based epidemiological study to examine prognosis published in 1979 provided a very different assessment of the nature and outcome of epilepsy. This study demonstrated that most individuals with epilepsy entered lasting long-term remission.[2] Gowers' characterization of epilepsy, and that derived from the epidemiological studies, both reflect important truths. Most people with epilepsy do have seizures that are well-controlled and may ultimately remit. Those who have the worst seizures and who are cared for in specialized referral centers often have inexorably progressive, nonremitting disorders. While this latter group reflects a relatively small minority of all individuals who ever have epilepsy, these are the patients who occupy the majority of the epilepsy specialist's endeavors and are the intense focus of research aimed at prevention and improved treatment of this disabling disorders.

To a large extent, the prognosis of epilepsy is determined by the type of epilepsy. The International League Against Epilepsy (ILAE) has made concerted efforts to identify distinctive forms of epilepsy and to arrange them into a practical classification of the epilepsies. Thoughtful and scholarly treatments of these efforts are available.[3–5] Although imperfect and as yet incomplete, the ILAE classification provides a useful framework for thinking about epilepsy[6,7] (Table 26.1). In children the most aggressively intractable forms of epilepsy arise from certain clusters of syndromes, some generalized, some localization-related, and some with combinations of features.

The emphasis in this chapter is on the intractable generalized epilepsies. This presents a few issues in definition and terminology that must first be addressed.

Generalized

While the term appears self-explanatory, in fact the apparently neat dichotomy between generalized versus focal really represents a continuum. Although the classification and terminology used to describe the epilepsies is under revision, at this point in time, it would be fair to consider, in the context of intractable generalized epilepsies, the epilepsies currently listed under the heading 'undetermined with both focal and generalized features'. These forms of epilepsies are complex but do have some distinctive generalized features and thus merit consideration here.

Intractable

There is no single operationalized definition for the concept of intractable or pharmaco-resistant epilepsy.[8] As it turns out, this is likely to be more of a problem for refractory partial epilepsies where the course of the epilepsy may be such that patients are seizure free for prolonged periods, and it is difficult to decide exactly when they are clearly intractable. Regardless, for the purposes of classifying a case of epilepsy as intractable, some minimum number of appropriate pharmacological treatments must be demonstrated ineffective, and a minimum criterion for seizure occurrence must be specified. Finally, knowledge of the natural history of the disorder is required as some forms of epilepsy, even those clearly refractory to medication, may go through relatively quiescent periods.

'Epileptic encephalopathy' and 'catastrophic epilepsies'

These terms have often been used in reference to many of these forms of severe epilepsy, localization-related as well as generalized and with both generalized and focal features. The concept of epileptic encephalopathy implies that the epileptic discharges associated with these disorders, which occur virtually exclusively in infants and young children, are thought to cause irreparable changes in brain development and function and result in lasting alterations in brain function. Children with these disorders may appear perfectly normal before onset but, with time, are frequently retarded or have pronounced cognitive deficits, are autistic, or both. The term 'catastrophic' epilepsy is restricted by some authors, to refer primarily to West, Lennox-Gastaut syndromes, and progressive myoclonic epilepsies.[9,10] Others consider catastrophic to be more expansive and use it to refer both to epileptic encephalopathies and to progressive encephalopathic conditions associated with epilepsy.[4] For the purposes of this discussion, the term catastrophic epilepsies will be used with the understanding that there is some variation in its use.

Intractable generalized epilepsies

Cryptogenic or symptomatic generalized epilepsies

These syndromes may or may not be preceded by a recognized symptomatic cause. The most common and best known of

Table 26.1 Outline of the classification of the epilepsies, 1989 report.[6]

Localization-related (partial, focal)
Idiopathic
Symptomatic
Cryptogenic
Generalized
Idiopathic
*Cryptogenic or symptomatic
*Symptomatic
Undetermined
*With both focal and generalized features
Without unequivocal focal or generalized features
Special situations

*Defined as catastrophic epilepsies for the purposes of this discussion.

these syndromes are West and Lennox-Gastaut. Myoclonic-Astatic Epilepsy (MAE or Doose syndrome) presents some difficulties in terms of classification. It was originally considered a form of idiopathic generalized epilepsy. In the 1989 classification, it was placed among the cryptogenic/symptomatic generalized epilepsies. This syndrome has been considered one of the epileptic encephalopathies.[11] More recently, it has been reintegrated into the idiopathic generalized epilepsies.[4,12] This reorganization in its classification does not indicate that MAE should be considered a benign disorder. In fact, fairly distinct subtypes with markedly different outcomes are described, suggesting that there is some complexity to this disorder that is not captured in the current approach to its classification.[13]

Symptomatic generalized epilepsies

This heading includes some well-recognized, although not necessarily entirely distinct, syndromes such as early infantile epileptic encephalopathy with suppression bursts (EIEE) or Ohtohara syndrome and early myoclonic encephalopathy (EME). Although typically associated with a specific symptomatic cause, occasional 'cryptogenic' cases are found.[14] In addition, there are epilepsies that result from very specific diseases in which the epilepsies tend to be characterized according to the disease rather than as a syndrome. As a group, these are often referred to as the progressive myoclonic epilepsies (PME). The better known among these include myoclonic epilepsy with ragged red fiber or MERRF, Lafora, and Unverricht Lundborg.[10,15,16] The report for the ILAE Task Force on Classification provides a current complete list.[7] In these disorders, the encephalopathic aspect of the disorder is a function of the underlying disease and not of the epileptic abnormality per se. Any one of these epilepsy diseases is exceedingly uncommon.

Undetermined with both focal and generalized features

Finally, well-recognized syndromes within the undetermined group should be considered in the context of catastrophic generalized epilepsy because they have generalized features and because it is important to differentiate them from other forms of intractable generalized epilepsy.

With the mounting evidence concerning its genetic basis, it seems increasingly apparent that that Dravet syndrome may represent the severe end of the spectrum of idiopathic epilepsy.[17,18] Dravet has also been linked to the familial clustering of epilepsies commonly known as GEFS+ (generalized epilepsy with febrile seizures plus). The finding of some cases of temporal lobe epilepsy with GEFS+ has resulted in the suggestion that the cluster be renamed autosomal dominant epilepsy with febrile seizures plus or simply FS+ (febrile seizures plus).[19] MAE has also been associated with the FS+ cluster and may well be part of this spectrum of idiopathic channelopathy epilepsies.[20,21] Landau-Kleffner syndrome and epilepsy with continuous spike wave in sleep (ESES) have a more localization-related presentation and may, in some cases, also represent the severe end of the localization-related idiopathic epilepsies. The two are not entirely distinct and some authors have suggested that they are manifestations of the same underlying process in different areas of the cortex.[22,23]

Basic epidemiology of epilepsy in the population

Overall incidence

For all epilepsy in the population, the estimates of the annual incidence range from a low of 24[24] to high of 64.1[25] per 100,000. The best overall population estimate from the US is based on the Rochester Epilepsy project and is 61/100,000 per year.[26]

Age at onset

From the population-based, epidemiological perspective, one of the most dramatic determinates of epilepsy is age (Figure 26.1).[26,27] In populations, the incidence of epilepsy is extremely high during the first year of life. It drops but remains relatively high throughout childhood and adolescence finally leveling off at a nadir in the third decade. It remains low into the sixth decade and then precipitously climbs in the elderly. The very elderly (>80 years) have

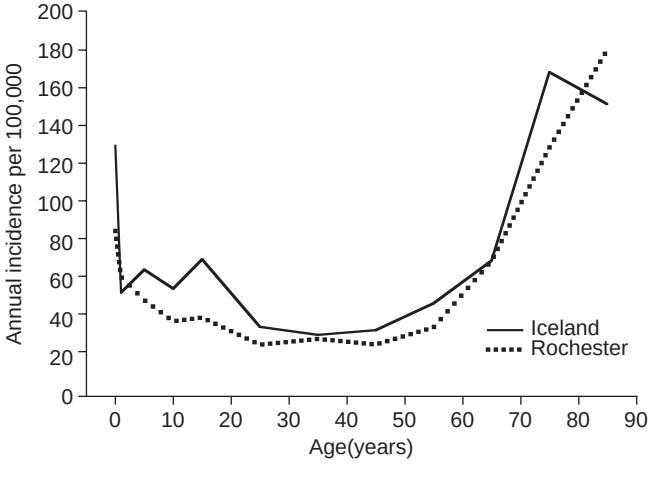

Figure 26.1 Incidence of epilepsy by age in Rochester, MN, US and Iceland. Data adapted from the original articles.[26, 27]

incident rates considerably higher than those seen in infants.[25–28]

Age and type of epilepsy

Part of the age-related pattern for the incidence of epilepsy is due to the occurrence of generalized seizures and epilepsies, many specific forms of which occur almost exclusively in infants, children, and young adolescents. This can be clearly seen in the Icelandic study where, for generalized seizures other than generalized tonic-clonic, the incidence is very high in infancy and drops precipitously in childhood, practically to disappear in adults.[27] The CAROLE study from France provides some of the most stable estimates of the relative occurrence of syndromes throughout the age span.[29] New onset generalized epilepsies of any kind account for little of epilepsy beginning in adults but are quite common in children and intermediate in adolescents and young adults.

Incidence of the catastrophic epilepsies

The Icelandic data provide incident rates by age and overall category of epilepsy.[27] The category for cryptogenic and symptomatic generalized epilepsy (dominated by West and Lennox-Gastaut syndromes) has an overall incidence of 0.7/100,000 per year in the general population; however, all cases observed in that population occurred in infants, and among infants (<1 year of age) the annual incidence rate was 43.4/100,000. For all the catastrophic epilepsies together, the population incidence rate was 1.7/100,000. The Icelandic study is a true prospective, population-based study. Because of the size of the population, the actual number of cases included in the study is fairly small (about 200 with newly diagnosed epilepsy and another 200 with first ever unprovoked seizures). The estimates for catastrophic disorders provided above were based on a total of 15 cases with such conditions.

Population-based estimates of the incidence or prevalence of some of the more common specific forms of catastrophic epilepsy are available from studies from a variety of countries. West syndrome is fairly consistently found to occur in 3 to 4 per 10,000 live births.[30–33] One study from Finland estimated the incidence of Lennox-Gastaut at 2/100,000 per year in the overall population.[34] A separate estimate more specific to children found the incidence to be 0.28/1000 live births.[35] Prevalence studies have provided fairly consistent estimates of the syndrome as being present in about 0.2 to 0.3 per 1000 children by age 10–15.[36,37]

Because this disorder often develops after West syndrome, incidence figures for Lennox-Gastaut must be made and interpreted with a little caution. Children who begin with one then evolve to the other cannot be counted twice in overall incidence estimates. For example, in separate reports from the US and Finland, about 25–40% of the children with Lennox-Gastaut first presented with West.[35,36,38] Up to half of children with symptomatic West syndrome may undergo an evolution to Lennox-Gastaut.[39]

One population-based estimate for Dravet syndrome comes from the United States. Based on the National Collaborative Perinatal Project, Hurst estimated that Dravet affects 1/40,000 children.[40]

Relative frequency of catastrophic epilepsies

The incidence figures provide a rough idea of how often some of the more common catastrophic epilepsies occur in the population. For understanding how common they are in the epilepsy clinic, other sources of information are more revealing.

The CAROLE study as well as other community- and population-based studies provide the distribution of types of epilepsy at initial diagnosis (incident cases) as well as in cross-section (prevalent samples). While these are not always strictly speaking 'population-based studies' and therefore precise incidence estimates cannot be obtained from them, the studies are representative of patients seen in the populations from which they come and can be reasonably used to estimate relative frequencies of different forms of epilepsy. In children, the encephalopathic disorders as a whole represent between 10 and 21% of epilepsies [29,41–43] although the highest estimate was based on the most clinic-based (referral center) of the reports.[43]

Syndromes such as West, Lennox-Gastaut, and MAE account for the majority of the children who have catastrophic epilepsies. Individually, each may account for 1–5% of pediatric epilepsy cases. Estimates from the rare syndromes are harder to come by. In a US study, Dravet was found in 0.5% of children recruited at the initial diagnosis of epilepsy. [38] Another study from Israel reported that syndromes such as Ohtahara and Landau-Kleffner accounted for 0.2% each of pediatric epilepsy.[44] Generally, such estimates are based on one or a few cases out of several hundred.

In all, what is apparent is that those forms of generalized epilepsies most likely to be intractable occur relatively rarely in absolute terms and represent a relatively small proportion of all individuals with epilepsy in the population although they represent an important minority of children.

Descriptive epidemiology of the catastrophic epilepsies

Available information is often based on case series from specialized treatment centers. Such cases may not entirely represent the disorder as it occurs in the population. On the other hand, true population-based estimates are difficult to obtain.

Age at onset

The catastrophic epilepsies tend to occur very early in life; however, each has a typical age at initial appearance. EME and Ohtahara have the earliest onset occurring during the neonatal period although they may first present later up through the first 3 months of life. West and Dravet syndromes generally occur within the first year with a peak around five months. Lennox-Gastaut, Myoclonic-Astatic Epilepsy, Landau-Kleffner, and Continuous Spike Wave in Sleep all occur mostly after the first year through about 7 to 8 years of age although CSWS may have its onset after the first decade.

Gender

For epilepsy overall, there does not seem to be much difference between boys and girls.[41,42] This lack of a gender difference overall, however, belies some rather distinct differences within in specific forms of epilepsy. For example, one of the most common forms of idiopathic generalized epilepsy, childhood absence, occur about twice as frequently in girls compared with boys.[4]

For the catastrophic epilepsies, there is some tendency for studies to report a predominance of boys relative to girls for several of the syndromes. For example, for West syndrome, 10/13 cases reported in Iceland [30] and 38/57 cases reported in Sweden (Sidenvall) were boys.[31] Lennox-Gastaut has also been associated with a predominance of boys[36] as have Dravet syndrome,[45] Landau-Kleffner syndrome,[4] and MAE[13] Ohtahara syndrome is very rare. To the extent it has been studied, there does not appear to be a tendency for boys or girls to be more susceptible than the other.[14]

Many of these encephalopathic conditions are secondary to known insults or other conditions each of which has its own epidemiology. Each of these symptomatic causes may tend to affect preferentially people of one gender or another. On the other hand, syndromes such as Dravet, Landau-Kleffner and MAE typically, if not always, occur in children who were previously neurologically and developmentally normal and in whom evaluations fail to reveal any explanation for their disorders.

Etiology

Many of the catastrophic epilepsies are often associated with and secondary to identified etiological factors. Because these are disorders that occur in infancy and early childhood, genetic as well as pre- and perinatal causes are particularly prevalent. Etiologic factors include a variety of brain malformations. These are often cortical; however not exclusively. Neurocutaneous syndromes (especially tuberous sclerosis), pre- and perinatal hypoxia and hemorrhage, and a variety of chromosomal disorders and genetic syndromes a common antecendants. Postnatal causes, particularly infections, are other potential causes but considerably less common, at least in developed countries. The specific findings vary between syndromes.

West syndrome

This disorder may be cryptogenic in about a fifth to a third of cases. In the Swedish series of 57 cases of West syndrome, 43 (75%) of the cases had recognizable symptomatic causes including four with neurocutaneous disorders, eight with various types of malformations of cortical development, and five with chromosomal disorders.[31] Pre- or perinatal asphyxia with or without evidence of intraventricular hemorrhage is another cause of West syndrome. Tuberous sclerosis receives considerable attention as a cause of West syndrome both because the possibility for surgical intervention and because of some evidence that West syndrome in this selected setting may be best treated with vigabatrin, a drug not available in the US but which has been approved in many other countries.

Lennox-Gastaut

This syndrome often develops in children who have had West syndrome and is associated with similar etiological factors.[35,36,38,39] As with West syndrome, however, a quarter to a third of the cases of Lennox-Gastaut are considered cryptogenic. That is there is no identified underlying cause and the infant or child was apparently 'normal' prior to the onset of seizures.

Myoclonic-astatic epilepsy

MAE is typically not associated with an identifiable symptomatic cause.[13] In part for this reason as well as the high proportion with family history of epilepsy, it has been grouped with the idiopathic epilepsies in the past and now again in the proposed update to the classification of the epilepsies.[7] In some cases, it may be part of the GEFS+ spectrum.[46]

Dravet syndrome

This disorder always occurs in infants who were previously considered neurologically and developmentally normal. It has increasingly become a prime example of a channelopathy, with many cases demonstrating severe functional mutations in the SCN1A gene coding for the alpha1 subunit of the sodium channel.[17,18,20] Other findings have implicated SCN1B as well.[47] This syndrome has also been considered part of the GEFS+ spectrum.[48]

Landau-Kleffner and CSWS

Landau-Kleffner syndrome occurs in children who were previously neurologically and developmentally normal. Some have speculated regarding the apparent continuum between this disorder and benign rolandic epilepsy with centro-temporal spikes.[22,23] The related phenonmenon, CSWS, is sometimes seen in association with pre- or perinatal insults, particularly certain types of cortical malformations as well as vascular lesions.[49,50]

Prognosis

In general, the prognosis of these disorders is extremely poor with respect to seizure outcomes, intellectual development, and mortality.

Seizure and intellectual outcomes

The catastrophic epilepsies, although accounting for only 10–15% of childhood onset epilepsy, account for half or more of all children with intractable epilepsy.[51] The absolute risk of becoming intractable depends on the definition of intractability. In a preliminary report from one prospective study, the risk was approximately 70% when failure of two appropriate antiepileptic drugs was considered and only somewhat less when more stringent criteria were applied.[52] Even within the catastrophic epilepsies, the risk of developing intractable seizures and the likelihood of entering a later remission depend on the specific type of epilepsy and, when applicable, whether there is an underlying symptomatic cause.

West Syndrome

The cryptogenic form of West syndrome is generally more likely to respond well to treatment with a complete cessation of seizures. Whether because of that or because there are no obvious structural abnormalities or other insults to the brain, these children also have the greatest likelihood of enjoying a

relatively normal development.[30,31,33,39] When associated with a symptomatic cause, the outcomes are very poor, with lasting seizure intractability and moderate to severe mental retardation being the rule. West syndrome with its characteristic epileptic spasms may remit for a period and then reoccur.[53] More typically, West syndrome evolves into Lennox-Gastaut syndrome or a focal epilepsy.

Whether the intellectual deficits are a result of the epilepsy or are an indication of the severity of the underlying insult is not entirely clear. A recent practice parameter from the American Academy of Neurology concluded that there was insufficient evidence to conclude that successful suppression of seizures resulted in substantially better cognitive and developmental outcomes.[54] The recent report from the UKISS study, a UK-wide randomized trial for treatment of infantile spasms and published since the practice parameter, found evidence suggesting the control of seizure was not necessarily all that was needed to secure better developmental outcomes. In that study, children with cryptogenic West syndrome responded equally well in terms of seizure control to ACTH and vigabatrin. Developmental outcomes were significantly better, however, in children who received ACTH.[55]

Lennox-Gastaut

Although this syndrome is often cryptogenic, it has an even more sinister outlook than West syndrome. Regardless of the presence or absence of a symptomatic cause, children with this syndrome rarely experience complete, lasting seizure remission, although it is not uncommon for the seizure occurrence to fluctuate. Developmental and intellectual outcomes in Lennox-Gastaut may be initially normal but are rarely so after several years.[56,57]

Myoclonic-astatic epilepsy

When considering the outcomes associated with MAE, it becomes less clear that this is a single entity.[13] Two groups distinguish themselves. In one form, seizures remit after a few years and development is fairly, if not completely normal. In the other, seizures are intractable and development and cognition are moderately to severely impaired.

Ohtahara and EME

These have extremely poor outcomes on all counts often because of the nature of the underlying cause of the epilepsy. Remission let alone normal intellectual outcomes are virtually never described. Dravet syndrome is similarly described as nonremitting and associated with severe intellectual disorders .

Landau-Kleffner and CSWS

Seizures tend to occur infrequently and generally remit. They are not the predominate concern. The language and other cognitive disturbances that develop after the onset of these disorders can be minimal but tends to be significant.[59–61]

Mortality

Almost all the excess mortality risk observed in children with epilepsy occurs in children with one of the catastrophic epilepsies or with severe neurological involvement, regardless of the type of epilepsy. In almost all cases, the death is due to the underlying cause of the seizures. Deaths due to seizures themselves are exceeding rare. In a US study, 13 deaths were observed in a cohort of 613 children. Eleven of the deaths occurred in children with catastrophic epilepsies.[62] Ten of the deaths were due to the underlying cause of the epilepsy and one was a sudden unexpected death (SUDEP) in a child with Dravet syndrome. In three population- or community-based studies (including the US study mentioned above), a total of 48 deaths were observed in 1777 children followed for a total of more than 15,000 person-years.[62–64] Only three deaths in this combined series were due to the occurrence of seizures, and 32 (67%) of the deaths occurred in the 10–15% of children with either catastrophic epilepsies or severe neurological impairment secondary to a symptomatic cause.

Table 26.2 provides a summary of some of the key epidemiological features of the syndromes discussed above.

Treatment options

By definition, many children with catastrophic epilepsies do not respond well to standard pharmacological therapies. Relatively small studies, some randomized, have provided a basis for selection or avoidance of specific drugs for specific syndromes. For example, lamotrigine may exacerbate seizures in Dravet syndrome[65] while being reasonably effective for Lennox-Gastaut.[66,67] West syndrome associated with tuberous sclerosis may respond better to vigabatrin than to ACTH, the generally preferred first line treatment for this condition.[54]

Surgical therapies, including stimulation devices, have been used in selective cases. In general, epilepsies with cryptogenic (possibly idiopathic) etiologies such as Dravet and MAE or that are due to progressive degenerative encephalopathic diseases are inappropriate for resective surgery. The greatest experience has been in the context of children whose epilepsy is secondary to identifiable and resectable lesions. Many of these catastrophic epilepsies are secondary to diffuse or multifocal lesions; however, they often limit the use of surgery in such cases. Callosotomies have been, and in places continue to be, used for Lennox-Gastaut syndrome.[68]

Vagal nerve stimulation has been used with guarded success in individuals with the Lennox-Gastaut and occasionally other severe generalized epilepsies.[69–71]

Summary

The catastrophic epilepsies occur at a very low frequency in the population overall and account for a small minority of cases of epilepsy. Their initial onset is concentrated in infants and young children and represent about 10–15% of childhood onset epilepsy. They account for half or more of all intractable epilepsy in children and about two-thirds of deaths occurring in association with epilepsy in children. Some of these epilepsies can occur in the absence of an identifiable preceding insult or conditions, and some may possibly represent the severe end of the spectrum of idiopathic epilepsies. Effective treatments for these conditions are largely lacking although, in selected cases, certain pharmacologic therapies as well as surgery may prove relatively beneficial. This is a group of epilepsies for which effective intervention could provide tremendous benefits by preventing life-long seizures, disability, and dependence.

Table 26.2 Summary of key epidemiological features of the more common and better known forms of catastrophic generalized epilepsy

	Proportion of pediatric epilepsy*	Typical age at onset	Gender	Etiology	Seizure outcome	Intellectual outcome
Ohtahara	<0.5% pediatric epilepsy	Neonatal – 2–3 months	No clear gender difference	Almost always symptomatic	Uniformly poor	Uniformly poor
EME	<0.5%	Neonatal – 2–3 months	No clear gender difference	Almost always symptomatic	Uniformly poor	Uniformly poor
West	2–3%	3–12 months	Boys usually more often than girls (studies vary)	1/4–1/3 cryptogenic	Variable – cryptogenic: can be good; symptomatic: uniformly poor	Tends to parallel seizure outcome
Dravet	<0.5%	<1 year	Boys maybe more often than girls	Channelopathy in most cases	Uniformly poor	Uniformly poor
MAE	1–2%	1–6 years	Boys more often than girls	Typically cryptogenic/idiopathic	Varies – either excellent or intractable	Intellectual outcome tends to parallel seizure outcome
Lennox-Gastaut	1–3%	1–7 years	Boys slightly more often than girls	1/3 cryptogenic	Uniformly poor	Uniformly poor
Landau-Kleffner	<0.5%	2–8 years	Boys more often than girls	Typically cryptogenic	Good, seizures usually remit	Variable, mild to significant impairments persist
CSWS	<0.5%	2 months –12 years	Boys more often than girls	Cryptogenic or symptomatic	Good, seizures usually remit	Variable, mild to significant impairments persist

* Estimates are based on citations throughout the literature. They should be interpreted with caution because the basis of these figures is not always sufficient for precise estimation of such rare disorders.

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27 Genetic factors contributing to medically intractable epilepsy

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Summary

- Medically intractable epilepsy may have genetic causes, mediated by pharmacogenetics or disease-related genetic effects.
- Two possible pharmacogenetic effects include overexpression of drug transporters and altered drug targets.
- Certain genetic epilepsy syndromes are characterized by medical intractability, although the relationship between phenotype and genotype is often complex.

Introduction

There is growing evidence that genetic effects contribute to medical intractability in epilepsy. Genetics can play a role in altering the pharmacology of an antiepileptic medication, and pharmacogenetics is the study of how genetic variation can influence individual drug response. In addition, genetics can play a role in the disease process itself. In some genetic forms of epilepsy, medical intractability is an inherent feature of the phenotype. To simplify the subsequent discussion, biological mechanisms of drug resistance will be grouped into two broad categories: drug-related (tolerance, ineffective mechanism, ineffective delivery, altered drug targets) and disease-related (etiology, progression/severity, altered neuronal networks).

Pharmacogenetics

Pharmacokinetics encompasses drug absorption, distribution, target interaction, metabolism, and excretion. At each step genetic variation has the potential to alter drug responsiveness. Drug resistance may result from decreased absorption or distribution, altered drug–target interactions, or increased metabolism and excretion. Medically intractable epilepsy patients are typically unresponsive to multiple antiepileptic drugs regardless of the drug's mechanism of action, suggesting that drug resistance is nonspecific, or at least not restricted to a single mechanism of action.

Altered metabolism and clearance

Historically, the metabolism of most drugs, including many antiepileptic drugs (AEDs), is classified into two pathways. Phase I reactions involve the additional of a functional group, through oxidation, reduction, and hydrolysis, which can be used as a site of conjugation in phase II reactions, involving acetylation, glucuronidation, sulfation, and methylation. In fact, phase II reactions can occur before or without phase I reactions. The P450 enzymes, a superfamily of microsomal drug-metabolizing enzymes, catalyze phase I reactions. Phenytoin is primarily metabolized by the polymorphic P450 CYP2C9 isoform with a minor contribution from CYP2C19. DNA variations in the genes coding for these enzymes can influence drug response by affecting metabolism. For instance, polymorphic variants that result in high enzymatic activity can lead to treatment failure due to increased drug metabolism and inadequate drug levels.

DNA variations (alleles or polymorphisms) have been associated with altered metabolism of several common antiepileptic medications. The CYP2C9*2 and CYP2C9*3 allelic variants show significantly reduced activity compared to the wild-type (normal) CYP2C9*1 allele.[1,2] The presence of an allelic variant correlates with the required maintenance dose of antiepileptic medication, in that, for equal serum levels, individuals with at least one mutant CYP2C9 allele require 30% less phenytoin than those individuals homozygous for the wild-type allele.[3] This pharmacogenetic effect on metabolism is not likely to be a significant contributor to medically intractable epilepsy, as AED dose would be adjusted to compensate for inadequate serum levels, in clinical practice.

Impaired central nervous system penetration

Overexpression of drug transport proteins

Medical intractability may also result from inadequate delivery of drug to the brain. There is mounting evidence for the upregulation of drug transport molecules in human epilepsy. This upregulation may be acquired (e.g., a consequence of repeated seizures) or inherited (e.g., functional variants of genes encoding drug transport proteins). Several genes have been identified that encode drug efflux pump proteins, including multidrug resistance genes MDR1 and MDR2, and the multidrug resistance-associated protein family, MRP1-7. The most well-studied example is the MDR1 gene product, P-glycoprotein, also known as the ATP-binding cassette subfamily B member 1 (ABCB1) transporter. Both MDR1 and several MRPs are expressed at the blood–brain barrier and act as pumps to export molecules to the vascular space away from neurons. Several AEDs are transported by MDR1 or MRPs.[4] Drug transporters are upregulated in human epilepsy, and this upregulation is associated with medical intractability.[5,6]

Interestingly, this overexpression of drug transporters appears to be localized to the seizure focus.[7] While appropriate brain tissue is difficult to obtain for human controls (drug-responsive epilepsy patients do not typically present for epilepsy surgery), experiments in a rat model of temporal lobe epilepsy (TLE) suggest that P-glycoprotein expression is increased in animals that are drug-resistant compared to those that are drug-responsive.[8] It is proposed that overexpression of drug transport proteins leads to lower brain tissue drug concentrations, and this is supported by indirect evidence that in culture, cells expressing MDR1 have lower intracellular phenytoin concentrations than cells not expressing MDR1.[5]

Role of MDR1 gene polymorphisms

A polymorphism in exon 26 of the MDR1 gene (C3435T) has been associated with a functional change in intestinal expression and activity of P-glycoprotein in normal Caucasian volunteers; specifically the TT genotype produces lower levels of expression compared to the CC genotype.[9] This finding does not appear to hold for other ethnic populations.[10] In any event, over the last several years there has been a great effort to correlate the C3435T polymorphism with disease, but the results have been conflicting for epilepsy. An initial study found an association between the CC genotype and medically intractable epilepsy in a British population from London ($N = 315$).[11] A similar finding was reported in a study from Austria ($N = 210$) restricted to TLE patients using three different categories of drug-resistance,[12] as well as in a Taiwanese study ($N = 331$) using definitions closer to the original study.[13] However, the original study's finding could not be confirmed in an Australian cohort of nearly twice the size and identical inclusion criteria as the original study ($N = 609$).[14] Additional attempts to confirm the original study in a Scottish cohort ($N = 400$),[15] and a Korean epilepsy patient population ($N = 171$)[16] have been unsuccessful.

The C3435T polymorphism occurs in a noncoding, nonpromoter region of the gene and is therefore unlikely to be causative itself, but thought to be linked to the causative allele. Conflicting reports are common in case-control association studies of this kind and may be due to differences in study design, case definition, and population ethnicity and genetic background. In addition, multiple testing, ascertainment bias, and small sample sizes lacking statistical power often play a role. While overexpression of MDR1 appears to play a role in medically intractable epilepsy, the role of MDR1 polymorphisms in producing this overexpression is unclear. It is not clear if the functional effect of the C3435T polymorphism on duodenal MDR1 expression is also true of MDR1 expression at the blood–brain barrier. Further, it seems counterintuitive that a genetic polymorphism, presumably present in all cells, could explain the finding that MDR1 overexpression is localized to the epileptic focus.

Role of other drug transport proteins

Other drug transporter proteins that may play a role in medically refractory epilepsy include MRP1,[17–19] MRP2,[17,19,20] breast cancer resistance protein (BCRP),[21,22] and major vault protein (MVP).[17,23] Increased expression of P-glycoprotein, MRP1, MRP2, and MVP was observed in surgical specimens of TLE patients with hippocampal sclerosis (HS), compared to TLE patients without HS and normal autopsy controls.[17] In another study, P-glycoprotein, BCRP, and MVP were found to colocalize on vascular endothelium in epileptogenic brain tissue.[21] This coexistent overexpression of several multidrug transporter proteins in epileptic brain tissue raises the question of whether these proteins are actually increased in response to seizures, as opposed to being the cause of drug resistance. Regional overexpression of drug transporters may serve as a protective mechanism in response to transient blood–brain barrier opening during seizures, for instance. Experimentally-induced seizures can produce overexpression of P-glycoprotein in animal models,[24,25] indicating that upregulation can be acquired as well as inherited. Clearly, much work needs to be done to clarify the role of drug transporter genes in medically intractable epilepsy.

Altered drug targets

Another possible mechanism for medical intractability is altered targets of AED action. AED targets can be divided into three broad categories: 1) voltage-gated ion channels, 2) proteins involved in synaptic inhibition (e.g., enhancing GABA neurotransmission), and 3) proteins involved in synaptic excitation (e.g., inhibiting glutamate receptors).[26] Clearly, a particular AED can have more than one target, and there are likely to be other targets that do not fall into the above categories.

Polymorphisms in genes encoding AED targets may affect drug response by altering target function, a pharmacodynamic effect. In one study the effect of carbamazepine was enhanced in mutated neuronal nicotinic acetylcholine receptor subunits (a mutation observed in autosomal dominant nocturnal frontal lobe epilepsy, which is typically responsive to carbamazepine) compared to wild-type subunits.[27] In another study, the sensitivity to phenytoin was reduced in neurons expressing a mutant voltage-sensitive sodium channel (VSSC) beta-1 subunit (a mutation associated with generalized epilepsy with febrile seizures plus (GEFS+)) compared to those expressing normal beta-1 subunits.[28] Similarly, a splice-donor site polymorphism in the VSCC alpha-1 subunit (SCN1A) was associated with maximally tolerated doses of phenytoin and carbamazepine.[29] These results await replication in larger, independent cohorts, but they provide preliminary evidence that altered drug targets can contribute to medical intractability.

In addition to gene mutations, AED drug targets can develop 'acquired' alterations, perhaps as a result of seizures. For example, there is reduced carbamazepine (CBZ) sensitivity in hippocampal CA1 neurons compared to neocortical neurons, in patients with TLE and HS.[30] Further work suggests a loss of effect of carbamazepine on VSSCs in ten patients with CBZ-resistant epilepsy compared to two patients with CBZ-responsive epilepsy.[31] Additional evidence suggests that changes in the distribution and density of sodium channels is related to epileptogenicity.[32] In addition to changes in voltage-sensitive ion channels, there is evidence that GABA-A receptors are altered in human TLE and post-status epilepticus animal models of TLE, and that these changes are associated with receptor pharmacology and drug resistance.[33,34] Genetic polymorphisms in the promoter regions of these genes play a potential role in seizure-induced receptor changes through effects on transcriptional regulation.

While there is some evidence for a role of altered drug targets in medically intractable epilepsy, the overall importance of

this mechanism is unclear. It is interesting that many of the genes identified as epilepsy-causing genes are also the targets of antiepileptic medications. Although not a major contributor, variants of SCN1A have been associated with increased risk for development of idiopathic generalized epilepsy.[35] This suggests that mutations in a single gene can increase the risk for development of both epilepsy and drug-resistance in epilepsy.

Gene–gene interactions

The pharmacogenetics of medically intractable epilepsy are clearly complex and likely involve multiple genes and gene–gene interactions. For example, drug transporter genes are regulated by other genes, as well as the environment.[36] In particular, transcription of MDR1 is regulated by a ligand-activated nuclear receptor, the pregnane X receptor (PXR), which is activated by many commonly prescribed medications.[37] It is unclear whether this upregulation is neuroprotective or whether it contributes to epileptogenesis, drug resistance, or both. The above proposed pharmacogenetic mechanisms are not mutually exclusive, nor are they the only possible pharmacogenetic explanations for drug resistance in epilepsy. As more and more candidate genes are identified, attempts to tease apart the specific contribution of each gene would benefit from prospective data collection of drug dose, concomitant medications, serum levels, efficacy, and adverse effects.

Disease genetics

Certain epilepsy syndromes are characterized by medical intractability, the prime examples being the progressive myoclonic epilepsies, the malformations of cortical development, and the epileptic encephalopathies (e.g., Lennox-Gastaut Syndrome, Othara Syndrome, West Syndrome). Many of these disorders are now known to be caused by genetic defects. In many cases it is not clear how the genetic defect leads to epilepsy or medical intractability, but it is clear that there are many genetic pathways to the common final phenotype of medically intractable epilepsy.

Progressive myoclonic epilepsies

The progressive myoclonic epilepsies (PMEs) are characterized by intractability, inherent in their progressive nature. Five disorders are typically included in this group: Unverricht-Lundborg disease, Lafora body disease, neuronal ceroid lipofuscinoses, sialidosis, and myoclonic epilepsy with ragged red fibers. Many of the genetic defects underlying these disorders have been identified, although the details of their relationship to epilepsy pathogenesis remain unclear.

Unverricht-Lundborg disease is an autosomal recessive disorder characterized by stimulus-sensitive myoclonic and generalized tonic-clonic seizures, as well as progressive ataxia, tremor, dysarthria, and cognitive decline. The disease is due to mutations in EPMI on chromosome 21q22, which encodes the protein cystatin B (CSTB), a protease inhibitor.[38] The most common mutation contains an unstable GC-rich dodecamer repeat in the promotor region, leading to reduced amounts of cystatin B. Wild-type alleles contain 2–3 tandem copies of this dodecamer repeat, while individuals with Unverricht-Lundborg disease have 30–150 copies. There is no clear correlation between the number of repeats and the severity of disease or age of onset. Cystatin B is thought to play a neuroprotective role, inhibiting neuronal apoptosis.

Lafora body disease is an autosomal recessive disorder with similar clinical features to Unverricht-Lundborg disease, onset between 6 and 22 years of age of myoclonic and generalized tonic-clonic seizures and progressive cognitive decline. It is characterized by the formation of Lafora bodies in brain, skin, liver, cardiac, and skeletal muscle. Two genes have been identified to date, EPM2A which encodes the protein laforin,[39] and EPM2B which encodes a protein called malin.[40] Laforin is thought to prevent accumulation of polyglucosans.

The neuronal ceroid lipofuscinoses (NCL) are a group of autosomal recessive lysosomal storage disorders, although adult-onset NCL (also known as Kufs disease) in some families shows an autosomal dominant pattern of inheritance. NCL is characterized by myoclonic seizures, visual loss, progressive cognitive decline, and motor abnormalities. To date, eight different forms have been identified, CLN1 to CLN8. Genes have been identified for nearly all the different forms, and most are lysosomal proteins of unknown function.

Sialidosis, also known as 'cherry-red spot myoclonus syndrome' is another autosomal recessive lysosomal storage disorder. Sialidosis types I and II are caused by a mutation in the gene encoding neuramidase (NEU1). Over 30 mutations have been described in the sialidase gene with clinical severity roughly correlating with genotype. Those with frameshift mutations or mutations resulting in premature truncation of protein generally have a severe form of sialidosis.[41]

Myoclonic epilepsy with ragged red fibers (MERRF) has variable clinical presentations but is typically characterized by myoclonic and generalized tonic-clonic seizures, ataxia, deafness, optic atrophy, and ragged red fibers on muscle biopsy. Mutations in multiple genes have been associated with this syndrome, but the most common defect is in mitochondrial DNA, in the gene encoding transfer RNA for lysine (MTTK).[42,43] These mutations cause a global defect in mitochondrial protein synthesis and subsequently a wide range of respiratory chain abnormalities.

It is striking that such varied molecular defects, from glycogen storage to energy production, can each result in myoclonic seizures. In general terms, these genetic defects produce irreversible or progressive neuronal damage which in turn produces multiple clinical manifestations, one of which is epilepsy. They differ in this respect from 'idiopathic' epilepsies with myoclonic seizures, such as juvenile myoclonic epilepsy, which are typically drug responsive and not associated with neurological deficits. While many consider the idiopathic epilepsies to also be genetic, an important difference may lie in the severity of the genetic defects. The idiopathic epilepsies are considered to be polygenic, due to multiple 'small' defects in several genes (each alone insufficient to produce disease), as opposed to the PMEs which are often the result of 'major' mutations in single genes (each alone sufficient to produce disease).

Malformations of cortical development

Malformations of cortical development (MCDs) are a frequent cause of medically intractable epilepsy in both adults and children. There is evidence that overexpression of drug transporters plays a role in focal cortical dysplasia.[7,44] In addition,

a number of genes have been described associated with malformations of cortical development, involving neuronal proliferation and/or survival, neuronal migration, and cortical organization.[45,46] The list of genes associated with MCDs is ever growing, as evidenced by a recent report of a group of Amish children with cortical dysplasia and intractable focal epilepsy in which mutations in the gene encoding contactin-associated protein-like 2 (CASPR2) were discovered, although the precise of role of CASPR2 in human cortex is unknown.[47] Active research in this area provides insight into mechanisms of epileptogenesis as well as the genetics of brain development.[45,46]

GEFS+/SMEI familial syndromes (SCN1A mutations)

Neuronal voltage-sensitive sodium channels play an important role in several human genetic epilepsy syndromes. Mutations in the alpha-1 subunit have been associated with a spectrum of disorders thought to form a continuum, from the relatively benign generalized epilepsy with febrile seizures plus (GEFS+) to the intractable severe myoclonic epilepsy of infancy (SMEI). Many of the mutations associated with SMEI produce nonfunctional channels (nonsense or frameshift mutations), as opposed to the predominantly missense mutations seen in GEFS+. This suggests that the ultimate functional consequence of these mutations is a loss of sodium channel function. These disorders demonstrate an overall correlation between severity of phenotype and genotype in that the most severely affected individuals appear to have the most severe genetic defects. Within families, however, genotype–phenotype correlations are complicated by incomplete penetrance and variable expressivity.[48] Approximately 5% of SMEI patients with identified mutations have inherited SCN1A missense mutations, and their family members typically have mild GEFS+ phenotypes.[49]

Conclusion

Drug resistance in epilepsy is clearly a complex phenomenon that likely involves multiple mechanisms, both genetic and non-genetic. Among pharmacogenetic mechanisms there is evidence for a role of multidrug transporter proteins, but the full extent of their involvement is not clear. Other mechanisms are likely to be important, such as altered drug targets. Intractability due to 'disease genetics,' as in the progressive myoclonic epilepsies and malformations of cortical development, may result from 'altered neuronal networks' as is hypothesized in TLE with HS, ultimately a very difficult hypothesis to prove. Regardless of the mechanism, medical intractability in epilepsy is clearly associated with significant morbidity and mortality and as such, is an important area of research. Identifying genetic mechanisms for medically intractable epilepsy may provide improved methods of diagnosis and prognosis, as well as new targets for pharmacological treatment.

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28 Informed consent

FL Vale and S Benbadis

Introduction

'Every human being of adult years and sound mind has the right to determine what shall be done with his own body; and a surgeon who performs an operation without the patient's consent commits assault'.[1] Since 1914, the legal system established the principle of informed consent between physicians and patients in the medical practice.

Informed consent is a legal document that defines the patient–physician relationship in a legal and ethical (personal) way. Critical to the medical system as physicians are, informed consent is a necessary document that testifies for a process of communication and understanding. A basic understanding of this process is necessary for any treating physician.

Epilepsy is a chronic disease with specific and significant clinical and cultural connotations that require special understanding and evaluation. In particular, uncontrollable epilepsy can cause severe social limitations, decline in cognitive function and even the potential for sudden death. This disease can be as devastating as uncontrolled hypertension and diabetes for any individual, but unfortunately is less well understood in our society. Specifics to this process will be discussed in this chapter to allow a better understanding of the disease process and need for adequate communication during informed consent.

Basic process

The pinnacle of the patient–physician relationship is not better exemplified than by obtaining a thorough and clear informed consent. Physicians are medical and technical experts, while patients are concerned with their own personal values and life goals. Obtaining consent requires an effective exchange of ideas with the patient and (usually) with their closest family members. This requires good rapport, communication, and empathy. Trust has to be developed for a successful long-term relationship.

The basic element of informed consent takes into consideration the need to disclose and understand the medical plan and alternatives. Obtaining an informed consent assumes that the patient and/or surrogate has full capacity to make medical decisions, free from coercion and persuasions that will interfere from full authorization to perform the proposed treatment.[2]

Decision making has to take into consideration the patient's right and self-determination. Active participation in health care decisions is expected in the current situation. Education through an exchange of ideas is the only way to achieve success. The process of education involves direct communication and understanding of the social and family dynamics. Mutual respect, collaboration, and negotiation have to occur for a successful interaction.

The key point in this interaction requires a clear understanding of the procedure to be performed. Informed consent is a process of education that involves discussing the following:

(a) options and alternatives to the procedure
(b) details of the procedure
(c) risks and benefits of the procedure
(d) results, including 'quality of life' issues.

Not only do physicians have to discuss what surgical procedure is going to be performed, but it is ethically necessary to educate the patient about possible alternatives to the surgical recommendation. It is also necessary to discuss success rates and complications as well as the consequences of declining or delaying the recommended procedure. Failure to cover these aspects could potentially be viewed as misinformation and result in a strain of the patient–physician relationship, with possible legal consequences. After a reasonable discussion, details of the selected procedure should be covered. Visual clues such as diagrams, physical models, and even physical description should be used for the sake of simplicity and clarity. All possible complications should be discussed in detail, including potentially life-threatening situations and rare events. Short- and long-term results should be discussed in a clear and concise manner. There should not be a bias in the information given to the patient. Finally, clear documentation is necessary for adequate social and legal understanding.

From the patient's point of view consent means the following:

(a) patient's capacity to make a voluntary decision
(b) acknowledgement of understanding relevant information.

Failure to understand the illness and consequences of the intervention are common causes for misunderstanding and stress to the patient and family. In our experience, patients' personal expectations are critical and can cause a tremendous amount of concern and stress if not discussed prior to the intervention.

Decision-making should promote active patient participation. Through a thoughtful dialogue between patient and physician, patients and families can receive an education about their illnesses and options, which will result in a better understanding and comprehension of the procedure to be performed.

Why epilepsy surgery?

Epilepsy is a chronic disease with clear social and medical connotations. It is no different than treating severe hypertension or diabetes. It may be controlled with medical management and behavioral modifications (avoid lack of sleep and alcohol abuse, etc.), but by definition the risk of seizures is always present and potentially dangerous, especially in cases of intractable epilepsy. In the medical community, surgery to treat a chronic medical disease is not common, and as a result not well established outside a small group of experts, which may explained the delay in referral to comprehensive epilepsy centers.[3] Brain surgery is sometimes viewed as an aggressive, usually life-saving procedure for diseases such as brain tumors, ruptured brain aneurysms, etc. It should not be forgotten that uncontrollable seizures can be potentially life threatening and more commonly can be devastating for the individual personal and social development. Epilepsy surgery performed by an experienced and well-trained neurosurgeon is a safe and successful intervention to control seizures. Unfortunately, it continues to be misunderstood in the medical community. Ethically, a neurologist should offer and discuss all potential alternatives to the affected individual. Currently, by the time a patient is sent to a center for evaluation, many years of uncontrolled seizures will have taken a toll on the functional abilities of this individual, medically and socially. The patient may or may not accept the clinical situation, but the chronic nature of the disease has most likely changed the overall performance of this person with a resultant decrease in quality of life issues.

Despite physical and social limitations caused by severe and intractable epilepsy, most patients have no major structural abnormalities on magnetic resonance imaging (MRI) and no physical stigmata to separate this individual from any other member of society. Thus, brain surgery to control epilepsy is viewed sometimes as a drastic maneuver and involves major decision making from the part of the patient and/or family. Psychosocial issues and lack of social support can also adversely affect patient–physician relationship. So, why offer epilepsy surgery?

To understand surgery, the patient must understand the current treatment and medical limitations from drug therapy. Surgical intervention should be offered when benefits outweighs the risks. Surgery should be offered in the context of medical failure such lack of seizure control and/or limiting side effect. Surgery may or may not result in complete medical (drug) withdrawal, but most likely offer seizure control with possible gain in independence in their role in society. Options should be discussed by the epileptologist prior to referral to a neurosurgeon. The surgeon should continue to educate the patient and their family without any bias toward the surgery. Understanding each individual psychosocial issue will help to establish good rapport and communication. A fair and clear conversation with open-ended questions will help develop trust in the relationship.

Surgery for epilepsy is an elective procedure. 'Elective' means that the patient can decide when this procedure can be performed. The local environment, family situation, and support play a key role in the decision-making process. Achieving seizure control is the goal. It is ethically necessary to discuss and offer this option to the patient that suffers from intractable epilepsy. If a patient has not responded well to medical therapy, it is the duty of the neurologist to discuss alternatives of treatment, such as surgery. In that case, referral to an epilepsy center by the local physician should be performed.

For example, sudden death in epilepsy is a known entity in intractable epilepsy and represents a much higher risk for the poorly controlled patient than the risk of surgical intervention. In fact there are more risks associated with intractable seizures than with epilepsy surgery. Temporal lobe epilepsy is a typical example of surgery for epilepsy. This represents a clear situation where benefits outweigh risks. In the case of mesial temporal lobe sclerosis, the success rate is as high as 80% for seizure control, which means that it offers better clinical outcome than any kind of medical intervention after initial drug failure. If drug failure is well documented, the chances of seizure control are less than 20% for polypharmacy,[4] and surgery may become the most effective approach. It is ethically correct in this situation to discuss this alternative early in the treatment plan for this group of affected individuals.

When mental capacity is in doubt

For specific clinical situations where mental (cognitive) capacity is limited, this will require a different approach to the problem. Mental retardation, severe psychiatric problems (severe depression, etc.), dementia, legally underage, etc, are conditions that require the appointment of a legal guardian to serve in the best interests of the patient. Nevertheless, the clear lack of decisional capacity is not an excuse to alienate the affected person from involvement in the decision-making process. Although the patient is not capable of giving a full and valid informed consent to surgery, he or she is able to give assent or dissent to the treatment being offered. The surrogate (usually the closest family member) should have a clear understanding of the patient's healthcare preferences, goals, and values, as well as the courage to uphold the decision despite any potential problems or misgivings.[5]

In situations where the patient lacks decisional capacity and yet is able to participate in the decision process at limited level, physicians should engage the individual in the process of decision-making. Physicians' efforts to educate, to determine understanding, and to solicit values, preferences, and goals should be targeted at the family and patient together as 'one voice'.

Epilepsy surgery in this situation is a valuable alternative for patients with intractable epilepsy, even in the case where total seizure control is not expected. Even though 'cure' might not be a feasible option, the potential for decrease in seizure frequency and, as a result, better quality of life should be considered by the surrogate as a reasonable alternative. In any case, surgery is an option that should be discussed when medical treatment offers a limited response.

Conclusions

Epilepsy surgery is a well-established alternative for the control of epilepsy, but unfortunately is underutilized and misunderstood in society as well as the medical community. The cognitive limitations that may accompany a severe and

intractable seizure disorder may interfere with the necessary skills for social development and understanding of the disease process. Extensive education and communication is required for decision-making. Involvement of the family in the education process is sometimes necessary for adequate communication. This process involves mutual trust and understanding. From the ethical perspective, disclosure and education are a requisite for the exercise of patients' independence in decision-making prior to any surgical intervention.

Surgery, despite the invasiveness of the procedure, is a clear alternative for patients that suffer from medically intractable epilepsy. Ethically it is necessary to educate and inform the patient and family members of the potentially hazardous alternatives and options regarding this disease. In summary, informed consent is a frank and open dialogue, permitting the physician to give the patient and/or family enough detailed information to make a decision regarding a specific treatment and alternatives.

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29 Epilepsy surgery: access, costs, and quality of life

MG Campos and S Wiebe

Introduction

Epilepsy is a common, serious, chronic neurological condition with high prevalence worldwide, but particularly in developing countries. Data suggest that 85% of the 50 million people with epilepsy worldwide live in the developing world.[1–3] The chronicity of epilepsy results in significant economic costs, especially in cases of medically refractory epilepsy, which requires continued symptomatic treatment. In addition, people's ability to work and develop vocationally can be affected, contributing to a significant social and psychological burden.[4,5] The advent of economic and cost analyses has resulted in a plethora of publications in this regard. However, there has been substantial variability in methodology. For example, the definition of cost can take on many different meanings, including that of a fee or tariff. Additionally, costs can be considered from many different perspectives, such as a third-party payer, society, the individual, or the healthcare system. From a purely economic viewpoint, costs should be defined as 'opportunity cost', i.e., the value of time or any other element in its highest value used in a cost of illness study. For the purpose of studies comparing different therapeutic alternatives, opportunity cost refers to the benefits lost because the next best alternative was not selected.

Confusion in terminology and variability in methods have fostered the creation of recommendations for adopting a 'reference case' type of analysis in economic evaluations, in which a standard set of principles is applied to the analyses, allowing for meaningful comparisons across studies.[4,6] These recommendations stipulate that costs should be expressed as a value of the goods, services, and other resources that are consumed in the provision of an intervention or dealing with other current and future consequences linked to it. These costs are often expressed in monetary terms. Even if a 'reference case' is not adopted in cost analyses, all studies should clearly describe the definition and perspective of the costs considered. Throughout this chapter we will use the term cost to refer to the fees related to epilepsy surgery, which is the most commonly reported metric, and not necessarily to the opportunity cost.

Because economic factors play an important role in healthcare worldwide,[7] it is important to analyze the main factors that influence costs of and access to epilepsy surgery, and some of the reasons behind differences in costs in various countries.

Determining the cost of epilepsy surgery

Although the effectiveness and safety of epilepsy surgery has a long tradition and has been established through various avenues, it remains underutilized. Several reasons underlie this phenomenon, including physicians' and patients' perceptions of its invasiveness and irreversibility, therefore making it a last-resort therapy.[8] In many parts of the world, the determining factor is a lack of physical resources and of expertise for the management of complex cases requiring presurgical evaluation with intracranial EEG.

The importance of defining the perspective from which costs are calculated is illustrated by the existing studies on the cost of epilepsy surgery. In many developed countries, patients rarely pay directly for treatments and instead receive healthcare that is paid for by national insurance schemes. From the patients' perspective, healthcare services cost little or nothing at the point of delivery, other than any user-charges or copayments that are made for drugs or hospital services. Consequently, economic analyses in North America and in most European countries often confine their analyses to the perspective of the major health insurer.[9–14] This contrasts with the organization of health services in most developing countries, where patients often pay for most or all of their epilepsy treatment at the point of delivery.[15,16] In these countries, it may be appropriate to consider a broader perspective that includes patient payments. From any perspective used, costs and savings are categorized in terms of their relationship to treatment. The most widely used classification of costs distinguishes between direct costs, indirect costs (productivity costs), and intangible costs.[17]

Direct costs

Direct costs and savings are those that arise in direct relation to an illness and its treatment. These include medical costs such as outpatient appointments, antiepileptic drugs (AEDs), hospital admissions, laboratory investigations, diagnostic procedures, surgical treatment, etc. Direct non-medical costs include payments required when patients receive treatment, such as transportation or childcare. Patients may also incur substantial expenditure traveling to clinics when services are concentrated in major cities, which is the typical pattern in the developing world. Other non-medical direct costs in epilepsy

patients include rehabilitation, vocational training, social services, volunteer services, etc. Direct costs and savings are easily understood in terms of their monetary value. Economic evaluations use the prices and charges made for these goods and services when calculating the overall cost of a treatment or program. In the USA, patients with uncontrolled epilepsy incurred direct costs of nearly $10,000 a year, while similar costs in patients with controlled epilepsy reached only about $2,000 a year.[18] These figures did not include direct non-medical costs, which in some countries can be substantial.

Indirect costs ('productivity costs')

Epilepsy can reduce productivity if patients perform less well at their jobs, take time off work, or become unemployed. Premature mortality can also be considered in terms of its effects on the workforce, as is the effect on productivity of caring for family members with epilepsy. These types of costs are typically referred to as indirect costs – a term that can create some confusion because of its different connotation in accounting, where it refers to overhead costs.

In most economic evaluations, productivity costs are estimated in terms of the average value of the work time missed. This process has its basis in the human capital method, which values a person's life in terms of future earnings.[19] This method has also been used to evaluate the effects of temporary illnesses on individuals' ability to do their job. For example, the cost of missing 10 days of work because of epilepsy would be valued as the equivalent of the loss of 10 days of average earnings for that individual worker.

Time is more difficult to value for the unemployed. For example, housework and childcare are important to the individuals concerned and also to the general economy, but such work is rarely paid for in a financial transaction. In the developing world, large numbers of people live in isolated and rural areas where work may also be unwaged. In these cases, either an arbitrary value is assigned, or 'shadow' pay rates are used – based on the prices charged for hiring workers to perform similar jobs.[3,20]

The human capital approach presents some problems. For example, older people typically have low indirect costs due to a shorter life expectancy, lower earnings, and lower expectancy of employment. Similarly, children's time is valued at a lower level for this reason. Nonetheless, the approach is practical, broadly used, and can be used if one acknowledges its limitations. Candidates for epilepsy surgery are most often school-age children or young adults, and the latter are often eligible to join the workforce. In the USA, the projected lifetime cost of epilepsy for an estimated 181,000 people with onset of epilepsy in 1995 is $11.1 billion, and the annual estimated cost for the approximately 2.3 million prevalent cases is $12.5 billion. Indirect costs account for 85% of the total costs and are highest in people with intractable epilepsy.[18]

Intangible costs

Intangible savings and costs pertain to the well-being associated with improved or worsening health, and their measurement is not straightforward. In chronic, socially stigmatized conditions such as epilepsy, intangible costs are likely to be significant. Unfortunately, no method of assessing the financial value of improved health and well-being in epilepsy has been agreed upon. Contingent valuation methods such as willingness to pay for a treatment or outcome can be used to estimate such costs from the patients' perspectives, but these techniques have not been widely used in healthcare.[3,21]

People with well-controlled epilepsy after surgery are more likely to be able to work and contribute to their personal and their society's wealth, thereby producing 'indirect' savings. Economic benefits may also accrue from the 'intangible' benefits of good health.

Cost in epilepsy surgery

Because the costs of presurgical evaluation and epilepsy surgery are highest at the outset, it is important to understand the time-course of costs incurred with various treatment modalities. Also, an assessment of direct, indirect, and intangible costs provides the necessary framework for assessing the costs of epilepsy surgery. The cost of intractable epilepsy is eight times higher than that of well-controlled epilepsy.[22,23] Twenty-five percent of patients comprising the more resistant epilepsy cases account for 79% of the total cost of incident cases.[18] Several studies have compared the costs of epilepsy surgery with those of medical treatment.[22,24–27] These studies demonstrate that, despite the high initial cost of presurgical evaluation and surgery, the benefits achieved in terms of clinical improvements and reduced requirements for medications and medical services outweigh the costs of surgery in the long term. A description of studies exploring the cost of epilepsy surgery follows.

A recent cost effectiveness study from France compared surgical and medical therapies in a 14-center prospective cohort of intractable patients with epilepsy who were candidates for resective surgery.[28] The mean cost of presurgical evaluation was €8,364 ($9,957) (25th, 75th percentiles = €3,286, €12,027). The mean cost of presurgical evaluation and surgery was €20,772 ($24,729) (25th, 75th percentile = €15,000, $25,310). An analysis of projected costs over several years concluded that epilepsy surgery became cost-effective within 9 years after surgery, i.e., surgery became a cheaper alternative to medical therapy. These results were based on direct costs only and on an assumption of seizure-free rates of 77% of patients at 2 years. Interestingly, these authors replicated the findings of an earlier Canadian study which found that, although the costs of epilepsy surgery were higher up front (during the first year), surgery became cheaper than medical therapy after 8.5 years because of averted costs of medical care due to the high rate of seizure-free patients with surgery.[24] In the USA, the estimated payback time for epilepsy surgery is approximately 6 years.[29] Whereas the Canadian study[24] comprised both intracranial and noninvasive presurgical evaluations, the USA figures apply particularly to noninvasive and uncomplicated temporal lobe resections. This figure is still germane because it is estimated that approximately 60% of all epilepsy surgeries needed in developing countries at this point require no intracranial or complex evaluation. Therefore, these data provide a strong support for establishing and expanding epilepsy surgery programs in developing countries. The cost difference in presurgical evaluation involving intracranial EEG versus that involving scalp recording is substantial.

A recent communication from the USA showed that the cost of patients requiring intracranial recordings ($72,032)

Table 29.1 Proportion of seizure-free patients treated with new AED and with surgery.

AED	Seizure-free*
VGB	5%
LTG	2–4%
TPM	10%
LEV	8%
PGB	5–17%
Surgery	58%

*Based on data from multicentre, placebo-controlled, add-on, randomized trials of new AEDs in pharmaco-resistant epilepsy (follow-up: 12 weeks), and one randomized trial of temporal lobe epilepsy surgery (follow-up:1 year).[54]

was almost twice that of those requiring only scalp recordings ($40,912) ($p < 0.01$).[29,30] In this study, seizure freedom was associated with a significant reduction in total healthcare costs from year one. By year two after evaluation, the total cost in seizure-free patients had declined to roughly half that of patients who continued to have seizures. This decline was due to a reduction in the number of inpatient admissions and AEDs prescribed, particularly the newer, more expensive medications (Table 29.1).[30] A few reports have compared the cost of epilepsy surgery between developed and developing countries. One such study compared the direct costs of epilepsy surgery programs in Colombia and Switzerland,[31] and showed that the average epilepsy surgery cost per patient in Colombia was a mere 5.5% of that in Switzerland. Thus, epilepsy surgery can be a relatively inexpensive and efficient treatment option for patients with epilepsy in developing countries.

Although empirical data are not available, it would appear that, in developing countries, epilepsy surgery may even be considered as an earlier therapeutic alternative for patients who cannot afford the lifetime costs of medical therapy. Some studies show that the costs (or fees) of epilepsy surgery vary by a factor of up to ten between developing and developed countries. For example, in the public healthcare system, epilepsy surgery without invasive investigations costs between $5,000 and $6,000 in Chile or Brazil,[32,33] and it may be even cheaper in Colombia or India.[7,31,34] The same surgical procedure can be 8–10 times more costly in the USA, and 6–8 times more costly in Germany.[35] The pertinent question at this point is, what explains such wide between-country variability in costs.

Why are costs different among countries?

To answer this question, we need to consider several variables that play a role in this discrepancy.

(a) *Price of instruments*: The cost (price) of instruments such as magnetic resonance imaging (MRI) and video-EEG equipment, before taxes, is similar at the place of origin (FOB price). However, the price of equipment at the place of destination varies due to a number of factors, such as transportation, insurance, or national taxes. However, these elements play a small role in the overall between-country price variation and do not fully explain it. On the other hand, the price of an examination using these technologies varies tremendously by country and within countries. For instance, the cost of an MRI in Chile is $350, whereas in Miami it is $3,438, i.e., ten times more costly. This difference could be explained because the examination in Miami incurs high overhead, salary, research, maintenance, or renewal expenses, and, no less important, the requirement of high profitability.

(b) *Drug prices*: These vary if we consider brand-name or generic drugs.[36] A comparison of the annual costs of brand name AEDs in Germany and Chile shows that almost all AEDs cost twice as much in Germany, but original valproic acid is more expensive in Chile, where it is also considered a first-line drug.[32] The reason is the different industry politics in merchandise between different continents.

(c) *Medical supplies and technology*: This is clearly the main factor underpinning the vast cost differences in epilepsy surgery between developed and developing countries. It reflects the elevated cost of high-end technologies, which are the gold standard in developed countries, but only exceptionally used in the average epilepsy surgery centers in developing countries.

(d) *Professional salaries*: In general, the salaries of physicians in university and publicly-funded hospitals are low in developing countries. This stands in stark contrast to the situation of their peers in developed countries. As a result, most doctors in developing countries need to complement their meager salaries by working in private practice settings. This has important implications in the analyses of the cost of epilepsy surgery. First, the cost disparities between surgical procedures performed in public versus private settings is apparent. Second, the large number of graduating physicians and specialists can drive the demand–supply curve in directions that may affect the cost and provision of medical and surgical services. Finally, a crisis in the demand–supply of medical services would necessitate the creation and implementation by regulatory bodies of epilepsy surgery guidelines to avoid the potential problem of surgery performed with suboptimal expertise, for questionable or inappropriate indications, or without sufficient investigations to allow adequate patient selection.

(e) *Malpractice insurance*: This is another important aspect contributing to the differences in surgical costs between developed and developing countries. For example, in the USA, an average neurosurgeon requires malpractice insurance that costs about $84,151 a year, a sum many times higher than that required by their peers in developing countries.

(f) *Administration costs*: The administration costs are difficult to assess, but in general they are considered to be low.

Are surgical results different in developing countries and developed countries?

The general answer is 'no'. Analysis of the evidence shows that surgical results in Europe, USA, Latin America, or Asia are practically the same. A recent systematic review found no difference in surgical results for common procedures among large world regions.[37] The simplest explanation is that surgeons' skills are similar worldwide. An exception to this generic statement could apply to surgeons specializing in rare pathologies, special surgical techniques, or in those dealing

with exceptional epilepsy cases (e.g., hypothalamic hamartomas, insular epilepsy, etc.).

On the other hand, an important challenge facing clinicians in developed countries is globalization. Conceivably, the surgical management of epilepsy patients in the future will see private health insurance companies paying for patients to travel to selected centers in developing countries for epilepsy surgery.

Access to epilepsy surgery

The problems surrounding increasing costs of treating epilepsy are magnified in developing countries, where healthcare resources are scarcer. Excellent neurology and neurosurgery services exist throughout Asia and South and Central America, but they tend to be concentrated in major cities. Public health insurance systems are not as prevalent or sufficient in developing countries as compared with Europe and North America, and many patients who could benefit from treatment cannot receive it. This 'treatment' gap is due in part to economic factors such as the relatively low average income of much of the population,[3,5,7,36] although political, social, and organizational factors are also highly relevant.

Twenty years ago, only ten countries had epilepsy surgical programs; in contrast, 26 countries had such programs in the year 2000,[38] the majority of which were in developed countries. However, epilepsy surgery remains underutilized even in developed countries. For example, it is estimated that only 1,500 of the nearly 100,000 eligible patients in the USA undergo such surgical procedures each year.[39] Also, clinical investigations for epilepsy surgery are often delayed, ranging from 8 to 20 years.[24,27] This inappropriately long waiting time and underutilization stands in stark contrast to the proven benefits of epilepsy surgery[40,41] and to the poorer quality of life and increased risk of death during the waiting period.

The macro-economic viewpoint

In Latin America, the average family member earns $2 a day ($60/month or $740/year), whereas in the USA, income under $17,500/year is considered 'poverty'. This is equivalent to less than half of the per-capita gross domestic product (GDP), which is $36,056 in the USA (http://www.who.int/en/). The GDP is defined as the per-capita market value of the total final output of goods and services produced in a country over a specific period. The international dollar (ID) is a common currency unit that takes into account differences in the relative purchasing power of various currencies. Figures expressed in ID are calculated using purchasing power parities (PPP), which are rates of currency conversion constructed to account for differences in price levels between countries. For example, the Chilean annual domestic gross was approximately $7,200 in 2002, but the corresponding amount in ID was $11,086 (Table 29.2).

Table 29.2 Per-capita gross domestic product (GDP) in international dollars (ID), total expenditure on health as a percentage of GDP, and per-capita total expenditure on health in ID (2002), in representative countries of each continent

Country	GDP ($ID)	% of GDP spent on health	$ID per capita for health
United States of America	36,056	14.6	5,274
Luxemburg	49,228	6.2	3,066
Germany	25,842	10.9	2,817
France	28,094	9.7	2,736
Australia	28,277	9.5	2,699
Japan	26,860	7.9	2,133
Israel	20,780	9.1	1,890
Republic of Korea	19,523	5.0	982
Lebanon	6,081	11.5	697
South Africa	7,935	8.7	689
Russian federation	8,588	6.2	535
Mexico	8,979	6.1	379
China	4,460	5.8	261
Chile	11,086	5.8	246
Brazil	7,762	7.9	206
Egypt	3,891	4.9	192
Cambodia	1,607	12.0	192
Philippines	5,231	2.9	153
Equatorial Guinea	7,645	1.8	139
Georgia	3,260	3.8	123
India	1,568	6.1	96
Peru	5,101	4.4	93
Senegal	1,202	5.1	62
Sudan	1,171	4.9	58
Nigeria	984	4.7	43
Haiti	1,093	7.6	29
Democratic Republic of the Congo	352	4.0	14
Liberia	520	2.1	11

- Total health expenditure per capita is the sum of public and private expenditure on health.
- Quelle: Website of the World Health Organization (WHO) (http://www.who.int/en/)

Nations differ in the percentage of their GDP they invest in healthcare. For example, the USA invests 14.6%, Georgia invests 3.8%, and Africa Equatorial Guinea invests only 1.8% (Table 29.2). This translates into a total per-capita expenditure on healthcare of $5,274 in the USA and only $11 in Liberia in 2002 (Table 29.2) (http://www.who.int/en/). However, 17% of the USA population has no health insurance, nor access to epilepsy surgery programs. This means that in many countries health expenditures are almost entirely out-of-pocket at the point of service delivery. Out-of-pocket spending is defined as the direct outlay of households, including gratuities and payments in kind made to health practitioners and suppliers of pharmaceuticals, therapeutic appliances, and other goods and services whose primary intent is to contribute to the restoration or to the enhancement of the health status of individuals or population groups. It includes household payments for public services, and to nonprofit institutions or nongovernmental organizations. It excludes payments made by enterprises that deliver medical and paramedical benefits, mandated by law or not, to their employees.

In summary, resources are scarce, particularly in developing countries, which makes it essential to obtain robust data on economic evaluations of epilepsy surgery. This would ensure that limited resources are efficiently and appropriately allocated, and that they are used in a rational manner. The main differences in the costs of epilepsy surgery between developing and developed countries arise from a low GDP in developing countries and a low expenditure on healthcare in relation to their GDP.

Quality of life (QOL)

Epilepsy presents multiple complex problems to everyday life.[3,42-44] The primary goal of surgical treatment is to control seizures, but the treatment must also be targeted to overcome the broad spectrum of physical, psychological, cognitive, and social effects of the disorder. Health-related QOL is a comprehensive multidimensional construct, and in epilepsy patients many factors affect it negatively. These include seizures themselves, drug adverse effects, psychosocial consequences, social stigma, etc.[45]

Although there is no standard definition for QOL, an operational definition includes:

> a state of well-being that is a composite of two components: (1) the ability to perform everyday activities that reflect physical, psychological, and social wellbeing, and (2) patient satisfaction with levels of functioning and control of disease and/or treatment-related symptoms. [46]

In assessing these constructs, one must take into account that QOL deals largely with the individual's (subjective) perceptions and experiences of health and disease. In addition, instruments used to measure QOL must satisfy the general measurement (psychometric) properties of validity, reliability, reproducibility, responsiveness to change, and ability to detect small but clinically important differences. Several analyses have assessed the specific properties of QOL instruments, such as validity of generic (non-targeted) instruments to be used in epilepsy,[47] as well as the minimum clinically important change[48] for specific instruments, and the minimum change that instruments can detect reliably in epilepsy.[49] These important parameters can help clinicians assess whether observed changes in QOL are clinically meaningful and statistically reliable in individual patients. QOL instruments can be classified as generic (non-targeted), targeted (epilepsy-specific), and as utility instruments (those measuring health state preferences).

Over the last decade, numerous instruments have been developed to assess QOL in epilepsy, as well as specific aspects of QOL. For example, different epilepsy-specific scales have been validated for children, adolescents, and adults, to assess AED adverse effects, severity of epilepsy, effects of surgery, impact of epilepsy, and other domains. For a catalogue of epilepsy-specific QOL instruments, see Cramer *et al.*[47]

Epilepsy surgery and QOL

Adults

Studies of QOL in adults after epilepsy surgery have shown improvements in QOL, e.g., employment, functional status, role activities, social functioning, emotional status, cognition, health perceptions, and general life satisfaction.[50–53]

The only randomized trial comparing medical and surgical therapy demonstrated statistically significant superiority of QOL after surgery ($P<0.001$), occurring as early as 3 to 6 months after surgery, and improving over time ($P<0.003$).[54] Although more patients in the surgical than in the medical group were employed or attending school at 1 year (56.4% vs. 38.5%), this difference did not achieve statistical significance ($P=0.11$).[54] Recent cohort studies have reported similar findings, with regard to early improvements in QOL after surgery, but without control comparisons.[55]

Postoperative QOL is clearly related to seizure improvement,[56] as well as to reduction of the stigma and handicaps associated with epilepsy.[51] Patients who are not seizure-free after epilepsy surgery generally have little regret about undergoing surgery, but are less likely to be satisfied and have a poorer psychosocial profiles.[57] Other important determinants of QOL postoperatively include mood, anxiety, and AED adverse effects.

Psychiatric function is an important predictor of QOL after surgery. A study compared seizure-free patients with temporal lobe epilepsy and extratemporal patients. Temporal patients reported significantly higher levels of depression (26%), anxiety (42%), and psychosocial adjustment difficulties (64%) at the 1-month review than did extratemporal patients. Mood disturbance was significantly associated with adjustment difficulties in both groups, but was not related to seizure outcome at any review period. A general increase in mood disturbance was evident after surgery, particularly in temporal resection patients at the 1-month review. Site of surgery and psychosocial adjustment showed significant associations with postoperative mood disturbance, supporting the role of both neurobiological and psychosocial factors in mood outcome.[58]

There is substantial variation in outcome definition, methodology, and interventions among the many reports on postoperative cognitive outcomes. Psychosocial benefit is substantial after surgery, but so is memory loss incurred with dominant temporal lobe resection. The only controlled study in this regard, from the University of Bonn, involved adults

with temporal lobe resections. After a mean follow-up of 5 years, memory decline occurred in 50% of patients in the medical group and 60% of patients in the surgical group, and it was worse in those undergoing left temporal lobe resections.[59] However, there was no change in intelligence.

A recent Australian study of psychosocial outcomes following epilepsy surgery ($N=89$) reported good outcomes in 58% of patients by 24 months post-surgery, characterized by improved family dynamics, enhanced vocational and social functioning, and driving. Associated prognostic variables included early postoperative adjustment difficulties. In contrast, 31% of patients perceived their outcomes as poor, reporting affective disturbance at 12 months and difficulties discarding sick role behaviors. Early anxiety served as a marker of poor outcomes, while resolution of early anxiety and vocational change at 12 months were indicators of good outcomes at 24 months. The remaining 11% of patients reported minimal adjustment features. This means that, for most patients, seizure surgery results in a process of postoperative adjustment that leads to distinct outcome trajectories.[60]

No differences have been found in the satisfaction of patients with epilepsy of different countries (developed vs. developing), based on their aspirations and needs. For example, a controlled study in a Middle Eastern population (Beirut, Lebanon) showed improvements 1 year after epilepsy surgery, similar to those reported in Western populations after a similar period. Patients had marked improvements in overall QOL, health perception, well being, and cognitive functioning. They had less remarkable improvements in social functioning and role limitations.[61] The results were similar for Turkish epilepsy patients, but independence seemed to be the most important concern and gain.[62]

In summary, compared with medical management, epilepsy surgery has a significant positive impact on QOL and psychosocial outcomes in terms of employment, independent living, driving, and financial independence in patients who are refractory to AEDs. Additionally, patients who are not entirely seizure-free still achieve beneficial psychosocial outcomes if their seizures are significantly improved.[63] Moreover, QOL improvements early after epilepsy surgery are both statistically and clinically significant.[64]

Children

There is a long-held view that epilepsy surgery during childhood results in sustained improved psychosocial function and QOL. There is little data on long-term outcomes, but a recent Canadian communication showed that early surgery results in better QOL in young adulthood for those who are seizure-free,[65] confirming the results of previous studies.[66] The studies also point out the importance of the number of AEDs and psychological functioning in determining QOL. In children and adolescents, epilepsy surgery sets the stage for improved QOL and for social integration. It appears that most of the QOL improvement occurs in the first 6 months after surgery.[67] However, against the classical results of better QOL after epilepsy surgery, a prospective study was performed in children with intractable epilepsy who underwent epilepsy surgery ($N=51$) for evaluation of cognitive, psychosocial and family function. The results showed that 1 year after surgery, 57% of the surgical group was seizure-free. Seizure status after surgery did not predict change over time in any of the areas measured. Cognitive and psychosocial status did not change over time in either group, and the strongest predictor of individual change in psychosocial status in the surgical group was baseline level of function. Within the surgical group, a trend toward an increase in independence was noted in the family, but the children's satisfaction with the family declined. These findings challenge the assumption that elimination of seizures will result in improved cognitive, psychosocial, and family functioning, at least within the first year after surgery.[68]

Conclusion

Epilepsy surgery must be considered as soon as drug resistance is reached: 'surgery does not need to be a last resort',[8] because it is the most effective treatment in cost/effectiveness for refractory epilepsy, i.e., in temporal lobe epilepsy. In addition, the improvement of QOL after surgery is clearly established in adults.

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30 Epilepsy surgery: patient selection

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Introduction

In this chapter, we will outline how adult patients with medically refractory epilepsy are selected for resective epilepsy surgery. Due to specific management,[1] primarily pediatric epilepsy surgery topics that include hemispherectomy and corpus callosotomy will not be covered. We will deal only with resective (supposed to be curative) surgery, so palliative procedures such as subpial transection procedures and vagus nerve stimulation will also not be covered.

Identification of surgical candidates

Eligibility criteria for resective surgery are far from being clearly defined, since they depend on many individual factors (type of epilepsy, presence or absence of an epileptogenic lesion, age, comorbidities, etc.), as well as on the exams that are considered mandatory for deciding whether an epileptic patient is a good epilepsy surgery candidate. Yet, there is only one randomized study that has demonstrated the superiority of (temporal lobe) surgery versus medical treatment,[2] so that it appears difficult to give evidence-based recommendations on who are the ideal candidates for surgery in general. Therefore, if there exists a relatively large consensus on the effectiveness of temporal lobe surgery, especially in the so-called mesiotemporal lobe epilepsy syndrome,[3] whether epilepsy surgery is really effective in other focal epilepsy types remains a debatable issue.[4] Many nonrandomized studies, however, strongly suggested that epilepsy surgery may lead to seizure-freedom in a substantial number of extratemporal and/or cryptogenic cases, and this has long been confirmed by daily practice.

Therefore, it seems legitimate to consider epilepsy surgery as a therapeutic option, whatever the type of *partial* epilepsy, provided that it is *drug-resistant* and *disabling*, and provided that the *benefit/risk ratio* for surgery *is* a priori acceptable.

Focal seizures

Up-to-date, resective surgery is exclusively considered when seizures are focal, i.e., when they arise from a limited portion of one hemisphere, and when they represent unequivocally the electroclinical expression of a nonidiopathic partial epilepsy syndrome. The minimum required for answering to these issues includes a good description of seizure semiology, interictal EEG data, and a good MRI scan. There exist, however, some situations where the distinction between partial epilepsy and generalized epilepsy is not so easy. For instance, asymmetric or focal interictal EEG abnormalities, as well as clinical signs suggesting a focal onset of the seizures, can be observed in generalized epilepsy syndromes.[5–7] Also, partial epilepsies, especially frontal, can manifest with bilateral interictal EEG discharges and with seizures that mimic absence seizures, or generalized tonic or tonic-clonic seizures.[8–10] In any case, when there exists a doubt, these patients should be referred to a specialized center for long-term video-EEG monitoring.

Drug-resistance

There is a general agreement to consider a patient medically refractory (or pharmacoresistant) if two or three appropriately selected and managed AEDs failed to control the seizures. This is in accordance with the prospective study of Kwan and Brodie,[11] who showed that a patient with focal epilepsy had only a 47% chance of achieving full seizure control with the first anticonvulsant taken, a 9% chance with the second anticonvulsant, and a dismal 4% chance with a third or multiple anticonvulsants. This clearly means that it is not necessary or reasonable to try all the 'older' and 'new' anticonvulsants either in monotherapy or polytherapy before considering surgery. However, the number of AED trials, as well as the minimum duration of the epilepsy (1 year, 2 years, more?) that are required before considering surgery depend on many factors, among which the type of epilepsy and the likelihood of rendering the patient seizure free after surgery are of particular importance. For instance, it seems legitimate to consider surgery very early in patients suffering from temporal lobe seizures associated with hippocampal sclerosis, since seizures are very often refractory,[12] and because surgery proved particularly effective,[13–15] especially when the delay between epilepsy onset and surgery is short.[16] Also, patients suffering from 'lesional' epilepsies should be considered quickly for surgery, mainly when the lesion is relatively well-limited in space, and/or when it appears to be of tumoral origin.[17]

Disability

Seizure frequency and severity are the most commonly used factors to account for epilepsy disability. Undoubtedly, they greatly participate to the assessment of the handicap, and they

have a major impact on the quality of life. However, this does not necessarily mean that a patient having frequent and devastating seizures is a good epilepsy surgery candidate. For instance, surgery for frontal lobe epileptic 'drop attacks' is often disappointing or not feasible, especially in cryptogenic cases, so that the decision to begin or not a presurgical evaluation must take into account this low likelihood of seizure alleviation. By opposition, a patient may suffer from relatively low frequent seizures which do not appear disabling for the physician (e.g., automotor seizures once a month), but this condition may have a major professional impact due to driving prohibition of, so that surgery should be considered rapidly. Thus, it is clear that many factors must be taken into account, including not only the frequency and severity of the seizures, but also the underlying pathology, the associated neurological or neuropsychological deficits, the AEDs toxicity and, above all, the socioprofessional and familial impact of the disease, as well as its psychological consequences.

Benefit/risk ratio

As a rule, mortality and morbidity of epilepsy surgery are small. No surgical mortality was reported in the Class I randomized controlled trial of Wiebe *et al.*[2] In the recent report of Engel *et al.*,[4] two out of 556 patients (0.4%) from seven centers died within a month after surgery, but deaths were unrelated to the surgical procedure. True, epilepsy surgery carries risks but, in actuality, the risk of surgical death following anterior temporal lobectomy is <1%.[18] As compared to this surgical risk, patients with uncontrolled seizures have a significant risk of death by injuries, drowning, suicide, and especially sudden unexpected death of epilepsy (SUDEP). The risk of SUDEP in medically refractory patients has been estimated as high as 0.5 to 1.5% per year and the risk is cumulative[19]. Sperling *et al.*[20] recently reported that following successful epilepsy surgery the risk of death was 0.85 per 1,000 person-years which is approximately the same as the general population while patients with unsuccessful epilepsy surgery had a mortality rate of 11.4 per 1,000 person-years. Surgical complications, as assessed in the report of Engel *et al.*,[4] were found to occur in 11% of 556 patients from seven centers, 3% experiencing permanent neurological deficits. In this report, postoperative cognitive and behavioral disturbances were described in 6% of patients of three series, and were permanent in 3%. Obviously, the risk and morbidity of epilepsy surgery depend on the specifics of the particular surgery planned for each patient.

For example, the risk of significant memory decline following removal of an atrophic, sclerotic, nondominant hippocampus is low compared to the significantly higher risk of removing a normal, dominant hippocampus. The risk of visual field deficit is high with removal of an epileptic occipital lobe and essentially nonexistent with a frontal lobe resection. In any cases, however, risks cannot be realistically estimated until the seizure semiology, EEG/video monitoring, and MRI findings, neuropsychological and/or functional MRI results are known. Patients and many non-neuroscience physicians have considerable misinformation about epilepsy surgery. As an example, multiple medically refractory persons with epilepsy have told one of the authors (HHM) they were informed by medical professionals that they should not consider having a dominant temporal resection because of the high risk of 'being unable to speak' following surgery.

Other factors

Role of age

Patients older than 45 years may benefit from epilepsy surgery, at least for temporal lobe seizures.[21–23] Postoperative results, however, are poorer than in younger patients in terms of seizure control and quality of life.[21,23,24] Overall, the risk of postoperative cognitive deficit does not seem higher than for younger patients.[23] A greater age at surgery, however, seems predictive of a stronger decline in verbal memory for surgery of the dominant hemisphere for langage.[25] Also, the risks of major complication of surgery might be higher in patients older than 35 years.[26]

Psychiatric problems

The cumulative incidence of mental problems in drug-resistant partial epilepsy patients referred to epilepsy surgery centers is especially high, ranging from 50% to 80% (for a review, see ref. 27). Such mental problems, however, do not seem to have any influence on the postoperative seizure outcome,[28] and it is much more common to observe their stabilization or improvement after surgery, than their aggravation.[29,30] Patients with personality disorders, however, might be at higher risk of suffering from severe postoperative psychiatric complications.[31] Overall, postoperative psychiatric problems are found in up to 50% of temporal lobe cases.[32] They consisted the most often in transient anxiodepressive states, especially in patients undergoing right hemispheric surgery and who had a high presurgical depression-related morbidity.[33] Nevertheless, the occurrence of such problems is lower in those patients who become totally seizure free after surgery.[34] Therefore, and based on our actual knowledge, it would certainly be unwise to reject a patient simply on the grounds of psychiatric problems.

Other associated diseases

Epilepsy is a common disease, and the coexistence with other pathological conditions, either neurological or non-neurological, is not so rare. Whether the comorbidity may interfere with presurgical evaluation and surgery may be an important issue, for instance when the patient is suffering from a disease (or takes medication) which makes impossible (or at least very difficult) any surgical act (e.g., hematologic problems). Also, some pathological conditions may aggravate the seizures (e.g., sleep apnea syndrome), so that the treatment of the associated disease may be necessary before considering surgery. As a rule, caution is required before considering surgery whenever the patient's health suggests that epilepsy is an epiphenomenon.

Presurgical evaluation: general principles

Once the history of disabling medically refractory focal seizures is clearly established, the principal requirement for resective epilepsy surgery is the identification and accurate localization of the epileptogenic zone,[35] the removal (disconnection, irridiation, or coagulation) of which will not create a new unacceptable handicap. To answer these issues, many examinations are available, the use of which is usually

complementary and will define various cortical zones: symptomatogenic zone, irritative zone, ictal onset zone, eloquent cortex, functional deficit zone, and the epileptogenic lesion.[35] All examinations are not utilized systematically, and the presurgical evaluation process must be conducted step by step, according to the individual anatomo-electro-clinical features of each patient (Figure 30.1).

Basically, epilepsy surgery candidates must have at least the following evaluation

(1) A *detailed history and neurological examination* are the obvious starting place and guide which studies will be required. Historical details regarding aura and seizure semiology and the sequence of events during a seizure should be sought (from both the patient and family members) and later compared, when performed, with the videotaped seizures recorded during EEG/video monitoring. Questions regarding birth history, febrile convulsions, head injuries, CNS infections, and other possible causes of seizures should be asked. Medication trials and their side effects should be reviewed. A detailed family history should be taken with particular reference to seizures and other neurological illness(es).

(2) A *high-resolution MRI scan* that includes at least volume acquisition T1-weighted and FLAIR sequences to document the presence of hippocampal sclerosis or other potentially epileptogenic brain lesion(s) should be performed. Neuroradiologists active in epilepsy surgery programs have a higher detection rate than do neuroradiologists in nonepilepsy surgery centers.[36] In most instances, gadolinium is not necessary unless a tumor or mass lesion is found. While a lesion seen on MRI is very helpful in the epilepsy surgery evaluation and may correlate with a good surgical outcome, a normal MRI does not by itself exclude a patient from epilepsy surgery; it does, however, make the presurgical evaluation significantly more complicated and expensive.

(3) *Repeated interictal EEGs* are very helpful to grossly evaluate from where seizures are expected to arise. Particular attention must be paid to the constant or variable location of interictal spikes, the possibility that their topography has evolved with time, and their unilateral, bilateral (asynchronous or not) or multifocal origin. Also, the type of interictal abnormalities, especially in the so-called cryptogenic cases, may be particularly informative when they strongly suggest the possibility of an underlying brain lesion (e.g., well-localized fast rhythms or repetitive fast spikes in focal cortical dysplasias).

(4) *Neuropsychological evaluation* must be done to determine the patient's baseline cognitive function and to help estimate the risk to those functions if a surgical resection were to be done. Neuropsychological results by themselves are not reliable enough to localize the epileptogenic zone. (The reader is referred to these topics in this book for more detailed discussions.)

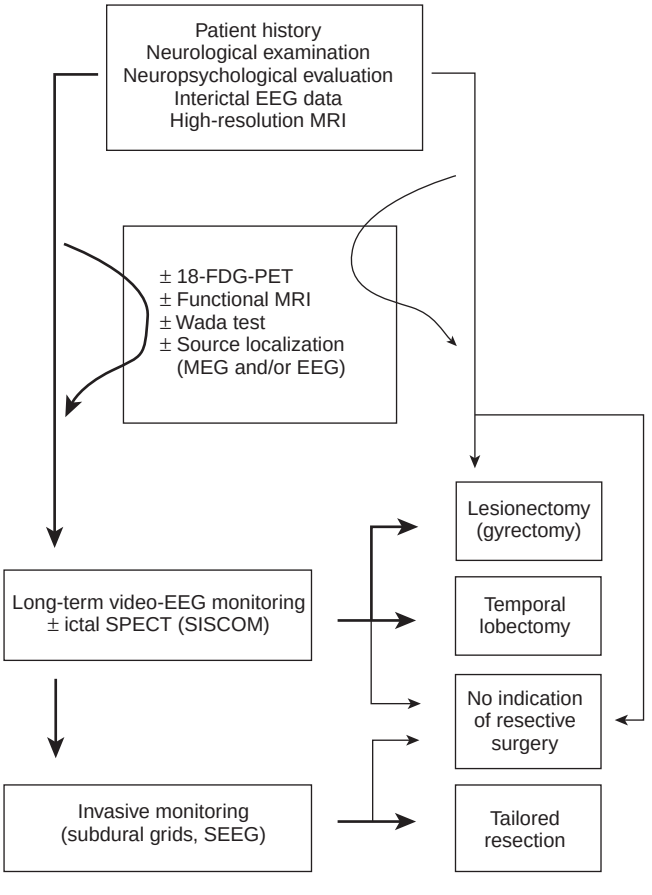

Figure 30.1 Strategies for presurgical evaluation.

In a few lesional cases, these data proved sufficient enough to decide whether surgery can be performed, even without additional EEG/video monitoring. This should concern only those patients with a recent history of drug-resistant seizures associated with a well-limited brain lesion (e.g., dysembryoplastic neuroepithelial tumor, cavernoma, etc.), providing that a good concordance exists between the localization of the lesion, the clinical semiology of the seizures as reported by the patient and/or his/her family, and the interictal scalp-EEG abnormalities. Also, brain imaging study, interictal EEG, and ictal clinical findings may sometimes be sufficient to exclude the patient from surgery. For instance, surgical possibilities are very low in a patient without neurological deficit who experiences simple motor clonic seizures of the right arm, whose interictal EEG shows well-localized left central spikes, and whose MRI does not demonstrate any lesion. Caution is required, however, to ascertain whether a patient is a good epilepsy surgery candidate, without having previously recorded seizures during EEG/video.

In general, noninvasive scalp EEG/video monitoring should be done in a majority of cases

EEG/video monitoring allows the localization of interictal epileptiform discharges (the irritative zone) and, above all, localizing the seizure onset zone and documenting the seizure type(s). It is helpful to the physicians working in the EEG/video monitoring unit to have the MRI scan before the monitoring is done. The information from the history, neurological examination, and MRI scan are helpful in planning the monitoring. For example, a patient with an olfactory aura, automotor (complex partial) seizures, and right hippocampal atrophy on MRI probably should have closely spaced bitemporal electrodes (International 10/10 System) applied with the standard International 10/20 scalp electrodes and sphenoidal

electrodes inserted at the beginning of EEG/video monitoring. In this patient, only a small number of seizures (one or two) would need to be recorded if they were of right temporal origin. A second patient with a sensory aura of the left hand and right hippocampal atrophy on MRI scan should have 10/10 electrodes placed over the right posterior frontal/anterior parietal region in addition to the temporal and sphenoidal electrodes (because of the distinct possibility of an extratemporal epileptogenic zone). A third patient with bihippocampal atrophy on MRI scan and bitemporal spikes would have electrodes placed the same as the first patient, but multiple seizures would be recorded (because of the higher risk of bitemporal independent seizures). At Cleveland Clinic Epilepsy Center most patients with suspected temporal lobe epilepsy undergo monitoring, employing closely spaced scalp electrodes placed bitemporally (10/10 international system) and with sphenoidal electrodes. Hopefully, there will be concordance between the seizure semiology, MRI, and EEG findings; if so, the patient's evaluation will involve fewer days in the hospital, less testing, and significantly less cost.

Selected candidates for epilepsy surgery may also have the following studies depending on the particular issues at hand

(1) *Fluorodeoxy glucose positron emission tomographic scans* (FDG-PET) and *intracarotid sodium amobarbital/methohexital tests* (WADA tests) are considered 'routine' in many epilepsy centers but are no longer done on every patient at Cleveland Clinic Epilepsy Center. For example, in a right-handed patient with right hippocampal sclerosis and agreement of semiology and EEG, the patient would most likely proceed to surgery without a PET scan or a WADA test. However, a PET scan may be of substantial interest to look for a localized hypometabolism in cryptogenic cases, and/or to help to define what the preferential spread pattern of seizures can be when invasive recordings are planned.

(2) A subtraction *ictal SPECT scan co-registered with MRI* (SISCOM or related technique) image may be most helpful in those patients who suffer from focal epilepsy but with normal MRI and in those with extensive focal cortical dysplasia.[37,38]

(3) Some centers employ *magnetoencephalography* (MEG) and/or *EEG dipole source localization* of interictal discharges in an attempt to further localize the irritative zone (area of interictal spiking). These studies are not required on all patients but may be helpful when the location of the epileptogenic zone is in doubt after the routine studies. As yet the exact role of MEG in evaluation of patients for epilepsy surgery is undetermined. MEG is used principally for the localization of interictal epileptiform activity as the chance of recording a seizure during MEG is very small unless the patient is having frequent daily seizures.

(4) *Functional MRI* (fMRI) may help localize some functional areas of the brain and their relationship to a suspected epileptogenic zone. Functional MRI may replace the WADA test in the future for determination of side of language dominance and may possibly be useful for memory assessment. A potential advantage of speech fMRI over WADA is its ability not only to lateralize speech but to anatomically localize cortical speech regions (both anterior and posterior speech areas). fMRI is also a promising technique for cortical localization of interictal epileptiform activity, but EEG recordings with time-locked functional MR imaging are technically challenging and the significance of interictal spiking in ictal onset zone localization is not entirely clear.

Invasive recordings may be needed when noninvasive data remain insufficiently concordant, discordant, or inconclusive, and when they suggest an early involvement of highly eloquent areas

In the 1980s, before high-quality MRI was available, many epilepsy centers performed invasive EEG studies in almost all patients. Some centers favored subdural grid and/or strip evaluations, while others favored depth electrode evaluations. Currently, most centers reserve invasive recordings for those patients in whom the location or extent of the epileptogenic zone is not well defined or those who require localization of eloquent cortex by electrical stimulation of the cortex.

While surgical techniques and the invasive electrode technology have improved, invasive electrodes do carry additional risks of infection, hemorrhage, and sometimes mass effect. Risk of the invasive study increases with the number of electrodes, length of time they are in or on the brain. It markedly increases if another craniotomy is done to move the electrodes. The task at hand then is to use the smallest number of electrodes for the shortest period of time (typical length of invasive electrode monitoring at Cleveland Clinic Epilepsy Center is 2 weeks, but some electrodes were left in for up to 4 weeks).

Most major epilepsy centers in North America employ grids, strips, and depth electrodes, or a combination of them depending on the task at hand. Invasive recordings with subdural grids are extremely helpful in the accurate localization of epileptogenic regions located on the cortical surface but are inaccurate in the definition of EcoG patterns arising from deeper generators such as the insula (that is not well covered by subdural electrodes because of anatomo-technical reasons), and the amygdalo-hippocampal complex (see appropriate chapters in this book). The hippocampus poses major problems, as recording of epileptic activities from an electrode covering the parahippocampal gyrus may point to an epileptogenic neocortex or hippocampus. Alternatively, some epileptic activities arising from the hippocampus may not be detected on subdural electrodes (author's personal observation, IN). The limitations of the subdural/cortical surface electrode mapping in the definition of deep epileptic foci are at least in part addressed in the technique of intracerebral depth electrodes (stereoencephalography, SEEG) that was introduced by Bancaud and Talairach and later was extensively used in many European epilepsy surgery centers (see appropriate chapters in this book). The advantages of SEEG include its ability to sample deep areas of the brain and anatomically distant regions and both hemispheres.

There are no set criteria that can be systematically used to decide whether or not invasive recordings should be performed. Nevertheless, some factors, such as the type of epilepsy (temporal vs. extratemporal), or the presence/absence of a lesion (lesional vs. cryptogenic), may influence to various

degrees the need of invasive recordings (see Chapters 28 and 29). In any case, such recordings must be planned on the one condition that the questions derived from the noninvasive protocol are clear, that the positioning of the electrodes will be able to answer to these questions, and that the patient is likely to benefit from surgery. In other words, since the precise site of the epileptogenic zone is usually uncertain, considerable thinking and planning should be done before the electrodes are placed. Placement of the invasive electrodes requires a hypothesis about where the epileptogenic zone is likely to be.

Temporal lobe epilepsy

Temporal (TLE) is the most common surgical epilepsy diagnosis. Although various pathologies (including cortical dysplasia, tumors, vascular malformations, etc.) may underlie TLE, hippocampal sclerosis remains the most common pathological diagnosis.

Typical cases

The best surgical outcomes are obtained when the localization by seizure semiology, the EEG interictal focus, the EEG seizure onset zone, and an MRI lesion are all functionally and anatomically concordant. An example would be a right-handed patient with an aura of *déjà vu*, followed by an automotor seizure (complex partial with automatisms) during which the patient demonstrates ictal speech, left hand dystonic posturing, that are followed by head version to the left and secondary generalization. A high-resolution MRI in this hypothetical patient reveals right hippocampal atrophy on T1-weighted images and the FLAIR sequence shows increased signal in the right hippocampus. A right anterior temporal lobectomy (with resection of the mesial structures) in this patient would carry low risk for language and memory dysfunction with a likelihood of seizure freedom of approximately 75% at 1 year and 55% 10 years later.[39] The likelihood of seizure freedom following surgery is high because the principal determinants of seizure localization are all in agreement. The ictal semiology suggests the right hemisphere because of the left hand dystonic posturing, ictal version to the left, and ictal speech in a right-handed patient. Both the interictal and ictal EEG findings point to the right temporal lobe and the MRI lesion is right mesial temporal. The surgical risk is low because the patient is almost certainly left-hemisphere dominant for language (because he is right-handed and exhibits ictal speech, suggesting left-hemisphere language dominance) and removal of a nondominant anterior temporal lobe with MRI evidence of hippocampal sclerosis is unlikely to result in clinically significant post operative memory impairment.

Cryptogenic cases

Contrast the above patient with another hypothetical case identical to the first, but whose high-resolution MRI scan is normal. This second patient would also be a surgical candidate but would be somewhat less likely to be seizure free because of the absence of a MRI abnormality and would have a higher risk of postoperative memory decline because the right temporal lobe did not have evidence of hippocampal atrophy; i.e., the resection would include a 'normal' hippocampus by MRI evaluation. This second patient probably should have a PET scan and a SISCOM study to obtain neuroimaging confirmation of the location of the ictal onset zone. More than likely, this patient would require invasive electrode studies and the EEG, PET, and SISCOM findings would help guide the placement of invasive electrodes. The reader should note that in this worst-case scenario, epilepsy surgery is *not* contraindicated, but there is a need for invasive monitoring in most patients (depth electrodes, subdural grids, and/or stereotactically placed depth EEG electrodes). Seizure outcome analyses in patients who underwent invasive evaluation suggest that the chances of seizure freedom after temporal lobe resection is lower (48% seizure free) than in those patients who did not undergo surgical evaluation (65% seizure free).[39] We feel strongly that issues such as these must be discussed with the patient before surgery, and the final decision for or against surgery should be a joint one made by an informed patient and a knowledgeable multidisciplinary team of physician experts.

Dual pathology

Dual pathology usually implies the presence of a neocortical lesion (most commonly a low-grade tumor or focal cortical dysplasia involving temporal or extratemporal (often occipital) neocortex and hippocampal sclerosis. If both lesions are not surgically addressed, the chance of seizure freedom is low. Invasive study may be required, depending on location of the associated lesion. The questions to be answered are: (1) where is the seizure beginning, and (2) to where does it spread?

Pitfalls

In patients suspected to have TLE, the following possibilities should be investigated and answered: (1) temporal versus 'pseudotemporal' epilepsy, (2) unilateral versus bitemporal lobe epilepsy, (3) mesial versus 'neocortical' lateral temporal lobe epilepsy, and (4) temporal versus 'temporal plus' epilepsy.

(1) *Temporal versus 'pseudo-temporal' lobe epilepsy*. This possibility is raised when a patient is suffering from pharmacoresistant epilepsy with EEG and semiological features pointing to the anterior temporal/fronto-temporal regions, but whose MRI scan is normal, and whose memory function is not deficient. As the epileptogenic zone in these cases may be in one of following regions: the temporal lobe, the orbito-frontal region, the temporo-occipital junction, or the mesial parietal/posterior cingulate/posterior interhemispheric areas, there is a need for invasive evaluation with a combination of grids and depths. As it is extremely difficult to lateralize the side of the epileptogenic zone in mesial/interhemisphere epilepsy, hypothesis generation in these cases should be aided by neurophysiologic cues such as the presence of bilateral independent interictal and/or ictal temporal epileptic patterns, and by additional studies that may include an ictal SPECT (with SISCOM).
(2) *Unilateral versus bilateral temporal lobe epilepsy*. Bilateral interictal temporal spikes are present in up to 40% of patients with unilateral hippocampal sclerosis.[40] The findings of typical MRI features of unilateral hippocampal

sclerosis with hypometabolism on ictal FDG-PET with concordant ipsilateral ictal EEG patterns help in making the diagnosis of unilateral mesial temporal lobe epilepsy. If the ictal patterns are bilateral anterior temporal, and the MRI is within normal limits, there will be a need for a confirmation of the seizure lateralization through the use of bilateral depth electrodes to be implanted in amygdalo-hippocampal regions bilaterally. If seizures recorded on surface EEG arise independently from left and right temporal lobes, the patient still may be a surgical candidate, but will require bitemporal depth electrodes for invasive recordings and chance of seizure freedom will be lower still if invasive studies proved bitemporal independent seizure onsets.

(3) *Mesial versus neocortical lateral temporal lobe epilepsy*. This is illustrated by a case that we recently reported:[41] a 42-year-old right-handed male who presented with recurrent daily seizures that were resistant to antiepileptic drugs. Multiple noninvasive (scalp) video-EEG evaluations revealed focal epilepsy arising from the left fronto-temporal region. Multiple high-resolution MRIs failed to show any abnormality. PET scan showed extensive left antero-mesial temporal hypometabolism and ictal SPECT showed increased perfusion in the left insula in addition to the left mesial and anterior temporal pole. Neuropsychological and Wada testing revealed excellent memory to the left dominant side. A two-stage invasive evaluation with subdural grid electrodes followed by depth electrode recordings allowed the localization of the epileptogenic region to the temporal pole. A selective resection of the left temporal pole (that spared the hippocampal formation) resulted in seizure-free outcome (>2 year follow-up) with no significant consequences on the memory function. The management of this case shows that targeted invasive recording techniques should be used for the accurate localization and delineation of the extent of the epileptogenic zone in cases of suspected nonlesional dominant hemisphere temporal lobe epilepsy with preserved memory function. The use of the staged invasive approach may increase the chances for memory (function) sparing through tailored temporal resection.

(4) *Temporal versus temporal 'plus' epilepsy*. Temporal 'plus' seizures are characterized by seizures involving a complex epileptogenic network including the temporal lobe and the closed neighbored structures such as the orbito-frontal cortex, the insula, the frontal and parietal operculum, and the temporo-parieto-occipital junction.[42] There are only a few data on this topic,[43–45] thus making the identification of this form of seizures largely ignored. Thus, some patients submitted to temporal lobe surgery who continue to experience seizures postoperatively might suffer from temporal 'plus' seizures and identifying those patients by means of invasive recordings, might lead to performing a more extensive and effective cortectomy, according to surgical possibilities and limits.[45] Recently, Barba *et al.*[46] have found that when compared to 'pure' temporal lobe patients, patients suffering from temporal 'plus' seizures more frequently had gustatory hallucinations, rotatory vertigo, and auditory illusions at seizure onset; they exhibited more frequently contraversive manifestations of the eyes and/or head, piloerection and ipsilateral tonic motor signs, and they were more often dysphoric in the postictal phase; also, they had more frequently bilateral or precentral interictal scalp-EEG abnormalities, and ictal scalp-EEG more frequently pointed over the anterior frontal, temporo-parietal and precentral regions.

Extratemporal epilepsy

In general, patients with extratemporal epilepsy surgery are less likely to be seizure free following epilepsy surgery, as compared to those who have temporal lobe resections. As a rule, the delineation of extratemporal epileptogenic network is much more difficult than that of temporal lobe seizure origin, so that many patients suffering from extratemporal lobe epilepsy have to undergo invasive EEG recordings. Indeed, there are no clear extra-temporal lobe epilepsy 'syndromes', no equivalent of hippocampal sclerosis on MRI, scalp EEG is often mislocalizing and even mislateralizing, and there are no standardized resection techniques.

Lesional cases

The complete removal of a well-limited lesion (and at least its surrounding neocortex) can prove effective against extratemporal lobe seizures, providing that there is a good concordance between the site of the lesion, the clinical semiology of the seizures, and the scalp EEG data, and subject to the one condition that it can be done without significant neurological deficit. Partial lesionectomy is significantly less likely to result in postoperative seizure freedom, notably in patients suffering from dysembryoplastic neuroepithelial tumors.[47] Invasive recordings may be necessary when the relationships between the lesion itself and the region of seizure generation remain unclear, and/or when there is a need to clarify the relationships with eloquent cortical areas. This is especially true for focal malformations due to abnormal cortical development, as the epileptogenic area is frequently larger than the visually-identified lesion, and as a large proportion of patients with such lesions have the diagnosis of focal epilepsy arising from the frontal or perirolandic regions. In any cases, the decision to perform or not invasive recordings in lesional cases must be based on 'anatomo-electro-clinical grounds', and the goals from the invasive evaluation, if decided, should be clear (mapping of epileptogenicity and function) with the understanding of the limitations and risks of the evaluation.

As an example of a straightforward case, a patient, left hemisphere dominant for language, has a small lesion (cortical dysplasia or low-grade congenital tumor) on a MRI scan located in the posterior aspect of the left inferior frontal gyrus. His seizures begin with a slight muscle twitch of the right lip. It is obvious that the lesion is related to the seizures. The questions to be answered are: How extensive is the epileptogenic zone, and exactly where is it located. Does the epileptogenic zone involve Broca's area or the motor strip? Depth electrodes would not be very helpful in this patient. A subdural grid could be used to cover the lesion, the motor strip, and Broca's area in order to record seizures and interictal epileptiform activity. In addition, subdural grids evaluation would enable functional cortical mapping with trigeminal/median nerves,

somatosensory evoked potentials, and physiologic localization of Broca's area and the primary somatosensory cortex by electrical cortical stimulation. As an alternative, fMRI might assist with localization of the eloquent cortex, but it would not localize the epileptogenic zone. Craniotomy under local anesthesia with electrocorticography and localization of the primary motor cortex by cortical stimulation in the operating room would be another alternative. However, this approach may be limited by the lack of ictal recordings (as the significance of some interictal patterns, besides the continuous rhythmic discharges remains unknown), and at times the technical difficulties associated with cortical mapping in the operating room. Surgical management recommendations should be made after a thorough discussion in a multidisciplinary patient management conference with the active participation of epileptologists, epilepsy surgeons, neuroimagers, neuropsychologists, psychologists/psychiatrists, and clinical nurses. The final decision should be made with active input from the patient after a long discussion of the multidisciplinary group's recommendations.

Cryptogenic cases

As with the temporal lobe surgical cases, the likelihood of seizure freedom with extratemporal resection is somewhat lower if the MRI scan is normal.[48,49] In such cases, the use of intracranial recordings remains essential, as illustrated in the following example of a left hemisphere language dominant patient with a left frontal interictal and ictal focus on EEG and with seizure semiology suggesting a left frontal epileptogenic zone. His MRI is normal, as is his interictal PET scan. His ictal SPECT scan is nonlocalizing. Because no lesion is found on neuroimaging, his chance of seizure freedom with surgery is lower. These cases present a challenge for both ictal onset cortical seizure localization and mapping of the functional regions that may be overlapping with the seizure onset zone. The electrode placement in these types of cases is typically guided by ictal semiology and EEG interictal and ictal patterns. In this patient, in addition to subdural grid electrode recordings from the mesial fronto-central region, the lateral convexity, and the inferior orbito-frontal region, multiple depth electrodes could be used to sample the mesial posterior orbital frontal cortex and medial frontal lobe.

Conclusions

The risks of the evaluation and surgery, and the likelihood of seizure freedom should be discussed with the patient. Risk-aversive patients may decline to proceed, while others may be more adventuresome. These complicated decisions are not black or white. A patient management multispecialty conference is very helpful in decision making concerning which patients are good epilepsy surgical candidates, which require additional noninvasive study, which require the use of invasive recordings and the type of electrodes and where they should be placed. At Cleveland Clinic, all epilepsy surgery candidates are discussed at a patient management conference before epilepsy surgery or invasive recordings. The epileptologists, epilepsy neurosurgeon, neuroradiologists, nuclear medicine physician, neuropsychologists, and epilepsy nurses are all in attendance. In addition to providing a group discussion with a variety of inputs before a decision is made, a benefit is that the conference plays an important educational role for epilepsy fellows and staff.

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31 Exclusion criteria

EMT Yacubian

Introduction

Surgery is an alternative for some patients whose seizures cannot be controlled by medication. It has been used for more than a century, but its use dramatically increased in the 1980s and 1990s, reflecting its effectiveness as an alternative to seizure medicines. Recent advances in epilepsy surgery can be traced to many factors, including progress in video-EEG monitoring and neuroimaging, advances in surgical techniques, and a better understanding of brain biology, including that of pediatric patients. Results from pediatric surgical series suggest that children should be referred for surgical evaluation at whatever age they manifest severe intractable focal epilepsy, even in infancy. Also, substantial experience in neuropsychological preoperative evaluation limiting any unwanted impact of surgery on normal brain function, development of a wide array of pharmacological agents that can be useful to manage psychiatric symptoms and comprehension of the social consequences of disabling seizures have contributed to the expansion of this treatment modality. It is now clear that specialized centers with extensive epilepsy surgery experience and the availability of progressively more accurate diagnostic techniques and safer surgical procedures resulted in a progressive shrinking of exclusion criteria for surgery.

Who is a surgical candidate?

Not every patient is amenable to surgical treatment. Patients, both adults and children, must fulfill the following criteria:

1. Recurrent seizures that continue despite adequate trials of antiepileptic medication. Medical intractability is one of the absolute indications in considering epilepsy surgery, although there are no widely accepted or uniformly applied definitions of 'refractory epilepsy' and the criteria used to determine medical intractability are either quite heterogeneous or rather vague.
2. Disabling seizures which must be a significant detriment to the patient life.
3. Anatomic localizability, meaning that the epileptogenic zone must reside in a specific area of the brain that can be removed safely.
4. No identifiable, resectable, single epileptogenic zone and very poor prognoses when a palliative surgical intervention is conceivable and might help the patient and caregivers. Any patient with medically refractory disabling epileptic seizures should be referred to an epilepsy center since epilepsy specialists are the best qualified to conclude that surgical treatment is not a treatment option.

Who is not a surgical candidate?

Not only must the patient fulfill the above criteria, but there are also some contraindications to surgery that must be assessed. Absolute and relative contraindications for epilepsy surgery must be considered as listed in Table 31.1.

Absolute

Idiopathic age-related epileptic conditions

This group comprehends focal and generalized epileptic syndromes. Among the first, Benign Childhood Epilepsy with Centrotemporal Spikes (BECTS) is the most common idiopathic partial epilepsy syndrome of childhood. Typically presenting between the ages of 3 and 13 years, it is characterized by a well-recognized seizure pattern related to sleep (brief, simple, partial, hemifacial motor seizures, frequently having somatosensory symptoms) arising in a normal child with blunt high-voltage centrotemporal spikes, often followed by slow waves that are activated by sleep and tend to spread or shift from side to side.[1] In the second-most prevalent type of idiopathic focal epilepsies, Idiopathic Childhood Occipital Epilepsy, occipito-temporal discharges present the same electrographic characteristics. Seizure control is usually, but not always, easily achieved, and prognosis is believed to be uniformly good. Some authors have suggested that individuals fitting these parameters need not undergo neuroimaging. However, symptomatic partial epilepsies may mimic this electroclinical phenotype configuring the 'pseudo-BECTS' or 'BECTS-like electroclinical type.'

Table 31.1 Epilepsy surgery contraindications

Absolute
Idiopathic age-related epilepsies
Diseases underlying epilepsy
Incapability to comprehend and cooperate with the procedure
Relative
Unrealistic expectations
Psychopathology
Mental retardation
Involvement of eloquent cortex
Bilateral, independent interictal and/or ictal EEG
Progressive underlying neurological diseases

BECTS and lesions, pseudo-BECTS or BECTS-like electroclinical picture

Occasionally, BECTS 'phenotype' has been associated with nonevolutive cerebral lesions not located in the rolandic area,[2] unilateral opercular migration disorder,[3] low-grade astrocytoma and cavernous angioma[4] and a malignant rolandic-sylvian epilepsy characterized by sensoriomotor seizures, medical refractoriness, normal MRI and cognitive problems.[5] Variable atypical features were present in most of these rare case reports. In such cases, epilepsy may or may not be ascribed to the lesions.[6,7] As in BECTS, symptomatic occipital epilepsy such as cortical malformations, mitochondrial disorders, Lafora disease, and celiac disease often imitates Gastaut type-Idiopathic Childhood Occipital Epilepsy.[8] Unusual bilateral occipitofrontal sharp waves, increasing in frequency and distribution during sleep suggestive of benign focal epileptiform discharges of childhood were reported in two children with refractory mesial temporal epilepsy related to hippocampal sclerosis.[9] The postoperative freedom from seizures in each case confirmed that hippocampal sclerosis was the primary epileptogenic process and that benign focal epileptiform discharges were incidental or an atypical secondary manifestation. Therefore, since children with lesions can be dismissed as candidates for epilepsy surgery because of the EEG pattern, caution is necessary in the interpretation of the criteria of absolute contraindication of epilepsy surgery in patients whose electroclinical data are initially suggestive of benign focal childhood epilepsies.

Coexistence of idiopathic generalized and symptomatic focal epilepsies

Idiopathic generalized epilepsies are an absolute contraindication to surgery. However, idiopathic generalized epilepsies may also coexist with focal epilepsies, although this is certainly an uncommon event. Out of 350 consecutive patients who had temporal resections, Koutroumanidis *et al.*,[10] described two cases with clear electroclinical evidence of coexisting temporal lobe epilepsy related to mesial temporal sclerosis cured by resective surgery and idiopathic generalized epilepsies. In one, spontaneous and photically induced generalized spike-wave discharges preceded temporal lobectomy by 5 years. In this patient, clusters of bilateral and arrhythmic clonic jerks of the limbs, mainly on awakening, suggestive of juvenile myoclonic epilepsy, started shortly after the surgical resolution of complex partial seizures. In the second, temporal lobe epilepsy and juvenile absence epilepsy occurred together for almost 7 years. In two other case reports, juvenile myoclonic epilepsy only appeared after successful anterior temporal lobectomy for complex partial seizures.[11,12] Coexistent idiopathic generalized epilepsies should not affect decision for epilepsy surgery.

Diseases underlying epilepsy

Progressive degenerative, neurometabolic and systemic diseases that may underlie the seizures are contraindications to epilepsy surgery.

Incapability to comprehend and cooperate with the procedure

Candidates for surgery need to be able to fully comprehend the procedure and to cooperate with a prolonged hospitalization for monitoring; for many, there will be further tests that require cooperation, such as MRI scanning, angiogram, invasive monitoring and even awake craniotomy with cortical localization studies.[13] Participation and involvement in decisions, even when being made on their behalf, to provide informed consent for preoperative investigations and surgery is highly desirable. After surgery, acceptance and involvement in the rehabilitation program aiming at psychosocial integration is also necessary.

Relative

Unrealistic expectations

Expectation that surgery will correct all the losses associated with chronic epilepsy that are unyielding, despite repeated attempts to correctly inform the patient of the risk-to-expected-benefit ratio of surgery, represent a relative contraindication.[14]

Psychopathology

The importance of this topic is highlighted by the fact that preoperative behavioral problems occur in approximately 67% of candidates for anterior temporal lobectomy, depression, anxiety, and/or suicidal tendencies in 20%, and psychosis in 16%.[15] Disputes have continued over whether presurgical evaluation may adversely influence the psychiatric disorder, whether psychiatric symptoms may be aggravated postsurgically, and whether these patients would benefit from surgery with respect to quality of life.[16] The NIH Consensus Statement suggested that severe psychiatric disorders should be included for consideration in recommendation of epilepsy surgery.[17] However, recent reports have indicated that the psychiatric status is little influenced by surgery and preexisting psychiatric problems may improve in half of the patients and could even disappear in about one third.[16] In the beginning of the 1990s, Fenwick[18] already noted a decrease in the number of patients with postoperative psychopathology, presumably because of rejection of patients with preoperative psychiatric disorders or presurgical identification of patients who were vulnerable psychiatrically. There are few definitive psychiatric contraindications to elective epilepsy surgery. Surgery is contraindicated in patients with severe psychiatric illness refractory to psychopharmacological treatment that cannot be managed safely on a nonpsychiatric award. Also, when there is a significant danger for suicide and aggressiveness during presurgical evaluation given the risk of self-injury, injury to personnel and other patients. Untreated psychopathology, including depression and psychosis, which is not always resistant to psychiatric treatment, may also preclude evaluation because of the patient's inability to cooperate and the difficulty in postoperative rehabilitation. Proper risk management warrants delay of the surgery until these risks have been abated.[19,20]

Psychosis

Chronic psychosis has been considered a contraindication to surgical treatment in the past. Whereas many centers prefer not to accept patients with fixed psychosis as surgical candidates because the psychosis remains even when the patient becomes seizure free, episodic psychoses that are seizure

related, usually as postictal phenomena, often disappear.[19] Actually, postictal psychosis has been considered a factor favoring rather than opposing surgical treatment of refractory epilepsy.[16,20] Another concern is exacerbation of psychosis with seizure remission after surgery, analogous to 'forced normalization'. Although aggravation may occur in a few cases, patients with chronic psychosis may benefit if they become free from seizures after operation, even though psychosis persists. Reutens *et al.*[21] reported that chronic psychotic patients might be able to provide informed consent, cooperate during preoperative investigation, have an uneventful course after surgery, and achieve an improved quality of life. Therefore, it would be unwise to make a decision on whether to reject a patient for surgery on the grounds of psychosis, and a detailed psychiatric evaluation should be performed for each individual case.[19]

Depression

The greatest predictor for postoperative depression is preoperative depression, and a third of patients with baseline depression will still be depressed after surgery. However, depression, as postictal psychosis, as mentioned above, improves in the majority of patients who become seizure free after surgery.[22] Therefore, preoperative depression is not a reason to withhold surgical treatment. Since untreated depression will produce lasting effects on a person's quality of life and postsurgical outcome, identification and treatment of depression should be an integral aspect of presurgical care to stabilize patients optimally before epilepsy surgery.

Substance abuse

Substance abuse represents a relative contraindication to epilepsy surgery. If it contributes to poor seizure control preoperatively and the patient is unmotivated to achieve abstinence, it may well contribute to poor seizure control postoperatively.[14]

Additional psychogenic seizures

Patients with epilepsy who have additional psychogenic seizures represent a particular diagnostic and therapeutic challenge and have been excluded from some epilepsy surgery programs. Epilepsy surgery should be offered only to patients predominantly disabled by epileptic rather than psychogenic seizures. In a series of 13 patients with both types of events who had epilepsy surgery, 11 had a relevant improvement and seven became free of both epileptic and psychogenic seizures. However, there was no definite link between the postoperative prognosis in terms of epileptic and psychogenic seizures.[23] Although a diagnosis of additional psychogenic seizures should not be considered an absolute contraindication to epilepsy surgery, patients should undergo careful preoperative psychiatric evaluation in which a diagnosis should be formulated, a psychological intervention programmed and a prognosis recorded.

Mental retardation

The NIH Consensus Statement suggested that profound mental retardation should be included for consideration in indication of epilepsy surgery.[17] In adults, mental retardation has been considered a poor prognostic sign for localized cortical resection because of the assumption of more diffuse brain damage and the likelihood of multiple epileptogenic regions as well as being considered a poor prognostic indicator. Additionally, the ability to compensate for surgically induced deficits is supposed to depend on the integrity of brain regions beyond the epileptogenic zone and these patients would be at risk with respect to their postoperative outcome. Different series have shown that the rate of success, although not as high as usually reported in patients with IQ >70, appears sufficiently high to justify the treatment. On the other hand, no deterioration of cognitive functioning or of psychosocial adjustment postoperatively has been observed.[24,25,26]

Involvement of primary language, motor, or sensory cortex in the epileptogenic zone

Participation of eloquent cortex in the epileptogenic zone has been considered a contraindication to surgical resection, since removal of these cortical areas can result in permanent neurological deficits. There are exceptions, however. When permanent deficits already exist, surgery introduces no additional risk; for instance, hemispherectomy is commonly performed in individuals who have a hemiparesis and a useless hand. Small areas of the lower sensoriomotor cortex can actually be removed at any age without inducing significant motor deficits, even in the dominant hemisphere.[27] Surgical resections that involve primary language cortex in infants and small children up to about the age of seven do not result in appreciable aphasia because contralateral cortex takes over this function. The nonablative technique of subpial transection of the primary cortex has been reported to have a beneficial effect on habitual seizures without inducing neurological deficits.[28]

Bilateral, independent EEG spikes and/or electrographic ictal onsets

In patients with mesial temporal sclerosis, interictal EEG findings include unilateral or bilaterally independent mesial temporal spikes. Initially, the latter would seem a contraindication to surgery. However, the majority of the authors concluded that, although associated with less favorable outcome (50–77% seizure freedom) compared to patients with pure unilateral discharges, the presence of bilateral independent interictal discharges is not necessarily a sign of bilateral epileptogenesis.[29] Some centers contraindicate surgery for bitemporal epilepsy, defined as clinical seizures arising independently from both temporal lobes on scalp EEG. Nevertheless, invasive monitoring reveals unilateral or preponderant (≥80%) ictal onsets in a significant proportion of cases with very satisfactory surgical results, with ≥75% of the patients becoming seizure free. Identification of lateralizing factors during the noninvasive phase of evaluation is crucial to the indication of invasive recordings in this group of patients. They are represented by at least one of the following factors concordant with the side of surgery: ≥75% preponderance of interictal scalp EEG discharges to one temporal lobe, unilateral temporal lesion on MRI, or lateralizing verbal or visual reproduction memory deficits on neuropsychological tests. Other methods of noninvasive assessment such as lateralizing factors on positron emission tomography, single-photon emission tomography, or magnetic resonance spectroscopy could be as useful as the factors mentioned above.[30]

A series of temporal lobe indolent tumors have also shown that contralateral interictal discharges are dependent on the epileptogenic side.[31] On the other hand, patients who experience a variety of clinical ictal onsets may still have seizures originating in one area of the brain with multiple spread patterns.

Progressive underlying neurological diseases

Although a clearly progressive underlying disease process is usually a contraindication to surgical intervention, early hemispherectomies can be an effective treatment for instance in Rasmussen's encephalitis and Sturge Weber syndrome. Yet, caution is again necessary. Bilateral involvement, mainly seen in children with unusually early onset and in adolescents and adults, has been reported in a few cases of Rasmussen syndrome.[32] Progressive features in other neurological conditions that reflect secondary epileptogenesis, drug effects, or psychosocial factors, should not exclude patients from surgery.

Additional special issues in children

In children other issues, as timing, widespread EEG abnormalities, psychopathology and mental retardation need special consideration.

Timing

Precocious onset of intractable epilepsy within the first 24 months of life is a significant risk factor for mental retardation independent of etiology.[33] Despite the recognition that the earlier the surgery is performed in the subgroup of infants with frequent and severe seizures, the better the long-term outcome relative to cognition and behavior taking advantage of neuroplasticity, surgical indications in extremely young children are still debated. Timing of surgery is a critical decision facing technical challenges at this age for an 'elective' procedure. The most serious risk of epilepsy surgery is perioperative mortality. The risk may be higher in infants, because of their tendency to require extensive surgery in the face of small blood volume. For each patient, the timing of surgery must carefully be considered based on a full assessment of the relative risks and benefits, derived from a detailed presurgical evaluation.[34]

Bilateral, independent EEG spikes and/or electrographic ictal onsets

Widespread pathology as well as electrographical interictal and ictal findings are very common in presurgical evaluation of children. Still it has been demonstrated that selected individuals with drug resistant epilepsy may benefit from epilepsy surgery. Despite multiple structural abnormalities on MRI and multifocal EEG abnormalities, stereotyped seizures may arise from a single tuber in patients with tuberous sclerosis. The same is seen in hemimegalencephaly, where hemispherectomy may improve a significant percentage of cases in spite of bilateral interictal discharges and ictal onset in more than half of them.[35,36] Even secondary generalized epileptic syndromes do not represent a formal contraindication for epilepsy surgery, since corpus callosum section may improve drop attacks in patients with Lennox-Gastaut syndrome and localized resections may benefit infants with infantile spasms.[37]

Psychopathology

Children's psychopathology differs from that of adults. Higher rates of psychopathology (83%) with over-representation of autistic spectrum disorders and unusual disruptive behavior disorders have been described in children who had undergone temporal lobe resection for temporal lobe epilepsy.[38] In adults, improvements in mental health problems are directly related to good seizure control postoperatively. On the contrary, epilepsy surgery in children may have a variable effect on psychopathology since preoperative psychiatric disorders may improve, deteriorate, or remain unchanged, independent of seizure freedom. This unpredictability reinforces the importance of a careful counseling to parents and children about the range of mental health outcomes after surgery.

Mental retardation

Substantial global mental delay is common in young children treated with surgery and about 80% of patients present moderate or severe mental retardation.[39,40] In a series of 50 consecutive preschool children, surgical prognosis was related to mental development since 80% of those with IQ ≥70 became seizure free. However, the same was observed in almost half of the severely retarded children. Therefore, profound mental retardation should not be an exclusion criterion for epilepsy surgery selection in small children. Postoperatively, gains in IQ have been related to seizure outcome being observed in seizure-free children and in those with shorter duration of epilepsy.[40]

Conclusion

There are contraindications to epilepsy surgery and a reference center has to provide a full range of established presurgical assessment, surgical treatment, and rehabilitation program. In children and especially in infants, it is critically important that epilepsy surgery be reserved only for patients with severe epilepsy, and performed at specialized pediatric centers.

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SECTION 3

Epilepsies remediable by epilepsy surgery

32 Classification of epileptic seizures and epilepsies

HO Lüders

Introduction

Already Hippocrates in his descriptions of the 'Sacred Disease' discussed several types of epileptic seizures. The majority of the descriptions of epilepsy since Hippocrates also includes detailed classifications of the epileptic seizures.[1] In most of these cases the seizures are simply classified by their main ictal symptomatology. Until relatively recently, however, no clear attempts were made to differentiate between epileptic seizures and epilepsies, i.e., the epilepsies were similarly subdivided according to the ictal symptomatology the patient was suffering from. The 1969-proposals by Gastaut[2,3] was the first attempt to clearly differentiate between the classification of seizures and the classification of epilepsies. The initial proposals by Gastaut in 1969[2,3] and the international classifications which essentially were modeled following Gastaut's philosophy were all adhering to the following principles:

a. Epileptic seizures are paroxysmal events defined by the ictal symptomatology and by a characteristic interictal and ictal EEG.
b. Epilepsies, on the other hand, are defined by a cluster of signs and symptoms (*syndromes*) which usually include one or more types of epileptic seizures, associated neurological deficits, a certain age of seizure onset, and a typical prognosis regarding frequency of seizure recurrence and persistence of seizures with age.

In most cases, however, the seizure type (seizure semiology and EEG) was the main factor which characterized a certain 'epilepsy syndrome'. Therefore, the distinction between epileptic seizures and epilepsy syndrome was frequently unclear. In most cases also, there was a one-to-one mapping from seizure type to epilepsy syndrome. Typical examples are absence seizures and absence epilepsy or infantile spasms and 'West syndrome'. Besides, over the years researchers described a progressively larger number of epilepsy syndromes which they felt tended to occur in clusters. This culminated with the recent 'diagnostic scheme' for the classification of epileptic seizures and epilepsies,[4] which again includes so many different syndromes that even neurologists subspecialized in epilepsy would have difficulties in applying it in everyday practice. This is also most probably the reason this 'diagnostic scheme,' even if approved by the ILAE, has never been implemented.

It is clear that the international classifications of epileptic seizures or epileptic syndromes played a major role in the development of clinical epileptology and have been extremely useful in everyday clinical practice. However, recent diagnostic advances in the epilepsies (including particularly neuroimaging and genetics) point to the need of a completely different approach regarding classification of the 'epilepsies.' Epileptic seizures can now be understood as a *neurological symptom* that occurs in association with an infinite type of insults to the human cortex. We now also know that all epileptic seizures are produced by *multiple etiologies* which converge in producing a particular type of epileptic seizures.[5] In this sense, epilepsy as a symptom is not too different to for example spasticity. Both can be produced by multiple lesions in different parts of the nervous system, both can be the consequence of multiple etiologies, and both respond to medications that are somewhat independent from the location of the lesion or the etiology of the symptom.

These observations lead us to propose a 5-tier 'classification' system.[6] Two of these five tiers (semiological characteristics of the seizures and seizure frequency) define the *symptom*, namely the epileptic seizures. The other three tiers (etiology, associated neurologic deficits, location of the epilepsy) define *what is producing the epilepsy* and the *location* of the brain abnormality.

It is also very important to clarify the terminology as it applies to epileptic seizures and epilepsies. As will become clear below, in the classification system proposed here, epileptic seizures are defined exclusively by ictal semiological features. Therefore, all the modifiers of the term 'seizures' refer to ictal semiology and anatomical modifiers (left, right, etc.) refer to the location of these semiological characteristics. For example, in the expression 'left hand clonic seizures', left refers to location where the clonus occurs. On the other hand, anatomical modifiers of the expression 'epilepsy' refer to the location of the epileptogenic zone, i.e. generalized epilepsy implies that the whole brain is epileptogenic, whereas left paracentral epilepsy implies that the epilepsy originates from the left paracentral region of the brain.

We will now give a short summary of the five-tier classification system. Detailed description of this system can be found elsewhere.[5–16]

Tier 1: Epilepsy

This tier defines the location of the epileptogenic zone. The precision with which we can define the location of the

epileptogenic zone varies depending on the number and type of diagnostic procedures we perform (interictal EEG, ictal EEG, MRI, PET, SPECT, invasive EEG studies, etc.). The following subdivisions can be defined:

1. Focal: epileptogenic zone located within one cortical lobe
   a. Frontal
   b. Perirolandic
   c. Temporal
      i. Neocortical temporal
      ii. Mesial temporal
   d. Parietal
   e. Occipital
   f. Other
2. Multilobar: epileptogenic zone affects more than one brain lobe
   a. Bilobar homotopic: epileptogenic zone affects two homotopic brain lobes (bitemporal, bifrontal, etc.)
   b. Other
3. Generalized: epileptogenic zone is bilateral, diffusely distributed affecting most or all of the brain cortex.

Classical 'epilepsy syndromes', which are a shortcut for a constellation of clinical features, almost invariably refer to generalized epilepsies. Most, if not all epilepsy syndromes, are clearly defined by listing the characteristics of the five tiers that are outlined her. However, for many experienced epileptologist the 'syndromic expression' is a useful shortcut expression. Therefore, we felt it would be useful to list the epilepsy syndrome in parenthesis after specifying the epileptogenic zone. For example; *Epilepsy: Generalized (Lennox-Gastaut Syndrome)*

Tier 2: Semiological seizure classification

The ictal semiology is, by definition, the clinical expression of a patient with epilepsy. Until the discovery of the EEG in 1930, epileptic seizures were defined exclusively by clinical semiology.[17] However, with the discovery that the EEG could localize the origin of the seizures investigators felt that the combination of the EEG findings and the seizure semiology could add significant precision to an 'epilepsy classification'. This was the first step towards an 'epilepsy syndrome' classification. Later, additional factors like MRI findings, associated neurological deficits, etiology, etc. were added leading to our modern definition of epileptic syndromes. At the same time, as mentioned above, in many instances in which the epilepsy syndrome was defined almost exclusively by the semiology/EEG findings, there was no distinction between semiology/EEG 'syndrome' and 'epilepsy syndrome'.

In the five-tier epilepsy classification shown here, the second tier classifies the epileptic seizures exclusively by clincial semiology, *independent of the results of any other tests* (interictal EEG, ictal EEG, MRI, PET, SPECT, neurological and neuropsychological examination, etc.). This leads to a clear distinction between epileptic seizures (*refers to the ictal semiology*) and epilepsy (*refers to the epileptogenic zone*). The tests used to define the epileptic seizures is exclusively *clinical observation* by the physician (video recordings) or by the patient itself or other direct observers (anamnesis). On the other hand, to define the location of the epileptogenic zone (epilepsy) we use the results of all available tests.

Details of the semiological seizure classification can be found in previous publications.[8,10,11,13,15,18–21] The main categories included in the semiological seizure classification are listed below.

Semiological seizure classification

1. Auras
   a. Somatosensory auras
   b. Visual auras
   c. Auditory auras
   d. Gustatory auras
   e. Olfactory auras
   f. Autonomic auras
   g. Abdominal auras
   h. Psychic auras
2. Autonomic Seizures
3. Dialeptic Seizures
4. Motor Seizures
   a. Simple Motor Seizures
      i. Myoclonic seizures
      ii. Clonic Seizures
      iii. Tonic Seizures
      iv. Versive Seizures
      v. Tonic-Clonic Seizures
      vi. Epiletic Spasms
   b. Complex Motor Seizures
      i. Automotor seizures
      ii. Hypermotor seizures
      iii. Gelastic Seizures
5. Special Seizures
   a. Atonic seizures
   b. Akinetic seizures
   c. Astatic seizures
   d. Negative myoclonic seizures
   e. Hypomotor seizures
   f. Aphasic seizures

Each seizure type listed above is considered a seizure component. Each seizure component can be modified by somatotopic modifiers, for example, *generalized tonic-clonic seizures* or *left visual auras*. In this case the somatotopic modifier always refers to the clinic semiology. The evolution of a seizure is expressed by linking two to four seizure components by arrows. Alterations of consciousness during a seizure is indicating by inserting (*AOC*) after the seizure component during which the patient had a clear alteration of consciousness. Besides, lateralizing signs not specified by listing the seizure evolution can be added. Example: *Left visual aura → left hand clonic seizure* (*AOC*) → *generalized tonic-clonic seizure. Lateralizing sign: postictal aphasia.*

Tier 3: Etiology

It is becoming more and more clear now that epilepsies are always produced by multiple etiologies. In some cases one of

the etiological factors might play a clearly dominant role (for example, seizures secondary to a tumor) whereas in other instances it is almost impossible to isolate a single etiology that is responsible for the epileptic seizures (for example, patients with 'genetic' epilepsy in which multiple genes contribute to the generation of epileptic seizures). However, there are always multiple contributing etiologies even if there is a single clearly dominant etiological factor. For example, the studies of Andermann and Metrakos[5,22,23] show that the incidence of seizures, epilepsy, and EEG abnormalities is significantly higher in close relatives of patients with surgically treated epilepsy than in the general population. This indicates that even in patients who were treated surgically for epilepsy, genetic factors still play a significant role in the etiology of focal, symptomatic epilepsy.

To facilitate entering the seizure/epilepsy classification into a database, Lodeenkemper et al. suggested the following classification of seizure/epilepsy etiologies.[6]

1. Hippocampal sclerosis
2. Tumor
   a. Glioma
   b. Dysembrioplastic neuroepithelial tumor
   c. Ganglioglioma
   d. Other
3. Malformations of cortical development (MCD)
   a. Focal MCD
   b. Hemimegalencephaly
   c. MCD with epidermal nevi
   d. Heterotopic grey matter
   e. Hypothalamic hamartoma
   f. Hypomelanosis of Ito
   g. Other
4. Malformations of vascular development
   a. Cavernous angioma
   b. Arteriovenous malformation
   c. Sturge–Weber syndrome
   d. Other
5. Central nervous system infections
   a. Meningitis
   b. Encephalitis
   c. Abscess
   d. Other
6. Central nervous system inflammation
   a. Rasmussen encephalitis
   b. Vasculitis
   c. Other
7. Hypoxic-isquemic brain injury
   a. Focal ischemic infarction
   b. Diffuse hypoxic-ischemic injury
   c. Periventricular leukomalacia
   d. Hemorrhagic infarction
   e. Venous sinus thrombosis
   f. Other
8. Head trauma
   a. Head trauma with intracranial hemorrhage
   b. Penetrating head injury
   c. Closed head injury
   d. Other
9. Inheritable conditions
   a. Presumed genetic cause
   b. Tuberous sclerosis
   c. Progressive myoclonic epilepsy
   d. Metabolic syndrome
   e. Channelopathy
   f. Mitochondrial disorder
   g. Chromosomal aberration
   h. Other
10. Structural brain abnormality of unknown cause
11. Other
12. Unknown etiology

Tier 4: Seizure frequency

The management of a patient with epilepsy is primarily focused on reducing the frequency and intensity of epileptic seizures. Therefore, at each office visit the health-care provider needs precise information about the type of seizures the patient is actually suffering from (given by the semiological seizure classification) and the number of seizures the patient had since the last visit (given by seizure frequency). In the seizure classification we can just list the average seizure frequency since the last visit or use broad categories which we also defined in previous publications.[6]

1. Daily seizures
   One or more seizures per day
2. Persistent seizures
   Less than one seizure per day but at least one seizure/6 months
3. Rare or no seizures
   Fewer than one seizure every 6 months
4. Undefined
   Seizure frequency can not be specified because of unknown seizure frequency, recent onset of epilepsy or recent surgery of epilepsy

Tier 5: Related medical conditions

Here we provide additional information (free text) about major non-etiological medical conditions the patient may be suffering from. Example: mental retardation, hemianopia, depression, previous surgical procedures, etc.

Examples of classifications

Case 1

Epilepsy: Left mesial temporal
Seizures: Psychic aura → automotor seizure (AOC) → Right face clonic seizure
Lateralizing sign: postictal aphasia
Etiology: Left mesial temporal sclerosis
Seizure frequency: Persistent
Related medical condition: Depression, poor verbal memory

Case 2

Epilepsy: Right frontal
Seizures: Left hand clonic seizures → generalized tonic-clonic seizure
Etiology: Right frontal malformation of cortical development
Seizure frequency: Undefined
Related medical conditions: Postsurgical left hand paralysis, right frontal lobectomy (January, 2008)

Case 3

Epilepsy: Generalized (Lennox-Gastaut syndrome)
Seizures: Generalized astatic seizures
Dialeptic seizures
Generalized tonic seizures
Generalized tonic-clonic seizures
Etiology: Diffuse hypoxic-ischemic injury
Seizure frequency: Daily
Related medical conditions: Severe mental retardation, left hemiparesis

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33 Mesial temporal sclerosis

HO Lüders

Already in the late nineteenth century, investigators realized that in patients with epilepsy, mesial temporal sclerosis was frequently found.[1] However, it was the development of modern neurodiagnostic techniques and the growing interest in surgery of epilepsy (particularly for patients suffering from mesial temporal sclerosis) that has greatly advanced our understanding of mesial temporal sclerosis. In spite of all these advances, there still are many unanswered questions.

Mesial temporal sclerosis is defined by its anatomical characteristics, namely gliosis and loss of neurons in the hippocampus, subiculum, parahippocampal gyrus, and inferomedial temporal cortex. Consistently the main change is seen in CA1, CA3, and hilus with relative sparing of CA2 and the granular cells of the dentate gyrus.[2] These changes are associated with typical sprouting of the dentate granular cells,[3] as well as of neuropeptide Y, substance P, and somastatin fibers.[4] Many authors consider these cellular reorganizations as an indispensable feature in the neuropathological diagnosis of mesial temporal sclerosis.

From an epileptological point of view, mesial temporal sclerosis is of special interest because of its high prevalence and its association with a relatively uniform clinical syndrome of high epileptogenicity. The high epileptogenicity of mesial temporal sclerosis is most probably related to the relatively selective loss of mossy cells in the hilus, essential for an inhibitory feedback to the main hippocampal input pathway, namely the dentate gyrus granular cells,[5] and the sprouting of the granular cells, which essentially establishes an excitatory feedback to the dentate gyrus granular cells.[3] Direct neurophysiological studies of resected tissue have actually confirmed the hyperexcitability of the granule cells as also the loss of inhibition.[6]

The characteristic clinical syndrome is mainly an expression of the fact that mesial temporal sclerosis is a highly epileptogenic lesion that affects selectively a constant region of the brain, namely the hippocampus and the immediately adjacent cortex. There certainly are other focal epilepsies also characterized by a constant pathological substrate (cortical dysplasias, heterotopias, etc.), but none of the other entities affects consistently the same anatomical region. Most of the characteristics of focal (regional) epileptic syndromes, namely semiology of the seizures and interictal and ictal EEG abnormalities, are defined by the location of the epileptogenic zone.

The abdominal aura, one of the most characteristic initial clinical semiology of seizures arising from the hippocampus, is most probably determined by spreading of the epileptogenic discharge to the closely adjacent insular cortex. In other words, as for most focal epileptogenic lesions, the epileptogenic zone and the symptomatogenic zone does not overlap. Depth recordings have shown that in patients with mesial temporal sclerosis, most of the seizures arise from the hippocampus. However, electrical stimulation suggests that the symptomatogenic area, for most of the symptoms associated with mesial temporal lobe seizures, was due to spread of the epileptiform activity to adjacent structures. Fear, the other typical aura, is most probably produced by activation of the amygdala. Other of the typical auras observed in patients with mesial temporal sclerosis are also most probably an expression of epileptogenic activation of paramesio-temporal regions (basal temporal region for psychic auras, amygdala for olfactory auras, etc). Most of the ictal as well as postictal symptoms observed in patients with mesial temporal sclerosis can also be attributed to a typical spreading pattern of seizures arising from the mesial temporal region (automatisms possibly produced by activation of the cingulate gyrus, postictal aphasia due to 'Todd paralysis' of the basal temporal and/or Wernicke's area, etc.). Certainly all the lateralizing signs seen with seizures arising from the mesial temporal region are also an expression of seizure spread with involvement of adjacent brain regions (basal ganglia for the contralateral dystonia, language areas for the postictal aphasia, ipsilateral motor strip for the contralateral version and clonic seizures, etc.).

Patients with mesial temporal sclerosis also have a typical interictal and ictal EEG, which again is just an expression of the constant localization of the epileptogenic zone to the mesial temporal region. Surface recordings show spikes and sharp waves localized primarily to sphenoidal and nasopharyngeal electrodes or in the anterior temporal–inferior frontal region (F7-F8). These surface spikes are most probably an expression of epileptiform activity in the parahippocampal cortex as opposed to hippocampal spikes itself. Spikes limited to the hippocampus, which is a closed field, are usually 'invisible' to surface electrodes. With depth electrodes, however, the main spiking is detected in the hippocampi. Ictal EEGs, when recorded with surface electrodes, tend to lateralize the seizure onset but only infrequently show localized seizure onset to the anterior temporal–inferior frontal electrodes (Sp1, Sp2, F7, F8). This is an expression of the surface electrodes' inability to detect hippocampal spikes and the relatively rapid spread of the ictal discharge once a seizure has been initiated. On the other hand, depth electrodes and electrodes placed directly on the hippocampal gyrus (foramen ovale and subdural electrodes) usually demonstrate extremely localized seizure onsets at a time when no alterations are evident when recording simultaneously with surface electrodes.

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There are, in addition, functional alterations typical of patients with mesial temporal sclerosis that are also due to the typical location and neuropathological characteristics of the lesion in these patients, namely a relatively selective loss of neurons usually affecting, to different degrees, both hippocampi. Neuropsychological testing of patients with mesial temporal sclerosis (including particularly pre- and posttemporal lobectomy studies) has greatly contributed to our understanding of the function of the hippocampus. The results of these studies have been complemented by the Wada test and also correlation studies between neuropsychological tests and MRI or neuropathological findings. The results of all these studies show that the dominant (usually left) hippocampus is essential for anterograde verbal memory, whereas the right hippocampus is most probably related to anterograde nonverbal memory. These conclusions come from studies that observed verbal memory deficits in patients with left mesial temporal sclerosis and the degree of deficit was a function of the degree of hippocampal volume loss on MRI studies[7–9] or neuronal loss on pathological studies.[8,10] This also explains why the postsurgical deficit is most marked in those patients that had the least hippocampal atrophy presurgically, namely patients with (1) intact memory function presurgically[11–15]; (2) relatively limited atrophy of the hippocampus on MRI[16–18]; (3) limited histopathological neuronal loss,[19–22] and (4) relatively preserved memory of the temporal lobe to be resected on Wada test.[23, 24] All these studies also showed that one hippocampus can compensate for most of the functions of the contralateral hippocampus. This is the reason that resection of one hippocampus, if the other hippocampus is relatively intact, leads only to mild to moderate memory deficits. On the other hand, it is well known that bilateral lesions of the hippocampus (e.g., herpes encephalitis) consistently produces devastating anterograde memory deficits.[25–27]

It is clear from this discussion that mesial temporal sclerosis is a focal epileptic syndrome that presents an unusually stereotyped clinical picture because the underlying pathology is extremely constant and it consistently affects the same neurological substrate (hippocampus and immediately adjacent cortex). However, it is unlikely that mesial temporal sclerosis is the consequence of a single etiology, the indispensable criterion to classify it as a disease. There is extensive evidence in the literature that the hippocampi are easily damaged by a variety of noxious stimuli. Patients with mesial temporal tumors or hamartomas usually have a mild degree of mesial temporal neuronal loss attributed to the excitotoxic effect of hippocampal seizures. This conclusion is supported by evidence that generalized, or focal status, in adults may induce swelling and eventually may lead to mesial temporal sclerosis.[28,29] It has also been shown that patients with mesial temporal sclerosis (shown on pathological studies or by MRI) have a significant higher incidence of febrile convulsions[30–34] and that mesial temporal sclerosis occurs more frequently in patients who had suffered febrile convulsions.[35,36] This evidence again suggests that the febrile convulsions itself could have led to damage of the hippocampus, perhaps by a mechanism of excitotoxicity. However, we should not forget that mesial temporal sclerosis occurs in a high percentage of patients (close to 70%) with no evidence of febrile convulsions. This again suggests that mesial temporal sclerosis is just the 'final pathological pathway' to a number of different hippocampal insults.

The hypothesis that mesial temporal sclerosis is not a unique disease with a single etiological factor is further supported by the observation that meningitis can frequently lead to mesial temporal sclerosis in children. These studies also suggest that the hippocampus is particularly susceptible to the excitotoxic effects of seizures in children of less than 5 years of age,[37–39] corresponding with, a period during which the hippocampus grows rapidly and, there-fore, may be particularly vulnerable. This special susceptibility of the immature brain to damage has also been proven experimentally by Wasterlain and Plum[40] and Hattori and Wasterlain.[41]

Summarizing, focal epileptic syndromes are currently classified according to the location of the epileptogenic zone. However, patients with an epileptogenic zone in a similar brain structure frequently present with very dissimilar epileptic syndromes because many etiologies can produce epileptogenic zones in a similar or identical brain region. Mesial temporal sclerosis, however, not only affects a clearly defined set of neurons but is associated with an extremely uniform pathological picture. Growing evidence in the literature suggests that mesial temporal sclerosis is the result of excitoxicity to hippocampal neurons at a relatively young age (less than 4–5 years). This explains why these patients frequently have a history of febrile convulsions or another illness associated with convulsions at a young age, followed then by a 'silent period' of 5 to 10 years before the actual seizures emerge. A better understanding of the pathogenesis of mesial temporal sclerosis will be essential to eventually prevent the occurrence of such a frequent and devastating disease.

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34 Neocortical temporal lobe epilepsy

A Ebner

Introduction

Temporal lobe epilepsy is usually divided into two different forms, depending on from which part of the temporal lobe the seizures actually originate. The division into mesial temporal lobe epilepsy (MTLE) and neocortical temporal lobe epilepsy (NTLE) is especially important since each of these epilepsies requires a distinct surgical strategy.

Compared to MTLE in which the seizure origin is rather circumscribed and essentially confined to the mesial structures, seizures in NTLE may arise from many different foci. Therefore, NTLE resembles other neocortical extratemporal focal epilepsies.

Historically, the concept of a distinct syndrome of NTLE has developed over recent decades, essentially based on the increasing interest in surgical treatment of intractable focal epilepsies of temporal lobe origin. The distinction between mesial and lateral temporal lobe epilepsies has been made possible through the availability of detailed analyses of seizure symptoms stored on video, together with surface and invasive EEG recordings, as well as the increasingly higher resolution of structural imaging techniques. The most convincing proof of the existence of lateral temporal lobe epilepsy is the successful resection of a neocortical temporal focus leading to seizure freedom.

Anatomy of the temporal neocortex

Figure 34.1 shows the distribution of various types of cortices found in the medial and lateral part of the temporal lobes adapted from Engel.[1]

The medial temporal lobe comprises several neural structures, such as the amygdala; the hippocampus together with the adjacent entorhinal and perirhinal cortex; and the parahippocampal cortex, also called the paralimbic areas, including the temporopolar cortex (area 38 from Brodman). Bordering the paralimbic areas are the inferior temporal gyrus containing Brodman area 20 in its anterior and middle part, and area 37 lying in the temporo-occipital junction. Areas 20 and 37 belong to modality-specific association areas. Between the entorhinal area and the inferior temporal gyrus, a strip of high-order association cortex (Brodman area 36) is located.

The medial temporal gyrus with Brodman area 21 also represents modality-specific association cortex. A second strip of high-order association cortex (Brodman area 36) is located between the middle and the superior temporal gyrus. The superior temporal gyrus contains the primary auditory cortex (Heschl area) with the medial transverse temporal area (Brodman area 41) and the lateral transverse temporal area (Brodman area 42). The other part represents a modality specific association area (Brodman area 22).

Functional anatomy

The main functions ascribed to different regions of both temporal lobes are depicted in Figures 34.2 and 34.3 (adapted from refs 2 and 3). These functions comprise verbal and nonverbal memory, emotional behavior, smell, and hearing.

Semiology of seizures arising from temporal neocortex

Aura

The content of auras in NTLE is produced by ictal activation of functional cortex in which the seizure originates. An auditory aura, for example, is the consequence of ictal activation of the primary or secondary auditory cortex and may indicate that seizure onset is in the Heschl area. However, it is also possible that the seizure origin is in a silent cortical area and spreads from there to the auditory cortex where it produces the first clinical symptom. Thus, the presence of an auditory (or any other sensory) aura always has to be interpreted cautiously in terms of localizing the seizure onset zone. In addition, it is important to be aware of the possibility that seizure activity, especially with neocortical origin, may spread very rapidly, leading to almost simultaneous co-activation of more widespread areas including mesial temporal structures. Thus experiential phenomena, as they were called by Penfield and Jasper, may not be specific for the lateral temporal neocortex. Rather, as was proposed by Gloor,[4] reciprocal connections between the limbic structures and the temporal isocortex have to be activated in order to obtain these phenomena. This has also been proposed by Blume *et al.*,[5] who concluded that ictal experiential phenomena represent simultaneous epileptic discharges of the temporal neocortex and the limbic system.

Types of auras reported in NTLE

Auras described in NTLE depend on the functional areas being activated at seizure onset or early during a seizure. According to the functional anatomy shown in Figures 34.2 and 34.3, several types of experiential or psychical auras[6] may occur due to activation of the memory system and, the auditory system, or the visual system.

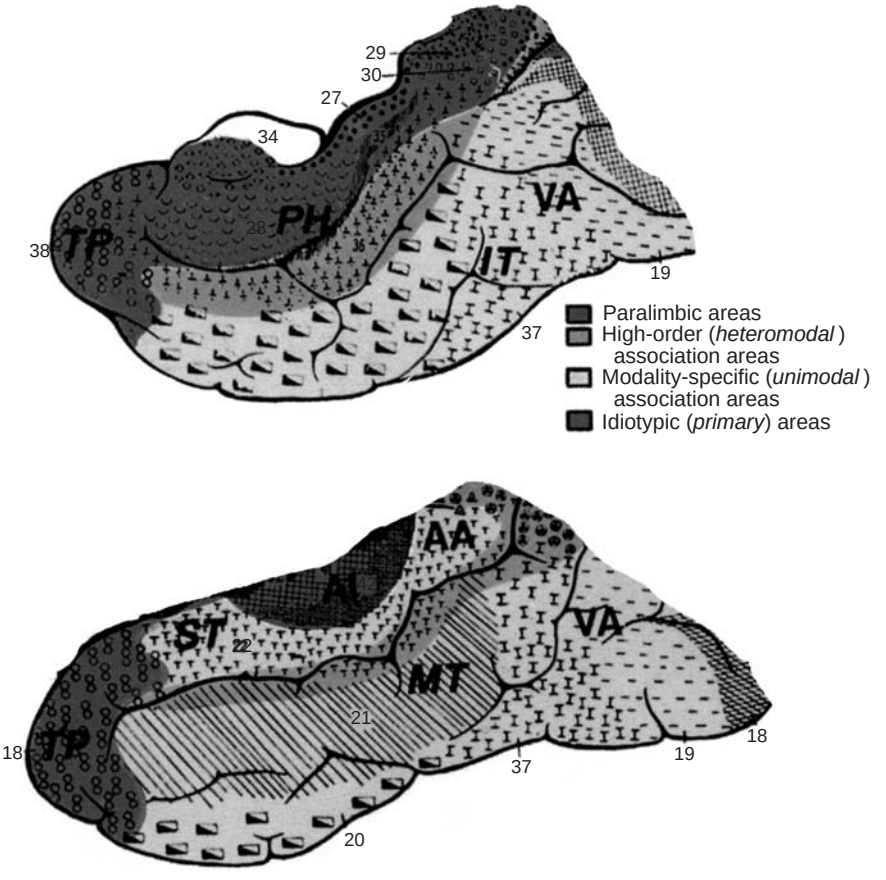


Figure 34.1 Medial (top) and lateral aspect of temporal lobes showing the supposed distribution of paralimbic (green), high-order (pink), modality-specific (yellow), and idiotypic or primary (blue) areas. This information is mainly based on experimental results in animals. AI: primary auditory cortex, AA: auditory association cortex, IT: inferior temporal gyrus, MT: medial temporal gyrus, ST: superior temporal gyrus, TP: temporopolar cortex, PH: parahippocampal area, VA: visual association cortex. The numbers indicate cytoarchitectonic areas following Brodman's map of the human brain (from Engel 1989, with permission). (See Color plates.)

These consist of memory illusions (*déjà vu, jamais vu, déjà entendu, jamais entendu*, feeling of strangeness) and memory hallucinations (memory flashbacks, dreams of past). Auditory auras can occur as unformed hallucinations (ringing, buzzing, chirping, machine-like) or as more elaborate sounds (voices, music). Auditory illusions can be perceived as advancing or receding, louder or softer, clearer or fainter sounds. Visual hallucinations originating in the posterior temporal association cortex consist of the perception of scenes, objects or faces. Illusions may occur as macropsia, micropsia, seeing objects nearer or farther, clearer or blurred.

Several reports support the assumption that patients with NTLE have different types of auras when compared with patients with MTLE. Maillard *et al.*[7] investigated 187 stereoencephalography-recorded seizures of 55 patients who were classified into three groups according to their electrophysiologic findings. There were 24 patients whose seizure onset was in the mesial temporal structures, 13 in the lateral temporal cortex, and 18 patients in both medial and lateral temporal areas. Auditory and other sensory hallucinations or illusions occurred significantly more often in the lateral group and viscerosensory and emotional auras in the medial group. However, with the exception of fear and dreamy states, which were not seen in the lateral group, all other auras also occurred in all three groups.

Gil-Nagel and Risinger[8] compared a group of 16 patients with hippocampal seizure onset (proven by seizure freedom after surgery) with a group of 19 patients with extrahippocampal temporal seizure onset. In the first group, 13 patients reported one of the following auras: five reported epigastric auras, three fear, two smell, two somatic, and one gustatory. In the NTLE group 11 patients reported auras mostly of the psychical type, none reported epigastric or emotional auras. Pfander *et al.*,[9] on the contrary, found a relatively high number (33%) of epigastric auras in a group of 36 patients with NTLE.

O'Brian *et al.*[10] found no statistically significant differences in the incidence or nature of auras in a group of 31 patients with MTLE compared to 15 patients with NTLE.

The difference might be explained by different patient populations studied. Psychical auras are more common in patients suffering from NTLE but they are in no way specific to NTLE. In our series of 14 patients with circumscribed lesions affecting the temporal neocortex as revealed by MRI (neocortical temporal lobe epilepsy group: nTLE, Figure 34.4a, b), significant differences were found in auditory/visual auras and epigastric auras: auditory/visual auras were more frequent in the nTLE and epigastric auras more frequent in the mTLE group consisting of 18 patients who were seizure free after temporal lobectomy (Figure 34.5). There was no difference between the two groups regarding other auras (memory illusions, fear, gustatory or none).[11]

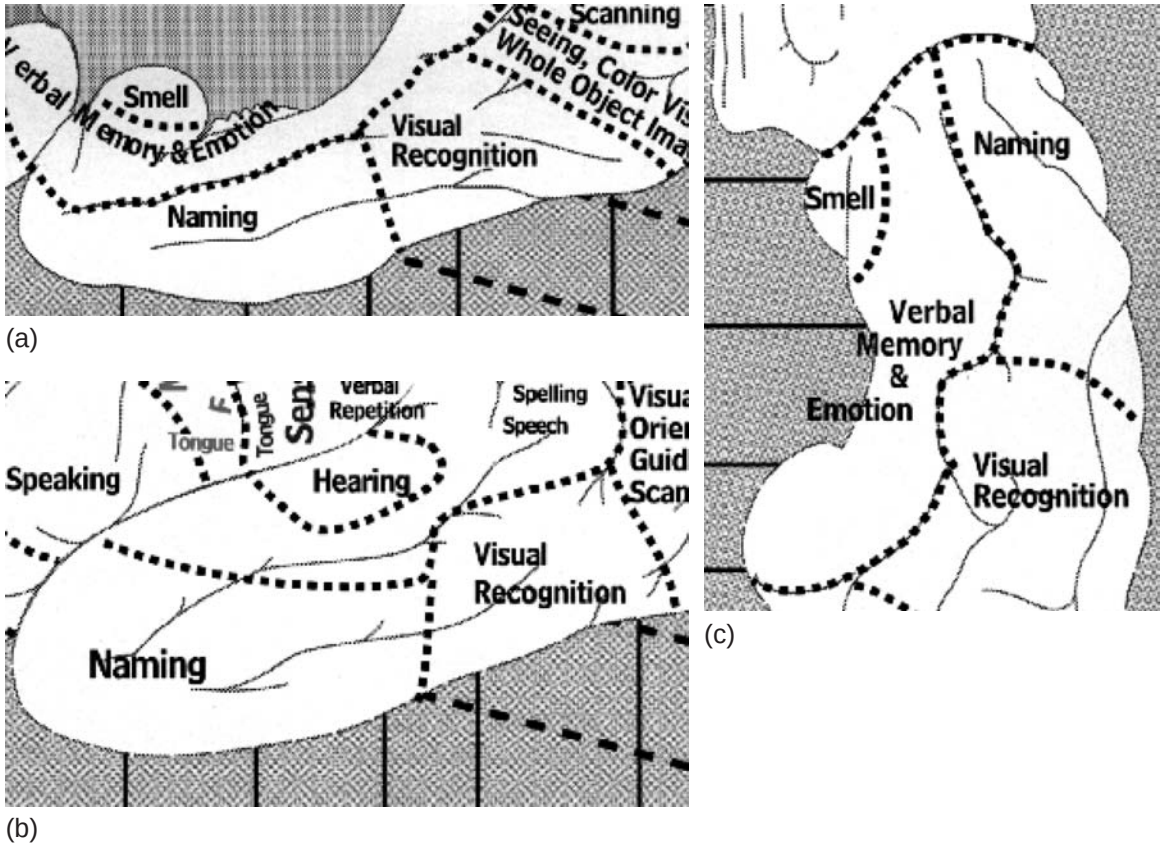


Figure 34.2 (a) Functional anatomy of the mesial part of the left temporal lobe. (b) Functional anatomy of the lateral portion of the left temporal lobe. (c) Functional anatomy of the basal aspect of the left temporal lobe. Adopted from Ardaman[2,3] *et al*. with permission.

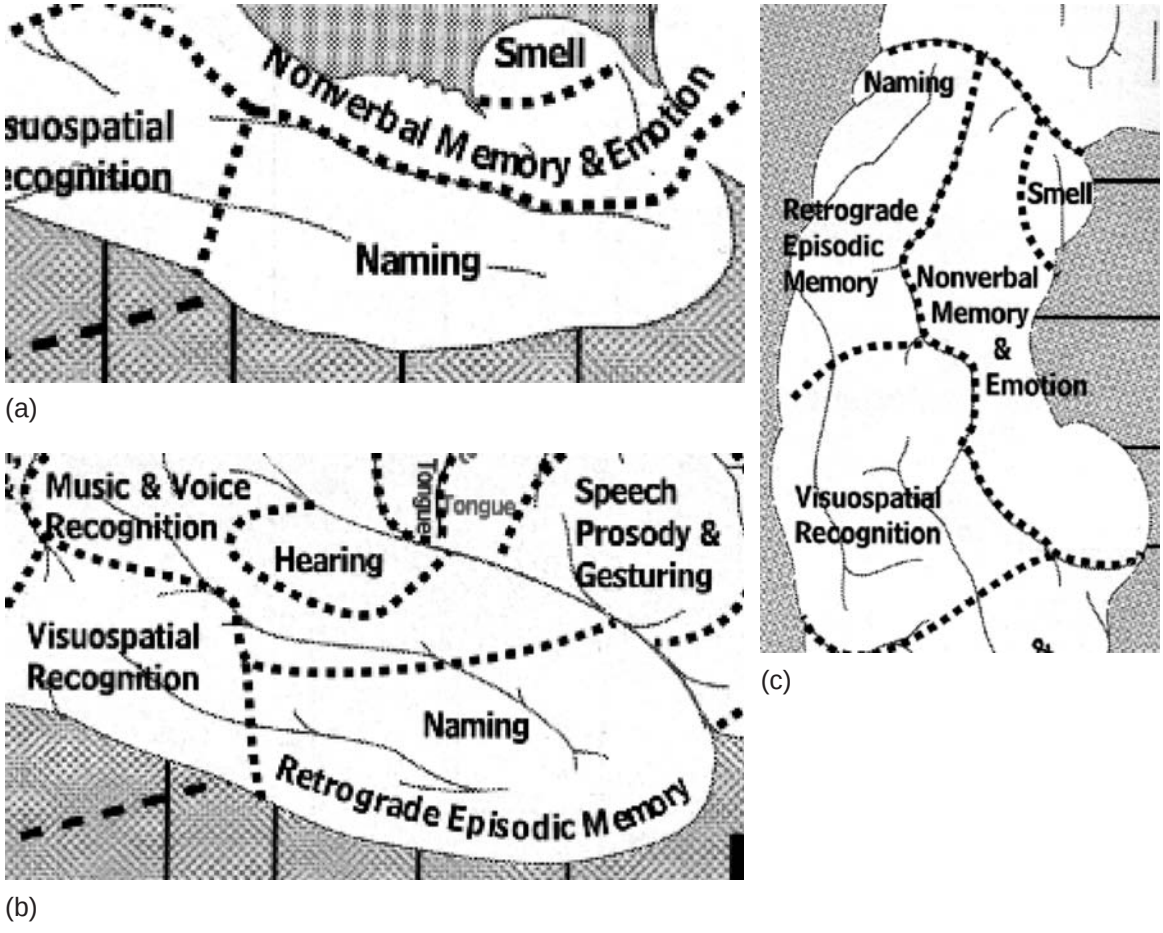


Figure 34.3 (a) Functional anatomy of the medial portion of the right temporal lobe. (b) Functional anatomy of the lateral portion of the right temporal lobe. (c) Functional anatomy of the basal aspect of the right temporal lobe. Adopted from Ardaman[2,3] *et al*. with permission.

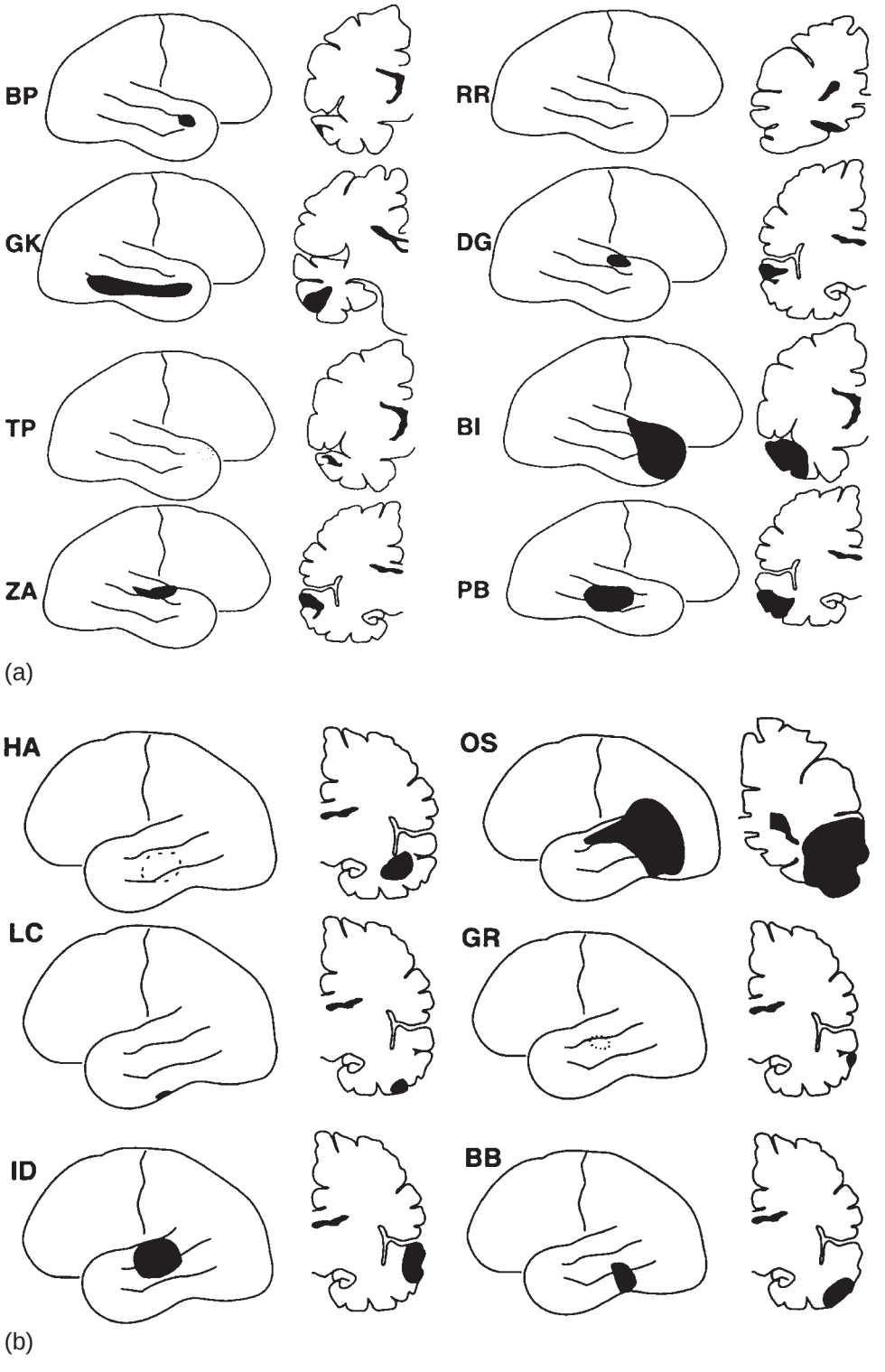


Figure 34.4 (a) Site of the neocortical temporal epileptogenic lesions of the right side traced from MRI scans in 8 patients.[11] (b) Site of the neocortical temporal epileptogenic lesions of the left side traced from MRI scans in six patients.[11]

Seizure semiology

Epileptic auras occur isolated, i.e., stop before other seizure symptoms follow, or progress to seizure signs that can be observed and analyzed when recorded on video. Many ictal motor manifestations have been described, such as version, clonic and tonic activity, unilateral epileptic spasms, dystonic posturing and unilateral automatisms, automatisms with preserved responsiveness, ictal spitting and vomiting, emotional facial asymmetry, unilateral eye blinking, ictal nystagmus, and akinesia. Furthermore, loss of consciousness, ictal language manifestations and postictal features, such as Todd's palsy, postictal aphasia, postictal nosewiping, postictal memory dysfunction, as well as peri-ictal water drinking, peri-ictal headache, and ipsilateral tongue biting have been analyzed.[12]

Several studies addressed the question whether seizures arising from temporal neocortex exhibit ictal signs that can help to differentiate them from seizures originating in other regions of the brain, most specifically the mesial temporal region.

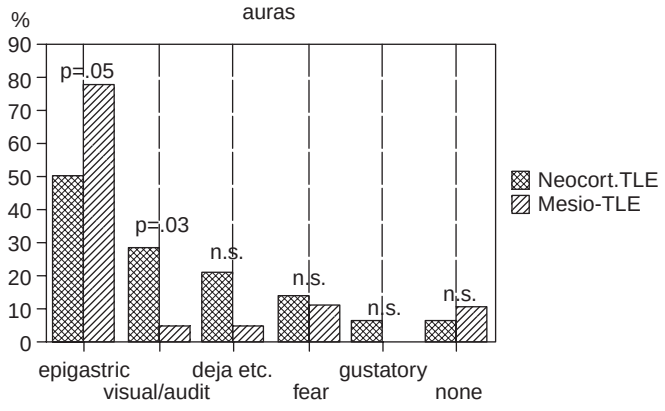


Figure 34.5 Comparison of the frequency of auras reported in the mesial and neocortical TLE group. Only epigastric and visual/auditory auras showed a significant difference (Fisher's exact test).[11]

In the study of Maillard *et al.*[7] only initial loss of contact, shorter duration, and more frequent generalizations were associated with neocortical temporal lobe seizures, whereas other investigated signs (oro-alimentary automatisms, vocalizations, verbal automatisms, upper limb automatisms, upper-limb tonic posturing, head and/or eye deviations) when occurring early or late during the seizures were either observed significantly more frequently in seizures of mesial temporal origin or did not show any difference between NTLE or MTLE.

Gil-Nagel and Risinger[8] found that early oral automatisms were significantly more frequent in MTLE than NTLE, whereas early motor involvement of the contralateral upper extremity without oral automatisms occurred significantly more often in NTLE. No difference between NTLE and MTLE was found in arrest reaction, vocalization, speech, facial grimace, postictal cough, late oral automatisms, and late motor involvement of the contralateral arm and hand.

Pacia *et al.*[13] found a motionless stare at ictal onset the most common behavioral manifestation in NTLE.

Pfander *et al.*[9] observed early clonic activity following automatisms significantly more frequently in NTLE.

Holl *et al.*[14] investigated 80 seizures (51 MTLE and 29 NTLE) of 30 patients (20 MTLE and 10 NTLE) with regard to dystonic posturing of the upper limb. Ictal dystonia was subdivided into different subtypes according to distinct clinical features. Their frequency and latency from the clinical onset of seizure were assessed. Frequencies of all subtypes were similar in MTLE and NTLE. Concerning the latencies, contralateral dystonic posturing characterized by sustained muscle contractions with flexion of the wrist and fist closure occurred significantly earlier in NTLE than in MTLE seizures.

Dupont *et al.*[15] reviewed the videotapes of 60 patients with well-defined MTLE, NTLE, or both to assess the presence and the localizing value of unilateral dystonic posturing associated with motor automatisms. Twenty-eight of the 60 patients exhibited unilateral dystonic posturing. This sign was observed in patients with MTLE and NTLE. It was mostly contralateral to the seizure focus in patients with MTLE and exclusively ipsilateral in patients with NTLE. Unilateral motor automatisms occurred in 26 of the 60 patients with MTLE or NTLE. It was predominantly ipsilateral to the seizure focus in patients with MTLE and exclusively contralateral in patients with NTLE. The association of ipsilateral motor automatisms and contralateral dystonic posturing was found in 14 patients with MTLE but in none of the patients with NTLE. Two patients who had medial and neocortical seizure onset also exhibited this clinical feature. The authors concluded that the association of ipsilateral motor automatisms and contralateral dystonic posturing may help to differentiate MTLE from NTLE with a reliable lateralizing value.

Contralateral motor automatisms were described by Mirsattari *et al.*[16] in a patient with right temporal neocortical seizures. The authors concluded that early onset unilateral motor automatisms without dystonic posturing can localize the seizure origin to the contralateral temporal lobe neocortex.

In our own study,[11] there was no difference in clinical ictal symptoms when patients with NTLE were compared to patients with MTLE (Figure 34.6).

The literature about clinical semiology in neocortical temporal lobe seizures shows heterogeneous results, sometimes with contradictory findings. Most studies compared seizures arising from the temporal neocortex with seizures of mesial temporal origin due to hippocampal sclerosis or other mesially located etiologies. At best, what can be concluded from the above cited publications is that experiential auras with auditory and visual content, early behavioral arrest, and rapid generalization may speak in favour of a neocortical seizure origin although this is, by far, not a common finding in all studies reviewed. Ictal symptoms of seizures arising in the mesial temporal structures exhibit a rather uniform pattern, especially when the sequence of symptoms and signs is regarded.[17]

Theoretically, neocortical temporal lobe seizures may arise from numerous foci with clinical symptoms and signs reflecting the functional properties of the activated area(s) as well as the different possibilities of spread that are predetermined by the cortico-cortical and cortico-subcortical connections.

Etiology of neocortical TLE

In the Epilepsy Surgery Program Bethel 910 patients received resective surgery between 1991 to April 2002. Among those, 610 patients (67%) had temporal lobe resections of which 60% had pure mesial temporal lobe surgery due to hippocampal

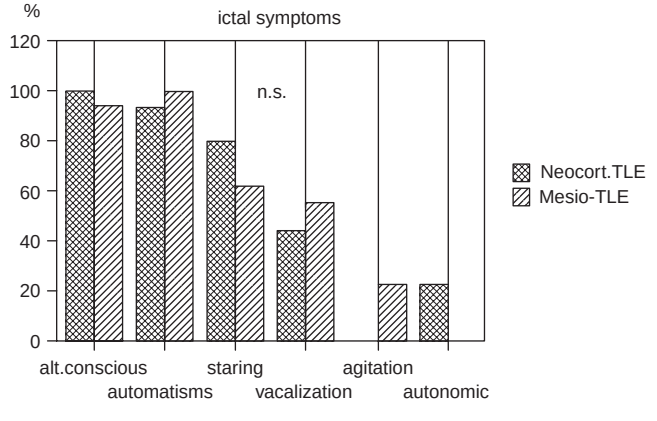


Figure 34.6 Comparison of the frequency of ictal symptoms observed in the mesial and neocortical TLE group. There is no significant difference between the two groups (Fisher's exact test).[11]

sclerosis and another 122 (20%) had other mesially located etiologies. There were 122 patients (20%) who had neocortical temporal resection without mesial structures (unpublished data).

Tumors of benign dignity such as gangliogliomas, dysembryoplastic neuroepithelial tumors or neurocytomas, vascular malformations (mostly cavernomas), and malformations of cortical development are among the most frequent chronic structural abnormalities found in neocortical temporal lobe resections.[18]

Figures 34.7 (a–f) show examples of different lesions in the MRI scans. Other etiologies encompass posttraumatic and postinflammatory defects.

Extrahippocampal temporal lesions may coexist with hippocampal sclerosis, a finding which is called dual pathology. It is not clear whether hippocampal sclerosis is the consequence of ongoing epileptic activity originating from a neocortical focus or a coincidental concurrence. Whenever this constellation is found in a patient it creates diagnostic problems when surgery is regarded. The following case should demonstrate this.

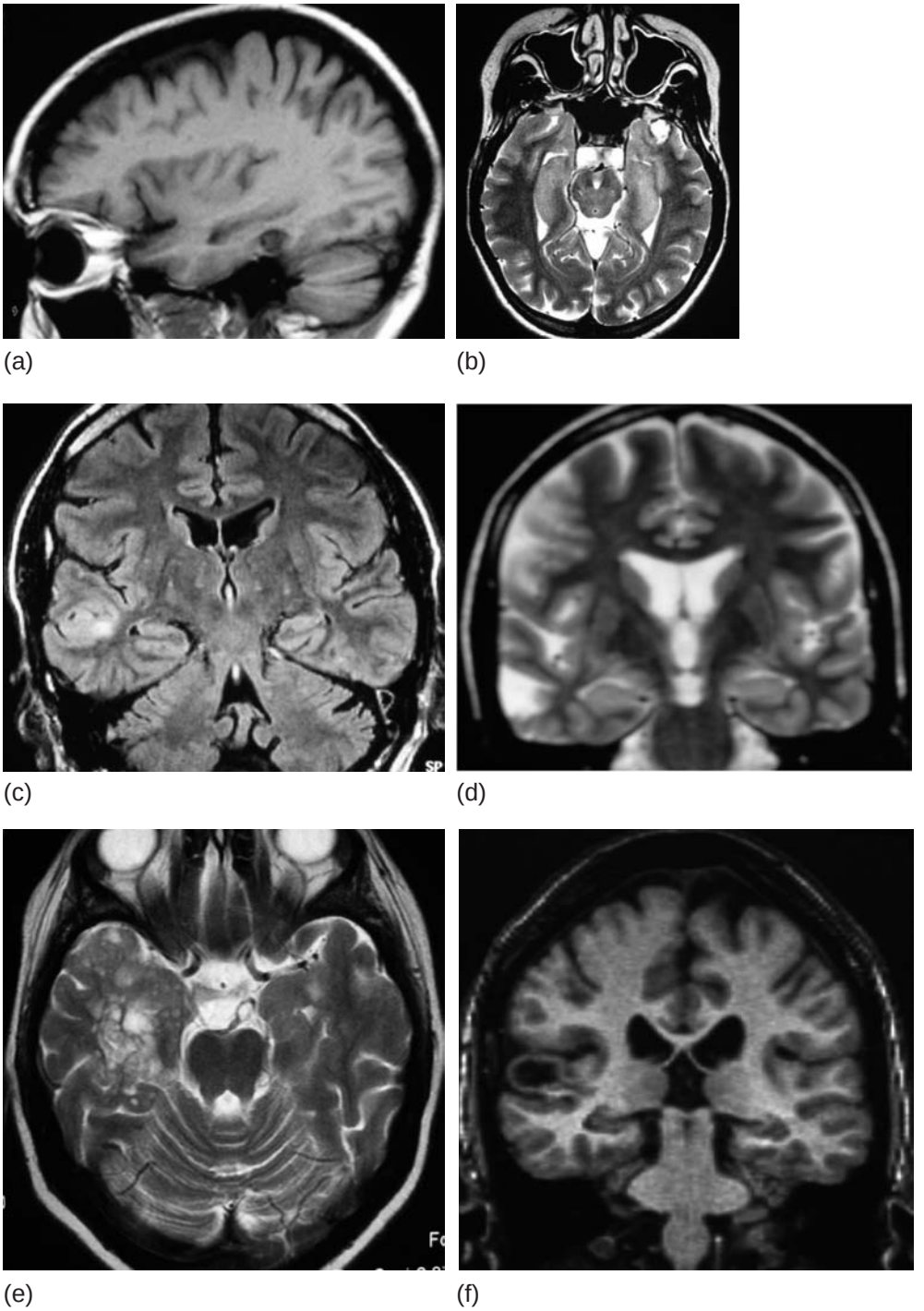


Figure 34.7 Examples of various histologically proven lesions found in patients with neocortical TLE located in different regions of the temporal lobes: (a) cavernoma in the right inferior temporal gyrus; (b) cavernoma in the left temporal pole; (c) focal cortical dysplasia in the right medial temporal gyrus; (d) post-traumatic defect in the right middle temporal gyrus; (e) dysembryoplastic neuroepithelial tumor affecting mainly the right inferior temporal gyrus; (f) gangliocytoma in the right superior temporal gyrus.

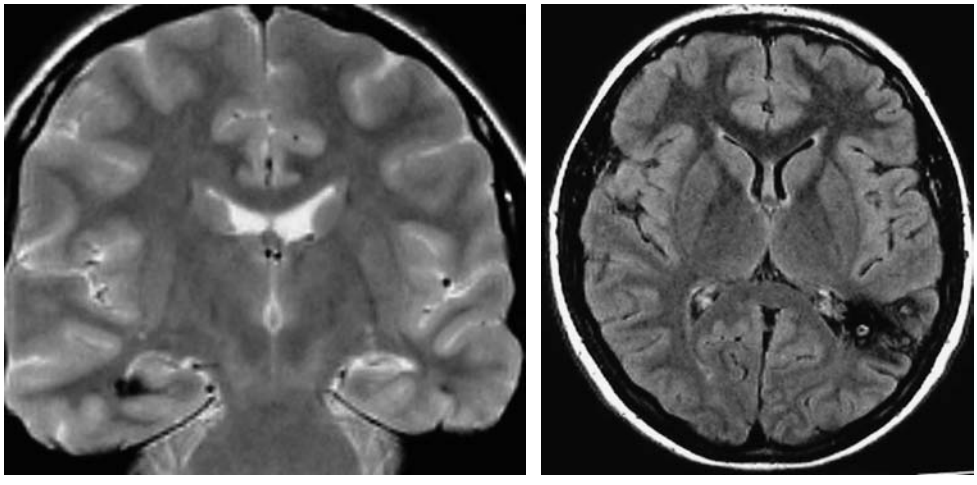


Figure 34.8 Coronal (left) proton density MRI showing the right subhippocampal cavernoma and the left sided hippocampal sclerosis, and axial FLAIR image showing a large left posterior temporal cavernoma.

Case report

A 19-year-old girl suffered from epilepsy since she was 6 months old. Until the age of 15 she occasionally complained about epigastric sensations before seizures, accompanied by loss of consciousness, heavy breathing, and stiffening of the right leg. She had an average of four seizures a month and she failed three first line AEDs before preoperative evaluation was carried out. The neurological examination was normal; her intellectual functions were above average. Her MRI revealed three lesions (Figure 34.8), the largest a cavernoma at the left posterior temporal area, the second a left-sided hippocampal sclerosis, and the third a cavernoma located immediately under the right hippocampus, which was otherwise normal.

During intensive EEG Video Monitoring over 5 days, three of the habitual seizures were recorded. Interictal EEG showed sharp waves over the left temporal region with a phase reversal either at the left sphenoidal electrode (Figure 34.9a) or at electrode T7 (Figure 34.9b) indicating that the maximum negativity of the interictal discharges occurred at the mesiobasal or the temporal lateral region.

Ictal EEG consistently started with low voltage fast activity over the left hemisphere maximal at the posterior electrodes (Figure 34.10a) then evolved into a rhythmic 4–5Hz theta pattern over the left temporal region (Figure 34.10b).

Intracarotid amobarbital test and fMRI for language revealed that the right hemisphere was dominant for speech and memory (Figure 34.11).

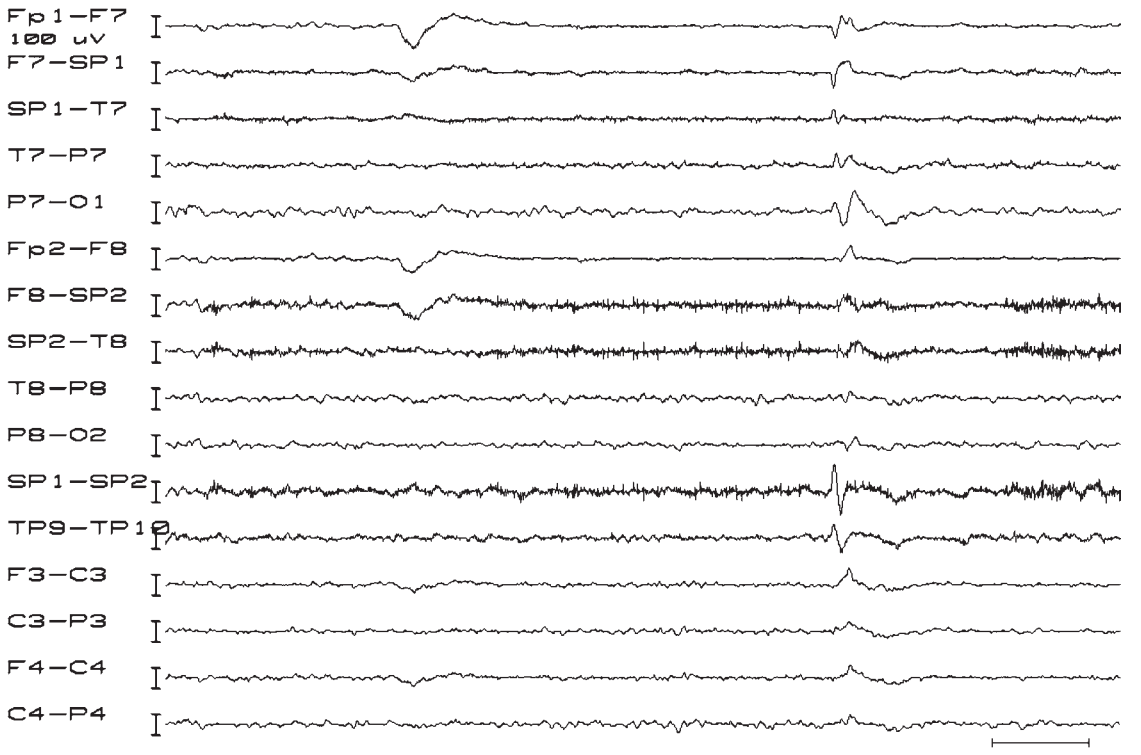
Mainly based on the ictal EEG showing a seizure pattern unusual for mesial TLE but in favor of a neocortical left temporal origin an extended lesionectomy of the left posterior vascular malformation guided by intraoperative electrocorticography was carried out.

The patient has been seizure free for 2 1/2 years despite bitemporally located lesions (see Figure 34.12 corresponding to preoperative MRI and Figure 34.12 showing the postoperative MRI scans).

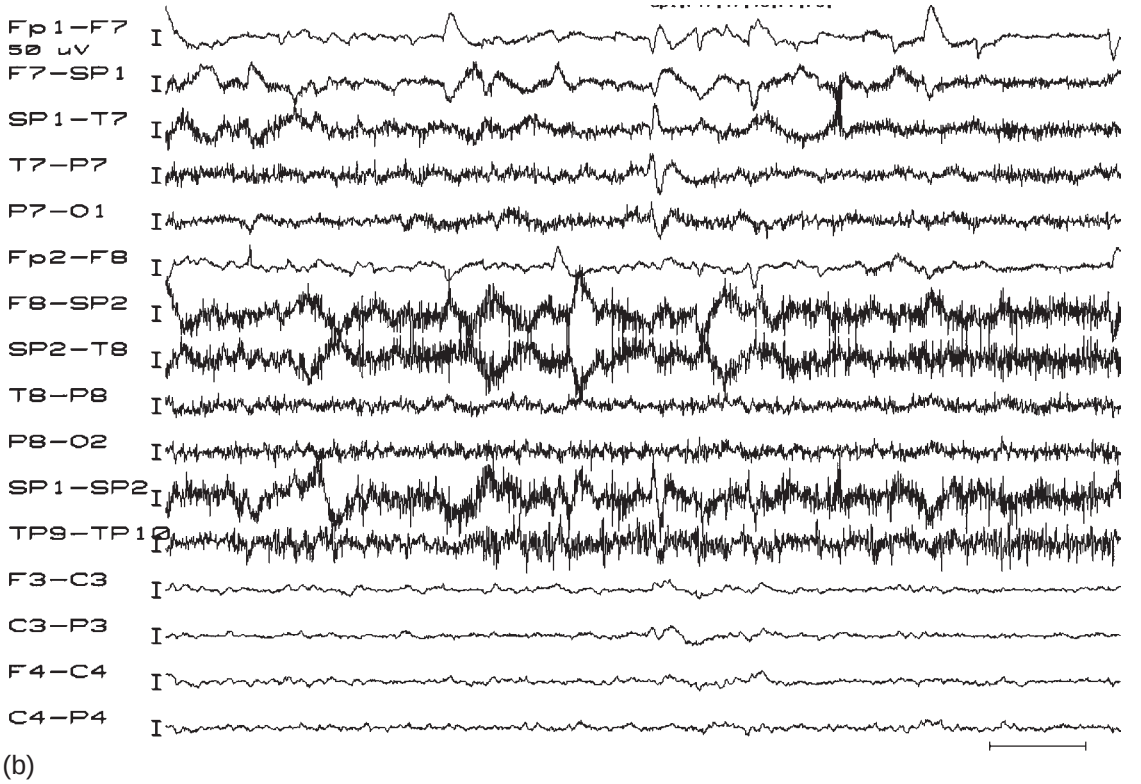
Electrophysiology of neocortical TLE

As was shown in the case report, surface EEG can provide essential information regarding the seizure origin in some patients. Although there is certainly an overlap in interictal and ictal EEG findings in patients suffering from MTLE and NTLE, interictal epileptiform activity in MTLE usually shows a predominance of discharges at the anterior temporal or sphenoidal electrodes and less often at the mid-temporal or posterior temporal electrodes. Pfander *et al.*,[9] and O'Brien *et al.*[10] investigated electroclinical differences in patients with NTLE and MTLE. Regarding the EEG findings, they found no difference in the interictal EEG. There was an increased frequency of fast rhythmic sharp waves (>4 Hz) in the ictal-EEG of MTS patients (mean 81% vs 60%, $P = 0.05$). The patients with NTLE developed bilateral ictal EEG changes more often (mean 55% vs 26%, $P < 0.05$) and more rapidly (mean 23s vs 74s, $P < 0.005$). The onset of ictal EEG seizure activity was bilateral more often in patients with NTLE (20% vs 4%, $P < 0.005$). There were no significant differences between the two groups for any of the video-EEG features, in terms of whether or not the feature occurred at least once in an individual patient. They concluded that there are a number of clinico-electrical differences between patients with mesial MTLE and patients with NTLE, but that none of these are sufficient to allow a distinction to be made in an individual patient. Foldvary *et al.*[20] found a lower mean frequency of lateralized rhythmic activity (LRA) in NTLE ictal EEG recordings that frequently had a hemispheric distribution, whereas LRA in MTLE seizures was maximal over the ipsilateral temporal region. They concluded that it may be possible to differentiate lesional NTLE from MTLE on the basis of historical features, seizure symptomatology, and ictal surface EEG recordings.

In summary, interictal and ictal surface EEG are important to prove (or disprove) the epileptogenicity of a structural abnormality in the temporal neocortex in patients with epilepsy. Some EEG features are more in favor of a neocortical

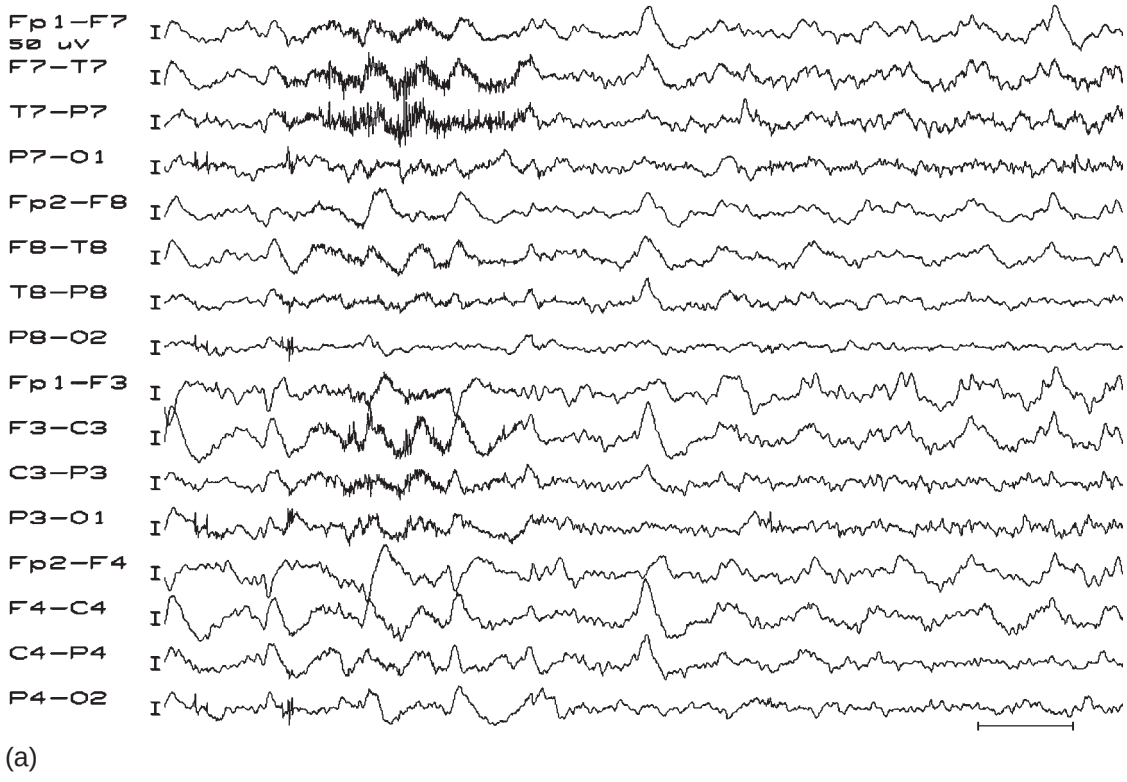


(a)

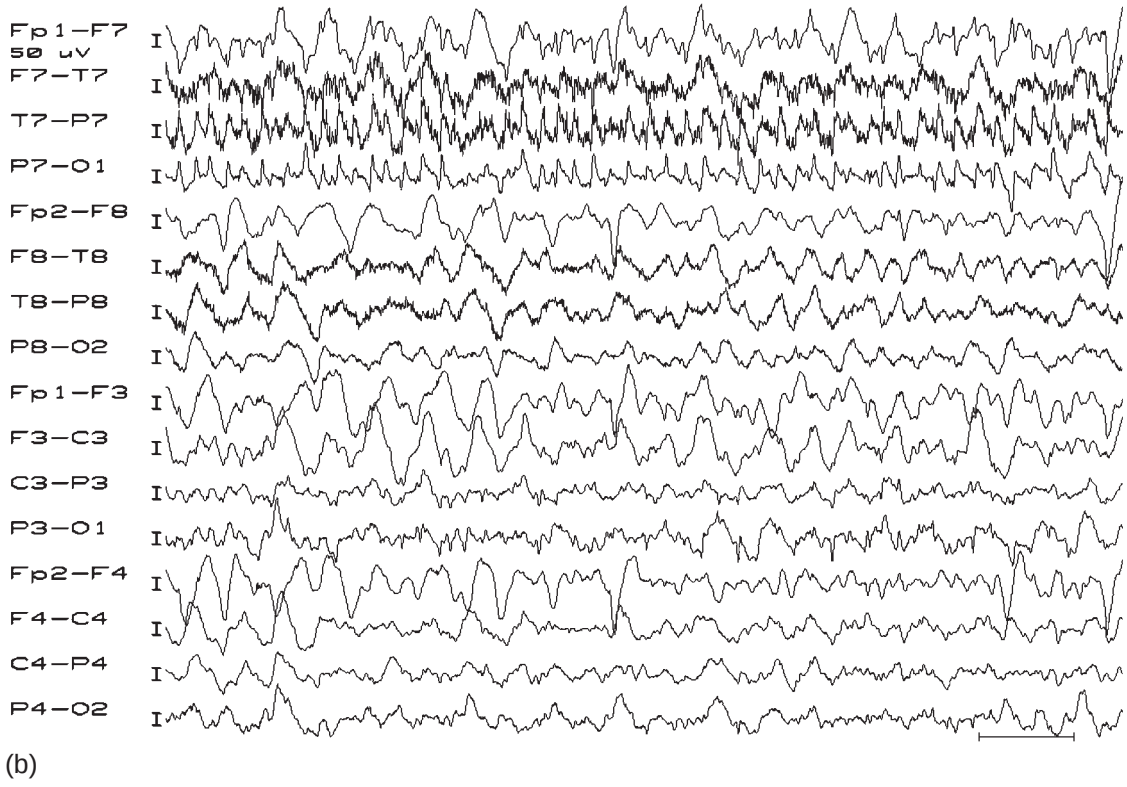


(b)

Figure 34.9 (a) Interictal sharp wave phase reversing at the left sphenoidal electrode. Calibration: horizontal bar corresponds to 1 sec. (b) Interictal sharp wave phase reversing first at the electrode T7 then at SP1.



(a)



(b)

Figure 34.10 (a) Onset of ictal EEG with low voltage fast activity over the left hemisphere maximal over the electrodes P3, P7, and O1. (b) Ictal EEG 30 sec after onset (a) showing a rhythmic 4–5 Hz theta activity over the left temporal area.

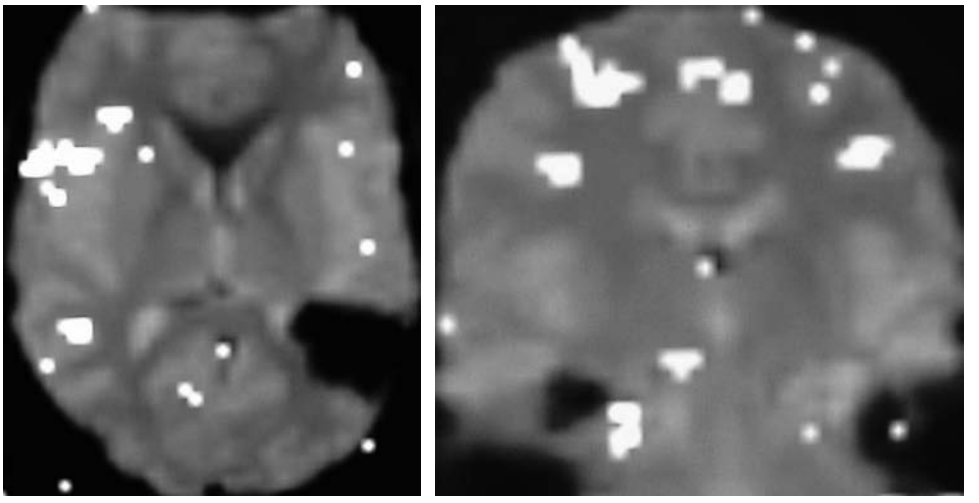


Figure 34.11 Functional MRI for speech (left) and memory (right) showing activation of anterior (Broca) and posterior (Wernicke) speech areas as well as memory-related mesial temporal areas located at the right hemisphere.

seizure origin and it might help to place invasive electrodes in patients without an MRI-visible lesion in order to clarify the situation.

Prognosis

The postoperative outcome in patients with NTLE due to MRI visible lesions is as good as in patients with MTLE. Patients with clearly identified nonlesional NTLE who were operated on and became seizurefree postoperatively are probably rare and nonexistent in the Bethel series comprising more than 1500 operated cases.

Two recent studies have investigated prognostic factors in NTLE. In the study of Janszky *et al.*,[19] more than two-thirds of the patients with NTLE became seizure-free postoperatively. Lateralized/localized EEG seizure pattern and tumors on the MRI were associated with postoperative seizure-freedom, while focal cortical dysplasias (FCD) were associated with a poor outcome. The 6-month postoperative outcome was a reliable predictor for the long-term outcome. Yun *et al.*[31] found that the presence of a focal lesion on MRI, correct localized hypometabolism on FDG-PET, or localized ictal rhythms on EEG are predictors of a seizure-free outcome.

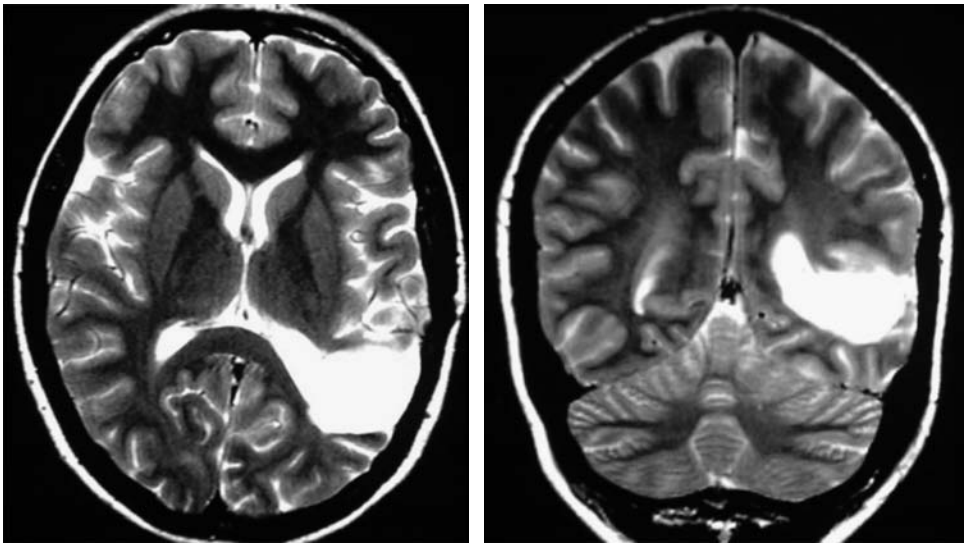


Figure 34.12 Postoperative MRI scans in axial (left) and coronal T2-weighted cuts showing the left posterior temporal defects (cf. also Figure 34.8).

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35 Premotor and central lobe epilepsy

S Bauer, HM Hamer, and F Rosenow

Anatomy

Structural anatomy

Premotor cortex is part of the lateral frontal lobe, which extends from the central sulcus to the frontal pole. Its upper and lower limits are the fissura longitudinalis and the sulcus lateralis, respectively. The surface is formed by the gyrus precentralis between central and precentral sulcus and the superior, medial and inferior gyrus frontalis, which are divided by the superior and inferior frontal sulcus. The inferior frontal gyrus again is subdivided into the triangular, orbital, and opercular part.

The lateral surface of the *central lobe* consists of gyrus precentralis and postcentralis, which are located between sulcus precentralis and postcentralis and divided by the sulcus centralis. The mesial part of the central lobe consists of the lobulus paracentralis between the precentral sulcus and the ramus marginalis of the cingulate sulcus.

Microanatomically, the frontal lobe cortex is part of the neocortex. Therefore, its cortex consists of six neuronal layers. Brodmann subdivided and numerated 52 areas of different cytoarchitectural patterns.[1] Considerable variability has been found in the extent of cytoarchitectonic areas in relation to macroanatomical landmarks, especially in the premotor region.[2–4] Cytoarchitectonic findings and their relationship to gyri and sulci connect the structural anatomy to localization of cortical functions as described below.

Functional anatomy

The *central lobe* contains the somatotopically organized primary *motor and sensory cortex* (Brodmann area 4 and 3, respectively). Historically, the sulcus centralis was thought to be the border between motor and sensory areas,[5] but more recent studies suggested both motor (tonic or clonic and 'negative motor', i.e., motor arrest) and sensory responses after electrical stimulation of the gyrus precentralis as well as in gyrus postcentralis.[6]

In primates, central lobe neurons receive their main input from thalamus and secondary motor and sensory regions, while their efferences form a considerable part of the pyramidal tract: 30–50% of the pyramidal tract fibers arise from primary motor and around 25% from primary sensory cortex. These neurons control kinematic and dynamic parameters of movement rather than single muscles.[4]

The *lateral frontal cortex* is usually subdivided in *premotor* and *prefrontal* cortex.[7]

The *premotor cortex* contains the secondary motor area (Brodmann area 6 in the posterior parts of the frontal gyri), the frontal eye field (Brodmann area 8 at the intersection of sulcus precentralis and superior frontal sulcus) and Broca's language region (Brodmann areas 44 and 45 at the opercular and triangular parts of the inferior frontal gyrus in the dominant hemisphere).

In primates, the secondary motor area is organized roughly somatotopically, receives input from thalamus, primary motor cortex and parietal lobe and sends projections to the spinal cord, the superior colliculus, and the reticular formation. It is involved in planning and controlling movements in response to somatosensory and visual information.[4]

The frontal eye field (Brodmann area 8) is located at the intersection of sulcus precentralis and superior frontal sulcus.[8] Its main function is the control of intentional saccades. Therefore, it receives input from occipital and parietal lobe.

Broca's language area (Brodmann areas 44 and 45) is located at the opercular and triangular parts of the inferior frontal gyrus in the dominant hemisphere.[2] Connections with Wernicke's temporal speech area and primary motor cortex are necessary for its function in speech production.

The supplementary sensorimotor are a (SSMA) also belongs to the premotor cortex and is located in the mesial frontal lobe.

The lateral frontal lobe surface between premotor cortex and frontal pole is sometimes referred to as *prefrontal cortex*. Its function is only vaguely defined and covers executive control, monitoring in working memory, learning, temporal structuring of behavior and control of behavior by context.[9] Few specific regions were identified which were recruited by different demands indicating a prefrontal network involved in solution of diverse cognitive problems.

Epidemiology

Data on incidence and prevalence of frontal lobe epilepsy (FLE) differ widely between general population, patients referred to epilepsy centers, and surgical series. Additionally, various criteria of estimating the location of the epileptogenic zone are used which hampers comparison of study results.

Population-based studies

In 594 patients with newly diagnosed epilepsy, 42% were found to suffer from partial epilepsy.[10,11] In this patient group, the *symptomatogenic zone* was localized as follows:

- primary motor cortex 12%
- primary sensory cortex 4%

- overlapping (motor and sensory) central regions 8%
- one or more frontal regions anterior to the primary motor cortex 14%
- frontotemporal 4%
- (together: 42%).

However, EEG and CT results revealed a strong variance with the seizure semiology in 20% of the patients. This shows the limited value of seizure semiology as single feature for localization of the epileptogenic zone. Reasons for overestimation of frontal lobe epilepsies defined by seizure semiology might be the large extension of eloquent cortex in the frontal and central lobe and the impressive presentation of motor signs in the course of seizures compared to more subtle symptoms of seizures that start in other cortical areas.

Another population-based prospective study[12] used seizure semiology, EEG, and imaging results for classification of epilepsy syndromes according to ILAE criteria.[13] Of 1,016 patients with newly diagnosed epilepsy, 43% suffered from either symptomatic or cryptogenic partial epilepsy. Of those, 26% had frontal lobe epilepsy and 5% parietal lobe epilepsy which included the postcentral part of the central lobe.

In general, the frontal or central lobe appear to be involved in 30–40% of all newly diagnosed partial epilepsies.

Hospital-based studies

Patients with extratemporal epilepsies might be referred less frequently to presurgical video-EEG monitoring compared to temporal lobe epilepsies due to unclear results in seizure semiology and interictal EEG and MRI findings that make eligibility for surgery difficult. Frontal lobe epilepsy was found in 10–27% of adult patients[14–17] and in 18–21% of children[18–20] who were referred to epilepsy centers.

Using a newly-proposed five-dimensional epilepsy classification [21] instead of the ILAE classification, the epileptogenic zone was found to be localized in the frontal lobe in 4% and in the perirolandic area in 3% of 94 randomly selected adult patients of a tertiary epilepsy center; in 7% of 91 children the epileptogenic zone could be localized to the perirolandic area and no child with frontal lobe epilepsy was identified.[22] The differences with previous evaluations may reflect the influence of various classification systems on assessing the diagnosis.

Surgical series

Underrepresentation of frontal lobe epilepsy in surgical series might occur due to the same reasons as stated for presurgical monitoring. A serial of 2177 patients who had undergone epilepsy surgery stated central lobe epilepsy in 7% and epilepsy of (remaining) frontal lobe in 18%.[23] Another study included 124 consecutive patients and found frontal lobe epilepsy in 15% of the patients.[24]

Etiology

Brain tumors

Of all patients with brain tumors, 25–75% develop seizures.[25,26] Infiltrating well-differentiated tumors localized in the forebrain have the highest risk to be accompanied by seizures.[25] Frontal lobe involvement was accompanied by a high epilepsy risk of 40–45%. Patients with tumors involving both frontal and parietal lobe (therefore including central lobe) showed seizures in 58% of the cases.

Presurgical and surgical series of patients with extratemporal neocortical[27] or frontal lobe[23,28–31] epilepsy reveal an incidence of brain tumors of 13–35%. In particular, astrocytoma was found in 10% (with higher incidence of low grade tumors), ganglioglioma in 5–10%, oligodendroglioma in 3–10%, and dysembryoplastic neuroepithelial tumor (DNET) in 1–5% of all frontal lobe epilepsy patients. In other surgical series, 15–30% of DNET were found to be located in the frontal lobe.[32,33]

Focal cortical dysplasia (FCD)

FCD are cortical lesions that contain architectural abnormalities like dyslamination, immature or giant neurons, balloon cells of neuronal or glial origin, and/or dysmorphic neurons. In frontal lobe epilepsy, cortical malformations were found in 20–84%[18,28–31,34,35] and are associated with positive family history of seizures, lower IQ, neurological deficits, multiple seizure types of early onset, and frequent status epilepticus.[36] A series of 14 consecutive children <7 years with frontal lobe epilepsy revealed FCD in all cases.[37] These data were consistent with earlier seizure onset in patients with FCD compared to other etiologies.[28]

FCDs can be divided into two subclasses: type 1 without dysmorphic neurons or balloon cells, and type 2 containing dysmorphic neurons and/or balloon cells ('Taylor-type FCD').[38] Type 1 FCDs were found to be located frequently in the temporal lobe while type 2 tends to occur more often extratemporally, especially in frontal and central lobes.[39] Patients with FCD type 2 have a higher seizure frequency.[40]

Vascular malformations (VM)

Vascular malformations include arteriovenous malformations (AVM), cavernomas, teleangiectasias, and venous malformations and occurred in 7–15% of patients with frontal lobe epilepsy.[30,31,41]

Arteriovenous malformations (AVM) were detected in 6% of frontal lobe epilepsies.[28]

About 20–40% of all supratentorial cavernomas are located in the frontal lobe.[42–44] 25–80% of cavernoma patients develop seizures[42,43,45]; accordingly, in 9% of FLE patients cavernomas were found.[28] Frontal lobe cavernomas presented less frequently with seizures than temporal lobe cavernomas did (45% vs. 70%).[44] Compared to other locations, frontal lobe cavernomas might have a higher probability of causing generalized seizures.[43]

Venous malformations and dural AVM do no seem to cause seizures.[45]

Genetic causes

There are two types of idiopathic focal epilepsies related to frontal or central lobe: Benign epilepsy with centro-temporal spikes (BECTS) and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).

ADNFLE is genetically heterogeneous and can be caused by mutations of genes coding for subunits of the neuronal nicotinic acetylcholine receptor.[46] BECTS has been classified as idiopathic (and therefore with a presumed genetic etiology) by the ILAE[13]; however, the lack of concordance in twin studies makes the classification doubtful.[47]

Other etiologies

Other etiologies include gliosis, e.g., due to head trauma (11–28% [23,28–30]), postinflammatory scars (up to 10%[23]), and birth trauma (up to 8%[23]). Frontal lobe arachnoid cysts were detected in 4 of 867 epilepsy patients (0.5%), but only 1 of the cysts was located near the irritative or seizure onset zone[48] which makes their relationship with epilepsy unlikely.

In up to 20% of frontal lobe epilepsy cases, no underlying pathology can be found.[23,29]

Diagnostic evaluation

Determination of the symptomatogenic zone–Seizure semiology

Most clinical studies concerning seizure semiology in frontal lobe epilepsies estimate location of the epileptogenic zone by defining the symptomatogenic, irritative, or seizure onset zone as well as epileptogenic lesion and may therefore include patients with epileptogenic zones outside frontal or central lobe, whereas studies of patients who became seizure free after frontal lobe resection are not representative for the group of patients who can be treated nonsurgically.[35] Moreover, many studies do not distinguish between certain regions of frontal lobe.

According to functional anatomy described above, *central lobe* seizures may be accompanied by focal somatosensory auras and focal motor signs:[49,50]

- *Focal somatosensory auras* are specific for involvement of central lobe. On the other hand, nonspecific auras occur in the majority of patients with frontal lobe epilepsy.[29,51]
- *Focal motor signs* contain *tonic, dystonic, clonic* and *complex motor* symptoms. Asymmetric tonic limb posturing occurs more frequently during seizures with temporal onset than in frontal lobe seizures.[7] Using EMG and subdural EEG electrodes, it has been shown that clonic seizures are preceded by a tonic phase which is sometimes too short to be recognized clinically.[52] Repetitive EEG spiking in primary motor areas during the initial tonic phase is followed by spike wave complexes and synchronous clonic contraction of both agonistic and antagonistic contralateral muscles. EEG spiking matches muscle contractions whereas relaxation occurs synchronized with EEG slow waves.

Seizures involving the lateral *premotor cortex* may present with the following symptoms:[49,50]

- *Contralateral version* that precedes secondary generalization in half of the seizures.[53,54]
- Version has to be distinguished from the rarer nonforced *head-turning* of unknown pathophysiology without any clonic or pronounced tonic component which frequently appears at seizure onset.[53] Both forms can appear successively in the same seizure.
- *Aphasia, dysphasia or vocalization* may occur if Broca's language area is involved. Pure vocalization other than those caused by cloni or apnea sound was seen in 40%.[55] Another study of 26 FLE patients reported articulate vocalization with uttering of words or swearing in 31%, while 42% of the patients produced other sounds.[56] Surprisingly, prolonged postictal dysphasia occurred in less than 10% of 118 complex partial frontal lobe seizures of 24 patients.[57] The dysphasia was of short duration even if the seizure onset zone was located in the dominant hemisphere; on the other hand, seizures starting in the frontal lobe of the dominant side and spreading to the ipsilateral temporal lobe caused long-lasting postictal dysphasia in >90%. Low distance between seizure onset zone and anatomical location of Broca's speech area (determined by electrical cortical mapping) did not correlate with appearance of postictal language disturbances. This finding suggests a disruption of temporal speech networks rather than direct influence on cortical speech areas as the cause for dysphasia.

  Seizures involving *prefrontal cortex* can present with *complex motor seizures* including automotor, hypermotor and gelastic seizures.[58]
- *Hypermotor seizures* (complex movements involving trunk and proximal limb segments, e.g., bicycling movements, as well as screaming, jumping, running around, or aggressive sexual automatisms), which are considered to be specific for frontal lobe epilepsy with special relation to lesions of frontopolar and orbitofrontal cortex,[49] occur frequently at night and tend to cluster.[29] It can be difficult to distinguish hypermotor seizures from psychogenic seizures. Behavioral symptoms like mood change, unexpected quietness, subtle change of awareness or awakening are other features of prefrontal seizures.[59] Unlike seizures involving primary motor or sensory areas, the complex semiology of prefrontal seizures may be caused rather by disruption of neuronal synchrony between different brain regions than by excitation of single cortex areas (Table 35.1).[60]

Cluster analysis of seizure evolution

Because the described seizure semiology usually does not occur isolated, the analysis of characteristic clusters has be performed.[49] Three seizure patterns have been found to be of localizing value in lateral frontal or central lobe epilepsy:

- Somatosensory aura with or without Jacksonian march, often followed by tonic posturing and head version or clonic seizures (*Video*). Automatisms and vocalization are rare in this seizure pattern. As expected, there is a strong association with central lobe lesions.
- Focal (tonic-)clonic seizures with Jacksonian march without secondary generalization, usually accompanied by ipsilateral head version and followed by postictal paresis. This seizure pattern is also associated with central lobe lesions.
- Version or posturing occurring early during the seizure evolution, frequently followed by other motor manifestations like simple automatisms. This seizure sequence is associated with lesions of the premotor cortex.

Table 35.1 Frequency and lateralizing value of some seizures symptoms and signs in lateral frontal lobe epilepsy

Symptom	Frequency in patients with lateral FLE	Lateralizing value (positive predictive value)	Literature
Postictal headache	41–53%	None (in contrast to temporal lobe epilepsy)	61,62
Unilateral tonic posturing	37–48%	Contralateral (67–100%)	50,54–56,63
Vocalization	37–77%	Probably none (contradictory data)	54,55
Postictal paresis	27–37%	Contralateral (100%)	29,54
Unilateral clonic seizure	23–37%	Contralateral (83–100%)	29,50,54,64
Head-version	22–60%	Contralateral (66–100%)	29,50,53,54,56,64
Complete loss of consciousness	19%	Nondominant	24
Focal somato-sensory auras	16–31%	Contralateral (100%)	31,50,54
Unilateral automatisms	16%	Ipsilateral (67%)	54
Hypermotor seizures	11–38%	None	29,31,50,54,55
Nonforced head-turning	11–31%	None	50,53,54
Postictal nose rubbing	10–37%	None	50,65
Unilateral dystonic posturing	0–21%	Contralateral (100%)	50,54,56

General features of frontal and central lobe seizures

Seizure frequency varies within a wide range. At least in surgical series, high frequency of several seizures per day is not rare in FLE,[29] but in patients with newly diagnosed epilepsy no significant differences in average seizure frequency were found between various partial epilepsies.[10]

Frontal lobe seizures tend to *cluster especially at night times*. More than half of the patients experience *status epilepticus* in their history which may even appear periodically in some patients.[29]

The *duration* of partial seizures arising from the frontal lobe is reported to be significantly shorter than the duration of temporal lobe seizures and does usually not exceed 1 minute.[29,51] Another study[49] did not confirm these results concerning the average seizure duration, but noted also that extremely short seizures (<10 s) were more likely to occur in frontal lobe epilepsies.

Secondary generalization occurs in up to 70% of the patients during lifetime.[29] However, the hypothesis that secondary generalization was more frequent in frontal lobe epilepsy than in other epilepsies could not be confirmed in more recent studies.[51]

Frontal lobe seizures were found to occur more frequently during non-REM-*sleep* than temporal lobe seizures.[66] However, this feature is of little clinical value to distinguish both syndromes in individual patients, because patients who develop seizures during sleep are seen in both epilepsy syndromes.[29,66,67]

Postictal headache (migraine-type, tension-type or unclassified) occurred in 41–53% after frontal lobe seizures.[61,62] The more posteriorly the seizures start, the more frequent is the migraine-type postictal headache (occipital lobe 20%, temporal lobe 10%, frontal lobe 5%).[61] In contrast to temporal lobe epilepsy in which the side of the headache was found to be ipsilateral to the seizure onset zone in 90%, there seems to be no lateralizing value of postictal headache in frontal and central lobe epilepsy.[62]

In *children* with FLE, the immature cortex architecture might influence seizure semiology; the lack of automatisms and secondary generalization has been attributed to this feature.[37]

Determination of the irritative zone

Interictal EEG

Interictal spikes or sharp waves appear in 60–80% of frontal lobe epilepsies (Figure 35.1); they are considered to be of less localizing value than in temporal lobe epilepsy because they can be bilateral, multilobar, or even generalized.[26,35,68–70] However, as far as the lateral frontal lobe is involved both interictal and ictal EEG findings are of higher localizing value.[71] Concordance of the epileptogenic zone with the irritative zone was found in 72% of the patients with lateral FLE compared to 33% with mesial FLE.[72] Possible reasons for this difference are the smaller distance between lateral cortex areas and scalp electrodes and the fact that tangential dipoles in mesial FLE cannot be detected by EEG.

The use of closely spaced surface electrodes other than those of the 10–20-system may improve localization if the irritative zone but did neither increase EEG sensitivity in 23 patients with frontal or central lobe epilepsy nor did it help in lateralizing the irritative zone in those patients who had bilateral epileptic discharges in conventional EEG.[73]

The sensitivity of interictal EEG is higher in intracranial subdural than in scalp recordings. Due to the closer distance to cortex, subdural electrodes may reveal a smaller extent of the irritative zone in some patients than surface electrodes do. However, a sampling bias remains in invasive monitorings.[69]

Pre-excision epileptiform activity during intraoperative electrocorticography recorded from >2 lateral frontal lobe gyri and central lobe predicts a poorer surgical outcome while postresection absence of spikes or sharp waves other than those at resection borders strongly correlates with a favourable surgical result.[74,75]

Magnetoencephalography (MEG)

Registration and localization of interictal discharges using magnetoencephalography (MEG) and magnetic source imaging (MSI; MEG co-registered with MRI) has been shown to be of predictive value for surgical outcome in some FLE patients.[76] Of 21 FLE patients who were considered for invasive monitoring, nine had no epileptic EEG discharges.[77]

In three of these patients, MEG showed interictal epileptic discharges. Especially patients with lateral neocortical localization of the irritative zone and patients whose epilepsy was caused by focal cortical dysplasia seemed to benefit from MEG investigation. Hence, combination of MEG with EEG can be helpful for tailoring the placement of invasive electrodes.

Determination of the seizure onset zone

Ictal EEG

Short seizure duration, fast cortical spreading and frequent muscle artifact in seizures with early motor signs as well as the large portion of frontal lobe cortex that is 'hidden' to scalp electrodes due to its far distance and vertical orientation restrict the value of ictal EEG recordings in frontal lobe epilepsy.[78] Again, this restriction applies more to mesial than to lateral frontal lobe epilepsy: seizures originating in the mesial frontal lobe were found to propagate faster than dorsolateral frontal seizures.[79] Ictal scalp EEG in 127 seizures of 15 patients with lateral frontal lobe epilepsy showed correct localization of the epileptogenic zone in 65% of the patients, while 26% of the seizures started with generalized EEG activity and 3% were mislateralized in the EEG analysis.[80] Only 1.5% of the seizures were obscured by artifacts or did not show EEG changes at all. The most frequent EEG patterns at seizure onset were repetitive epileptiform activity (36%) (Figure 35.2), rhythmic delta (26%) and EEG suppression (14%). Rhythmic theta activity, the most frequent seizure pattern in temporal lobe epilepsy, was seen in only 9%. A smaller study of nine patients also comparing medial and lateral frontal lobe epilepsy found that absence of focal electrographic seizure activity excluded the possibility of dorsolateral frontal lobe seizures with a negative predictive value of 93%.[71]

Although scalp electrodes showed widespread seizure onset and MRI was read as normal or nonlocalizing, the use of subdural grid electrodes that covered extensively frontal areas were reported to localize the seizure onset zone in >90% by several authors.[79,81]

Ictal single photon emission computed tomography (SPECT)

An early report about exploration of the seizure onset zone in 22 children with frontal lobe epilepsy using ictal 99Tc-HMPAO-SPECT showed hyperperfusion in 91% and correct localization in 95% of the cases.[82] However, newer data on adults did not confirm these promising results. Localization of seizure onset was found in only 33–43% of frontal lobe epilepsy patients.[83–85]

Subtraction ictal SPECT co-registered to MRI (SISCOM) as well as the combination of ictal SPECT with near-infrared spectrospcopy (NIRS) has increased diagnostic sensitivity,[86–88] but sufficient data on frontal lobe seizures are not yet available.

Determination of the epileptogenic lesion

Magnetic resonance imaging (MRI)

Surgical series showed MRI-lesions in 46–97% of the patients[28,29,31,68,89–91] (Figure 35.3). In 38 children, the rate of lesions detected by MRI were found to be only 32% compared to 97% in 17 children with mesial temporal lobe epilepsy.[20] Presence of an MR lesion strongly correlates with a good surgical outcome: 25–41% of patients without MRI lesions became seizure free or had only nondisabling seizures after surgery as compared to 67–72% of MR-positive patients.[70,89,90] According to the frequent etiologies of frontal lobe epilepsies, inclusion of FLAIR and proton weighted series for detection of dysplasias and blood products is recommended.[51,92,93]

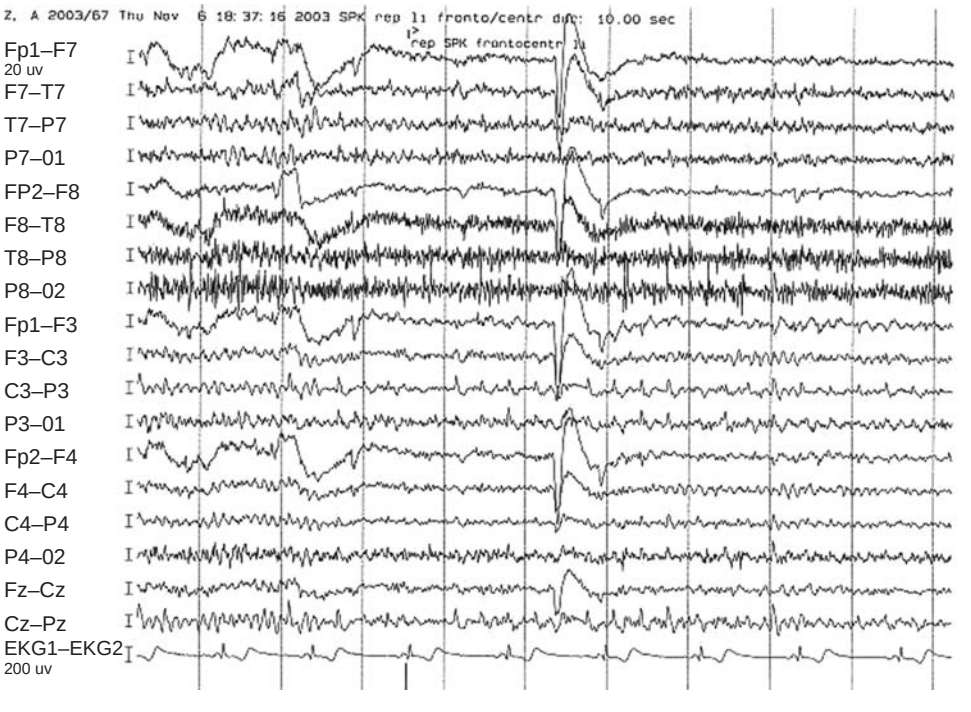
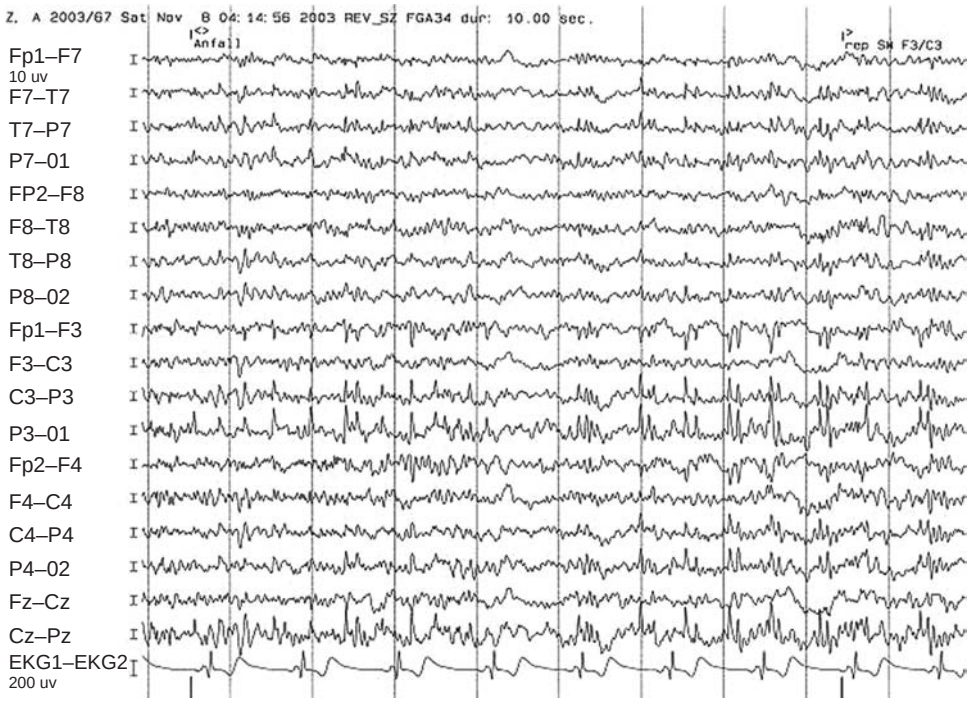
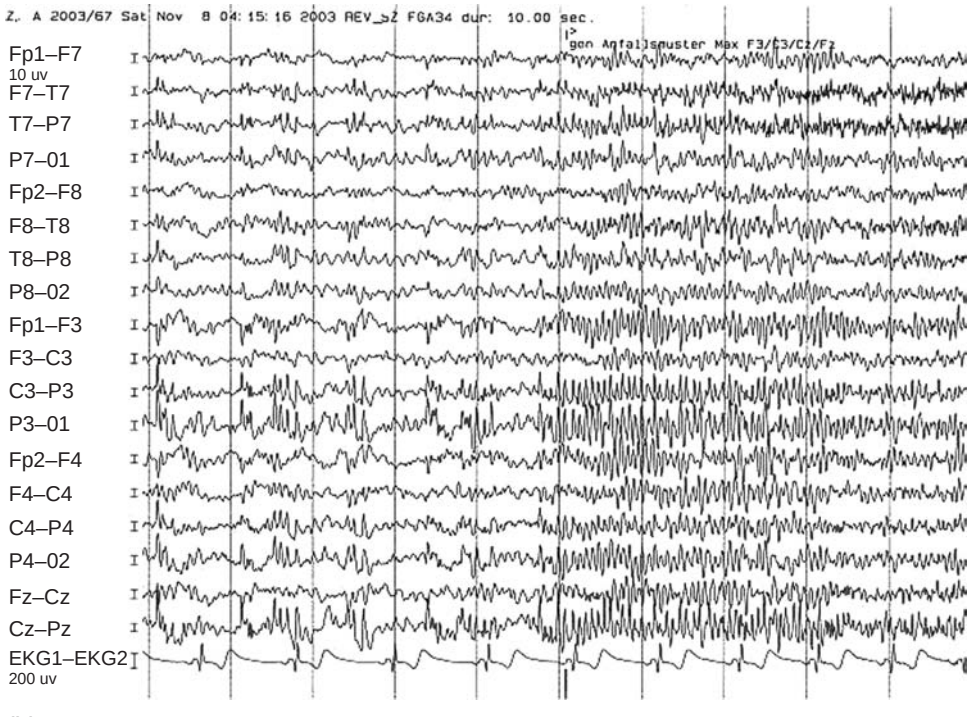


Figure 35.1 Interictal EEG recording of a 35-year-old man with lateral frontal lobe epilepsy caused by a left frontal cavernoma. The EEG shows repetitive spikes left frontocentral (F3 = C3 > P3, 5Fp1).



(a)



(b)

Figure 35.2 (a,b) Ictal EEG recording of the same patient as in Figure 35.1. The seizure starts with repetitive spikes, regional left frontocentral (F3,C3) and propagates toward a generalized beta-activity with left frontocentral (F3,C3,Fz,Cz) maximum.

MRI review by experienced neuroradiologists can remarkably improve its sensitivity.[94]

Additional and experimental methods

Despite its low spatial resolution, *MR spectroscopy* can help to lateralize and even localize epileptogenic frontal and central lobe lesions by detection of reduced N-acetylaspartate levels.[95,96] The area of decreased N-acetylaspartate concentration frequently exceeds the epileptogenic lesion as seen in MRI.[97]

Diffusion tensor imaging may be helpful for detection of the epileptogenic lesion in patients without structural changes on conventional MRI, especially in patients with focal cortical dysplasia.[98–100] Furthermore, multiplanar reconstruction and curvilinear reformatting were shown to improve the localization of focal cortical dysplasias in the frontal lobe.[101]

Unlike in mesial temporal lobe epilepsy, postictal *diffusion weighted MRI* may be helpful in detection of the seizure onset zone in selected patients with FLE.[102]

Determination of the functional deficit zone

Interictal single photon emission computed tomography (SPECT)

Interictal 99Tc-HMPAO-SPECT is of little value in neocortical epilepsy: areas of hypoperfusion have been found in only 24% of patients without MR-abnormalities, and these areas did not match the epileptogenic or seizure onset zone.[103] In 22 children with frontal lobe epilepsy, only two had interictal localized hypoperfusion that was concordant with clinical, EEG, MRI, and pathological findings.[82] Therefore, performance of interictal SPECT seems to be reasonable only together with ictal SPECT.

Positron emission tomography (PET)

The overall sensitivity of ^{18}F-fluorodeoxyglucose-PET (FDG-PET) scans in frontal lobe epilepsy was reported to be 46–96%.[104] There is a correlation between MRI lesions and pathologic results in FDG-PET: hypometabolism was found in about 75% of patients with unilateral frontal lobe epilepsy and MR abnormalities.[14,105] However, only in 29–45% of patients without MR-detectable lesion but electroclinical features of unilateral frontal lobe epilepsy localizing hypometabolism were seen in FDG-PET.[14,83,105] In a prospective study PET revealed pathological findings in no patient with bifrontal epilepsy and normal MRI.[14] Flumazenil-PET for detection of low benzodiazepine receptor density showed only a slightly higher sensitivity to lateralize cryptogenic unilateral frontal lobe epilepsy. The method did not contribute significantly to localization of the epileptogenic zone.

The sensitivity for ^{18}F-fluorodeoxyglucose-PET was found to be 92% in children with frontal lobe epilepsy while the specifity for frontal lobe lesions was only 62% and additional hypometabolism outside frontal regions could be detected frequently.[106] Hence, the value of ^{18}F-Fluorodeoxyglucose- and flumazenil-PET seems to be restricted in frontal lobe epilepsy compared to temporal lobe epilepsy,[14] although sensitivity can be slightly increased by use of statistical parametrical mapping.[107] The role of alpha-[^{11}C]methyl-L-tryptophan-PET remains to be determined because only small case series have been published.[108]

Neuropsychological examination

The published studies on neuropsychological deficits in frontal lobe epilepsy do not differentiate between certain cortical areas. Impaired motor programming and coordination together with reduced response inhibition can be found in about two-thirds of frontal lobe epilepsy patients and may contribute to differentiate them from patients suffering from temporal lobe epilepsy, while speed, attention, and memory span does not differ between the epilepsy syndromes.[109] An exception might be the patients with right-sided frontal lobe epilepsy and early seizure onset (<6 years) in whom motor skills were found to be less impaired than in patients with frontal lobe epilepsies of the left side or later onset.[110]

Estimation of the epileptogenic zone

Ictal EEG, seizure semiology, and MRI are most important for estimation of the localization and extent of the epileptogenic zone. If seizure semiology, MRI, PET, and SPECT results are pointing to a certain frontal lobe region, intracranial EEG may be abdicable.[111] In MR-positive cases, pure lesionectomy without further attempt of locating the epileptogenic zone led to at least 95% seizure reduction in 13 of 14 patients with central lobe epilepsy.[112]

Difficulties arise especially

- if non-invasive investigations reveal equivocal results;
- in patients without MRI-detectable lesion;
- in patients with close relation of the epileptogenic zone with eloquent cortex; and
- in patients with focal cortical dysplasia because of the ill-defined lesion margins.

In those patients, invasive EEG monitoring is frequently required.[17,113,114]

Determination of the eloquent cortical areas

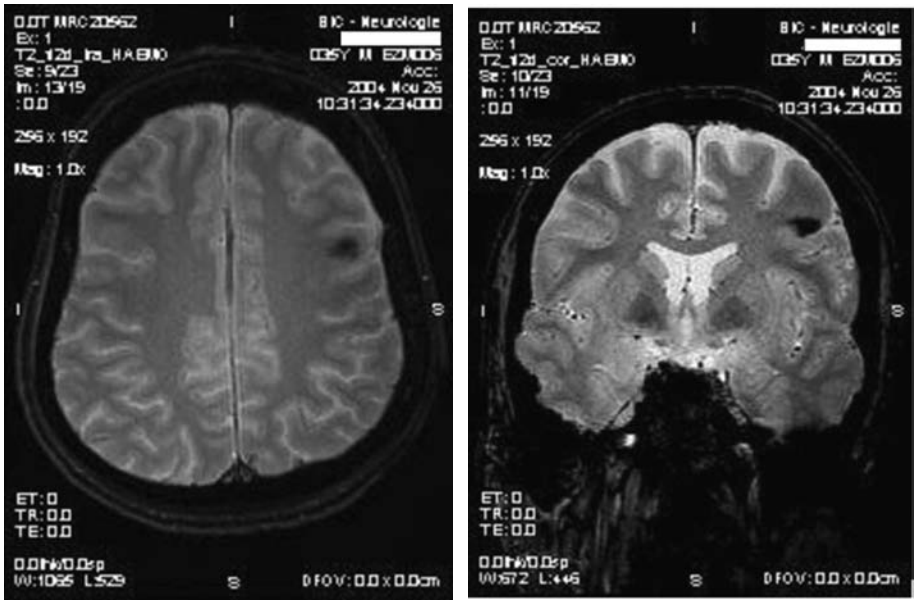
The detection of eloquent cortical areas is crucial prior to and during resection of central lobe cortex due to the motor representation in this area.

Pre-and intraoperative localization of the central sulcus by use of SEP is possible in >90% of the cases; however, the method may fail in patients with tumor etiology in which the anatomical cortex structure is deranged.[41,69,115] Magnetoencephalographic responses evoked by electrical stimulation of the median nerve can also help to locate the central sulcus.[116] Electrical cortical stimulation via implanted grid or strip electrodes has the highest validity for cortical mapping. Reproducibility of seizure symptoms during cortical stimulation is associated with good outcome in extratemporal epilepsy, if these areas were included in the resection.[81]

Therapy and outcome

Medical therapy

In general, medical therapy leads to seizure freedom in about two-thirds of patients with newly diagnosed focal or generalized epilepsy.[117] There are few data on medical therapy of frontal lobe seizures. Medical therapy led to seizure freedom in 37% of 200 patients with difficult-to-treat frontal lobe epilepsy who were referred to a tertial epilepsy centre.[15] In one open-labeled nonrandomized study, a combination of valproate and lamotrigine was used in 21 patients, of whom 48% were seizure free after 1 year of treatment and another 29% experienced seizure reduction of at least 50%.[118] However, the use of additional antiepileptic drugs was allowed. A similar seizure freedom rate of 50% was



(a) (b)

Figure 35.3 (a,b) 3T-MRI scans of the patient whose EEG is shown in figures 35.1 and 35.2(a,b). The gradient echo sequences show the cavernoma as a hypointense left frontolateral lesion. (Courtesy of Dr. S. Knake, Marburg and Dr. K. Krakow, Brain Imaging Center, Frankfurt).

seen in 22 retrospectively observed children with frontal lobe epilepsy.[119]

Surgical therapy

Resective surgery: seizure outcome and prognostic factors

In older series, 13–55% of patients with frontal lobe epilepsy had a favorable outcome after surgery;[23,28,35] a meta-analysis showed an overall seizure freedom rate of 27%.[120] However, since diagnostic capabilities (especially neuroimaging) improved, seizure freedom, or an outcome with nondisabling or very rare seizure was reported in up to 60–70%.[28,29,68,121–123] In patients without MRI-detectable lesions, Engel class I outcome was achieved in 43% of 35 FLE patients.[83]

Acute seizures within the first week after resection occurred in around 25% of patients after frontal lobe epilepsy surgery, particularly in patients who develop intracerebral hematomas; an association with long-term outcome could not be proven.[124] During five postoperative years, seizure outcome improved in 15% and deteriorated in 5% of frontal lobe epilepsy patients.[125]

Neuropsychological benefits (e.g., improvement of short term memory) may occur in patients who become seizure free after frontal lobe resection.[126]

The following factors have been found to be associated with good postoperative outcome in patients with frontal lobe epilepsy by several authors:[30,70,122,123,127–132]

- Tumor or post-traumatic etiology;
- Focal MRI lesion;
- Focal lesion or normal result in FDG-PET;
- Focal ictal β-activity in EEG at seizure onset;
- Slow spreading of EEG seizure pattern;
- Localization of the resection in lateral frontal lobe;
- Seizure control within first year after resection.

On the other hand, the following factors seem to be associated with poor outcome:[30,31,70,114,123,127]

- Autonomic seizure symptoms;
- Etiology of focal cortical dysplasia;
- Contralateral head version;
- Eye deviation (any direction);
- Incomplete resection;
- Generalized slowing or generalized interictal epileptiform discharges (IED) in presurgical EEG;
- Postsurgical IED in scalp EEG;
- Additional extrafrontal lesions;
- Localization of the resection in medial frontal lobe;
- Childhood febrile seizures.

Some factors could not be shown to correlate with the outcome:[30,31,83,122,123,127,129]

- Age at operation;
- Age at onset;
- Epilepsy duration;
- Seizure frequency;
- Seizure duration.

However, it has to be pointed out that the prognostic value of several above mentioned features was not corroborated by other authors. For example, most studies revealed a strong correlation between presence of MRI-detectable lesions and favorable seizure outcome,[30,122,127] while other data showed no correlation[123,132] or even better results in patients with normal MRI.[29]

Complications

Neurological deficits after lesionectomy (paresis, hypesthesia, dysphasia, abulia, incontinence) appeared in 15–40% after frontal lobe resection, but only 1–3% of the deficits persisted.[28,35,123]

Resection of primary hand and arm motor cortex leads to contralateral paresis. Functional recovery starts within 1–3 weeks, but fine motor skills do not recover completely.[133] Due to crossing fibers leading to bilateral representation, resection of axial, face, and tongue motor areas usually recovers completely, and so does sensory function after removal of postcentral cortex.[133,134]

Vagus nerve stimulation

Vagus nerve stimulation reduces seizure frequency by at least 50% in 30–40% of patients, whereas efficacy increases over time.[135] No specific data on premotor or central lobe epilepsy are available.

Other and experimental methods

If resective surgery is impossible due to overlap of the epileptogenic zone and eloquent cortex, multiple subpial transsections (MST) and callosotomy remain as further surgical approaches.

Three months after MST in the frontal lobe, 30% of the patients were seizure free in one study.[126] However, the long-term seizure freedom rate is probably far lower.[120]

In patients without localizing diagnostic results, callosotomy is a palliative option.[136] Freedom of most disabling astatic seizures can be achieved by this procedure in 35%.[120]

Other methods like deep brain or cortical stimulation or focal cortical cooling are still experimental.

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36 Mesial frontal epilepsy

A Bleasel and D Dinner

Introduction

The unusual semiology of seizures arising in the frontal lobes; frenetic asynchronous movements, bilateral posturing and partial awareness often presents diagnostic challenges to physicians. Epilepsy surgery assessments are beset by the brevity of the seizures, the speed of seizure propagation within and beyond the frontal lobe and the limitations to resection imposed by sensorimotor and language cortex. Seizure foci within the mesial frontal lobe add to the challenge by their remoteness to scalp EEG electrodes, propensity to transcallosal spread and bilateral hemisphere involvement and difficult surgical access.

A clinical syndrome of mesial frontal lobe epilepsy is not easy to define because of the anatomical complexity and interconnectivity of the mesial frontal lobe, the non-specific seizure semiology and the diverse pathologies of symptomatic frontal lobe epilepsy. The mesial frontal lobe contains primary motor cortex for the lower limb, the supplementary sensorimotor area, and the anterior cingulate motor area. Each of these motor areas is interconnected, within and between hemispheres, and receives input from subcortical nuclei and the parietal lobe. There are non-eloquent anterior cortical regions that give no clue to seizure onset before propagation within and beyond the mesial frontal lobe. Despite the potential pitfalls a knowledge of the anatomy of the mesial frontal lobe and its connections, typical seizure semiology, scalp EEG patterns and surgical experience can guide the assessment of patients with intractable partial seizures suggesting mesial frontal lobe involvement or identified mesial frontal lobe pathology.

Anatomy of mesial frontal lobe

Cortical surface

The mesial frontal lobe contains portions of each of the major divisions of the frontal lobe; primary motor cortex, premotor cortex and prefrontal cortex. Conventional MRI scans in sagittal and axial views can identify critical boundaries between primary motor and premotor cortex (Figure 36.1 and 36.2). The cingulate gyrus can be identified above the corpus callosum and curves around the genu of the corpus callosum anteriorly (Figure 36.1). The cingulate sulcus is easily identified above the gyrus. It may be divided anteriorly with the two sulci running roughly parallel around the genu of the corpus callosum.[1] Posteriorly the cingulate sulcus ceases to run parallel to the corpus callosum and travels superiorly as the marginal ramus to the parasagittal surface of the brain. The marginal ramus is the posterior boundary of the frontal lobe mesially and divides the primary sensorimotor cortex of the paracentral lobule from the precuneus (mesial parietal lobe). The most rostral aspect of the central sulcus can be identified immediately anterior to the marginal ramus in sagittal MRI views.[2] The central sulcus usually does not enter the interhemispheric fissure[3] and sagittal planes just lateral to the midline are best used to locate it in relation to the marginal sulcus. The superior frontal gyrus occupies much of the mesial surface of the frontal lobe anterior to the paracentral lobule. It is divided from the paracentral lobule by the paracentral sulcus, in continuity with the cingulate sulcus, and passes forward to form the frontal pole. Inferior to the anterior portion of the superior frontal gyrus a number of gyri run obliquely toward subcallosal region becoming parallel with the gyrus rectus of the orbitofrontal cortex. The anterior inferior aspect of the mesial frontal lobe is contiguous with the orbitofrontal cortex. The superior frontal gyrus and central sulcus are also seen well in axial MRI views of the brain (Figure 36.2). The superior frontal sulcus, the lateral boundary of the superior frontal gyrus, ends posteriorly in the precentral sulcus, an interrupted sulcus when traced laterally. The uninterrupted central sulcus can be followed laterally in successive caudal axial images and a characteristic '**Ω**' shaped bend in the central sulcus identified.[4] This feature of the precentral gyrus has proven to be a reliable cortical landmark for the hand region of the motor cortex based upon cortical stimulation and evoked potential studies.[4,5]

Functional anatomy

Classical functional divisions of the frontal lobe motor areas into primary, premotor and supplementary motor regions do not adequately convey the complex reciprocal connectivity of mesial frontal motor areas with lateral frontal regions, striatum, thalamic nuclei and the parietal lobe.[6] The mesial surface of the frontal lobe includes primary sensory and motor cortex for the lower limb, the supplementary motor area, the anterior cingulate motor areas, anterior cingulate cortex and the prefrontal cortex.[7] Because of the coincidence of motor and sensory responses with cortical stimulation of the supplementary motor area, the term supplementary sensorimotor area has been proposed.[8] Specific subregions of these cortical areas can be distinguished based upon the inputs and projections between these mesial frontal areas and subcortical nuclei, the parietal lobe and lateral frontal motor areas.

The supplementary sensorimotor area (SSMA) is found in the mesial portion of the superior frontal gyrus anterior to the

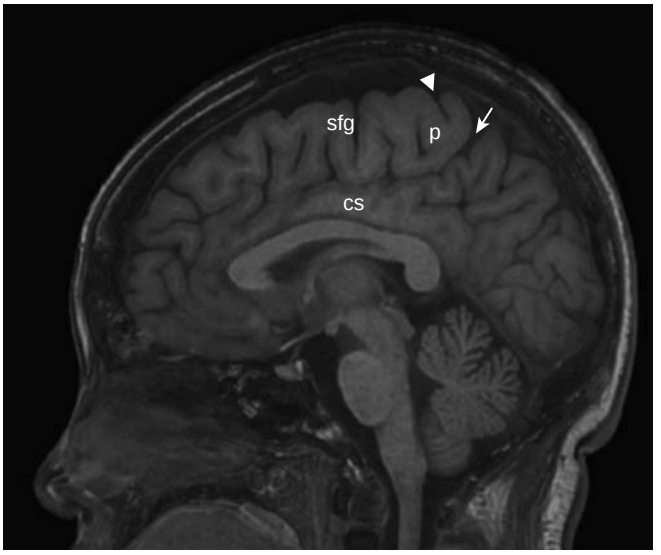

Figure 36.1 The midline sagittal plane of a 3D reconstruction of an MRI of the brain showing the mesial surface of the hemisphere. The paracentral lobule (p), the mesial surface of the superior frontal gyrus (sfg) and the cingulate sulcus (cs) are labelled. The central sulcus, indicated by the arrow head, lies immediately anterior to the marginal ramus (arrow) of the cingulate sulcus. The supplementary sensorimotor area is found on the mesial surface of the superior frontal gyrus anterior to the paracentral lobule.

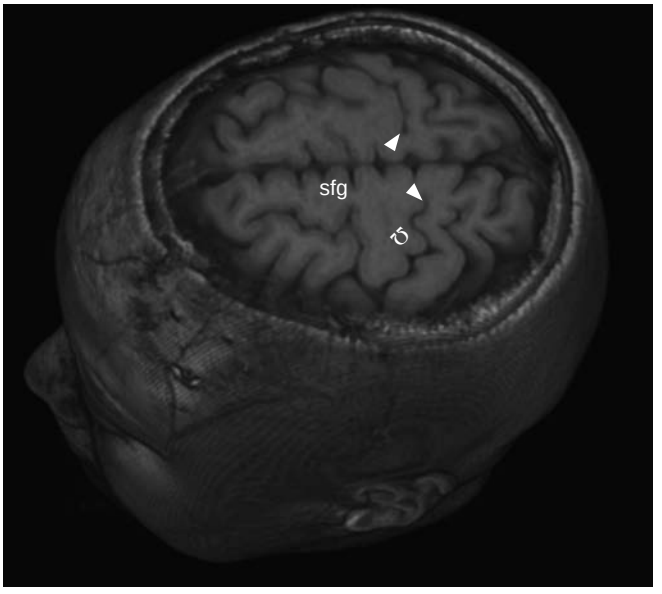

Figure 36.2 Axial cut of a 3D reconstruction of an MRI of the brain showing frontal and parietal lobes. The rostral end of the central sulci are indicted (small arrow heads) in the right and left hemispheres. The superior frontal gyrus (sfg) occupies the parasagittal region. The characteristic Ω shaped bend in the central sulcus is seen in the left hemisphere, the Ω symbol lies over the precentral gyrus at this point. This portion of the precentral gyrus is a reliable anatomical landmark for the hand motor cortex.

primary motor area for the lower limb extending to approximately the level of the genu of the corpus callosum. The inferior border is formed by the cingulate sulcus but the superior border has no clear cortical landmark. Cortical stimulation studies have suggested the SSMA extends onto the dorsolateral aspect of the superior frontal gyrus[8–11] although Talairach and Bancaud[12] concluded that the SSMA was only found on the mesial surface. The precentral sulcus may be a more reliable landmark defining the border between the primary motor foot area and the SSMA than the paracentral sulcus as the primary motor cortex may not occupy a great portion of the paracentral lobule.[2,13,14]

Motor responses to electrical stimulation of the SSMA are characterised by the simultaneous activation of axial, proximal and distal muscle groups. Tonic muscle contraction with posturing of the trunk and limbs is usually seen rather than focal clonic activity.[8,11,15–17] Simultaneous activation of more than one extremity is common and bilateral movements of the limbs occur.[8,11,16] Arrest or slowing of voluntary motor activity occurs[11,18] and these negative motor responses result from the anterior portion of the SSMA.[8] Sensory responses to cortical stimulation can be obtained from the mesial frontal cortex and parietal cortex inferior and posterior to the paracentral lobule.[11,18] These 'supplementary sensory' responses are not as precisely localised by the patient as those occurring in response to stimulation of the primary sensory cortex in the postcentral gyrus. Motor responses have also been obtained posterior to the paracentral lobule.[8]

The SSMA is located in the mesial portion of area 6 of Brodmann's cytoarchitectonic map of the brain corresponding to the Vogts' areas 6aα and 6aβ.[18,19] Immunohistochemical and microstimulation studies in primates and functional imaging studies in humans have shown that the anatomical SSMA is not a single functional region.[6,19] There is an anterior ('pre-supplementary motor area') region, interconnected with the prefrontal cortex and anterior cingulate motor areas, involved in motor processing of other parietofrontal circuits. Detailed cytoarchitectural studies in human brains has shown this region corresponds to the mesial portion of area 6aβ and a more posterior 'supplementary motor area-proper' is formed by the mesial portion of area 6aα.[14] In the primate the supplementary motor area-proper has significant connections with the primary motor cortex and spinal cord and important reciprocal connectivity with the mesial parietal regions.[20] The SSMA is a non-primary motor area involved in preparing voluntary movements with the primary motor area responsible for the execution of the movement.[19] The supplementary motor area-proper seems more important for postural control and movement execution while the rostral pre- supplementary motor area has more 'supramotor' programming function.[20]

Human cortical stimulation studies have found a topographic representation of the body within the SSMA. Motor responses are more concentrated within the posterior portion of the classically defined supplementary motor area,[12] and within this region eye movements responses lie most anteriorly followed by upper limb and then lower limb movements as one moves posteriorly. Negative motor responses are located anterior to positive motor responses.[8] Support for this somatotopic organisation of the SSMA can be found in functional neuroimaging studies of cerebral blood flow

with motor activation[21] and recording of movement-related cortical potentials.[22]

The anterior cingulate cortex lies inferior, rostral and superior to the corpus callosum and accounts for a significant portion of the mesial frontal cortex. It is made up of Brodmann areas 32, 24, 25 and 33. In addition to the premotor functions of the anterior cingulate motor areas, lying deep within the cingulate sulcus, the anterior cingulate cortex is involved in the regulation of autonomic and endocrine function, affect, emotional vocalisation, pain perception and cognitive processing for response selection.[1] The anterior cingulate cortex receives input from multiple thalamic nuclei. Its projections reach the skeletomotor system via the spinal cord, red nucleus and pons, the striatum, the limbic system via amygdala and the midbrain periaqueductal grey, and the autonomic system via the solitary tract and dorsal motor nucleus of the vagus.[1] It is not surprising that electrical stimulation of the human anterior cingulate region has produced an enormous variety of autonomic, emotional and complex motor responses. Cingulate stimulation may produce changes in heart rate, blood pressure, facial flushing, pupillary dilation and may induce nausea, salivation, bladder or bowel evacuation.[1,23,24] Emotional responses such as fear, agitation, pleasure and euphoria and repetitive simple and complex motor actions may occur.[1,23,24] The prefrontal cortex anterior to the SSMA and cingulate motor cortex is relatively silent when subject to cortical stimulation although reciprocally connected to the pre-supplementary motor area.

Vascular anatomy

The anterior cerebral artery is the major arterial supply of the mesial frontal lobe with only a small contribution from distal branches of the superior division of the middle cerebral artery to the lateral aspect of the superior frontal gyrus. The anterior cerebral artery courses from the circle of Willis to the parieto-occiptial area and shows great anatomical variation between individuals.[25–27] The orbitofrontal cortex, the mesial anterior frontal lobe, the superior frontal gyrus, cingulate gyri, paracentral lobule and anterior corpus callosum are all supplied by branches of the anterior cerebral artery.[25,26] The proximal anterior cerebral arteries may be very asymmetric with dominance of left or right, and branches of the callosomarginal or pericallosal may cross the midline to supply the contralateral mesial frontal lobe.[26] Thus the occlusion of one anterior cerebral artery may lead to bilateral mesial hemispheric infarction and is a potential complication of surgery in the mesial frontal regions.

A 'C' shaped inferior portion of the mesial frontal surface surrounding the corpus callosum, including cingulate gyrus and inferior aspect of the superior frontal gyrus, drains in to the deep cerebral venous system to the straight sinus. The more rostral and anterior arc of mesial frontal cortex and the parasagittal lateral convexity drains via the superficial cortical veins to the superior sagittal sinus. The superior anastomotic vein of Trolard travels between the superficial middle cerebral vein in the sylvian fissure and the superior sagittal sinus. It can be identified on lateral venous phase angiograms and the surface of the cerebral convexity at craniotomy. It runs parallel and adjacent to the central sulcus. The superficial venous system is very important in planning the placement of subdural electrode arrays and cortical resections in the mesial frontal region. The passage of proximal superficial cortical veins to the sagittal sinus anchors the parasagittal convexity to the dura at several points and may indeed limit what can be introduced in to the interhemispheric fissure. These large but distensible veins are exposed to any subdural electrode arrays and may be compressed and thrombose especially if patients are not kept well hydrated postoperatively.[13]

Seizure semiology

The seizures associated with mesial frontal lobe epilepsy share the common features of frontal lobe seizures; abrupt onset, short duration and clusters of multiple daily seizures. The bilateral asymmetric tonic seizure[28] is most often linked to the mesial frontal lobe. These seizures have attracted different labels over the years; 'postural seizures',[29] 'supplementary motor seizures',[30] or asymmetric tonic motor seizures.[31,32] This seizure semiology is not specific for mesial frontal lobe onset and other distinct semiologies may also be seen with mesial frontal lobe onset. These include the uncommon 'frontal lobe absence seizures'[33] with motionless staring, 'frontal lobe complex partial seizures'[34–36] with hyperkinetic motor automatisms, repetitive vocalisations and agitation, focal clonic seizures of the lower limb and negative myoclonus. Focal clonic seizures involving the face and upper limb, or versive seizures are not typical of a mesial frontal onset. Complex partial seizures with oral and manual automatisms (psychomotor seizures typical of mesial temporal lobe onset[37] are not typical but may be seen with seizure onset within the cingulate gyri.[1]

Bilateral asymmetric tonic seizures

Bilateral asymmetric tonic seizures are characterised by an abrupt onset of tonic posturing, maintained for 10-40s and not followed by any postictal stupor or confusion.[38–40] Typically the tonic posturing appear to be bilateral from the onset but careful analysis has revealed it may begin in one part of the body and move rapidly to the other limbs.[41] Less often posturing may be unilateral or restricted to a single limb but proximal limb and axial muscle involvement is always prominent.[39] Most often all 4 limbs are involved with abduction of the upper limbs and asymmetric flexion of the elbows. The lower limbs are abducted at the hips with the knees extended or semi-flexed.[39] Penfield described 'the arm being raised and the head and eyes turned as though to look at the hand' and this has been referred to as the 'fencing posture'.[18a] Clinical series show the assumption of a true fencing posture is uncommon.[34, 38, 42]

The patient's posture may change during the seizure if the distribution and intensity of muscle contraction changes. Patients may also attempt to change their position during the seizure and show coarse incoordinate movements of their tonically postured limbs. They may cry out (perhaps cursing) or moan loudly at the onset.[43] Patients are unresponsive during the tonic phase of the seizure but do not lose consciousness during brief bilateral asymmetric tonic seizures and words or

instructions given during a seizure can be recalled. Longer seizures, as may be seen with antiepileptic medication withdrawal during prolonged video/EEG studies, may be associated with some ictal amnesia and postictal confusion.[44] Focal clonic activity may occur due to involvement of the primary motor cortex[34,42] and may appear late with seizure spread or precede the tonic phase if the epileptogenic zone includes the primary motor cortex.

A somatosensory aura may immediately precede the tonic seizure. This may be a feeling of tension, pulling or heaviness in a limb or the sense of the limb 'being about to move'[18,39,45] or more simply a 'tingling' feeling. The symptoms may arise from the sensory representation within the supplementary sensorimotor area[8,16] or may be the awareness of tension developing in muscle groups involved in the tonic contraction. The sensation may be relatively focal involving a portion of a limb, lateralised with both upper and lower limbs involved simultaneously or a less well defined bilateral sensation in the head or body.[18,39,45]

Although evidence exists to support ictal involvement of the supplementary sensorimotor area in producing bilateral tonic posturing, the seizure onset may be outside the mesial frontal region or outside the frontal lobe itself. Subdural and depth electrode monitoring has shown the seizure onset zone and epileptogenic zone commonly extends beyond the supplementary sensorimotor area to primary motor cortex, the dorsolateral premotor cortex, the cingulate gyrus, the mesial prefrontal cortex and the mesial parietal lobe.[34,35,38,46] Patients with seizures arising exclusively from the SSMA are rare[34,35,38] and the seizure semiology of such patients can not be distinguished from that occurring in patients with ictal onset's that included adjacent cortical areas.[34,38] Surgical series have shown the typical bilateral asymmetric tonic postural seizures described above may occur in patients with ictal onset, confirmed by surgical outcome, in lateral frontal, parietal or occipital lobes.[40,47–52] Similar observations have been made in a clinical series comparing seizure semiology to clinical localisation based upon lesion location.[53] Detailed analysis of the evolution of seizure semiology in patients with bilateral tonic seizures can provide some features to distinguish between focal onset within frontal and parieto-occipital regions[54] but one must consider an extra-frontal onset in all cases of non-lesional epilepsy.

These observations suggest that the epileptogenic zone in patients with bilateral asymmetric tonic seizures may be outside the mesial frontal lobe with this seizure semiology arising by propagation of ictal discharges to the one or both SSMA in the mesial frontal lobe. This concept is well supported by the primate anatomical studies of fronto-parietal connectivity.[6] Evidence for such propagation has been limited in human studies[45,55] as invasive electrode placement will always be concentrated in the proposed area of resection and there will be limited sampling regions of seizure onset and propagation.[56] More recently Ikeda *et al*[52] found good evidence of seizure propagation to the SSMA from epileptogenic regions outside the mesial frontal region to coincide with the asymmetric tonic semiology. Dorsolateral frontal regions and mesial parietal cortex gave rise to seizures which immediately spread to electrodes implanted over the SSMA.

A more challenging question is whether ictal involvement of cortical (dorsolateral premotor areas and cingulum) and subcortical motor regions (basal ganglia) other than the SSMA may be capable of producing the bilateral asymmetric tonic seizure semiology.[34,57,58] Apparently isolated ictal involvement of either the lateral premotor area or the primary motor area can produce tonic motor activity.[34] The tonic motor activity was manifest as unilateral posturing of a limb or limbs (contralateral to the ictal activity) and usually associated with clonic motor activity. Unilateral tonic limb posturing without clonic activity was seen in 2/13 seizures in the patients with ictal discharges limited to the primary motor area.[34] Cortical stimulation of frontal convexity premotor areas in primates can produce contralateral tonic motor activity in proximal muscle groups but not bilateral or ipsilateral motor responses.[59-61] Intraoperative[62,63] and extraoperative[64,65] cortical stimulation studies in humans have not revealed convexity premotor (Broddman area 6, or Vogt and Vogt area 6a alpha) responses distinct from primary (area 4) motor responses but the convexity premotor motor responses are not bilateral. At present there seems to be good evidence for a central role for the SSMA as the symptomatogenic zone for bilateral asymmetric tonic seizures with preserved awareness but questions remain regarding the participation of other cortical motor areas and subcortical systems.

Hypermotor seizures

Complex partial seizures characterised by vigorous sometimes bizarre motor automatisms, vocalisation and relatively minor postictal confusion are often seen in frontal lobe epilepsy and have been distinguished from those associated with mesial temporal lobe seizure onset.[35,66,67] The complex movements resulting in repeated changes in posture and asynchronous perseverative proximal limb movements, have been termed 'hypermotor seizures' in the semiological seizure classification proposed by Lüders *et al*.[68] Patients may have wild repetitive movements of the outstretched hands, kicking or pedalling of legs, hopping, pelvic thrusting or genital mani pulation.[69,70] Vocalisation is common and may be loud and intrusive and socially disabling.[66,70,71] The vocalisation is often primitive consisting of grunting or barking sounds but can consist of intelligible phrases repeated over and over. Patients may be partially responsive during the episodes, occasionally have some recall of the events and often have minimal postictal disorientation. Because of the bizarre character of the episodes and the rapid recovery these seizures may be mistaken for pseudoseizures or behavioural outbursts.[70,72] However, the stereotyped nature of the events and the loss of awareness should point an experienced physician toward epilepsy. There may be an overlap between the hypermotor and the bilateral asymmetric tonic postural seizure semiology as axial tonic activity may be present whilst the patient struggles and attempts to change position.[58] Both hypermotor and tonic postural seizure types may be brief lasting less than 30-40s, may be predominantly nocturnal, and have minimal or no postictal confusion although completely preserved awareness is not as common with the hypermotor semiology.

This seizure semiology is not well localised within the frontal lobe and has been described with orbitofrontal seizure onset[73–76] and lateral frontal seizure onset.[42,77] While seizure onset in a number of frontal regions may produce this seizure semiology the anterior cingulate region has most often

been discussed as the cortical region responsible for the clinical signs and symptoms.[78] Seizures with onset in the anterior cingulate gyrus are characterised by these vigorous automatisms and vocalisations[78] and stimulation induced complex motor behaviours are similar to these automatisms when the anterior cingulate region has been explored with invasive electrodes.[1,23] Ictal single photon emission computerised tomographic scans (SPECT) studies have demonstrated hyperperfusion of the frontopolar regions in children with complex gestural automatisms, vocalisation and hyperventilation.[76,79] The hypermotor seizure has been though to have some specificity for a frontal lobe onset[35] but more recently seizure onset within temporal neocortex[80] or insular cortex[81,82] has been shown to also produce the typical hypermotor seizure semiology.

Frontal lobe absences

Motionless staring with amnesia may occur in seizures arising from the mesial frontal cortex, so called 'frontal absences'.[33,83] Bancaud and Talairach described seizures characterised by impairment of consciousness, speech and movement arrest, simple gestural automatisms and immediate recovery of consciousness.[33] The duration varies, they may be as brief as 10s and are usually between 15-45s. Compared with the absences of childhood absence epilepsy frontal lobe absences may have subtle repetitive vocalisation, rocking movements, small degrees of head and eye turning and some brief postictal confusion.[1,33,84,85] The patient may report awareness of a motor arrest without loss of consciousness.[86] The staring may evolve into a secondarily generalised tonic clonic seizure via version of the head and eyes, focal tonic posturing of an upper limb or bilateral tonic posturing.[33] Episodes of status epilepticus are characterised by subtle alteration in responsiveness or mood, and variable degrees of stupor may occur.[86–88] Patients with absence seizures in frontal lobe epilepsy seem to have a more anterior epileptogenic zone than those with bilateral asymmetric tonic seizures.[33] The clinical semiology has been ascribed to bilateral cingulate gyrus involvement in the seizure[1,89] via the callosal route.[90] However, the common association of bilateral synchronous frontal interictal discharges and the coincidence of clinical and scalp EEG seizure onset suggest a rapid entrainment of both frontal lobes in the ictus possibly via thalamocortical pathways involved in the production of idiopathic generalised absence seizures.[33]

Negative myoclonus

Epileptic negative myoclonus is characterised by brief lapses of postural tone usually with dropping of an outstretched limb. The muscles need to be activated for the clinical manifestation and it is not seen when muscles are at rest. Frontocentral epileptiform discharges immediately precede the atonia. Most commonly focal negative myoclonus occurs in association with a central seizure onset in cases of idiopathic focal epilepsy of childhood.[91] In symptomatic partial epilepsy foci have been demonstrated in primary sensorimotor cortex[92] and dorsolateral premotor areas.[93] The association focal negative myoclonus and asymmetric tonic seizures has been noted with mesial frontal seizure onset.[94] The electromyographic correlate of negative myoclonus is a brief (<500ms) silent period not preceded by any electromyographic evidence of myoclonus.[95] It has been reported with direct cortical stimulation via subdural electrodes the primary sensorimotor cortex could produce a silent period but not the SSMA.[96] Rubboli *et al.*[95] performed cortical stimulation via depth electrodes of premotor cortex, primary motor cortex, primary somatosensory cortex and the supplementary sensorimotor area at low frequency. They found a motor evoked potentials most often preceded the silent period for primary motor and premotor cortex, low but not high intensity stimulation produced an isolated silent period from primary sensory cortex but the SSMA consistently produced only a silent period.[95]

Lateralising and localising signs

It is true that all of the frontal lobe seizure semiologies discussed with this chapter have limited localising value for subdivisions of the frontal lobe.[58] It is most important to be aware the distinctive semiology of the bilateral asymmetric tonic seizures does not have localising value for an onset within or adjacent to the SSMA.[52,97] Lateralising signs have not been well studied in frontal lobe epilepsy. Consistently unilateral sensory symptoms are usually contralateral to the hemisphere of onset. Focal clonic activity reliably lateralises seizure onset to the contralateral hemisphere[34,42] and focal tonic posturing has a similar lateralising value.[58,98,99] Unilateral tonic posturing is not as common as bilateral asymmetric tonic posturing. The position of the arms, elbow extension vs flexion, is not a reliable guide to lateralisation of seizure onset. Head turning as part of a bilateral asymmetric tonic seizure is not a reliable lateralising sign.[58] Head turning occurring early in the seizure may be contralateral[18,34] or ipsilateral[44,100] to hemisphere of seizure onset. Head version, with clonic movement, occurring immediately prior to secondary generalisation to a generalised tonic clonic seizure is more reliable lateralising sign.[101] Unifocal or unilateral somatosensory aura is a reliable sign appearing contralateral to the hemisphere of onset.[58]

Interictal and ictal EEG

Several factors often combine to reduce the localising value of interictal and ictal scalp EEG in frontal lobe epilepsy; the inaccessibility of mesial frontal and orbitofrontal cortex to scalp EEG electrodes, the rapid propagation of seizure discharges within and between frontal lobes and movement artefactc.[35,56,102,103] The interictal EEG in patients with mesial frontal lobe epilepsy most commonly shows an abundance of nonlateralised epileptiform activity or none at all.[38,70,85,89,104–108] Quesney and colleagues from the Montreal Neurological Institute[109] have examined interictal epileptiform activity in 34 patients seizure free after selective frontal lobe excisions and compared parasagittal resections with anterofrontal and fronto-opercular resections. None of the parasagittal group (10 patients) had focal discharges, 5 had exclusively bilateral or generalised discharges, 4 had regional frontocentral discharges and one had no discharges. Localised epileptiform activity appears to be more common in lateral frontal lobe foci.[108,109] Quesney *et al.*[109] found only two of 18 anterior resections and none of 6 fronto-opercular resections had exclusively bilateral or diffuse discharges. In another series scalp EEG revealed no interictal epileptiform discharges

in 7/9 patients with mesial frontal lobe epilepsy confirmed by intracranial EEG.[107] An absence of interictal discharges has not been reported in the lateral frontal lobe resections.[108,109]

Focal interictal spikes and sharp waves at or adjacent to the midline have been reported in other series of patients with tonic postural seizures.[39,45] In a group of 16 patients with bilateral asymmetric tonic seizures, scalp EEG's recorded during long-term video/EEG monitoring showed midline frontocentral interictal epileptiform discharges in 50% of the patients.[45] Blume *et al.*[106] found a similar incidence of midline (Fz, Cz) (5 patients) or frontal (F4, F3) (2 patients) spike foci in a group of 13 patients with 'supplementary motor area epilepsy'. Examination of the EEG with montages using the midline electrodes, Fz, Cz and Pz, is essential as discharges maximal at these electrodes may have a very limited field.[39,105,110] Midline discharges present only during sleep can be difficult to distinguish from vertex sharp waves of sleep. Polyspikes and spikes with a prominent aftergoing slow wave will suggest epileptiform activity rather than sleep transients.[105] Normal sleep transients have a broad symmetric field and the addition of parasagittal 10-10 system electrodes may be helpful in documenting a persistent asymmetry of the electrical field of midline epileptiform discharges.[39,105] Identification of the same midline sharp waves or spikes during wakefulness will of course distinguish them from sleep transients.

Bilateral synchronous discharges are characteristic of but not specific to mesial frontal epilepsy[85,111] having been reported in orbitofrontal, lateral frontal foci and extrafrontal parietal lobe epilepsy.[74,76,112,113] Subtle lateralisation may be present in patients with bilaterally synchronous frontal discharges and recording during sleep is important if lateralising information is not to be missed.[106,111,114,115] Such lateralisation may be misleading, Blume and Oliver found interictal discharges maximal contralateral to the hemisphere of seizures origin in 2/8 patients with mesial frontal lobe epilepsy and secondary bilateral synchrony. Subtraction techniques may reveal consistent lateralisation in bi-frontal discharges not obvious when examined in bipolar montages.[116] Epileptiform discharges and regional slowing may also be present in frontopolar, parietal and occipital regions. This may be an indicator of seizure onset in extrafrontal regions[106] but it has also been reported as a misleading finding.[108]

The interictal EEG may show only non-epileptiform slowing in mesial frontal lobe epilepsy.[39] Intermittent rhythmic midline frontocentral slowing is seen in patients with bilateral asymmetric tonic seizures[38] and in patients with midline parasagittal epileptic discharges.[105] Ciganek[117] described a similar activity in patients with temporal lobe epilepsy although an association between this pattern and epilepsy was not confirmed in a large series of routine EEG studies.[118]

Muscle activity is prominent from the onset of bilateral asymmetric tonic seizures and the EEG is frequently contaminated with considerable electromyographic (EMG) and movement artefact. Electroencephalographic seizure patterns may still be evident at the vertex where EMG activity is least and transverse montages will usually demonstrate this best. Characteristic findings include an initial high amplitude slow wave transient or midline sharp wave followed by bilateral frontocentral low voltage fast activity or electrodecrement.[38,39,105,111,115,119] Electrodecrement will usually evolve into low voltage fast activity and then bilateral frontocentral or generalised rhythmic theta slowing.[38] The low voltage fast activity and the rhythmic slow activity may either be localised to the vertex or be more diffuse. Subtle lateralisation of these rhythms may occur but in general the lateralising information from ictal EEG is minimal.[106–108] This was the case in an excellent study looking at the localising and lateralising value of ictal scalp EEG recording in well defined focal temporal and extratemporal epilepsy.[120] Seizures from mesial frontal lobe foci most commonly showed paroxysmal fast activity (33%) or electrodecrement (29%) as the initial ictal pattern whereas seizures of lateral frontal lobe epilepsy showed repetitive epileptiform discharges (36%) or rhythmic delta at onset (26%). Foldvary and colleagues found only 25% of mesial frontal lobe epilepsy seizures correctly localised or lateralised and 75% had nonlateralised patterns.[120] Lateral frontal lobe epilepsy showed 65% of seizures to be correctly localised with an additional 6% correctly lateralised. Bautista *et al.*[108] found seizures originating in the dorsolateral region had focal ictal EEG patterns correctly localising to the region of seizure onset[108] but none of their 5 patients with mesial frontal lobe seizure onset had focal ictal EEG patterns.[108] An absence of any ictal or immediate postictal EEG slowing has been reported in patients in mesial frontal lobe epilepsy.[39,108] In Foldvary's study just over 50% of the seizures examined were obscured or showed no EEG change in the mesial frontal lobe group, an uncommon occurrence in the other focal epilepsy subsets.[120] The demonstration of an EEG seizure pattern may require examination of multiple recorded seizures to detect a subtle but reproducible pattern.

Aetiology of mesial frontal epilepsy

In symptomatic focal epilepsy arising from mesial frontal lobe the surgical specimens have the range of pathologies associated with all extratemporal surgical series. No unique pathologies exist for the mesial frontal lobe. Encephalomalacia, developmental tumours and malformations of cortical development predominate. There are seizure free surgical cases with non-specific findings presenting a cryptogenic category and raising the possibility of sporadic cases of autosomal dominant nocturnal frontal lobe epilepsy appearing in the refractory series.

Early surgical series excluding tumours have identified 'meningocerebral cicatrix' or gliosis as the commonest pathology related to a past history of head trauma, postinfectious scarring or birth injury.[121] Talairach *et al*[122] reviewed the aetiology in 100 patients with frontal lobe epilepsy undergoing surgery and also found a large percentage of patients with birth injury (18%), encephalitis (15%), and postnatal head injury (15%). Tumours were present in 10 patients in the Paris series.[122] A variety of neoplasms have been associated with intractable partial seizures in frontal lobe epilepsy including gangliogliomas, gliomas (low grade gliomas, astrocytoma, oligodendrogliomas) and hamartomas.[70,77] An aetiology could be identified in 15/18 patients with refractory tonic postural seizures undergoing surgery at the Cleveland Clinic Foundation;[43] 7 had tumours including ganglioglioma and astrocytoma, 5 had regional cortical dysplasia and 3 had encephalomalacia related to remote infarction, previous

cerebral abscess and head injury. In another series of 5 patients with mesial frontal lobe onset seizures; 3 had cortical dysplasia, 1 oligodendroglioma and 1 gliosis with a normal MRI.[108] Other pathologies include vascular malformations (cavernoma, thrombosed arteriovenous malformation)[123] and tuberous sclerosis.[124]

The literature on FLE is dominated by patients seen in comprehensive epilepsy centres with intractable seizures being assessed for epilepsy surgery. There are more benign frontal lobe epilepsies with tonic postural and hypermotor seizure semiology.[125–127] Vigevano and Fusco[125] described 10 children with 'hypnic tonic postural seizures', without neuroradio logical lesions who became seizure free with carbamazepine treatment. The seizures began at an early age and there was a family history of epilepsy in 8 of the patients. Frontal lobe epilepsy with autosomal dominant inheritance has been described with clusters of brief nocturnal motor seizures with tonic postural semiology or the hypermotor semiology.[126,128,129] While one cannot be sure of a mesial frontal lobe onset on the basis of seizure semiology alone, ictal SPECT evidence of regional hyperperfusion in the fronto polar and mesial frontal regions has been reported in these patients.[130] Onset is usually in childhood, mean 11.7 year, but a wide range of ages at onset is seen from 2 months to 52 years.[126] Not all of these patients are well controlled, the family history of epilepsy can be difficult to elicit and sporadic cases are thought to occur.[126,127] It is possible patients with idiopathic frontal lobe epilepsy are included in non-lesional surgical series.[131] A consistent feature in surgical series of frontal lobe epilepsy is the report of patients with no identified aetiology and non-specific findings in surgical specimens, yet some of these patients become seizure free in long term follow-up.[122,124]

A clinical syndrome of mesial frontal lobe epilepsy?

Tonic postural seizure semiology has often been presented as evidence for a diagnosis of mesial frontal lobe epilepsy.[39,115,125,126,132] However the tonic postural seizure is not specific for a seizure onset within the mesial frontal region or even the frontal lobe itself.[35,97] Additional evidence to support a mesial frontal lobe seizure onset may provided from structural neuroimaging studies showing circumscribed lesions[53,123] or functional neuroimaging such as positron emission tomography (PET)[133] and ictal SPECT.[76] Vertex or anterior frontal scalp EEG abnormalities[105,114] may be misleading and are not sufficient alone as support for a mesial focus.[35,134] Evidence of mesial frontal lobe seizure onset and

Table 36.1 Surgical outcome, mesial frontal resections

Series	Patients	Outcome
Talairach *et al.*, 1992[122]	31	Successful outcome[1] Anterior 50% Middle 18% Posterior 80%
Veilleux *et al.*, 1992[135]	8	4 patients Engel I and II no details on the other patients
Van Ness *et al.*, 1993[143]	20	4 patients Engel I 7 Engel II-III
Olivier, 1996[124]	28	6 patients Engel I, 7 Engel II-III, 6 Engel IVa, 9 Engel IVb
Smith & King, 1996[136]	12[2]	6 patients no or rare seizures, 2 >90% reduction in seizures, 4 < 90% reduction[3]
Mihara *et al.*, 1996[123]	5	4 patients seizure free 1 90% reduction in seizures
Spencer & Schumacher, 1996[138]	8	4 patients excellent outcome, 3 good outcome, 1 typical seizures continued
Toczek *et al.*, 1997[107]	9[4]	6 patients Engel I 2 Engel II 1 Engel III
So, 1998[145]	11	5 patients Engel I, 1 Engel II, 3 Engel III, 1 Engel Iva[5]

[1] Successful included those patients seizure free, with only rare seizures and with >75% reduction in seizures
[2] Four patients with structural lesions. Four of eight nonleisonal cases had previously undergone anterior corpus callosal sections to aid in localising EEG seizure onset.
[3] 12 month follow-up, subsequently; 2 patients lost to longer follow-up, 1 patient had sudden unexplained death, 1 (< 90% improvement) had second more successful surgery.
[4] All patients had section of the anterior portion of the corpus callosum
[5] One patient died in follow-up, drowning

involvement on the basis of invasive subdural or depth electrode studies is more rigorous a basis of case selection than semiology and scalp EEG.[33,34,43,45,50,135–137] However, intracranial electrode evaluations suffer from inherent sampling errors. Frontal epileptogenic regions are often large and there is rapid and complex seizure propagation patterns between cortical and subcortical regions.[35,50,134,134a] Series based upon seizure free outcome after frontal resections are the 'pure culture'[42, 121] from which seizure syndromes might be derived but the patients are not always separated into anatomical subsets such as mesial or lateral frontal lobe epilepsy and the patients only represent intractable symptomatic partial epilepsy with diverse aetiologies.

These caveats should caution us against accepting too readily a clinical syndrome of mesial frontal lobe epilepsy as there is remarkable diversity in terms of aetiology and prognosis once one gets beyond seizure semiology. The brevity, frequency and nocturnal occurrence of tonic postural seizures are not exclusive to the mesial frontal lobe epilepsy.[70,77] The predilection for tonic postural seizure onset during sleep may mitigate the disability arising from intractable epilepsy. There are several series examining surgical strategies in patients with seizures involving the supplementary sensorimotor area that provide some additional clinical details relevant to symptomatic mesial frontal lobe epilepsy.[13,45,123,124,136–138] In patients with medically refractory epilepsy tonic postural seizures very often occur daily and clusters of 5–20 seizures per day are not uncommon.[45,123,138] The majority of patients in surgical series have seizure onset at an early age: at the Cleveland Clinic; 17 patients, mean 10.4 years, range 3.5 to 22 years,[139] in Grenoble; 18 patients, mean age 7 years, range 6 months to 22 years,[137] at Yale University School of Medicine; 7/8 patients, had onset at 15 years or younger.[138] Normal neurological examinations and average intelligence are more commonly reported than focal signs or severe intellectual disability[138,139] although others have found a higher incidence of abnormal neurological signs. In the series of 100 frontal lobe surgery cases from St. Anne's Hospital in Paris 60% had motor or sensory signs and a third of these had intellectual deficits.[122] Specific neuropsychological deficit profiles have not emerged for mesial frontal lobe epilepsy to distinguish it from other subsets frontal lobe epilepsy.[140–142] A high incidence of abnormal interictal behaviour and psychiatric illness has been reported in patients with cingulate epilepsy.[1,85]

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37 Basal frontal lobe epilepsy

AV Alexopoulos and N Tandon

Introduction

For neuroscientists and clinicians alike the basal frontal cortex is one of the least explored and least understood regions of the cerebral cortex.[1] Studies of the connectivity of the orbitofrontal region by invasive tract tracing in animals, and less invasive methods in humans, suggest that this region is part of a widely distributed network involving cortical and subcortical projections within the frontal lobes and limbic system.

Unlike seizures arising from other cortical sites, seizures originating from within the orbitofrontal region have not been extensively characterized in the existing literature. Several factors have tempered our understanding of basal frontal lobe epilepsy including the lack of a characteristic semiology and electroencephalographic findings, the inaccessibility of this region to surface electrodes and the resulting need for invasive recordings in order to demonstrate ictal onset within the orbitofrontal region. Not surprisingly, surgical experience in patients with pharmacoresistant epilepsy is relatively limited, when it comes to resections restricted to the basal frontal area.

The functional heterogeneity and widely disseminated connections of the basal frontal areas account for the protean clinical manifestations of seizures arising from this region. In this chapter we will review the anatomical and functional aspects of the orbitofrontal region and examine the characteristics of the few cases of basal frontal lobe epilepsy that have been reported in the literature.

Anatomic considerations

The basal surface of the frontal lobes (Figures 37.1 and 37.2a) is anatomically divided from front to back into right and left orbital cortices, right and left anterior perforated substances (which are partially covered by the temporal poles) and the midline interpenduncular (or intercrural) area.[2] The orbital surface of each frontal lobe is literally located 'above the orbit' and houses the orbitofrontal cortex, which is part of the prefrontal cortex.

Given that there is no single functional role or cytoarchitectonic structure common to all portions of the basal frontal area (as opposed to, say, the primary motor area or the primary visual cortex) the term orbitofrontal cortex may be somewhat misleading. The region is perhaps best described as *the orbitofrontal region*. Another term that is occasionally used to define this area is the term 'basal frontal lobe'. While this terminology intuitively suggests the anatomic location of the region under consideration, it may be confused to incorporate components of the basal ganglia that are intimately related to the fiber tracts of the frontal lobe. Therefore, we prefer to refer to this collection of structures as the orbitofrontal region (OFR).

Gross anatomy

Sulcation patterns in this region are highly variable. In most cases however, three principal sulci are noted on the basal (orbital) surface of the frontal lobe: the lateral and medial orbital sulci and the H-shaped sulcus. The two longitudinal orbital sulci (lateral and medial) divide the orbitofrontal region into lateral and medial orbital gyri and an intermediate orbital cortex[3] (Figure 37.1).

- *The lateral orbital sulcus* separates the orbital lobe from the lateral surface of the frontal lobe (from the inferior frontal gyrus).
- *The medial orbital sulcus* is synonymous with the olfactory sulcus – the longitudinal sulcus in which the olfactory tract and bulb are located. At its caudal end, the olfactory tract divides into the medial and lateral olfactory striae. Between these two striae lies a rhomboid-shaped region, the anterior perforated substance, whose other two boundaries are the optic tract (posteriorly) and the proximal anterior cerebral artery (ACA) postero-medially. Posterolaterally, it continues into the uncus and medially, it is continuous with the subcallosal gyrus. The anterior perforated substance is perforated by several minute blood vessels (including some lenticulo-striate arteries) arising from the ACA and the carotid artery and supplying several deep subcortical structures.[4]
- *The H-shaped orbital sulcus* lies in the largest section of the OFR – the intermediate region – and varies significantly among individuals. The typical H-shape is formed by two longitudinal rami, which are linked by a transverse ramus (the latter is also known as arcuate orbital or transverse orbital sulcus). This H-shape is not commonly seen; rather the name 'H-shaped sulcus' encompasses the complex sulci situated in the central region of the orbital lobe.[2,3]

The orbital sulci form five gyri on the basal surface of the frontal lobe. These are (from lateral to mesial):

(1) *The lateral orbital gyrus*, located between the lateral orbital sulcus and the H-shaped sulcus;
(2) and (3) *The anterior and posterior orbital gyri* situated on each side of the transverse ramus within the confines of the longitudinal rami of the H-shaped orbital sulcus;

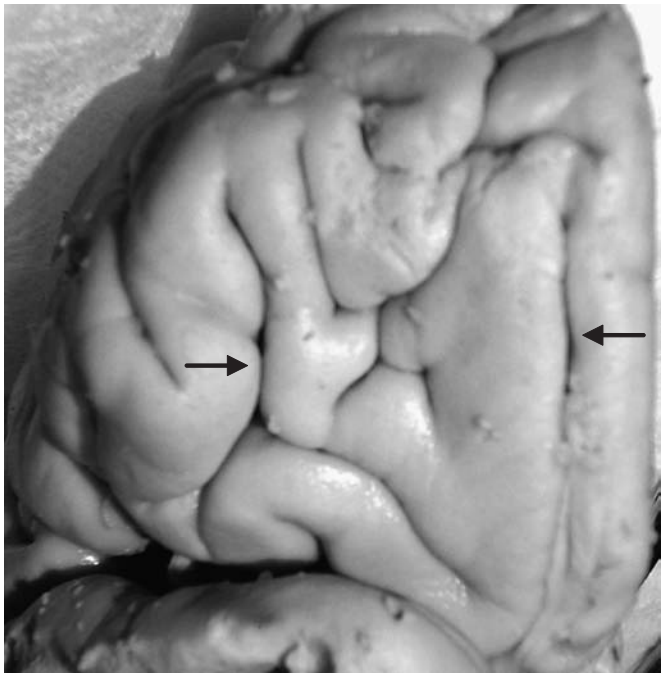

Figure 37.1 The basal surface of the frontal lobe – fresh cadaveric specimen. The two longitudinal orbital sulci (lateral and medial) – black arrows – divide the orbitofrontal region into lateral and medial orbital gyri and an intermediate orbital cortex.

(4) *The medial orbital gyrus* located between the H-shaped and the medial orbital sulcus; and
(5) *The gyrus rectus*, which lies along the medial margin of the orbital lobe and extends over the medial surface of the frontal lobe

Given the considerable variability with regards to the shape of the orbital sulci and gyri, some neuroanatomists prefer to generically label the convolutions between the olfactory sulcus and the inferior frontal gyrus (F3) as *orbital gyri*, and all of the corresponding sulci as *orbital sulci*.[5]

The anterior and posterior limits of the OFR are the frontal pole and the anterior perforated substance respectively. The frontal pole is a transitional area between the lateral, medial, and orbital surfaces of the frontal lobe.[2] The three longitudinally oriented frontal gyri (superior, middle and inferior) are interrupted by transverse folds, the *transverse frontopolar gyri*. A fairly constant and deep sulcus, the *frontomarginal sulcus*,[3] separates the *transverse frontopolar gyri* dorsally from the *frontomarginal gyrus* ventrally. The *frontomarginal gyrus*, can therefore be considered to constitute the inferior part of the frontal pole and to mark the boundary between the fronto-polar and orbital regions.

The inferior frontal gyrus (F3) merges into the orbital region, where *the pars orbitalis* (the most rostral part of the inferior frontal gyrus) continues into the *caudal part of the lateral orbital gyrus* and the *posterior orbital gyrus*. The continuation of the superior (F1) and middle frontal (F2) gyri in the orbital lobe is considered arbitrary.[2] In general, *the medial orbital gyrus* and *the gyrus rectus* are linked to *the superior frontal gyrus* (F1). Similarly, *the anterior orbital gyrus* and *the rostral part of the lateral orbital gyrus* are considered part of *the middle frontal gyrus* (F2).

Cytoarchitecture

Several investigators have developed cytoarchitectonic maps of the OFR in humans and monkeys. The pioneering investigations of Brodmann,[6] while detailed in other brain regions, were relatively cursory in the OFR. His maps of this region were essentially restricted to charting areas 10, 11, and 47.[7]

Subsequent studies of the same region in primates revealed that the cortex on the orbital surface of the frontal lobe can be categorized as Brodmann Area (BA) 14 medially (corresponding to the gyrus rectus), and 13 caudally. As it extends laterally to the inferior convexity the orbitofrontal cortex corresponds to BA area 12 caudally and 11 anteriorly (anterior orbital surface). Finally, the frontal pole corresponds to BA 10. There is now general agreement that the cyto-architecture of the orbital cortex is similar in humans and primates and earlier discrepancies have been largely reconciled.[8,9]

A recent detailed cyto-architectonic investigation of the human orbital and medial PFC (Figure 37.2b) revealed that all of the subdivisions recognized in the macaque have counterparts in humans.[10] The rostro-caudally organized granular to agranular gradient seen in the rest of the frontal lobe also manifests itself in the orbitofrontal region: The posterior orbital cortex is dysgranular in contrast to the anterior granular areas.[10] The lateral orbital cortex is recognized as BA 47/12. The rostral (anterior) orbital cortex is labeled as BA 11; it consists of a strongly granular cortex that is contiguous with the frontal pole (BA 10). Area 13 occupies the posterior medial orbital surface. Finally, area 14 embodies the cortex of the gyrus rectus at the ventromedial convexity of the frontal lobe. Thus, the OFR constitutes a region of cytoarchitectural transition between the agranular piriform olfactory cortex and the granular cortex of the dorsolateral PFC.[11]

The medial wall of the prefrontal cortex comprises of agranular areas 24 (anterior cingulate cortex), 25 (most posterior/subgenual portion of the medial wall) and 32 (paracingulate cortex).[10] These areas share some functions with portions of the OFR, but will not be discussed further in this chapter.

Connectivity and functional considerations

As described above, the primate orbitofrontal region occupies the entire ventral surface of the frontal lobe and is considered part of the prefrontal cortex.[7] The granular prefrontal cortex (PFC) receives projections from the medio-dorsal nucleus of the thalamus and constitutes a large expanse of cortex situated in front of the motor and premotor regions of the frontal lobe (Brodmann areas 4 and 6).[12] The PFC reaches its highest level of development in the human brain.[13]

The PFC can be sub-categorized on the basis of divisions of the medio-dorsal nucleus of the thalamus,[14,15] a critical relay structure, which in turn receives input from almost all other cortical areas:[16]

(1) The medial part of the medio-dorsal nucleus (pars magnocellularis) projects to the orbital (ventral) surface of the PFC, the so-called 'orbitofrontal cortex' or orbitofrontal region (OFR).
(2) The lateral part (pars parvocellularis) projects to the dorsolateral prefrontal cortex (DLPFC). This part of the PFC receives input from the parietal cortex and is involved in spatial short-term memory tasks.[14,15]

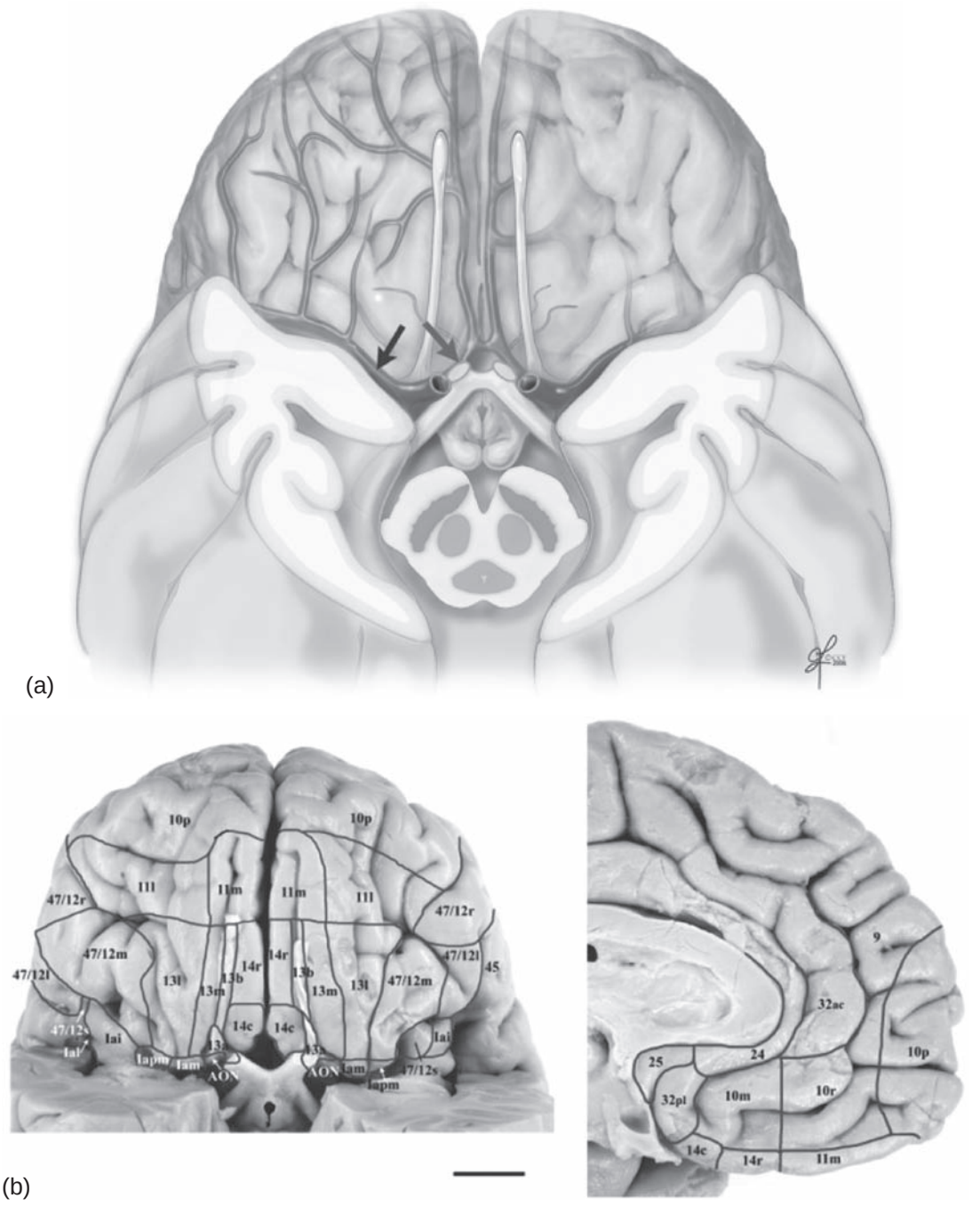

Figure 37.2a Relationships of the OFR with the olfactory tracts and the middle and anterior cerebral arteries arrows revealed after removing the right temporal pole. b: Architectonic subdivisions of the human orbitofrontal region (left) and medial frontal surface (right); scale bar = 10mm. Reproduced with permission from ref. 10.

(3) The pars paralamellaris (the most lateral part of the mediodorsal nucleus of the thalamus) projects to the frontal eye fields (Brodmann area 6).

In humans, indeed in all primates, the posterior part of the OFR is continuous with the rostral part of the agranular insula and abuts upon the para-olfactory component of the cingulate cortex, the anterior olfactory nucleus, and the piriform cortex. This part of the OFR is more primitive architectonically (non-isocortical OFR), and is hence regarded as more 'limbic' in character.[17] On the other hand, the rostrally-placed isocortical OFR has the appearance of granular isocortex and blends into the dorsolateral heteromodal components of prefrontal cortex.[17,18]

In addition to visceral information the OFR receives direct and indirect inputs from all sensory modalities (gustatory, olfactory, somatosensory, auditory and visual). Therefore, the OFR stands out as perhaps one of the most 'polymodal' brain regions.[7] As a rule, cortico-cortical connections are densest among areas with comparable architecture: the more anterior isocortical OFR is mostly linked with isocortical prefrontal, premotor and sensory (somatic, auditory and visual) cortical areas. By contrast, the more posterior nonisocortical sectors of the OFR are mainly

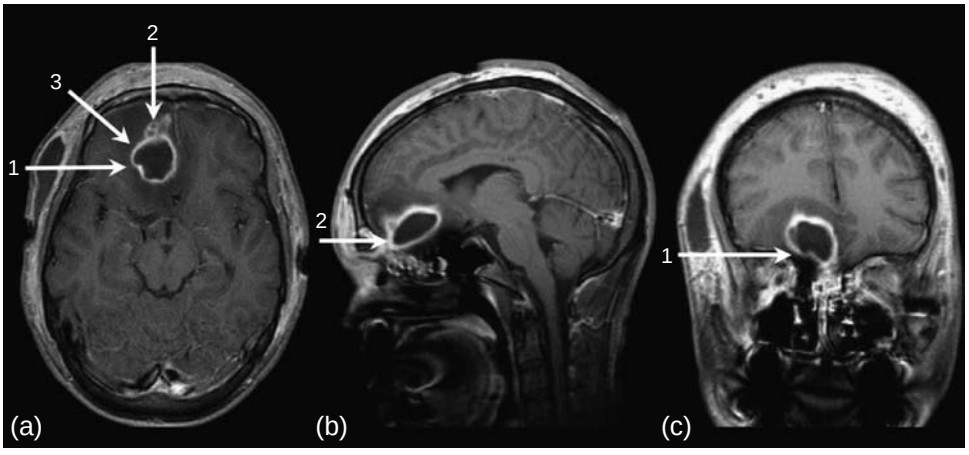

Figure 37.3 The three generally accepted surgical approaches to the OFR. These images show a brain abscess in the gyrus rectus, which could be approached by three possible directions: (1) Lateral approach: commonly performed when OFR resection is carried out after a period of extraoperative invasive recordings using subdural electrodes. (2) Anterior approach: used predominantly for lesionectomies in cases of smaller focal lesions. (3) Antero-lateral approach: may be used for larger lesions of the OFR and possibly combined with an orbito-zygomatic osteotomy. A principal advantage of the anterior and antero-lateral approaches is that the inferior frontal gyrus may be more easily spared.

connected with nonisocortical areas of the insula and temporal lobe, and with primary olfactory and gustatory cortices.[18]

The posterior orbitofrontal cortex receives gustatory and olfactory input through direct connections that originate from the primary taste and olfactory cortices or indirectly via the thalamus. The afferent pathways through the thalamus to the orbitofrontal cortex are thought to mediate conscious perception and discrimination of odors. As a consequence, patients with lesions of the orbitofrontal cortex may lose the ability to discriminate odors.[19]

The OFR has reciprocal connections with the amygdala both through the ventral amygdalofugal tract and through the

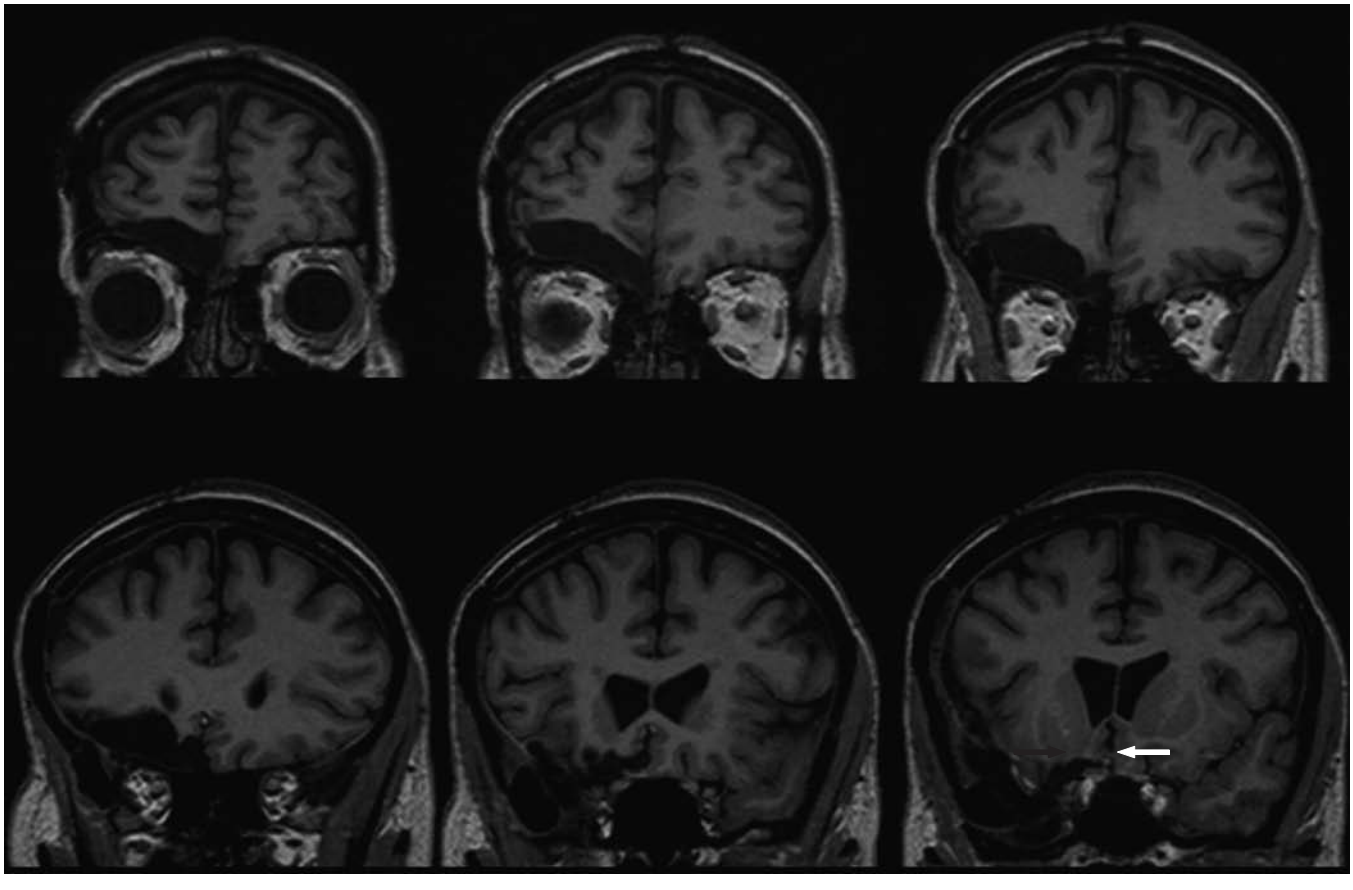

Figure 37.4 Coronal MRI views following extensive resection of the OFR and anterior temporal pole in patient with pharmacoresistant focal epilepsy. Note the preservation of the ventro-lateral prefrontal cortex and resection extending to the subcallosal gyrus (white arrow). Also note the proximity of the supero-medial edge of the posterior margin of the resection to the nucleus accumbens (black arrow).

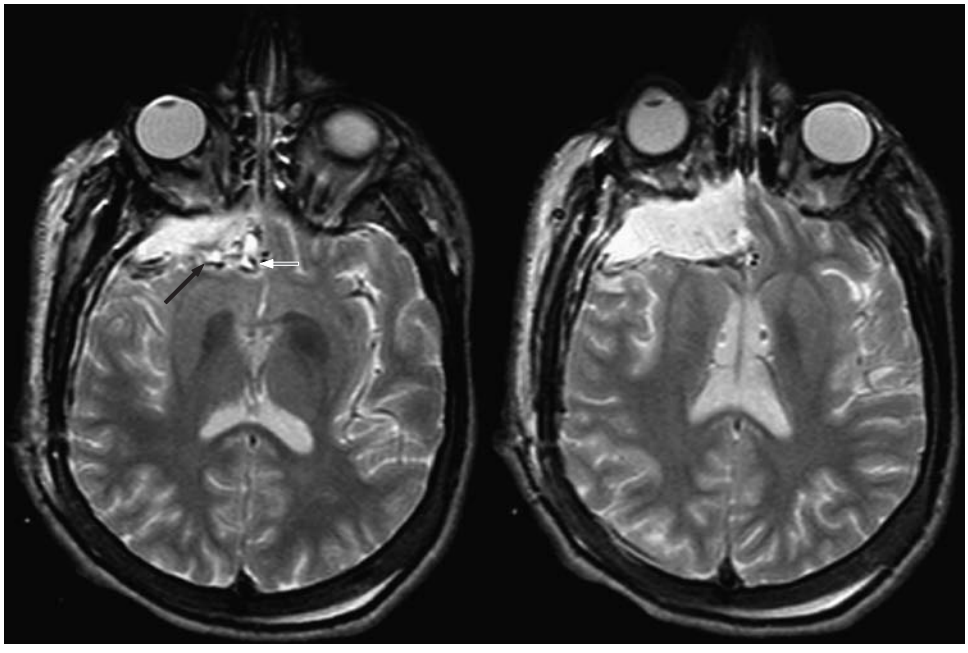

Figure 37.5 Axial views of a T2-weighted MRI after a 'complete' OFR resection. The posterior edge of the resection abuts the middle cerebral artery (black arrow) and the postero-medial edge abuts the anterior cerebral arteries (white arrow).

stria terminalis,[16] and projects back to the inferior temporal cortex, amygdala, as well as to the entorhinal cortex, which serves as 'the gateway to the hippocampus'. In addition the OFR has projections to the hypothalamus and various brainstem structures (including the periaqueductal gray matter, and ventral tegmental area), the caudate nucleus and the cingulate cortex.[18,20]

Epileptologists should be familiar with the main *bidirectional* association pathways linking the OFR with the temporal lobe and limbic system: the uncinate fasciculus and the so-called ventral and dorsal limbic pathways:[13]

- The fibers of the uncinate fasciculus arise from the most rostral part of *the superior temporal gyrus* (T1). They run as part of the uncinate fasciculus and terminate in areas of the OFR and the medial PFC.
- The ventral limbic pathway originates from *the parahippocampal gyrus* (T5). It consists of two segments: The rostral segment runs through the uncinate fasciculus towards the OFR and medial PFC. The caudal segment terminates in areas of the dorsolateral PFC.
- The dorsal limbic pathway arises from *the cingulate cortex* and runs as part of the so-called cingulum bundle. Some components of these association fibers are directed towards the PFC (and terminate in the OFR, as well as medial and dorsolateral PFC).[13]

In a recent stereo-EEG study Catenoix and co-workers investigated the functional anatomic connectivity between the hippocampus and OFR in humans by means of intracerebral hippocampal electrical stimulation[21] in three patients. Low frequency (≤ 1 Hz) bipolar stimulation of adjacent hippocampal contacts was found to result in reproducible evoked responses in the OFR with a mean, first peak latency of 222 ms, and confirmed the existence of functional connections between the hippocampus and the OFR in humans. The long latency of the main response indicates a polysynaptic projection from the hippocampus to the ipsilateral OFR, which, the authors speculate, may play a role in the interhemispheric propagation of discharges arising from mesial temporal structures. This hypothesis is supported by previous studies of ictal recordings obtained using bilateral mesial frontal and temporal depth electrodes, which show that the ipsilateral OFR is frequently and rapidly involved during propagation of seizures arising from the mesial temporal region.[22] In a series of eight patients, who were studied with bilateral, multicontact, orbitofrontal depth electrodes, Wilson and Engel observed that 5 mAmp stimulation of the OFR on one side was effective in evoking contralateral homotopic responses (responses recorded from the OFR on the other side) in the majority of cases.[23] The authors recorded an initial, short-latency, ipsilateral OFR response in contacts adjacent to the stimulated electrodes, followed by a clear response of slightly longer latency in the contralateral OFR. The ease, with which the contralateral OFR response was elicited and recorded, has led to the hypothesis that spontaneous seizure activity may in fact use similar interhemispheric pathways to propagate contralaterally.[23]

Lesions or damage to the OFR have been associated with significant changes in emotion, personality, behavior and social conduct. Patients often exhibit signs of disinhibition, impulsivity, inappropriate jocular affect (witzelsucht), emotional lability, poor judgment, lack of initiative and reduced concern for social conventions.[24] It has been suggested that these patients may suffer from impaired detection of emotional reinforcers such as voice or face expression, and exhibit impaired responses to changing reinforcers.[7] Indeed, the classical case of Phineas Gage, who was injured by a penetrating foreign object that lodged in both medial frontal lobes, may reflect the consequences of orbito-frontal region damage.[25,26] Many signs evident in the early months after head injury to the basal frontal regions seem to fade away with the passage of time, suggesting plasticity involving othermbic regions or the

contralateral homolog. The likelihood of residual personality changes is mainly determined by the severity of the injury.[27] Autonomic and visceral changes including intermittent vasomotor instability and gastrointestinal or cardiac abnormalities may also occur following lesions of the OFR.[28]

Functional imaging of the human OFR has generally confirmed its role in the assessment of potential reward and punishment as has previously been suggested by neurophysiological recordings in nonhuman primates. Additionally, a recent meta-analysis of 87 published functional imaging studies of the OFR suggests that there may be two trends of neural activity in the OFR. The first is a medio-lateral distinction, whereby the medial OFR activity is implicated in monitoring reward potential of different reinforcers – whereas lateral OFR activity is more related to the evaluation of punishers, which may lead to a change in ongoing behavior. The second is a posterior–anterior distinction in which complex or abstract reinforcers (such as monetary gain and loss) appear to be represented more anteriorly in the OFR compared to more simple (or visceral) reinforcers such as taste or pain.[7]

It is evident that the OFR has extensive connections with medial temporal structures as well as thalamic regions involved in various stages of memory processing. Nonetheless, the functional role of the OFR in relationship to memory is not well understood.[18] Dysfunction of the orbitofrontal cortex has been implicated in a number of psychiatric disorders. Neuroimaging studies have repeatedly implicated the OFR in the pathophysiology of obsessive-compulsive disorder (OCD) and depression. It has been consistently demonstrated that patients with OCD show increased uptake of tracers with SPECT and PET imaging measuring cerebral blood flow and metabolic activity.[11,16] Interestingly, this hyperactivity of the orbitofrontal area has been found to normalize following successful pharmacological or behavioral therapy.[29,30] On the other hand, hypometabolism of the OFR and adjacent brain regions has been observed in patients with secondary depression.[31]

Basal frontal lobe epilepsy

It is difficult to estimate the prevalence of basal frontal epilepsy. The true percentage of patients in the general population, who have seizures originating from the basal frontal lobe, is unknown. The literature contains only a handful of patients with pharmacoresistant epilepsy, whose seizures were clearly shown to arise from the orbitofrontal region.

The most reliable evidence for accurate localization of the epileptogenic zone is seizure freedom after epilepsy surgery.[32] This gold standard can only be applied to a small fraction of patients with focal epilepsy, namely patients with medically intractable seizures who are referred for surgical therapy and undergo successful surgical resections. One should remember, however, that a larger number of patients with basal frontal lobe epilepsy may not seek medical attention, may respond well to medications or may be misdiagnosed as having paroxysmal nonepileptic events.

The epileptogenic zone is most precisely defined as the area of cortex generating seizures, the complete removal of which is necessary in order to abolish seizures.[33] Therefore, under ideal circumstances the orbitofrontal origin of the epilepsy is deduced postoperatively on the basis of a surgical resection restricted to the OFR and leading to long-term cessation of seizures after surgery.

When patients do not undergo resective surgery, or are not completely seizure free following resection, or in cases where surgical resection extends beyond the boundaries of the basal frontal lobe, the origin of seizures within the OFR is surmised by intracranial ictal EEG recordings and/or by the presence of a structural lesion. It should be emphasized, however, that these latter criteria (localized intracranial ictal recordings and/or presence of a demonstrable lesion) can not be used as surrogates to the concept of the epileptogenic zone.[34]

Invasive recordings are currently required to demonstrate ictal onset within the OFR. In the subgroup of patients referred to tertiary epilepsy centers, estimates about the frequency of epilepsy arising from this region will depend on how frequently the OFR is investigated invasively.[35] A large stereo-EEG study of 60 patients, who presented with electroclinical patterns requiring differentiation between frontal or temporal seizure onset and underwent exploration with at least one orbital frontal electrode, was reported by Munari and Bancaud in 1992. Ictal discharges were felt to be 'primarily localized' in the OFR in eight patients.[36] The majority of patients in this highly selected group underwent 'acute' investigations lasting for less than 6 hours. Moreover, the authors did not comment on further surgical decisions, and extent of surgical resection and postsurgical outcome, when applicable. In a later review, Munari and co-workers concluded that their original stereo-EEG approach to the OFR 'was not entirely satisfactory', because it did not necessarily target the orbitofrontal cortex.[37]

Jobst and co-workers presented a series of 26 patients with intractable frontal lobe epilepsy. Of these, seven patients were deemed to have seizures arising from the orbitofrontal region.[38] All seven underwent tailored resections with excellent seizure outcome in five (mean follow-up was 52.2 months for the entire series). Individual results of scalp EEG, invasive recordings and brain MRIs were not listed. Similarly, the extent of surgical resection in each case was not provided. Given these limitations, patients from these two series are not included in our further discussions.

The authors of one of the best-documented cases of orbitofrontal epilepsy[39] set strict criteria to establish that seizures indeed arise from the OFR. These include: (1) the OFR should be the source of interictal and ictal activity, as defined by intracranial recordings; (2) resective surgery should be limited to the OFR, and (3) postoperatively the patient should remain free of seizures for at least 5 years. They also propose a fourth relative criterion: it would be preferable to include cases in which the resected surgical specimen from the orbitofrontal focus displayed specific histopathologic abnormalities.[39]

Table 37.1 presents a compendium of cases of presumed orbitofrontal epilepsy as reported in the literature.[37,39–53] An attempt has been made to include most, if not all, cases previously associated with the OFR (initial historical reports as well as more recent descriptions from the MRI era), and to retain the description of seizure semiology, results of neurophysiology, imaging and surgery, as provided in the original reports. Seizure outcome, when available, has been adapted according to the Wieser proposal for a new classification of outcome with

Table 37.1 A compendium of published cases of presumed orbitofrontal epilepsy (from 1951–2005)

Authors/ Year/ Center	Age/ Sex/Han dedness	Onset (yrs)	Aura	Ictal Semiology	IED	IOZ	Imaging	Resection	Histopathology	Outcome	Location/ Comments
Penfield and Kristiansen *1951 MNI, Canada Case #1(M.C.)	35F/-	N/A	Perceptual illusion 'slow motion sensation': slowing down of moving objects or of person's speech; impression that walking person is suspended in air	N/A (only aura reported)	N/A	- eCS-induced Aura of slow motion reproduced in intermediate frontal region. eCS-induced 'one attack' from the same - area (details not provided)	N/A	Resection of large tumor	Tumor (type unknown)	Unknown	Large tumor extending inward over the Rt orbital surface
Case #2(H.B.)	19M/-	14	'indescribable terrible feeling'; 'things going away'	weak feeling in Lt arm/ leg → LOC	N/A	N/A	N/A	Tip of Frontal pole adherent w/old abscess tract entering in the anterior basal part of Rt Frontal lobe	Adherent old frontal abscess tract	Controlled for few months, then recurred (lost to f-up)	Rt anterior basal frontal pole/s/p Rt frontal brain abscess at 9yrs; retained consciousness at onset of attacks
Penfield and Jasper 1954 MNI, Canada Case #1 (P.T.)	30-/-	N/A	No	Sudden LOC w/ Lt head/ eye deviation →GTC	- Scalp EEG: Asymmetrical B/L2Hz SWC Lt> Rt, max Lt Anterior/ Lateral Frontal- ECoG: Sporadic Spikes near the cicatrix on orbital surface & rhythmic sharp and slow complexes on adjacent gyrus	N/A	Pneumoence-phalogram: deficiency of bone overlying Lt frontal sinus w/ slight enlargement of the anterior horns of both lateral ventricles Rt>Lt	Lt orbital surface w/ removal of cicatrix& bone spicule	Bone spicule ~1 inch posterior to frontal pole & meningocerebral cicatrix	Unknown	Hx of depressed fracture of Lt frontal bone; szs started 3 yrs later
Case #2 (D.Tr.)	18M/-	15	No	Automatisms (throat clutching, tearing clothing) w/ occasional	- Scalp EEG: discharge in the Frontal lobe (uncertain if Rt/Lt)-B/L Frontal SDG	-B/L Frontal SD grids: discharge across Lt OFC w/out clinical	N/A	N/A	Not described	Unknown	Hx of skull fracture 3mos prior to sz onset; also previous psychiatric hospitalization

Continued

Table 37.1 cont'd

Authors/ Year/ Center	Age/ Sex/Han dedness	Onset (yrs)	Aura	Ictal Semiology	IED	IOZ	Imaging	Resection	Histopathology	Outcome	Location/ Comments
				Rt head/eye deviation & Rt arm jerks → amnesia, confusion	(total of 4) i Rt/Lt Mesial Frontal ii. Rt/Lt OFC	**change**, then 2:40min later spread to Rt Hemisphere w/ Rt head/ eye turning & Rt arm jerk					for 'peculiar behavior'
Schneider 1961 Ann Arbor, MI Neurology Case #1	30F/Rt	30	Hallucinations: -Visual formed in Rt field: headless persons, circles, bars, colored butterflie - Auditory: whistling like sound of wind - Olfactory: odor of foul cigar smoke	Auras only	- Scalp: B/L high-voltage delta in prefrontal regions, also Lt Anterior & mid Temporal - Subcortical electrodes in i) Superior Temporal: few slow waves ii) Superior Frontal 'Nl alpha' iii) Anterior Midfrontal gyrus: slow waves at 2cm level; no waves at 4cm (mass on palpation)	- eCS of Lt Temporal lobe: no auras were elicited (Lt Frontal lobe not stimulated; pt became uncooperative)	- Skull X-rays Nl; - Carotid arteriogram: Rt shift of Lt ACA - Ventriculogram: Rt shift of ventricular system w/ posterior displacement of Lt frontal horn c/w Lt frontal space-occupying lesion inferior to the lateral ventricles	Complete excision of firm 2.5cm mass at the tip of Lt Frontal pole w/ firm stalk projecting from track originating in roof Lt orbit w/ osteomyelitis of Lt orbital bone (*)	Encapsulated brain abscess w/ purulent exudate of coagulase (+) hemolytic Staph aureus	Class 1(f-up = 10 months)	Hx of MVA 5 yrs prior a/w Lt eye injury requiring enucleation & Lt orbital prosthesis (*) Postop course complicated by extradural abscess requiring bone flap removal, abscess evacuation, debridement & delayed cranioplasty
Niedermeyer* 1971 Baltimore, MD	22M/-	20	No	Oroalimentary automatisms; occasionally tonic body posturing or 'grand mal'	- Scalp: Generalized, irregular slow SWC 1-2.5Hz, max Lt Frontal, Lt Frontopolar & Anterior Temporal - Depth: Spikes Rt Orbito-Frontal, Rt Caudate Nucleus & B/L Amygdala; also Lt OFC during sleep	Depth: lowest ADT in Rt OFC	N/A	Rt Frontal lobectomy	Encephalomal acia & multiple cystic cavities and calcifications within area of disorganized & gliotic	'much improved' sz frequency but developed marked hyper-sexuality post-op cortex	Hx of Rt Fronto-Parietal skull fracture at 20yrs s/p removal of extradural hematoma & debridement of Rt Frontal lobe
Tharp* 1972 Stanford, CA Epilepsia	11M/-	6	No	Facial flushing, piloerection, frightened look → Complex motor w/	Scalp: Periodic, asymmetrical B/L Sharp/Slow wave complexes Rt>Lt (Fp2> Fp1& F4>F3)	2 surgeries: i) I/Op ECoG: Multifocal Spikes & Polyspikes over	Nl skull X-rays, Pneumoen-cephalo gram & B/L carotid arteriograms	2 surgeries: i) resection of area w/ max ECoG abnormality ii) Rt Frontal	Nl cortex & dural vein (varix) → reop: Firm 'gliotic' tissue in the Rt lateral	Class 1 >2 yrs	Rt lateral OFC Clusters ≥ 50/day, for several months w/ long sz-free intervals

				screaming. Able to follow simple commands, but amnestic of events	every 0.5–6 sec resembling SSPE, enhanced by sleep	Anterolateral Rt Frontal lobe ii) I/Op Depth in orbital: **Active spiking lateral OFC;** also sharp-slow waves, but no **seizures recorded**		lobe resection anterior to precentral gyrus including mesial frontal & anterior cingukate	at surgery (no histological examination)		Duration: few sec to min
Ludwig* 1975 NINDS, MD Epilepsia Case #1	38M/Lt	18	Cephalic aura = 'unusual' feeling	Sudden loss of responsiveness w/ staring → Automatisms (fumbling, blinking, sitting up from recumbent) sometimes a/w pallor, lasting for 30 sec → oriented & fluent but amnestic	-Scalp: 1. SWC or Sharp/Slow over Lt Anterior + Middle Temporal 2. Spikes Lt >> Rt Basal leads 3. Bisynchronous Sharp/Slow Frontopolar, max Lt - Extradural flaps Depths: Spikes independent & equal Posterior OFC & Hippocampus - I/Op ECoG: Spikes in posterior OFC	- Scalp: 1. Obscured or Nonlocalizable 2. Rhythmical 10Hz Sharp Waves Lt Frontal) -Extradural flaps (Temporal & Frontal & Depth (Hippocampus + posterior OFC): **build- up of Spikes in posterior OFC** → rhymical 15MH → 25–30Hz for 15sec **exquisitely localized to OFC** - eCS-induced Automatisms in Hippocampus; No AD or clinical changes in OFC	Pneumoencephalogram: mild symmetric dilatation of ventricular system	Resection of posterior OFC & Gyrus rectus, Amygdala & Hipocampus, 3cm of Superior TG & 5cm of Middle, TG + Inferior TG No ECoG discharges postresection	N/A	N/A 'recently operated'	
Case #2	32M/Lt	9	Feeling 'off balance', 'choking' or feeling the room 'closing in'	Unresponsiveness → kicking & cursing (rarely hears voices or sees faces) lasting <1min → oriented & fluent but amnestic	- Scalp: 1. Intermittent Rt Temporal theta 2. Rare sharp transients Rt frontal (F8, Fp2)	- Scalp: 1. No EEG changes concomitant w/ spontaneous szs. - PTZ-induced sz: 1 sec burst of 3Hz bisynchronous SWC - Epidural electrodes Rt Frontal, Temporal: Low-voltage fast 25Hz Rt Frontal - Flap, Needle & Cortical electrodes: rhythmic 20Hz trains exclusively Spike to posterior OFC flap	Pneumoencephalogram: slight dilatation of lateral ventricles Lt > Rt; N1 B/L carotid arteriograms	#1. Rt posterior OFC #2. I/Op ECoG: Lateral Inferior TG w/ eCS-induced Automatism → Rt Temporal lobectomy	N/A	#1. Class 4 #2. Class 4	At onset given diagnosis of 'psychoneurotic hysteria' and treated w/ ECT Initial invasvive evaluation w/ bitemporal superficial & depth electrodes: no epileptiform activity even during clinical sz

Continued

Table 37.1 cont'd

Authors/ Year/ Center	Age/ Sex/Han dedness	Onset (yrs)	Aura	Ictal Semiology	IED	IOZ	Imaging	Resection	Histopathology	Outcome	Location/ Comments
Case #3	26M/Lt	6	No	Unresponsi veness w/ facial pallor → Complex motor (foot stamping, kicking, running) ± Lt oculocephalic deviation, lasting <1–2min	- Scalp: B/L synchronous Sharp/Slow over Anterior Head areas w/ Lt predominance and shifting max (Fp1, F3, F7) - B/L Extradural: Spikes in OFC > Lt Anterior Temporal	- Scalp: PTZ-induced → Obscured rhythmical 12Hz waves over Lt hemisphere - B/L Extradural OFC + Anterior Temporal: PTZ - induced w/ brief flattening → 2–3Hz SWC over Lt OFC w/ spread to Rt OFC - I/Op ECoG: Anterior parts of Lt Middle + Inferior TG & middle FG	Nl Pneumoence-phalogram & B/L carotid arteriograms Wada: Rt hemisphere dominance for speech	extensive Lt Temporal lobectomy: 7 cm along Middle + Inferior TG & 5.5cm along Superior TG & Hippocampus 2.5cm	N/A	Class 3 'very few' seizures 'short follow-up'	
Case #4	13M/Lt	7	Visual - hallucination or Perceptual illusion (feels as if smiling/ unable to speak)	Upward mouth movement (either side) w/ 'silly laugh' → unresponsi-veness w/ Lt head turning & Lt arm waving purposelessly → Complex motor (moves about, undresses self) Rare generalized motor szs	- Scalp: B/L synchronous Sharp/Slow & SWC over Frontal + Frontopolar, max Rt (F4/ Fp2) - SD: Mesial Rt OFC rhythmical 2Hz waves & independent Sharp waves from Rt superior Frontal convexity	- Scalp: PTZ-induced 'diffuse Rt-sided activation' - Rt-sided SD: OFC, Superior + Inferior Frontal & Midparasagittal: No spontaneous szs * eCS-induced typical sz only w/ Rt OFC stimuation* * PTZ-induced: flattening → rhythmical 2.5–3Hz SWC Rt OFC w/ spread to Lt OFC → rhythmic SWC well localized over Rt Superior frontal (F4)	Pneumoence-phalogram: moderate dilatation of entire ventricular system	No resection (aborted because of Suspicion of skull infection) Felt to have 'at least two independent epileptogenic foci'	N/A	No resection	History of purulent Rt ear infection at 6yrs
Williamson 1985 Yale, CT Ann Neurol	-/-	N/A	'buzzing noise & visceral sensation'	Staring → Complex motor (kicking, thrashing, pelvic thrusting) w/ genital manipulation & alleged retention of awareness, lasting ~15sec	**	Depth: **Rt OFC** localization	**	Rt Frontal lobectomy	'dense orbi-tofrontal gliosis'	Class 4 Sz-free × 1yr, then recurred w/ frequency of 8/yr	**

Rougier and Loiseau 1988 Bordeaux, France JNNP	29M/-	10	No	- Staring w/ semi-purposeful & thrashing movements; shouting incoherent words (occasional laughter) & amnesia for events - Occasional GTC out of sleep	- Scalp EEG: Sharp waves Rt Fronto-temporal (F8-T4) - sEEG: Spikes localized to Rt OFC (w/ occasional propagation to contralateral Lt OFC)	- Scalp EEG: Sudden attenuation of background followed by movement artifact - sEEG: Repetitive Spikes localized to Rt OFC only	CT: Nl (also N1 Ventri-culography & Carotid angiogram)	Rt Orbital gyri, gyrus rectus & subcallosal area	No abnormal-ities	Class 1 18 months	Rt OFC / clusters 5–10/d w/ sz-free intervals up to 1–2 weeks Initial sEEG w/ depths in Rt mesial Frontal, mesial Temporal & Anterior Cingulate (failed to identify area of ictal onset)
Chang 1991 Seattle, WA Epilepsia	36M/-	8	Sensation of whole body numbness starting in the feet → flash backs from past/butterflies in stomach or feelings of fear or	- Cessation of activity areas w/ → Right body/ head turning → Complex motor behavior (struggling, kicking) & vocalizations indicating fear, lasting ~30 sec w/ abrupt return of consciousness - GTC out of sleep &	- Scalp EEG: 1.Bisynchronous asymmetric IEDs anteriorly w/ shifting Rt or Lt preponderance; 2. IEDs widely distributed over Rt Fronto-temporal - Sphenoidal: Bisynchronous Basal IEDs maximal Rt - Infraorbital: IEDs maximal infraorbitally strips: Spikes Rt Infraorbital - I/Op ECoG: Spikes in entire Rt OFC & Anterior portion of Inferomedial Temporal	- Scalp EEG: Obscured by artifact (only one Aura w/ Rt Temporal rhythmic theta) - SD strips (B/L Temporal; & Medial + Lateral Frontal): Rt Infraorbital rhythmic fast activity w/ attenuation in all contacts	CT: Nl	Tailored resection of Rt OFC & adjacent portion of Rt Lateral Frontal -Postresection ECoG: some Frontal discharges Superior & Posterior to the excision considered insignificant	Gliosis & areas w/ Intracyto-plasmic neuronal inclusions of PAS(+) granules c/w focal lipofusc-inosis	Class 1>- 6 yrs -off AEDs for > 5 yrs -apparent resolution of premorbid psychiatric problems	Positive FH of seizures Psychiatric comorbidity: - Depression - Violent outbursts
Munari 1995 Grenoble, FL France Adv. Neurol.	25M/Rt	6	Rare: Sensation of cold & Piloerection on Back & Thorax or feeling as if 'my brain is being crushed'	Sudden loss of contact → Ambulation & Automatisms: Oral / Gestural ('as if trying to catch things in the air') / Verbal (incomprehen-sible utterances) → rotation of trunk Lt> Rt & eyes rolling to the Lt → rare GTC	Scalp-EEG: Theta-delta activity & occasional Spikes over Rt Fronto-temporal region	- Scalp EEG: Rt anterior onset; evolution c/w initial Frontobasal onset → very rapid spread to anterior & mid-temporal regions - sEEG: Low-voltage fast on Rt mesial & lateral OFC w/out clinical signs for first 35sec except for some brady-cardia (from 77 to 63 beats /min); szs	Large signal change on Rt Frontopolar & Frontobasal regions, w/out evidence of progression	- Inferior Frontal region including Forntal pole - Temporal pole & uncus - Anterior & mid-Temporal neocortex (including first, second & third temporal gyri)	N/A	Class 1 (26 months)	* Hx of Rt Frontal Frontal tumor s/p resection at age 7 (details N/A) followed by chemo- & radio-therapy;

Continued

Table 37.1 cont'd

Authors/ Year/ Center	Age/ Sex/Han dedness	Onset (yrs)	Aura	Ictal Semiology	IED	IOZ	Imaging	Resection	Histopathology	Outcome	Location/ Comments
						become symptomatic after spread to inferior frontal, temporal pole, anterior & mid-temporal neocortex					
Roper and Gilmore 1995 Gainesville, FL J Epilepsy Case #1	17F/Rt	15	Bad taste or smell & awareness of accelerated heart rate	Staring w/ occasional manual automatisms	- Scalp/sphenoidal EEG: Spikes Rt mesial (Sp2) & midtemporal (T8) - I/op ECoG: Spikes localized to lateral OFC portion	- Scalp/sphenoidal EEG: 2Hz δ at F4 & T8 → bifrontal & Rtmidtemporal δ w/ Sharp waves at Sp2 - B/L SD: Central & Lateral contacts of Rt OFC strip w/spread to Rt subtemporal	MRI: Nl hippocampal volumetry	Both the central OFC (SD strip) + lateral OFC (ECoG abnormality) w/ firm mass of slightly discolored tissue	Maloriented cells of glial & neuronal origin c/w focal MCD	Class 1 17 months	No significant post-op neuro-psychologyical deficits
Case #2 unrelated	42F/Rt	13	None reported	Staring w/ unresponsiveness & oral automatisms mostly out of sleep	- Scalp/sphenoidal EEG: Independent bitemporal Spikes Lt >> Rt (20:1) - I/op including ECoG: Spikes in Lt OFC + Lt posterior mesial Temporal	- Scalp/sphenoidal EEG: (i) Bi- fronto-temporal 3/6 (ii) Lt mesial temporal -B/L SD & Depth: hippocampal 4/8 & (ii) Central contacts of Lt OFC strip w/ spread to Rt OFC	MRI: Nl including hippocampal volumetry; PET:↓10% FDG in Lt Temporal (i) Focal Lt	- 4cm lateral temporal neocortex -3cm of hippocampus & parahippocampal -Uncus & lateral posterior OFC	- Hippocampus: no evidence of sclerosis but missing portions gyrus - OFC: NI amygdala 2×3	Class 3 15 months of CA3	Single seizure type w/ respect to ictal semiology Mild word-finding difficulties post-op Only 2 szs on day of
Case #3	34M/Rt	13	'feeling of déjà vu' → sensation of disorientation	N/A (only aura reported)	None reported	- Scalp/sphenoidal EEG: Rt Fronto-Temporal - Unilateral SD (Rt Fronto- temporal): Medial contacts of OFC SD strip w/ spread to Dorsolateral Frontal	MRI: ATL defect 4.5cm from tip w/ complete resection of Mesial structures	Rt OFC -	'unremarkable'	Class 1 19 months	surgery 11 months post-op (gliosis w/ out cell loss), age 16 → sz-free × 6yrs age w/ recurrence of habitual szs
Shihabuddin 2001 Vanderbilt, TN Seizure	28F/Rt	19	feeling of 'butterflies in the stomach' a/w fear	Restless, hyperkinetic w/ UE automatism (Rt>Lt), drinking, dressing, & later oroalimentary automatisms a/w LOA + ictal speech →	- Scalp/sphenoidal EEG: Rt Inferomesial Temporal Spikes (Sp2) & 'atypical trains of polyspikes' (Sp2) postictally- SDG: frequent	- Scalp/sphenoidal EEG: Regional, Rt Inferomesial Temporal (rhythmic theta) Spikes & Polyspike- SDG: (i) Clinical szs: Rt mesial Frontal	- MRI: Lesion 20 × 8mm^2 in Rt mesial OFC (Nl hippocampi) - PET: ↓FDG in Rt Temporal (both mesial + lateral) - SPECT: ↑uptake	Rt mesial OFC Lesionectomy	Pilocytic astrocytoma	Class 3 - Cluster of habitual szs post-op day#1 - sz free × 1yr- then 3 'atypical' szs in	Positive FH of szs in 1st degree cousin Sz frequency: -CPS: 20/month - 2° GTC:10/mo

				GTC sz	Spikes Rt mesial OFC; also Spikes Rt Lateral & Basal Temporal	(inferior/anterior aspect) (ii) Subclinical szs: Rt OFC (mesial aspect)	Rt Temporal (injection 15sec after sz onset)			1mo & sz-free for another 6 months	
Rugg-Gunn FJ 2002 London, U.K. Lancet	36F/-	23	No	Sudden LOA a/w truncal rocking mvts, reperated grabbing hand mvts & aimless wandering	- Scalp: Rt F-T slow waves	-Scalp: Regional Rt Frontal- -Intracranial: 4 typical & 10 subclinical szs w/ Rt OFC onset	-Conventional high-resolution MRI: Normal -DTI: Area of ↑ Diffusivity in Rt OFC	Image- guided Rt Inferior Frontal resection	Substantial diffuse gliosis w/ astrocytosis (predominantly in the white matter w/ mild intracortical gliosis w/out dysgenesis)	Class 4 Recurrence after 6 mos sz-free → 'shorter & less disabling' 'Engel IIA'	No identifiable risk factors
Smith 2004 Augusta, GA & Munich, Germany SFN Case #1	-/-	N/A	Metallic taste, head tingle, 'déjàvu'	Unresponsiveness or arrest of activity → vocalization (shouting, laughing)	- Scalp: Lt Frontal convexity tF3)	-Scalp: Nonlocalized - Depth: 'Electrodecremental' Lt posterior OFC w/out clinical change for ~16sec until spread to B/L Mesial Temporal	MRI: Nl 'nonlesional'	Complete resection ictal + interictal focus as defined by Depths = posterior 3.5cm OFC	Gliosis in the molecular layer + white matter w/ mild & patchy gliosis in other layers	Class 1	
Case #2	-/-	N/A	No	Unresponsiveness or arrest activity → oromanual automatisms	- Scalp: 'Diffuse discharges'	-Scalp: Nonlocalized (No invasive studies)	MRI- identifiable lesion (posttraumatic)	Complete resection old posttraumatic cavity & surrounding sclerotic tissue	Old posttraumatic hematoma cavity w/ surrounding sclerotic tissue	Class 1	
Rheims 2005 Lyon, France Epil Disord	21F/Rt	9	Lt Temporo-parietal cephalgia	Behavioral arrest → Lt & downward oculocephalic deviation w/ grimacing & vocalization→ hypermotor	- Scalp EEG: Lt Frontal Spikes & slow waves - sEEG: active Spike focus Lt Frontopolar	-scalp EEG: low-voltage fast Lt Frontal → B/L Frontal SWC - sEEG: (i) Localized Lt Frontopolar onset w/ spread to Lt OFC (ii) Onset & predominant evolution in Lt OFC	MRI: circumscribed MCD Lt Frontopolar suggesting 'minor form' of TSC	Lt Frontopolar & OFC (resection of sEEG-defined area)	Cortical Dysplasia 'typical of those seen in TSC'	Class 1 > 2 yrs	Mother w/ TSC & epilepsy Patient w/out TSC stigmata

Abbreviations:
AD = Afterdischarge; AEDs = Antiepileptic Drugs; Angio = Angiography; ATL = Anterior Temporal Lobectomy; a/w = associated with; B/L = Bilateral; c/w = consistent with; eCS = Electrical Cortical Stimulation; ECoG = Electrocorticography; ECT = Electroconvulsive therapy; EEG = Electroencephalography; F = Female; FG = Frontal Gyrus; FH = Family History; f-up = follow-up; GTC = Generalized Tonic-Clonic; Hx = History; IEDs = Interictal Epileptiform Discharges; I/Op = Intraoperative; IOZ = Ictal Onset Zone; Lt = Left; LOA = Loss of awareness; LOC = Loss of consciousness; M = Male; max = maximum; max = maximum; MCD = Malformation of Cortical Development; min = minutes: mo = month; MRI = Magnetic Resonance Imaging; MVA = Motor Vehicle Accident; N/A = Not available; Nl = Normal; post-op = postoperatively; Rt = Right; s/p = status post; sec = seconds; sEEG = stereo-encephalography; OFC = Orbitofrontal cortex; PAS(+) = Periodic Acid-Schiff positive; post-op = postoperatively; PTZ = Pentylenetetrazol; SD = Subdural; SDG = Subdural Grid; s/p = status post; SSPE = Subacute Sclerosing PanEncephalitis; SWC = Spike & Wave Complex; sz = seizure; TSC = Tuberous Sclerosis Complex; TG = Temporal Gyrus; UE = Upper Extremity; w/ = with; w/out = without; yrs = years; 2° = Secondarily; -/= not provided; δ = delta

respect to seizures following epilepsy surgery.[54] Careful review of these cases, with the above criteria in mind, reveals that in most instances localization of the epileptogenic zone within the OFR is either presumed or unconfirmed. Our inability to determine the extent of the epileptogenic zone and its relationship to the OFR, when surgical resection involves extra-orbital areas adjacent to the basal frontal lobe or when an extensive frontal lobectomy has been performed reflects a well-recognized inherent limitation of most human surgical studies.[35]

Seizure (clinical) semiology

The most widely used system for classification of epilepsies was revised in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE).[55,56] The 1989 Proposal for the Classification of the Epilepsies and Epileptic syndromes describes a separate anatomically defined seizure pattern in regards to the orbitofrontal area: 'The orbitofrontal seizure pattern is one of complex partial seizures with initial motor and gestural automatisms, olfactory hallucinations and illusions, and autonomic signs'.[55]

The commission prefaces the 1989 report with a cautionary note: '... inferences regarding anatomical localization must be drawn carefully'. Attempts to classify seizures according to location (anatomic lobes or sublobar regions) are confounded by the fact that seizures usually give rise to ictal manifestations by virtue of propagation to eloquent areas of cortex. Large cortical areas in the anterior neocortex such as the prefrontal cortex may be clinically silent, when activated by seizure discharges or electrical stimulation. Consequently, the first clinical evidence of a seizure may reflect propagation to areas remote from the region of seizure origin.[57] Seizures arising from a distinct focus within the frontal lobe may rapidly involve multiple frontal lobe regions concealing specific seizure patterns.[58] On the other hand, extensive, nondiscrete, or multifocal epileptogenic zones and rapid spread patterns within the ipsilateral or contralateral frontal lobe will lead to overlapping, coincidental clinical phenomena. As a result of these limitations, attempts to classify frontal lobe seizures on the basis of distinct anatomic subdivisions may be restrictive and potentially misleading.[35,59]

Moreover, only a handful of patients with unequivocal focal epilepsy arising from the orbitofrontal area have been reported in the literature, as is evident from the earlier discussion and the cases listed in Table 37.1. In their comprehensive review of 'complex partial seizures of extratemporal lobe origin' Swartz and Delgado-Escueta remarked that only eleven cases of 'orbitofrontal complex partial seizures' existed in the literature in a period spanning almost 20 years (from 1957–1975; all 11 cases are included in Table 37.1). And only nine of these were thought to carry 'strong proof'.[60]

Electrical stimulation studies

Direct electrical stimulation of the cortex has been used to study the results of epileptic activation of various cortical sites.[61] Stimulation studies with an effective stimulus intensity reveal that the majority of human cortex is symptomatically silent, and provide further evidence to suggest that cortical activation by epileptiform discharges will not produce symptoms, unless the electrical activity spreads to adjacent eloquent cortical sites.[34]

Stimulation of the OFR has been reported to produce a variety of responses. Smith and co-workers report that stimulation of the lateral and mesial posterior OFR (including the apparent ictal onset zone in a patient with pharmacoresistant focal epilepsy) did not produce any observable clinical phenomena. Such findings lend support to the hypothesis that clinical manifestations of basal frontal epilepsies may in fact begin outside the basal frontal area.[51] The same group stimulated 13 posterior orbitofrontal sites using laterally placed depth electrodes in nine patients, who did not have evidence of focal epilepsy arising from the OFR. An assortment of sensations were elicited in this group including 'body tingling' on six occasions, and 'a spaced-out, confused feeling' on four; 'an unpleasant feeling', an ill-defined smell, an olfactory hallucination, a cephalic sensation, lightheadedness, and 'fuzzy vision' were reported on one occasion each.[51] In their series of orbitofrontal stereo-EEG depth electrode investigations Munari and Bancaud report that an olfactory hallucination can be elicited in the presence or absence of 'a localized afterdischarge' following posterior orbitofrontal stimulation.[36] Smith and co-workers postulate that such provoked olfactory symptoms may actually reflect activation of the adjacent lateral olfactory striae,[51] which is possible, given that afterdischarges related to electrical stimulation often activate a more extensive cortical region beyond the cerebral tissue surrounding the directly stimulated electrode.[61]

Lastly, autonomic responses resulting from OFR stimulation in humans were reported in older studies;[62,63] these include blood pressure elevation or bradycardia,[64] respiratory arrest or increased amplitude of respiration, and increased esophageal contractions or decreased gastrointestinal motility.

Ictal manifestations

As discussed earlier, the large prefrontal cortical region can be viewed as a collection of heteromodal association areas, which share elaborate connections with other frontal and extrafrontal cortical and subcortical structures.[65] Hence, seizures arising from several regions within the anterior part of the frontal lobe – including the orbitofrontal, frontopolar, anterior cingulate, and medial intermediate frontal regions – may display overlapping clinical characteristics as a result of the rapid and simultaneous activation of cortical sites within the PFC and its connections.[58,66] In general, seizures arising from the frontal lobe may start and end abruptly with little if any postictal confusion, and tend to have a shorter duration (lasting less than 30 seconds) and higher frequency (oftentimes occurring in clusters) compared to seizures of temporal lobe origin.[35] Ictal behavior is commonly characterized by prominent and often complex motor manifestations. Because of their bizarre appearance at times, frontal lobe seizures are not infrequently mistaken for nonepileptic, psychogenic events.[67] The somewhat circuitous and dichotomous term 'frontal lobe complex partial seizures' has been proposed by some authors to describe these events.[53,68,69] Stereotypic recurrence of the various clinical components in individual patients is key in establishing the correct diagnosis of seizures arising from the frontal lobe.[53,67]

Again, it is important to recognize that the observed seizure semiology reflects epileptic activation of the symptomatogenic zone.[34] When seizures originate from silent areas of the brain there will be no outward manifestations without propagation of seizure activity to the symptomatogenic zone. Studies with

depth electrodes have shown that ictal onset within the OFR may precede the onset of clinical manifestations by as much as 60 seconds suggesting asymptomatic activation of this area.[37,51,70] Two separate groups of investigators have observed that patients may in fact remain completely asymptomatic, when the epileptic discharge stays localized within the OFR.[37,47] Summarizing their experience of more than 150 patients, in whom the orbitofrontal region was investigated using stereo-EEG, Munari and co-workers concluded that 'the only clinical from characteristic of well-limited discharges in the orbital cortex was the absence of any objective clinical symptomatology'.[71]

Based on these observations, the limited number of well-documented published cases, and the functional heterogeneity of the OFR, it is difficult to assume a unique seizure semiology that is characteristic for this part of the frontal lobe. A review of reported cases reveals some common themes: lack of aura or nonspecific auras, autonomic changes, behavioral arrest and/or impaired awareness, complex motor and 'hypermotor' activity, vocalization, oculocephalic deviation, olfactory or gustatory hallucinations, occasional secondary generalization.[55,66,72] Occurrence in clusters, nocturnal preponderance, relatively brief duration and brief if any postictal confusion are also observed.

Based on the cases reported by Ludwig[41] (see Table 37.1) Bancaud and Talairach identified two 'recognizable seizure patterns' associated with seizures of orbitofrontal origin,[73] as follows:

(1) Olfactory auras, defined as seizures beginning with an olfactory hallucination or illusion. The olfactory symptoms may be accompanied by gustatory auras, autonomic changes, oroalimentary and/or gestural automatisms and 'thymic alterations'. These associated symptoms have been attributed to propagation of ictal discharges to the adjacent opercular-insular-amygdalar region (autonomic manifestations, gustatory hallucinations or illusions, and oroalimentary activity) and/or to anterior cingulate region (complex gestural activity 'automatic gesticulations', and mood changes).[36] Other studies have shown that olfactory auras usually point to seizures originating from the limbic mesial temporal structures, which are also involved in olfactory function.[74,75] In fact, published reports suggest that olfactory auras constitute an uncommon manifestation of seizures arising from the basal frontal region.[76]
(2) Autonomic seizures, defined as seizures of prevalent 'vegetative components'. They present with a variety of paroxysmal autonomic disorders including cardiovascular (heart rate changes, facial flushing, pallor), respiratory (apnea), digestive (sensation of hunger and/or thirst), urogenital (urge to urinate and periictal urination) and thermoregulatory disturbances (sensation of cold with piloerection and/or sensation of heat). Ictal 'vegetative' manifestations are thought to result from activation of the orbitofrontal and opercular insular regions.[35,73]

The so-called 'hypermotor seizures' constitute another ictal pattern commonly associated with this region. According to the Semiologic Seizure Classification hypermotor, seizures are defined as seizures manifesting with complex motor automatisms – organized motor activity, which primarily affects the proximal body segments and results in relatively large amplitude movements.[77] The term 'organized' refers to movements that imitate natural movements as opposed to dystonic, tonic or clonic movements, but does not specify whether they are voluntary, involuntary or semipurposeful (e.g., evoked in response to environmental stimuli).[78] When rapidly executed these movements may appear violent, for example thrashing, bicycling, vigorous kicking, frenetic striking or flailing of limbs and other rather peculiar motor behaviors.[76] The repetitive character of these motions has been attributed to the central role of the prefrontal and premotor areas of the frontal lobe in the sequential design of movements.[79]

In a large series of suspected frontal or temporal lobe epilepsies Manford and co-workers identified 13 patients with a CT and/or MRI-demonstrable lesion ('lesional focal epilepsy') and hypermotor seizures, characterized by early 'motor agitation'. The authors noted that the structural lesions involved the OFR in the majority of cases (7 out of 13). Lesions extended to the frontopolar cortex in Six of these Seven patients.[80] The remaining Six cases with early motor agitation showed no consistent lesion localization (their lesions resided in various other frontal or temporal areas). Such observations may support the 1989 ILAE classification of anatomically defined seizure types of possible orbitofrontal origin. It should be noted however, that this was not a series of patients undergoing resective epilepsy surgery, and that the definition of the presumed epileptogenic focus was based on somewhat loose and often discordant clinical, EEG and MRI/CT localization criteria. In his review of structural lesions in the frontal lobe Goldensohn found '… too few cases with discrete lesions with sufficiently detailed seizure descriptions of possible orbitofrontal and cingulate origin to allow separate categorizations'.[66] The author concluded that symptoms and signs commonly linked to orbitofrontal and/or cingulate epilepsy (such as autonomic or mood and affect changes, gestural automatisms, and versive movements preceding automatisms) do not appear to differentiate between lesion cases involving the orbitofrontal, anterior cingulate or other areas of the anterior third of the frontal lobe.[66]

Finally, it should be emphasized that epileptogenic foci within the OFR can give rise to seizures, which are electroclinically indistinguishable from temporal lobe seizures given the widespread connections between the limbic system and the OFR.[39,47,50] In other words, basal frontal epilepsy may manifest itself with seizure spread outside the lobe of origin, as illustrated by Shihabuddin and colleagues in their case of a small right orbitofrontal pilocytic astrocytoma. Invasive recordings demonstrated seizure generation in the right OFR with spread to the ipsilateral mesial-basal temporal region – seizures were eliminated almost completely following right mesial orbitofrontal lesionectomy.[50]

Electroencephalography

Surface EEG

The ability of the scalp EEG to detect interictal activity depends on the extent of the irritative zone, the location and proximity of the generator in relation to the scalp and the orientation of the dipole.[81] In general, interictal or ictal surface EEG studies are not very helpful in identifying epileptogenic foci residing in the basal frontal lobe because of the hidden, distant location of this part of the cortex with relation to scalp electrodes. Even long-term sleep-deprived interictal EEG

recordings may be completely normal despite activation procedures. This apparent lack of interictal and/or ictal EEG abnormalities is a well-known weakness of electroencephalography.[74]

When detected on scalp EEG, interictal epileptiform discharges are helpful in establishing the diagnosis of epilepsy. Prolonged daytime EEG studies with recordings of 1–2 hours of sleep, as well as nocturnal sleep recordings increase the yield of interictal epileptiform abnormalities in individuals with epilepsy.[82–84] Increased sampling using special electrodes (such as sphenoidal, anterior temporal or ear electrodes)[85,86] and closely spaced additional scalp electrodes[87–89] may be helpful in distinguishing temporal from frontal lobe foci.

Home videotape recordings, when available, can provide valuable diagnostic information by capturing ictal manifestations. Prolonged inpatient video-EEG monitoring is indicated in patients with pharmacoresistant epilepsy as well as patients with paroxysmal events of unclear etiology. Careful video analysis of ictal semiology may lend support to the diagnosis of frontal lobe epilepsy, even in some cases where EEG is inconclusive. Polysomnographic recordings with additional EEG montages should be considered, in cases of predominantly nocturnal paroxysmal phenomena.[90,91]

Typically, abnormalities that are detectable on scalp EEG do not allow for topographic localization of foci residing in the basal frontal lobe. When present, spikes or sharp waves may have a regional distribution or appear generalized as a result of secondary bilateral synchrony.[87] False localization to the anterior temporal region is not uncommon in patients with basal frontal epilepsies, who present with anterior temporal interictal epileptiform discharges (Figure 37.6) on their scalp EEG.[57] Occasionally, propagated epileptiform activity can be present over central or frontolateral regions.[76] Moreover, epileptiform abnormalities may have a misleadingly widespread appearance, because of the large distance and intervening cortical area that separates the epileptogenic zone from the scalp EEG electrodes.[81,92] Interictal sharp waves may be reflected over a wide bifrontal region as a result of volume conduction (Figure 37.7) such bilateral discharges may sometimes exhibit a shifting right or left preponderance or a misleading contralateral maximum.[35] The inaccessibility of the basal frontal surface and other areas of the frontal lobe to scalp electrodes, the widespread connectivity of the OFR, the variable size and location of epileptogenic foci within this region and the potential for bilateral epileptogenicity as a result of bifrontal injuries are among the factors accounting for the lack of adequate topographic scalp EEG localization in basal frontal lobe epilepsies.[33]

Large and somewhat blunted sharp waves were demonstrated by Tharp in his patients with presumed orbitofrontal epilepsy.[52] Case reports by Ludwig and co-workers highlighted the occurrence of bilaterally synchronous, paroxysmal epileptiform discharges, with a bifrontal or frontopolar maximum, as well as discharges involving one anterior quadrant, with or without evidence of additional temporal lobe involvement.[41] In the single patient described by Chang and colleagues sphenoidal recordings exhibited a consistent preponderance on the side of the epileptogenic OFR. In this well-documented case report the addition of sphenoidal and infraorbital scalp electrodes revealed that the observed bisynchronous discharges had a more basal distribution with a maximum in the infraorbital regions.[39]

The close anatomical connections between the mesial temporal and orbitofrontal regions have already been discussed. In their classic (1958) paper, Kendrick and Gibbs used the technique of strychnine neuronography in the course of temporal

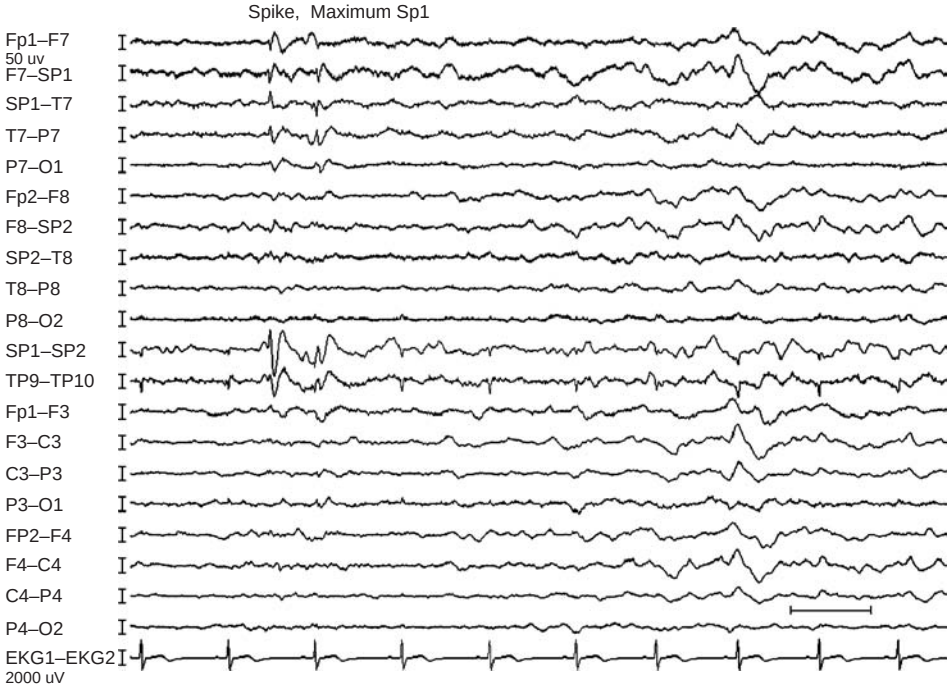

Figure 37.6 Interictal scalp EEG tracing. Predominant spike focus in the left anterior temporal region, maximum in the left sphenoidal electrode (Sp1), as seen on this longitudinal bipolar montage (the temporal chains have been extended to include the left and right sphenoidal electrodes).

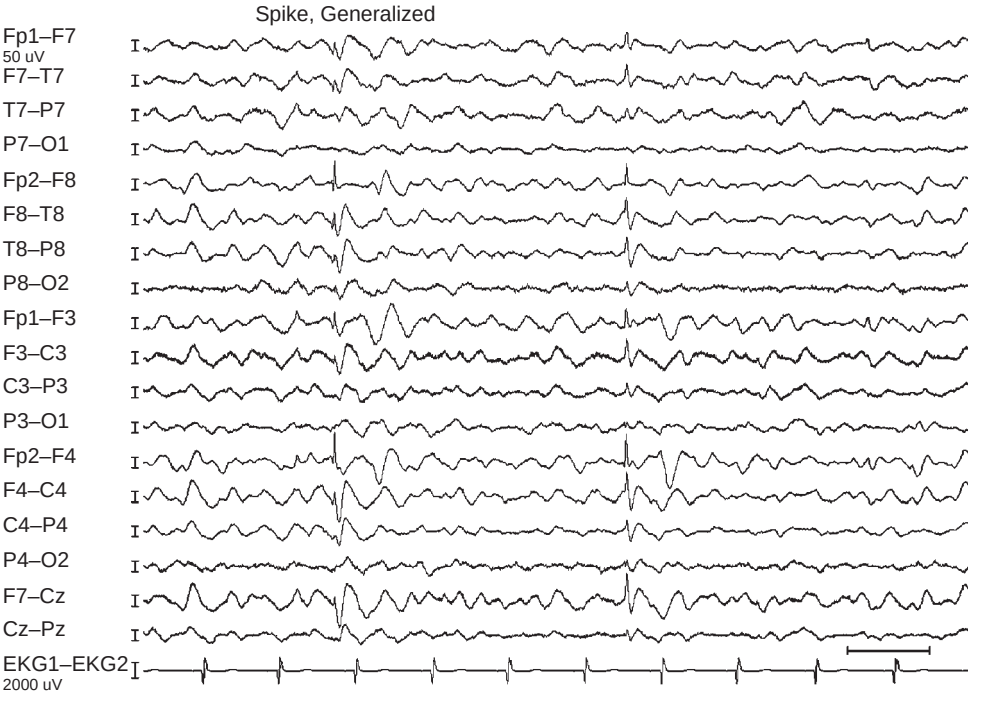

Figure 37.7 Interictal scalp EEG tracing. Less frequently, generalized epileptiform discharges (with a shifting bifrontal maximum; higher on the right side in this instance) were seen during prolonged video-EEG recordings, as illustrated on this routine longitudinal bipolar montage.

lobectomies to demonstrate the bidirectional interrelationship between these two regions in humans.[93] Local application of strychnine through needle electrodes produced 'artificial' spike foci in the frontal and temporal lobes of 34 patients. The authors observed that strychnine-induced spikes in the mesial temporal region commonly spread to the mesial orbital surface of the ipsilateral frontal lobe as well as to the tip of the ipsilateral temporal lobe. On the other hand, strychnine injected into the mesial OFR resulted in spike discharges that propagated first to the ipsilateral mesial temporal cortex, and later to the contralateral mesial OFR and to a lesser extent to the frontal poles. The authors concluded that discharges may spread in either direction – depending upon whether strychnine is first applied in the mesial temporal or orbitofrontal area – and implicated the 'pathway afforded by the uncinate fasciculus' to explain the observed spread patterns.

Ictal scalp EEG recordings (Figure 37.8) during seizures of frontal lobe origin, as a whole, may provide poorly localizing[94,95] or misleading information.[96] Seizure duration is usually short and muscle artifact often obscures ictal EEG activity. Furthermore, observed patterns and frequency of activity at the time of electroencephalographic seizure onset do not correlate with the cortical area generating seizures.[97] When ictal EEG is inconclusive or normal, diagnosis will rely on the history and ictal semiology. In cases where the clinical pattern does not provide additional clues with respect to lateralization to one hemisphere, detailed analysis of clinical seizure onset may be helpful in disclosing a clearly defined focal symptomatology.[98]

The localizing value of ictal scalp EEG is generally inferior in extra-temporal epilepsies.[33,99] Using lateralized rhythmic discharges, postictal slowing and EEG activity at seizure onset only 47–65% of extratemporal seizures are correctly lateralized, as opposed to 76–83% of temporal lobe seizures.[99] Surface ictal EEG recordings were retrospectively analyzed in a recent series of 46 patients with neocortical focal epilepsy, who became seizure free after surgical resection of a single lobe (lateral frontal=15, mesial frontal=8, neocortical temporal=10, parietal=7 and occipital=6). In this series, virtually all seizures that were either obscured by artifact or had no identifiable EEG change had a frontal lobe origin.[33] Localized EEG patterns were more common with seizures arising from the dorsolateral frontal region.

Intracranial EEG

Patients with suspected pharmacoresistant focal epilepsy should be referred to a comprehensive epilepsy center for a thorough presurgical evaluation, which includes prolonged video-EEG recordings, high-resolution structural and functional imaging and neuropsychological assessment. When results of presurgical studies are inconclusive or incongruent and epilepsy surgery is being considered, invasive EEG recordings with subdural grid and/or depth electrodes may be necessary to delineate the epileptic focus.

Invasive approaches to verify the location of the epileptogenic focus include: intraoperative electrocorticography, extraoperative invasive electrode recordings (using extradural, subdural and/or intracerebral electrodes), and stereo-electroencephalography.[60] It is important to emphasize that invasive electrodes record from limited parts of the cortex only, and do not provide the global picture of brain activity afforded by scalp electrodes.[100,101] Hence, intracranial electrode monitoring should only be utilized, once a reasonable hypothesis

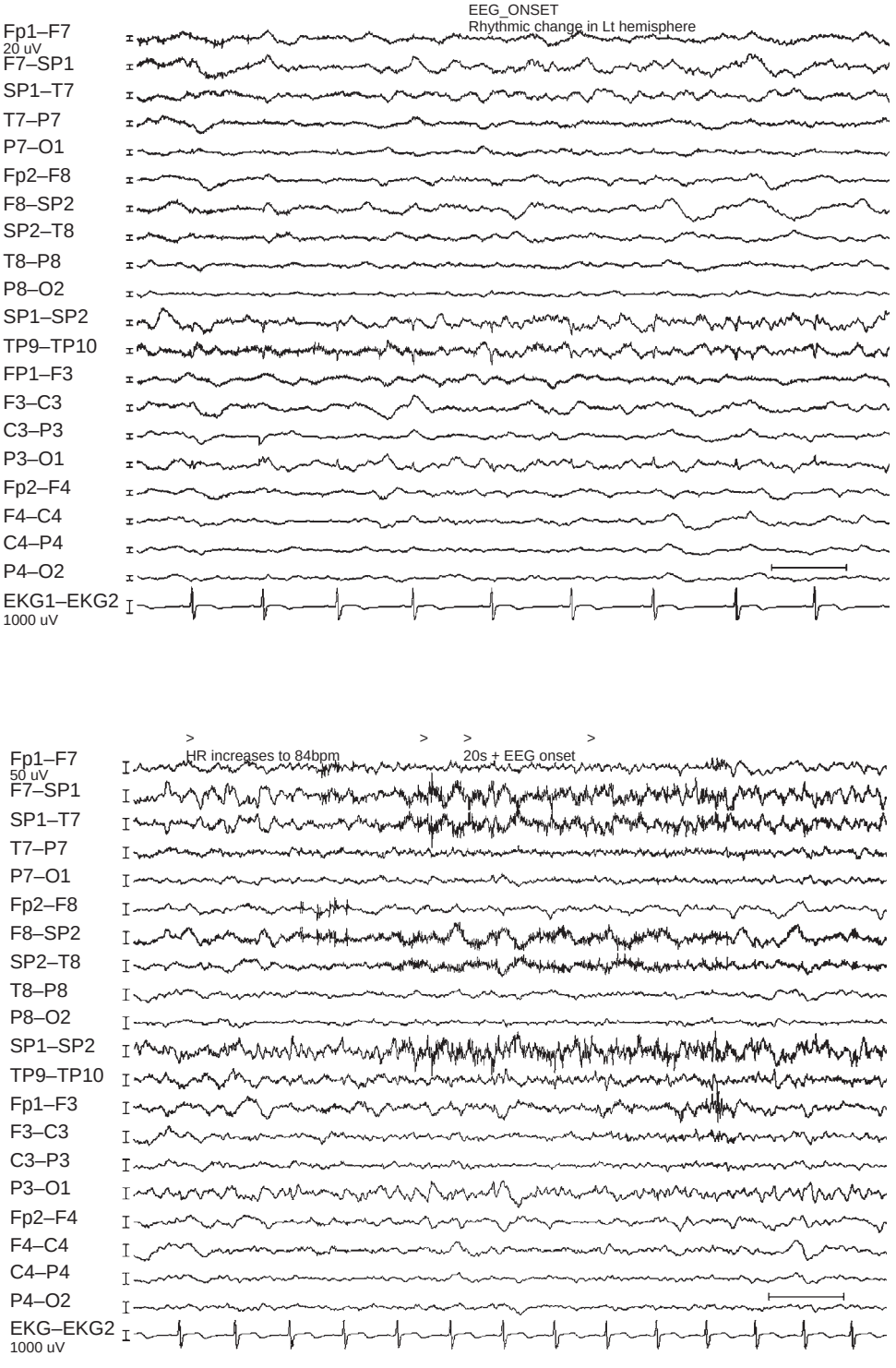

Figure 37.8 Ictal scalp EEG tracings on a routine longitudinal bipolar montage during a typical nocturnal seizure: (a) The electrographic onset (EEG onset) is punctuated by the appearance during sleep of an initial low voltage semi-rhythmic activity, which gradually evolves into more rhythmic and sharply contoured delta slowing over the left hemisphere; (b) 20 seconds later repetitive spikes within the ill-defined slowing.

about the possible location(s) of the epileptogenic zone has been made based on the results of a detailed presurgical evaluation.[102] When epileptogenicity involving the basal frontal lobe is suspected, electrode coverage of both the frontal and the temporal lobe may be necessary, to better localize the epileptogenic zone and differentiate between frontal and temporal involvement (Figures 37.9 and 37.10). Furthermore, use of bilateral frontal electrodes may be contemplated as a means of improving the investigators' ability to study lateralization and mode of propagation of ictal discharges.[103]

Stereotactically placed depth electrodes are useful in accurately targeting/evaluating deep structures, but sample only a restricted area. On the other hand, subdural electrodes provide better spatial resolution and can sample a larger expanse of cortex as they record directly from the cortical surface that underlies the pia matter. However, only about one-third of the

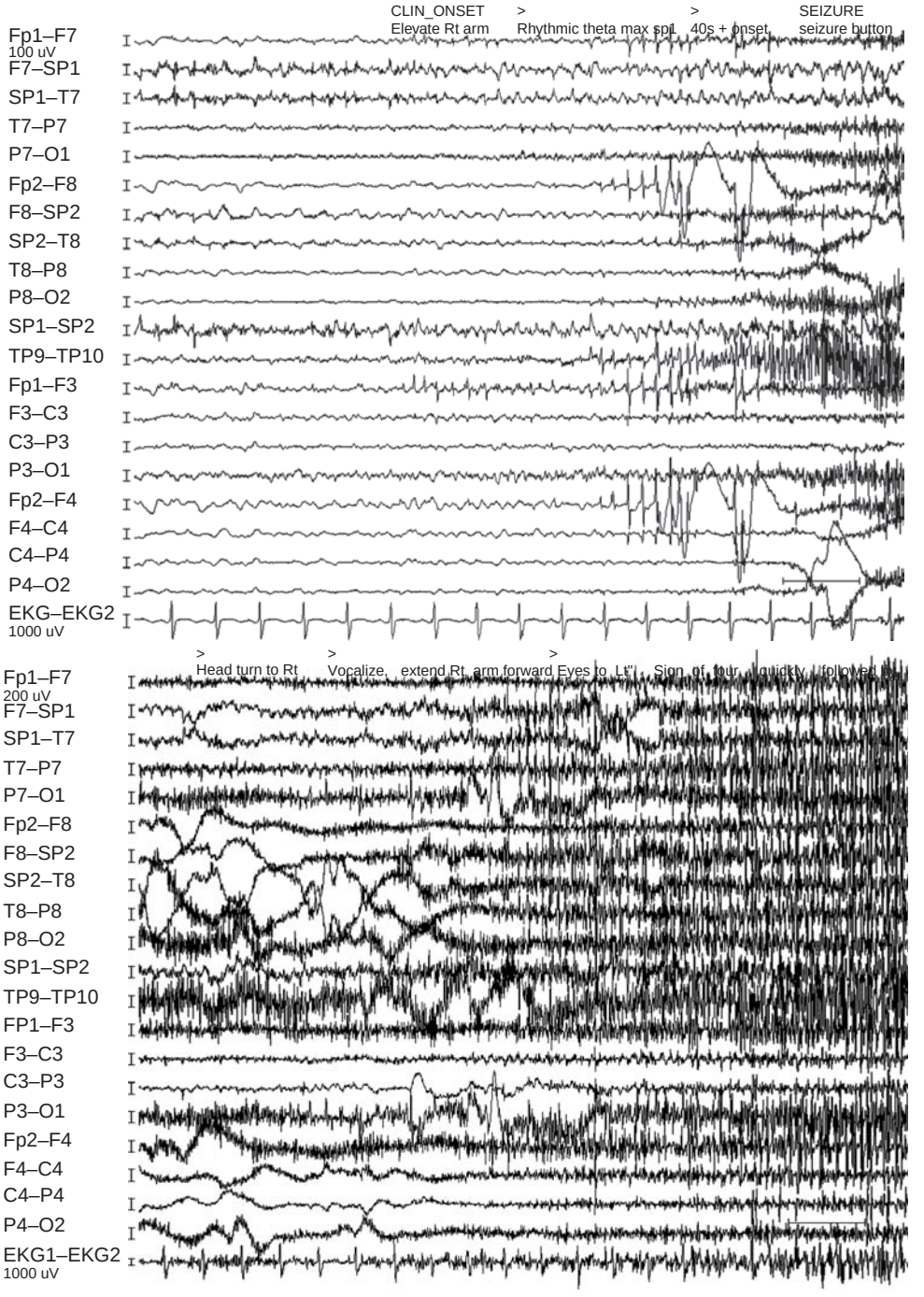

Figure 37.8, (c) low-amplitude repetitive spiking (~5–7Hz) seen over the left temporal region at the time of clinical onset, which occurs approximately 40 seconds following EEG onset. (d) muscle artifact obscuring EEG activity at the beginning of secondary generalization, which occurs approximately 50 seconds following EEG onset.

cortex is exposed, and generators located within the depth of a sulcus cannot be sampled adequately unless they extend to the cortical surface or crown.[104] Subdural grid or strip electrode arrays are inserted under general anesthesia following craniotomy and incision of the dura. Such arrays are usually slid under the edges of the exposed dura, in contact with the brain surface, without direct visualization for the purposes of recording from the orbitofrontal and adjacent inferior temporal areas.[105] The current approach at both the Cleveland Clinic Epilepsy Center and at the Texas Comprehensive Epilepsy Program is to sample the basal frontal region using a 4 × 4 subdural electrode array (Figure 37.9); made of four rows and four columns of platinum-iridium disk electrodes, each of which has a 4 mm diameter and is separated from neighboring electrodes by a center-to-center distance of 1 cm.[106]

As described above, the OFR has widespread connections with the anterior and mesial temporal regions, the insula, opercular areas and cingulate gyrus. Adequate sampling of these areas is recommended during invasive recordings in patients with suspected basal frontal epilepsies.[107,108] Good communication between the neurosurgeon and the epileptologist/neurophysiologist involved in the clinical management and interpretation of presurgical studies is essential during the planning stage. In addition, functional mapping by means of electrical cortical stimulation may be necessary to identify eloquent cortex such as language areas and motor cortex.

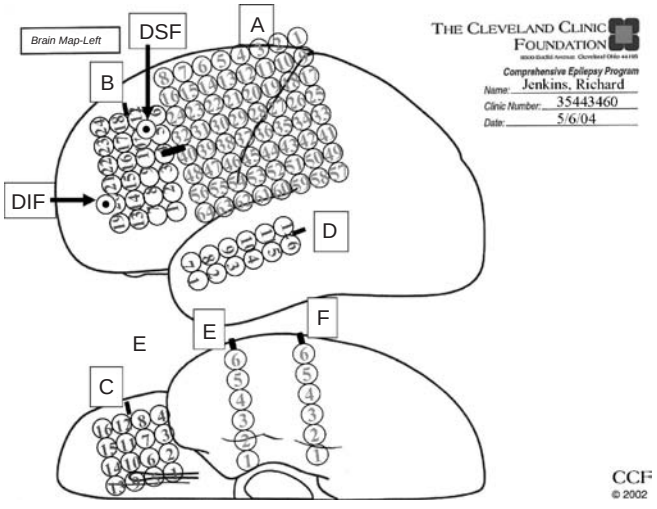

Figure 37.9 Invasive EEG evaluation using a combination of multiple subdural electrodes covering the left frontal and temporal lobes along with two intracerebral depth electrodes targeting the area of encephalomalacia. Subdural electrode arrays: A=8×8 plate, covering the left perirolandic region; B=4×6 plate, covering the left dorsolateral frontal region, anterior to the A plate; C=4×4 plate, covering the orbitofrontal area; D=2×6 plate, covering the lateral aspect of the temporal lobe; E and F=1×6 strips, covering the anterior and mid subtemporal regions. Intracerebral depth electrodes targeting the encephalomalacic area: DSF with entry point in the superior frontal gyrus, and DIF with entry point in the inferior frontal gyrus, as seen in this schematic representation.

Roper and Gilmore used a single subdural strip electrode to sample the orbitofrontal cortex in all cases of limbic epilepsy referred for invasive monitoring during a period of 1 year.[46] A total of 15 patients underwent invasive evaluations during this period (unilateral investigations with temporal, frontal, and orbitofrontal subdural electrodes were performed in eight and bilateral studies using bitemporal depth electrodes along with bilateral inferolateral temporal and orbitofrontal subdural electrodes were performed in seven patients). Three patients out of the 15 patients with intractable limbic seizures were found to have seizures originating from within the OFR (see Table 37.1). Subdural strip electrodes identified the OFR as the site of seizure origin (ictal onset zone), but were insufficient to define the actual boundaries of the epileptogenic zone. To better delineate the boundaries of the epileptogenic area the authors supplemented their investigations with the use of intraoperative electrocorticography (ECoG). These investigations and subsequent surgical excisions led the authors to conclude that unilateral OFR resections can be beneficial in a subset of patients with orbitofrontal epilepsy and can be performed without significant neuropsychologic impairment.

Stereo-electro-encephalography (stereo-EEG, sEEG) refers to the methodology of stereotactically-guided depth electrode recordings, which was originally developed by Bancaud and Talairach in France. Ictal anatomo-electro-clinical correlations based on sEEG recordings are utilized in identifying the cortical area(s) primarily involved in the generation of spontaneous ictal discharges, and provide a guide to tailored cortical resection.[109] For the school of stereo-EEG investigations *individualized* planning of electrode implantation is critical. The surgical team is assigned with the task of finding the best compromise between the 'ideal' position of the electrode and the constraints introduced by the various vascular segments, which the electrode may encounter along the length of its trajectory from the surface to the deeper brain targets.[103,110]

In their review of the electroclinical features of orbitofrontal seizures Munari and Bancaud summarized their experience in a series of 60 patients, who underwent stereo-EEG investigations with at least one orbitofrontal depth electrode. The majority of these stereotactically implanted multilead electrodes (total of 10 contacts, each 2 mm in size and 1.5 mm apart) were inserted via an orthogonal, lateral approach and aimed to explore both the medial and lateral aspects of the OFR.[36] An oblique approach was used in a few cases and a vertical approach was utilized in a single patient.

Spread between OFR and temporal lobe may occur extremely rapidly via the uncinate fasciculus as documented by stereo-EEG investigations of spontaneous seizures arising from the basal frontal lobe.[36] Other investigators have observed that 'orbitofrontal seizures' propagate more slowly compared to seizures arising from other extratemporal locations.[101] This observation comes out of a fairly small study of 10 patients with extratemporal neocortical epilepsy. A total of 25 seizures were studied with intracranial recordings using a combination of subdural strips, subdural grids, and depth electrodes implanted 'as clinically indicated'. Two patients in this group were thought to have seizures arising from the OFR and both underwent bilateral intracranial EEG investigations. A total of eight 'orbitofrontal seizures' were studied, although details on individual seizures were not provided. The authors defined the ipsilateral and contralateral propagation time as the time elapsed from electrographic seizure onset to first spread either to an adjacent ipsilateral lobe or to the contralateral hemisphere. For 'orbitofrontal seizures' spread to the ipsilateral temporal lobe occurred within a period ranging from 12.5 to 85 seconds, and to the contralateral frontal lobe within a period ranging from 9.8 to 92 seconds (compared to a more rapid ipsilateral or contralateral spread, as early as within 0 to 0.4 seconds, in some seizures arising from other frontal or parieto-occipital locations).[101] The small patient number and the potential spatial sampling limitations of invasive recordings need to be taken into account, when interpreting these results.

Structural and functional imaging

Structural imaging

High resolution anatomical MRI should be performed to search for focal intracerebral lesions, and ideally interpreted by expert radiologists, experienced in imaging of the epilepsies.[111] Identification of a structural abnormality by MRI adds substantially to the process of localizing the site of seizure onset and selecting favorable candidates for resective epilepsy surgery.[112] Structural abnormalities may be found in up to 80% of patients with refractory focal epilepsy using optimal anatomical MRI imaging.[113]

Structural MRI can provide reliable information about the pathology of the suspected epileptogenic lesion. Common MRI-identifiable pathologies include disorders of cortical development and foreign-tissue lesions (such as

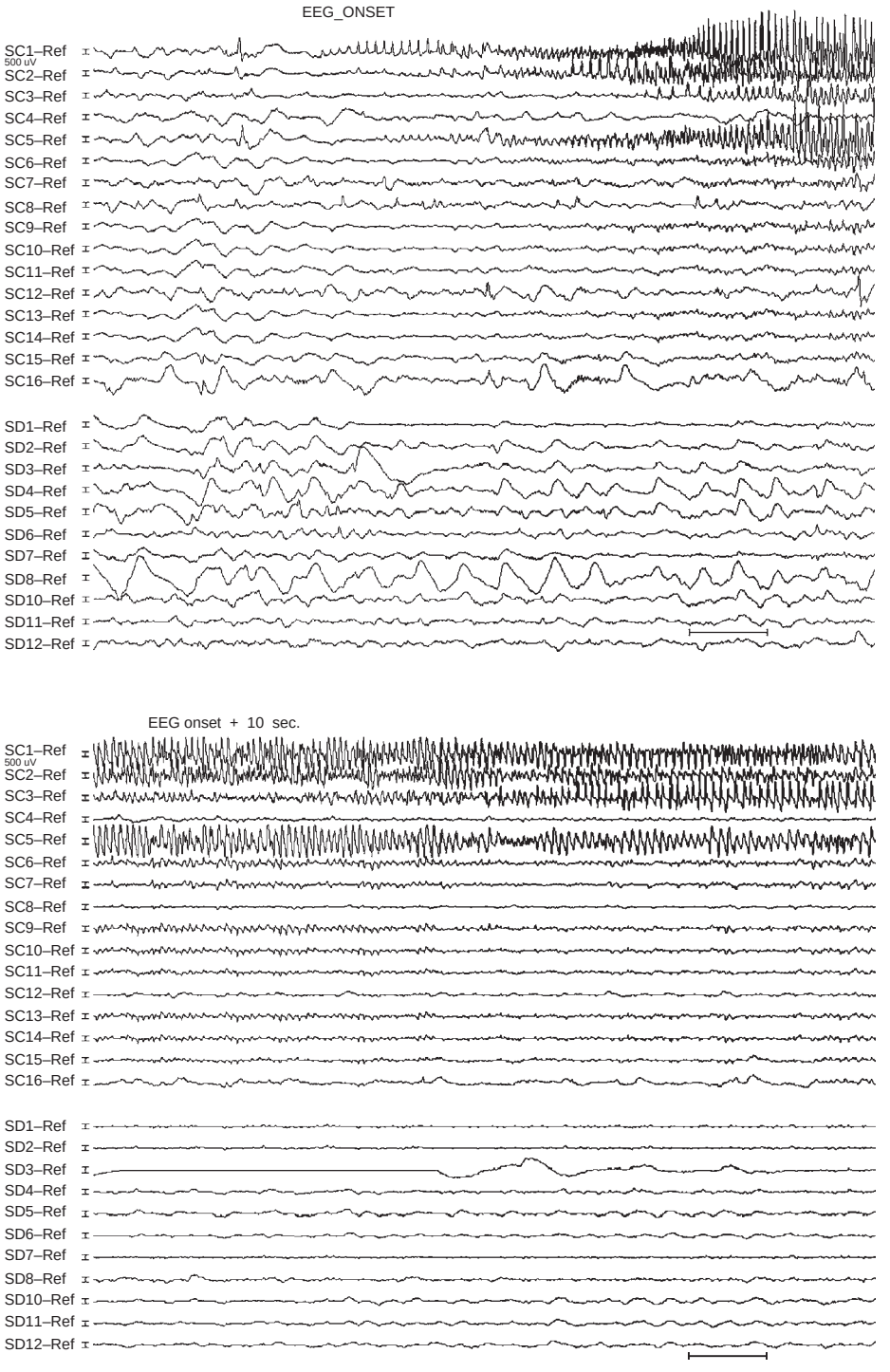

Figure 37.10 Ictal invasive EEG recordings on a referential montage displaying the electrode contacts on the C (orbitofrontal) and D (lateral temporal) plates: The electrographic onset is punctuated by the appearance of focal repetitive spiking involving the mesial, posterior corner of the orbitofrontal plate (electrodes C1 followed by electrodes C2 and C5). This activity remains confined to the orbitofrontal area without evidence of concurrent involvement of other electrodes for several (~25) seconds.

tumors and vascular malformations). Furthermore, findings on MRI help tailor the surgical procedure and assess the extent of resection postoperatively.[112] A particular challenge for T2 weighted MRI sequences investigating the human OFR using is the potential for susceptibility artifacts resulting in signal dropout or geometric distortion as a result of the close proximity of the OFR to the air-filled sinuses.[7]

When MRI is negative but EEG or other testing points to a potential area of focal epileptogenicity, dedicated MRI sequences[114] with thin cuts through the region(s) of interest should be obtained. Imaging with higher magnetic fields or three-dimensional MRI techniques may further increase the yield and allow for presurgical identification of epileptogenic lesions.[115] As illustrated in the case reported by Rugg-Gunn and colleagues[48] the use of diffusion tensor imaging and advanced postacquisition processing analyses can enhance the detection rate of subtle abnormalities in patients with so-called 'nonlesional' focal epilepsies.[116,117]

Functional imaging

Functional imaging with interictal PET and/or ictal SPECT studies may be employed as a means of identifying seizure foci in the basal frontal lobe and guiding surgical resection.

Interictal studies of brain metabolism using ^{18}FDG-PET (fluoro-deoxyglucose positron emission tomography) may disclose areas of hypometabolism in up to 60% of patients with frontal lobe epilepsy. However, almost 90% of these patients will have an underlying MRI-identifiable structural abnormality.[118] In neocortical epilepsy it is often difficult to interpret small or subtle focal areas of hypometabolism of questionable clinical relevance in the absence of a structural lesion.[119] Consequently, ^{18}FDG-PET studies may be of limited value in nonlesional frontal lobe epilepsies.

Single photon emission computed tomography (SPECT) has been used in patients with focal epilepsy to assess alterations of cerebral perfusion that may reflect the approximate location of the epileptic focus. Ictal SPECT is the only available, noninvasive modality practically suited for functional brain imaging during an actual seizure.[119] Digital subtraction techniques allow for comparison of an individual patient's interictal (baseline) and ictal SPECT images. The relatively low-resolution subtraction images afforded by SPECT can then be coregistered to the patient's anatomical MRI for more precise localization.[119] This computer-aided process was found to be diagnostically superior, when compared to routine side-by-side visual inspection of ictal and interictal SPECT scans.[120] Recent studies suggest that subtraction SPECT images are useful in guiding the location and extent of surgical resection in patients with extratemporal epilepsy.[121] There have been no specific reports related to subtraction/ictal SPECT imaging in patients with seizures arising from the basal frontal lobe. Because of their sometimes brief duration and propensity of frontal lobe seizures for rapid secondary generalization it may particularly difficult to obtain and interpret ictal SPECT studies.

In contrast to the aforementioned nuclear imaging techniques, magnetoencephalography (MEG) is a neurophysiological method with high temporal and spatial resolution. Results of MEG source localization can be co-registered to structural MRI data and produce the so-called magnetic source imaging (MSI), which is currently explored as a means of improving noninvasive localization of epileptogenic foci. The conjugation of noninvasive neurophysiology and anatomical neuroimaging using MEG/EEG along with MRI can provide important insights into the generation and spatiotemporal evolution of neocortical discharges. However, the results obtained require careful clinical analysis, integration and comparison with available preoperative testing and further validation.[122] MSI[123] along with ictal SPECT studies[124] may play an increasingly important role in directing placement of electrodes in patients with suspected frontal lobe epilepsy, being considered for resective surgery.[125] At this time, however, the role of MSI in the presurgical evaluation of patients with suspected basal frontal lobe epilepsies remains unclear.

Etiologies of basal frontal lobe epilepsy

Out of the 23 cases assembled in Table 37.1, a brain abscess was identified in two patients, and a tumor in another two (one had a pilocytic astrocytoma; the tumor type was unknown in the second case). Two more patients were found to have cortical dysplasia, while four patients were suspected to have a posttraumatic etiology. Histo-pathological examination showed nonspecific 'gliosis' in five patients and no abnormalities in three. Details on histopathology of resected tissue were not provided/not known in the remaining five cases.

The OFR is a common site for closed-head injury. Nonpenetrating head traumas may produce forces that move the basal frontal brain parenchyma across the underlying uneven surface of the orbital roof.[126] Falls or blows on the front of the head produce direct frontal lobe damage, while trauma to the occipital region produce basal frontal and fronto-polar injury by a contre-coup mechanism. Hence, posttraumatic epilepsy following closed head injury often involves the frontal and/or temporal lobes. The diffuse nature of nonpenetrating head injuries often limits localization of the epileptogenic focus, especially in patients without distinct, MRI-identifiable focal lesions.[127] It should also be noted that extensive cortical abrasions and/or lacerations in the orbitofrontal region may not be easily detected by CT and/or MRI because of the relatively limited three-dimensional volume of these lesions and the artifacts introduced by the surrounding bony irregularities of the cribriform plate.[128]

The prognosis and risk of later epilepsy depends on the severity of the trauma and concomitant cerebral complications.[129,130] Post-traumatic epilepsy refers to the recurrent, unprovoked seizures developing more than one week after penetrating or closed head injury.[131] Nearly 40% of seizures appear within the first 6 months, and 70–80% by the first 2 years after the injury.[132] The risk of posttraumatic epilepsy falls rapidly as the post-injury seizure-free interval increases, but does persist for more than 15 years after the injury, especially in cases of moderate to severe trauma.[130]

The olfactory nerves are located immediately below the OFR and are similarly susceptible to injury following closed head trauma. Post-traumatic anosmia usually results from shearing of the olfactory nerve fascicles as they traverse the cribriform plate to enter the olfactory bulb.[133] Because of this shared mechanism of injury posttraumatic anosmia may serve as an important clinical sign of concomitant orbitofrontal damage. Significant hypoperfusion in the OFR has been demonstrated with the use of HMPAO-SPECT in a series of 18 patients, who had been rendered completely anosmic as a result of a remote head injury.[134] In a similar study of 11 anosmic patients with a history of prior head injury quantitative PET studies showed evidence of hypometabolism in the OFR as well as in the medial temporal region compared with controls.[135]

In a similar series of 20 head-injury patients the finding of marked post-traumatic anosmia was taken as a strong indication of damage to the OFR.[128] Most of these patients appeared intact on psychometric neuropsychological testing and were generally preserved in areas such as intelligence, memory and language. Nevertheless, they faced major psychosocial difficulties; most of them were unemployed and showed evidence of poor empathy, poor judgment and absent-mindedness. It is not uncommon for patients with OFR injuries to perform normally on a variety of standard neuropsychological tests.[128,136] More specialized testing is required to expose deficits related to decision making and executive planning. The authors concluded that posttraumatic anosmia has a close and specific relationship with a particular locus of injury (OFR) and a

specific set of neurobehavioral symptoms that constitute the so-called 'orbitofrontal syndrome'.

Another common insult with predominant temporal and/or orbitofrontal localization that deserves mentioning in this section is herpes simplex encephalitis. Herpes simplex virus (HSV) is the cause of the most common sporadic viral encephalitis in adults and children older than 6 months.[137] Encephalitis due to HSV infection (both primary and recurrent infection) is a serious disease with an untreated mortality approaching 70% and substantial morbidity despite antiviral therapy.[138] Pathological studies of HSV encephalitis have shown predominant viral-related damage in limbic structures as well as neighboring areas including the mesial temporal lobe (hippocampal formation, amygdala, parahippocampal gyrus, and perirhinal cortex), orbitofrontal region, insula and cingulate gyrus.[139] The selective and often remarkably segregated involvement of temporal and orbitofrontal locations may in part reflect the route of entry of the virus into the host. In primary infection HSV may gain access to the brain via an olfactory route reaching the olfactory bulbs through the cribriform and subsequently spreading along the base of the frontal lobe. In reactivation of latent HSV infection the virus may spread from the trigeminal ganglion along meningeal branches of the trigeminal nerve.[137,140]

The long-term sequelae of rigorously confirmed HSV encephalitis in the era of antiviral therapy (with acyclovir) were investigated in a retrospective study from New Zealand, in which a total of 42 acyclovir-treated patients were followed for a period of up to 11 years.[141] The mortality rate was 12% at 1 month and 14% at 6 months. All but one of the surviving patients had persistent neurological impairment. The most common and most disabling complication was that of memory dysfunction (especially short-term memory). Personality and behavioral disorders occurred in almost half of the long-term survivors, albeit less severe compared to reported disability before the introduction of acyclovir. Epilepsy was present in 24% of surviving patients. Of note, two-thirds of survivors were found to have unilateral or bilateral anosmia, although may of these patients were unaware of the deficit.[141]

Other common substrates of extratemporal focal epilepsy include tumors, vascular anomalies and developmental disorders. The importance of MRI-identifiable lesions involving the deeply situated orbitofrontal region should not be underestimated. Studies of anatomically defined lesions in various locations of the brain cortex indicate that these lesions will more often than not harbor the site of the epileptogenic focus.[142] In this case complete excision of the lesion along with the surrounding 'epileptogenic tissue' provides an excellent chance for a seizure-free outcome.[38,66] Studies have shown that one of the best prognostic factors in epilepsy surgery is in fact the completeness of such lesionectomies.[143] Poor surgical results are more common in cases, where postoperative MRI provides evidence of incomplete resection of the lesional pathology.[144]

With improvements in neuroimaging, cortical dysplasias and other developmental disorders are increasingly recognized as causes of pharmacoresistant focal epilepsy. It is estimated that nearly 30% of surgical specimens from patients with neocortical epilepsy contain some type of malformation of cortical development.[145] In fact, dysplastic lesions (ranging from heterotopias to subtle cytoarchitectural abnormalities) are the most common histopathological finding in some surgical series of frontal lobe epilepsies.[38]

Among the various vascular anomalies, cavernous angiomas (cavernous malformations, CM) and arteriovenous malformations (AVM), are more likely to cause seizures. The epileptogenicity of these lesions is believed to result from pathological changes imparted on tissue surrounding the vascular malformation due to ongoing microhemorrhage and hemosiderin deposition.[146] Therefore, surgical excision should not only target the lesion but extend to the adjacent hemosiderin-stained tissue.[147]

Frequently encountered tumoral pathologies associated with pharmacoresistant epilepsy include gangliogliomas, dysembryoplastic neuroepithelial tumors (DNETs) and low-grade gliomas. In cases involving the basal frontal lobe, a gross total resection to clear margins provides the best chance for control from both the oncology and epilepsy standpoint.[148]

Gliosis as a result of previous anoxia, head trauma, or other unknown causes may be the only identifiable in pathology in surgical specimens obtained from patients with focal epilepsy. Lastly, a curious clinicopathologic entity of intracranial choristomas involving the gyrus rectus has been reported recently in two adult patients with seizures. In both cases the epileptogenic lesions were composed of heterotopic epithelial, glial and mesenchymal components. The histogenesis of these lesions is unclear, but the preferential involvement of the gyrus rectus, which is in close proximity to the frontal bone, led the authors to speculate a common origin from neural crest progenitors.[149]

Medical therapy

Seizures arising from the basal frontal region may respond to standard anticonvulsant agents (AEDs). As the seizures are focal in origin carbamazepine (or phenytoin) has been recommended as first line of treatment.[150] Alternatively monotherapy with a newer AED such as lamotrigine, oxcarbazepine, topiramate or gabapentin could be considered based on drug-drug interactions and side-effect profile.[151] If patients do not respond to monotherapy trials at maximum tolerated doses a second agent may be added. Valproic acid may have a role in preventing secondarily generalized seizures. Other adjunctive agents include levetiracetam, zonisamide and tiagabine.[152] Approximately 65% of patients with focal epilepsy respond to appropriate anticonvulsant therapy.[153,154] When medical therapy provides inadequate control of seizures or unacceptable side effects, the possibility of resective surgery should be explored. Patients with evidence of pharmacoresistant focal epilepsy should be referred to a specialized epilepsy center for presurgical evaluation and management. Patients who are not favorable surgical candidates or have failed surgical resection may be considered for implantation of a vagus nerve stimulator (VNS). Unfortunately, it has not been possible to predict which patients will benefit from chronic VNS before implanting the device.[155]

Surgical approaches to the OFR

The surgical anatomy of and surgical approaches to the orbitofrontal region have not been well characterized in the published literature. One possible reason for this may be

the fact that prior to the widespread application of invasive electrophysiology in surgical epilepsy programs the OFR has generally not been viewed as a target for resection. While portions of the basal frontal lobe are routinely retracted during neurosurgical procedures for vascular or neoplastic abnormalities, resections of the OFR itself are uncommon. A notable exception is the resection of the gyrus rectus that is carried out to facilitate exposure during pterional/subfrontal approaches to aneurysms involving the anterior communicating artery and proximal A2 segment of the anterior cerebral artery. The epilepsy surgeon accessing the OFR should, therefore, familiarize him/herself with the anatomy of the region and discuss the goals of the planned procedure with the treating epileptologist.

Invasive monitoring of the OFR

The investigation of nonlesional basal frontal lobe epilepsy is challenging, yet necessary, given the 'buried' nature of the cortex in this region. We prefer the use of subdural electrodes to depth electrodes to investigate the OFR. If a fronto-temporal craniotomy is planned, it is extended anteriorly to expose most of the frontal operculum; if burr holes and strip electrodes are planned, one burr hole is placed over the pterion ('the keyhole'). In the case of a craniotomy, a 4×4 electrode array, with its lead situated laterally, is placed over the orbital roof, to cover a significant portion of the OFR. If burr holes are used, a 4-contact strip electrode is placed over the posterior portion of the OFR.

Resections of the OFR

The surgical approach to the OFR is dictated by the surgeon's familiarity with a particular approach, the pathologic process being treated (lesion resection versus regional OFR excision for intractable epilepsy), the location of the lesion, and whether or not the resection involves the (presumed or apparent) dominant hemisphere. Another important consideration during surgical planning should be the connections of this region with the anterior and medial temporal lobe and the cingulate gyrus. Incomplete resection of epileptogenic cortex left attached to these structures, may compromise surgical outcome. Given that these connections extend from the posterior edge of the OFR, and that the posterior boundary is intimately linked to multiple structures (anterior perforated substance, optic nerve and anterior cerebral artery) – damage of which can result in significant deficits – an intimate knowledge of the anatomy of the OFR is crucial to successful surgical outcomes.

Prior descriptions of surgery in the OFR have variously delineated the posterior extent of orbito-frontal excisions as being about 1–2 cm in front of Broca's area in the language-dominant hemisphere or extending posteriorly to the ipsilateral internal carotid artery[156] and the intersection of the optic and olfactory nerves.[107] We find a subpial approach combined with intraoperative frameless stereotactic navigation to be safer, and prefer to use the proximal anterior and middle cerebral arteries (viewed through intact pia) to delimit the resection margins (Figure 37.2).

The OFR may be approached using three possible trajectories, depending on the nature and location of the lesion (Figure 37.3):

- Lateral frontal;
- Anterior frontal; and
- Intermediate or anterolateral approach, which may be combined with orbito-zygomatic osteotomy.

The lateral frontal is by far the commonest approach for an OFR resection in the context of epilepsy surgery. This is because many such resections occur in the context of a large fronto-temporo-parietal craniotomy performed for placement of subdural electrodes for invasive electrophysiology. The resection is usually carried out at the time of electrode removal, and the orbital cortex is therefore approached from its lateral aspect. An en bloc resection of all, except the most posterior aspect, of the lateral, posterior and medial orbital gyri, and a portion of the anterior inferior frontal gyrus is carried out. This is followed by subpial aspiration of gyrus rectus. The ipsilateral anterior cerebral artery (ACA) is identified and traced posteriorly to the rostrum of the corpus callosum. Finally, the posterior limits of the orbital gyri and the subcallosal (rostral) cingulate gyrus are aspirated using a subpial technique (Figures 37.4 and 37.5). Identification of the ACA helps determine the posterior extent of the medial resection. The M1 segment of the middle cerebral artery (MCA) may be used to define the posterior edge of the resection. Use of a subpial technique during the medial and posterior aspect of the resection is crucial in minimizing risks to the anterior perforated substance, olfactory tract, and optic nerves.

The anterior approach is principally used for excisions of overt OFR lesions and resections in the context of depth electrode recordings. Preoperative placement of a lumbar drain minimizes the need for retraction. A bicoronal scalp incision is made, following which a frontal craniotomy bone flap is elevated – from just above the frontal sinus, just lateral to the midline (and anterior sagittal sinus) and extending laterally to the anterior attachment of the temporalis muscle. A frameless stereotactic system may be used to demarcate the edges of the craniotomy and facilitate approach to the lesion. The dura is opened, with its base on the sagittal sinus, following which the lesion is resected. Subpial techniques should be used when there is a need to remove abnormal (gliotic, hemosiderin stained etc.) cortex surrounding the lesion. A principal advantage of the anterior and antero-lateral approaches is that the inferior frontal gyrus is more easily spared (Figure 37.7).

The antero-lateral approach, combined with an orbito-zygomatic osteotomy may be useful in cases where a large lesion is situated in the postero-medial OFR, and the intention is to minimize dissection and retraction of uninvolved cortex. A frontal craniotomy incision extending to the contralateral midpupillary line is used, following which a frontal craniotomy and orbito-zygomatic osteotomy are carried out. The dura is then opened with its base on the orbital contents, and resection of the lesion is performed. A lumbar drain placed prior to the craniotomy further helps in minimizing retraction.

Occasionally invasive recordings may suggest independent ictal onsets originating from both the medial temporal and orbitofrontal regions. These cases can be managed with concurrent resections, possibly guided by the judicious use of intra-operative electro-corticography (ECoG) to measure the impact on electric activity in one region after the other is resected. Routine resection of the OFR concurrent with a temporal lobectomy is not recommended – although some authors have adopted a combined approach guided solely by the apparent location of interictal abnormalities.[157]

Possible complications related to surgery in the OFR include: infection of the surgical site, osteomyelitis and/or CSF fistulae from opening the frontal sinus mucosa during craniotomy; hemorrhage from injuring the anterior sagittal sinus; venous infarcts when sacrificing veins leading into the sinus; visual deficits following injury to the optic nerve; ischemic events following injury to perforating vessels in the anterior perforating substance; CSF rhinorrhea through the cribriform plate and anosmia if the olfactory nerve and tracts are destroyed; and inadvertent injury to the contralateral frontal lobe if the medial frontal pial layer is not recognized and respected. In addition, there may be impacts upon personality and social behavior following OFR resections – such deficits are not adequately assessed with the current, standard neuropsychological measures employed in patients undergoing epilepsy surgery.

Outcome

There is no systematic study of outcomes related to resections for the treatment of basal frontal lobe epilepsy, and studies examining neuropsychological function in patients with epilepsy arising from this region are lacking. In general, just as for other extratemporal epilepsies, outcomes following resective epilepsy surgery anywhere in the frontal lobe are considered to be 'not as good' as those after temporal lobectomy.[121,144]

The presence of a lesion on neuroimaging increases the chances for seizure-freedom or significant improvement.[35] Cumulative results of surgical treatment for various frontal lobe epilepsies in the pre-MRI era have been characterized as 'unsatisfactory' or 'mediocre'.[103] As a rule, results following removal of discrete frontal lesions are superior to those with more diffuse lesions or without demonstrable lesions.[66] In a study of 68 consecutive patients, who underwent epilepsy surgery involving the frontal lobe good outcome at last follow-up was reported in 72% of patients with evidence of a lesion on neuroimaging, as compared to only 41% of the 'nonlesional' cases.[158]

We recently performed a retrospective review of all frontal lobe resections performed by a single neurosurgeon for the treatment of pharmacoresistant focal epilepsy at the Cleveland Clinic Foundation during a 6-year period (from 1998 to 2004). All cases had undergone a comprehensive presurgical evaluation including high-resolution preoperative MR imaging and presentation at a multidisciplinary patient management conference. Out of a total of 130 patients, who had frontal resections during the study period, basal frontal lobe epilepsy was suspected in eight patients.[159] In these patients, MRI demonstrated a lesion restricted to the OFR, and/or invasive recordings provided clear evidence for ictal onset within the OFR. Patients with more extensive MRI lesions were excluded. Only two cases were nonlesional (i.e., there was no identifiable structural abnormality on high-resolution anatomical MRI); in three of the six 'lesional' cases the MRI detected blurring of the gray-white junction in the medial OFR. Histopathology revealed malformations of cortical development in the majority of patients (5 of 8); cavernomas were found in two, and gliosis in one patient. Resections were restricted to the OFR only in four of the eight patients; the other four underwent larger resections that extended into the lateral frontal region. In this study median follow-up was only 14 months. Seven patients were seizure free, while one had rare seizures postoperatively (Wieser class 3).[54]

Illustrative case presentation

The patient is a 33-year-old, right-handed young man with frequent pharmaco-resistant seizures dating back to the age of 26 years. The patient has a history of a motor vehicle accident at the age of 21 years, when he drove into a telephone pole. He lost consciousness upon impact, and had peritraumatic amnesia and a left-sided skull fracture. He did not require neurosurgical intervention and did not experience seizures at the time of the accident.

Seizures started approximately 5 years later. Initial seizures were primarily nocturnal occurring out of sleep. Family members described 'whole body convulsions' followed by stertorous respirations and loss of urine control lasting for less than 1–2 minutes. Postictally the patient reported tiredness, muscle soreness and occasional tongue biting. These seizures have been disabling and have persisted despite several trials of antiepileptic agents with an average frequency of at least one to four per month.

A second 'mild seizure type' was reported. During wakefulness he would have a warning described as 'feeling unwell' or having 'a funny feeling in the head' lasting for a few seconds, and followed by loss of awareness. Family members described staring and unresponsiveness for 2–3 minutes. During this period the patient had been observed to have complex movements involving the legs and hands. Patient was not sure as to the frequency of this second seizure type. He reported having auras at least once a month.

He had no history of prolonged, unremitting seizures or physical injury as a result of seizures. He has been unable to work for the last 7 years, because of seizures.

Examination and investigations

Physical and neurological examinations were normal. Routine outpatient EEG was normal. Magnetic resonance imaging revealed an area of focal encephalomalacia in the ventral and basal aspects of the left anterior frontal lobe abutting the roof of the left orbit. The patient was admitted for video-EEG monitoring. Background EEG was normal. Interictal epileptiform activity was recorded predominantly arising from the left temporal region (maximum at the left sphenoidal electrode (Figure 37.6). Less frequent generalized epileptiform discharges with a shifting bifrontal maximum were also present (Figure 37.7). In addition, rare right temporal sharp waves were described.

Three typical nocturnal seizures were recorded during sleep. They were characterized by an early change in facial expression and unresponsiveness, followed by tonic stiffening and elevation of the right arm (sign of four, right arm extended with the left arm flexed at the elbow), and right head turning preceding the onset of the secondarily generalized tonic-clonic seizure.

Interictal FDG-PET showed mild decrease of FDG uptake in the left orbitofrontal region, corresponding to the area of MRI abnormality. Wada testing (with intracarotid administration of methohexital) demonstrated left hemispheric dominance for language and bilateral memory representation. Baseline neuropsychological evaluation suggested bilateral frontotemporal dysfunction. The patient appeared to have greater difficulties with verbal than visuospatial intellectual measures. He exhibited evidence of compromised executive function in the course

of problem solving, impaired verbal memory performance and some deficiencies in vocabulary, naming and reading.

The case and results of presurgical studies were discussed in a weekly, interdisciplinary patient management conference attended by experts in clinical epileptology, electroencephalography, structural and functional neuroimaging and neuropsychology. The impression was that the patient's epilepsy may be arising from the left orbitofrontal region 'perhaps deep in the area of encephalomalacia'. A temporal onset could not be excluded. An invasive evaluation with a combination of chronically implanted subdural and depth electrodes was recommended to further delineate the seizure onset zone, and its relationship to the encephalomalacic lesion (Figure 37.9). In addition, this approach would allow functional mapping of adjacent eloquent cortex (anterior language area) by means of extraoperative electrical cortical stimulation.

Six typical nocturnal seizures were recorded in the span of 8 days of invasive recordings. All seizures were characterized by focal EEG changes restricted to the mesial, posterior edge of the orbitofrontal plate (Figure 37.10). Based on three-dimensional MRI reconstructions of the electrode location and underlying epileptogenic lesion the area of seizure onset was found to correspond to the posterior edge of the encephalomalacia.

Treatment and outcome

A resection of the left orbitofrontal and anterior ventral frontal regions was performed. Postoperatively the patient experienced a single breakthrough seizure at 3 months and a cluster of three seizures within one day (in the context of a flu-like illness) at approximately 6 months. At his last follow-up the patient has been seizure-free since for more than a year on a stable combination of lamotrigine and levetiracetam.

Summary

The basal frontal lobe is perhaps one of the least explored and least understood regions of the human cerebral cortex. This highly multimodal area is characterized by its functional heterogeneity and widespread connections within the frontal lobes and limbic system. The anterior part of the OFR has the appearance of granular isocortex and is connected to the heteromodal prefrontal cortex. The posterior OFR has a more primitive, dysgranular architectonic appearance and is intimately connected with the limbic system.

Localization of epileptogenicity arising from the basal frontal lobe is particularly difficult because of the absent or potentially misleading information derived from scalp EEG recordings, and the lack of distinct ictal manifestations. The advent of sophisticated neuroimaging techniques (especially high-resolution anatomical MRI) and the increasing capability to perform invasive recordings from the OFR has made it possible to delineate epileptogenic foci within this region. A limited number of patients with identifiable lesions in the orbitofrontal area and very few patients without evidence of MRI abnormalities have been reported to be seizure free after localized surgical resections. The intimate spatial and functional relationship of the OFR with limbic structures and the reported successes following targeted resections underscore the utility of evaluating this region closely in cases of focal epilepsy presumed to originate in the frontal or temporal lobes.

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38 Parieto-occipital lobe epilepsy

V Salanova

Introduction

Occipital lobe epilepsy was first recognized by Gowers in 1879[1] when he described a 30-year-old man with 'epileptoid attacks with visual aura'. The patient described a very brilliant image before him 'like a gold serpent'. This patient at other times had episodes of transient blindness. The patient was found to have an occipito-parietal tumor at autopsy. Gowers interpreted the aura as follows: 'at first there was apparently an over action of the center – a bright light; afterwards paroxysmal defective action, due to temporary exhaustion or inhibition, shown in the narrowing of the field of vision'.

When Gowers examined his records,[2] he found that 84 of his 1000 patients with epilepsy exhibited a 'special sensory aura' which was referred as 'the organ or sense of sight', he subdivided these 'ocular and visual warnings' into five categories: a sensation in the eyeball itself, diplopia, an apparent increase or diminution in the size of the objects, loss of sight, and distinct visual sensations such as elementary visual hallucinations.

The symptomatology of occipital epilepsy was further defined in 1927 by Gordon Holmes[3] when he studied patients who had sustained gunshot wounds to the occipital region who exhibited occipital auras, characterized by elementary visual hallucinations or transient blindness, and in 1941 by Penfield and Erickson,[4] who described the clinical manifestations of several patients with 'visual seizures', including blindness, and coloured moving lights, and were able to elicit the auras by cortical stimulation.

In 1951 Penfield and Kristiansen[5] reported that 11 of 222 patients with focal epilepsy treated surgically had 'visual sensations' as the first manifestation of their seizures, characterized as sensations of lights, darkness of colour, and five patients reported that the visual image was 'revolving' or 'rotating'.

Penfield and Jasper,[6] described several patients with 'visual seizures', including the patient C.Fr. with a traumatic scar of the pole of the right occipital lobe who had an incomplete left homonymous hemianopia. The patient felt that the seizures were induced by a bright light, to the point that he refused to have the examiner shine a light in his eye. Wilder Penfield stated that 'This is an example of sensory precipitation of a visual seizure'. The patient described lights followed by blurring of the vision progressing to complete blindness and then a sensation of stiffness in the left hand, and right hand, followed by a generalized seizure. Penfield stated 'The somatic sensation in both hands suggests that the spread of discharge was from the calcarine cortex to the supplementary area within the sagittal fissure. At the onset of the generalized seizure the head and body turned to the left'.

Penfield and Jasper[7] also reported two patients whose spontaneous seizures began with elementary visual hallucinations, followed by complex visual images. In both patients the habitual complex visual hallucinations were elicited at surgery by stimulation of the right posterior temporal region, suggesting that during the spontaneous attacks the hallucinations probable represented spread of the ictal discharge to the temporal lobe.

Ludwig and Ajmone Marsan[7] reported the clinical manifestations in 55 patients with electrographic evidence of occipital lobe involvement, and noted that as many as two-thirds had lateralized visual manifestations, Blume *et al.*[8] found that in 13 of 19 (68%) of their patients the most common initial ictal symptoms were visual phenomena, and Williamson *et al.*[9] reported that in 22 of 25 patients (88%) with occipital lobe epilepsy, early signs or symptoms 'would had provided clues for the correct diagnosis'. In the series from the Montreal Neurological Institute[10] in more than two-thirds of the patients the clinical manifestations indicated the occipital onset of the seizures.

Functional anatomy

Von Economo[11] divided the occipital cortex into striate, peristriate, and parastriate regions. The striate cortex contained within the walls of the calcarine fissure, constitutes Brodmann's area 17, and it is recognized by the thick strip of granular cells in layer IV that is split by the geniculocalcarine band of Gennari. All layers of this cortex reveal marked granularization.

All six layers of cortex are delineated in the peristriate and parastriate cortices (areas 18 and 19). Numerous pyramidal cells are found in layers II, III, and V and giant pyramidal cells populate area 18, immediately bordering on the striate cortex.

Jones and Powell[12] studied the distribution of projection pathways emanating from areas 17, 18, and 19 by selectively ablating these areas in adult rhesus monkeys. The striate cortex projected to areas 18 and 19, whereas areas 18 and 19 projected fibers to area 8 in the frontal lobe and the adjacent temporal and parietal association cortices. The pathways include the superior longitudinal, the inferior longitudinal and the fronto-occipital fasciculus. Areas 18 and 19 also project deep fibers to the midbrain tegmentum.

Further elucidation of the occipital lobe functional anatomy arose from electrical cortical stimulation studies in

humans undergoing epilepsy surgery. Wilder Penfield and Theodore Rasmussen in the Cerebral Cortex of Man,[13] found that 22 patients reported gross visual sensations as the result of stimulation. These visual responses were elementary sensations of light, darkness, and color. They also reported that 'complicated visual hallucinations do occasionally result from epileptic or electrical stimulation, but these are phenomena of another order and are associated with activation of the temporal lobes'. They observed that 'the visual responses appear in the secondary visual areas of Brodman (18 and 19) as well as in the primary calcarine area 17. They noted that 'in general, it would appear that the calcarine image was more often colored while images produced from the secondary visual zone more often consisted of colorless light'.

Symptomatology and pathophysiology of occipital lobe seizures

An analysis of 42 patients with refractory occipital lobe epilepsy treated surgically at the Montreal Neurological Institute (MNI) between 1930 and 1991[10] showed that the clinical features of occipital lobe epilepsy can be divided into those representing seizure phenomena of occipital lobe origin, which include elementary visual hallucinations, ictal blindness, blinking and ocular movements and those resulting from ictal spread to adjacent cortical areas.

Fifty-nine percent had visual field deficits. Seventy-three percent of the patients had visual auras. In those patients where the data were available, the elementary visual hallucinations were contralateral to the epileptogenic area. One patient with left occipital microgyria and a right homonymous hemianopsia described 'dancing lights, whirling lights to the right' followed by right head and eye deviation, and right head and eye clonic activity. Another patient with left occipital microgyria and a right homonymous hemianopsia described a slowly rotating disk of light in the right visual field. Others described flashing colors, and change in perception of shapes and colors. Another patient with left occipital cortical dysplasia and right upper quadrantanopsia described 'circles, triangles squares, all colors', and a visual sensation of movement, followed by conscious right head and eye deviation and right arm posturing. A patient with left occipital gliosis described 'colored squares of light' followed by blindness, right head and eye deviation and postictal dysphasia.

Four patients had elementary visual hallucinations followed by complex visual hallucinations: a 12-year-old with a history of birth trauma and right occipital gliosis had elementary visual aura characterized by colored triangles followed by a complex hallucination in which he saw a robber, or a man with a gun; sinister characters from comic books, followed by conscious adversion to the left, nystagmoid eye movements, left arm clonic activity and postictal left hemiparesis. Another patient with a left hemianopia described 'a square with a circle in it', faces, pictures like Rembrandt's self portrait. The reason for these complex visual hallucinations is most likely ictal spread to the posterior temporal region, as Penfield and Perot[14] found that complex visual hallucinations could be elicited by posterior temporal stimulation near the occipital cortex, and Gloor *et al.*[15] reported that experiential phenomena (visual and auditory) 'did not occur unless a seizure discharge or electrical stimulation involved limbic structures'.

Ictal blindness has been a consistent symptom of patients with occipital lobe epilepsy. Twenty-eight percent of patients from the MNI had ictal blindness as an initial manifestations of their seizures which lasted as long as a few minutes. A 24-year-old patient with left occipital gliosis described a shadow moving to the right, 'ombrage' followed by blindness, and conscious adversion to the right.

Russel and Whitty[16] reported blurring or extinction of vision in 40% of their patients with traumatic occipital lobe epilepsy, and Williamson *et al.*[9] reported that 10 of 25 (40%) of their patients with occipital lobe epilepsy exhibited ictal amaurosis. Barry *et al.*[17] reported five patients with ictal blindness and electrographic (EEG) monitoring revealed that complete blindness occurred with ictal spread to the contralateral occipital lobe, demonstrating that ictal blindness is caused by seizure induced bilateral occipital lobe dysfunction.

Other authors have also reported lateralized visual auras in patients with occipital lobe epilepsy, Sveinbjornsdottir and Duncan,[18] Aarli and Engelsen,[19] Geller *et al.*,[20] Boesebeck *et al.*,[21] Taylor *et al.*,[22] and Blume *et al.*[23]

Other occipital manifestations in the MNI series included eye pulling or moving sensations, blinking, nystagmoid eye movement and contralateral eye movements. Nineteen percent of the MNI patients exhibited blinking and 7% had contralateral nystagmoid eye movements. In one patient, studied with depth electrodes, the nystagmoid eye movements were contralateral to the seizure discharge.

Munari *et al.*[24] described 16 patients with stereo EEG who had seizures with ocular deviation within the first 10 seconds of the seizure onset. In 14 patients the ocular deviation was tonic and in all was contralateral to the ictal discharge, which generally originated in the medial occipital structures. Cortical stimulation studies in animals and humans demonstrate that eye movements can be initiated by occipital mechanisms.[25,26]

Contralateral head and eye deviation was present in half of the MNI patients. Two of these patients were studied with depth electrodes and had contralateral head and eye deviation while the seizure remained localized to the occipital lobe. Ludwig and Ajmone-Marsan[7] reported contraversive movements of head and eyes in 29% of their 55 patients.

Automatisms similar to those from patients with temporal lobe epilepsy occurred in 50%, and focal motor activity in 38% of the MNI patients, and one-third of the patients had more than one seizure type. Ajmone-Marsan and Ralston[27] suggested that seizures originating in the occipital lobe could have multiple spread patterns. Subsequently this was confirmed by intracranial recordings in humans[28,29] and animal experimental data.[30] The inferior longitudinal, superior longitudinal and the fronto-occipital fasciculus are involved in this spread.

Etiologies of occipital lobe epilepsy

Rasmussen,[31] identified the etiology of refractory occipital lobe epilepsy, established by history and pathological findings in 23 patients; one-third had a history of head trauma or anoxia; 9% had gliomas and 13% postinflamatory brain scarring. In 26% of patients no cause could be determined. The remaining patients had other lesions including pial angiomatosis. In the updated series of 42 patients from the

MNI, 21% had a history of significant head trauma with loss of consciousness, 24% had a history suuggestive of birth trauma or hypoxia, 7% had a history suggestive of encephalitis, and 10% had slow growing glial tumors. Others had focal cortical dysplasia.

Ludwig and Ajmone-Marsan[7] reported that 24% of their patients had a history of birth injury, hypoxia, and severe head trauma; 13% had a history of encephalitis or meningitis; 14% vascular lesions, and 7% expanding lesions. In 25% the etiology was unknown. A recent series from the Yale Epilepsy Center, of 35 patients with intractable occipital lobe epilepsy treated between 1986 and 1995, reported that most of their patients had developmental abnormalities or tumors,[32] and Lee *et al.*[33] reported that 20 of 26 of their patients with occipital lobe epilepsy had a pathological diagnosis of cortical dysplasia.

EEG findings in occipital epilepsy

In the MNI series, the most common location of interictal epileptiform discharges was the posterior temporal-occipital region (46%). Interictal epileptiform discharges were localized to the occipital lobe in only 18% of patients. One-third of the patients had synchronous lower amplitude epileptiform discharges from the contralateral homologous head regions, suggesting secondary bilateral synchrony. Bitemporal interictal epileptiform discharges were recorded, in 24% of the patients. This is probably a manifestation of secondary bilateral synchrony and/or secondary epileptogenesis.[34,35]

The most common type of surface ictal onset was regional involving the posterior temporal occipital region. Ictal onsets on surface recordings restricted to the occipital lobe were seen in only four out of 24 patients (17%). Six patients had intracranial recordings with depth electrodes. Ictal onsets were predominantly regional rather than focal and involved widespread areas of the mesial and lateral occipital cortex, often involving the supra and infracalcarine structures and, in some seizures, the posterior temporal region. The most common pattern of spread involved the ipsilateral temporol-mesial structures.

Aykut-Bingol *et al.*[32] found that of 35 patients who had occipital lobe epilepsy surgery between 1986 and 1995, interictal scalp EEG was localized to the occipital, temporal, and occipitotemporal regions in 17%, 27%, and 24% of patients, respectively. Ictal events were recorded in 30 patients. Ictal onset was localized to the occipital lobe in 30%, and temporal and occipitotemporal in 27%; in the rest it was more diffuse. Nineteen patients underwent intracranial EEG studies. Foldvary *et al.*[36] analyzed the localizing value of ictal EEG in focal epilepsy, and found that 'false localization/ lateralization occurred in 28% of occipital seizures.'

Parietal lobe epilepsy

Historical background, and functional anatomy

Wilder Penfield, Theodore Rasmussen, and their colleagues divided their patients with refractory epilepsy into those whose epileptogenic areas involved the frontal, central (sensorimotor area), parietal and occipital regions.[4,6,13]

Patients with epileptogenic lesions involving the pre- and post-central gyrus were grouped together, because lesions in this cortex produced sensorimotor deficits, and as Penfield and Erickson[4] stated 'the precentral and postcentral gyri in man constitute a functional unit. Close interrelationship of motor and sensory cortical areas is established by the numerous connecting U-shaped fibers which pass under the bottom of the central fissure'.

Penfield and Rasmussen,[13] noted that 'by Parietal area is meant that portion of the classical parietal lobe which lies behind the post central gyrus', 'if the lower parietal area which constitutes the parietal speech area on the dominant side be excluded, the superior parietal cortex could be removed with a comparatively small functional penalty'. Penfield and Erickson[4] had described that ablation of the parietal association cortex left little obvious functional deficits though 'disturbances of speech and disturbances in perception of form in the opposite homonymous visual field has been noted'.

Rasmussen[37] continued to use the functional division of the brain developed by Foerster and Penfield,[38] since their definition of the parietal lobe differs from the generally employed in reviewing the MNI series of parietal lobe epilepsy, we refer to 'parietal association area' to define the region behind the postcentral gyrus and in front of the occipital lobe.

Foerster and Penfield,[38] described patients with epileptogenic lesions and 'parietal field attacks', characterized by painful sensations, vertigo, paresthesias, head and eye deviation, a sense of movement of one extremity, visual illusions, and complex movements of arms and legs, and reproduced these symptoms by faradic stimulation.

Cushing[39] expanded on these observations when he described 12 patients with parietal meningiomas; nine of them had a contralateral sensory aura, described as numbness, tingling, painful sensation or a feeling of warmth or heat. Since then few series of patients with parietal lobe epilepsy have been reported.

Clinical manifestations and pathophysiology

Patients with parietal lobe epilepsy with epileptogenic areas in the parietal cortex behind the postcentral gyrus, comprised 6% of patients operated at the Montreal Neurological Institute (MNI) between 1929 and 1980.[40,41]

Eighty-two patients had nontumoral parietal lobe epilepsy (Figure 38.1), with a mean age of seizure onset of 14.1 years and mean duration of epilepsy 8.1 years. Twelve patients had contralateral sensory deficits which were found during detailed examination and consisted of contralateral impaired two pointpoint discrimination, isolated diminished stereognosis, without two point discrimination, was reported in only two patients. Sixteen percent of patients had smallness of the contralateral extremities, 8% contralateral visual field deficits, most commonly inferior quadrantic defects. Impairment of spatial orientation and right–left disorientation were described in three patients, disturbance in the field of written language, and mild aphasia in two others.

Ninety-four percent of patients exhibited auras. The most common were somatosensory, described by 52 patients as tingling or numbness; they were contralateral to the epileptogenic zone in 51 patients and bilateral in one; 13 of these patients described a painful, and five a thermal sensation. The second most common auras were disturbances of body

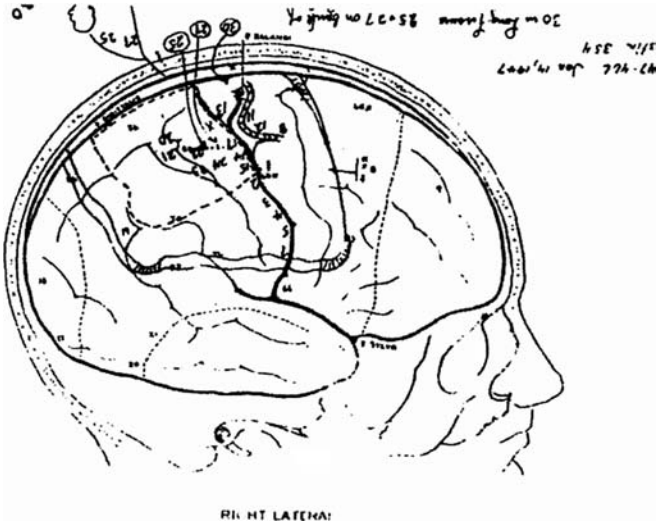

Figure 38.1 Original operative map of patient A. H. operated on by Dr Penfield in 1946. 25 year old with history of head trauma. The seizures were described as 'does not know where he is, cannot concentrate, cannot see well', followed by turning to the left.

image exhibited by nine patients; three patients mentioned a sensation of movement in one extremity, and another a sensation that the leg was absent. Twisting or turning sensations of the extremities were also described.

Visual illusions were reported by nine patients as 'figures look larger' or 'things on the wall turning'. A few patients exhibited complex visual or auditory hallucinations, suggesting ictal spread to temporo-limbic areas.[15] Eighty patients underwent intraoperative cortical stimulation studies and the habitual auras were reproduced in 55% of patients. These included auras with a disturbance of body image or visual illusions, indicating an epileptogenic zone in the parietal association cortex. However, somatosensory auras also occurred in patients with lesions limited to the parietal association cortex, suggesting ictal spread to the somatosensory cortex. Thus, the symptomatogenic zones were distant from the epileptogenic zones in the parietal association cortex, Luders and Awad.[43]

Other seizure characteristics

The other clinical manifestations were due to ictal spread. The ictal semiology indicated several dominant spread patterns, including spread to the sensorimotor cortex, the premotor eyefield, supplementary motor area, and the temporolimbic region. Twenty-eight percent had tonic posturing of the extremities, 57% had focal motor activity, 17% had oral-gestural automatisms, and 4% had complex automatisms. Forty-one percent had head deviation, 22% had Todd's paralysis and 7% had postictal dysphasia.

Many patients had more than one seizure type reflecting the different spread patterns. Sixty-one percent of patients with tonic posturing had epileptogenic zones which included the superior parietal lobule, and 79% of those with automatisms had epileptogenic zones extending into the inferior parietal lobule. This suggest preferential spread with ictal activity from the superior parietal lobule more commonly spreading to the supplementary motor area, and the one from the inferior parietal lobe to the temporo-limbic areas. This pattern of spread is supported by Reesnick *et al.*,[44] who used subdural electrodes in the evaluation of patients with refractory epilepsy, and is a reflection of the connection of the parietal lobe with the supplementary motor area, and with the temporo-limbic region,.[45,46]

Other authors and recent reviews have also reported asymmetrical tonic seizures and automatisms in patients with parietal lobe epilepsy, and have emphasized that many of these patients have more than one seizure type.[18,47–50]

Etiologies of nontumoral parietal lobe epilepsy

Thirty-five patients from the MNI series had a history of head trauma, and 16% had a history of birth trauma. The remaining patients had a history of encephalitis, febrile convulsions, gunshot wounds to the head, forme fruste of tuberous sclerosis, hamartomas, vascular malformations, tuberculoma, arachnoid or porencephalic cysts, microgyria and post-traumatic thrombosis of the middle cerebral artery.

Tumoral parietal lobe epilepsy

Thirty-four of 116 patients (29%) from the MNI series with parietal lobe epilepsy had slow growing tumors (Figure 38.2), most commonly astrocytomas (62%) and meningiomas (14%). The remaining patients had hemangiomas, oligodendrogliomas, and mixed astrocytoma and oligodendroglioma.

Forty-seven percent had impaired two point discrimination in the contralateral fingers, 38% had mild contralateral weakness, 6% aphasia, 3% smaller extremities contralateral to the epileptogenic zone, one right to left disorientation and acalculia and two spatial disability. Only one patient exhibited definite astereognosis without coexisting primary sensory cortical deficit.

Seventy-nine percent exhibited auras, most commonly somatosensory, contralateral to the the epileptogenic zone in

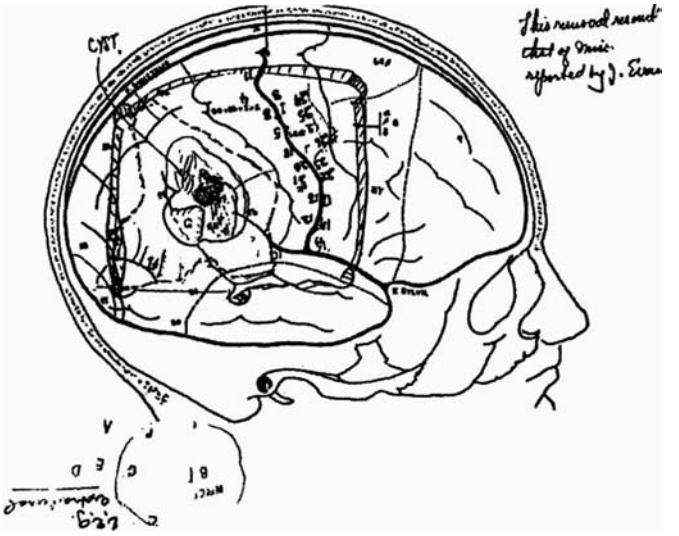

Figure 38.2 Original operative map of patient E. O'k. operated on by Dr Penfield in 1947. 25 year old with weakness of left foot and absent two-point discrimination in left leg. The seizures began by a sensation in the left great toe, tingling in the left vulva, spreading to left breast (not sexual), followed by left leg and left arm jerking.

all except for one patient. Four described a painful sensation. Twelve percent had visual illusions, 9% aphasic aurae, 6% disturbance of body image, 3% complex auditory hallucinations, and 3% a feeling of movement in one arm. Some patients had two or more auras.

The clinical manifestations indicated different spread patterns; 21% had tonic posturing of the extremities, 28% had focal clonic activity always contralateral to the epileptogenic lesion, 15% had head deviation, 9% automatisms, and 6% difficulty speaking. Thirty-two percent had Todd's paralysis and 18% had post-ictal dysphasia.

EEG findings in parietal epilepsy

Surface EEG was available in 66 patients of the nontumoral parietal lobe epilepsy MNI series and seizures were recorded in 36 patients. The interictal epileptiform discharges were recorded from the fronto-centro-parietal region in 33% of patients, parieto-posterior temporal in 14%, parietal in 14%, parieto-occipital in 9%, fronto-centro-temporal in 4.5%, fronto-temporal-parietal in 4.5%, hemispheric, maximum posterior head region in 9%, and bilateral in 4.5%. No interictal epileptiform discharges were recorded in 7.5% of patients. Secondary bilateral synchrony was described in 32% of patients. Ictal discharges were predominantly lateralized, in some patients the maximum ictal activity was recorded over the centro-parietal region and in others over the posterior head region. Localized parietal seizure onset was recorded in four patients.

Williamson *et al.*[47] and Cascino *et al.*[48] emphasized that surface EEG monitoring is often non-localizing in parietal lobe epilepsy, and Foldvary *et al.*[36] reported false localization/lateralization in 16% of parietal lobe seizures.

Conclusions

In more than two-thirds of the patients with occipital lobe epilepsy, clinical manifestations indicated the occipital onset of the seizures. Visual auras were reported in 47–73% of patients. Most patients exhibited contralateral elementary visual auras, and a few exhibited ictal blindness. Seven to nine percent of patients exhibited nystagmoid eye movements. Many of the disabling clinical manifestations resulted from ictal spread to adjacent cortical structures, 29–88% of patients exhibited automatisms typical of temporal lobe epilepsy, and 38–47% had focal motor activity. Some patients had more than one seizure type reflecting these different spread patterns. Contralateral visual field deficits were reported in 20–59%, and abnormal imaging studies in 37–72% of patients. EEG recordings often showed posterior temporal-occipital interictal epileptiform discharges, and ictal onsets were regional often involving the posterior temporal region. A quarter of patients had bitemporal independent interictal epileptiform discharges, and one-third had bilateral synchronous epileptiform discharges over the posterior head regions.

Ninety-four percent of patients with parietal lobe epilepsy exhibited auras. The most common auras were somatosensory, including painful sensations. However the auras experienced by some patients, like disturbance of body image may have indicated an epileptogenic zone in the association parietal cortex. The ictal semiology indicated several dominant spread patterns; 28% had tonic posturing of extremities, 57% focal motor clonic activity, and 17% had oral-gestural automatisms. The surface EEG was often lateralizing rather than localizing. Brain tumors are often the cause of parietal lobe epilepsy and were found in one-third of 116 MNI patients.

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39 Insular epilepsy

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Introduction

The concept of insular epilepsy was debated in the early fifties when it was observed that insular stimulation could evoke symptoms very similar to those of temporal lobe seizures. This similarity could be such that confusion between insular and temporal lobe seizures might explain some of the failures of temporal lobectomy. In 'Historical background and basic concepts' we review the historical background and concepts on which are grounded recent depth Stereotactic EEG (SEEG) studies aiming at identifying the actual symptoms reflecting discharges located in the insular lobe. 'The insula as an ictal symptomatogenic area' is devoted to the description of an ictal symptomatic sequence, which occurs in full consciousness, and is highly suggestive of an epileptic discharge in the insular lobe. Based on SEEG recordings of spontaneous seizures and stimulation data, this sequence includes an initial pharyngeal and/or laryngeal discomfort with thoracic oppression or dyspnea, unpleasant paresthesiae, warmth or pain sensation in the perioral region or spreading to a large somatic territory, followed by dysarthric or dysphonic speech and ending by focal somato-motor manifestations. Several cortical areas, with which the insula is connected, are involved in most of the focal seizures originating in, or spreading to, the insula. Based on clinical observation of ictal symptomatology, invasive EEG investigations must be targeted to explore the whole extent of the suspected epileptogenic network in order to assess the role of the insula in seizure development. 'The insula as a mode in distributed epileptogenic networks' provides the arguments supporting identification of three major epileptogenic networks (temporo-perisylvian, temporo-limbic and mesial-orbital frontal) where the insula participates as a node in the building of ictal symptomatology, including that of nocturnal frontal hypermotor seizures where the antero-superior part of the insula can be a clinically silent seizure onset zone. The final three sections are devoted to the review of etiologies, presurgical evaluation and treatment of insular epilepsies. Most cases reported in the literature as insular epilepsies are symptomatic of a focal epileptogenic lesion located in the insula, some of which were successfully operated upon, while the few cases of cryptogenic epilepsies hitherto available are those reported in this chapter. EEG plays a minor role for investigating insular epilepsies because interictal paroxysms and seizures originating in the insula are unlikely to be detected by scalp recordings. The roles of MEG and functional interictal neuroimaging remain incertain as well as the results of insular surgical resection based on SEEG data or of SEEG-guided thermo-coagulation in cryptogenic cases. Conversely seizure freedom can be obtained after surgical resection of the lesion in symptomatic cases, provided that ictal symptoms are compatible with an epileptogenic zone located close to the lesion in the insular lobe.

Historical background and basic concepts

The insula as the fifth lobe of the brain

In an article published in 1896 that was devoted to the comparative anatomy of the insula, Clark[1] quoted 39 synonyms used in anatomical literature to name the fifth lobe of the brain buried in the lateral sulcus and covered by the opercular parts of the frontal, parietal, and temporal lobes, among which the term insula, first proposed by Reil in 1804, has prevailed. The anatomical situation of the insula and its cytoarchitectonic organization lent some substance to the view that it might be an isolated lobe of the brain mostly devoted to the processing of body and visceral sensation including gustation, pain and other emotions, and to viscero-motor and autonomic control. In monkeys the insula includes Brodmann's areas 13 to 16 and shows a caudo-rostral sequence of distinct cytoarchitectonic areas namely; a granular cortex, at its upper and posterior part, very similar to that of the second somatosensory (SII) area and involved mostly in somatosensory, pain and auditory functions; a transitional dysgranular field localized in its antero-superior part involved in gustation and and viscero-sensitive functions; an antero-ventral agranular field, which is in continuity with the temporal pole and olfactory proisocortex, and related to olfactory and autonomic functions (see ref 2 for a review).

For the past 10 years the question of insular physiology has been addressed by numerous studies using neuroimaging, evoked potentials and direct stimulation in humans as well as microelectrode studies in monkeys. These studies have confirmed the role of the insula in:

- Somatosensory and pain sensation as assessed by numerous anatomical,[3,4] functional imaging studies[5–8], as well as by our recent studies of somato-sensory and pain evoked responses[9] and direct electric stimulation of the Insular cortex[10, 11]
- Visceral sensation and viscero-motor control[12–14] including processing of visceral pain[15]
- Cardiovascular function as demonstrated by insular stimulation in epileptic patients before temporal lobectomy that produced changes in heart rate or in blood pressure

in 50% of cases,[16] thus leading to suspect a role of insular discharges in cardiac arrhythmias causing sudden death during epileptic seizures.
- Gustation as assessed first by the stimulation studies of Penfield and Faulk[17] and further confirmed by neuroimaging studies[18, 31] as well as by microelectrode recordings of a large number of insular neurons in monkeys,[20] these physiological findings being consistent with the altered taste perception observed in patients with insular lesion.[21]
- Audition and language, in particular allocation of auditory attention, tuning in to novel auditory stimuli, temporal and phonological processing of auditory stimuli.[22] Furthermore several studies suggest that both right and left insulae are involved in the control of speech production.[23–28]

More recently, some studies suggested that the insular lobe could belong to the mirror-neuron system that characterizes regions of the brain that are able to respond when the subject performs an action and when the subject observes another individual doing a similar action (see ref 29 for a review), but also regions able to encode for a sensation (or emotion) perceived by the subject and to respond to the observation of others experiencing that sensation (or emotion). In the human insula regions involved in visceral sensation or viscero-motor responses also respond to faces expressing disgust.[30,31] Similarly the human insula responds to both pain perception and empathy for others' pain.[32]

From what precedes one can conclude that the insula represents a highly organized lobe with specific functions comparable to the other lobes of the brain and, therefore, consider that an epileptogenic zone located in this area will cause seizures characterized by a specific ictal symptomatology. This point is addressed in details in the second section of this chapter where we discuss the localizing value of a sequence of ictal symptoms that are highly suggestive of an epileptic discharge affecting the insula.

The insula as a node in distributed cortical networks

As the other lobes of the brain, the insula is characterized by anatomical borders that are defined by a limiting sulcus (the circuminsular fissure) but also by fuzzy cytoarchitectonic borders with neighboring cortical areas and by a dense network of cortico-cortical connections with adjacent or more distant cortical areas. Therefore its function, as well as its implication in epileptic seizure development, cannot be sketched as an isolated functional center, as suggested by the term 'insula'. A complete description of insular connections is given in the review by Augustine[2] showing that the insula is connected with the limbic areas, the amygdalar nucleus, the basal ganglia, and all of the cortical lobes, except the occipital lobe. Several attempts have been made to identify functional networks in which the insula could play the role of a functional node.[33–35] Among these networks the perisylvian-insular, the temporo-limbic-insular, and the mesial-orbito-frontal-insular networks deserve the attention of epileptologists because epileptic discharges propagating in each of them will produce seizures where the symptoms attributable to the insula will reflect only part of the ictal symptomatology. In part III of this chapter we discuss the difficulties in identifying insular epilepsy among epilepsies where the epileptogenic zone spreads outside the limits of the insular lobe, and the utility of the concept of epileptogenic networks for planning the depth electrodes implantation in the presurgical evaluation of these patients.

The concept of insular epilepsy

In the late forties and early fifties Guillaume et al.[36] followed by Penfield and Jasper[37] were the first authors to call attention upon the concept of insular epilepsy. Penfield and Faulk[38] concluded the review of their personal experience of insular stimulation by noting that the majority of the positive responses to stimulation of the insula consisted either in sensations resembling that produced by stimulation of the superior bank of the sylvian fissure (SII area), or in abdominal feeling secondary to motor change in the gastrointestinal tract. This latter finding suggested that seizures originating in the insular cortex were able to mimic temporal lobe seizures to such a degree that confusion between the two types of seizures might explain part of temporal lobectomy failures.[36] This concept was mostly based on data from electrocorticography (EcoG) carried out during the surgical treatment of patients suffering from temporal lobe epilepsy (TLE) under local anaesthesia. Moreover EcoG recordings revealed a rich interictal spiking paroxysmal activity in about half of these patients.[34] However, in spite of an EcoG strategy exploring systematically the insula, Penfield and his collaborators never succeeded to record spontaneous epileptic discharges with a focal onset in the insular cortex. Furthermore they were unable to provide the argument that insular cortectomy, as a complement to conventional temporal lobectomy in TLE patients, could improve the surgical outcome.[39] Thus the concept that specific symptoms could reflect insular discharges into the insular lobe fell into dereliction. More recently, several case reports showed that seizures could be stopped by the surgical removal of insular lesions[40–42] and reactivated the research for identifying the insula as a symptomatogenic area in focal epilepsy.

The insula as an ictal symptomatogenic area

Identification of a given cortical area as a symptomatogenic zone is mostly based on correlations between the ictal symptomatology and data from ictal discharge recordings using invasive EEG procedures.[43] In the case of the insular lobe such correlations are often uneasy because, even though the insula is frequently involved during temporal lobe seizures, most insular discharges develop concomitanty in the temporal, perisylvian, or frontal cortex, so that symptoms reflecting discharges in the insular cortex are difficult to disentangle from those related to the involvement of these neighboring areas in the building of ictal symptomatology. The patients' file of our department reflects the rarity of focal seizures involving exclusively, or preferentially, the insular lobe. Of the 180 patients with temporal lobe epilepsy (TLE) referred to our department for presurgical evaluation since 1996, 83 were explored using depth electrodes implanted in the lateral and mesial regions of the temporal lobe, of whom 50 also had depth electrodes implanted in the insular. We have been able to identify an ictal symptomatic sequence associated with a focal discharge restricted to the insula in only eight of them (16%).

Ictal symptoms reflecting seizure activity in the insula

What we know about the electroclinical manifestations of insular seizures mostly stems from SEEG data from a few patients referred mostly for TLE surgery. Electrode implantation in the insula is usually decided on the basis of ictal symptoms or scalp video-EEG data suggesting an early spread of seizures either to the suprasylvian opercular cortex, such as tonic or clonic mouvements of the face, dysarthria or motor aphasia, gustatory hallucinations, hypersalivation, post ictal facial paresis,[44] or to the infrasylvian opercular cortex such as auditory hallucinations or early sensory aphasia.[45] For the description of insular ictal symptoms we selected seizures that were characterized by a SEEG discharge involving selectively the insula at any moment of the seizure development. In six patients discharges originated from the insula itself (cases 3 to 8 in Figure 39.1) and in two (cases 1 and 2 in Figure 39.1) discharges originated in the hippocampus but propagated exclusively to the insular cortex without spreading to any other cortical structure. Video recordings of patients' behavior during insular seizures are illustrated in Figure 39.1. The five ictal features that were invariant in repeated seizures in a given individual and observed when the ictal discharge selectively involved the insular cortex are the following:

(a) Consciousness and contact with the environment are fully preserved
(b) Paresthesiae (lines B and C in Figure 39.1) represent the second feature that is reported by all patients during insular discharges. They are described as an unpleasant sensation of electricity or warmth that can be painful (2/8). They are either restricted to peri-or intra-oral areas (line B in Figure 39.1), or distributed to a large cutaneous territory (face-shoulder-arm and trunk, upper limb-trunk-lower limb) most often opposite to the insular discharge (line C in Figure 39.1), or bilateral (2/8) affecting either territories close to midline, such as mouth and oral cavity (1B and 2B in Figure 39.1), or more distal somatotopic areas such as both lower limbs (3C in Figure 39.1). Although the onset site and spreading of paresthesiae can vary from one seizure to the other, there is usually no somatotopic Jacksonian march as often reported in SI somatosensory seizures.[46]
(c) Motor and sensory pharyngo-laryngeal symptoms are other frequent manifestations (6/8) that are accompanied by the spontaneous gesture of seizing the neck with the hand ipsi- or contralateral to the discharge, or with boths hands, as illustrated in patients 1–6 in Figure 39.1 (line A). This sensation can be isolated or preceded, or followed, by other sensations such as a retro-sternal or abdominal heaviness that can be accompanied by rumbling noises and vomiting (image 1B in Figure 39.1), or a short breath with dyspnea as reported in the early descriptions of anterior insular stimulations by Penfield and Faulk.[38] Its intensity is variable according to patients and is described either as an unpleasant sensation of throat constriction, or as the sensation that the salivary glands are under pressure preceding hypersalivaltion (image 2A–5A in Figure 39.1), or even as a terrifying sensation of strangulation with suffocation (images 1A and 6A in Figure 39.1).
(d) A dysphonic and dysarthric speech evolving progressively toward a complete muteness is as frequent as the laryngeal sensation described above (6/8). It may persist several tens of seconds after the end of the discharge.
(e) Finally, the clinical manifestations of insular seizures often (5/8) end with motor symptoms (cases 4–8, line D in Figure 39.1) that are either lateralized and opposite to the discharge (tonic spasm of face and upper limb), or more diffuse (head and eyes rotation, generalized dystonia). In a given patient the occurrence of motor symptoms is usually inconstant from one seizure to the other.

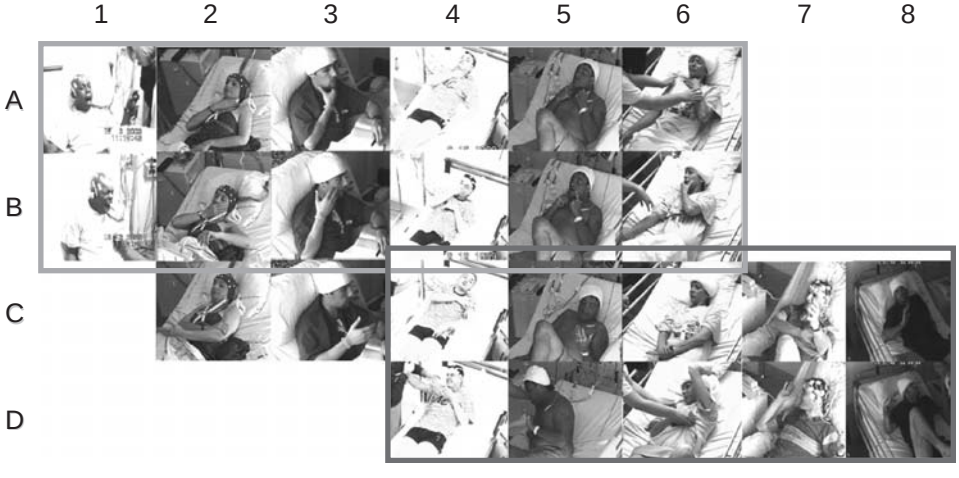


Figure 39.1 Video sequence of ictal symptoms in the eight patients with insular seizures. Empty areas correspond to missing symptoms in the sequence. All illustrated seizures are simple partial seizures with complete preservation of contact during phases A, B, and C of the sequence. A brief loss of contact occurred in phase D for patients 6 and 7 in association with intense somatomotor convulsive symptoms. A: Laryngeal constriction (6 patients). B: Paresthesiae in the perioral region (6 patients). C: Lateralized somatosensory symptoms in upper limb (7 patients). D: Focal somatomotor symptoms (5 patients). *For patient 3 somatomotor symptoms(D) did not occur during the three Video-SEEG recorded seizures, while most of spontaneous seizures in patient's history ended by this type of symptoms. Colored frames distinguish rostral (green) from caudal (red) insular seizures. Green frame: symptoms associated with anterior insular ictal discharge Red frame symptoms associated with posterior insular ictal discharge.

When observed at any given moment in the seizure such symptoms suggest that the insular lobe is included in the symptomatogenic zone; when observed at the onset of seizures they indicate that the insula should be involved in the surgically resected area to achieve postsurgical control of seizures; when an insular lesion is present their occurrence at seizure onset suggests that the epileptogenic zone is close to the lesion. This latter statement is illustrated by the patient whose brain MRI is shown in Figure 39.2. This female patient, aged 22, had suffered since the age of 16 from seizures beginning by unpleasant and intense paresthesiae that involved a large proportion of the left side of her body including face, whole upper limb and trunk followed by a 'strange taste' in her mouth. Her seizures ended with hypersalivation and clonic jerks in her left face. MRI showed a cavernous angioma located in the posterior insular cortex, the removal of which was followed by the disappearance of seizures. Since surgery this patient has remained free of seizures and antiepileptic drugs, with a postsurgery follow-up of two years.

Localization specificity of insular ictal symptoms: data from direct electric cortical stimulations

Electric stimulation of the insula in patients presenting with one or more of the above listed ictal symptoms is useful for mapping the symptomatogenic area when it reproduces symptoms that are immediately identified by the patient as identical to their spontaneous ictal symptoms. Thus lateralized and widely distributed paresthesiae could be triggered by stimulation in five of the eight patients whose ictal behavior is shown in Figure 39.1 (cases 1, 3, 5, 6 and 8), focal perioral paresthesiae in four (cases 1, 2, 3, and 6), laryngeal sensation in three (cases 2, 4, and 5), dysarthric speech in one (case 5) and abdominal pain in one (case 1).

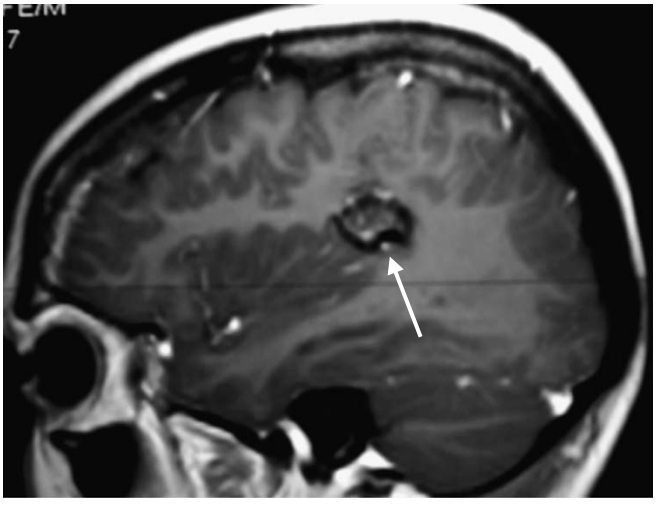
More generally direct stimulation of the insula, even in patients whose seizures are of extrainsular origin, is able to elicit all of the ictal symptoms of insular seizures. In our experience, the insula is one of the most eloquent cortical areas when electrically stimulated by shocks[47] or trains[11] at low intensities (1–3 mA). Insular stimulation sites explored in our group of 50 consecutive patients are plotted in Figure 39.3. Of these 144 sites, 125 were clinically responsive to stimulation in the absence of any after discharge, and a total amount of 139 evoked clinical responses could be collected (Figure 39.3b). Thirty-one of them were identified by the patients as identical to one of the ictal symptoms of their spontaneous seizures, 108 were reported as unknown and not belonging to the usual ictal symptomatology. As for ictal symptoms, these responses can be subdivided into five main categories: somatosensory (Figure 39.3Ca), viscerosensitive (Figure 39.3Cb and c), auditory (Figure 39.3Cd), dysarthria and missing words (Figure 39.3Ce), others including sensation of unreality, whole body sensations, olfacto-gustatory hallucinations, and vegetative responses (Figure 39.3Cf).

Somato- or viscero-sensory responses represent nearly two-thirds of evoked responses, of which more than half concern the cervical-laryngeal region. There is thus converging evidence from seizure analysis and stimulation data that these somatosensory symptoms, particularly in case of warmth or pain sensation, suggest an ictal involvement of the posterior insula.

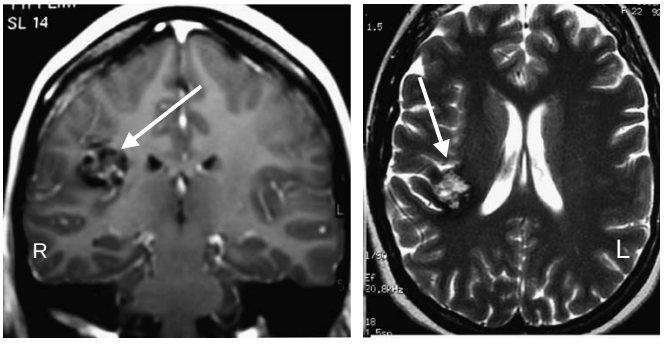
Similarly the laryngeal and visceral sensations reported by our patients during their seizures, and reproduced by electric stimulation suggest an anterior insular propagation of the epileptic discharge. This conclusion contrasts with the commonly accepted view that visceral and laryngeal ictal sensations indicate a hippocampal or amygdalar origin when observed in the context of TLE seizures.[48, 49]

Auditory symptoms and dysarthric speech immediately follow somatic and visceral sensations, in terms of frequency, in the list of responses evoked by insular stimulation. Auditory symptoms are currently attributed to ictal discharges in the temporal operculum and first temporal gyrus. Our data suggest that they may also reflect an insular propagation of the discharge. However, there are no types of auditory illusions or hallucinations that can be considered as specific to insular ictal semiology, because stimulation of the Heschl's gyrus can evoke auditory symptoms very similar to those produced by insular stimulation. Conversely, though dysarthria is considered to reflect frontal opercular discharges,[50] we never observed this symptom in isolation when stimulating this region outside Broca's area. Moreover, ictal dysarthria was associated with discharges in the nondominant hemisphere for language in the three patients whose insular seizures included this symptom, and it was reproduced as often in the right or left hemisphere by direct cortical stimulation.

Somato-motor ictal manifestations differ from others in that they usually cannot be reproduced by insular stimulation and reflect seizure propagation outside the insular lobe. They have been considered as predictors of a bad outcome in



(a)



(b) (c)

Figure 39.2 Sagittal (a), coronal (b) and axial (c) MRI slice showing a right posterior insular cavernous angioma in a patient with painful seizures on the left side of the body, who became seizure free after lesionnectomy (see text for details).

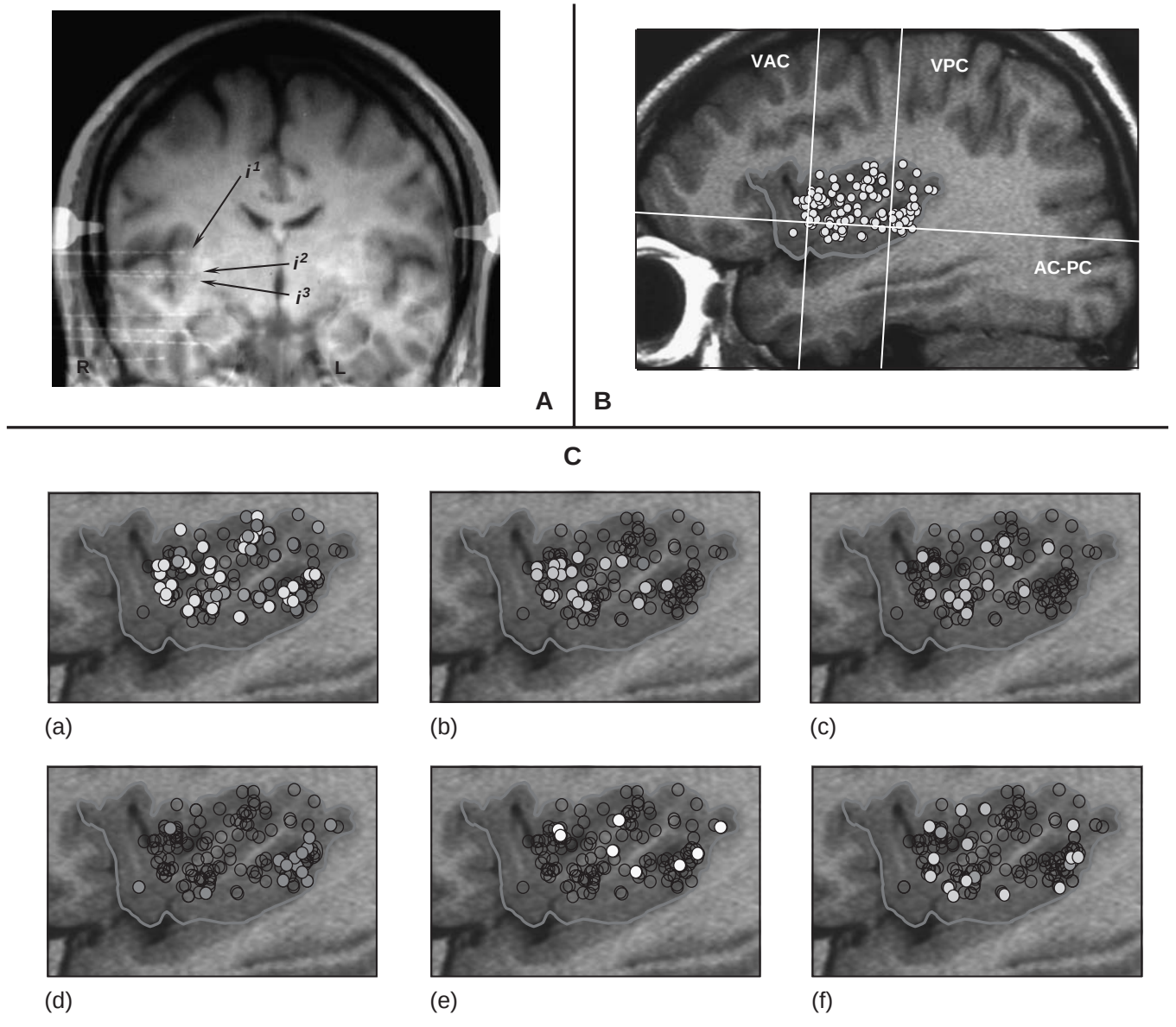


Figure 39.3 SEEG exploration of the insular lobe. A: Fusion of skull radiography and coronal MRI slice in the anterior commissure vertical plane at scale 1. This picture illustrates the positions and trajectories of the electrodes exploring the insular cortex (i1, i2, and ***i3***) in an individual patient. The two deepest contacts of each electrode are located in the insular cortex. The more superficial contacts are located in the suprasylvian (i1) and infrasylvian opercular cortex (i2 and i3). (R: right, L: left). B: Plotting of the 144 insular contacts (yellow dots) in the 50 patients on a sagittal MRI slice of the insula. The borders of the insular lobe are drawn in red. Most of the insular surface has been explored except its most anterior part. The white lines represent the axis of the bicommissural stereotactic space of Talairach and Tournoux.[97] AC-PC: anterior commissure-posterior commissure horizontal plane; VAC: vertical anterior commissure plane orthogonal to the AC-PC plane; VPC: vertical posterior commissure plane orthogonal to the AC-PC plane C: Functional mapping of the insula. This figure illustrates data from direct electrical stimulations of the insular cortex in the 50 patients of this study. In each of the six Ca to Cf insets all of the 144 stimulated points are plotted as black circles (see ref. 11 for details on stimulation procedure, safety and accuracy). The 138 responses evoked by electrical stimulations are represented according to the functional categories detailed in the results section. Ca: Somatosensory responses. Simple paresthesiae are represented in yellow, paresthesiae with warmth sensation in orange and painful paresthesiae in red. Cb: Viscero-sensitive responses are in blue, of which one was painful (in red). Cc: Sensations of laryngeal constriction are in green, of which two were painful (in red). Cd: Auditory responses (lilac). Ce: Dysarthric speech and missing words (cream white). Cf: Miscellaneous responses: Sensation of unreality (light blue); Olfacto-gustatory responses (orange); Vestibular responses (pink), Vegetative responses (purple). From Isnard et al. 2004 with permission.[69] (See Color plates.)

temporal lobectomy and their occurrence makes questionable the diagnosis of TLE.[51] Indeed such symptoms are exceptional in seizures originating in the mesial temporal lobe, while they occur at the end of nearly two-thirds of insular seizures. Thus, in patients whose ictal symptomatology is compatible with TL seizures, their occurrence during the development of the seizure strongly suggests a seizure onset in the insular lobe.

Finally, 10% of the responses evoked by insular stimulation (Figure 39.3Cf) reproduce ictal manifestations that are only occasionally observed in spontaneous insular seizures such as vegetative responses, feeling of unreality, olfacto-gustatory and visceral sensations. The insular origin of these rare symptoms is in agreement with the functional role of the insular lobe in the control of taste[52–56] and visceral functions.[31, 57]

None of our patients with SEEG documented insular seizures reported vertigo or sensation of body tilting as part of their ictal symptomatology and insular stimulation exceptionally produced a vestibular sensation (3/139: 2.1%, purple points

in Figure 39.3Cf). This finding contrasts with some observations where parieto-insular strokes manifested by such sensations.[58–60] It is in line with cortical stimulation data by Penfield and Jasper[37] and more recently by Kahane et al.[61] showing that vestibular sensations are mostly observed after stimulation of the superior temporal neocortex and lateral aspect of the inferior parietal cortex.

What, if anything, is an insular seizure?

Based on the above detailed observations is it possible to add an 'insular' category to the list of epileptogenic zones that can be used as one of the dimensions of a patient-oriented epilepsy classification?[62] In other words, is there any sequence of symptoms that are specific enough to locate the epileptogenic area in the insula and to predict that the removal of the insular cortex is necessary to make the patient seizure free? Even though SEEG-documented seizures are scarce an affirmative answer can be given to this question when, during spontaneous seizures, the patient experiences in full consciousness a symptomatic sequence made of a pharyngeal and/or laryngeal discomfort with thoracic oppression or dyspnea, unpleasant paresthesiae, warmth or pain sensation in the perioral region or spreading to a large somatic territory, followed by dysarthric or dysphonic speech and ending in focal somato-motor manifestations. Knowing that in patients illustrated in Figure 39.1, most of the antero superior quadrant of the insula has not been explored (see Figure 39.3), two variants can be distinguished according to whether the insular discharge originates from the anterior or posterior part of the insula. In rostral insular seizures viscero-motor and laryngeal symptoms are predominant (green frame in Figure 39.1), while in caudal insular seizures the ictal symptomatology is dominated by somato-sensory symptoms, which are all the more so specific that they affect a large, eventually bilateral, territory and manifest as a warm or painful sensation (red frame in Figure 39.1)! Thus most of the insular seizures can be described as a combination of vegetative and somatosensory auras according to the semiological seizure classification proposed by Lüders et al.[63]

The insula as a node in distributed epileptogenic networks

As for any other types of partial seizures, the concept of a distributed epileptogenic network can be applied to describe insular seizures where the insular cortex is involved as a node, or as a relay in seizure propagation, and not as a single focus. This situation is likely to be more frequent than that where seizures remain confined to the insular cortex. The occurrence of a sequence of ictal symptoms reflecting the insular involvement at seizures clinical onset, as described above, proves effective to delineate the various clinical situations where epileptic discharges might originate in the insula. It must be reminded, however, that identification of these symptoms does not allow to firmly conclude on the insular origin of seizures, since they might as well follow the primary involvement of noninsular portions of a larger epileptogenic network where the seizure onset zone can keep clinically silent.[64] Thus, apart from the situation where a clear-cut epileptogenic MRI lesion, such as a cavernous angioma or a low grade tumor, is observed within the insula, invasive EEG investigations, based on clinical observation of ictal symptomatology, must be targeted to explore the whole extent of the suspected epileptogenic network in order to assess the exact role of the insula in seizure development. Three major types of epileptogenic networks involving the insula can be distinguished:

- Temporo-perisylvian-insular networks that include the various brain regions bordering the sylvian fissure, i.e., the frontal, parietal and temporal operculum, together with the insula;
- Temporo-limbic-insular networks, which primarily involve the mesial temporal structures and/or the temporal pole;
- Mesial and orbito frontal-insular networks, in the context of the so-called nocturnal frontal lobe epilepsy.

This subdivision remains partly artificial, however, since some patients combine electro-clinical features that belong to at least two of these networks, as detailed below.

Temporo-perisylvian-insular networks

The concept of 'perisylvian epilepsy' was originally introduced by Munari et al.,[50] in an attempt to distinguish this form of epilepsy from temporal lobe epilepsy proper. It should be noted, however, that in perisylvian the epileptogenic zone often encompasses the first temporal gyrus, accounting for the frequent presence of simple auditory hallucinations in this form of epilepsy, and explaining why the term 'temporo-perisylvian' is preferable to that of 'perisylvian'. Apart from simple auditory hallucinations, temporo-perisylvian seizures are characterized by the presence of symptoms reflecting the involvement of the frontal and parietal operculum (hemifacial motor or somato-sensory symptoms, gustatory hallucinations, hypersalivation), the secondary somato-sensory area (various types of ipsilateral, contralateral or bilateral somatosensory symptoms), and the temporo-perisylvian vestibular cortex (vertigo).[61]

Part of the semiology initially ascribed to frontal or parietal opercular ictal discharges in the early study of Munari et al.,[50] which did not benefit from the placement of depth electrodes within the insula, does in fact reflect the involvement of the insular cortex. One such example is that of gustatory hallucinations, previously thought to reflect a fronto-parietal opercular discharge,[52] but that can be elicited by stimulating the insula rather than the opercular region.[17] Furthermore, both the insular cortex and parietal opercular somato-sensory (SII) cortex can be responsible for similar ictal somato-sensory symptoms affecting large cutaneous territories, even though the somatotopic fields are much larger in the insula than in SII[65] Finally, the tight anatomical connections and cytoarchitectonic continuum observed between the fronto-parietal and temporal perisylvian cortex on one hand, and the insula on the other, also militates for including all these brain regions within the temporo-perisylvian network that must be explored by SEEG recordings before surgery. For instance, in two of the patients presented in section II (#4 and #5), one of whom presented with a parietal cortical dysplasia (#4), the SEEG involvement of part of the

opercular regions was judged important enough to lead to a surgical resection or a thermolesion of that structure together with the posterior insula, resulting in seizure control in both patients (class Ib of Engel).

In another recent series,[66] the role of the insula in a temporo-perisylvian epileptogenic network can be suspected in six patients in whom temporal lobe surgery was unsuccessful in controlling seizures despite intracranial EEG evidence that the temporal lobe participated in seizures genesis. In these patients a somato-sensory aura was interpreted as reflecting a discharge in the parietal lobe and the inferior parietal region was indeed also involved at ictal onset on intracranial EEG recordings, but its secondary removal did not result in better seizure control. The authors acknowledged that the insula might have participated to the complex epileptogenic network observed in their patients, inasmuch as one presented with an insular hyperperfusion on ictal SPECT. They could not confirm this hypothesis, however, due to the lack of intracerebral electrodes directly placed within the insula.

Temporo-limbic-insular networks

One major challenge in epilepsy surgery remains to understand the origin of postoperative seizure recurrence in a still significant proportion of operated patients, despite the presence of typical clinical and MRI features of mesial temporal lobe epilepsy. Part of these surgical failures might reflect the involvement of the insular cortex within a larger epileptogenic network encompassing the sclerotic mesial temporal structures.[67] This issue is well illustrated by patient #6 in Figure 39.1, whose history has been further detailed in a recent review.[68] Indeed, this patient fulfilled the major criteria used to define mTLE, including a rising and distressing epigastric sensation at seizure onset rapidly followed by oroalimentary automatisms, MRI signs of unilateral hippocampal sclerosis; ipsilateral temporo-limbic interictal FDG-PET hypometabolism, and an anterior temporal scalp-EEG ictal discharge. However, other ictal signs and symptoms suggested a rapid involvement of the perisylvian region, including early simple auditory hallucination and rapid occurrence of mastication and left face tonic contraction, leading to the decision of performing an invasive SEEG monitoring. The latter revealed that the patient suffered two seizure types, one arising from the sclerotic mesial temporal structures that secondarily propagated to the ipsilateral insula and opercular regions, and another arising from the posterior insula before invading the ipsilateral mesial temporal and opercular regions. Interestingly, the insular seizure type, but not that arising from the temporal lobe, selectively occurred during sleep. Resection of the epileptogenic temporal lobe controlled daytime seizures type for a few months only, whereas nocturnal seizures have continued unchanged. Overall, this case report illustrates the possibility of observing insular seizures in a patient with the major clinical and MRI features of mesial temporal lobe epilepsy, suggesting an epileptogenic zone encompassing the temporo-limbic regions and the insula. This patient also demonstrated an intense and rapid involvement of other temporo-perisylvian regions, suggesting that these different networks might be intermingled and overlapping in the same patient.

Other patients might present with comparable ictal semiology, EEG and neuroimaging data, and will eventually prove to have an epileptogenic zone limited to the temporo-limbic cortex. This alternative situation is illustrated by another patient from our series (#2 in Figure 39.1) whose intracerebral EEG recordings demonstrated a mesial temporal ictal discharge that invaded the insula very rapidly and intensively, suggesting that the insular cortex might be part of the epileptogenic zone.[69] However, long-term seizure freedom was achieved after an anterior temporal lobectomy. More generally, seizures originating in the mesial temporal lobe are likely to propagate to the ipsilateral insula, though less rapidly and intensively than in the above patient, and this propagation[70] does not preclude seizure freedom after temporal lobectomy.

Several issues remained unsolved regarding the connections involved in the propagation of ictal discharges between the temporo-limbic system and the insula. Due to the frequent participation of the temporal pole at ictal onset,[71] we prefer using the terminology 'temporo-limbic' rather than 'mesial temporal', knowing that part of this brain region is located outside the mesial aspect of the temporal lobe and is closely connected to the insula.

In fact, according to Mesulam's description of the paralimbic regions, two major belts should be considered, one including the orbito-frontal cortex, the temporal pole, and the insula, while the parahippocampal and cingulate gyrus form the other.[33] Indeed, as already discussed, the insula has strong reciprocal connections with the temporal pole, but also with the entorhinal cortex and the amygdala. In addition, it projects to the anterior hippocampus but does not receive major direct afferents from this structure. It is yet unclear which of the above regions is predominantly involved in the insular propagation of temporo-limbic ictal discharge. Conversely, the posterior and anterior-inferior aspects of the insular cortex are predominantly involved in seizures propagating to the mesial temporal structures.[68,69]

Mesial and orbital frontal-insular networks

A recent issue concerns the role of the insula as a part of the epileptogenic network in fontal lobe epilepsies and, more precisely, in NFLE, which is is primarily characterized by seizures occurring exclusively or predominantly during sleep, the semiology of which suggests a frontal lobe origin, as for example nocturnal paroxysmal dystonia (NPD) or hypermotor seizures.[72] An autosomal dominant inheritance (ADNFLE) is found in 8–43% of patients, and several mutated genes have been identified.[72–76] However, many uncertainties persist regarding the neural networks underlying the cryptogenic and idiopathic forms of NFLE, inasmuch as very few patients have been investigated with intracranial EEG recordings.[77,78]

We have recently reported three patients with a typical form of nocturnal hypermotor seizures suggesting cryptogenic NFLE in two, and autosomal dominant NFLE (ADNFLE) in another, whose ictal onset zone proved located in the antero-superior portion of the insula.[79] In the two patients presenting with a seemingly cryptogenic NFLE, intracerebral EEG recordings demonstrated a very focal interictal focus in that same region, consisting of frequent bursts of high frequency discharges and high amplitude spikes (Figure 39.4). In the ADNFLE patient, the epileptogenic zone appeared larger, extending to the frontal operculum.

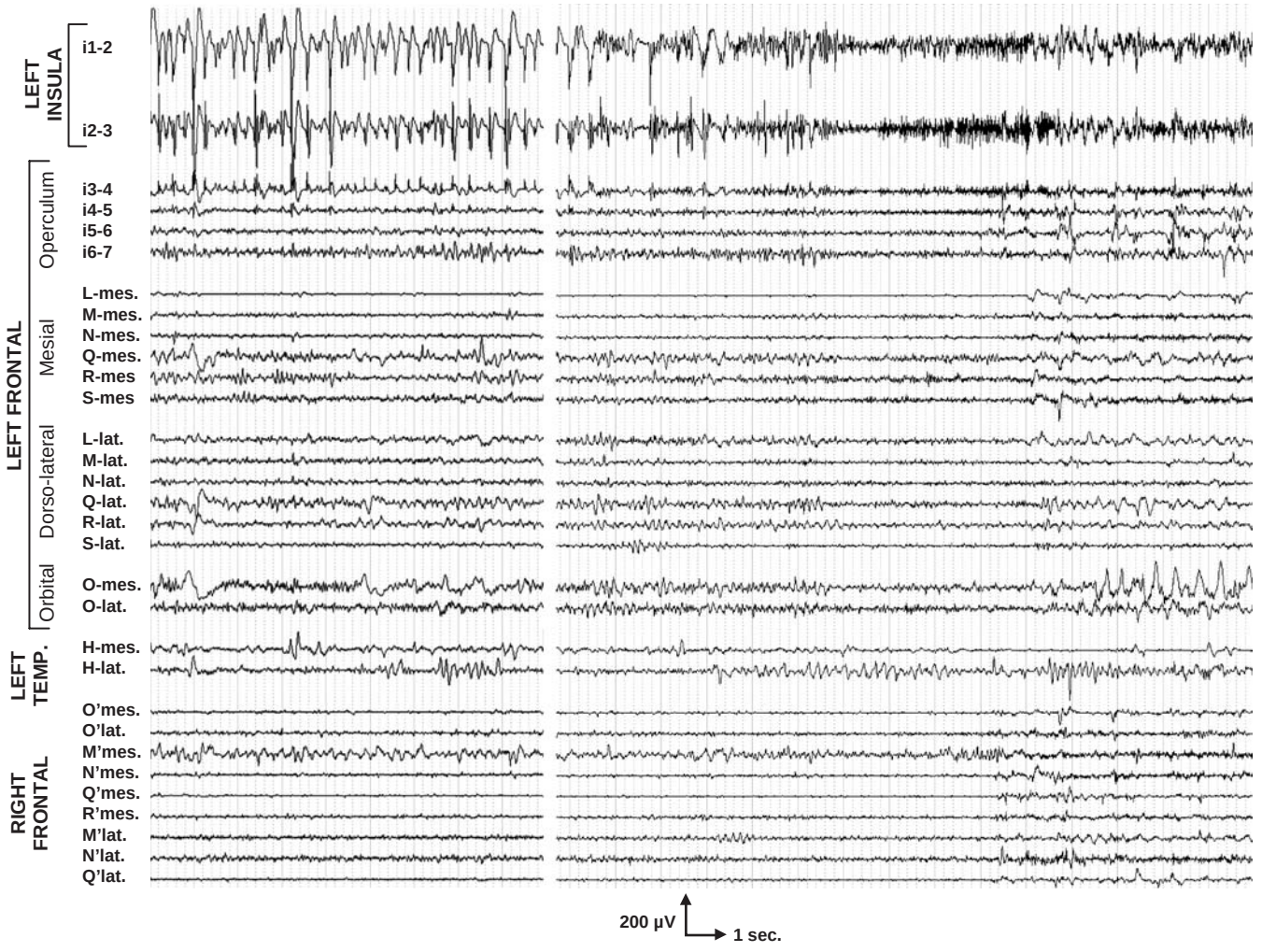


Figure 39.4 Intra-cerebral EEG investigation of a patient with a clinically-defined cryptogenic nocturnal frontal lobe epilepsy showing almost permanent high amplitude spikes (left EEG traces), and a high frequency discharge at ictal onset (right EEG traces) in the antero-superior portion of the left insula (i1,i2), slightly diffusing to the nearby deepest aspect of the frontal operculum (i3–4), but not to more lateral probes. Note that all leads are displayed with a similar amplification.

High frequency electrical stimulation of the antero-superior portion of the insula, but of no other region, could elicit a typical aura or full-blown seizure in two patients. However, because none of the three patients underwent epilepsy surgery, we cannot firmly conclude on the precise extent of their epileptogenic zone. Interestingly, these three patients represent 30% of all those with nocturnal hypermotor seizures and no MRI brain lesion who underwent an intracerebral EEG investigation in our study. Among the seven other patients, a mesial or anterior frontal seizure onset was demonstrated and resected, but three continued to suffer postoperative seizures. One might speculate on the role of the insula in these patients seizures, provided that it was not investigated during their intracerebral EEG recordings.

Overall, an insular seizure onset zone might be responsible for a significant proportion of so-called cryptogenic NFLE, at least among those resistant to antiepileptic drugs. At the present time, no clear indicator other than intracerebral EEG recordings allows to distinguish these patients from those presenting NFLE proper. In fact, our patients with an antero-superior insular ictal onset started their hyperkinetic behavior only when the mesial frontal cortex was invaded.

The propensity for insular seizure to occur during sleep has not been previously reported. However, it is interesting to note that this propensity was also observed in one of our patient with temporo-insular epilepsy (see previous section). The role of the insula in sleep physiology is not known, but recent functional neuroimaging studies have shown a marked deactivation of the anterior insula during sleep.[80, 81]

Overall, insular seizures might be associated with various types of ictal semiology, reflecting the subregion of the insular cortex primarily affected, as well as the related multilobar network: the posterior and antero-inferior aspect of the insula appears to be mostly involved in temporo-perisylvian and/or insulo-temporo-limbic epileptogenic networks mimicking the different forms of TLE; the antero-superior portion of the insula seems to play a more important role in the insulo-frontal networks mimicking NFLE. At the present time, there is no available data suggesting a primary role of the insular cortex in seizures originating from other brain areas than those listed above.

Etiology of insular epilepsy

Lesional insular epilepsy

The majority of cases reported in the literature as insular seizures or epilepsies derives from patients with an obvious

epileptogenic brain lesion located in the insula, some of which were subsequently and successfully operated upon. [41,42,54,69,82,–85] These lesions primarily included low grade brain tumors, including gliomas and dysembryoplastic neuroepithelial tumors, cavernomas, and cortical dysplasia. However, all potentially epileptogenic brain lesions might be observed in the insula, such as stroke or encephalitis.[86,87]

Cryptogenic and idiopathic epilepsy primarily involving the insula

To our knowledge, the only published cases of cryptogenic epilepsy primarily involving the insula are those published by our group.[68,69] They represent a very limited number of patients, none of whom underwent a surgical resection of their epileptogenic but MRI negative insula. No pathological data is thus available, but SEEG findings suggested the possibility of a MRI occult cortical dysplasia in a minority of patients. For instance, one of our patients with NFLE of insular origin presented an intracerebral SEEG pattern typical of an underlying cortical dysplasia, with very focal and permanent high amplitude spikes intermingled with bursts of high frequency discharges (Figure 39.4).[79] In the same series, one who presented with a typical form of ADNFLE, but none of the known mutation of the α 4 and β 2 subunits of the nicotinic acetyl-choline receptor, should be considered to suffer an idiopathic form of partial insulo-opercular epilepsy, according to the familial inheritance of his epileptic disorder and the result of his SEEG investigation.[79,88] To our knowledge, no other patient with ADNFLE has undergone an intracerebral EEG investigation, and we therefore ignore the proportion of such patients who might also demonstrate an insular epileptogenic zone.

Presurgical evaluation

Noninvasive investigations

EEG and MEG

According to the deep location and specific gyral organisation of the insula, interictal or ictal epileptiform discharges originating in this lobe are unlikely to be detected by scalp-EEG recording, unless these discharges propagate to lateral neocortical regions. This has been shown in our first description of insular discharges[70] and is also illustrated by Figure 39.4. Accordingly, neither interictal nor ictal scalp-EEG abnormality could be recorded in this patient, accounting for the fact that the epileptic origin of his seizure disorder has been strongly debated.

However, scalp-EEG recordings might provide some clue regarding a temporo-perisylvian epileptogenic zone, indirectly reflecting the potential involvement of the insular cortex. In particular, both interictal and ictal EEG abnormalities will display a more widespread distribution over the infra- and supra-sylvian elecrodes.

To our knowledge, a single case report has assessed the diagnostic value of MEG in a patient with an insular epileptogenic DNET, and concluded that MEG could detect epileptiform abnormalities within the concealed insular cortex.[82]

Functional interictal neuroimaging

In patients with typical TLE, [^{18}F]FDG-PET and [^{11}C] Flumazenil-PET studies have reported that interictal hypometabolism and decreased benzodiazepine receptor density observed in the temporal lobe could extend to the insula in some patients.[89–92] At the present time, the presence of such insular abnormalities have not been clearly associated with a higher risk of postoperative seizure relapse, but this issue still needs to be addressed in larger populations.

In the few well-documented cases of insular epilepsy, [^{18}F]FDG-PET, [^{11}C]Flumazenil-PET, and ictal SPECT did not demonstrate distinctive features from those encountered in TLE or NFLE, and in particular no clear cut insular abnormality.[67,68]

Finally, [^{18}F]FDG-PET and ictal SPECT have shown abnormal findings in the insula of a few patients with uncertain epileptogenic zone, where one might speculate on the involvement of the insula.[66,93,94] These include patients with nocturnal hypermotor seizures,[93,94] as well as one patient with somato-sensory aura and a seemingly temporo-parietal ictal onset zone not controlled by surgery sparing the insula.[66]

Overall, whether functional imaging will eventually prove useful in the clinical assessment of insular epilepsy remains an open issue.

Invasive investigations

In the stereotactic implantation technique first described by Talairach and Bancaud,[95] intracerebral electrodes are implanted perpendicular to the midsagittal plane using Talairach's stereotactic grid and can be left in place chronically up to 15 days.[96] The position of each contact can be plotted on the corresponding slice of the atlas of Talairach and Tournoux[97] and by fusing the frontal skull radiography with the coronal MRI slice, both at scale 1/1, corresponding to the electrode trajectory (Figure 39.3a). Oblique electrode trajectories can be also useful to explore the insula.[79]

Interictal insular recordings

The few available data from literature on interictal insular paroxysmal activities in surface or depth recordings were reported in the fifties.[36,98,99] These early studies showed that spikes or spike-waves are recorded in the insula of nearly 50% of TLE patients. In SEEG recordings they are present in all patients with insular seizures. They are sporadic or intermittent in TLE and most often frequent in patients with insular seizures, particularly in those with focal dysplasia.[91] Since the early study of Silfvenius et al.[39] it has been acknowledged that their presence is not predictive of a poor outcome of temporal lobectomy in TLE, so that they do not indicate an insular epileptogenic zone. Spikes in the amygdala, hippocampus or temporal pole usually co-exist, and are most often asynchronous, with insular paroxysms. Contacts located in supra- or infrasylvian opercular cortex or adjacent amygdalo-hippocampal structures are often blind to insular paroxysms, which are thus unlikely to be recordable by subdural electrodes grids placed over the sylvian fissure or on the mesial surface of the temporal lobe (Figure 39.5).

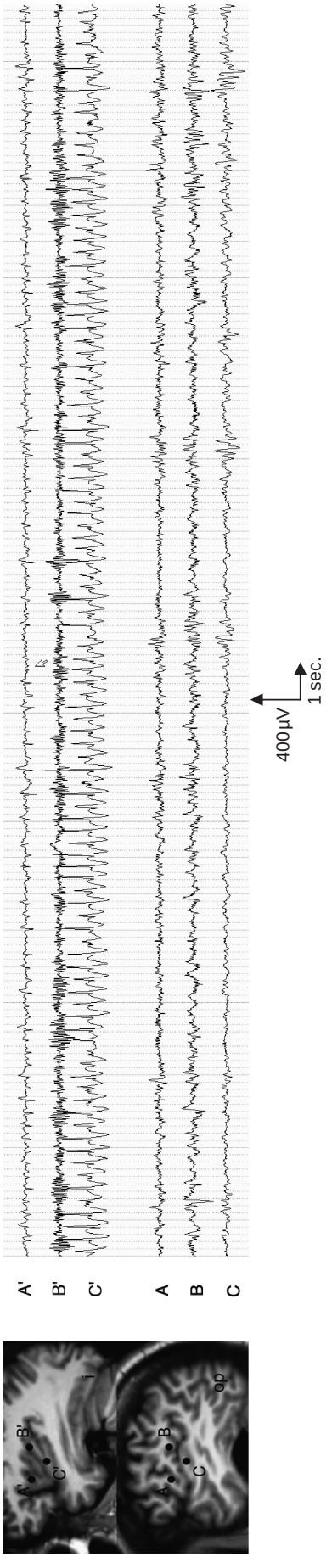


Figure 39.5 SEEG recordings in patient 8 using three transopercular electrodes exploring the right insular lobe (cf Figure 39.3a). An abundant paroxysmal interictal activity made of subontinuous spikes and spike-waves is picked up by the insular contacts (A', C'), to which which more superficial opercular contacts are blind. (i) MRI sagittal slice in the insular plane. (op) MRI sagittal slice in the opercular plane. A, B and C: postions of the insular contacts; A', B' and C': positions of the opercular contacts.

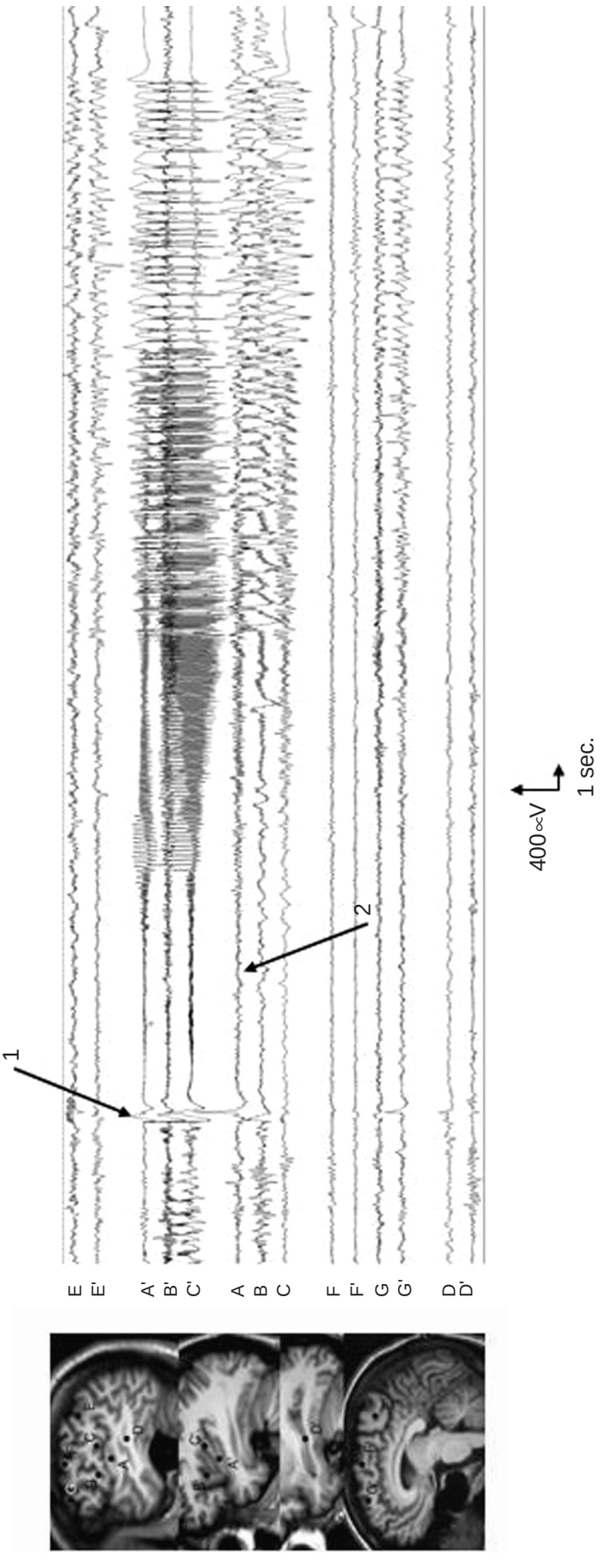


Figure 39.6 SEEG recording of an ictal discharge in patient 8 beginning in the insular cortex (Arrow 1) by a large spike-wave complex followed by a low voltage fast activity and a recruiting discharge of high frequency spikes and spike-wave affecting preferentially the posterior insula. This ictal spiking activity reaches the opercular cortex 8 seconds after the insular onset time (Arrow 2). This discharge spreads later on to the frontal (G, G') and parietal (E, E') lobe, sparing the temporal lobe (D, D').

Ictal insular SEEG recordings

In terms of onset site, propagation and morphology, the insular discharge patterns are very similar from one seizure to the other in a given patient, suggesting an individual organization of the insular epileptogenic neuronal network. They are made of a low voltage fast activity (LvFA) that may begin abruptly, or be preceded by changes in interictal activity. These preictal changes manifest by an increase in the frequency of spikes that become more regular or rhythmic and/or by the appearance of spikes and poly-spike-waves. Ictal LvFA can remain confined in the insula during several tens of seconds, or spread outside the insula in a few hundreds of milliseconds. During their intrainsular development LvFAs are not detectable by SEEG contacts located in neighbouring structures, in particular in the temporo-parieto-frontal opercular cortex, the activity of which is either unchanged or shows only rhythmic slow waves without sharp paroxysms during insular LvFA discharges (Figure 39.6).

We have never observed an insular LvFA not spreading, either step by step to perisylvian cortical areas, or more abruptly at distance to ipsilateral amygdala, hippocampus or posterior mesial frontal cortex. Lastly, in two patients with a bilateral SEEG exploration we could observe that an insular LvFA can propagate to the contralateral insula. This anecdotal observation does not allow any conclusion as to the frequency of insular seizures bilateralization, but suggests that the insula is not only a possible relay for intrahemispheric propagation of focal seizures (see section III), but also a route for their interhemispheric transfer.

Treatment

Based on electrocorticography, insular resections were attempted as early as the late forties to improve the surgical outcome of temporal lobectomy.[36,39,98,99] This procedure has been abandoned because it proved to have a much greater morbidity than the usual temporal lobectomy alone without improving significantly the seizure control. Progress in surgical techniques now allows, with an acceptable risk level, the removal of focal epileptogenic lesions located in the insula, such as tumors[42] and cavernous angiomas.[100,101] The outcome in terms of seizures control is usually good,[102] so that a lesionnectomy can be proposed, without presurgical invasive EEG recordings, whenever an insular lesion manifests clinically by seizures with insular ictal symptomatology, as in the case illustrated in Figure 39.2.

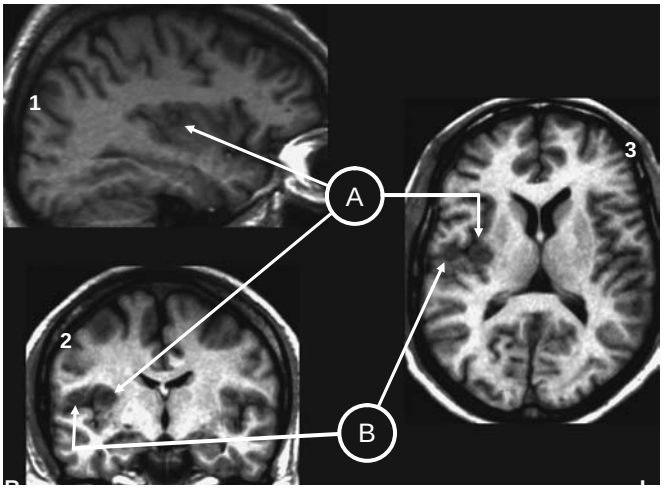


Figure 39.7 Sagittal (1), coronal (2) and axial (3) control brain MR images after insular radio frequency thermo lesions using the SEEG electrodes contacts implanted in the epileptogenic areas of patient 5. This procedure was performed immediately before SEEG electrodes removal and thus did not entail the risk of additional electrodes implantation. These RM images acquired 15 days after this procedure show the thermo-lesions located at the insular onset site of seizures (A), and in the parietal opercular cortex (B), which was the first propagation relay of insular discharges.

Partial or subtotal resection of the insular cortex is also feasible in a patient without a space-occupying lesion (case 4 in Figure 39.1). However, this remains an aggressive procedure that necessitates the removal of part of the opercular parieto-frontal or temporal cortex, and entails a lesional risk in the deep territory of the middle cerebral artery. In the absence of a lesion no tailored insular cortectomy can be undertaken without presurgical SEEG exploration of the entire cortical network suspected as epileptogenic (see the third main section), with recordings of several spontaneous seizures and insular stimulations.

An alternative to cortectomy is represented by SEEG guided radio-frequency (RF) thermocoagulation.[71] RF thermocoagulation is performed using adjacent contacts of SEEG electrodes in sites where discharges have been recorded. It produces focal lesions of 5–7 mm diameter with minimal risk (Figure 39.7). Two of the eight patients reported in this chapter (see the second main section) have benefited from RF thermocoagulation (# 5 and 8), with a follow up of 36 and 17 months, respectively. Both are free of disabling seizures (class Ib of Engel).

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40 Cingulate epilepsy

E Garzon and HO Lüders

Introduction

Between the 1940s and 1950s, studies on experimental animals and observations on human beings with destructive lesions led to the discovery of a possible relationship between the anterior portion of the cingulate gyrus (CG) and behavioral disorders. Those studies also led to the use of surgical ablation of the anterior portion of the CG or of cingulum disconnection for the treatment of severe behavioral illnesses. Many advances have been made in the last 20 years and, even if a clear understanding of all its connections and functions is still far in the future, the CG has been shown to be, indeed, a heterogeneous structure.

Because of peculiarities of its vascular irrigation (the pericallosal artery and its branches irrigate the medial portion of the frontal lobe and part of the medial portion of the parietal lobe), ischemic or hemorrhagic lesions circumscribed to the CG are rare. Small tumors or malformative lesions relatively restricted to the CG are also uncommon. These facts limit our ability to study CG function based on lesional observations.

Noninvasive neurophysiological studies provide only partial or inconclusive data because of the anatomical location of the CG (medial and distant from the cerebral surface, with significant portion of the CG buried in the depths of the pericallosal and cingulate sulci). This makes it difficult to define the ictal clinical manifestations of the CG as a symptomatogenic zone.

The objective of the present chapter is to describe the clinical characteristics of epileptic seizures most probably originating in the CG. As an introduction a brief review of the cytoarchitecture, connections and functions of the CG of humans and experimental animals will be presented.

Cytoarchiteture

Brodmann's cytoarchitectural map of the cerebral cortex has been used as the standard for human brain research. The CG is divided into anterior and posterior parts (Figure 40.1). The anterior part consists of the perigenual portion, areas 25 and 33, and of the midcingulate portion, areas 24 and 32. The posterior cingulate consists of the posterior cingulate cortex, areas 23 and 31, of the retrosplenial portion, areas 29 and 30, and the ectosplenial portion, area 26. Areas 29, 30, and 26 are narrow and located in the isthmus of the CG.[1]

More recent cytoarchitecture studies have confirmed that an important part of the CG cortex is buried in the depth of the sulci (Figure 40.1). The anterior cingulate cortex (ACC) is agranular, with a prominent Va layer. Not all the cortex of area 24 is exposed on the surface[2] and histological differences exist between the caudal and rostral parts of area 24, which is, therefore, subdivided into 24a, 24b, 24c, and 24d.[3] The main difference resides in the composition and thickness of layers Va and Vb.[3] Area 24c lies primarily within the ventral bank of the cingulate sulcus.[2] This area is called the cingulate motor cortex, since pyramidal Betz cells have been demonstrated in layer Va.[4] Compared with the Betz cells of the primary motor field, those of the cingulate area display numerous primitive traits.[5]

In non-human primates, in addition to cytoarchitectural differences there are differences in inputs. While the rostral portion of area 24 receives substantial input from the amygdala, the caudal portion receives a large component of parietal lobe afferents.[6]

The posterior CG consists of the posterior cingulate cortex (PCC), areas 23 and 31, and the retrosplenial and ectosplenial areas 29, 30, and 26. Areas 29, 30, and 26 are buried in the depths of the pericallosal sulcus. Area 23 is located in the caudal portion of the CG and extends into the caudal part of the cingulate sulcus before it arches to form the marginal sulcus. The PCC is characterized by granular layers II and IV,[2] except for area 30 whose layer IV is dysgranular.[7]

Area 23 is subdivided into 23a, 23b, 23c, and 23d as a function of the degree of differentiation of layer III and of the size and distribution of neurons of layers IV and Va.[3]

Connections

The cingulate cortex is considered to be part of the limbic system and is also a component of the Papez circuit. Outputs from the amygdala, septal area, entorhinal cortex, and hippocampus travel via the fornix to the mammillary bodies of the hypothalamus; from there via the mammillothalamic tract, to the anterior thalamic nucleus (anteroventral subdivision); and via the thalamocortical fiber system to the CG, and then back to the hippocampus via the cingulum and entorhinal areas. This closed circuit of connections was described by Papez[8] and became known as the Papez circuit.

Studies in rhesus monkeys using retrograde tracer horseradish peroxidase have shown that both the ACC and the PCC receive thalamic inputs. Although each area of the CG receives inputs from distinct thalamic nuclei, the anterior thalamic nucleus (anteromedial subdivision) sends afferent fibers to areas 25, 24, and 23, thus forming a certain connectional link between all cingulate areas.[9]

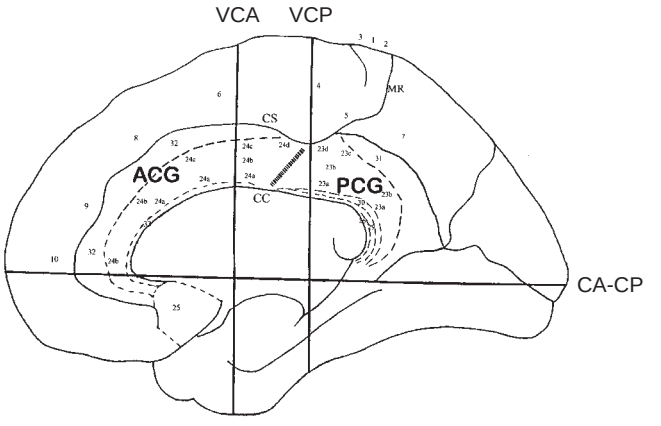

Figure 40.1 Cingulate gyrus cytoarchitectural areas. Areas 24, 25, 23, and 31 are located on the mesial surface. Small portions of areas 24 and 23 are buried in the depth of the cingulate sulci. Areas 32, 33, 26, 29, and 30 are buried in the depth of the cingulate and pericallosal sulcus (ACG = anterior cingulate gyrus; PCG = posterior cingulate gyrus; CC = corpus callosum; CS = cingulate sulcus, MR = marginal ramus)

The ACC and PCC also receive a large contingent of afferents from the frontal lobe, especially the dorsolateral and orbital areas, and also from the parietal lobe. Most of the frontal cortical afferents reach area 24, whereas area 23 preferentially receives inputs from the parietal lobe.[6] The ACC also receives afferents from the insula cortex and the PCC receives a small proportion of afferents from the occipital lobe, area 19.[6]

The CG also has extensive efferents connections. Studies on rhesus monkeys have shown that areas 23 and 24 have extensive and widespread projections to several regions of the cerebral cortex (Figure 40.2). Area 24 projects to the premotor region (areas 6 and 8), the orbito-frontal cortex (area 12), the rostral part of the inferior parietal lobe, the anterior insular cortex, the perirhinal cortex, and the laterobasal nucleus of the amygdala. Area 23, likewise, sends its connections to the dorsal prefrontal cortex (areas 9 and 10), the rostral orbital cortex (area 11), the parietotemporal cortex (posterior part of the inferior parietal lobule and the superior temporal sulcus), the parahippocampal gyrus, the retrosplenial region, and the presubiculum.[10]

The anterior cingulate cortex also sends projections to brainstem motor systems including the caudate, pontine, and red nuclei.[11,12]

Functions

Structural lesions, surgical ablations, or functional alterations due to electrical stimulation of the CG in animals and humans shed some light on the function of the CG. These studies have been complemented by microelectrode recordings, and positron emission tomography in experimental animals and human beings.

Changes in behavior can occur due to lesions in area 24, although in many of these reports on humans and experimental animals additional damage was also evident in the adjacent areas 6, 8, 9, 10, and 25 and in the corpus callosum.

In monkeys, ablation of area 24 was marked by increased restlessness, hyperactivity, loss of their previous apprehension to certain aspects of their environment, apparent loss of fear, increased

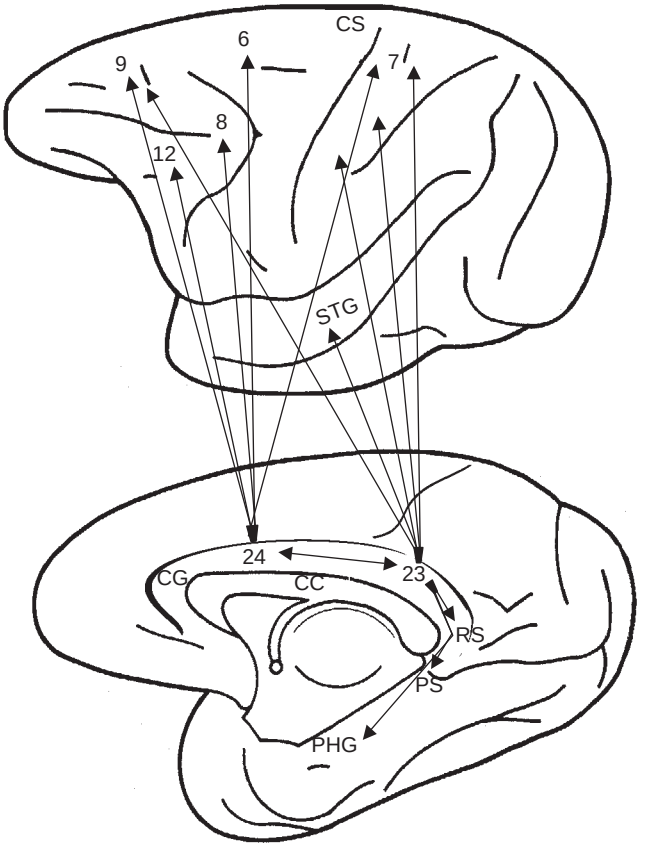

Figure 40.2 Cingulate gyrus simplified sketch showing efferent connections from areas 23 and 24 in the monkey's brain (CC = corpus callosum; CG = cingulate gyrus; PHG = parahippocampal gyrus; PS = presubiculum; RS = retrosplenial area; STG = superior temporal gyrus).

tameness, and reduction of aggression.[13] In animals with a longer survival time these changes tend to be reduced or to disappear.

Behavioral changes such as indifference, docility, inappropriate urination, severe lack of attention, lack of social restraint, heightened sexuality, bulimia, and aggressiveness have also been reported to occur in humans as a consequence of unilateral[14] or bilateral[15] lesions in the anterior portion of the CG.

Bilateral lesions of area 24 also cause the so-called anterior cingulate gyri syndrome which clinically manifests as apathy, akinesia, mutism, urinary incontinence, and indifference to pain.[16]

Structural lesions and studies of cortical stimulation have also correlated the anterior cingulate with autonomic phenomena such as piloerection,[13] changes in blood pressure, tachycardia, mydriasis, and increased respiration frequency.[17,18,19] The structural basis for involvement of area 25 in visceromotor activity is well known. Area 25 projects directly to the parasympathetic nucleus of the solitary tract,[20] dorsal motor nucleus of the vagus, and to the sympathetic thoracic intermediolateral cell column.[21]

The anterior cingulate is also involved in the emotional aspects of pain perception.[22,23]

The ability of the anterior cingulate to participate in or execute motor functions has been studied extensively. The presence of Betz cells in area 24 supports the hypothesis of the possible existence of a motor area in the CG. In experimental animals the lower bank of the anterior cingulate sulcus is involved in self-initiated movements.[24] There is also evidence

that areas 24c and 23c send inputs to the motor and supplementary motor cortices in a somatotopic distribution.[25]

Additionally, there are reports that cortical stimulation of the ACC evokes motor responses in man.[26–29] The nature of the responses obtained differ among the various studies, but include repetitive movements of the hands, fingers, and lips that can be classified as automatisms, tonic contractions involving the hands and arms, or an irresistible urge to grasp something.

The posterior CG probably integrates visual information recognized in the visual cortex and an emotion-related substrate is processed in the anterior cingulate.[30]

Electrical activity of PCC is detected during eye movements in several species while assessing large visual field patterns. The activity is linked to the position of the eye in the orbit and the direction and amplitude of saccadic eye movements.[31–33] Several observations have suggested that the PCC contributes to orientation of the animal in the environment and to spatial memory. Lesions of the posterior cingulate disrupt a rat's ability to swim to a hidden platform.[34] The observation of the deficits due to lesion of the retrosplenial region of rats has led to the assumption that the damage may disrupt the integration and transmission of both movement-related information and visuospatial information from cortex to hippocampal formation. The hypothesis is that the retrosplenial region is important not for memory of landmarks or other visuospatial cues, but rather the functional role of this region may be to purposefully organize the movements with respect to surrounding visual landmarks.[35]

Cingulate seizures

Overview

The semiologic characterization of epileptic seizures originating in the CG cortex is a challenge in epileptology. As mentioned before, the anatomical location of the CG makes neurophysiological studies with scalp electrodes difficult. Similar problems are encountered with invasive neurophysiological recordings. The presence of large caliber blood vessels on the medial surface of the brain and the fact that a considerable proportion of the cortex is located inside sulci make invasive evaluation of this area difficult.

Ideal cases for the study of ictal clinical manifestations would be small medial epileptogenic lesions practically limited to the CG. These cases are relatively rare and literature data are limited to case reports or relatively small series. Thus, the semiologic aspects of the epileptic seizures of this region are still poorly defined. Most cases in the literature do not provide direct evidence that the epileptogenic zone was in the CG or actually limited to the CG. The gold standard would be cases in which a resection of an epileptogenic zone limited to the CG renders the patient free. Such cases do not exist in the current literature. Therefore, the following review of the literature refers to cases in which the lesion was mainly in the CG, even if there was no direct proof that the seizures originated from the CG, i.e., patients were not necessarily seizure free after surgery and/or the surgery was not limited to the cingulated gyrus.

Although auras are considered rare,[36] autonomic symptoms such as tachycardia, mydriasis, and changes in respiratory frequency are considerate common.[37] Other descriptions are sensation of fear, dizziness,[37] and painful sensations.[38]

In general, reports in the literature tend to stress that seizures originating from the cingualte gyrus are frequent, brief, nocturnal and do not include significant preictal or postictal alterations.[36]

The ictal semiology that has been related to the anterior cingulate is relatively varied. Some ictal manifestations like complex automatisms, laughter, and altered level of attention or consciousness have been described more frequently.

Table 40.1 summarizes literature cases with seizures originating in the anterior portion of the cingulate, as confirmed by scalp video-EEG evaluation and/or invasive recording in lesional and non-lesional cases. Complex gestural movements,[36–40] laughter,[36,38,39,41] tonic contraction,[36] lapses of attention, blinking, and oroalimentary automatism[40] were the most common clinical manifestations.

For comparative purposes, on the basis of described data, we reclassified the seizures according to the semiological seizure classification (Table 40.1).[42] The most frequent types of epileptic seizures reported as originating from the anterior portion of the CG were bilateral asymmetric tonic seizures, gelastic seizures, hypermotor seizures, and complex motor seizures. In two cases the seizures were preceded by a somatosensory and autonomic aura respectively. In one case an autonomic seizure was documented (mydriasis).

Dialeptic seizures were reported in only one report. This patient by history had atonic and complex motor seizures, but dialeptic seizures were documented during evaluation by video-EEG.[40]

Stimulation with depth electrodes have shown that continuous movements may be elicited by electrical stimulation of the anterior region of the CG. These movements were classified as automatisms and primarily involved the fingers, hands, lips, and tongue. The movements were 'primitive' and simple such as touching, leaning, rubbing, stretching, or sucking. The movements were frequently integrated with more complex movements that were adapted to the situation and thus represent, as a whole, what the authors called 'types of behavior'.[19,26]

Cleveland clinic series

In an attempt to better define the semiology of seizures originating from the CG, we reviewed the Cleveland Clinic Epilepsy database. To analyze the semiology and the electroencephalographic findings of seizures originating from the CG, patients of any age range evaluated by video-EEG and with symptomatic focal epilepsy secondary to a single structural lesion identifiable by magnetic resonance and localized in the CG, anterior, or posterior region were selected. No attempt was made here to define if the observed ictal semiology was due to direct activation of the CG (symptomatogenic zone in the CG) or due to spread an activation of extra-CG symptomatogenic areas such as, for example, the adjacent supplementary sensory-motor area.

Only cases in which at least 90% of the lesion was located in the CG were included. Patients with extensive lesions with a small proportion in the CG or with extensive lesions widely involving the CG and adjacent regions as also non-lesional cases were excluded.

Of patients evaluated between 1990 and 2005 who had received a diagnosis or a diagnosis of probable cingulate epilepsy, 76 were selected. The clinical data and the

Table 40.1 Literature studies

Study	Type	Sex Age at seizure onset	1.Description semiology 2. Video recording	Duration Frequency	Semiological Seizure Classification	Surface Evaluation Ictal EEG	MRI	Invasive Evaluation Ictal EEG	Procedure Evolution Pathology
Chassagnon *et al*., 2003[38]	Case report	Male 4 yrs	1. Painful sensation of tightness in the right shoulder, raising of the right arm, bilateral tonic posturing of the arms, swinging movements of trunk and laughter. Consciousness preserved. 2. Bilateral tonic posturing of upper limb and swinging-twisting movements of trunk, laughter preceded by brief choreoathetosic movements of the right hand. Consciousness preserved.	10–30 sec 30/day	1. Somatosensory aura (right, arm) → Bilateral Asymmetric Tonic seizure → Hypermotor seizure 2. Bilateral Asymmetric Tonic seizure → Hypermotor seizure → Gelastic seizure	Regional over the precentral regions and vertex (slight predominance on the left hemisphere)	Normal	Depth electrodes Ictal recording at SSMA contacts. Cortical stimulation at MCG evoked typical seizures	Stereotactic monopolar electric radiofrequency lesions over contacts of SSMA and MCG Seizure free:follow-up 27 mo
McConachie & King, 1997[39]	Case report	Male 4 yrs	1. Sudden inappropriate laughter and kicking movements of the lower limbs. 2. Screaming, falling to the ground, holding his right arm in the air, thrashing his other limbs and wetting himself.	<30 sec most over 100/day	1. Gelastic seizure →Hypermotor seizure 2. Hypermotor seizure	Regional, right frontocentral	MCD, right CG and medial frontal lobe	–	–
Devinsky *et al*., 1995[36]	Review and 2 cases description	Male 28yrs	Laughter, repetition of the phrase 'Oh my God', small repetitive neck and trunk flexion, and bilateral arm extension, repeated touching of the forehead and mouth. Amnestic for the seizures	<10 sec 10–20/ day	Gelastic seizure → Bilateral Asymmetric Tonic seizure → Complex motor seizure	Regional, bifrontal	Mild/ diffuse cortical atrophy	Depth and subdural strips Ictal recording at right ACG	Resection right ACG Seizures have resolved over the first year of follow- up Low grade glioma
		Male 29yrs	Grotesque facial contortions (tongue thrusting, a strangulated yell), neck and trunk flexion, bilateral arm and leg extension with side-to-side thrashing and occasional progression to a generalized tonic-clonic seizure Consciousness preserved	<1 min 10–20/ night	Hypermotor seizure → Tonic clonic seizure (generalized)	Regional, bifrontal	Left parietal cryptic AVM	Depth and subdural strips Ictal recording at right ACG	Resection right ACG and anterior corpus callosotomy More than 90% reduction in seizures

Continued

Table 40.1 cont'd Literature studies

Study	Type	Sex Age at seizure onset	1.Description semiology 2. Video recording	Duration Frequency	Semiological Seizure Classification	Surface Evaluation Ictal EEG	MRI	Invasive Evaluation Ictal EEG	Procedure Evolution Pathology
Arroyo *et al.*, 1993[41]	Out of 3 cases with gelastic seizure, one with lesion in the mesial	Female 15 yrs	1. Speech arrest, grimacing and laughing or crying, sometimes associated with incontinence Consciousness preserved 2. Speech arrest, grimacing and laughing or crying. Some evolved to clonic seizure with right arm, mouth and head version to the right	15–35 sec 10–20/day	1. Gelastic seizure 2. Gelastic seizure → Clonic seizure (right arm, mouth) → Versive seizure (right)	3 types of ictal recording - EMG artifact → Regional, left posterior temporal - Regional, left frontotemporal - Regional, bitemporal	CA, left superior parasagital, frontal region	Subdural grid and strips Ictal recording over the left ACG	Resection mesial frontal lesion and region of ictal onset at the ACG. Seizure free. Follow-up 16 mo. One typical seizure 12 mo after surgery when medication was stopped CA and gliosis
Bancaud & Talairach, 1992[37]	Series of 16 cases, just one complete description	Female 19 mo	1. Aura: extreme fear, malaise, rapid frequency of heart rate felt as strong chest palpitations, mydriasis, intense pallor or the same aura followed by leaning head on her chest, arms bent, whimpering, calling her mother, giving the impression of fright, becoming agitated, rubbing the epigastric region with her right hand Consciousness returned in less than 30 sec. 2. (scalp evaluation) Seizure 1 Sensation of heart beating, stretched out on the examining bed, raised herself, folded her arms over her face, clonic jerks on the left distal upper extremity and left side of the face, frightened, whimpering, facial pallor, rubefaction, rubbed her left leg with her right hand and manifested chewing motions and salivation. A return of consciousness was delayed	1–2min 1–4/day 1–2 min 1–4/day	1. Physic Aura → Autonomic seizure Physic Aura → Motor seizure → Complex motor seizure 2. (scalp evaluation) Seizure 1: Autonomic Aura → Complex motor seizure → Clonic seizure (left hand and face) Seizure 2: Motor seizure → Clonic seizure (generalized) → ? Versive seizure (right) or? paradoxical version 3. (invasive evaluation) Autonomic seizure → Hypermotor seizure	Lateralized, right hemisphere	Normal	Ictal recording over the genu of the right CG	Resection of anterior portion of the medial surface of the right frontal extending as far as possible toward the posterior portion of the orbital surface and around the genu of the CG. Seizure free Follow-up 5 year

			Seizure 2. Sagged and lay down, bilateral clonic jerks with secondary deviation of the head toward the right 3. (invasive evaluation): Pupils dilated and eyes deviated to the left and upwards. Uncoordiante violent and agitated movements of te lower half of the body and trunk accompanied sign of language and gestures of intense fright. Several unsystematized and belated buccal movements.						
Levin & Duchowny, 1991[40]	Case report	Female 2.5 yrs	1.Brief atonic seizures, gradually diminished over several months and then started with 2.lapses of attention with stereotyped automatisms including humming, lip smacking, bruxism, and hair fixing 3.Behavioral arrest, associated with eye blinking and oroalimentary automatism	up to 40 sec 10–15/day 2. 10–20 sec	1.Atonic seizure 2. Complex motor seizure 3. Dialeptic seizure	Generalized, maximum right frontal	–	Depth electrode Discharges at right ACG	Resection of right ACG. Seizure free follow-up 15 mo.

ACG = anterior cingulate gyrus, AVM = arteriovenous malformation, CA = cavernous angioma, CG = cingulate gyrus, MCD =malformation of cortical development, MCG = midcingulate gyrus, SSMA = somatosensory supplementary motor area

neuroimaging exams were reviewed. Only eight of 76 patients satisfied the inclusion criteria listed above.

To correlate the semiologic data with the location of the lesion, sagittal sections of MRI were selected and the best section for the visualization of the anterior and posterior commissures and of the structural lesion was chosen for each individual. The horizontal plane, anterior commissure-posterior commissure line (AC-PC) and the vertical anterior commissure line (VAC) and the vertical posterior commissure line (VPC) of the vertical plane of the Talairach and Tournoux[43] coordinates were traced.

The CG was thus divided into three portions: anterior, middle, and posterior. The anterior portion is located rostral to the VAC line, the middle portion is caudal in relation to the VAC line and rostral in relation to the VPC line, and finally the posterior portion is caudal in relation to the VPC line.

The lesion was then carefully identified on the three magnetic resonance planes – sagittal, coronal and axial – and their rostrocaudal and ventrodorsal extension was represented on a map on the sagittal plane.

Considering the cytoarchitectural data, area 24 occupies a large part of the anterior and middle portion (Figure 40.1), so the anterior and middle portions of the CG were considered to be anterior cingulate.

According to the location of the structural lesion, the cases were divided into anterior CG lesion group (ACGL-group) when the lesions were located in the anterior cingulate (the entire extension rostral to the VPC line) and posterior CG lesion group (PCGL-group) when the lesions were located in the posterior cingulate (caudal portion in relation to the VPC line).

Clinical data such as age at the onset of seizures, semiologic description provided by the patients and their relatives and complaints of behavioral changes, seizures recorded during video-EEG monitoring, and interictal and ictal recordings were reviewed. Wieser *et al.*'s classification of outcome following epilepsy surgery was used for the classification of surgical outcome.[44]

Demographic data

Of the eight patients, six were males and two were females. Age ranged from 8–52 years, with a mean of 23.7 years. Five of the eight patients were 14 years old or younger. Age at the onset of seizures ranged from 7–44 years, with a mean of 18.2 years. Three patients had a recent history of onset of seizures (<1 year) and the interval between the onset of seizures and evaluation ranged from 0–22 years, with a mean of 4.7 years (Table 40.2).

All patients had a normal neurological examination and seven had normal intelligence; only one was in the mentally deficient range.

Four patients (1, 2, 3, and 4) had anterior CG lesions (ACGL-group), and four (5, 6, 7, and 8) had posterior CG lesions (PCGL-group) (Figure 40.3).

The results of the anatomopathological analysis of the seven patients who had surgery were low grade astrocytoma in five cases, reactive astrocytosis in one case, and ganglioglioma in one case.

Four of the eight patients reported mood changes, depression, and reduced school performance. Of these four, only one belonged to the ACGL-group, while the remaining ones belonged to the PCGL-group. The data obtained by psychiatric evaluation or using the back depression inventory are presented in Table 40.2. The patient from the ACGL-group had adjustment disorder with depressed mood. Only one of the three patients from the PCGL-group had a more severe psychiatric disorder (major depressive episodes and reduced school performance). The remaining two patients of the PCGL-group had affective distress and emotional distress with mild to moderate feeling of depression, respectively.

Seizure characteristics

The ictal semiology data obtained from the clinical history were provided by patients and relatives and are listed in Table 40.2.

All patients presented frequent – daily or weekly – seizures. Only patient 1 (ACGL-group) had a lower frequency of seizures – one to four seizures per month.

By history, the seizures' duration varied from seconds to minutes in both groups. The most prolonged seizures reported lasted about 2–3 minutes, namely patients 1 and 2 from the ACGL-group and patients 5 and 8 from the PCGL-group. Shorter seizures lasting 10–20 seconds occurred in patient 3 from the ACGL-group and patient 6 from the PCGL-group

Auras

Five patients reported auras, two in the ACGL-group and three in the PCGL-group. The two patients in the ACGL-group presented clinical manifestation lateralized contralateral to the structural lesion. One patient described pins and needles in the contralateral arm and the other complained of a heavy contralateral leg. The latter also reported a nonspecific complaint described as dizziness.

The three patients in the PCGL-group who reported auras described them as tingling in both legs, and dizziness (patient 5), depersonalization feelings (patient 7) and abdominal sensations (patient 8).

Semiologic analysis of the seizures by video-EEG examination

Semiological seizure classification

When auras were excluded and the initial presentation of the epileptic seizures was evaluated as documented in the video-EEG, the following types of seizures were observed: ACGL-group: complex motor seizures, hypermotor seizures and bilateral asymmetric tonic seizures; PCGL-group: automotor seizures and dialeptic seizuress (Table 40.3).

Analysis of the seizure evolution (Table 40.3) shows that all the patients, except for patient 6, showed a changing seizure manifestation. Regarding the motor manifestations, we shall first consider the initial pattern of the seizure and then the seizure evolution.

Motor manifestations

ACGL-group

All four patients in the ACGL-group exhibited motor manifestations. In two patients the seizures were characterized by relatively complex movements that imitated natural movements involving different parts of the body (patients 1 and 2). In patient 2 the movements were more abrupt and ample and

Table 40.2 Cleveland clinic series: clinical data and seizure description by history, MRI, and anatomopathological findings

Anterior/Midcingulate Lesions									
Patient	**Age (years) Sex**	**Seizure onset age (years)**	**Seizures Descriptions Seizure (s) Classification (s)**	**Seizure Frequency**	**Seizure Duration**	**Neurological Examination IQ Full Scale**	**Psychological, Psychiatric Data**	**MRI**	**Surgical Anatomopathology**
1	49 M	44	A. First episode was a nocturnal generalized motor seizure. Four additional similar episodes throughout 3 years. He was amnesic for those events. B. No aura. Seizure starts with mumbling simple words like 'thank you' or 'OK' → stare → unresponsiveness → lip-smacking automatism Seizures Classifications: A. Motor seizure (generalized) B. Dialeptic seizure	A. 1–2/ year B. 1–4/ month	A.1–2 min B.2–3 min	N 68	Adjustment disorder with depressed mood	Left anterior cingulate lesion, immediately anterior to the genu of the corpus callosum. Approximately 1 cm in diameter	Low grade astrocytoma
2	13 M	13	A. Seizures while awake: pins and needles sensation in the right arm → stiffening right arm without loss of consciousness B. Seizures while asleep: arousal → right arm pins and needles sensation → loss ofconsciousness → sits up in his bed → twists around in bed, makes forced vocalization noises → bangs his bed1 or 2 times with his right arm Seizure Classifications: A. Somatosensory aura (right, arm) → Tonic seizure (right, arm) B. Somatosensory aura (right, arm) → Hypermotor seizure	A. 2–3/ week (while) awake) B. 1–2/ night (during sleep)	A, B. 1–2 min. 92	N 92	–	Left midcingulate lesion. Approximately 3 cm in extension	Low grade astrocytoma
3	10 M	10	The first and single episode was described as a generalized motor seizure, and 2 months later the recurrent seizures started: Aura described as dizziness and right leg heavy → right leg stiffening and falling to the right. Consciousness preserved during episodes. Seizure Classification: A. Somatosensory aura (right leg) → Tonicseizure (right leg)	1–3/week	10–15 sec	N 99	–	Left midcingulate lesion. Approximately 2.2 cm in extension	Low grade astrocytoma

Continued

Table 40.2 Cont'd

Patient	Age (years) Sex	Seizure onset age (years)	Seizures Descriptions Seizure (s) Classification (s)	Seizure Frequency	Seizure Duration	Neurological Examination IQ Full Scale	Psychological, Psychiatric Data	MRI	Surgical Anatomopathology
4	8 M	7	A. Episodes of staring for 10–20 seconds and inability to respond and move but preserved awareness B. The staring episode is followed by a slow fall to the ground followed by clonic head jerks to the right. Some seizures: postical left arm paralysis Seizure Classification A. Akinetic seizure B. Akinetic seizure → Atonic seizure → Clonic seizure (right, head) Lateralizing sign: postictal Todd's paralysis (left arm and hand) Posterior Cingulate Lesion	A. 10/day B. 5–10/ month	A. 10–20 sec B. 30 sec	N 108	-	Right midcingulate lesion 2 cm in extension	Low grade astrocytoma
5	12 M	10	A. Aura: tingling sensation in both legs and dizziness B. Aura → silly grin → decreased responsiveness → bilateral hand automatisms and incoherent speech. At times he walks during a seizure and slumps over to the floor. Seizure Classifications: A. Somatosensory aura (legs) B. Somatosensory aura (legs) → Automotor seizure	A, B: 2–6/ day	1–2 min	N 100	Major depressive episodes. Parents state that he has had significant disabilities in school	Left posterior cingulate lesion 4.6 cm in its largest extension Extending posterior to the occipital lobe and superior	Low grade astrocytoma
6	52 M	30	The first and single episode was a generalized motor seizure. Recurrent seizures: no aura, change in expression → pupils dilate → looks around → can say 'how are you' → apparently remains responsive following commands but does not respond and he is amnestic for most of these events	1–3/day	B. 10 -20 sec	N Not tested	–	Right posterior cingulate lesion 3.5 cm. Extending superior to the supramarginal sulcus	No surgery

			Seizure Classification: Dialeptic seizure						
			Anterior/Midcingulate Lesions						
7	32 F	18	A. During sleep, movements of the whole body for few seconds. B Awake: Feeling of depersonalization → cessation of activity and stare → confusion Seizure Classification: A. Motor seizure (generalized) B. Psychic Aura → Dialeptic seizure	A. 1–2/year B. 1–4/week to 1/day	A. Not precisely determined < 5 min B. 30–60 sec	N 97	** Significant affective distress	Left posterior cingulate Approximately 3 cm in diameter	Gray and white matter with mild reactive astrocytosis. Tissue adjacent to a neoplasm cannot be excluded
8	14 F	14	Aura: weird sensation in the epigastric region lasting 30 seconds → confusion 'she does not know where she is' → she covers her eyes with both hands, is able to hear but can answer only in monosyllables or may say 'hold on' or 'I am having a spell'. She appears to be partially unresponsive and she has no automatisms or tonic/dystonic posturing Seizure Classification: Abdominal Aura → Dialeptic seizure	1–2 per day	60–90 sec	Normal Not tested	**Significant emotional distress, mild to moderate feeling of depression	Right posterior cingulate lesion Approximately 2.5 cm diameter	Ganglioglioma

A and B means different seizures types, N = normal neurological examination, * Physical examination revealed: multiple subcutaneous neurofibromas at skin, ** Beck depression inventory.

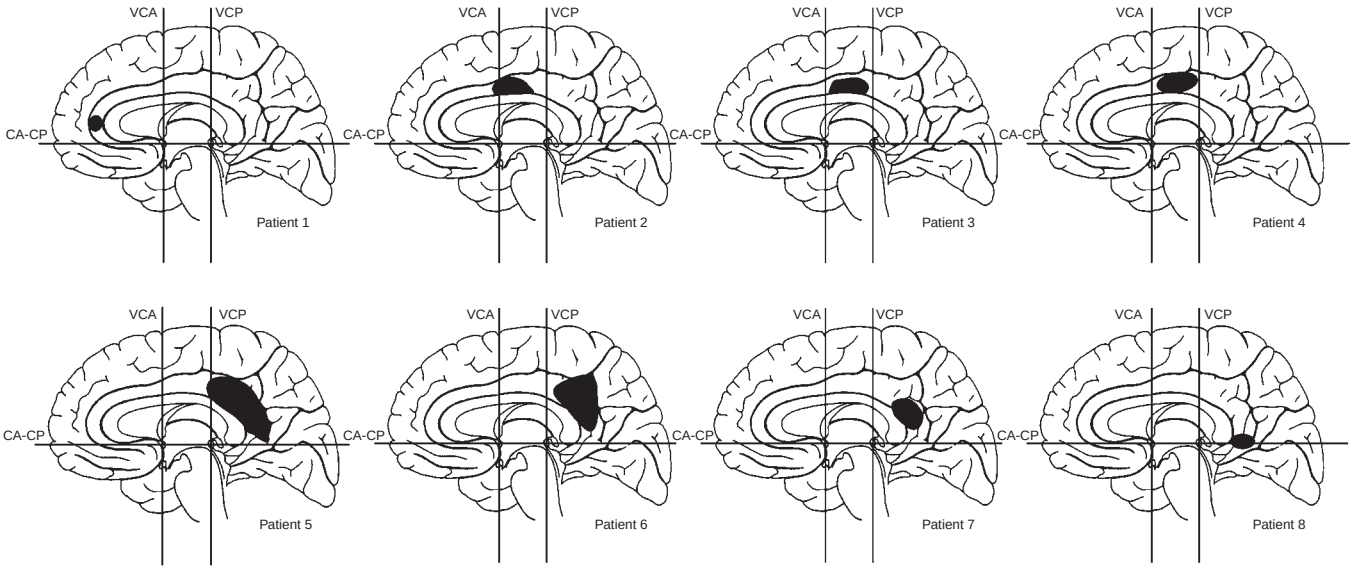

Figure 40.3 Schematic representation of cingulate gyrus lesions in the sagital plane.

predominantly involved the trunk. The initial seizure of patient 1 was classified as complex motor seizure and that of patient 2 as hypermotor seizure.

The motor manifestations of the other two patients were characterized by bilateral and asymmetric tonic contractions mainly involving the upper limbs, i.e., bilateral asymmetric tonic seizure.

The initial seizures progressed to clonic or focal tonic seizures contralateral to the structural lesion or to seizures with complex automatisms, i.e., complex motor seizures. In patient 1 the initial motor seizure evolved into a predominantly unresponsive phase (dialeptic seizure). In patient 2 the initial hypermotor seizure progressed to a focal tonic seizure involving the contralateral arm and the leg. Patient 3 progressed from a bilateral asymmetric tonic seizure to a contralateral clonic seizure involving the shoulder and the arm or the arm and the leg. Patient 4 progressed from a bilateral asymmetric tonic to complex motor seizure manifesting as complex movements of lower limbs, trunk and head.

Patients 2 and 3 progressed to secondary generalization, which was tonic-clonic in both cases. Patient 2 presented relatively asymmetric clonic movements during the phase of clonic seizure. While the side contralateral to the lesion was more tonic, the ipsilateral half of the body, and mainly the upper limb, presented more evident clonic contractions.

PCGL-group

Of the four patients in this group, only three had seizures that were documented by video-EEG. Two of them had motor manifestations during the initial phase of the seizure, characterized by automatisms of the distal segments of the body, particularly the fingers and hands (patients 5 and 7). These automatisms were characteristic of automotor seizures.

In patient 6, the seizure was characterized by impairment of consciousness, with minimal motor manifestations, i.e., a dialeptic seizure.

No seizure was recorded for patient 8 but the clinical history revealed that his seizures consisted predominantly of impairment of consciousness, without clear motor manifestations (dialeptic seizure).

The initial automotor or dialeptic seizures of this group progressed to contralateral focal clonic or versive seizures.

Patient 5 progressed from automotor seizure to focal clonic seizure in four of eight recorded. automotor seizures. Of these four seizures, three manifested with clonic jerks involving the proximal portion of the contralateral upper limb, shoulder, and trunk. The upper limb exhibited clonic contractions simultaneous with elevation and abduction movements. In one seizure, the clonic contractions involved the trunk bilaterally and the proximal region of the arm ipsilateral to the side of lesion.

Patient 7 progressed from automotor seizures to contralateral versive seizure.

Two of the three patients in this group presented secondary generalization.

Patient 5 presented a secondarily generalized tonic-clonic seizure. The tonic seizure started in the arm contralateral to the side of lesion and this arm remained extended. The clonic phase also started in the contralateral arm and became generalized but asymmetric, predominating in the body half ipsilateral to the lesion. At the end of the generalized seizure, this patient presented a clonic seizure in the arm ipsilateral to the side of lesion (paradoxical clonic seizure) which lasted approximately 5 seconds.

Other motor manifestations

Other motor manifestations associated with the main seizure type described above were also observed. These motor manifestations consisted of head deviation ipsilateral to the side of lesion during a generalized clonic seizure (patient 3) or during an automotor seizure (patients 5, 7), grimacing during a hypermotor seizure and dialeptic seizure (patients 2, 6), looking around during a hypermotor seizure and dialeptic seizure (patients 2, 6), blinking during a bilateral asymmetric tonic seizure (patient 4), and grinning (patient 5) during an automotor seizure.

Automatisms

ACGL-group

The automatisms of the patients in this group were predominantly characterized by complex movements involving the

Table 40.3 Video-EEG: semiologic and electrographic findings

Patient	Background	Non-Epileptiform Abnormalities	Epileptiform Abnormalities (%) Frequency (*F*)	Clinical Symptoms	Seizures duration	Seizure (*s*) classification (*s*)	A Range of EEG versus Clinical Onset B. EEG Description C. EEG Classification
1	Slow	IS, generalized	SW, regional, left temporal (85%) F:1 every 30–40 minutes. SW, regional, right temporal (15%) F: 1 every 2 hours.	2 seizures both recorded out of sleep. Awakening → Complex motor seizure (sudden generalized jerk → intermittent body wiggling → sighing → bilateral hand and leg automatism (open hands, palm of the left hand over the right and alternating this position with interlaced hands; wide leg movements as if straightening the sheet that covers him) → brief episode of lip-smacking) Dialeptic seizure (motionless and fixed gaze for about one minute). Tachycardia during the seizure (HR=120, basal HR 60–70). Total amnesia of events. Postictal confusion for 20 minutes, with automatisms, scratching head and genitals.	70 sec	Complex motor seizure → Dialeptic seizure	A. 0 to (+) 2 seconds B. Arousal → Diffuse EMG intermixed with irregular theta 4–6 Hz → Diffuse regular delta (2 Hz) activity C. Non-localizable
2	N	–	–	3 seizures recorded out of sleep. A. Suddenly awakened → Hypermotor seizure (turned around → looked around and looked scared → flexed the trunk → grimace → made noises (grunts) → tremor of the right hand → sat up in bed → moved his trunk → grabbed the bed rails) (2 seizures). No LOC in 2 seizures. No postictal confusion. B. A → Tonic seizure (right arm, right leg) → Tonic seizure (generalized: bilateral upper limbs flexed, right leg extended, face deviation to the left, eyes to the right) → Clonic seizure (generalized, but asymmetric. Clonic jerks more marked in the left arm) (1 seizure). LOC no postictal confusion.	A. 25 sec B. 90 sec	A. Hypermotor seizure B. Hypermotor seizure → Tonic seizure (right arm, leg) → Tonic seizure (generalized) → Clonic seizure (generalized)	A. 0 to (+) 21 seconds B. Ictal EEG was somewhat obscured by EMG. Delta activity in the bilateral centroparietal region with maximum on the left (C3-P3) C. Regional, left centroparietal
3	N	–	SPK, regional, vertex (100%) F: 3 in total	4 seizures recorded, all out of sleep A. Arousal from sleep → Bilateral asymmetric tonic seizure (isolated bilateral shoulder myoclonic jerk, he looked uncomfortable, grimaced, bilateral and asymmetric tonic contraction of upper extremities: right arm extended, left slightly flexed and with internal rotation movement, raised his shoulder and head with eyes deviation to the left, moaning) (2 seizures). No LOC. No postictal confusion	A. 30sec B. 90sec	A. Bilateral asymmetric tonic seizure B. Bilateral asymmetric tonic seizure → Clonic seizure (right, shoulder, arm, leg) → Tonic seizure (generalized) → Clonic seizure (generalized)	A. (–) 4 to (+) 14 seconds.. B. Electrodecremental pattern lasting 4 seconds followed by a 4–5 Hz theta activity intermixed with delta at frontovertex region (Fz-Cz) C. Regional, midline frontal and vertex

Continued

Table 40.3 Cont'd

Patient	Background	Non-Epileptiform Abnormalities	Epileptiform Abnormalities (%) Frequency (*F*)	Clinical Symptoms	Seizures duration	Seizure (*s*) classification (*s*)	A Range of EEG versus Clinical Onset B. EEG Description C. EEG Classification
				B. A → Clonic seizure (right arm and shoulder in one seizure and right arm and leg in the other) → Tonic seizure (generalized: turned the body to the left, left arm extended, right arm elevated) → Clonic seizure (generalized: clonic jerks more marked in the lower limbs, head to the left) (2 seizures). LOC			
4	N	IS, generalized, maximum posterior regions IS, lateralized, right hemisphere ST, regional, right frontocentral	–	4 seizures recorded out of sleep. Awoke → eyes opened → bilateral asymmetric tonic seizure (tonic contraction, right arm elevated, left arm elevated with elbow flexed, blinking, moaning) → Complex motor seizure (tongue protrusion, restless movements of the legs, tried to sit up, balanced his head) not responding during the seizure. LOC, immediately after the seizure he was reponsive and went back to sleep quickly Seizure 4: Postictal left arm and hand weakness	40 sec	Bilateral asymmetric tonic seizure → Complex motor seizure Lateralizing sign: postictal Todd's paralysis (left, arm, hand)	A. (–) 1.9 to (+) 1.6 seconds. B. High voltage slowing with a 4–6 Hz rhythm for 1–4 seconds, followed by high voltage (1–3 Hz) rhythmic delta activity that was generalized but maximum over midline frontal, vertex, parietal. C. Non localizable
5	N	IS, regional, left temporal	SW, regional, left temporal (100%) F: 1 every 3 min during sleep	16 seizures recorded A. Aura described as dizziness and tingling and numbness in both legs (8 recorded) B. A → Automotor seizure (grinning, sighing, decreased responsiveness or unresponsiveness, bilateral hand automatism (mainly involving the hands, grabbed closest objects, rubbed the sheet with the palm of the hand moved and turned the identification bracelet and rubbed rubbed the suprapubic region), head turned (non-versive) to the left (4 seizures). LOC. No postictal confusion. C. A→B→ Clonic seizure (right arm with elevation, abduction and clonic jerks no right shoulder including superior portion of the trunk) (3 seizures). In one seizure the initial clonic manifestation involving the right shoulder and trunk was followed by flexion of the left leg with some clonic shaking. LOC.	A. Hard to define precisely the duration B. 70 sec D. 80 sec E. 85 sec c	A. Somatosensory aura B. Somatosensory aura → Automotor seizure (LOC) C. Somatosensory aura → Automotor seizure (LOC) → Clonic seizure (right, shoulder, trunk) D. Automotor seizure (LOC) → Clonic seizure (trunk) → Tonic seizure (generalized) → Clonic seizure (generalized)	A. (–) 26 to (+) 10 seconds B. Rhythmic sharp waves in the parietal-vertex region, maximum at Pz electrode, lateralized slightly toward the right side. These evolved to high amplitude sharp waves, intermixed with delta activity over the centroparietal region, maximum in the left superior parietal region (electrodes, P3, P1). C. Regional, midline parietal-vertex

				D. B → Clonic seizure (head deviating to the left, trunk with clonic contractions apparently more marked on the left, left leg flexed) → Tonic seizure (left arm extended, right arm and head flexed to the left) → Clonic seizure (generalized, but with more marked clonic contractions on the left. (1 seizure). LOC			
6	N	–	SPK, regional, vertex (100%) F: max 2 per 10 sec during sleep	9 seizures recorded, all out of wakefulness. Dialeptic seizure → minor change in facial expression (as if he were absent minded), grimaced, looked around, unresponsive for a very brief period and sniffed frequently. He had total amnesia of events, but no postictal confusion.	25 sec	Dialeptic Seizure	A. (–) 3.4 to (+) 14 Seconds B. Paroxysmal fast activity in the right sphenoidal electrode for 2–4 seconds which evolved to a more widespread theta activity maximum Sp2. C. Regional, right temporal
7	N	IRS, regional, left temporal	SPK, regional, left temporal (100%) F: 0–1 per page	2 seizures recorded, both upon awakening Automotor seizure (the patient appeared confused → he tried to sit up in bed → left hand automatism: rubs the sheet between his thumb, index and middle finger) → Right versive seizure (vocalization, right version, left arm extension) → Tonic seizure (generalized: upper extremities extended, left leg flexed, evolving to bilateral leg extension) → Clonic seizure (clonic contractions started in the right arm and became generalized but asymmetrical,more marked on the left) → Clonic seizure (left arm) LOC.	85 sec	Automotor Seizure (LOC) → Versive Seizure (right) → Tonic seizure (generalized) → Clonic seizure (generalized) → Clonic seizure (left arm)	A. 0 – (–) 6.2 seconds B. Lateralized left rhythmic theta (4–5 Hz) activity, which spread to involve the right hemisphere in approximately 5–6 seconds and finally evolved to rhythmic slow 3–4 Hz generalized
8	N	IS, regional, right temporal	SW, regional, right temporal	No seizures recorded		Dialeptic seizure (by historical)	C. Lateralized left

HR= heart rate, IRS = intermittent rhythmic slow, IS = intermittent slow, LOC= loss of consciousness, SPK= spike, ST= sharp transient, SW = sharp wave.

upper and lower limbs and the trunk. In patient 1 the automatisms involved the hands, head, trunk, and legs. The hands remained open with the palmar surface of the left hand on the dorsal surface of the right hand, with the fingers interlacing intermittently. Under the sheet, the legs exhibited ample and alternating movements at times with the right leg and at times with the left leg. He also showed body and head wiggling and lip-smacking. The automatisms of patient 2 were characteristic of hypermotor seizures and involved the trunk (he sat up in bed, flexed his trunk and alternately turned it to the right and to the left) and upper limbs (he grabbed the bed rails). In addition, he also exhibited a repetitive tremor-like movement of the right hand. Patient 4 presented tongue protrusion and wide movements of the lower limbs and trunk and balanced his head, alternately turning it to the right and to the left.

PCGL-group

The automatisms of this group were characterized by more distal movements predominantly involving the hands. Patient 5 presented automatisms involving the hands bilaterally. The most frequent was smoothing the sheet that covered him with his open hand. The automatisms were also directed at nearby objects; for example, the patient handled the bracelet on his left hand while his left hand showed opening and closing movements. He also had scratching of the suprapubic region. Patient 6 sniffed several times during the seizure. In both seizures of patient 7 the automatisms involved the hand ipsilateral to the side of lesion. Holding the sheet between his thumb and fingers he made movements by rubbing the thumb and fingers together.

Vocalization

Excluding the vocalization typical of the beginning of secondary generalized seizures, only patients in the ACGL-group presented ictal vocalization. Patient 2 grunted and patients 3 and 4 moaned.

Facial expression

Changes in facial expression were more marked in patients 2 and 3 in the ACGL-group, who appeared to be scared. Patient 6 (PCGL-group) showed a discrete change in facial expression, looking more still and barely expressive.

Level of consciousness

Excluding the auras, in the ACGL-group, one patient presented total amnesia of all his seizures, two patients could remember some motor manifestations during the seizures, and one patient was very sleepy and poorly responsive after seizures recorded by video-EEG, although by history this patient was aware during his motor manifestations. In the PCGL-group, out of the three patients whose seizures were recorded, two had loss of consciousness and one had total amnesia of seizures.

Autonomic phenomena

Patient 1 presented tachycardia, with his basal heart rate of 60 reaching 120 during the seizure. On the basis of history data, patient 6 had mydriasis, which was not documented during the video-EEG.

Duration of seizures

In the ACGL-group the seizures without secondary generalization lasted 30–70 seconds, while those with secondary generalization lasted on average 90 seconds. In the PCGL-group, the duration of seizures without generalization ranged from 25–80 seconds, while the duration of seizures with secondary generalization lasted about 85 seconds. Patient 3 only presented seizures with secondary generalization which lasted on average 85 seconds.

Postictal manifestations

Except for the seizures with secondary generalization, one patient in the ACGL-group presented a prolonged period of postictal confusion lasting as long as 20 minutes and another presented Todd paralysis involving the leg and arm contralateral to side of the lesion.

Lateralizing signs

Lateralizing signs were frequent both in the ACGL-group and in the PCGL-group. In five of the eight patients, it was possible to infer the side of the lesion on the basis of the clinical characteristics of the seizures.

Of the four patients in the ACGL-group, two had focal tonic or clonic seizures involving the arm, leg, or shoulder contralateral to the side of structural lesion. One patient presented Todd paralysis involving the arm and leg contralateral to the lesion. On the basis of clinical history, in this group the auras were unilateral, involving the arm or leg also contralateral to the side of lesion.

Of the four patients in the PCGL-group, one presented a focal clonic seizure contralateral to the lesion (shoulder and trunk) and one presented a versive seizure preceding secondary generalization, also contralateral to the side of lesion, and a paradoxical clonic seizure at the end of a seizure with secondary generalization.

Relation of the seizures to the wakefulness-sleep cycle

All patients in the ACGL-group had seizures during sleep.

All the three patients in the PCGL-group with recorded seizures had seizures while awake, although one seizure occurred shortly after the awakening.

Eletroencephalogaphic recording

Interictal epileptiform findings

Interictal epileptiform abnormalities were recorded in six of the eight cases (75%). Among these six patients, the epileptiform discharges were exclusively ipsilateral to the side of lesion in three, independent bilateral in one but with a marked predominance (85%) also ipsilateral to the side of lesion, and on the vertex region in two (Table 40.3).

Among the ACGL-group, only two patients showed epileptiform discharge, one regional temporal (bilateral, but mainly ipsilateral to the side of lesion) and one regional on the vertex region.

All patients in the PCGL-group showed interictal epileptiform discharges, three regional on the temporal region (all of them ipsilateral to the side of lesion) and one regional at vertex.

Ictal findings

Among the seven patients with seizure recordings, the ictal EEG was regional in four, lateralized in one and non-localizable in two (Table 40.3).

Among the seven cases with seizure recordings, the ictal EEG would predict correctly the side of lesion in only three patients.

Regarding location, the ictal EEG was on the fronto-vertex-parietal areas with or without clues for lateralization also in three of seven cases (42.8%). In the remaining four cases, the ictal recording was non-localizable in two, lateralized and ipsilateral to the side of lesion in one and regional temporal and also ipsilateral to the lesion in the other.

Although the number of patients was small, we observed that there seemed to be a greater difficulty in lateralization in the ACGL-group. Only one of the four patients presented an ictal recording over the centroparietal region with lateralizing data. In another patient the recording was over the midline with no evidence for lateralization, and the last two cases were non-localizable.

Among the three patients in the PCL-group with ictal recording, the EEG was regional in two and lateralized in one. The regional ictal EEG was over the midline, involving the vertex and the parietal region without lateralizing data in one and over the temporal region ipsilateral to the side lesion in the other. The lateralized ictal recording was ipsilateral to the side of structural lesion.

The ictal rhythm consisted of varied patterns in both groups, with no predominance of any particular type. Theta or delta activities of regular or irregular morphology were observed, as well as rhythmical sharp waves and also paroxysmal fast and electrodecremental patterns.

In patient 5, the ictal recording preceded the clinical seizure by as much as 26 seconds. The most delayed electrographic recording started 21 seconds after the onset of the clinical seizure in patient 2.

Invasive recording

In this series, two patients were submitted to invasive evaluation, one in the ACGL-group and the other in the PCGL-group, patients 2 and 5, respectively.

In patient 2, the ictal recording was diffuse, involving all the recording contacts positioned in the mesial frontal region.

In patient 5, the ictal recording was focal in only one contact positioned over the lesion and later involved the adjacent contacts that were positioned over the lesion and outside the lesion.

Follow-up after surgery

Seven of the eight patients were submitted to surgery. Five had lesions in the hemisphere dominant for language (Table 40.4). Except for one who was lost to follow-up within a period of less than 1 year, the others had a follow-up of 2–5 years. No patient presented neurological deficits or behavioral alterations after surgery. Among the patients who were submitted to neuropsychological evaluation after surgery (full scale, verbal, and performance IQ), the scores obtained in the post-operative evaluation were basically unchanged compared to those obtained preoperatively (Table 40.4).

One patient was submitted to a second surgery for more extensive resection due to residual tumor after the first surgery.

Seizure outcome

Of the seven patients submitted to surgery, one patient had only a 6 month follow-up and was seizure free for 2 months. After seizures recurrence a modification in his drug treatment changes were made. In his last follow-up, 6 months after surgery, he was seizure free. Of the other six, one patient in the ACGL-group and one in the PCGL-group remained seizure free (outcome classification 1) up to the last evaluation (Table 40.4). The remainder did not become seizure free, two of them with outcome classification 3 (1–3 seizure-days per year) and two with outcome classification 4 (4 seizure-days per year to 50% reduction of baseline seizure-days) on the of the last follow-up.

Discussion

There are several ways to study the clinical symptomatology of epileptic seizures arising from a given cerebral cortical area. The so-called 'gold standard' is to analyze the seizure semiology of patients who became completely seizure free after a relatively restricted cortical resection.[45,46] Other methods used are based on information obtained from the onset of the ictal-EEG with intracranial electrodes,[47] or on the relationship between ictal semiology and the anatomical location of structural lesions, as long as the lesions are not extensive or diffuse.[48,49]

In the present series, all patients presented structural damage, with the lesion being of neoplastic nature in all cases but one.

Although the specific pathophysiological mechanism by which acquired and developmental brain tumors may cause epilepsy is unclear, there are several hypotheses including chronic changes in surrounding cortex, i.e., by direct mechanical or vascular mechanisms,[50] hemosiderin deposition,[51] and partial isolation of cortical areas.[52,53,54] These factors, separately or as a whole, possibly cause alterations in inhibitory and excitatory mechanisms in local circuits. In addition, developmental tumors may be associated with areas of cortical dysplasia[55] having intrinsic epileptogenic potential.[56] On the basis of these factors, it is quite probable that the clinical manifestations of the epileptic seizures described here were triggered by epileptic discharges originating in the cingulate gyrus and spreading to involve one or more symptomatogenic areas[57] close to the structural lesion.

Semiologic analysis of the epileptic seizures in the ACGL-group and PCGL-group studied here permitted us to conclude that, whereas the seizures of the anterior cingulate were predominantly motor (complex motor, hypermotor, and bilateral asymmetric tonic seizures), the seizures of the posterior cingulate were characterized by impairment of consciousness (dialeptic seizures) or automatisms of the distal portions of the limbs (automotor seizures), i.e., seizure types frequently present in patients with temporal lobe epilepsy.[58,59]

The supplementary motor area is considered to be the symptomatogenic zone for bilateral asymmetric tonic seizures,[27,60] whereas the symptomatogenic zone of hypermotor seizures, which frequently occur in patients with frontal lobe epilepsy, is uncertain but may be related to activation of the frontal lobe and/or anterior CG.[61,62]

It is not possible to determine if the semiologic ictal manifestations of these series are due to the activation of the CG or are related to the propagation of the ictal discharge. However, the semiology of some seizures, such as bilateral asymmetric

Table 40.4 Wada test, neuropsychological testing, and surgical outcome

			Neuropsychological Testing					
Patient	**Lesion**	**WADA Test**	**Handedness**	**Full scale IQ A.Pre-Op B.Post-OP ΔT (time interval between surgery and B)**	**Verbal IQ A. Pre-Op B. Post-OP ΔT (time interval between A/B)**	**Performance IQA. A. Pre-Op B. Post-OP ΔT (time interval between A/B)**	**Surgery Year Procedure**	**Surgical outcome classification [44] Year–classification**
1	Left anterior cingulate	Left speech	Right	*A. 68 B. –	A. 69 B. –	A. 73 B. –	2003 Stereotactic tumor lesionectomy	2004–4 2005–4
2	Left midcingulate	Left speech	Right	**A. 92 B. 99 ΔT: 15 months	A. 104 B. 106 ΔT: 15 months	A. 80 B. 93 ΔT: 15 months	Invasive monitoring evaluation 1st resection: 1993 Residual tumor after first resection extended resection: 1994	1993: free for 6 weeks following 1st resection. 1994-1 1995–3
3	Left midcingulate	–	Left	**A. 99 B. –	A. 98 B. –	A. 90 B. –	1999 Stereotactic tumor lesionectomy	Follow-up <1 year seizures recurred 2 months following surgery
4	Right midcingulate	Left speech	Right	**A. 108 B. –	A. 108 B. –	A. 107 B. –	1994 Stereotactic tumor lesionectomy	1995–1 1996–1 1997–1 1998–3 (when off medication) 1998–last visit (went back on medication)
5	Left posterior cingulate	Left speech	Right	**A. 100 B. 104 ΔT: 7 months	A. 88 B. 99 ΔT: 7 months	A. 100 B. 108 ΔT: 7 months	Invasive monitoring 1994	1995–4 1996–4 1997–4 1998–4
6	Right posterior cingulate	–	–	–	–	–	No surgery	
7	Left posterior cingulate	Left speech	Right	***A. 97 B. 99 ΔT: 8 months	A. 100 B. 104 ΔT: 7 months	A. 100 B. 106 ΔT: 8 months	Stereotactic tumor lesionectomy1997	1997–1 1998–1 1999–1 2000–1 2001–1
8	Right posterior cingulate	Left speech	Right	**A. – B. 91 ΔT: 24 months	A. – B. 89 ΔT: 24 months	A. – B. 96 ΔT: 24 months	Stereotactic tumor lesionectomy 1993	1994–3 1995–3 1996–3 1997–3 1998–3

* WAIS-III ** WISCIII *** WAIS R

tonic seizures, suggest that they were produced by involvement of the supplementary motor. Involvement of the temporal lobe may also explain the ictal semiology of those patients who presented dialeptic seizures or automotor seizures.

Although some of our patients presented lesions very close to what we define as a dividing line between the anterior and posterior cingulated (VPC), we should remember that this division is not arbitrary, but based on cytoarchitectural criteria. Namely, the anterior and posterior CG have cell layers with distinct neuronal populations and distributions and different connections. Even though the CG is extensively connected, each area has preferential efferent connections. In addition to these considerations, it should be pointed out that by selective criteria none of our cases presented large portions of the lesion involving areas outside the CG. These considerations may explain why the semiologic ictal manifestations of epilepsies arising from the anterior cingulated differed from the semiologic manifestations of seizures originating from the posterior cingulate. In other words, while the epileptic seizures of the anterior region most likely spread to involve areas in the adjacent frontal lobe, those of the posterior cortex of the CG tend to involve structures of the temporal lobe.

The cases reported in the literature support this hypothesis. In the anterior CG group, except for one case whose main clinical manifestation was alteration of consciousness,[40] all others suggested involvement of the frontal lobe with hypermotor seizures, tonic seizures, bilateral asymmetric tonic seizures, and gelastic seizures.[36–39,41]

It is also worthwhile to stress that the ictal scalp recordings only had limited localizing or lateralizing value in this series. The interictal discharges involved either the region of the vertex or the temporal electrodes in both groups. Only two patients had vertex spikes, four patients had temporal spikes and two patients had no epileptiform discharges. In the ACGL-group two patients had no epileptiform discharges, one had vertex, and one had bitemporal discharges. Of the four patients in the PCGL-group, three had regional interictal discharges in the temporal lobe and one had vertex interictal epileptiform discharges.

Ictal recordings correctly lateralized the lesion in only three cases No patient presented a contralateral ictal recording. Although the number of patients was small in each group, there seemed to be a tendency to greater difficulties of lateralization and localization in cases with lesion of the anterior cingulate.

The motor signs during the seizures were lateralizing in four of the eight patients and were characterized by a focal tonic seizure, focal clonic seizure, and versive seizure contralateral to the side of structural lesion. One patient also presented Todd's paralysis during the postictal period. Thus, the semiologic data of the seizures correctly predicted the side of the structural lesion in five of eight patients. The patient with a versive seizure also presented a focal paradoxical clonic seizure (clonus in the upper limb ipsilateral to the lesion) after the end of a secondarily generalized seizures.

In this series, in contrast to literature data which consider auras to be rare[36] in cingulate epilepsy, five of eight patients reported auras, two of four in the ACGL-group reported pin and needles in the contralateral arm or a heavy contralateral arm, one of four patient in the PCGL-group reported tingling in both legs. This is consistent with the finding that contralateral or bilateral somatosensory symptoms can be produced by electrical cortical stimulation in the superior portion of the mid-CG and in the supplementary sensorimotor area.[27,63]

Abdominal auras and psychic auras were also reported by patients in the PCGL-group. Cortical stimulation studies have shown that abdominal aura can be obtained when the superior bank of the sylvian fissure or the adjacent insula region were stimulated.[64] Besides, recent studies with stereo-EEG in patients with temporal epilepsy have demonstrated viscerosensitive manifestations characterized by nausea, pain and constriction of the abdominal and thoracic region when the ictal rhythm invades the insula.[65] Psychic auras are usually attributed to the temporal neocortex. More recently, structural lesions have been demonstrated in the parietotemporal transition zone of patients with depersonalization feelings.[66] All these considerations and the evidence that the posterior CG has extensive connection with the temporal lobe and to the insula, lead us to the conclusion that these auras are most probably due to extension of the epileptic discharges into the temporal lobe and insula.

All patients had frequent seizures whose duration, however, ranged from a few seconds to a little more than 1 minute in both patient groups. All patients in the ACGL-group had sleep-related seizures, whereas in the PCGL-lesion seizures had no clear relationship to sleep.

In the ACGL-group two patients were aware during the motor manifestation, while in the CGL-group all patients had loss of consciousness.

Brief and frequent nocturnal seizures with no impairment of consciousness during the initial motor manifestation (the patient remembers initial motor manifestation) are characteristic features of frontal lobe epilepsies. Therefore, these characteristics seen in seizures of patients with ACGL-group may reflect primarily the pattern of seizure propagation from the anterior cingulate to the frontal lobe.

Three of the four patients with an anterior lesion had vocalization. Stimulation of the region close to the rostrum of the corpus callosum provokes vocalization in experimental animals. Although the lesion of patient 1 was located exactly in this area, this was the only patient in the ACGL-group that did not produce vocalization.

The only autonomic manifestation documented was tachycardia. It has been demonstrated that tachycardia is a common phenomenon in focal seizures,[67,68] and the anterior cingulate cortex, as well amygdala, and anterior insula are the areas considered the central autonomic network.

Except for two patients who had invasive monitoring, the remaining ones had stereotactically guided tumor lesionectomy. Lesionectomy or small resections in the anterior or posterior CG did not cause neurological deficits or behavioral disorders; however, it is interesting to note that of the seven patients submitted to surgery, only two became completely seizure free.

The relation between the tumor mass or the epileptogenic lesion and the epileptogenic zone is extremely important for resections with a favorable outcome regarding seizure control. Although in the presence of tumors the area of ictal onset usually is not associated with a focus remote from the lesion[69] and a limited lesionectomy may result in a favorable outcome in selected cases, [70,71] it has been well determined that the area of ictal onset and the epileptogenic zone do not always fully coincide topographically with the structural lesion.[69]

There is no clear explanation for the relatively poor outcome for epilepsy surgery in this series. Invasive recordings, even when it localized the seizure onset to one electrode placed in close proximally of the MRI lesion, did not influence the final outcome.

Conclusions

Epileptic seizures secondary to structural lesions localized in the anterior portion of the CG present clinical manifestations relatively different from those of lesions localized in the posterior portion of the CG. Anteriorly localized lesions evolve with predominantly motor manifestations such as bilateral asymmetric tonic seizures, hypermotor seizures and complex motor seizures, while posterior cingulate cortex epilepsies tend to have predominantly alterations of consciousness (dialeptic seizures) and automatisms of the distal portions of the limbs (automotor seizures) as the main clinical manifestations.

This suggest that epileptic seizures of the anterior cingulate cortex are primarily an expression of seizure spreading into frontal areas, whereas seizures of the posterior cingulate cortex reflect involvement of the temporal lobes.

On the basis of the clinical characteristics (focal clonic, focal tonic, versive seizures, postictal Todd's paralysis, and paradoxical clonic seizures), it is possible to predict the side of the lesion in a high percentage of the patients.

On the other hand scalp interictal and ictal EEG only lateralize or localize the seizures correctly in less than 50% of the cases.

Lesionectomy in the CG does not cause a neurologic or behavioral deficit, but only a relatively small percentage of patients (29%) remained seizure free with surgical treatment.

These results suggest that most probably more extensive resection will be necessary to achieve seizure freedom in a higher percentage of cases.

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41 Hypothalamic hamartomas

AS Harvey

Summary

- Hypothalamic hamartoma (HH) are malformations of the hypothalamus that are associated with epilepsy and precocious puberty.
- Gelastic seizures arise from the HH are characterized by ictal laughter and autonomic symptoms, often with minimal change on concurrent scalp-EEG.
- Complex partial seizures with loss of consciousness, automatisms and focal motor features, and focal spike-wave on scalp-EEG, occur in some patients as a result of seizure propagation from the HH to frontal and temporal cortex.
- Generalized tonic/atonic seizures and generalized scalp-EEG abnormalities develop in many children with HH, seemingly as a result of secondary epileptogenesis affecting the neocortex.
- The neurobiological basis for the range of seizure severity and associated neurobehavioral disturbances seen in patients with HH is not understood.
- An important distinction to be made on MRI is between intraventricular HH attached to the mamillary bodies and infraventricular HH attached to the tuber cinereum, the former more commonly associated with seizures.
- Seizures associated with HH are invariably resistant to medication.
- The best published outcomes in HH surgery are with transcallosal, interforniceal resection or disconnection. Endoscopic procedures are being currently evaluated. Gamma Knife radiosurgery is promising but there is limited outcome data.

Hypothalamic hamartoma (HH) are tumor-like malformations of the hypothalamus which arise from the tuber cinereum and/or the mamillary bodies on one or both sides. The term HH was first coined by Le Marquand and Russell[1] in 1934 to describe such a lesion found at post mortem in a boy with central precocious puberty. HH vary in size, attachment and extension into the third ventricle and suprasellar cistern. Histologically, HH consist of gray matter in which there is some variation in neuronal size, shape, and aggregation.[2–9]

HH usually come to clinical attention through their association with central precocious puberty and epilepsy, characteristically epilepsy with gelastic (laughing) seizures. HH and gelastic seizures occur with a prevalence in childhood of approximately 1 in 200 000,[10] with a greater proportion of males affected.[11] The current literature is biased towards patients with refractory epilepsy and associated neurological problems, largely related to reports of surgical treatments, making it difficult to determine the true spectrum of neurological manifestations. Central precocious puberty occurs in about a third of patients with HH and epilepsy,[11,12] usually following the onset of seizures. HH may be asymptomatic, though the prevalence of this is unknown.

Seizure manifestations

The first report of epilepsy associated with a (likely) HH was in 1932,[13] in a boy with precocious puberty and mental retardation who died from status epilepticus. The first report of HH associated with gelastic seizures specifically was in 1938.[14] Numerous case reports and small patient series were published over the subsequent 50 years. In 1988, Berkovic and colleagues provided the first detailed electroclinical and imaging descriptions of what they proposed was a recognizable and possibly progressive epileptic syndrome of HH and gelastic epilepsy.[15]

Gelastic seizures occur in nearly all patients with HH and epilepsy. Onset of gelastic seizures early in life, even from birth, is characteristic.[7,10,11,15–19] Gelastic seizures are often described as attacks of inappropriate and mechanical or mirthless laughter. Many patients also have dacrystic (crying) seizures,[4,19–26] or seizures in which the facial expression, rhythmic quality of the respirations, and sound produced are discordant mixtures of crying and laughing. Consciousness is usually preserved during brief gelastic seizures.[15,19,27] Autonomic features such as flushing, pupillary dilation and breath holding often accompany laughter in gelastic seizures. Recurrent gelastic seizures during wakefulness and sleep are not uncommon in infancy, and when occurring in a relentless fashion have been described as 'status gelasticus'.[28,29] A mild form of gelastic epilepsy is described, usually in adults with small HH, in which seizures manifest with only a 'pressure to laugh'.[30,31] It should be remembered that gelastic seizures may also occur in patients with neocortical epilepsies of frontal and temporal origin,[32,33] as well as in patients with brainstem lesions and degenerative diseases.[34]

Hypermotor automatisms, oroalimentary automatisms, head and eye deviation, and tonic or clonic facial contraction are often seen in older patients during gelastic seizures. These additional clinical manifestations are invariably seen with impairment of consciousness and described as complex partial seizures, with the implication of frontal and temporal lobe involvement.[15,19] Lateralized motor manifestations are

typically contralateral to the side of greater hypothalamic attachment in asymmetric HH.

In more than half of patients with HH and epilepsy, there is a further 'epileptic progression' with development of generalized tonic/atonic seizures and tonic-clonic seizures.[11] Many patients develop a Lennox-Gastaut syndrome with disabling drop attacks.[7,15,35–38] Tonic seizures and spasms associated with HH are often asymmetric, and laughter may precede or follow them. Infantile spasms are reported as a presenting seizure type in patients with HH.[10,37,39,40]

Neurobehavioural manifestations

Cognitive disturbances in patients with HH and epilepsy are common, especially those in whom seizures begin in childhood. Global developmental delays are particularly common in patients with refractory seizures that begin in infancy and evolve rapidly to partial and generalized seizures with associated generalized EEG disturbances. Cognitive disturbances vary in severity from patients with normal cognition, to patients with impairments of memory, attention, and learning,[10,15,31,30,41,42] through to patients with moderate-severe intellectual disability.[7,10,35,36,38] Deficits in memory and new learning are most commonly reported but the exact nature of the memory dysfunction is difficult to determine from the reported studies, due to the variable nature of testing and the often associated intellectual impairments. One study suggested cognitive deficits are correlated with seizure frequency and size of HH.[42]

Aggressive behavior, rage attacks, anxiety disorder, autism, and other psychiatric comorbidities are widely reported in patients with HH.[10,15,35,38,43,44] The relationship between behavior disturbances, seizures and intrinsic hypothalamic dysfunction is uncertain.

Sleep disturbance is common in patients with HH and epilepsy. In infants and young children, gelastic seizures may occur every few minutes and impair normal sleep-wake cycling.[17,19] Similar manifestations are reported in adults,[40,45] whereby frequent subclinical gelastic seizures are associated with recurrent sleep arousals. Sleep disturbance may be further exacerbated by continuous epileptic activity on EEG and antiepileptic drugs.

Electroencephalographic findings

Scalp EEG findings in patients with HH vary depending on the age of the patient and the evolution of the seizure disorder. In infants and young children with gelastic seizures only, and in adults with the mild phenotype characterized by only an 'urge to laugh', the interictal and ictal EEG are usually normal.[46] Such normal EEG findings with gelastic seizures are not widely appreciated and often lead to delayed or incorrect diagnosis.

Interictal scalp EEG abnormalities may not appear until later childhood,[47] often coinciding with the appearance of complex partial and generalized seizures.[11] Initially the EEG may only show epileptiform activity when asleep.[27] Spike-wave activity predominates over the frontal and temporal regions, either in a bilaterally-synchronous or predominantly unilateral fashion.[11,48] Unilateral EEG abnormalities tend to occur on the side of predominant HH attachment in asymmetric and unilateral HH. In patients with tonic/atonic seizures, background slowing is common and multifocal or generalized spike-wave activity, paroxysmal fast activity, and electrodecremental patterns are recorded, often with electrical status in sleep.[37]

Scalp EEG recordings of seizures in patients with HH and chronic epilepsy usually show suppression of interictal discharges and attenuation of background rhythms, with or without widespread low voltage fast activity.[10,15,49] Lateralized and regionalized ictal rhythms or spike-wave activity may follow, potentially giving the misleading impression of frontal or temporal lobe origin of seizures.[48] Computerized source analysis of scalp EEG may reveal subcortical sources of early rhythmic activity prior to more superficial cortical sources.[49]

Depth EEG recordings from HH[4,18,45,50,51] show gelastic seizures are associated with an ictal discharge within the HH that, in most cases, remains confined to the HH. Electrical stimulation of HH using depth electrodes may provoke characteristic ictal laughter. In contrast, depth EEG recordings of tonic seizures reveal ictal onset in cortical regions remote from the HH,[4] with medial frontal and lateral temporal areas being prominent.[50]

Neuroimaging findings

HH vary in size from 5–40 mm and vary in their attachment and extension (Figure 41.1). MRI is far superior to CT brain in revealing and characterizing HH.[15] Small HH may be difficult to detect unless the hypothalamic region is specifically examined. T2-weighted sequences in the three orthogonal planes are well suited to displaying the HH in relation to the heavily-myelinated hypothalamic nuclei and tracts. HH usually have increased signal on T2-weighted and FLAIR sequences and low signal on T1-weighted sequences, compared to grey and white matter. They do not enhance with contrast and on serial imaging remain in proportion with the rest of the brain.[12] HH associated with Pallister-Hall syndrome are often larger than sporadic HH and are isointense with gray matter on T2-weighted images.[52] Proton magnetic resonance spectroscopy (MRS) demonstrates relatively decreased N-acetylaspartate and increased myoinositol levels compared to normal gray matter,[12,53] suggesting neuronal attenuation and relative gliosis. Increased signal on T2-weighted images is correlated with gliosis on MRS and histological examination.[53]

Several anatomically-based classifications of HH based on MRI features have been proposed, distinguishing different sizes and patterns of hamartoma attachment to the hypothalamus.[2,36,54–58] The most important categorization from clinical, pathophysiological and surgical perspectives is the distinction between HH within the third ventricle that are attached to the mamillary bodies and/or the medial hypothalamus (sessile, intraventricular, intrahypothalamic), from HH beneath the third ventricle with attachment to the tuber cinereum (pedunculated, extraventricular, parahypothalamic).

In a systematic review of MRI in 72 patients with epilepsy and HH, Freeman and colleagues reported mamillary body attachment in all, with intrahypothalamic extension between

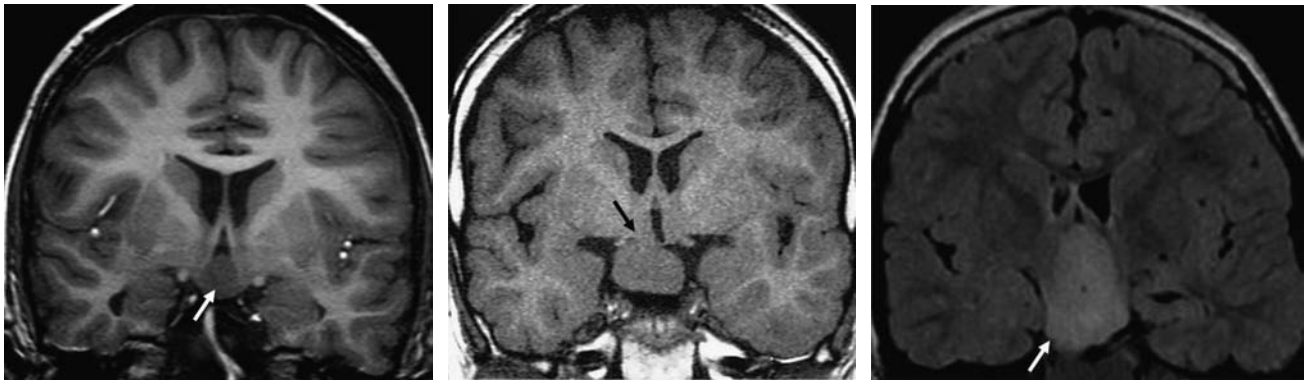

Figure 41.1 Coronal MRI scans of HH in three patients with gelastic epilepsy. (a) and (c) show intraventricular HH attached to the medial hypothalamus bilaterally; (B) shows a pedunculated HH attached predominantly to the tuber cinereum on the right, although still with a small intraventricular connection. The HH in (a) and (b) are relatively isointense with gray matter on the T1-weighted images, while the HH in (c) is hyperintense on the FLAIR image compared to the rest of the cerebrum.

the fornices and mamillothalamic tracts seen in the majority.[12] In contrast, HH associated with isolated precocious puberty tend to be pedunculated and not involve the third ventricle.[59] The association of HH size with endocrine versus neurological manifestations is variably reported, with no consistent relationship identified.[12,30,52,59] A possible interpretation of the data is that large HH are associated with the combination of endocrine and neurological manifestations, due to attachment and distortion of multiple hypothalamic regions; conversely, small pedunculated HH are more commonly associated with isolate precocious puberty[59] and small intrahypothalamic HH are more commonly associated with isolated[12] and sometimes milder epilepsy.

Occasionally, HH are seen in association with dysgenesis of the corpus callosum, gray matter heterotopias, arachnoid cysts, and microgyria.[2,12,60] Anterior temporal lobe white matter changes are seen in a minority of patients with HH, but despite the severity and frequency of seizures in many patients, hippocampal sclerosis is not reported.

Positron emission tomography (PET) studies are few but report areas of cortical hypometabolism, lateralization usually being concordant with the side of HH attachment.[7,61] PET during a period of 'status gelasticus' revealed hypermetabolism in the HH.[29] Ictal single-photon emission computed tomography (SPECT) during gelastic seizures have consistently reported focal hyperperfusion in the region of the HH (Figure 41.2).[17,18,62,63] Asymmetric cerebral perfusion during seizures is common in patients with HH,[10] with hyperperfusion ipsilateral to the side of predominant HH attachment, suggesting preferential cortical spread of seizure activity from the HH.[64] Group analyses of seizure propagation with ictal SPECT suggest preferential cortical spread to medial frontal and lateral temporal regions,[64] consistent with depth EEG studies.[50]

Epileptogenesis associated with hypothalamic hamartoma

HH usually occur sporadically and in isolation. Rarely, HH may occur as part of the autosomal dominant Pallister-Hall syndrome which includes HH, hypopituitarism, polydactyly, midline defects, and imperforate anus.[65] Patients with Pallister-Hall syndrome have mutations of the transcription factor gene *Gli3*,[66,67] but the role of *Gli3* in patients with sporadic HH is unknown[68] and thus the etiology of sporadic, nonsyndromic HH remains uncertain.

Distortion of the hypothalamus or brainstem by HH was originally believed to be the basis of seizures in this syndrome,[22] as irritation of the third ventricular floor and mamillary bodies was known to induce laughter.[69,70] With later appreciation of the severe and often generalized nature of seizures and neurological disturbances in many patients with HH, it was later proposed that patients with HH had widespread occult cerebral dysgenesis.[15,71] This view that HH were perhaps just an epiphenomenon of more significant epileptic disturbance in the neocortex led to unsuccessful temporal and frontal resections in many patients with localized EEG patterns.[8,20,72,73]

From the mid-1990s, evidence accumulated proving that gelastic seizures arose from HH, evidence coming from stereotactic depth EEG recording of seizures from HH,[4,18,50,51,74] reproduction of ictal symptoms with electrical stimulation of HH,[4,18,50] and demonstration of HH hyperperfusion with ictal SPECT[18,62] and PET.[29] HH have been shown to be intrinsically epileptogenic,[75] with pacemaker-like spontaneous repetitive firing demonstrated in small HH neurons within cell clusters.[76]

The reasons for the variability in onset and severity of epileptic manifestations of epileptogenic HH is however unknown. As discussed above, the attachment of HH is more important than their size in determining endocrine versus neurological manifestations, with mamillary body involvement and third ventricular distortion being strongly correlated with epileptogenicity,[12,54,55,59] however variability of neurological manifestations between patients with epileptogenic HH is not understood.

Clinical evidence suggests that complex partial seizures in patients with HH result from seizure propagation to medial frontal and lateral temporal cortical regions,[49,50,64] and that generalized tonic seizures represent independent neocortical phenomena.[4,50] Similarly, interictal scalp EEG abnormalities arise from secondary cortical regions, either independently or triggered by discharges arising in the HH.[4,37,50] In patients with

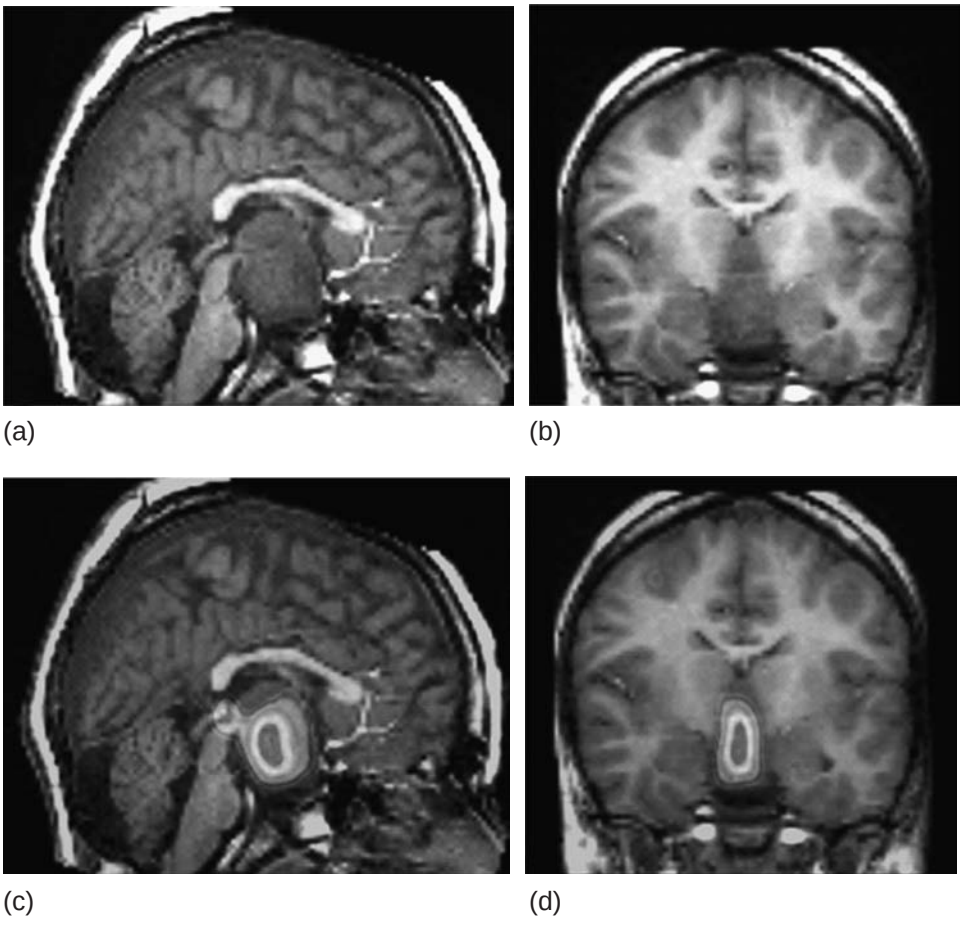

Figure 41.2 Sagittal (a) and coronal (b) T1-weighted MRI scans in an intellectually disabled boy with gelastic epilepsy showing a large HH occupying and distorting the third ventricle and interpeduncular cistern. Subtraction ictal-interictal ^{99m}Tc-HMPAO SPECT of a gelastic seizure coregistered with the sagittal (c) and coronal (d) MRI scans, showing relative hyperperfusion in the HH. (Courtesy Dr Jeremy Freeman, Royal Children's Hospital, Melbourne).

symptomatic generalized epilepsy (SGE), generalized and multifocal interictal epileptiform discharges persist over the neocortex and scalp immediately following resection of the HH,[37] frequently reducing in the weeks and months that follow, providing further evidence of the independent nature of scalp EEG abnormalities. The apparent epileptic progression in many patients with HH, and in particular the electroclinical and behavioral features of SGE, may in fact represent a process of secondary epileptogenesis affecting the cerebral cortex,[4,37,50] perhaps mediated through mamillo-halamo-cingulate pathways.[50]

Surgical treatment

Antiepileptic medications are generally ineffective in the treatment of seizures associated with HH.[10,15] While they may have some impact on the severity or frequency of partial and generalized seizures, antiepileptic drugs usually have little impact on gelastic seizures. Some patients gain partial benefit from vagal nerve stimulation.[10,77] The management of precocious puberty associated with HH is no longer surgical, with patients now treated with gonadotrophin releasing hormone agonists.

In the last two decades, there have been numerous reports of successful surgical treatment of epilepsy associated with HH, with more than 200 operated patients reported in the English literature by 2006. Today, epilepsy due to HH is considered a surgically-remediable condition.[75,78–80] Many microsurgical, endoscopic, and radiosurgical techniques for resection, disconnection, and ablation of HH are reported and a brief review is provided below. The diagnostic evaluation for patients with HH undergoing epilepsy surgery is similar to that for patients with refractory epilepsy of cortical origin except for the need for perioperative endocrine assessment, the need for high-resolution imaging of midline brain structures, and a reduced emphasis on scalp EEG localization of seizures and interictal discharges.[81]

Pterional and frontotemporal resection and disconnection

Pterional and frontotemporal craniotomies provide access to the inferior part of the HH via subtemporal, subfrontal, transsylvian or transcortical approaches, sometimes performed with temporal pole or orbital cortical resection.[7,36,47,55,82,83] These approaches to epileptogenic HH are often ineffective in controlling seizures, as only the infraventricular portion of the HH can be resected, leaving the important intraventricular component attached to the mamillary bodies and medial hypothalamus.[7,75,78] Furthermore, endocrinopathies, stroke and third nerve palsies are not infrequent complications with these approaches.[7,36]

Transcallosal, anterior interforniceal resection, and disconnection

An interhemispheric, transcallosal approach to resection of HH was first reported by Rosenfeld and colleagues.[84] This approach passes between the columns of the fornices and leaves of the septum pellucidum to enter the third ventricle, allowing direct vision of the intraventricular component of the HH. With microsurgical technique, the neurosurgeon can obtain complete or near-complete resection or disconnection of the HH at its attachment to the mamillary bodies and medial hypothalamus, down to the floor of the third ventricle (Figure 41.3). In the 56 reported patients who have undergone transcallosal resection or disconnection of HH at two centers,[35,38] seizure freedom or >90% seizure reduction is reported in 80% with associated improvement in behavior and learning in the majority of these. Most striking in these series was the improvement in patients with SGE, in whom there was often marked improvement or remission of tonic seizures, generalized spike-wave discharges on EEG, and language and behavioral problems.[35,37,38] Morbidity in these series consisted of short term memory impairment, weight gain, hypothyroidism, and transient hypernatremia,[35,38,85] with neurovascular complications being rare.

Stereotactic radiosurgery

Several radiosurgical approaches to treatment of epilepsy associated with HH are reported. All deliver ionizing radiation to a stereotactically defined intracranial target, with a steep radiation fall-off outside of the treated volume, the aim being to cause tissue damage or physiological change in the HH. Gamma Knife is reported in 46 patients,[56,57,86–90] but seizure outcome is reported in only 16 (6 seizure free or > 90% seizure reduction). Stereotactic radiosurgery with the linear accelerator[4,91] and implantation of ^{125}I seeds[92,93] are reported by a few centers, with seizure-free or near seizure-free outcomes reported in about half. Minimal morbidity and short hospital stay are clear advantages of stereotactic radiosurgery, whereas delayed seizure reduction is a potential disadvantage and certainly limits outcomes presently reported in the literature. Radiosurgery may be best suited to the treatment of smaller HH, or perhaps the intrahypothalamic component of large HH.

Minimally-invasive stereotactic techniques

Radiofrequency thermocoagulation, via stereotactic or open approaches, produces small necrotic lesions in the HH by radiofrequency heating of the tip of an electrode, often following recording and stimulation of seizures. Relatively low

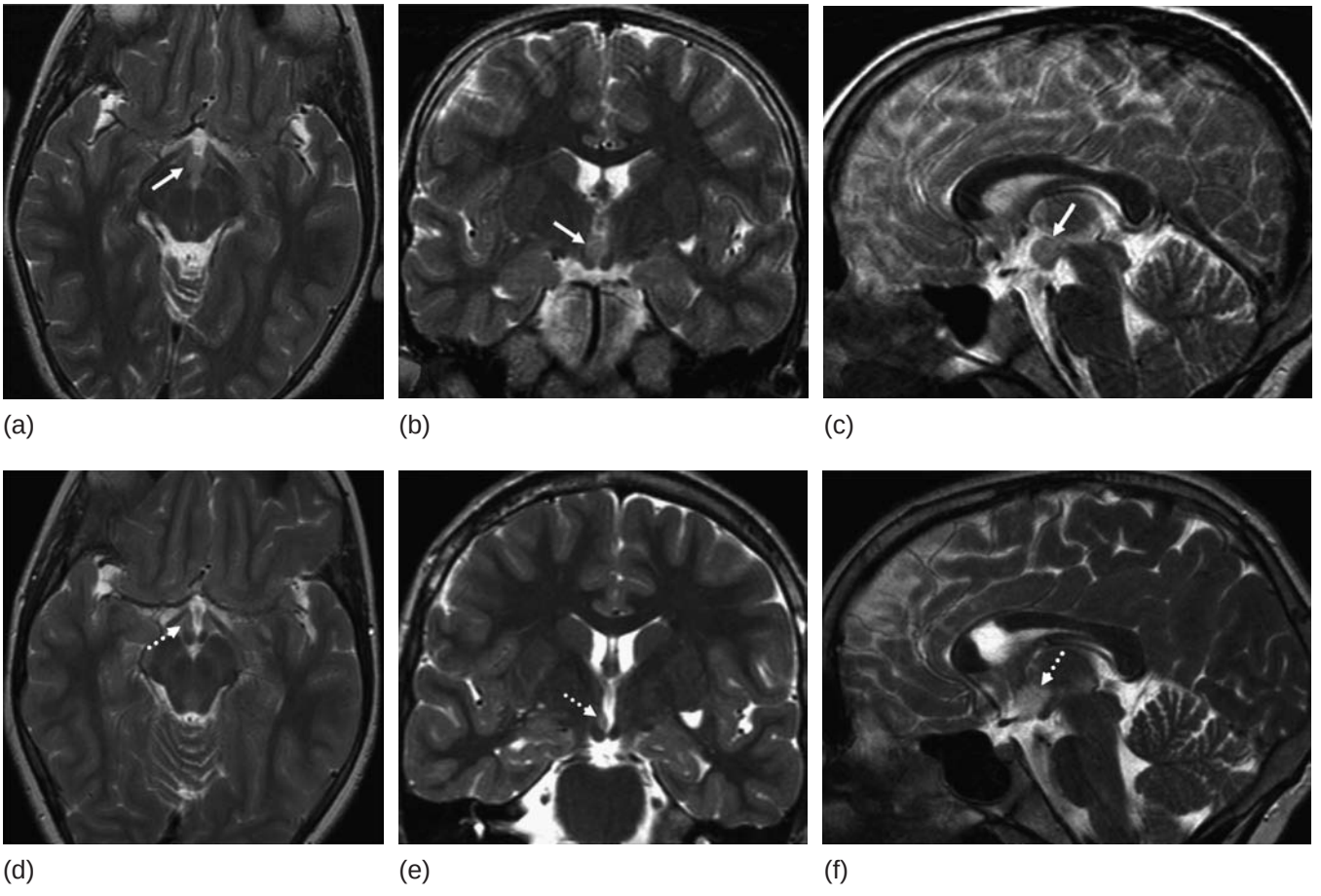

Figure 41.3 Axial (a,d), coronal (b,e) and sagittal (c,f) T2-weighted MRI scans in an intellectually normal girl with a small intraventricular HH. The top row are preoperative scans. The bottom row shows postoperative scans following transcallosal resection of the majority of the HH; there is residual HH attached to the right mamillary body (e). The patient suffered no endocrine or memory impairments following surgery and is seizure free with short follow up. (Courtesy Ms Wirginia Maixner, Royal Children's Hospital, Melbourne).

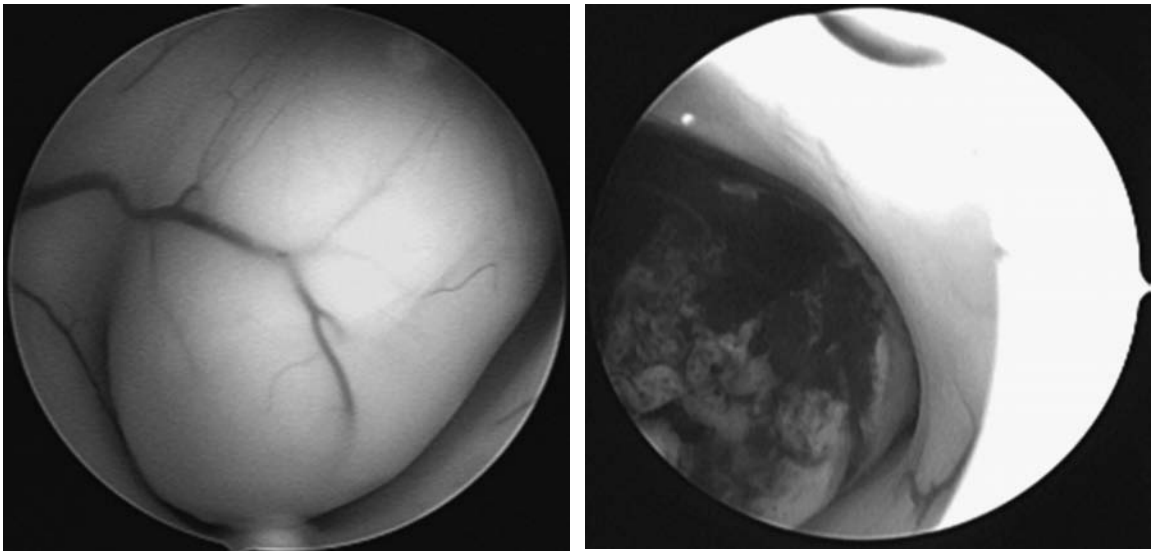

Figure 41.4 Endoscopic view of a small intraventricular HH attached to the left medial hypothalamus before (left) and after (right) partial endoscopic resection. (Courtesy Drs John Ragheb and Glenn Morrison, Miami Children's Hospital).

seizure-free rates are reported (only half being seizure free or having >90% seizure reduction) and repeat procedures are not uncommon.[18,23,40,94,95] Like stereotactic radiosurgery, radiofrequency thermocoagulation may be best suited for small HH.

Neuroendoscopy is being increasingly reported as a means of resection or disconnection of HH (Figure 41.4),[7,36,95–97] with seizure freedom or >90% seizure reduction reported in about 60% patients. Third ventricular access is generally transcortical, through the lateral ventricle and foramen of Monro. Delalande employs both frontotemporal and transcortical endoscopic approaches to disconnection of infraventricular and intraventricular components of HH.[36] Endoscopic surgery is presently limited by tools for safe and complete resection of HH tissue, though recent technical advances are reported.[97,98] Postoperative hospital stay is reduced but there is limited data on efficacy and safety to compare third ventricular endoscopic surgery with transcallosal surgery and stereotactic radiosurgery.

Overall, short-term Engel class I or II outcomes are reported in about two thirds of patients undergoing transcallosal or endoscopic resection and/or disconnection of HH from within the third ventricle, these approaches being superior in efficacy to reported outcomes from pterional and frontotemporal resections and radiofrequency ablative techniques. When greater than two year seizure outcomes are reported from a prospective study of Gamma Knife surgery in HH,[56] it may become apparent that stereotactic radiosurgery is an equal or superior technique, at least in older patients with small HH and time to wait for seizure improvement. Callosotomy, neocortical resection and pterional/frontotemporal HH resections are inferior surgical approaches that are no longer advocated.[36,48,99]

Conclusions

Previously an uncommon, poorly-understood, neurologically-devastating and untreatable epileptic syndrome, HH and gelastic epilepsy is now better understood and surgically-remediable. Optimum management of patients requires awareness of pathological laughter as a potential seizure symptom, acceptance of normal scalp EEG findings early in the course of the epilepsy, careful imaging and inspection of the hypothalamic region with MRI, recognition of the potential detrimental effects of seizures on neurological development, and early referral to a neurosurgical center with experience in treatment of HH. Further studies of surgical outcomes, with large patient numbers and adequate follow-up, are awaited to compare the merits of different approaches and timing of surgical interventions.

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42 Rasmussen syndrome

CG Bien

In 1958, the Montreal neurosurgeon Theodore B. Rasmussen published a report on three pediatric patients under the title 'Focal seizures due to chronic localized encephalitis'.[1] This is an unusual condition typically developing in childhood, and is characterized by the occurrence of refractory partial epilepsy, often with *epilepsia partialis continua* (EPC), associated with progressive hemiparesis and cognitive impairment. Neuroimaging reveals progressive unilateral hemispheric atrophy. The Montreal Neurological Institute continuously treated patients with this disorder. However, it took another about thirty years until reports started to appear from other parts of the world. From this time on, most researchers and clinicians have adopted the term Rasmussen syndrome (RS) or (Rasmussen encephalitis) for this condition.[2,3]

Clinical presentation and seizure semiology

Typical features

The 'typical RS patient' can be described as follows: he or she (there is no gender predominance in RS) starts experiencing intractable unilateral focal motor seizures or temporal lobe seizures at the age of six years. Later on, when the disease process spreads across the affected hemisphere, new seizure semiologies indicating new epileptogenic areas are often observed. EPC is not infrequently seen. This type of focal motor status epilepticus is characterised by repetitive, brief, regular or irregular, quite monomorphic myoclonic jerks. Distal rather than proximal muscle groups are affected. Physical exercise, sensitive stimulation or psychic exertion may increase the amplitude and frequency of the myoclonic jerks. The upper half of the body is more frequently affected than the lower one. EPC more often continues during sleep – sometimes in a milder form – than does it stop.[4] This seizure type is not a unique feature of RS.[5–7] However, in childhood, RS is its most frequent cause. Within a few months of the manifestation of epilepsy, progressive loss of neurological function associated with one hemisphere starts. Typical features are hemiparesis, hemianopia and (if the dominant side is affected) aphasia.[8,9] After on average eight months, the main decline is over, and the patient passes into a residual stage with a rather stable neurological deficit and cerebral hemiatrophy.[9] Seizure frequency is still high but not as much as during the previous 'acute stage'.[9] In reality, this 'average' or 'typical' RS patient is rarely seen. Due to the complexity of potential symptoms, the presentation of RS can take a variety of different forms.

Less common presentation forms of RS

Since the original description of RS, a variety of other presentations have been recognized. Although RS typically develops in children, the condition has also been described in adult life.[10–12] In the majority of these cases the course appears to be slower and less severe. Villani *et al.* distinguished two phenotypes in adults: an 'epileptic' form, characterised by focal motor epilepsy refractory to antiepileptic drug treatment, and a 'myoclonic' form, in which EPC and/or unilateral cortical myoclonus (focal or multifocal) are the prominent features. Although secondary spread of seizures to the contralateral side, or a minor degree of contralateral atrophy is sometimes seen in patients with RS, true bilateral involvement in the form of bilateral inflammation has only rarely been described.[13–15] The bilateral nature of these unusual cases became apparent within 13 months of disease onset. Of note, no case of subsequent spread to the opposite side has been reported following the successful hemispheric surgical treatment of unilateral RS.

Dual pathology, i.e. a second cerebral abnormality such as cortical dysplasia, vascular abnormality or tuberous sclerosis in association with RS has been found in approximately 10% of patients,[16] leading to speculation that a breach in the blood–brain barrier may play a part in the genesis of the disease.

Patients with an otherwise typical RS course have been observerd who experienced delayed seizure onset,[17] or even the absence of seizures.[18]

In a few patients, movement disorders including hemiathetosis and hemidystonia have been described in addition to EPC.[19,20]

Diagnostic tests

Brain imaging

Magnetic resonance imaging (MRI)

Brain MRI has become a mainstay of diagnostic evaluation and follow-up in RS.[21,22] Serial investigations reveal focal cortical and subcortical T2/FLAIR signal increases followed by progressive, centrifugal hemiatrophy of the cerebral hemisphere contralateral to the affected side of the body. The onset of MRI visible first changes is usually noted around the Sylvian fissure. The head of the ipsilateral caudate nucleus is usually included in this hemiatrophic process, and is particularly easily ascertained.[21,22]

Other neuroimaging techniques

Positron emission tomography (PET), single photon emission computed tomography (SPECT) and magnetic resonance

spectroscopy (MRS) are techniques not suitable for defining the inflammatory nature of the condition (for a literature survey, see ref. 23). However, these techniques may be helpful in confirming the unihemispheric nature in patients with suspected recent onset disease.

Electroencephalography

The most characteristic EEG abnormalities in RS are polymorphic delta waves over the affected hemisphere. These waves are for the most part found in temporal and central leads. Epileptiform abnormalities with frequent evolvement into electrographic seizures are regularly observed. During the disease course, background activity shows progressive flattening. In the majority of patients, contralateral asynchronous slow waves and epileptiform discharges occur.[24] Later on, these contralateral abnormalities may be even more frequent than the ipsilateral ones.[25,26] It must be emphasized that these contralateral abnormalities are not sufficient to make the diagnosis of bilateral disease. They are likely to arise from rapid spread from the primarily affected hemisphere, and they should not be taken as a cause to reject an otherwise suitable patient from hemispherectomy. As with other conditions with cortical epileptic myoclonus, EPC in RS is not always accompanied by ictal contralateral EEG discharges on surface EEG.[25]

Laboratory tests

CSF studies

Only about 50% of RS patients have abnormal cerebrospinal cell counts (16–70 cells/μl, predominantly lymphocytes) and protein content (50–100 mg/dl).[8,27] Oligoclonal bands have been an inconsistent finding, ranging from 0–67%.[24,28,29] Standard CSF studies (in combination with serological tests) are helpful to rule out a CNS infection by a known neurotropic agent during the process of excluding differential diagnoses. Stand-alone standard CSF tests, however, are not sufficient to exclude or confirm the diagnosis of RS.

Blood tests

The serum test for antibodies to the glutamate receptor subunit 3 antibodies (GluR3 abs), published in the mid-1990s,[30] is no longer considered sensitive of specific for the diagnosis of RS. This has become evident from several recent studies.[31–33] To conclude, this test can no longer be regarded as a useful diagnostic method. At present, no other diagnostically helpful blood test is available for patients with suspected RS.

Brain biopsy

Recently, an international consensus has been made on the role of brain biopsy in the diagnosis of RS.[23] It is indicated only in patients in which the diagnosis of RS is suspected but can neither be sufficiently supported by cross-sectional, non-invasive assessment (part A criteria of the European consensus criteria, see Table 42.1) nor by demonstration of the progressive nature of the condition (part B criteria, #1 and 2). This is usually the case in patients with very recent onset of clinical symptoms suggestive of RS – e.g., in a patient with otherwise unexplained recent onset EPC. Such a patient may profit from rapid definite diagnosis by brain biopsy because subsequent timely initiation of long-term immunotherapy (see below)

Table 42.1 Diagnostic criteria for Rasmussen syndrome (with permission from ref. 23). Rasmussen syndrome can be diagnosed if either all three criteria of part *A or* two out of three criteria of *B* are present. Check first for the features of part *A*, then, if these are not fulfilled, of part *B*

Part A:		
1.	Clinical	Focal seizures (with or without Epilepsia partialis continua) *and* unilateral cortical deficit(s)
2.	EEG	Unihemispheric slowing with or without epileptiform activity *and* unilateral seizure onset
3.	MRI	Unihemispheric focal cortical atrophy *and at least one of the following:* gray or white matter signal T2/FLAIR hyperintense signal, hyperintense signal or atrophy of the ipsilateral caudate head
Part B:		
1.	Clinical	Epilepsia partialis continua *or* progressive* unilateral cortical deficit(s)
2.	MRI	Progressive* unihemispheric focal cortical atrophy
3.	Histopathology:	T-cell dominated encephalitis with activated microglial cells (typically, but not necessarily forming nodules) and reactive astrogliosis. Numerous parenchymal macrophages, B cells or plasma cells or positive signs of viral infections (viral inclusion bodies or immunohistochemical demonstration of viral protein) exclude the diagnosis of RS.

*'Progressive' means that at least two sequential clinical examinations or MRI studies are required to meet the respective criteria. To indicate clinical progression, each of these examinations must document a neurological deficit, and this must increase over time. To indicate progressive hemiatrophy, each of these MRIs must show hemiatrophy, and this must increase over time.

may prevent irreversible loss of brain tissue and related neurological functions. An open brain biopsy collecting a piece of brain with an intact relation of meninges, gray and white matter is preferable. Stereotactic biopsies have a relatively high probability of leading to false negative results (frequent sampling error due to small specimen size). In RS brains, pathological and seemingly normal brain areas may lay closely together. Even in the case of an open brain biopsy, extensive neuropathological evaluation of serial sections may be necessary to detect the characteristic inflammatory changes. The biopsy should ideally be obtained from a non-eloquent brain area with increased T2/FLAIR MRI signal.[21] A systematic study of a large sample of hemidecortication specimens revealed that frontal or temporal lobe areas are more likely to contain diagnostically valuable inflammatory infiltrates than more posteriorly collected specimens.[34] There are less histopathological differential diagnoses than sometimes assumed. Main alternative diagnoses are chronic viral encephalitides[35] and – in adults – paraneoplastic encephalitis[36,37] and nonparaneoplastic limbic encephalitis.[38] These disorders can be distinguished by the clinical presentation, neuroimaging and additional laboratory studies. If the results of brain biopsy are not clearly abnormal and therefore considered inconclusive, this may be due to the above mentioned sampling error. In this case, further clinical and MRI follow-up studies (e.g. every 6 months) are needed to establish or exclude the progressive nature of the condition.

Neuropsychology

Neuropsychology testing does not provide positive diagnostic evidence in favour or against a diagnosis of RS. Repeated testing, however, may provide highly valuable information on the progression of cognitive decline. Language studies are of particular importance because aphasic disturbances may suggest involvement of the language dominant hemisphere. If hemispherectomy is considered, language laterality must be determined. Language functional MRI testing may in selected cases be an adequate tool for this purpose. However, its applicability can be impaired in RS patients by their frequently reduced ability to follow the instructions and by the limited morphological comparability of the two hemispheres due to unilateral atrophy and subsequent hemispherical asymmetry.[39] Determination of language lateralisation therefore mostly requires the performance of a Wada test.

Diagnostic criteria of RS

The most characteristic and unique features of RS are the progressive unilateral loss of function and the progressive hemispheric atrophy occurring over several months or a few years. This acute stage is followed by a quite stable residual stage. Prior to the acute stage, a non-specific prodromal period with less frequent seizures and sometimes a mild neurological deficit can be observed.[9]

To standardize the diagnosis of RS, a European consensus panel recently proposed formal diagnostic criteria,[23] which are given in Table 42.1

Differential diagnoses

Lists of potential differential diagnoses are long. In reality, however, most can be relatively quickly checked and ruled out or confirmed. The major alternative diagnoses are those of non-inflammatory unilateral epileptic syndromes such as malformations due to abnormal cortical development, Sturge-Weber syndrome, stroke, hemiconvulsion-hemiplegia-epilepsy syndrome, and tumours including gliomatosis cerebri. Rarely, other causes of EPC have to be excluded, particularly: metabolic disorders (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; renal or hepatic encephalopathy) or inflammatory conditions (vasculitis, HIV, Russian spring-summer meningoencephalitis and a few others). For an extensive list, see the recent consensus statement.[23]

Pathophysiology

The neuropathological hallmarks of RS are inflammation, neuronal loss, the presence of microglia activation, microglial nodules and astrogliosis. These characteristics have been described as early as in the index publication;[1] they have been elaborated in more detail by the Montreal group.[40] Pathological investigations in RS have been focused on the nature of the inflammatory response. Many earlier studies have dealt with (herpes-)viruses as potentially causative factors.[41–46] Still, although these reports suggested the presence of viruses, and treatment with ganciclovir decreased seizures temporarily in some patients,[47] a causal association of RS with a specific virus was never found. As mentioned above, neuronal damage by an antibody-mediated immune response through antibodies directed to the glutamate receptor subunit 3 (GluR3) was postulated.[30] Subsequent studies suggested that such antibodies not only killed neurons via an antibody or complement mediated attack,[48] but also that such antibodies might kill neurons via direct activation of the receptor ion channel.[49] Later, it became clear that anti-GluR3 antibodies were not present in all RS patients and were also found in other forms of epilepsy.[31–33] However, there is continuous evidence that plasmapheresis or immunoadsorption are effective in some patients. It seems likely that in these patients indeed autoimmune antibodies contribute to pathogenesis. The antigenic specificity of the underlying antibodies remains unclear. Recently, antibodies against the neuronal alpha7 acetylcholine receptor have been found in two RS patients.[50]

Recent reports have analysed the composition of the immune cells in the brains of patients with RS and found evidence that cytotoxic T cells play a role in RS. The T lymphocyte fraction in the brain parenchyma is mainly composed of $CD8^+$ cells. $CD4^+$ cells are present, but accumulate in the perivascular space of blood vessels rather than migrate into the parenchyma.[51] Other immune cells coming from the bloodstream, like macrophages, B cells, plasma cells and natural killer cells are present in low numbers.[36,51] The infiltration of T lymphocytes and density of microglia nodules (focal accumulations of activated microglial cells) are inversely correlated with disease duration as well as with neuronal loss.[21] Whereas during the course of disease neuronal loss increases, the presence of T lymphocytes gradually subsides to a level which,

however, is still well above that found in normal individuals.[21] About one tenth of the T cells in the inflammatory lesions are GranzymeB$^+$ cytotoxic T lymphocytes.[51] Some of these cells were found in close apposition to neurons with polarisation of the cytotoxic granules towards the neuronal membrane. This suggests that a cytotoxic T cell response against neurons might be responsible for neuronal loss. Further evidence suggests a specific T cell mediated destruction of neurons in RS: restricted T cell populations have expanded from a few precursor T cells specifically directed against distinct antigenic epitopes.[52]

Another prominent feature of RS is astrocyte activation. Moreover, a recent study showed that in RS there are also areas that reveal a dramatic loss of these astrocytes.[53] These astrocytes apparently also die by apoptosis induced by Granzyme-B$^+$ cytotoxic T cells. Astrocytes support neurons by many different functions, such as maintenance of potassium homeostasis and regulation of GABA and glutamate, neurotransmitters critically involved in epileptic processes. Therefore astrocytes are indispensable for normal functioning of neurons. Both the presence of hypertrophic astrocytes as well as their loss may have a serious impact on the disease severity.

Treatment

Treatment in RS has two aims: first, to reduce (or ideally: eliminate) the epileptic seizures, and secondly, to counteract the progressive tissue loss during the acute disease stage in order to improve the functional long-term outcome of patients.

Anti-seizure treatment

Antiepileptic drugs are started as soon as seizures start, but the seizures are often refractory to treatment. These drugs have no effect on the underlying course of the disease. Treatment should be adjusted to cause only a minimum of side-effects.[54] Injections of botulinum toxin have been successfully applied against localised EPC and other involuntary movements.[55,56]

The most efficient treatment against seizures has been hemispherectomy with seizure freedom rates of up to 85% (for a summary of outcome studies, see ref. 23). The anatomical hemispherectomies originally performed have now been largely superseded by functional hemispherectomy, involving disconnection techniques. Most neurosurgeons agree that in experienced centres, the individual technique of deafferentation should not influence seizure outcome, but only the rate of complications (lower with less invasive procedures). The exclusion of one hemisphere leaves the patient with a spastic hemiparesis without fine finger movements but usually with preserved walking ability (if there has not been a major surgical complication, if the patient was ambulatory prior to the operation and if he is not left with extremely frequent seizures afterwards).[57] In addition, a hemispherical procedure inevitably leads to a homonymous hemianopia. Patients seem to adapt rather well to this kind of disability.[58] Exclusions of the dominant hemisphere lead to high-grade aphasias. Whereas in such patients some receptive abilities may be regained postoperatively, no more than a telegraphic speech output is achieved by them.[59] The cognitive performance beyond the language aspect is not relevantly impaired by exclusion of the diseased hemisphere.[60] Sometimes (apparently because of the postoperatively lowered or even totally eliminated drug load and seizure activity), patients achieve a strong relief and a clear improvement in their day-to-day abilities.[61] The mortality of hemispherectomy in its modern variants (in RS and other conditions) has been 0–4%, the complication rate (including hydrocephalus requiring shunt placement) 0–44% [57,58,60,62–65]. Such a wide range in complications is striking. One important variable that accounts for this is the surgical methodology utilized, whether based on resection or disconnection. Disconnective techniques (functional hemispherectomy and hemispherotomy) are associated with a lower incidence of complications.[65–68] It must be noted that more focal resections have never been reported to be successful. They lead to an improvement in seizure control only in the short term, if at all.[62,69]

Treatment directed against hemispheric cerebral degeneration

Existing data indicate that in RS brain cells degenerate because of chronic inflammatory processes. Immunosuppressive or immunomodulatory treatments are therefore promising candidates to prevent tissue loss and improve the functional long-term outcome of affected individuals. Several treatment approaches have been reported in case reports or small, usually uncontrolled patient series, mostly with beneficial effects. As judged from these publications, most positive experience exists with long-term corticosteroids,[13,70,71] intravenous immunoglobulins (IVIG),[70–72] plasmapheresis or protein A immunoabsorption, [71,73,74] and oral tacrolimus.[75]

Suggestions for individual treatment regimens

The majority of RS patients suffer from epileptic seizures. Therefore, anticonvulsive pharmacotherapy is usually indicated. Epilepsy due to RS is often refractory to treatment and EPC is notoriously difficult to control: it is important to avoid excess treatment, and particularly polytherapy with multiple antiepileptic drugs, with their associated adverse effects, most prominently sedation.[54] Injections of botulinum toxin may be helpful in the management of involuntary movements and localised myoclonus associated with RS.[55,56] If, as is common, intractable seizures persist, the option of hemispherectomy should be considered and the potential benefit should be weighed against the deficits that are to |be expected. Most centers would not perform this operation in patients with still functional fine finger movements or patients with language representation within the affected hemisphere. If, however, the condition or its treatment causes such severe impairments that the expected benefits of surgery appear to outweigh the likely deficits, hemispherectomy may be offered.

In those patients in whom hemispherectomy is considered inappropriate, long-term immunotherapy with one of the above named treatments is indicated if the condition is still progressive (as judged by the clinical and neuroradiological course over the previous 6–12 months). The principal aim of this type of intervention is prevention of structural and functional

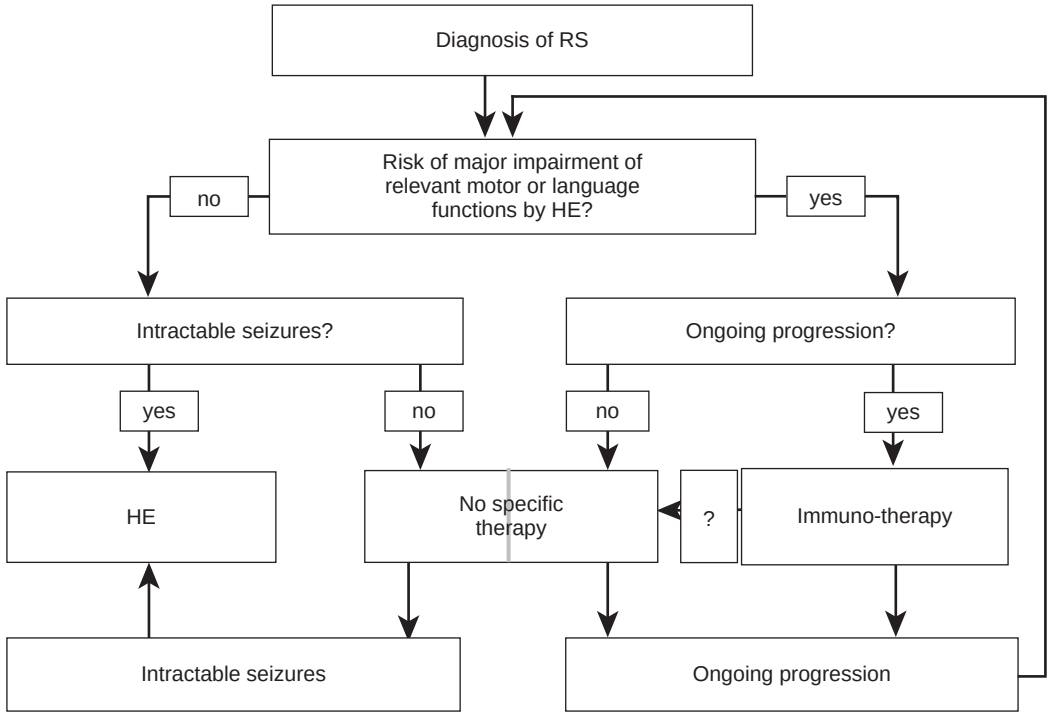

Figure 42.1. Therapeutic approach to a patient with Rasmussen syndrome (with permission from ref. 23). HE = hemispherectomy in one of its modern variants.

decline of the affected hemisphere. There is insufficient evidence to recommend any specific regimen. The most frequently reported successful regimens are: (1) long-term corticosteroids[13,70,71,76]; (2) intravenous immunoglobulins (IVIG)[70–72,77–79]; (3) corticosteroids plus IVIG[70,80,81]; (4) plasmapheresis or protein A IgG immunoadsorption[71,73,74,82]; and (5) tacrolimus.[75]

In general, the tolerability and the effect of long-term immunotherapy should be evaluated every 6–12 months. If the disease progresses during this time in the form of additional neurological deficits or increasing cerebral hemiatrophy, the treatment should be changed. When treatment is able to prevent further disease progression, it is unclear when immunotherapy may be discontinued. One might estimate that it would be reasonable to continue treatment until the patient's condition has been stable for at least 3 years (rather, for a longer period of time).

Management algorithm

The European consensus recommendations for therapeutic management of RS[23] are shown in Figure 42.1.

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43 The Landau–Kleffner syndrome

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Introduction

The Landau-Kleffner Syndrome (LKS) is an acquired epileptic aphasia or verbal auditory agnosia of childhood that results from an epileptogenic lesion in speech cortex (or that impacts speech cortex) during a critical period of language development. LKS is a disorder that occurs in children who have already developed age-appropriate language function and it is one of the epileptic encephalopathies with the electrographic pattern of Continuous Spikes and Waves during Slow Sleep (CSWS). The LKS was described in 1957 by William Landau and Frank Kleffner[1] in a report of six children, five of whom developed an acquired aphasia in association with an epileptic seizure disorder consisting of 'petit mal' 'grand mal' and myoclonic seizures. The aphasia had developed over days to months and persisted from 2 weeks to several years. These authors attributed the language dysfunction to the impact of the epileptic activity in language cortex. Indeed, they identified bilateral epileptiform activity in the children's EEG recordings pointing out the predominant involvement of the temporal lobes and suggested a relation between the severity of the paroxysmal discharges on EEG and the severity of language disturbance. In 1989, LKS was included in the International Classification of Epileptic Syndromes,[2] giving it legitimacy as a recognized clinical entity.

Epidemiologic aspects

The actual incidence and prevalence of LKS remains unknown at this time. Its prevalence is rare if the strict clinical diagnostic criteria proposed by Landau and Kleffner are applied. Recognition of LKS has increased over time as 81 cases were reported between the years of 1957 and 1980 and 117 cases between 1980 and 1990. Yet, the reported cases are more likely to include children with the more severe forms of the disease, while those in whom language disturbances remit spontaneously after a short period of time are less likely to be recognized and reported.

Ascertainment of the actual prevalence and incidence of LKS has been further complicated by the 'dilution' of its diagnostic criteria in the last decade. Indeed, the term 'LKS-look-alike' disorder has been applied to children with language disturbances who in the past would have been considered to suffer from an Autistic Spectrum Disorder (ASD) or children with the CSWS syndrome.[3] This diagnostic confusion has significant implications when the surgical option is being considered, as epilepsy surgery is thought to be more likely to improve language disturbances in children with 'true' LKS, while this does not appear the case in children with LKS-look-alike or those with CSWS syndrome or ASD (see below).

Etiology of LKS

The LKS does not have a single etiology. For example, an analysis of neuropathologic specimens of 22 consecutive children that underwent epilepsy surgery at the Rush Epilepsy Center revealed a variety of abnormalities: astrocytosis was identified in 11 (52%), ectopic neurons in two (9.5%), focal displasia in another two (9.5%), while no abnormal findings were identified in six patients (29%); no specimen was available for analysis in one child. Likewise, Cole and collaborators[5] have identified a variety of pathologic entities in their series of children with LKS including neurocysticercosis, encephalitis, vasculitis, subpial gliosis and neuronal migration disorder. It should be noted that the absence of pathologic findings in several of these children may be a function of having taken an insufficient amount of tissue for neuropathologic analysis as there is hesitation to remove tissue from presumed language areas, even if they show the most active epileptic discharges and the mapping of eloquent cortex is not an option when language is so severely impaired.

Clinical manifestations of LKS

The diagnosis of LKS is based on a set of clinical, electrographic and neuropsychological characteristics.

Clinical criteria

The clinical manifestations of LKS include language disturbances, behavioral problems with or without sleep disturbances, epileptic seizures (and/or very abnormal EEG recordings with epileptiform activity), and abnormal findings in verbally mediated cognitive functions with sparing of visually mediated functions.[6–9] The symptoms of LKS appear between the ages of 2 and 8 years in children who had a normal language development with an acute or subacute onset, though occasionally they may take a stuttering initial course.

Language disturbances present initially as problems with verbal comprehension that progress in severity to a total inability to understand what is being said to them as well as to recognize common sounds (auditory agnosia). It is not

infrequent for these children to be initially misdiagnosed with acquired deafness.[6,7] Concurrent with, or a short time after the onset of receptive language disturbances the child starts displaying signs of expressive language deficits such as paraphasias and phonological errors. The establishment of normal language development is of the essence in distinguishing children with LKS from children with other types of language disturbances including children with an autistic spectrum disorder (ASD). In fact, it is not infrequent that parents may give an 'erroneous impression' of normal cognitive developmental milestones in their child. Yet, a careful analysis by speech pathologists of home video-tapes during the 'asymptomatic' development of these children can often reveal delayed expressive and/or receptive language functions relative to the chronologic age.

The onset of language disturbances (and of other clinical symptoms) has been linked in-time with the onset of clinical seizures or a short time after. Electrographic evidence of epileptiform activity presenting as a pattern of CSWS or long runs of bisynchronous or unilateral epileptiform discharges in temporo-parietal and frontal derivations can be identified in patients without obvious clinical seizures at the time of onset of language disturbances. These electrographic data coupled with the language disturbances help clinicians to consider the possibility of LKS.

Language disturbances can progress in a steady or fluctuating manner to a state of complete mutism in the course of a few days to a few weeks, or as stated above, in a few children, they may follow a stuttering course.[8,9] The duration of language disturbances may vary among patients. At one end of the spectrum are children that are symptomatic for periods of only days to weeks followed by complete spontaneous remission.[6] At the other end, are children whose language disturbance progresses to a global aphasia and auditory agnosia, occasionally with a waxing and waning course but with no meaningful recovery of any functional language despite multiple pharmacologic interventions.[9–17] In some children a careful history can often reveal fluctuations in the severity of language disturbances with intermittent periods of improvement in expressive and/or receptive language functions of variable magnitude. These fluctuations in symptom severity can often, but not always be associated with a parallel improvement or worsening of seizure frequency.

Children with LKS are often able to communicate through nonverbal means such as sign language. For example among 22 consecutive children with classic LKS evaluated at the Rush Epilepsy Center for epilepsy surgery, 11 (50%) had learned to use sign language.[4]

There have been unfortunately few studies that have investigated the long-term course of language disturbances in LKS patients. Mantovani and Landau[10] found a significant recovery in language functions in four of nine patients who were re-evaluated 10–28 years after the onset of their symptoms. On the other hand, only one of seven patients followed by Deonna *et al.*[11] into adulthood recovered language functions completely; a second patient recovered functional language but was left with severe dyslexia, a third patient exhibited significant deficits in comprehensive language while the other four patients continued to suffer from global aphasia. Various investigators have concluded that spontaneous recovery of functional language in the long-term is unlikely in patients with persistent language disturbances for more than one year.[9,10,12–17]

While the onset of language disturbances can be in general temporally linked to the onset of seizures, their remission does not immediately follow the control of seizures or abolition of epileptiform activity with steroids or epilepsy surgery (see below).[18]

Seizures are usually of mild severity and are often nocturnal; their clinical manifestations vary widely ranging from generalized tonic-clonic seizures (GTC) to complex partial and simple partial seizures often displaying very subtle clinical signs such as brief clonic deviation of the eyes, at times associated with eye blinking, head dropping, and minor automatisms.[18] Up to 20–30% of patients with LKS are never found to have epileptic seizures[8] and in some children seizures are identified for the first time in the course of a prolonged video-EEG monitoring study (V-EEG). Unlike the language disturbances, seizures tend to respond readily to pharmacotherapy with AEDs,[8,9] and generally subside by the age of 15.[19]

Behavior disturbances are very common in patients with LKS; their onset can precede, appear concurrently or follow the language disturbances. Motor hyperactivity, impulsivity and poor frustration tolerance are among the most frequently reported symptoms seen in up to 50% of children[8,9] and this cluster of symptoms is often indistinguishable from a severe Attention Deficit Hyperactivity Disorder (ADHD). In a study of 18 children with LKS, Robinson *et al.*[20] found behavioral disturbances in nine children, which was associated with frontal lobe discharges in *awake* EEGs.[18] Sleep disturbances can also be common and present as difficulty falling asleep and/or middle of the night awakenings associated with bouts of screams and agitation.

At the height of the auditory agnosia, some children have been reported to exhibit autistic-like features such as withdrawn and self-stimulatory behaviors. Nevertheless, children with LKS do not loose their social relatedness to others. Failure to recognize this important difference has resulted in the misdiagnosis of children with an ASD as suffering from LKS.

Behavioral disturbances can often be extremely disruptive at home and in school often requiring the use of symptomatic treatment with psychotropic drugs, such as central nervous system stimulants (methylphenidate and dextroamphetamine), antipsychotic (risperidone, haloperidol, etc.) and antidepressant drugs (i.e., selective serotonin-reuptake inhibitors [SSRI]) and alpha-adrenergic blockers such as clonidine, all of which have been found to yield mixed results. Behavioral disturbances can be expected to improve to various degrees in many but not all children following the remission of clinical seizures and/or of epileptiform activity on EEG recordings. Following epilepsy surgery, behavioral improvement can precede the recovery of language functions.

Pathophysiology

The relationship between epileptiform activity and language disturbances has been considered as the 'core' pathogenic mechanism of LKS,[1,12,18,21] but remains to be universally accepted by all investigators.[22] Deonna reviewed the arguments both for and against the role of epileptic causality of language disturbances.[21] Supportive evidence included speech recovery in some patients, coincident with the disappearance of EEG abnormalities when treated with steroid, antiepileptic agents or epilepsy surgery with multiple subpial transection (MST). Holmes *et al.*[22]

suggested that both the epileptic discharges and language disturbances were epiphenomena of underlying pathologic abnormalities in the speech areas. Arguments against an epileptic cause include the development of clinical seizures in some children long before or long after the onset of language dysfunction and the persistence of language disturbances after remission of electrographic epileptic activity. Additionally, some children never develop clinical seizures, although they typically do have abnormal EEG recordings with epileptiform activity.

Morrell suggested the following hypothesis to explain the development of LKS:[12,18]

> It is well known that different neural systems have critical periods in development during which the adult patterns of synaptic engagement are gradually established. At such times, there is first a superabundant outgrowth of axon terminals resulting in a temporary hyper-innervation of the synaptic target; this extravagant outgrowth appears to be entirely under genetic control. Over the remainder of the critical period, the synaptic contacts are extensively pruned. The pruning is selective; it is dependent on and controlled by synaptic use, i.e., environmental input. Synaptic contacts activated by use become cemented, so to speak, while those not environmentally engaged wither away.[23–29] Neural networks for linguistic function develop late and their circuitry remains malleable during the first 8 to 10 years of life.[30–33] We hypothesize, then, that the impact of epileptic activity originating from this anlage of speech cortex may result in chaotic and behaviorally meaningless activation of synaptic contacts that would have been 'pruned' under normal circumstances. Such epileptic activity may set up permanent, inappropriate and nonfunctional linkages.

Data from experimental studies in animals support Morrell's hypothesis showing that epileptogenic lesions induced during a critical period for circuit development cause the emergence and fixation of long-lasting or permanent aberrant connections.[34,35] Morrell's hypothesis and the data of Baumabach and Chow[34] and of Grigonis and Murphy[35] provide an explanation for the development of language deficits associated with the temporal gap between the onset of epileptiform activity (and/or seizures) and the failure to regain language functions after remission of electrographic epileptiform activity.

Diagnostic evaluations

An initial evaluation consists of a thorough and detailed clinical history aimed at identifying all the clinical signs and symptoms cited above and the temporal relation between the onset and course of language/behavioral disturbances and seizure activity. Auxiliary studies include a high resolution magnetic resonance imaging of the brain (MRI), an EEG study with awake and sleep recordings and a neuropsychological evaluation that includes a speech evaluation and evaluation of nonverbal cognitive functions.

EEG studies as part of an initial evaluation

As stated above, the CSWS pattern is the characteristic electrographic finding of LKS. It consists of runs of spike- and slow-wave that take up *at least 80% of slow-wave sleep* and hence the EEG study has to be scheduled to be of long enough duration to record slow-wave sleep. This may be facilitated by the use of 25 mgs of amytriptyline in a single dose. The epileptiform activity presents typically as 'apparent' bisynchronous runs of spike- and slow-wave with a wide distribution maximal in posterotemporal regions (see Figure 43.1), but in some patients it may have a unilateral distribution.

Mapping of the bisynchronous epileptiform activity can often reveal the unilateral source that propagates to the contralateral side with a 20–25 millisecond gap (see Figures 43.2a and 2b).[12,18,36]

Awake electrographic recordings may show epileptiform discharges with a focal distribution in frontal, temporal or parietal regions and usually in a discontinuous pattern,[18,19] though temporal spikes are most frequent. Background activity during wakefulness may be normal. Serial EEG recordings may vary within the same patient in the amount and degree of focality of epileptiform discharges.[9] Furthermore, a normal sleep record does not necessarily rule out the diagnosis of LKS, as fluctuation in the severity of EEG abnormalities is a rather common finding. The absence of epileptiform activity may be often encountered in children with steroids or benzodiazepines, even in the absence of any clinical improvement.

Electrophysiological studies as part of a presurgical evaluation

Epilepsy surgery for the treatment of LKS follows the same principles that any other type of epilepsy surgery: there has to be concordance between interictal and ictal data obtained during V-EEG and with other neurophysiologic studies such as MEG. Thus, the first study is a V-EEG with scalp electrodes with the aim of identifying the presence of a sylvian dipole and establishing whether the epileptogenic zone extends beyond the intra and perisylvian region. In addition, the goal of the V-EEG is to identify clinical seizures that may have gone unrecognized up to then by the parents (up to 30% of children with LKS are reported not to have seizures), because of their subtle clinical manifestations.

Sylvian dipole

As stated above, the mapping of epileptiform discharges with referential montages or with source localization programs can identify a dipole with negativity in the frontal regions and positive polarity in temporal electrodes.[37] Thus the epileptiform discharges in LKS reflect a generator source represented by a tangential dipole in the inferior bank of the sylvian fissure (on the superior surface of the temporal lobe); therefore we refer to this pattern as the sylvian dipole. The search of a sylvian dipole must be done in the first discharge of a run of epileptiform discharges, as subsequent discharges may reflect the area of spread of the epileptic activity beyond the perisylvian area.

Methohexital suppression test (MHXST)

The vast majority of patients' electrographic recordings reveal a CSWS pattern with 'apparent' bisynchronous discharges with a wide field of distribution but with maximal electronegativity in temporal lobe derivations. The onus of the

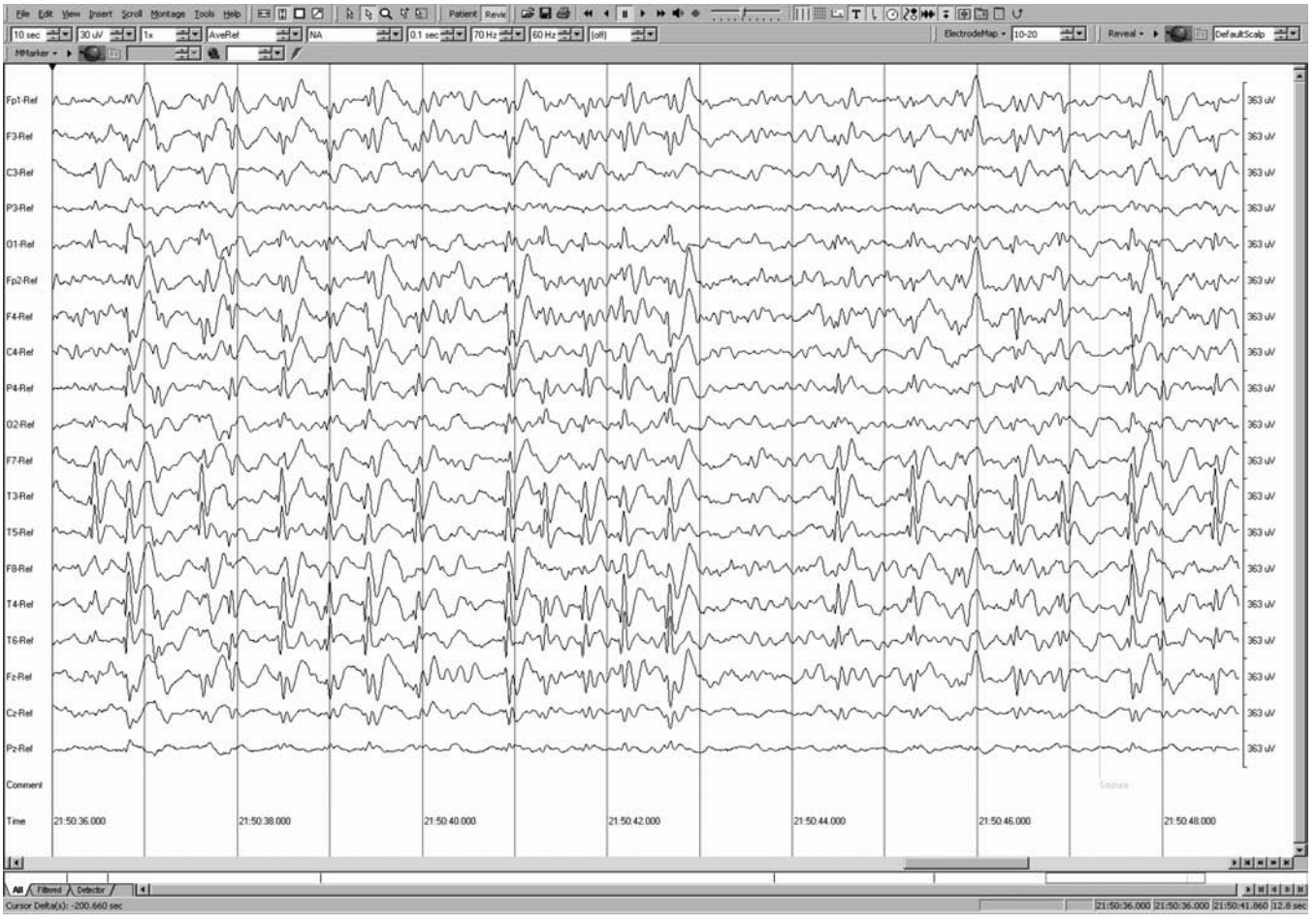


Figure 43.1 Electrographic pattern of CSWS.

electroencephalographer is to determine whether the epileptiform activity has a unilateral source within the sylvian region, or is of bilateral independent origin.

The use of methohexital (MHX) is aimed at identifying independent epileptiform activity within the CSWS; it is a barbiturate known to block excitatory synaptic transmission and, at low doses, to enhance inhibitory synaptic action.[38,39] During intravenous infusion of MHX at doses high enough to cause electrocerebral silence, almost all excitatory transmission is abolished, with the exception of a few oligosynaptic systems with high safety factors, such as the direct thalamocortical relay (see Figures 43.3a and 3b). Under these circumstances, autonomous and truly independent epileptogenic lesions show a marked resistance to synaptic blockade and continue to fire; the epileptiform discharges stand out sharply against a flat EEG background.

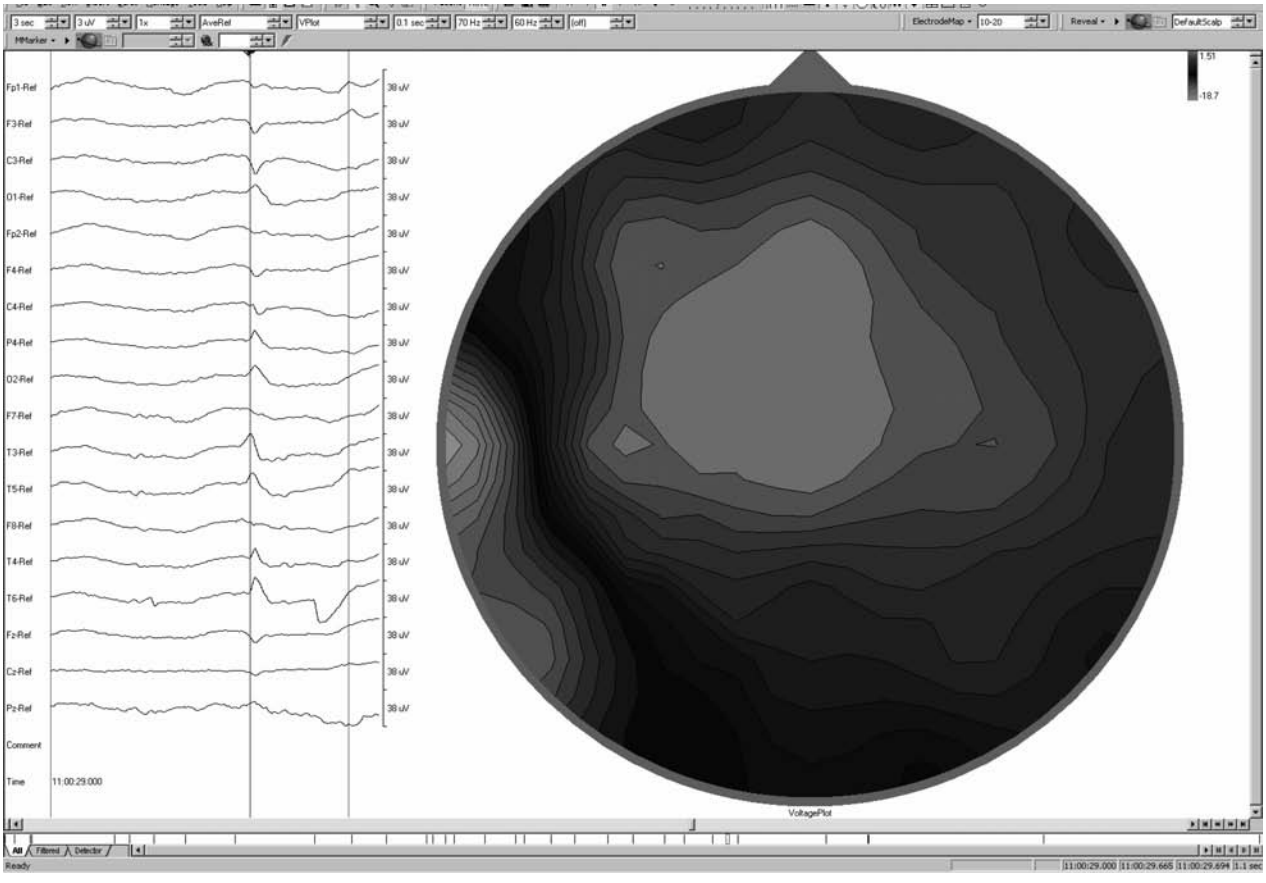
Conversely, epileptogenic lesions that are not independent and depend on synaptic input (i.e., epileptic discharges secondarily driven from a primary focus) are silenced along with the ongoing EEG rhythms.

The MHX suppression test (MHXST) is carried out by administering the drug at a rate of 100 mg/min until a 60 s period of total electrocerebral suppression is reached. The test is carried out in the V-EEG monitoring unit at the patient's bed side with an anaesthetist present, since at the deepest levels of MHX anaesthesia, a few minutes of apnoea occurs. The anaesthetist provides bag-breathing with room air. Intubation has never been necessary in more than 400 cases and the only morbidity has consisted of mild transient acceleration of the heart rate and transient hiccups.

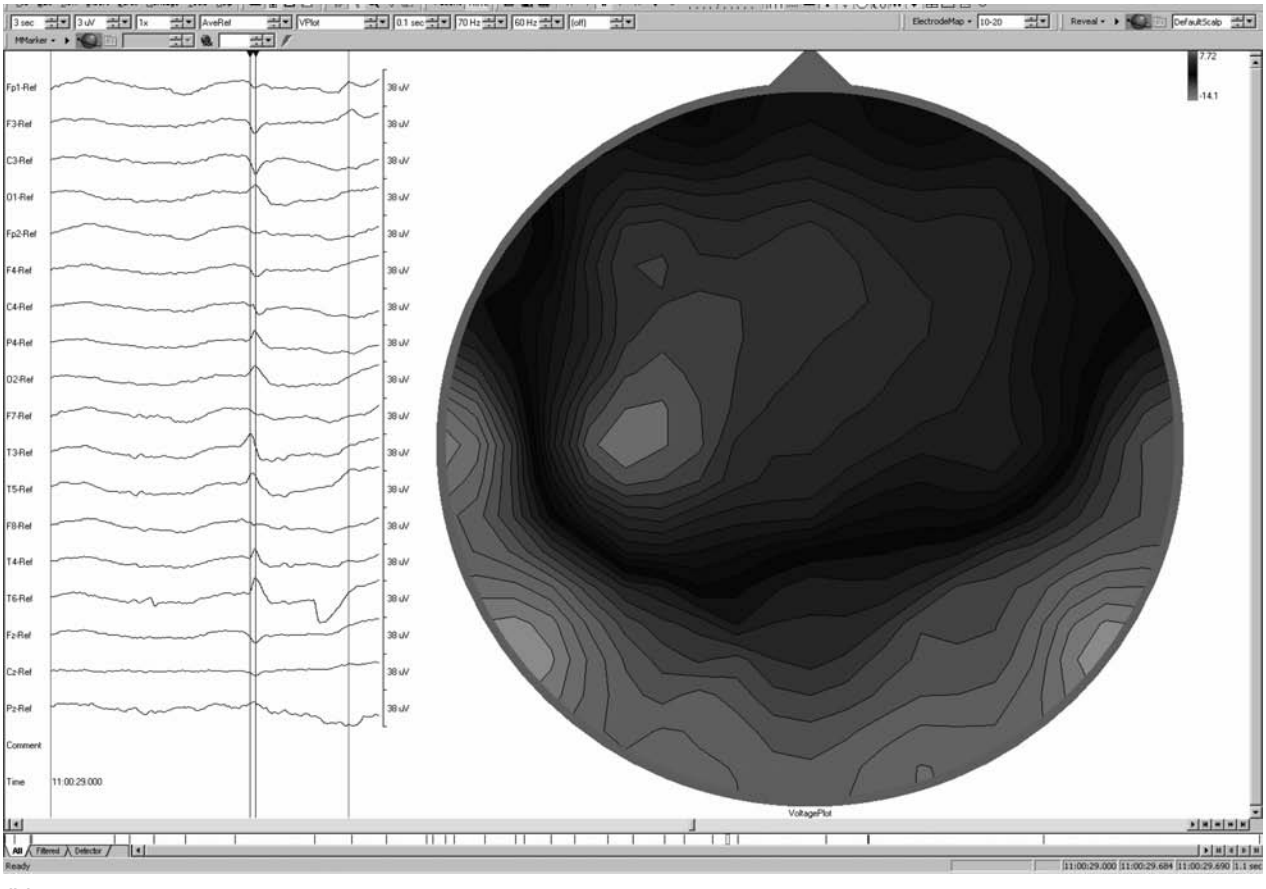
Magnetoencephalography studies

In the last ten years, MEG has become one of the presurgical tests of LKS. MEG is sensitive to epileptic activity originating from the depths of sulci, such as the sylvian fissure, because it reveals magnetic fields generated by transmembrane synaptic currents oriented in a plane tangential to the skull surface.[40–42] MEG performed on a small number of patients with LKS revealed a focus of epileptiform activity in the posterior temporal area adjacent to the sylvian fissure, supporting an origin in the dorsal surface of the superior temporal gyrus (see Figure 43.4a) and propagation to homotopic regions contralaterally (see Figure 43.4b).[12,42]

The use of MEG has been useful in identifying children with Autistic Spectrum Disorder (ADS) that may have been misdiagnosed as LKS. Indeed, Lewine *et al.*[40] compared the MEG data between six children with LKS and 50 children with ADS. In all the children with LKS, MEG revealed primary or secondary epileptiform involvement of the left intra/perisylvian region, with all but one child showing additional involvement of the right sylvian region. In all cases of LKS, independent epileptiform activity beyond the sylvian region was absent, although propagation of activity to frontal or parietal regions was seen occasionally. MEG identified epileptiform activity in 41 of the 50 (82%) children with an ASD that included intra/perisylvian regions in 85% of the cases and

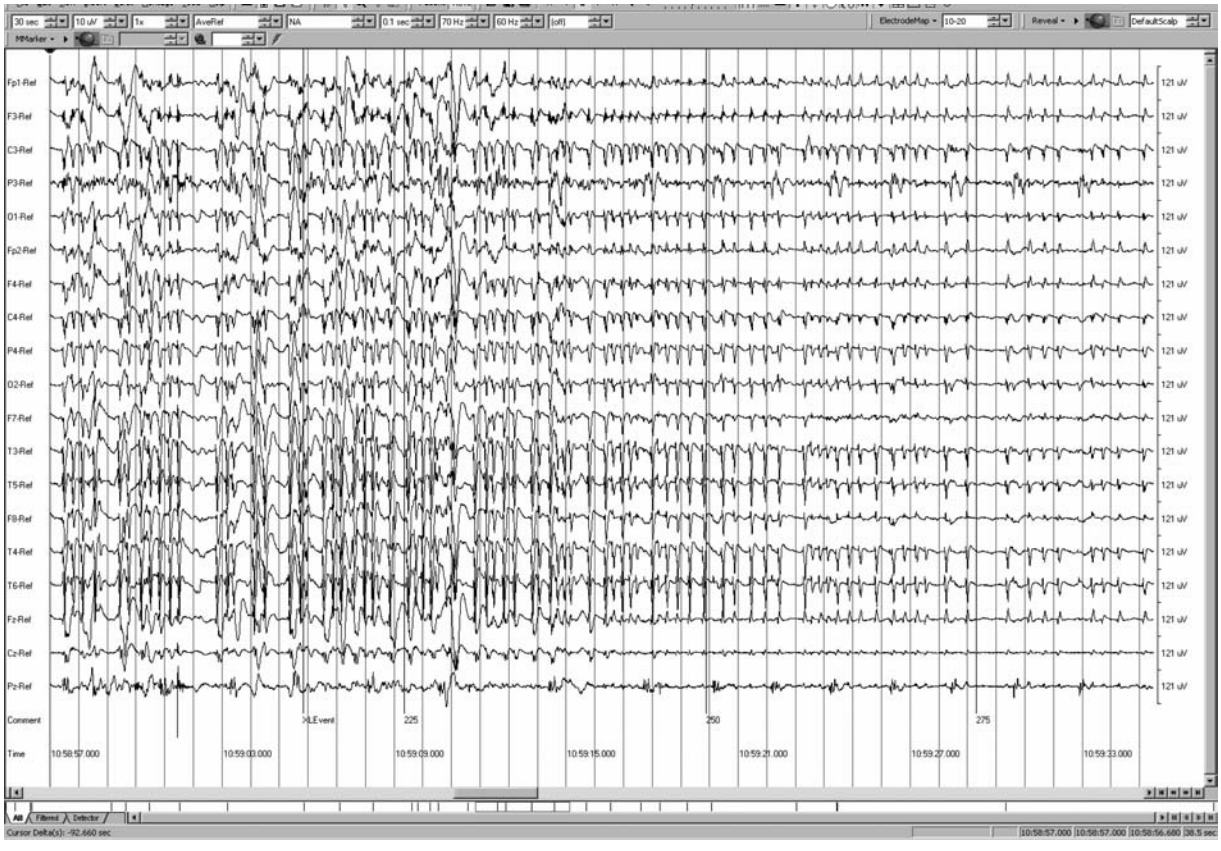


(a)

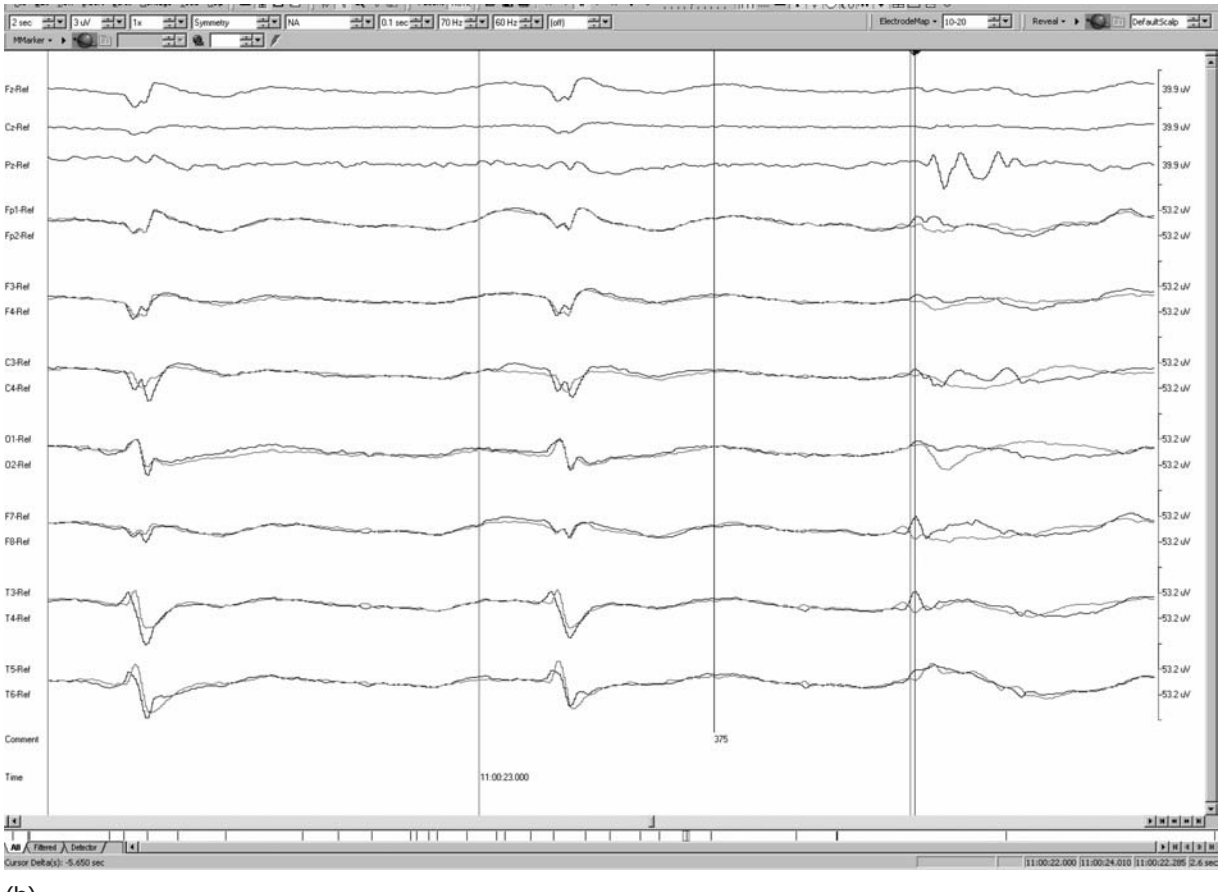


(b)

Figure 43.2 (a) Mapping of epileptiform discharge indicating a left temporal origin. (b) Propagation of the epileptiform discharge to homotopic regions in the right hemisphere.

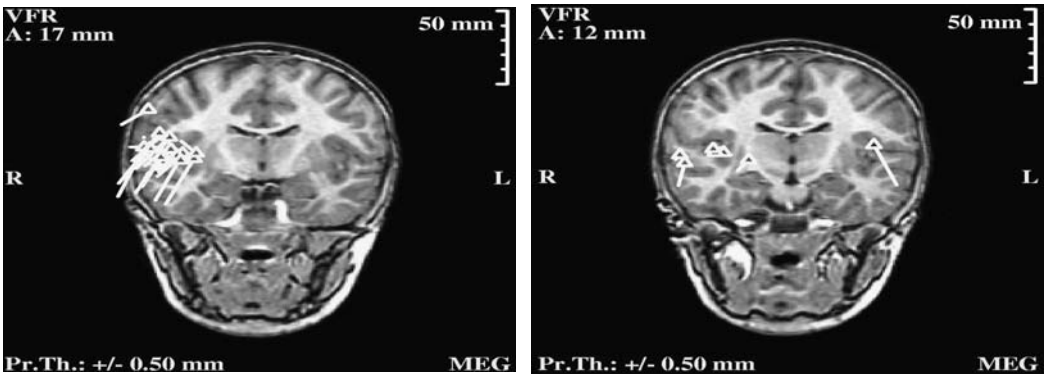


(a)



(b)

Figure 43.3 (a) Compressed recording of the initial phases of the MHXST. The initial segments of the recording reveal an activation of epileptiform activity followed by the appearance of periods of electrocerebral suppression of longer duration as the infusion of MXT progressed at a rate of 100 mg/min. (b) Following the disappearance of the background activity, a superimposition of recordings from homologous electrodes reveals an initial discharge in the left that rapidly propagates to the right side.



(a) (b)

Figure 43.4 (a) MEG dipole co-registered on MRI reveals a right intrasylvian source of epileptic activity. (b) Red triangles indicate the source of the epileptic activity in the right sylvian cortex, while the blue triangles represent the propagated dipole to the contralateral side.

75% of the ASD children with epileptiform activity demonstrated additional nonsylvian zones of independent epileptiform activity. Thus, this study documented the utility of MEG to identify different location(s) of epileptogenic zones in LKS and in ASD, as well as the different electrographic patterns of their recorded epileptiform activity.

The valuable use of MEG has been reported in other small case series of LKS children. Thus, Pateau *et al.*[41] carried out an MEG in four children. In all patients, the earliest spike activity originated in the intrasylvian cortex, spreading in one subject to the contralateral sylvian cortex within 20 ms. Secondary spikes occurred within 10–60 ms in ipsilateral perisylvian, temporo-occipital, and parietal-occipital areas. A single intrasylvian pacemaker initiated all epileptic activity in two patients, whereas the other two had independent left- and right-hemisphere circuits or focal spikes. MEG source dynamics predicted the results of the methohexital suppression test in two patients and was confirmed by surgery outcome in one patient, in whom all epileptic activity ceased after a small transection of the sylvian pacemaker.

Sobel and colleagues found that 13 of 19 patients with LKS had perisylvian MEG spikes.[42] In 10 of the patients, the spikes were bilateral, and in three they were unilateral. Four children had nonsylvian spikes. Interestingly enough, these children displayed various other behavior and cognitive dysfunction in addition to the aphasia, which questions their diagnosis of LKS and confirms the data reported by Lewine *et al.*

V-EEG with intracranial recordings

In the case of discordant data derived from MEG and scalp-V-EEG or if lateralization of the source of epileptic activity cannot be achieved with non-invasive studies, repeat V-EEG with intracranial electrodes is considered. At the Rush Epilepsy Center, two or three pairs of eight contact epidural electrodes are used. These are placed parallel to the sylvian fissure, one about 1 cm. superior to the fissure, the second over the fissure and the third about 1 cm inferior to the fissure. A repeat MHXST is carried out with these electrodes and at the time of surgery, the electrodes contralateral to the side of surgery are kept in place for recording of the epileptiform activity throughout the procedure.

Neuroimaging studies

MRI

High resolution MRI studies must be carried out in all presurgical evaluations of LKS, as they may reveal subtle malformations of cortical development that may go undetected with standard MRI. In addition, this new technology lends itself to volumetric measurements of various neuroanatomical structures. A case in point is illustrated in a recently published study by Takeoka *et al.* who compared the cortical volume of the superior temporal areas corresponding to the auditory association cortex in four children with LKS and four children with other types of focal epilepsy.[41] The authors divided the entire neocortex into parcellation units and counted the number of voxels in each parcellation unit. All children with LKS had a reduction of 36–51% in the cortical volume of the superior temporal areas. It is not clear, however, whether the smaller volume reflects a cause or consequence of this disorder.

Positron emission tomography studies (PET) have been carried out in a small number of patients with LKS. In studies performed in the awake state, PET with 2-[^{18}F] fluoro-2-deoxy-D-glucose (^{18}F-FDG) have shown an area of decreased blood flow or glucose utilization, while the opposite occurs when the radionucleotide is injected during slow wave sleep when recordings reveal a CSWS pattern. For example, Da Silva *et al.*,[44] evaluated 17 children with LKS with 18-FDG PET; 15 out of the 17 patients had bitemporal glucose hypometabolism and in two the area of hypometabolism was unilateral. The patients were awake for the uptake period of FDG. On the other hand, studies done on sedated patients with induced continuous spike-and-wave discharges showed a focal area of increased blood flow or glucose utilization.[12,45,46] Maquet and colleagues reported that some patients who underwent [^{18}F]FDG-PET after the resolution of the active phase of spike-and-wave discharges showed persistent hypometabolism in the areas that previously showed hypermetabolism, documenting long-lasting metabolic alterations.[45] Of note, areas of cortical hypermetabolism are not specific to LKS and can be seen as well in children with CSWS syndrome.[46]

Neuropsychologic and speech evaluation

The purpose of the neuropsychological and speech evaluations is twofold: to identify the type (i.e., expressive vs. receptive vs. both)

and severity of language disturbances; and to establish whether cognitive problems are restricted to verbally mediated functions or if there is involvement of nonverbal cognitive functions. Two tests are typically (but not exclusively) used for evaluation of language functions. The Peabody Picture Vocabulary Test-revised (PPVT-R) is a measure of receptive vocabulary. During the test the child is asked to point to one of four pictures displayed on a card as depicting the word spoken by the examiner. The Expressive One Word Picture Vocabulary Test-revised (EOWPVT-R) is a test of expressive vocabulary. The child is shown a picture and asked to name it.

The findings of neuropsychological testing have been associated with different discharge patterns of epileptiform activity. For example, Guilhoto and Morrell[47] carried out a retrospective analysis of 19 cases referred with a presumptive diagnosis of LKS, and with the EEG pattern of CSWS. They separated the children into two groups: group 1 included those erroneously thought to have LKS (also known as 'LKS-look-alikes', $n = 8$) and group 2 those with 'true' LKS (cognitive disturbances restricted to the verbal domains, $n = 11$). Mapping of the distribution of electrical abnormality revealed that 6/8 patients in Group I had widespread, multifocal discharge. One out of the eight cases had bilateral high parietal disturbance and 1/8 had a primarily left-sided abnormality that became bilateral and multifocal during slow-wave sleep. All of the patients in group 2 (11/11) showed discharges limited to the parietal-temporal region of both hemispheres which revealed the characteristic sylvian dipole with frontal negativity and temporal positivity, as described above.

Differential diagnosis

The differential diagnosis of LKS includes CSWS syndrome, the ASDs and secondary aphasias.

CSWS syndrome

As stated above LKS is not the only epileptic encephalopathy with a CSWS electrographic pattern. The CSWS syndrome has been recognized as a distinct entity by the Commission on Classification and Terminology of the International League against Epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy and by the International Classification of Diseases (ICD-10).[2,48] This syndrome was initially described by Patry *et al.* in 1971 as 'subclinical electrical status epilepticus during sleep'[49] and then retitled by Tassinari as electrical status epileptic during sleep (ESES) in a report of six children, aged 7 to 12 years old, five of whom were mentally retarded and all exhibited language disturbances, epileptic seizures and very abnormal EEG recordings consistent with a CSWS pattern described above. The epileptic seizures were of various types including tonic, atonic, clonic, generalized tonico-clonic and atypical absences. The severity of mental retardation was related to the age of onset.[48] Tassinari later changed the name of this syndrome to CSWS syndrome.[3]

The following differences between LKS and the CSWS syndrome can be identified based on data from publications by Beaumanoir[50] and Bureau,[51,52] that included analyses of clinical and electrographic findings in 71 children with LKS and 103 children with CSWS syndrome. Landau-Kleffner syndrome tends to affect a slightly younger population, presenting first with language dysfunction and behavioral deterioration. In CSWS syndrome, the affected children tend to be slightly older, presenting with more global neuropsychologic and behavioral deterioration in addition to the language dysfunction.[51,52] The severity of the seizures and EEG abnormality are more pronounced in CSWS syndrome in which seizures are more likely to be significantly more frequent of all types including atonic seizures with falls, absence and atypical absences, GTC and hemiclonic seizures. The spike-and-wave discharges are maximal in the centro-temporal or posterior temporal regions in LKS and in the frontal head region in CSWS syndrome. The seizures in CSWS syndrome are often difficult to control, primarily among the subgroup of patients with atypical absence seizures and drop attacks which are resistant to treatment with AEDs. The patients with CSWS syndrome had more frequent MRI abnormalities (33%) than children with LKS (13%). Interestingly enough, seizure remission was comparable between the two groups after resolution of the CSWS pattern.[49,52]

Autistic spectrum disorders are behaviorally defined syndromes with various etiologies that are manifested by deficits in verbal and nonverbal communication, social interaction deficits and repetitive behaviors or a restrictive array of interests.[53] About 30% of children with ASD experience a language regression and one-third develop epilepsy by the time they reach adolescence.[54] Furthermore, interictal epileptiform discharges in centro-temporal regions have been identified in a certain percentage of children with ASD that never go on to experience clinical seizures.[54,55] Recently, the term of autistic epileptiform regression has been coined to refer to children with autistic regression in the context of an epileptiform EEG.

Tuchman[54] has investigated the association of epileptic seizures and language regression in 585 children with ASD. No difference was found in seizure occurrence between the children with or without language regression. On the other hand, the EEG recordings of children with language regression were significantly more likely to exhibit interictal epileptiform discharges (14% vs. 6%, $p = 0.02$).

In contrast to LKS, a normal development of language cannot be traced in many children with ASD. Rapin[53] has also suggested that in patients with reported 'normal' language development, a careful history may in fact reveal that such was not the case. As stated above, a review of family video tapes may help the speech pathologist establish whether the child already exhibited a developmental delay before the 'more overt' evidence of language deterioration was identified by parents. Children with ASD have been found to exhibit a compromised drive to communicate, difficulty with comprehension of gestures, facial expression and tone of voice and immediate echolalia (pronoun reversal) delayed echolalia (scripts, formulaic speech) and perseveration. In addition they display self-stimulatory behavior, marked difficulty with adjusting to minimal changes and loss of social relatedness.[53,56] From a cognitive standpoint, these children display across the board cognitive deficits.

The differential diagnosis of LKS also includes differentiation with developmental language disorders with or without an epileptiform EEG, which consist of lack of development of age appropriate language skills in an otherwise cognitively and behaviorally normal child.[54] Finally, since hearing difficulties

may present as apparent language impairment, auditory function should be assessed by behavioral and/or electrophysiological means.

Nonsurgical treatment

Pharmacologic treatment

There is a dichotomy in the response to AEDs of clinical seizures and language disturbances. Indeed, remission of clinical seizures is readily achieved in a majority of patients, while the opposite is true when it comes to cognitive disturbances. Often, the improvement of language functions may be more an expression of a spontaneous remission than a real therapeutic effect of AEDs, above all in the early phases of the disease. Furthermore, due to the rarity of the disorder controlled clinical trials have not been done.

Pharmacologic treatment of LKS has included trials with AEDs, steroids and IV immunoglobulin (IVIG).

Antiepileptic drugs

Using the trial and error approach some investigators have suggested that AEDs like valproic acid (VPA) benzodiazepines and ethosuximide can yield (at least partially and/or temporarily) a therapeutic impact in both language and seizure disturbances while carbamazepine, and phenytoin can worsen the course of LKS.[57] In fact these two AEDs were found to increase the duration of spike-wave activity in sleep; phenobarbital was thought to have no therapeutic effect on language functions but to worsen the child's behavioral problems.

In most cases an initial trial with valproic acid is usually carried out before trying any of the other AEDs. Clobazam has been reported to significantly reduce continuous spike-wave discharges in several small studies, associated with language improvement.[57,58] Vigabatrin,[59] felbamate,[60] lamotrigine, and recently levetiracetam have also been reported as effective as well.

Diazepam has been successfully tried in the management of language and behavioral disturbances in children with LKS. In a protocol that calls for the administration of rectal diazepam (Diastat®) at a dose of 1 mg/kg under V-EEG on day one, Riviello *et al.* have found suppression or reduction of the epileptiform activity associated with an improvement of language functions in a small group of children with LKS. The child is then placed on a maintenance oral dose of 0.5 mg/kg/day and kept on this dose for three to six months (*Riviello JJ*, unpublished data). In the case of bisynchronous epileptiform activity, the administration of rectal diazepam resulted in suppression of the propagation of the epileptiform activity to the side contralateral to the seizure focus (*Kanner*, unpublished data).

Steroids

The use of steroids in LKS has included trials with prednisone and ACTH. Oral prednisone has been given as daily doses or as pulse doses on a weekly basis to minimize potential adverse events. Trials have ranged from 3–6 months to long-term trials, depending on clinical response, tolerability and the preferences of individual centers. Some reports have suggested a favorable acute and long-term response of short and long-term duration.[62–64]

The use of ACTH calls for 80 U/day with a three-month taper. Most centers have preferred the use of oral prednisone. At the Rush Epilepsy Center, it is started at a dose of 2–3 mg/kg/day and tapered down over the course of 3 months. The trial of prednisone may be extended at minimal effective doses, provided that the child has derived a significant improvement in language function and *in the absence* of significant adverse events such as behavioral problems (such as aggressive behavior, motor hyperactivity, impulsivity (beyond that already caused by the LKS), sleep disturbances, hypertension, diabetes, obesity. Long-term use of steroids can be frequently associated with the risk of developing the above-cited problems in addition to a Cushingoid appearance, cataracts and osteopenia/ osteoporosis.

Sinclair and Snyder[62] recently reported on their experience with long-term steroid therapy in eight children with LKS and two with CSWS; three were females and seven males and the age of onset ranged from 2–11 years (mean 7.5 years). The patients received prednisone 1 mg/kg/day for 6 months, 1 year, then yearly. After a mean follow-up period of 4 years (range 1–10 years), all but one patient manifested significant improvement in language, cognition, and behavior, which persisted after discontinuation of steroids. Side-effects were reported in four patients and were transient; they included weight gain (2), behavioral change (1), and hypertension (1). Tsuru *et al.*[63] have reported on the use of high-dose IV steroids in two children with LKS. Both patients were treated with high-dose methylprednisolone sodium succinate (20 mg/kg daily) for three consecutive days. This infusion was repeated three times with a 4-day interval between treatments, which resulted in a rapid improvement in speech ability. After intravenous therapy, prednisolone was given orally (2 mg/kg daily for 1 month, then gradually withdrawn), which maintained the clinical improvement in language functions. Lerman *et al.*[64] reported on the treatment of four children with LKS with early and prolonged ACTH or corticosteroid therapy, with high initial doses. In all four cases the EEG promptly became normal, with subsequent long-lasting remission of the aphasia and improvement of seizure control. Three to 6 years after discontinuation of hormone therapy the children were off medication and free from seizures and language disability. Marescaux[58] treated three children with LKS with steroid therapy which resulted in improved speech, suppression of seizures, and normalization of the EEG in the three. These authors advocated the administration of corticosteroids in high doses as soon as the diagnosis is established and to maintain on these doses for several months or years to avoid symptom recurrence.

While steroid therapy is the pharmacologic treatment most likely to yield to significant improvement in language disturbances, its discontinuation is often followed by symptom recurrence or loss of gains made. For example, in a study of 22 children with LKS evaluated at the Rush Epilepsy Center,[4] 20 underwent a trial with prednisone. Nine of these children (45%) regained functional language but steroids had to be discontinued because of adverse events. Of note, a recovery of functional language with steroids was a predictor of a recovery of functional language six months after epilepsy surgery.

Intravenous immunoglobulin

The use of IVIG has been reported in isolated cases or small patient series. Mikati *et al.*[65] reported the first case of a

31-month-old child with LKS treated with IV IG 500 mg/day for 4 days followed by remission of language disturbances and electrographic epileptiform activity. In one series of 11 patients, however, only two patients had long-lasting improvement of language functions.[66]

Clearly, pharmacotherapy of LKS has been disappointing with respect to the treatment of language disturbances, either because of lack of efficacy (of AEDs) or significant adverse events (of steroid therapy).

Surgical treatment

When should surgery be considered for the treatment of LKS?

The role of surgical treatment of LKS continues to be a source of debate among epileptologists and pediatric neurologists with some advocating[18,67] and others questioning it.[68] The aim of epilepsy surgery for LKS is to yield a remission of the language disturbances and render the patient free of any clinical seizures. In most patients, the latter goal can usually be reached with AEDs, thus the most frequent reason to consider the surgical option is to achieve the former aim. The authors that favor the use of epilepsy surgery base their decision on the favorable results of this treatment modality in a group of children in whom less aggressive treatments are not an option. Thus, in 1995, Morrell *et al.*[18] published the first series of 14 children with LKS who underwent surgical treatment consisting of MST of the epileptogenic area localized in intra and perisylvian cortex. Morrell's rationale for suggesting the use of MST in LKS included the following arguments: (1) children with LKS whose language disturbances failed to remit spontaneously after one year or longer were unlikely to have functional language in adulthood. (2) Pharmacotherapy with AEDs is more often than not unlikely to yield a remission of language disturbances, while therapy with steroids may result in significant improvement but is associated with potentially serious long-term adverse events. (3) The surgical technique MST was developed with the specific aim of abolishing epileptic activity from eloquent cortex. Thus, Morrell and his group suggested that epilepsy surgery could be considered in children with LKS that had failed to regain functional language for a period of at least 2 years despite multiple pharmacologic trials with AEDs and steroid therapy. The authors that oppose the consideration of surgery in LKS have questioned the effectiveness of MST which they claim 'does not substantiate the perioperative complications'. This section of the article will address this dilemma.

Experience from previous case series

In their case series of 14 children with LKS, Morrell *et al.*[18] found that seven children exhibited significant improvement of language functions, with four additional children having some improvement. Among the three children in whom the surgical procedure had no impact, two had bilateral independent (ictal) foci and below age appropriate nonverbal cognitive functions, while one child was found to have a focal Rasmussen's encephalitis. In a subsequent study, Grote *et al.*[69] reported on the language changes established with neuropsychological testing following MST in 14 children with LKS, 10 of whom were part of the initial series and four patients that had undergone surgery since the publication of the initial case series. Eleven of the 14 children exhibited significant postoperative improvement on measures of expressive or receptive vocabulary, but only four (29%) were in a regular class without receiving any special services at school. Grote identified a positive correlation between the pre- to postsurgical scores and the postsurgical follow-up duration. In contrast to observations made by Bishop[13] and Dulac[14] in nonsurgical case series, age of onset of LKS was not predictive of language recovery after surgery. On the other hand, Grote *et al.* found an inverse correlation between the time elapsed between onset of LKS symptoms and time of surgery and language improvement.

Irwin[70] reported a series of five children with LKS who underwent MST at Guy's Hospital in London. All five children experienced a significant improvement of language functions, but none had achieved an age-appropriate level. The CSWS pattern that was present in all patients before surgery was eliminated after MST.

The different postsurgical language outcome between Grote's[69] and Irwin's studies can be explained by a longer postsurgical follow-up in Grote's study, as he clearly demonstrated a correlation between degree of language improvement and duration of postsurgical follow-up. The second difference may reside in an earlier surgical intervention after the start of symptoms in Grote's study, as he shows an inverse relationship between recovery of receptive language functions and time between onset of symptoms to surgery. This observation seems to be in agreement with Irwin's observations made by his colleagues at Guy's hospital.[20] Indeed in a study of 18 children with LKS followed up for 67 ± 46 months, five of whom were treated with MST[70] and 13 with only pharmacotherapy, recovery of language functions either spontaneously or after pharmacotherapy or MST seemed to be unlikely after 3 years of a CSWS pattern.

In addition to MST, temporal lobectomy has been used for the treatment of LKS. Cole *et al.*[71] reported two patients with LKS both of whom were mute prior to surgery. One patient was speaking in full sentences after 10 months. The patient experienced a recurrence of language disturbances and was lost to follow-up. The second patient had surgery as an adult by which time she had learned to communicate by sign language. One year after surgery her language functions had improved but were not normal.

As with any type of epilepsy surgery, the proper selection of surgical candidates is of the essence to ensure a successful postsurgical outcome. Unfortunately, the total number of surgeries performed so far is too small to generate analyzable data that can help identify the variables associated with the best postsurgical outcome. Based on the experience of the first 14 patients operated at the Rush Epilepsy Center, Morrell *et al.*[16] concluded that the ideal surgical candidates are children that meet the following criteria: (1) acute (or sometimes stuttering) onset of aphasia and auditory agnosia in an otherwise normal child who has already developed age-appropriate language; (2) failure to show any signs of improvement of linguistic functions for 2 years; (3) severe, clearly epileptiform, EEG abnormality characterized by unilateral or bilateral spike-wave discharge in slow-wave sleep; (4) electrophysiological evidence of a unilateral origin of the bilateral epileptiform

discharge; (5) neuropsychological test findings indicating relative preservation of nonverbal cognitive capacities in the presence of devastating loss of verbal skills. Of note, the presence of clinical seizures is not mandatory. Morrell made a point of emphasizing the risk of considering surgery in children with the 'LKS-like' diagnoses, which in reality are likely to be suffering from a pervasive developmental disorder.

Surgical technique

Multiple subpial transection

Why MST?

In 1995 Morrell *et al.*[18] suggested using MST for the treatment of LKS, since this is a surgical technique developed with the aim of eliminating epileptic activity from eloquent cortex (i.e., language cortex) without interfering with its function. The technique is based on the following three principles: (1) interruption of intracortical horizontal fibers which are necessary for the propagation and synchronous discharge of epileptic activity without which a seizure cannot occur.[72,73] (2) The preservation of the vertical columnar organization of the cortex which constitutes the basic functional unit of cortical physiology.[74–77] (3) Transections done at 5 mm intervals throughout the epileptogenic area, since the critical mass of cortex for synchronization of epileptiform discharges is at least 5 mm.[78]

Operative procedure

As stated above, the typical source of epileptic activity involves intrasylvian cortex only or in conjunction with perisylvian cortex, though in occasional cases an additional epileptogenic area has been identified in frontal and anterolateral cortex. Accordingly, the extent of the craniotomy is aimed at exposing the sylvian fissure, anterior and posterior language areas, including the angular and supramarginal gyrus. Opening of the sylvian fissure must always precede any MST of perisylvian cortex as the edema ensuing from MST may make the opening of the sylvian fissure more difficult (see Figure 43.5). The location and extent of the opening of the sylvian fissure is based primarily on MEG data.

Transections are carried out with a transection hook, which has a handle, a malleable shaft and a tip that is 4 mm long (which parallels the cortical width) and 1 mm in width. The tip has been designed to be blunt and angled at a 105° in order to minimize the risk of snagging or injuring vessels (see Figure 43.6).[18,79]

In general, the cortex accessible for transection is limited to the crown of the gyrus, while that at the depth of the sulcus remains outside of the transected cortex. The gyral cortical pattern is fairly constant among individuals, but the microgyral pattern of individual gyri may vary considerably. Accordingly, a careful inspection of each of the gyri, its microgyral pattern and vascular supply is of the essence before the transections are carried out. Transections are done perpendicular to the long axis of the gyrus at 5 mm intervals. They are first performed in the more dependent areas to avoid the problem of subarachnoid blood obscuring the other areas. At the edge of the visible gyrus, in an avascular area, a 20-gauge needle is used to open a hole in the pia, through which the tip

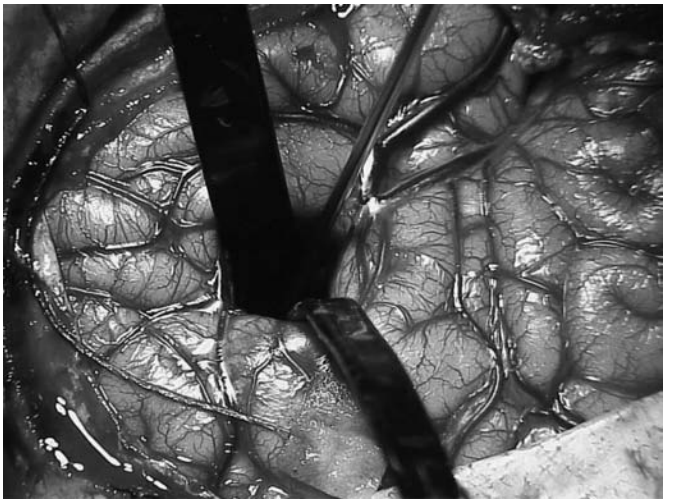


Figure 43.5 Opening of the sylvian fissure prior to the start of MST in intrasylvian and perisylvian cortex.

of the transector is introduced into the gray matter layer and advanced to the next sulcus in a direction perpendicular to the long axis of the gyrus. At the Rush Epilepsy Center, the neurosurgeon keeps the tip of the transector upward and visible immediately below the pia. At other centers, neurosurgeons have elected to introduce the transector with the tip oriented downwards with positive outcomes.[80] It is important that the pia be left undisturbed to minimize vascular injury and scarring. Furthermore it is essential that the surgeon keep the 4 mm tip of the transector within the gray matter layer to ensure that the white matter is undisturbed. Once the epileptogenic area is transected, the transection lines take on a striped appearance from the petechial hemorrhages along the way (see Figure 43.7).

The technique of MST appears to be relatively simple to the observer. Yet, it is more complicated than it actually appears, as transections must be done perpendicular to the cortical surface, not an easy achievement, given the variable microgyral patterns that can result in oblique or parallels transections.[81,82] Needless to say there is a learning curve in the acquisition of these skills. To that end, neurosurgeons are encouraged to carry out transections in brains of cadavers or

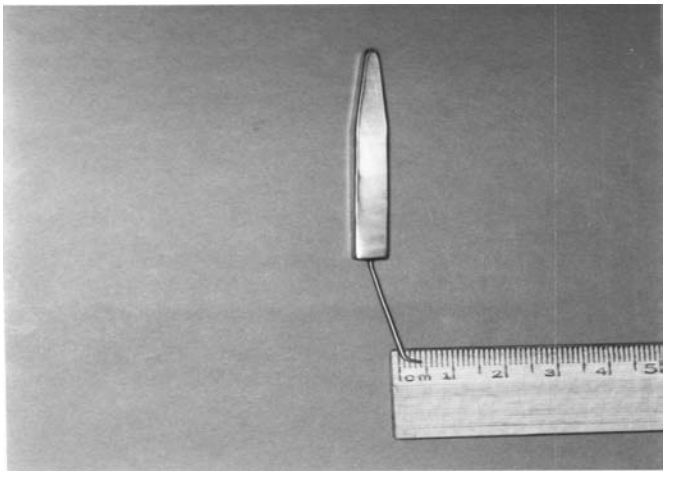


Figure 43.6 Transector used for MST.

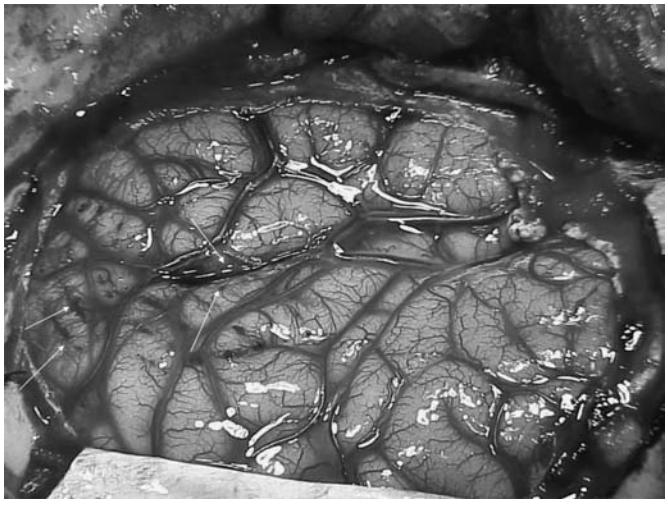


Figure 43.7 Appearance of transected cortex in perisylvian region. The sylvian fissure is open and the planum temporale has also been transected.

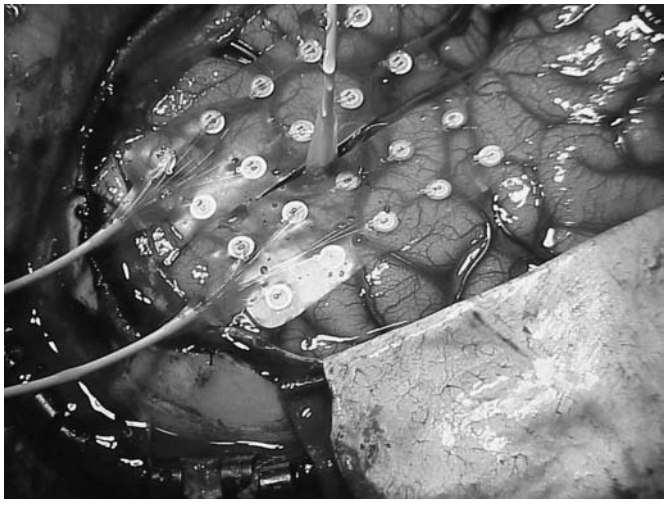


Figure 43.8 Electrodes typically used for intraoperative electrocorticography after the opening of the sylvian fissure.

in cortical tissues destined to be resected (i.e., antero-temporal resections) and examine the transected tissue under the microscope.

Anesthesia

At the Rush Epilepsy Center surgery has been carried out under general anaesthesia with MHX. While this drug can activate interictal epileptiform activity, activation is restricted to the epileptogenic zone.[83–87] Enflurane or isoflurane are avoided as anaesthetic agents at our centre, since the latter has been reported to suppress epileptiform activity in 26% of patients while enflurane can activate epileptiform discharges beyond the area of the epileptogenic focus in 30%.[88]

Intraoperative electrocorticography (ECoG)

Once exposure of perisylvian cortex and opening of the sylvian fissure are achieved ECoG is carried out to guide the extent of the transacted area. Mapping includes localization of the source of epileptic discharges, and the central sulcus. The central sulcus is identified by the recording of evoked potentials to electrical stimulation of median nerve, which aides in the localization of the pre- and postcentral gyri. Identification of the source of the epileptogenic area with ECoG is based on a spatial-temporal analysis of epileptiform discharges in which the onus on the electroencephalographer is to identify those spikes originating within 'abnormal cortex' (as evidenced by the presence of abundant focal slow-wave activity) that propagate to adjacent and/or distant cortical regions. It is therefore essential that electrodes cover the areas suspected to be the potential source of epileptic activity (i.e., planum temporale and superior cortical surface within the sylvian fissure and at times, perisylvian cortex) and areas of propagation (i.e., temporal lateral, frontal-lateral and perisylvian cortex). To that end, a 20-electrode pad is moved throughout the exposed lateral convexity of the hemisphere; in addition, one or two six-contact strips are placed within the sylvian fissure, three contacts covering the inferior and three the superior cortical areas (see Figure 43.8). On occasions, additional six-contact cylindrical electrode strips are used for coverage of subtemporal, mesial frontal and mesial parietal cortex.

The locations of pre- and postcentral gyri are ticketed. The extent of the epileptogenic area to be transacted is demarcated with an easily visible thread. Photographs are taken prior to, and following, the last transaction, so that reconstruction of the transected areas could be made. It is important to emphasize that opening of the sylvian fissure can be associated with technical difficulties in some children. Furthermore, in some children the source of the epileptiform activity can be established to be intrasylvian (i.e., before it propagates to perisylvian cortex) but no *discrete* source can be identified 'within' the exposed intrasylvian cortex; in such cases, the neurosurgeon needs to expand the opening of the sylvian fissure and transect both superior and inferior cortical surfaces in toto. Following a successful MST, the background activity of the transected cortex is expected to be attenuated.

Some epilepsy centers using MST, rely on extra operative data in determining the extent of the area to be transected. In our opinion, Intraoperative ECoG is of the essence prior to and following the transections, as epileptiform activity may not be necessarily abolished. Indeed, it is important to remember that only the cortex at the crowns of the gyri is usually accessible for transection, while the sulci remain untouched. Additional transections may be necessary in some cases after the initial ones fail to abolish the epileptiform discharges, in which case the possibility that these discharges are originating from a distant cortex or from within the depth of a sulcus should be considered. In order to transect the depth of a sulcus safely, the tip of the transector should be turned away from the sulcus as the instrument is advanced. Without post-transection ECoG, the neurosurgeon may not know whether the transection achieved the intended goal.

Results of MST

The interpretation of the surgical outcome of previously published surgical series has to take into account several methodological problems among which the most important include the small numbers and the inclusion of cases that may not meet the original diagnostic criteria of LKS. To overcome the first problem, multicenter studies using the same diagnostic

protocols, inclusion criteria for surgery and surgical technique is necessary given that classic LKS is a rare disorder. To overcome the second problem, we reviewed the surgical outcome of children who met the classic diagnostic criteria and who underwent epilepsy surgery at the Rush Epilepsy Center[4] between the years 1990 and 2003.

This study included 22 children, 14 boys and eight girls who were 6.95 ± 1.95 years old at the time of surgery. The mean age of onset of LKS was 4.3 ± 1.4 and the mean duration of the disease before surgery was 2.5 ± 1.3 years. Among the 22 children, 21 had nonfunctional language for a period of at least 18 months; one child had functional language but had been experiencing frequent and recurrent language regressions that failed to be prevented with pharmacotherapy with AEDs and steroids. The mean baseline score of the language test used for evaluation of expressive vocabulary, the Expressive One Word Picture Vocabulary Test-revised (EOWPVT-R) [expressed as age equivalent in months old] was 12.8 ± 9.0 months, while the mean baseline score of the Peabody Picture Vocabulary Test-revised (PPVT-R) which is used for evaluation of receptive language was 14.6 ± 12.9 months. Behavioral problems were reported in 19 children; four children had an abnormal MRI and three had never experienced any clinical seizures.

Among these 22 children, presurgical data obtained with noninvasive tests were sufficient to proceed to surgery, while in eight patients V-EEG with bilateral intracranial epidural electrodes as described above had to be carried out. In twelve patients (54.5%) only MST was carried out in intra- and or perisylvian cortex. In seven (32%) a combination of MST and resection of temporal lobe structures were carried out, while three children underwent a pure resection of the planum temporale.

Postsurgical neuropsychological and speech evaluation was carried out after a mean period of 34.1 ± 19.9 (7–75 months). At that point, the mean EOWPVT and PPVT scores were 144 ± 72.9 months and 144 ± 73.8 months, respectively ($p < 0.0001$ for both analyses) with mean gains of 124 ± 60.1 months and 129 ± 59.2 months, respectively. A significant correlation between improvement in the scores of these two tests was found ($r = 0.86$, $p < 0.0001$). There was a significant correlation between the duration of postsurgical follow-up and the gains made on the PPVT ($r = 0.56$, $p = 0.02$) and a statistical trend for the EOWPVT ($r = 0.4$, $p = 0.09$). At that point in time, 20 of the 22 patients were still receiving speech therapy. Following a mean postsurgical follow-up period of 48.3 ± 30.2 months, 16 children (72%) had regained functional language as defined by the ability to use complex sentences and understand what was being said to them. Despite these significant gains, only nine of these children (41%) were in a regular class without a need of assistance or further speech therapy.

Among the 19 children with clinical seizures before surgery, 15 (79%) had become seizure free, two had rare seizures, one had >90% and one had <90% seizure frequency reduction. Of note, residual spikes at the end of ECoG and at the last EEG were not associated with a worse postsurgical outcome. Behavioral improvement was reported in 17 of the 19 patients (89.5%).

Prior to surgery, a trial with prednisone was carried out in 20 children, nine of whom regained functional language defined by the ability to use sentences to express themselves. Response to prednisone was a predictor of functional language at 6 months after surgery, but not at the last follow-up.

Morbidity

Two patients sustained small infarcts caused by vascular manipulation, probably at the time of opening the sylvian fissure. These took place among the first cases in whom the opening of the fissure was done. In one patient, the infarct involved the posterior white matter and was not associated with any clinical deficits. The second patient had weakness of the right arm which cleared over a three-month period.

Conclusions

The data presented here suggest that MST can be an effective therapy for children with LKS who, after losing linguistic abilities, have failed to show any signs of improvement for at least 18 months to 2 years. However, not every child with a severe form of LKS may benefit from this surgery. We believe that demonstration of a unilateral, well-localized, source of the epileptic activity and a relative preservation of nonverbal cognitive functions in children who had a normal development of language functions are prerequisites for surgical consideration. The positive response to steroids in a significant percentage of children (9 of 20 in our study) raises the question of what criteria should be followed in the selection of surgery versus pharmacotherapy with steroids. No definite answer is available as no head-to-head comparison has been carried out between these two treatment modalities. In our center, surgery was considered for children who had not responded to steroids and in children who had responded but had experienced adverse events which precluded their long-term use. Thus, until the safety and efficacy of these two treatment modalities are compared in multicenter, randomized controlled head-to-head study, surgery should be considered in children with LKS who are not candidates for pharmacotherapy with either AEDs or steroid therapy.

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44 The Lennox–Gastaut syndrome: a surgically remediable epilepsy?

C Dravet

Introduction

Historically the Lennox–Gastaut syndrome is a generalised epilepsy. In the last international classification of epileptic syndromes and epilepsies,[1] it is listed as 'cryptogenic or symptomatic generalized epilepsy'. That means it is usually related to a known or suspected disorder of the central nervous system. In the new proposal published in 2001[2] it is listed under the heading of 'epileptogenic encephalopathy' which means a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function. Before discussing whether and when it could be considered as surgically remediable, I will briefly describe the syndrome.

Description

Among childhood epilepsies, the Lennox–Gastaut syndrome (LGS) is one of the most severe epileptic syndromes, due to the frequency of seizures, the occurrence of sudden falls, a marked pharmacoresistency, and the occurrence of mental and behavioral disturbances.[3] The physiopathogenic mechanisms of LGS are not well understood and the borderlines with other types of severe epilepsies are not easy to define. Without a precise knowledge of the clinical and electroencephalographic (EEG) characteristics of the patient concerned, it may be difficult to distinguish between LGS and other childhood epilepsies such as the Doose syndrome (myoclonic-astatic epilepsy), epilepsy with continuous spike-and-waves (SWs) during slow sleep, and focal epilepsies with bilateral secondary synchrony.

LGS is defined by several criteria:

1. polymorphous epileptic seizures, with mainly atypical absences, axial tonic and atonic seizures;
2. EEG patterns consisting of diffuse slow SWs and bursts of fast rhythms at 10–12 Hz during sleep; and
3. permanent psychological disturbances with psychomotor delay or personality disorders or both.

However, other seizure types can be seen (myoclonic, focal, generalized tonic-clonic). The seizure frequency is high and they often repeat themselves in episodes of status. Focal and multifocal abnormalities can be associated with diffuse slow SWs in the EEG. These electroclinical features can occur in a previously normal child, without pathological antecedents and without signs of brain lesion, usually between 1 and 8 years (constituting the *cryptogenic* form of LGS). They also can occur in a child with prior signs of brain damage, sometimes following another type of epilepsy, such as West's syndrome or a focal epilepsy (*symptomatic* form). In the latter, the age at onset can cover a wider range (between 1 and 15 years).

Etiological circumstances are various; ante-, peri- or postnatal: anoxo-ischemia, vascular accident, cerebral and cerebromeningeal infection, hemiconvulsion-hemiplegia-epilepsy syndrome, brain malformation and migration disorders, tuberous sclerosis, Down's syndrome, hydrocephalus, head trauma, brain tumor, radiotherapy for brain tumor. Neuroimaging studies show abnormalities related to etiology. In some cases, in spite of a psychomotor retardation before the onset of seizures, or of a cerebral atrophy demonstrated by computerized tomography (CT) scan and magnetic resonance imaging (MRI), there is no recognizable etiology. When epilepsy starts in the first year of life, it is often in the form of West's syndrome, followed by LGS. Otherwise the LGS can be preceded by focal seizures or can have the full-blown presentation from the very onset on. The typical features of LGS can be observed only transiently in some patients. In the cryptogenic forms, there is by definition no recognized etiology.

The underlying mechanisms are still unknown.[4] Pathologic studies are rare. They have shown anomalies mainly at the synaptic and postsynaptic levels: selective neuronal necrosis,[5] poor dendritic arborization and disturbed synaptic development,[6] perhaps related to an autoimmune process, also hypothesized by Eeg-Olofsson.[7] However, the immunologic approach[8] did not reach significant results. Even the neurophysiological pathways leading to the expression of generalized slow SWs on the scalp are not explained. The same processes as in the idiopathic generalized epilepsies could play a limited part, since abnormal sleep patterns seem to originate outside the usual thalamo-cortical circuit.[9] Secondary bilateral synchrony could be at the origin of the apparently generalized EEG changes. Recently, Bonnani *et al.*[10] have demonstrated that the spikes preceding the myoclonic jerks in the LGS were propagated from one frontal lobe, unlike in the idiopathic myoclonic astatic epilepsy where they were diffusely distributed without lateralization. LGS seems to be one specific age-dependent condition which looks like a diffuse encephalopathy, and we do not know the reason why it appears in either normal or brain-damaged patients.[4] However, LGS is not as strictly age-dependent as

West syndrome. When it has started in childhood it may continue in adulthood, and it may appear at various ages, from baby to adolescent and, exceptionally, to adult.

Ictal symptomatology

Tonic seizures constitute one of the main signs of this syndrome. They are axial, axial and proximal, or global, and symmetrical or asymmetrical. They involve sudden flexion of the neck and body, raising the arms in a semi-flexed or extended position, extension of the legs, contraction of the facial muscles, sometimes restricted to the lower lip, rolling the eyes, apnea and facial flushing. Enuresis can occur and pupils are usually dilated. This can lead to sudden falling. Loss of consciousness does not occur in all instances. Return to normal consciousness is always concomitant with the end of the EEG discharge. They are diurnal and nocturnal. During sleep, they are often short, with only rolling of the eyes and change in the respiratory rhythm, and they can escape attention. Alternatively, when they are long, they can culminate in a tremor pattern. In other cases they can be followed by a phase of gestural automatisms.

On the EEG, the tonic seizures correspond to a discharge of bilateral rapid rhythms, of variable voltage, higher in the anterior areas and in the vertex, sometimes preceded by a short flattening of the background, and followed by diffuse slow-waves or spike-waves (Figure 44.1). There is no postictal silence.

Atypical absences are also observed in the majority of cases. Often they are difficult to clinically detect because they begin and end progressively, and the loss of consciousness is incomplete. Eyelids and perioral myoclonias and drooling are usual. Decrease in muscle tone of variable intensity can lead either to a progressive head drop or complete fall ('atonic absences').

On the EEG, atypical absences correspond to irregular, diffuse slow spike-waves, at 2–2.5 Hz, more or less symmetrical, difficult to differentiate from the interictal slow spike-waves (Figure 44.2).

The third characteristic seizure type is represented by *the drop attacks*. This term is only phenomenological and does not correspond to an epileptic seizure type. It designates all the sudden falls, whatever their mechanism: atonic, myoclonic, myoclono-atonic or tonic, which are often impossible to distinguish without a video and polygraphic EEG recording (Figure 44.3). They correspond to various EEG patterns which can be combined: brief flattening, diffuse poly-SW or fast rhythms. It has been demonstrated that drop attacks were mainly due to a tonic mechanism.[11,12] However, in the literature the term 'atonic seizures' is often used to designate seizures with sudden fall without any demonstration of the mechanism responsible for the fall. That is confusing, and it is preferable to use 'drop attacks'.

All these types of seizures can be repeated in status, particularly atypical absences and tonic seizures.

Seizures of other types, not typical for the syndrome, focal and generalized tonic clonic, are observed in some patients.

Interictal symptomatology

Clinical

There is no neurological sign specific to LGS and those signs observed in some patients are due to the previous brain lesion in the symptomatic forms (hemiparesia).

Cognitive impairment and personality disorders are constant but different in the cryptogenic and in the symptomatic forms. In the latter they are often pre-existing to the LGS onset and will worsen during the course of the syndrome. In the former, the first changes seem to be slowness in the ideation and verbal expression. In children aged three to five, slow psychomotor development, instability and behavioral disorders occur. In older children, attention disorders preclude satisfactory school work and make further learning difficult or even impossible. Relationships with other children and adults are distorted by the high frequency of seizures, associated with slowness, verbal and comprehension difficulties,

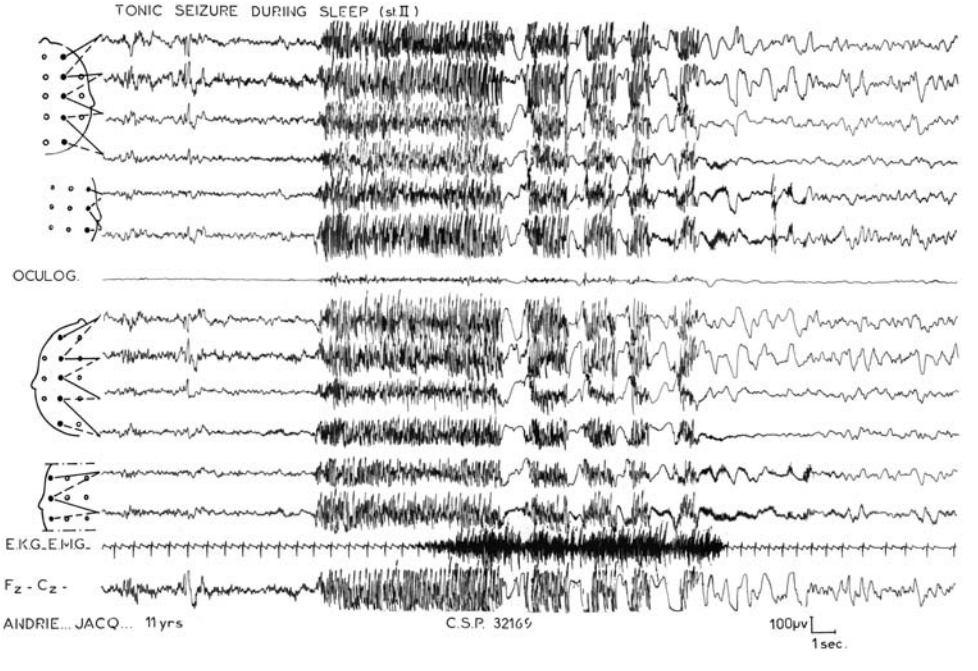

Figure 44.1 Axial tonic seizure during sleep in an eleven years girl, characterized by a burst of high voltage rapid rhythms, four times interrupted by a flattening, and followed by anterior slow waves. The EMG, recorded in the left deltoid (E.K.G. E.M.G.), shows a sudden increase in the muscular tone of the same duration as the EEG discharge.

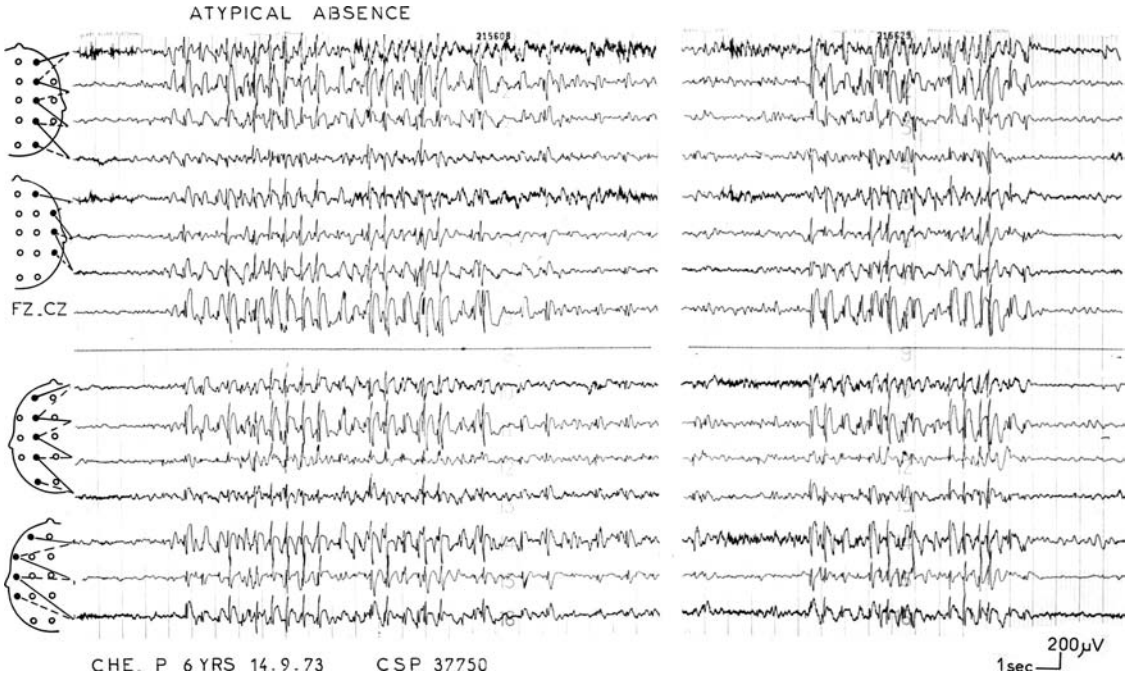

Figure 44.2 Atypical absence recorded in a 6-year-old boy, with diffuse SW of irregular frequency. There is no difference with the interictal discharge on the right of the figure.

which results in aggressiveness and a tendency to isolation. Personality disorders are nearly always present and, sometimes, evolve to a psychotic organization.

Electroencephalography

In awake patients, the EEG is abnormal in most cases, even in the early stages of the disease. Background activity is often slow and poorly structured with regards to the patient age. Interictal discharges of diffuse slow SWs, at 2–2.5 Hz, widespread over the two hemispheres, are recorded, isolated or grouped in bursts of variable duration, facilitated by hyperpnea (Figure 44.2). They can be associated to focal or multifocal slow waves, spikes and SWs, predominating in the fronto-temporal areas. Intermittent photic stimulation usually has no effect.

During sleep, cyclic organization remains normal or shows a decrease in the REM phases. Diffuse slow spike-waves become more and more repeated and their morphology changes, giving an aspect of poly-SW (Figure 44.4). Then they start with brief bursts of rapid rhythms, at 10 Hz, of high amplitude. There is no striking difference between these subclinical discharges and those accompanied by

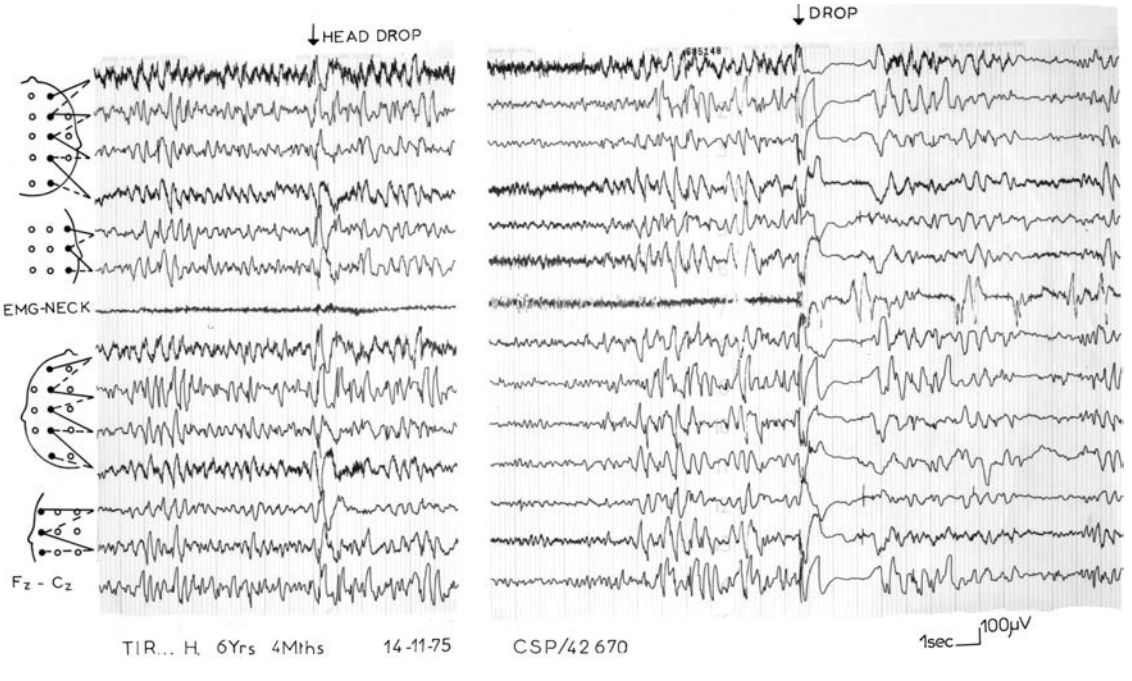

Figure 44.3 Drop attack in a 6-year-old boy. On the left, one head drop corresponding to a high voltage diffuse SW, without clear change in the EMG of the neck. On the right, fall onto the ground. The SW is followed by a flattening. The EMG seems to show a loss of tone but it is not valid because of artifacts.

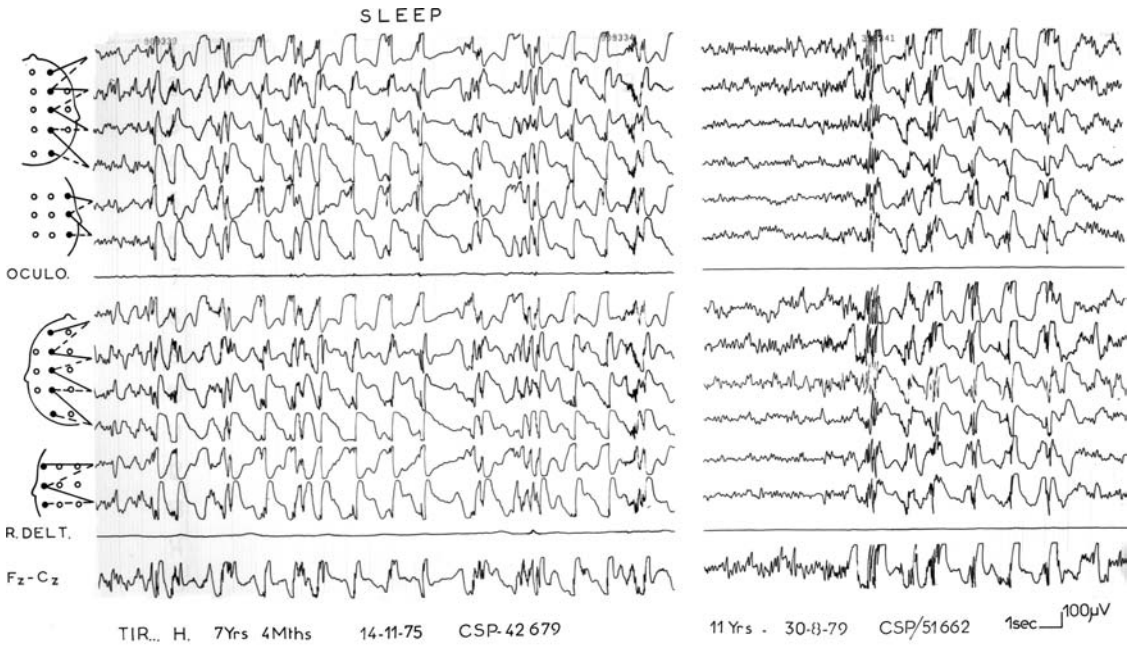

Figure 44.4 Sleep recording in a 7-years-4-month-old boy. On the left, very slow diffuse SW with brief flattenings. On the right, bursts of typical rhythms at 10 Hz.

clinical manifestations. It is important to emphasize that these discharges are the main diagnostic criterion for LGS.

Treatment

Treatment is disappointing. Seizures do not respond or respond transitorily to the antiepileptic drugs. Carbamazepine, valproate, and the benzodiazepines are useful. Results have also been obtained with some new drugs, such as vigabatrin, lamotrigine, felbamate, topiramate, and zonisamide (in Japan), but many patients are not improved by these drugs. Corticosteroids and immunotherapy can help at the onset or in worsening periods. Ketogenic diet has been used with satisfactory results in some patients.

Is LGS a surgically remediable syndrome?

According to its electroclinical characteristics LGS seems not to be considered for surgery. However, seizures are usually extremely pharmacoresistant, EEGs show numerous discharges and cognitive functioning gradually declines. Thus, it is legitimate to search for a surgical approach. Two situations in which LGS may be surgically remediable may be considered.

Surgically removable lesions

In the first situation, the patient presents with a known etiology consisting of a localized and well circumscribed lesion. In that case the removal of this lesion is able to make seizures disappear, EEG improves and behavior also. There are few examples of this type in the literature.

Angelini *et al.*[13] reported one patient who started at 4 years with atypical absences, followed six months later by tonic seizures. The EEGs showed long discharges of diffuse slow SWs without asymmetry, without focal predominance. No sleep recording was available. The CT scan was normal. Nocturnal tonic seizures increased in spite of various treatments and her behavior became abnormal. One year after the onset she presented with slight neurological impairments in the right side and EEG abnormalities clearly predominant from the left parietal region. One isotope brain scan and one left carotid angiography displayed the presence of a tumor in the parieto-temporal region, which was surgically removed. It was a type II astrocytoma. The child had no further seizures and SW disappeared in the EEGs. Two years later she was still seizure free.

More recently, Quarato *et al.*[14] published the case of one patient with an atypical, LGS suffering from atonic and tonic seizures, who was seizure free one year after the removal of a left parietal dysembryoplastic neuroepithelial tumour. In that case, EEG and clinical signs pointed to left hemisphere origin of the seizures.

We also have the case of S.G., who did not have family antecedent or a personal pathological history. At 10 years, he had a generalized tonic-clonic seizure, followed by atypical absences and tonic seizures. Sometimes his tonic seizures were preceded by a conscious onset with head and eye deviation to the right. He continued to go to school but he has increasingly poor results. At 16 years 6 months, despite antiepileptic drugs, seizures increased, becoming diurnal and nocturnal. He was referred to our center at this time. Clinical examination was normal in this right-handed boy, but his verbal expression and his ideation were slow. EEGs showed diffuse slow SWs, in bursts facilitated by hyperpnea (Figure 44.5), and numerous discharges of diffuse subclinical rapid rhythms predominant in the anterior areas (Figure 44.6). The CT scan displayed a left frontal tumor, which was surgically removed without complication and seizures disappeared. The boy's IQ was 94, with a slight

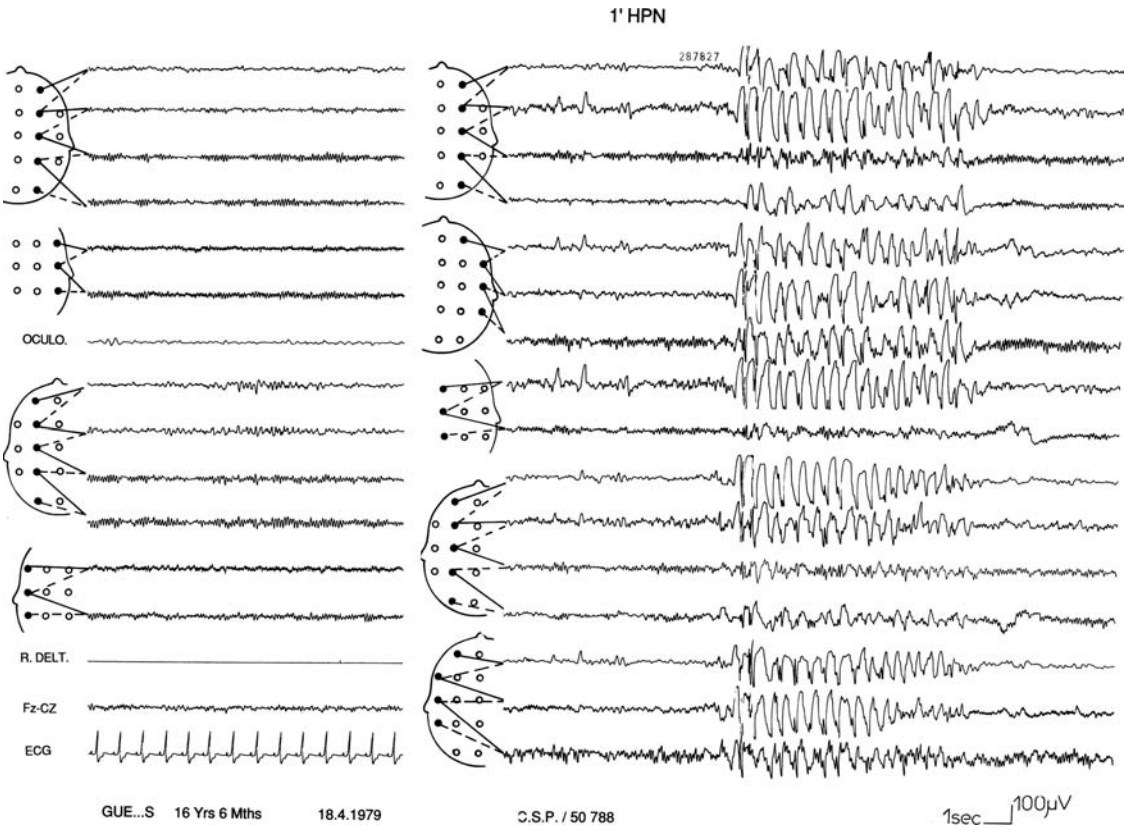

Figure 44.5 Awake EEG in a 16-year-old boy with a brain tumor. On the left, slight asymmetry with theta waves in the left anterior region. On the right, hyperpnea provokes a burst of diffuse slow SW, without clinical manifestation, preceded by sharp waves in the right fronto-central region and the vertex.

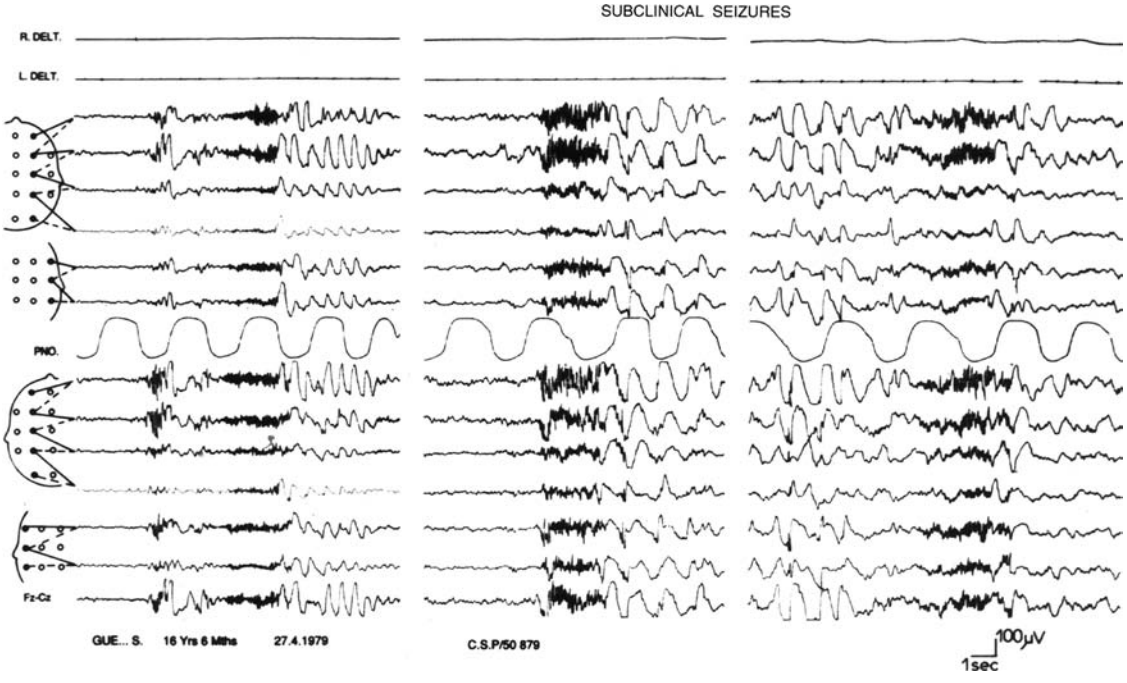

Figure 44.6 In the same boy, subclinical discharges of rapid rhythms, of variable voltage, followed by slow-waves.

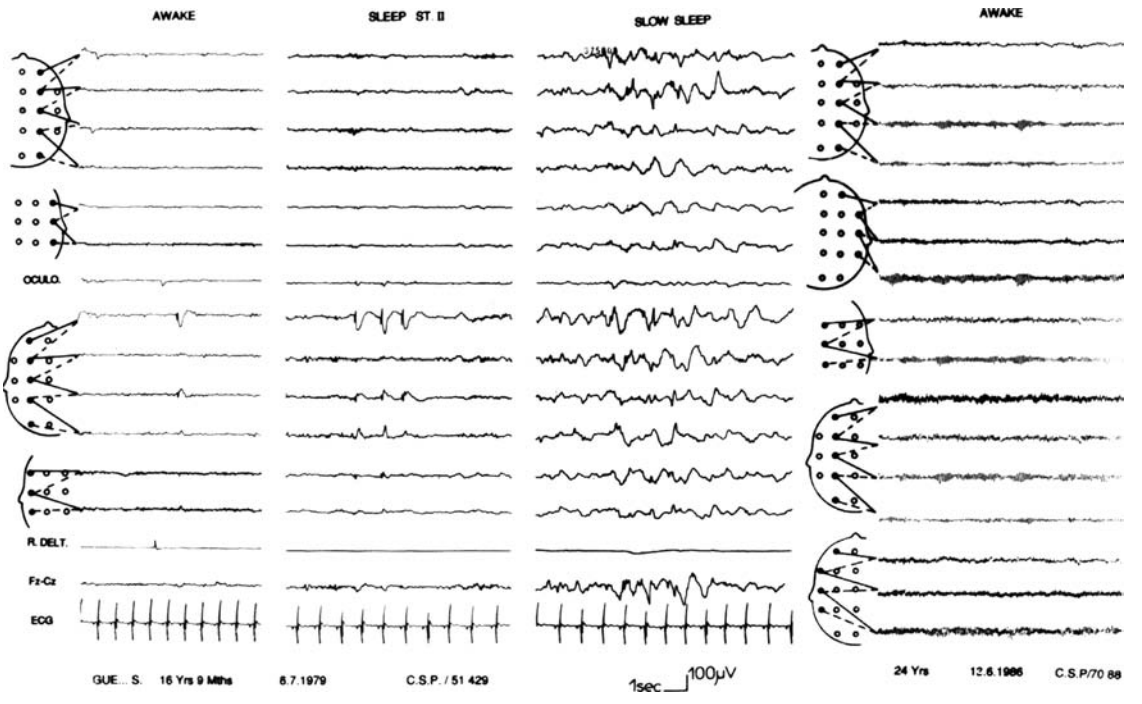

Figure 44.7 In the same boy, after the removal of the tumor. From left to right: fragment 1, rare small spikes in the left fronto-central area; fragments 2 and 3, the same spikes increased by sleep; fragment 4, normal EEG at 24 years.

frontal deficit. EEGs showed spikes localized in the left frontal region, without diffuse discharges, while awake and during sleep (Figure 44.7). Treatment was progressively reduced and stopped at 25 years. He now has a normal professional career. In this patient the LGS was related to a benign frontal tumor (low grade astrocytoma) and was cured by the lesionectomy, but this situation remains exceptional.

Other authors reported on patients with symptomatic LGS due to perinatal anoxo-ischemia resulting in porencephalic cyst who were successfully treated by surgery. However these patients were not separated from those with West syndrome and the diagnostic criteria for LGS were not well defined.[15,16] One paper by Ishikawa *et al.*[17] also reported one patient remarkably improved by this treatment.

Cryptogenic cases: lesions not surgically removable

In the second situation, by far the most usual, there is no lesion to be easily removed. Either one faces a cryptogenic case or lesions are extensive, diffuse, bilateral or not well defined: atrophy, ventricular dilation, cortical dysplasias, and other malformations. In these patients it is possible to discuss the indication of a palliative surgery, such as corpus callosotomy (CC) and vagus nerve stimulation (VNS).

Corpus callosotomy (CC)

First proposed by Luessenhop,[18] this procedure has the objective of preventing the interhemispheric propagation of the discharges presumably responsible for the falls and the generalized tonic-clonic seizures. Preoperative evaluation is of great importance to delineate the shape and integrity of the corpus callosum and to decide what will be the extent of the section.[19] In order to maintain sufficient connections for a good coordination of cognitive functions a certain amount of callosal fibers must be preserved. After several years' experience it has been determined that the anterior two-thirds callosotomy is the best procedure because the conservation of the splenium avoids the disconnection syndrome; subsequent completion of the section remains an option in patients who fail to obtain an adequate response.[20] However, recently Maehara and Shimizu[21,22] advocated for an initial complete callosotomy, arguing that in young children it gives the best results for seizure frequency as well as for psychomotor development. CC has been applied to children and adults presenting with different types of severe, pharmacoresistant, epilepsies, without possibility of resective surgery. They were focal or generalized epilepsies, with multiple seizure types, mainly drop attacks, and epileptic status, often associated with a mental deficit.

Rougier *et al.*[23,24] reviewed the literature in 1997. CC is principally effective in seizure types characterized by drop attacks, due either to a tonic axial phenomenon, or to an abrupt loss of tone. Sometimes they are completely suppressed. More often (70–80% of cases) their frequency is dramatically reduced, between 60 and 100%. Drop attacks are observed in different varieties of syndromes and are usually associated with other seizure types which are less susceptible to be improved by the operation. The best results are obtained when drop attacks are caused by a unilateral brain lesion, or when they are part of a bilateral frontal lobe epilepsy. A good result is observed in 65–75% of those patients. The results are comparable in adults and in children and the functional tolerance is higher in children, who are the best candidates.

It seems that this surgical procedure could be improved by using the gamma knife as reported by Pendl *et al.* in 1999,[25] who applied this technique to three patients, two of which with a LGS.

Results of CC for the Lennox–Gastaut syndrome

In the large body of literature concerning CC in intractable epilepsies the seizure types are usually described but the cases

of LGS are not always identified. For example, Maehara and Shimizu [21] have studied 52 patients who underwent CC for 'intractable generalized seizures' mainly represented by drop attacks, but we do not know the number of patients suffering from LGS and those from other epilepsy types. This study reported not only the seizure outcome, which was particularly good for drop attacks (80.8% seizure-free patients), but also the change in the daily life of the patients and the degree of satisfaction of their parents which was also high (57%) for the children's parents but not for the adults' parents (12%). In the series from Montreal [26] there were 73 cases of CC performed for a variety of cerebral seizures and clinical entities between 1981 and 1986. Fifty-six patients suffered from a secondary generalized epilepsy (SGE) and 14 were classified as LGS. The results were considered satisfactory. Nevertheless there was no case with complete cessation of all the seizure types. The tonic drop attacks emerged as the major indication for this procedure: they decreased between 75 and 100% in 11/23 patients (48%), with complete disappearance in seven, whereas generalized tonic-clonic seizures decreased >75% in 6/19 patients (31%) with complete disappearance in one. The authors assumed they had, at times, spectacular results in the cryptogenic LGS, with no clinical or EEG evidence of focalization, which contrasts with the results obtained by other authors. They also mentioned improvement in awareness and alertness, not attributable to changes in antiepileptic medication. In one patient, a new seizure type occurred after surgery, consisting of nocturnal focal adversive and clonic seizures. These data are consistent with the data reported by Spencer *et al.*[27,28] on the occurrence of more intense focal seizures after callosal section. In the same way Spencer *et al.*[29] have analyzed the EEG ictal patterns before and after CC, showing that the bilateral synchronous pattern was replaced by a unilateral or a focal onset, and that seizures newly localized to a lobe could occur, mainly in the frontal, sometimes in the parieto-occipital lobe. Quattrini *et al.*[30] observed the same changes in the postoperative ictal discharges. They also observed that after certain time, generally some months, lateralized discharges tend to generalize again, confirming that CC is replaced in discharge diffusion by other structures (brainstem, diencephalon).

Ritter *et al.*[31] reported 27 patients with LGS who underwent CC (19 complete, eight partial anterior). The selection criterion was the presence of drop attacks or frequent secondary generalized tonic-clonic seizures. Duration of follow up was 2–18 months (median 6 months). Overall, 70% of the patients had marked improvement in seizure control: tonic seizures decreased in frequency >80% in 14 of 23 patients (60%); GTC in nine of 15 (60%); atonic in seven of eight (87%), and seizures associated with dropping in 13 of 21 (61%). Repeated episodes of status epilepticus ceased in three of four patients.

Provinciali *et al.*[32] reported on the neuropsychological changes after partial CC in 15 patients with SGE, of which five were LGS. They tested memory, attention, visuo-motor ability, posture, motor dexterity, language, praxis and gnosis, as well as social behavior, one month before surgery, then 15–20 and 90–100 days postoperatively, without modifying the medical treatment. The short-term neuropsychological cost of this procedure appears to be low and seems to depend mostly on surgical parameters and brain conditions before the operation.

Nakatani *et al.*[33] and Sakaki *et al.*[34] reported respectively four and two patients operated upon in Japan with a satisfactory result with respect to the seizures for all, in spite of a disconnection syndrome in three patients, transient in one and lasting in two.

Gates [35] reviewed three series of CC, including 17, one and five patients with LGS in the respective series. Among them 15 achieved a satisfactory outcome. Gates reported that the presence of bilateral independent foci with capacity for secondary generalization was an indicator of good outcome.

Pinard *et al.*[36] had operated on 34 patients with more than three seizures a day, among whom eight patients were diagnosed as having LGS. Patients were followed prospectively for at least 2 years after anterior CC (19 patients) and for 1 year after complete CC (15 patients). The eight patients with cryptogenic LGS improved after anterior CC.

Septien *et al.*[37] emphasized the good results obtained in children with psychiatric problems. They had performed partial anterior CC in two children with LGS and major psychiatric troubles: frontal syndrome with hyperkinesia, distractibility, aggressiveness, alexithymia, loss of planning abilities. They observed a progressive improvement of this frontal syndrome during the 2 postoperative months, with the possibility of learning new skills, without a change in IQ. Associative functions depending on the posterior third of the corpus callosum were preserved. They thought this improvement was related to the reduction of seizures.

Claverie and Rougier[38] studied the outcome in terms of quality of life in 20 patients submitted to CC for intractable epilepsy, including three cases of LGS. In two of these three they observed a substantial change; they became capable of independent living, and one attended a specialized school. In the whole series it appeared that the psychosocial benefits obtained in 40% of the patients were linked not only to the seizure reduction but also to the precocity of the intervention.

Matsuzaka *et al.*[39] studied 22 consecutive patients who underwent an anterior CC for intractable epilepsy. Seventeen of these patients had SGE, of whom eight had LGS. A cross-correlation analysis and measurements of amplitude differences were performed between bilateral homologous regions pre-and postoperatively. The surgical outcome was excellent in 14 (63.6%), including a complete elimination of seizures in four; good in three (13.6%); and poor in five (22.7%) patients. After surgery, interictal generalized synchronous SW bursts in the SGE patients were disrupted and changed to unilateral SWs in 11 patients and to bilaterally independent SWs in six. The unilateral group had better surgical outcome than the bilateral independent group. Preoperatively the first group had significantly lower interhemispheric synchrony and fewer regional changes in the side leading in time and the side dominant for amplitude, suggesting unilaterally predominant epileptogenesis that triggered the secondary bilateral synchrony. These findings lead to the hypothesis that a considerable range of variation exists in the underlying condition of epileptogenesis in each hemisphere, even in SGE, affecting the postoperative EEG changes and surgical outcome. Preoperative quantitative EEG analyses enabled the authors to predict the underlying conditions of epileptogenesis and the surgical outcome. Unfortunately the authors were not precise in indicating to which group the patients with LGS belonged.

Kwan *et al.*[40] analyzed findings and acute changes in electrocorticograms (EcoG) obtained during CC, in order to identify any relationships with the postoperative outcome of seizure activity, in 48 patients with LGS, all followed postoperatively for more than 4 years. Of these patients, 31 (64.6%) had significant improvement in seizure control. EcoG displayed bisynchronous discharges in 79.2% of the 48 patients, and they were blocked during CC in 69.7%, who achieved the best postoperative outcomes. But the difference did not reach statistical significance. Therefore, the changes in preoperative EcoG are not predictive.

The largest series was reported by Cukiert *et al.*[41] who performed one-stage callosal section, leaving only the splenium intact, in 76 patients with Lennox–Gastaut ($n=28$) and Lennox-like ($n=48$) syndromes. However, the latter is not defined by the authors. All patients were severely mentally impaired. Mean follow-up time was 4.7 years. Worthwhile improvement (>50%) was noted in 69 patients, with 90% or more seizure reduction in 52, 100% in seven. As in other series, the drop attacks were the most responsive seizure type (92%), followed by atypical absences (82%), tonic-clonic (57%), and tonic (51%) seizures. Postoperative EEGs were obtained in 56 patients. In 42 they showed complete disruption of secondary bilateral synchrony, in six only partial disruption, in eight no change. But a postoperative acute callosal disconnection syndrome appears in 72 patients (apathy, urinary incontinence, right hemineglect, low verbal input, one mutism) which lasted for 8–50 days. After this period, the attention abilities were substantially improved.

Interestingly, in two patients who had LGS with reflex seizures these seizures were reduced by 60% in one (startle epilepsy) and disappeared in the second (tap epilepsy), unfortunately with a relapse after one year in the latter.[42]

In all series, postoperative complications and side-effects were rare. When it appears, the disconnection syndrome is transient. All the authors underline that in children CC is usually followed by an evident improvement in psychomotor development and behavior, though it is not measurable by usual assessment methods.[35,37,38]

At the end of this brief and incomplete survey, it appears that a number of patients with LGS can really improve with a partial anterior CC. In any case it is not a curative but a palliative treatment which can control the most ominous seizures represented by the drop attacks, mainly tonic in nature in this syndrome. Few papers give data on long-term results (more than 5 years' follow-up) but it is never mentioned that good results were transitory. Spencer *et al.*[26] followed patients postoperatively from 2–7 years. They indicate that 'the stability of generalized seizure control after CC continues over many years of follow up'. The problem is not knowing the factors which could allow predicting the result of this intervention. Most authors reported better outcome in patients with a lateralized lesion or lateralized EEG anomalies, but in one series[43] some cryptogenic LGS without asymmetry have been improved. Nevertheless, it is important to conduct a good preoperative EEG analysis in order to detect the type of electrogenesis in each hemisphere. The presence of a mental deficit is not a contraindication. Neuropsychological consequences are usually rare after partial section. It is recommended to perform surgery before the age of 10, in order to preserve a good intellectual outcome and to restore a good quality of life.

Vagus nerve stimulation

In the numerous publications studying the effects of VNS on epilepsy, the patients with LGS were often included in series of patients with 'refractory' or 'intractable' seizures, or with a low IQ. Few details were provided by the authors. The effect of VNS was evaluated at different times after surgery and was variable, from 50% and more seizure reduction in few patients[44,45] up to more than 90% seizure reduction.[46,47] Most of the authors also indicate some degree of improvement in behavior, such as alertness and social communication. The side-effects were never disabling, consisting of change in the voice, hoarseness, sometimes coughing, at the time of the stimulation, and usually persisted only for some weeks.

From the year 2000, LGS patients have been reported as a group and the conclusions are also variable. Moreover, the criteria for diagnosing LGS often lack and these groups include also cases designated as Lennox-like syndromes.

The best study of VNS in patients with LGS was published by Majoie *et al.*,[48] who gave the results of this procedure in 16 patients, aged from 7–18 years, accurately analyzed in terms of seizure and epilepsy type, frequency of the different seizure types, cognitive functions, quality of life and cost-effectiveness. This prospective, longitudinal cohort study included 16 'Lennox-like' patients, among whom 12 with LGS, three with myoclonic astatic epilepsy, and one with myoclonic absences, followed from 6–12 months. The overall results showed that 25% of the patients had a reduction of seizures of 50% or more, with a mean for the individual patient of approximately 20–30%. No patient was completely seizure free. There were no significant differences between the various seizure types and for patients with drop attacks ($n = 10$) only one was seizure free and one had more than 50% reduction. The effects were moderate on neuropsychological functioning, a slight improvement appearing in the group with the highest mental age and not correlated with the seizure frequency reduction. The effects on EEG were not studied, but the best results were obtained in the patients with the best EEG background activity. The side-effects were low and transitory. The cost-effectiveness analysis showed a decrease of 2876.06 € in the postoperative period of 6 months (1 € was approximately equivalent to 1 $). The same authors reported the results after a 2-year follow-up,[49] which were substantially the same with persistence of the seizure reduction rate at the same level and no more improvement in the neuropsychological functioning.

Frost *et al.*[50] reported a multicentric retrospective study of 50 LGS patients, aged from 5 to 27 years (median = 13 years), 42% younger than 12. Data were gathered at 1, 3, and 6 months after implantation. They had multiple seizure types, 66% presenting with drop attacks. At 3 months, data were available for 43 patients. Seizures had decreased by >75% in 15 (35%), and by =50% in 24 (56%), and they have increased by >50% in 3. After 6 months, data were available for 24 patients (due to the data collection cutoff point). Seizures had decreased by >75% in 9 (38%) and by =50% in 14 (58%), and no increase was reported. No patient was seizure free. According to the authors, drop attacks and atypical absences seemed to equally respond, but it was difficult to affirm that, since there was no prolonged video recording. They also mentioned an improvement in quality of life, which requires further studies because the scales they applied were very simple. The side-effects were similar to those in previous studies, but

hypersalivation and worsened behavior and hyperactivity were also noted in respectively 4 and 3 patients.

Buoni *et al* [51] reported a series of 13 patients, 7 with LGS of whom 6 with atonic seizures. Three had a 50% or more seizure frequency reduction, mainly for atonic seizures, which the authors considered one good responsive seizure type, in contrast with the results by Majoie *et al.*[48] However, their sample is small and atonic seizures are not always responsible for falls (drop attacks).

Data about the effectiveness of VNS in LGS as regards other epilepsy types are unclear. Some authors [46] found a high rate of seizure reduction (from more than 50% up to more than 90%) and others seem to indicate that it is equivalent[48] or lower. Labar, [52] in a survey of 269 patients with 1-year follow-up, concluded that VNS responsiveness was associated with older age, longer duration epilepsy and syndromes other than LGS.

As for CC, up to now there are no outcome predictive factors allowing the selection of patients with a good chance of improvment by VNS. Janszky *et al.*[53] conducted a study in 47 patients, with long-term ictal and interictal EEG recordings, with a 1-year follow-up. Only four patients had a symptomatic generalized epilepsy. They concluded that only two factors were predictive for a complete control of the seizures, the presence of a cortical dysplasia and the absence of bilateral interictal epileptiform discharges, the latter independently. These preliminary results would be rather discouraging for LGS patients.

Another group[54] also attempted to find prognostic electroclinical features and studied seizure patterns in 17 patients, mainly with focal epilepsies (16 with falls) and including four LGS patients. Only four patients had a significant seizure reduction, a better outcome occurring in those seizures with a temporal lobe onset, and the poorest outcome occurring in frontal and fronto-central seizures. In the LGS patients there were no significant improvement, except a diminution of retropulsive falls.

Conclusion

In conclusion, one must underline that none of the published patients treated by VNS for a LGS has been completely seizure free, even if one seizure type could have disappeared in few of them (atonic seizures).[51] For this reason, the choice between the two types of palliative surgery, CC and VNS, should be discussed case by case. It is known that a real improvement in quality of life is obtained only in patients who become seizure free and not in patients with a seizure frequency reduction <90%. That was demonstrated for temporal lobe epilepsy surgery[55] and for pharmacological treatment.[56] However, patients suffering from LGS are extremely handicapped and diminution of drop attacks from several per day to several per month should represent a real change in daily life and the mood of the patient and his family and caregivers. Thus, after failure of several antiepileptic drugs, if the patient is not eligible for a resective surgery, the two options should be discussed. One recent study[57] has compared the response to CC and VNS in a series of 77 patients, only 13 presenting with a LGS, for a follow-up duration of 9 months. Their results for the whole group showed better outcome after CC: 79% of patients had a 50% decrease in seizure frequency as compared with only 40% for those with a VNS ($p < 0.001$), and 57% of patients had a 80% decrease as compared with only 20% of those with VNS ($p = 0.007$). They do not indicate how many patients became seizure free. However, the number of complications was obviously higher in the CC (21%) than in the VNS (8%), as well as their severity. One patient died in the postoperative period.

CC is probably more likely to give a complete control of the most disabling seizures but is not lacking in serious risk, whereas the VNS gives less favorable results but is a safer procedure.

To be complete it is necessary to mention that deep brain stimulations have been tried in selected patients,[58] apparently with some positive results against atypical absences and tonic seizures [56,57] but this procedure does not appear to be actually used.

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45 Medically intractable epilepsies not remediable by surgery

NK So

Introduction

The very title of this chapter raises a number of questions on definitions and conventions. First is the term *medically intractable*. This has to do not only with observations documenting that a patient has failed to respond to past or current trials of medications, but also to the implied improbability of a future response to further drug trials. This issue is explored in several chapters in Section 2*: Overview*. Second is the definition of *remediation*. Complete freedom from seizures is unarguably what is hoped for, as supported by psychosocial and quality of life studies which showed that improvements in employment and self-reported quality of life is correlated with a seizure-free status. However, would a 90% reduction in seizures not sometimes be worthwhile, converting a patient with 10 seizures a month to one with one seizure a month? There is indeed data to show that patients with less than 12 seizures a year report better quality of life as compared to those with more seizures. But what about a 50% reduction in seizures? While this is considered far from ideal after resection surgery, a 50% reduction in seizure frequency is the realistic expectation with vagus nerve stimulation. These questions on outcome are explored in Section 17*: Surgical Outcome.* Third is the surgery itself. There are resection procedures, large and small; disconnection procedures; the technique of multiple sub-pial resection; and vagus nerve and brain stimulation. If we include all the above techniques, and we accept that a 50% seizure reduction rate is an acceptable threshold of remediation, then in fact there is no medically intractable epilepsy that is not a candidate for surgical treatment, save for those with terminal or degenerative disorders who are considered to have too short a life expectancy.

We will briefly discuss the generalized epilepsies but this is not the place to repeat a textbook account of these seizures and syndromes. The rest of the chapter surveys those partial epilepsies that have demonstrated sub-optimal outcomes after resection surgery for which caution and extra deliberation may be advised, and those patients with partial epilepsies who were not offered epilepsy surgery. Reports of negative outcomes in the literature are subject to publication bias, so when reports are available we need to give them perhaps even greater attention.

Generalized epilepsies

The idiopathic generalized epilepsies of childhood and adolescence (and sometimes adulthood) are usually responsive to medications and fully controlled in 80%–90%, provided that medications have been judiciously selected. Pseudo-intractability arises when treatment relies on drugs that do not cover the spectrum of generalized seizures, or drugs that can aggravate generalized seizures[1] (most commonly carbamazepine and gabapentin), or because of treatment non-compliance. A small minority remains with persistent seizures despite the best treatment and compliance. It seems that those epilepsies emerging later such as *juvenile absence epilepsy* and *juvenile myoclonic epilepsy* may be more likely to face some difficulties in obtaining complete seizure control as compared with those that present earlier. There are sometimes features suggesting an overlap with symptomatic generalized epilepsy in some of these patients with difficult to control epilepsy, such as a history of some prior neurological event, or of borderline intellectual function. When pharmacological treatment has failed, such patients may be candidates for vagus nerve stimulator implantation,[2] although its use is still *off-label*.

The secondary (symptomatic or cryptogenic) generalized epilepsies represent the opposite spectrum from idiopathic generalized epilepsy. Some also call these encephalopathic generalized epilepsies. Seizures often persist throughout life and many patients have significant mental impairment and other handicaps. These patients can constitute a sizeable proportion of the patients with medically intractable epilepsy at an epilepsy center. One prototypical example is Lennox-Gastaut syndrome which starts in childhood, manifests severe epilepsy with multiple seizure types, and has associated mental retardation. The most typical seizure types are tonic, atonic (drop attacks), and atypical absence seizures, although myoclonic, generalized tonic-clonic and partial seizures also occur. The EEG shows runs of 2–3 Hz (slow) generalized spike wave complexes, bursts of generalized paroxysmal fast (10 Hz) activity, and multifocal sharp waves.[3] Other patients in the category of secondary generalized epilepsy have other combinations of multiple seizure types and multifocal sharp waves. While cases can be attributed to a specific etiology such as perinatal hypoxic-ischemic encephalopathy, malformations of cortical development, or neurocutaneous syndrome, some remain of unclear etiology. Yet others have transitional or other assorted features, making it difficult to be more specific in delineating a disease or syndrome.

Of note in a book on epilepsy surgery, some patients with secondary generalized epilepsy can superficially look as though they may have partial seizures. Simple and complex

partial seizures can indeed occur but are rarely the predominant seizure types in contrast to the different generalized seizures, and can be interpreted to be a manifestation of the multifocal nature of the disease. In ictal recordings this would be confirmed by a localizable ictal onset that is in logical agreement with the clinical signs. However, in other cases, what looks like a complex partial seizure with psychomotor automatisms on the ictal EEG first shows a generalized ictal onset pattern followed by a delayed localization of a rhythm over the temporal regions. So these may not be partial seizures in the proper sense, but a delayed recruitment of the temporal limbic system.

First corpus callosotomy [4,5,6] and later vagus nerve stimulation[7] had been used to treat patients with secondary generalized epilepsy, most commonly with the Lennox-Gastaut syndrome. Tonic, atonic, and generalized tonic-clonic seizures seem to improve most after either of the procedures. There is less consensus to the degree to which myoclonic, atypical absence, or partial seizures improve after callosotomy. Both drop attacks and atypical absence seizures were reported to improve after vagus nerve stimulation.[7]

Partial epilepsies with reduced outcomes after resection

For the sake of this discussion, we will adopt a definition of a reduced or sub-optimal seizure outcome when there is a less than 50% chance of becoming seizure free or obtaining a substantial reduction in seizures after a cerebral resection procedure. The seizure-free group corresponds to Engel Class I, while substantial reduction would correspond to Class II, and also Class III if an earlier UCLA criterion of >90% reduction in seizures is used.[8] Difficulties arise when a Class III 'worthwhile' outcome is not specified either in number of seizures or percentage reduction from baseline. The substantial reduction group would also include the Duke 'Significantly Improved' outcome of <10 seizures a year,[9] and the category of <4 seizures per year in the 1993 proposed scoring system.[10]

Identification of the conditions that lead to a less than 50% chance of seizure-free or substantial seizure reduction outcome is not presented here as an exclusion for (resection) surgery. The final decision for or against surgery will rest on a full discussion of the patient's goals, expectations for success, and tolerance of adverse outcomes. Nevertheless it brings a perspective, and helps to separate the settings for success from those less likely, which can be useful when counseling patients considering surgery. This is admittedly a higher bar than that set for vagus nerve stimulation or drug trials, where a 40% to 50% chance of a 50% or greater reduction in seizure frequency is the expected measure of success and with only a few patients becoming seizure free. But as with many human decisions, we adjust the bar set for a goal based on its associated risks. Craniotomy and excision of brain tissue inherently carry more risks. The 50% seizure-free or significant reduction cut-off is probably also less meaningful when dealing with the sometimes 'catastrophic' or 'malignant' partial epilepsies seen in infancy or childhood, where daily seizures lead to developmental standstill, making palliation without complete control a desirable objective.

Bitemporal epilepsy

Repeated studies from some of the earliest on the surgery of temporal lobe epilepsy noted a reduced outcome for seizure control in patients with bitemporal spikes.[9,11] Bitemporal interictal spikes are only one of several and a non-specific measure of bitemporal disease. Bitemporal epilepsy is now rightly defined by independent seizures recorded from each temporal lobe.[12]

Bitemporal epilepsy does not by itself stand out as a distinct syndrome. Most importantly, one should separate bitemporal epilepsy with bilateral temporal lobe disease from falsely localizing interictal and ictal EEG findings in patients with extatemporal lesions. Patients with bitemporal epilepsy do show some differences from unilateral mesial temporal lobe epilepsy. First a history of febrile seizures is less than that in patients with unilateral temporal epilepsy,[13] while a history of encephalitis and other diffuse cerebral insults is increased. Nearly all will have bilateral independent EEG spikes with or without slow waves over the temporal regions if recorded for long enough. Extracranial EEG ictal recordings are more likely to show not only independent seizure onsets, but also bitemporal non-localizable onsets, asynchronous ictal rhythms of different frequency and morphology over the temporal lobes proceeding simultaneously, and ictal patterns that switch in amplitude predominance from one temporal region to the other.[14] They are more likely to show bilateral dysfunction in a range of measures: whether MRI, MRS, memory testing. As a group, their cognitive and memory scores are more impaired than for patients with unilateral disease, and may exhibit more personality problems.

The issue to be discussed here is not that patients with demonstrated bitemporal seizures are not surgical candidates. In a review of several published series, 54% obtained a good outcome (Engel Class I and II), somewhat less than that for patients with unilateral disease.[12] What is interesting here is to look at the reasons for a bad result. The rate of seizure control is much less in series which offered most patients with bitemporal epilepsy surgery,[15–17] as compared to those that exercised additional selection.[18,19] Additional selection had been based on independent measures of mesial temporal disease: MRI findings of hippocampal atrophy and sclerosis, PET hypometabolism, and lateralized neuropsychological dysfunction that included the findings of the intracarotid amobarbital test. When there is some degree of concordance between seizure predominance as recorded by intracranial EEG and these independent tests, seizure outcome is improved. When there is no clear predominance of seizures from one side, the absence of congruent lateralization or the presence of discordant lateralization from independent tests, herald a poor outcome. It is this latter group who should be counseled on the low yield of surgery.

Multifocal epilepsy

Epilepsy with multifocal seizure onsets from non-contiguous areas, whether from the same hemisphere, or from both hemispheres is generally held to be not treatable by resection surgery. However, as we shall see later, there may be exceptions. Originally, this prohibition against operation on more than one area was probably influenced by the disastrous outcome to memory functions after bilateral surgical removal of the

temporal lobes, leading to a permanent amnesic syndrome.[20] Undoubtedly, the same prohibition applies to bilateral removal of the frontal lobes.

The causes of multifocal epilepsy are sometimes evident and visible, a consequence of a multifocal disease such as encephalitis or tuberous sclerosis. At other times the potential for multifocal epileptogenicity is understood even though not necessarily anticipated, such as when MRI imaging shows only one area of cerebral malformation, or a single scar from head injury, but investigations reveal multifocal seizure onsets. Yet other cases remain difficult to understand.

The term 'multilobar' resection was used by Rasmussen,[2] but he included in this category the failure of piecemeal resections to improve seizures in Rasmussen's encephalitis, and some cases of infantile hemiplegia with widespread epileptiform abnormalities throughout the hemisphere. The same would apply to surgery for hemimegalencephaly. These are all widespread or progressive disease states. We know that epilepsy surgery can be successful in these conditions, but calls for a more radical removal or disconnection of the diseased hemisphere. Rasmussen also presented the results of 'frontal plus' surgery at Montreal Neurological Institute.[22] This very brief report did not detail the diseases or pathologies treated. What is notable is that of 63 patients who had removals from the frontal lobe and adjacent central or temporal regions, only 10% became seizure free and another 24% had 'marked reduction' of seizures. Then there were 13 patients who had reoperations on both the frontal and temporal lobes after a failed first operation. None of these patients became seizure free.[23]

The results from Montreal contrast with results collected at the 2nd Palm Desert Conference in 1992. Between 1986 and 1990, 166 multilobar resections were performed worldwide, and 89% were seizure free or had worthwhile (>90%) seizure reduction.[24] The pathological conditions treated by multilobar resections are not known. More intriguing is a recent report of the success of staged multifocal resections in children with tuberous sclerosis.[25] It raises the question that the success or failure of multifocal resections need to be re-evaluated based on the underlying disease process. In patients with non-progressive multifocal epileptogenic lesions, surgery may work provided it does not violate patient safety and lead to unacceptable deficits.

Dual pathology

Dual pathology refers the presence of hippocampal sclerosis with another identifiable lesion in temporal or extratemporal locations. It may be considered another facet of multifocal epilepsy. Dual pathology so defined is found in about 15% of patients with partial epilepsy.[26,27] It seems more common in congenital disorders or when there is a history of an early insult. The pathological entities most commonly found associated with hippocampal sclerosis include: malformations of cortical development, porencephalic cysts, and atrophic gliotic lesions from old infarcts or contusions. Less common associations are indolent tumors and vascular malformations.

Several studies reported on the surgical outcomes in patients with dual pathologies. The numbers of patients were by the nature of this condition small. Where only one of either the lesion or the mesial temporal structures was removed surgically, the chance of a seizure-free outcome was reduced to 10%–17%, although some had significant improvement.[28–30] While there was a paucity of studies to no studies proving independent ictal onsets from the separate pathologies, this had been implicit in the observations. Selected patients who failed first surgery, became seizure free when a second surgery was performed to remove the remaining pathology. This suggests that when there is dual pathology, the surgical strategy should plan for removal of both pathological substrates, although the surgical steps can be staged.

Partial epilepsies with normal MRI findings

Seizure outcomes after surgery are generally reduced in patients with temporal and extratemporal epilepsies and normal MRI.[31,32,33,34] Several studies showed that additional preoperative non-invasive findings are extremely important to help predict a good or a poor outcome. The presence of localized interictal discharges on scalp EEG, and localized hypometabolism by PET were statistically significant predictors, while ictal scalp EEG afforded a trend but was not statistically significant in patients with neocortical epilepsy and normal MRI imaging.[35] The presence of generalized interictal discharges in scalp was a bad omen in frontal lobe epilepsy, even if there were MRI abnormalities, as only one of ten (10%) patients became seizure free.[36] In MRI negative temporal lobe epilepsy, the presence of bilateral independent or multifocal interictal discharges in scalp EEG also predicted bad outcome, with only four of 14 (29%) seizure free.[32] There is additive value to the number of concordant non-invasive tests in prediction of outcome: when two or more tests are concordant, outcome is significantly better with 60% becoming seizure free. This contrasts with a 30% seizure-free rate in patients without any localizing findings on non-invasive testing.[35]

Thus patients with neocortical epilepsy and normal imaging should be counseled on the reduced likelihood of a good surgical outcome if there are no localizing findings on non-invasive testing by scalp EEG and FDG-PET scan.

Certain malformations of cortical development

In contrast to relatively the good outcomes after resection of focal cortical dysplasia, some other developmental pathologies have not responded well to surgical treatment, whether by localized resection or by multiple subpial resection, despite intracranial EEG investigations. Of eight women with subcortical band heterotopia (double cortex syndrome) who underwent surgery, only one had significant improvement.[37] Periventricular heterotopias also did not demonstrate a good surgical outcome particularly if there is bilateral disease. In a series of ten patients operated at Montreal (seven bilateral disease), only one had a significant reduction in seizures at long-term follow-up.[38] This patient had unilateral heterotopia, and most of the abnormality was included in the temporal resection. Admittedly the resections were corticectomies that often did not include the heterotopic tissue, now known to be intrinsically epileptogenic, and part of the ictal epileptogenic zone together with overlying cortex. In a more recent surgical series in which resection targeted both the heterotopic nodules and associated cortex, excellent results were obtained in patients

with unilateral heterotopias, but not in those with bilateral heterotopia.[39]

Other subtle indices of malformation in cortical development may also be important in surgical outcomes. In a study using segmentation analysis of gray and white matter volume distributions,[40] even a subtle abnormality outside of the temporal lobe is correlated with a reduced outcome after temporal lobectomy, with only four of 14 patients (28%) becoming seizure free, as against 11 of 13 patients (85%) without such extratemporal abnormalities.

Reasons patients are not selected for surgery

Inability to localize the epileptogenic zone

A proportion of patients are rejected from surgery in any surgical series after extensive investigations, either because the epileptogenic zone could not be localized, or because testing showed multifocal abnormalities. Non-localized, non-invasive testing is typically followed by intracranial EEG investigation in patients with suspected partial epilepsy, thus the published results of intracranial EEG investigations can give us some idea of how often patients are rejected from surgery for these reasons. Non-localizing intracranial EEG studies could be a result of inability to record seizures, mistaken investigation of generalized epilepsy, failure to target the epileptogenic zone from an incorrect hypothesis of its location, inadequate electrode coverage, true multifocal epileptogenicity, and perhaps abnormal networks that cause such rapid and widespread synchronization that confident interpretation of the site of seizure onset is not possible based on current understanding and technology.

In a review by Spencer in 1981, she found that 18% of patients investigated by depth electrodes were excluded from surgery.[41] The rates were even higher in two European centers with a notable history of depth electroencephalography in that era, 23% in Milan, and 35% in Paris. For subdural EEG recordings, rather similar results were found. In a series of 50 patients from Oregon, 12 (24%) were excluded from surgery because of multifocal onset, inability to determine an onset, or bitemporal independent seizures.[42] It can be argued that the rates for unsuccessful intracranial EEG would be expected to be higher in those earlier series that did not have the advantage of MRI and other imaging techniques now in use. A more recent report on the cumulative experience of 217 patients at Montreal Neurological Institute investigated by depth electrodes found that 37 (16.5%) were excluded from surgery afterwards, and that a further nine patients (4%) had technically unsatisfactory recordings.[43] The proportion of patients with a localized epileptogenic zone falls when the preoperative MRI is negative. Only 58% of a series of 43 MRI negative patients proceeded to resection surgery after intracranial EEG investigation between 1992 and 1999, using combinations of subdural and depth electrodes.[44] Thus 15%–40% of patients with complex findings that did not permit localization of the epileptogenic zone by non-invasive data and who underwent intracranial EEG investigation failed to obtain sufficient localization to recommend surgery, with the higher number when the MRI was normal.

Epileptogenic zone located in eloquent cortex

The number of patients who are not candidates for resective surgery because of this reason is probably smaller. There are several qualifiers that make the location of the epileptogenic zone in eloquent cortex more a relative contraindication than an absolute contraindication in many cases. *First* there is the risk benefit analysis undertaken by the patient and healthcare team as to whether the potential benefit of surgery outweighs the likely postoperative deficits. This is a highly individual decision. It seems there is some degree of rank ordering with some deficits considered more acceptable than others. Thus the deficits that follow resection of the primary sensory area in the postcentral gyrus, and of the visual areas in the occipital cortex are presumably acceptable to many as a trade-off for seizure control, if only because there are surgical series of such treatments. Experience also indicates that resection of the primary motor area of the face can be tolerated with only relatively minor problems.[45] This leaves resection of primary motor areas of the arm and leg, and the language areas, as the least acceptable. To that is added permanent anterograde memory loss that can result from resection of the mesial temporal structures on one side if the other side is also diseased. This has fortunately become very uncommon with present presurgical protocols to evaluate both the structure and the function of the temporal lobes. Indeed there is now more controversy on the validity of memory assessments by the different test methods, particularly the intracarotid amobarbital (Wada) test. What is acceptable or not can be modified by a *second* consideration, namely the permanence versus the potential of recovery of the neurological deficit. When a deficit is transient, it is not at all a contraindication. Thus resection of the supplementary motor area can lead to an akinetic mute state with contralateral hemiplegia that can last several weeks before recovery.[46,47] Although some minor deficits can persist, patients appropriately counseled and prepared for this possible outcome seemed to have come out at the other end with minimal discouragement. Reversibility is influenced by a *third* factor, namely the timing of the surgical procedure in the neurodevelopmental course of the individual. The earlier the resection, the greater the chance that even essential functions can be re-established. To illustrate, all three considerations are important when evaluating a patient for hemispherectomy or one of its 'disconnection' variants. Because the epileptic conditions (e.g., hemimegalencephaly, Rasmussen's encephalitis, Sturge-Weber syndrome) that call for hemispherectomy are usually progressive or cause a 'catastrophic' decline in function, the first consideration of benefit versus risk is usually in favor of surgery. The second consideration of functional recovery is supported by empiric experience that children can regain locomotor use of the hemiplegic side, and maintain language functions. The third consideration on the timing of surgery is also important in that there is some consensus that the chances for speech development after resection of the dominant hemisphere is more likely to be assured if operation is carried out by the sixth year of age, and less likely if carried out after the age of ten. It should be emphasized that the course of speech recovery after left dominant hemispherectomy can take 6 to 12 months or more.[48]

Adults with epileptogenic zones in eloquent areas not deemed candidates for resective can nevertheless be considered for other surgical procedures. The technique of multiple

sub-pial transaction was developed for this very reason (see Chapter 126). New neurological deficits can still take place, reported in 22% by one meta-analysis.[49] Vagus nerve stimulation can be considered for palliation. There are ongoing investigational protocols for brain stimulation, either targeting subcortical structures with a view towards interruption of seizure networks, or direct brain stimulation of the epileptogenic zone by implanted intracranial electrodes, delivering an 'abortive' electrical stimulus to terminate the seizure discharge. Abortive direct brain stimulation takes advantage of advances in microelectronics and computer systems to make a responsive 'closed-loop' system that detects a seizure discharge and delivers the therapeutic output.

No resection because of other surgical risks

Resective surgery may not be offered for other surgical risks. It could be because the patient has too many other serious medical or psychiatric comorbidities that would jeopardize surgical or social recovery. But more often it is because the location of a large lesion that not only impinges on eloquent cortical areas, but also on subcortical motor tracts or major blood vessels, renders its complete removal prohibitive in terms of risk of a major neurological deficit in an otherwise intact individual.

Summary

The decision for epilepsy surgery should always be a personal one informed by discussions between the patient and her doctors. Ultimately what constitutes a desirable result with regards to seizure control, and what constitute acceptable and unacceptable risks, have to be decided by the patient. There are however instances when the epileptic condition is *inoperable*, either because the risk of a major complication is considered too great, or because the seizure focus cannot be localized. Then there are situations in which a patient may not get operated on because the chance of a successful outcome is reduced below the expected threshold. It is of course the hope of all that further technological advances and scientific understanding will improve our ability to offer surgery to those who can benefit, increase the postoperative outcome, and at the same time identify others who may be best served by non-surgical therapies.

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46 Special characteristics of surgically remediable epilepsies in infants

A Gupta

Introduction

The selection of infants with surgically remediable epilepsy poses unique challenges due to several age related special characteristics.[1,2] The special characteristics span clinical presentation, seizure semiology, difficulties in examination, maturational aspects to the interpretation of scalp-EEG findings, anatomical and functional neuroimaging findings, pathological substrates, and decision making for goals, timing and type of surgery. Involvement of parents and guardians, and their level of understanding and informed consent for surgery add another dimension to the challenges. As in adults, the ultimate goal for surgical strategy in children is the identification of a focal, resectable epileptogenic zone. Surgical experience and postsurgical seizure outcome data in infants and young children from several centers around the world show encouraging seizure outcomes with low morbidity and mortality, and consensus is building on early evaluation for surgical management.[2–7] In this chapter, we focus our discussion on these special age-related differences that are important to recognize in the management of children who are likely to benefit from the surgical treatment of epilepsy. Table 46.1 compares common findings during diagnostic evaluation of pediatric and adult patients for epilepsy surgery.

Presurgical investigations in infants and young children

The presurgical investigations that are obligatory in all pediatric patients include a history and physical examination, long-term video-EEG monitoring, neuropsychological testing, and a high-resolution brain MRI (magnetic resonance imaging). Functional neuroimaging like brain FDG-PET (^{18}fluro-deoxy-glucose positron emission tomography) is often helpful as an adjunct tool, especially in patients with subtle or doubtful brain MRI findings. Other investigations such as ictal SPECT (single photon emission computerized tomography), MEG (magnetoencephalography), fMRI (functional MRI) and invasive intracranial monitoring remain challenging in this population, but may be considered in selected infants and young children. Dilated eye examination by an expert ophthalmologist, and other organ system investigations (for example, in infants with tuberous sclerosis) in consultation with other specialists such as geneticist and neurometabolic experts should be considered in appropriate circumstances prior to surgery.

Special characteristics in clinical presentation in infants

Surgically remediable epilepsy in infants often presents as catastrophic epilepsy with associated developmental regression or arrest. Medical treatment options are usually exhausted within few weeks to months of seizure onset due to rapid trials in the face of daily intractable seizures. History usually offers important clues to the etiology of epilepsy. Age of seizure onset, the course of neurological symptoms, presence of symptoms indicative of multiple organ system involvement, family history, and history of premature birth, hypoxic event, significant head trauma or central nervous system infection may offer clues to possible etiology, type of central nervous system pathology, and a possibility of bilateral or global injury. The presence of neurocutaneous markers, congenital anomalies involving multiple organ systems, stigmata of metabolic diseases, micro- or macrocephaly, and abnormal neurological findings may suggest a specific genetic diagnosis or a particular group of conditions.

Neurological examination is often challenging to elicit neurological deficits in this population. Neurological examination is helpful in presurgical evaluation if it shows unilateral hemispheric dysfunction with decreased use of one arm or side (hemiparesis), or gaze preference (homonymous hemianopsia). Recognition of subtle neurological abnormalities in infants requires experience and close observation during various activities. Mild hemiparesis may only present as early hand preference, reduced spontaneous movements of one side, poor grasp and dexterity of one hand, or unilateral small size of the limbs in early onset and long standing hemiparesis.[8,9] Subtle differences in the tone and deep tendon reflexes may also be difficult to confirm. This may be due to immaturity of the central motor systems and corticospinal tracts.

Special characteristics in evaluation of seizure semiology on video EEG

There are several differences between the semiology of partial seizures in children compared with adults. Seizure characteristics suggesting partial onset, such as specific auras in adult

Table 46.1 Comparison of common findings during diagnostic evaluation of pediatric and adult patients for epilepsy surgery. (modified from ref # 2)

Characterstic findings	Infants/young children	Adult patients
History, seizure semiology and exam		
Specific auras	Rare (unable to communicate)	Common
Seizure semiology	Stereotypic (like 'epileptic spasms' or 'bland stare')	May indicate symptomatogenic zone
Clincal seizure onset, ictal exam, postseizure recall	Unable or difficult to confirm	Easier
Ictal lateralizing features	Uncommon or unreliable	Common and reliable
Neurlogical deficit on exam	Difficult to elicit (mild hemparesis, visual fields)	Easy to elicit
Neuropsychology testing for surgical risk	Less objective (due to age, severe cognitive and behavior difficulties)	Helpful in pointing specific deficits
Scalp-EEG patterns		
Confounding factor of developmental EEG evolution	Present	Absent
Stereotypic and nonlocalizing interictal and ictal patterns	Common (hyperrhythmia, generalized or synchronous discharges)	Absent
Imaging and pathological substrates		
Confounding factor of developmental brain MRI changes	Present	Absent
Ictal SPECT	Difficult (brief frequent seizures, clusters, difficult ictal onset)	Easier
Common location and extent of lesions	Extratemporal large lesions	Temporal, smaller lesions
Common etiologies	Congenital (cortical dysplasia, malformation, tumor, perinatal stroke)	Hippocampal sclerosis, focal cortical dysplasia
Surgical considerations		
Morbidity and mortality	Higher (due to age, weight, larger resections, coexisting disablities)	Lower
Timing and best techniques for surgery	More controversial and require planning and experience	Less controversial
Invasive mapping (intracranial grids or depth electrodes)	Not practical in most infants and young children	Possible
Intraoperative neurophysiologic techniques	Limited utility, more challenging in infants	Very useful
Goals of surgery/successful seizure control	Cognitive improvement, schooling, behavior, productive adult life	Job, driving, independence

patients, are unidentifiable in infants.[10] Clinical seizure onset may be difficult to pinpoint with accuracy, especially in developmentally delayed and hypotonic infants, and this may create a challenge during scalp Video EEG and ictal SPECT.[11,12] Assessment of the ictal level of consciousness in infants is fraught with problems, and automatisms, when infrequently present, tend to be simple, bland, and predominantly oral. Furthermore, distinguishing oral automatisms from normal background behavioral activity in infants can be difficult.[13,14] Clearly identifiable and reproducible characteristics of localized seizure onset, such as clonic jerking or tonic/dystonic posturing of one extremity or one side, is rare in infants.[15] Partial seizures arising from temporal or temporo-parieto-occipital regions usually manifest with a decrease or arrest in behavioral motor activity, bland stare, with indeterminate level of consciousness and minimal or no automatisms. Partial seizures arising from frontal or fronto-parietal regions tend to present with symmetric or asymmetric bilateral tonic stiffening, sometimes preceded by or associated with bilateral eyelid blinking.[14,16] It is generally recognized that the classification of partial epileptic seizures of the International League Against Epilepsy [17] reflect experience in adult patients, and therefore, may not be as useful in children below the age of 3 years.

Special characteristics and maturational aspects of scalp EEG patterns

It is now well known that seizures in focal cortical lesions in infants may have no clinical or EEG findings to suggest partial epilepsy. Seizures are usually stereotypic infantile spasms, and scalp-EEG shows interictal hypsarrhythmia, diffuse electrodecrement during infantile spasms, and absence of focal EEG seizure patterns.[18–21] Yet, many studies have shown cessation or significant improvement in seizures after the resection of the focal cortical lesion seen on the brain MRI and PET.[4,7,19,22] Overall 65% of affected infants are free of seizures after surgery,[21] and infantile spasms with hypsarrhythmia are not predictive of poor surgical outcome. However, careful review of scalp-EEG in infantile spasms is still helpful as it may offer clues to a localized pathology by predominance of interictal sharp-waves over one region, localized slowing or decreased background activity, or absent sleep spindles over the affected region or hemisphere. Sometimes careful history and review of earlier video-EEG evaluations may show intermixing of infantile spasms with partial seizures (EEG and clinical) during early infancy eventually to be replaced or overwhelmed by infantile spasms. Ictal scalp-EEG in infants may offer clues to focal pathology by unilateral electro-decremental events, generalized but asymmetric electroencephalographic EEG patterns, or occurrence of partial EEG seizure patterns before, during, or after a cluster of infantile spasms.[2,23]

Generalized scalp-EEG patterns in the presence of focal lesion may not be limited to infants. More recently it has been recognized that scalp-EEG may show generalized and bilaterally multiregional interictal and ictal findings even in older children with an MRI lesion, and seizure freedom is possible after surgery[47]. Further, generalized discharges/slow spike and wave resolve postoperatively in such patients, and are likely to be a secondary phenomenon. Authors reported 10 children (age 3–16 years) with generalized and bilateral multiregional interictal and ictal EEG (without any solitary or predominant focal EEG) and a brain MRI lesion who were surgically treated. All had catastrophic epilepsy resistant to all possible medical treatment. Surgery was offered as a last resort after critical evaluation, parental consent and bioethics approval. MRI showed encephalomalacia in four, malformations in three, and remote stroke in three patients. On postoperative follow-up (mean 26 months), eight were seizure free, and two had rare seizures. All had remarkable improvement in quality of life. Postoperative EEG at 6 months showed resolution of generalized discharges/slow spike and wave in all patients. The authors concluded that generalized and multiregional epileptiform scalp-EEG findings (and without any single or predominantly focal EEG) may occur in older children in the presence of a brain insult early in life, and do not preclude benefit from surgery.

It is, therefore, not uncommon to see generalized EEG patterns in pediatric patients with surgically remediable epilepsy. This recognition is important, and every effort should be made to look for subtle clues to focal pathology in the EEG, and previous EEGs should be reviewed whenever available.

Special characteristics in anatomic and functional neuroimaging in infants

Brain MRI is a key investigation in planning surgical strategy at all ages, but in infants it assumes even a higher level of importance due to common occurrence of generalized or nonlocalized EEG patterns as discussed in the previous section. With the availability of high-resolution brain MRI and three-dimensional volume acquisition sequences, the brain MRI can demonstrate the presence of subtle cortical dysplasias, developmental tumors like dysembryoplastic neuroepithelial tumors, and other malformations of cortical development which are the most common pathological substrates in infants with surgically remediable epilepsy. The presence of subtle cortical dysplasia may only be evident as loss of gray-white matter junction, loss of normal white matter arborization, localized thickening of cortical ribbon, or abnormal morphology of gyri and sulci.[24]

Infants present a unique challenge in interpretation of brain MRI abnormalities that may be subtle or focal, like focal cortical dysplasias. This is due to immaturity of myelination and normal lack of gray-white matter distinction during the first year of life. The brain MRI during infancy shows a maturational dependent change in the signal intensity on T1- and T2-weighted images as the brain matures from caudal to cephalad and from dorsal to ventral surface.[25,26] The importance of finding a lesion on brain MRI can be demonstrated by several studies that showed that the complete resection of the brain MRI lesion resulted in the seizure-free outcome in a significantly higher percentage of patients when compared to those with only partial resection of the lesion or resection in the absence of a MRI lesion.[5]

Brain FDG-PET was shown to be an especially useful tool in identifying infants for epilepsy surgery, as it may show a region of abnormality that may be obscured on brain MRI due to its subtle nature and immaturity of the myelination process.[4,27,28] However, this is seldom the case these days due to improvement in MRI technology and increased expertise in detecting subtle cortical abnormalities. Other confounding factors that must be considered while interpreting brain PET in infants and young children with frequent seizures include the difficulty in accomplishing a true interictal study due to occurrence of clinical or EEG seizures just before or during the PET scan, dynamic nature of brain maturational process, and evolution of certain pathological substrates of seizures over time as in tuberous sclerosis, Struge-Weber syndrome or Rasmussen's encephalitis. Nonetheless, brain PET remains a valuable noninvasive supplementary tool in localization of the epileptogenic zone.

Ictal SPECT is increasingly being used as a diagnostic procedure for localizing epileptic seizure focus, especially in patients with extratemporal epilepsy and a normal brain MRI.[11] It has proven useful in some pediatric patients where the most common location of epileptogenic lesions is extratemporal. However, some special challenges exist in obtaining and interpreting the ictal SPECT studies in infants and young children with frequent seizures. These include difficulty in accomplishing a true interictal SPECT due to multiple daily seizures, difficulty in promptly recognizing the clinical onset of ictal behavioral changes due to age and coexistent mental retardation often resulting in a late injection, brief duration and rapid spread of spasms and other seizures of extratemporal origin, and two-time sedation that may be required for interictal and ictal study. The advent of techniques such as subtraction SPECT with co-registration on magnetic resonance imaging (SISCOM) and computer image-guided surgery has enhanced the clinical electrophysiologic evaluation of SPECT detected abnormalities in epilepsy. Recent studies have suggested that the probability of seizure-free outcome is significantly higher in patients with nonlesional extratemporal epilepsy when surgery involved the SISCOM focus than when it did not.[29–31]

The role of other neuroimaging modalities like magnetic resonance spectroscopy (MRS) and functional MRI (fMRI) in young children with catastrophic epilepsy has not been systematically studied.

Special characteristics of pathological substrates in pediatric patients

Pathological substrates of epilepsy are different in infants when compared with older children and adults. Hippocampal sclerosis, the most common etiologic factor in adult candidates for epilepsy surgery, is uncommon in infants. In pediatric epilepsy surgery series from the Cleveland Clinic Foundation,[7] hippocampal sclerosis was the cause in only 12% of 62 children (age 3 months to 12 years) and 15% of 74 adolescents (age 13 to 20 years). Whenever hippocampal sclerosis was found as the etiology of epilepsy, Pediatric patients appeared to have an especially high incidence of dual pathology with cortical dysplasia.[32]

In infants and young children, the predominant etiologies that lead to epilepsy are focal or multilobar malformation of cortical development (cortical dysplasia), and low-grade tumor. These were the cause of the epilepsy in 57% of adolescents, 70% of children, 90% of infants younger than 3 years in the Cleveland Clinic series,[7] and 90% of infants treated surgically in the series of Duchowny and colleagues.[5] Congenital hemispheric malformations of brain development such as hemimegalencephaly or extensive hemispheric malformations are also important etiologies in infants undergoing epilepsy surgery in the form of hemispherectomy.[9] Perinatal unilateral cerebral ischemic (vascular) insults, Sturge-Weber syndrome, and Rasmussen's chronic focal encephalitis are other etiologies where hemispherectomy may be indicated.[6,9] Less common indications for epilepsy surgery are etiologies like encephalomalacia related to remote trauma or infection.

The age-related differences in etiology result in an age-related spectrum of surgical procedures. Anteromesial temporal resections predominate in adults[33] but not in children. In pediatric series, extratemporal or multilobar resections or hemispherectomies composed 44% of the surgeries in adolescents, 50% in children, and 90% in infants.[5]

Special surgical characteristics in pediatric patients

Timing of epilepsy surgery

Recent pediatric series justify early epilepsy surgery in infants with catastrophic epilepsy, regardless of age.[6] Improvement in surgical techniques, anesthesia, and pediatric intensive care during peri- and post-operative periods significantly reduced the mortality and frequency of complications. The risk of proceeding with surgery must be weighed against the risk of continuing with uncontrolled seizures treated medically. If careful analysis yields a favorable risk/benefit ratio for surgery, then surgery should be considered. The usual delay from onset of seizure intractability to surgery is still in the range of 12–15 years at most centers, reflecting a reluctance to consider surgery during childhood. Complicated infants in need of epilepsy surgery should be considered for referral to specialized centers with extensive pediatric experience.[6]

Goals of epilepsy surgery

The goals of epilepsy surgery may vary according to age. In adolescents and adults, the main goals are usually related to driving, independence, and employment, and their achievement requires complete postoperative freedom from seizures.[34] For infants and children, the goals often center on relief of catastrophic epilepsy, resumption of developmental progression, and improvement in affect and behavior. For infants and young children with catastrophic epilepsy and daily seizures, even a postoperative outcome with rare or infrequent seizures may be gratifying with improvement in developmental progression. Seizures that begin in the first few years of life, regardless of etiology, constitute a risk factor for mental retardation.[8,35–37] Early surgical intervention may reduce this risk by allowing resumption of developmental progression during critical stages of brain maturation, but quantitative and prospectively collected data are scant.[5,6]

Postoperative new deficits and plasticity

Risks for occurrence and chances of recovery from new postoperative neurological deficits (e.g., hemiparesis or language impairment), may be reduced in pediatric patients as a result of developmental plasticity and potential for transfer of eloquent functions. In patients with Rasmussen's encephalitis involving the left (dominant) hemisphere, transfer of language has been described to the right hemisphere during the course of the illness.[38] Language may also develop in unusual regions of the left hemisphere in a congenital malformations or tumors involving the left frontal or posterior temporal region.[39,40] In these cases, the epileptogenic lesion may be resected or disconnected without worsening or producing new language deficits. Motor function may also partially develop outside a damaged or malformed rolandic region, so that resection of a perirolandic lesion results in little or no additional postoperative motor deficit. Factors favoring developmental plasticity include early onset of the lesion (e.g., perinatal infarction or congenital malformation) and surgery performed within the first few years of life.

Mortality in infants undergoing epilepsy surgery

Epilepsy surgery in infants has higher morbidity and mortality compared to adults due to several factors such as perioperative blood loss and hypothermia in the face of lower weight and smaller blood volume, radical surgeries with multilobar or hemispheric resections, and higher likelihood of metabolic derangements. The risk of death in recent larger series from several centers is around ~1–1.5%.[7,22,41–43] However, the mortality from epilepsy surgery in infants still compares favorably against the mortality from uncontrolled seizures treated medically. In a populationbased cohort study in children[44] (1–16 years of age) who developed epilepsy between 1977 and 1985, 26 (3.8%) of 692 children died by the year 1999. Majority (13 of 26) of the children who died had secondarily generalized seizures. Presence of neurological deficit was the only independent factor that determined mortality. Similar results have been reported from a Dutch study.[45,46] These epidemiological data reinforce consideration for early surgical intervention as children with surgically remediable catastrophic epilepsy often have neurological deficits and secondarily generalized seizures.

Conclusions

Presurgical evaluation in infants and young children entails a variety of special challenges, and requires a special set of skills for accurate interpretation of clinical data, EEG, and imaging studies. In addition, decision for surgery requires a careful study of the benefit/risk ratio in every child, keeping in mind the complicated interplay of age-related factors and parental understanding. All children with catastrophic epilepsy, regardless of age, must be promptly evaluated for the possibility of surgically remediable epilepsy. Management of infants with surgically remediable catastrophic epilepsy is best done at centers with experienced and dedicated team of pediatric epilepsy specialists, neurosurgeons, anesthesia, and intensive care staff.

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SECTION 4

Presurgical evaluation: general principles

47 General principles of presurgical evaluation

M Carreño and HO Lüders

The main goal of the presurgical evaluation in patients with intractable epilepsy has been the identification of the cortical area capable of generating seizures, and whose removal or disconnection will result in seizure freedom. This area is called the *epileptogenic zone*. It includes not only the actual area that is generating the patient's habitual seizures, but also those regions with potential epileptogenicity, which could give rise to seizures if they were left in place, even though the documented seizure onset zone is removed. The concept of the epileptogenic zone is a purely theoretical one, and its extent and location cannot be determined until we have actually made the patient seizure free after resective surgery. At that point it is possible to state that the epileptogenic zone was indeed included in the removed area.

To estimate where the epileptogenic zone is and what its boundaries are, epileptologists have been using different diagnostic tools of increasing complexity and technical difficulty. This includes careful analyses of seizure semiology, electrophysiological studies (noninvasive and invasive), anatomical neuroimaging, and functional neuroimaging. These diagnostic methods have led to the definition of several cortical zones (*symptomatogenic zone*, *irritative and ictal onset zones*, *epileptogenic lesion*, *and functional deficit zone*), each one of which is a more or less precise index of the epileptogenic zone. During modern presurgical evaluation of patients with intractable epilepsy, an attempt is made to locate and define the boundaries of these five zones. In the ideal surgical candidate, all five zones will show a high degree of overlap and the resection can be performed with a high likelihood of seizure freedom. However, in most patients the different cortical areas are somewhat discordant in location or extent and, in the final decision about surgery, the relative significance of each one of these areas (based on the information presented below) must be weighted carefully.

In this chapter we provide an overview of these five zones, the techniques we use to locate them, and their relative advantages and disadvantages to estimate the epileptogenic zone. We will start with the sympomatogenic zone, which was the first cortical area that epileptologists could define, just by analyses of seizure semiology. The rest of the zones will be reviewed in the order in which they were defined and used in clinical practice, thanks to the growing amount and accuracy of diagnostic techniques.

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Symptomatogenic zone

The symptomatogenic zone is the cortical area that, when activated by the epileptic discharge, reproduces the patient's typical ictal symptoms. The symptomatogenic zone that produces the initial ictal symptoms is usually most important when we use it as an index of the location of the epileptogenic zone. The concept that the symptomatogenic zone was a good index of the epileptogenic zone was a by-product of the pioneering work of John Hughlins Jackson in the nineteenth century. He was the one who first used ictal symptomatology to define cerebral localization in patients with partial epilepsies. Jackson's clinical observations and autopsy studies provided evidence about the role of the cerebral cortex in motor function and in epilepsy. His definition of epilepsy, which still stands today, was made in 1873: 'epilepsy is the name for occassional, sudden, excessive, rapid and local discharges of gray matter'.[1] Until the introduction of the electroencephalogram (EEG) by Berger, localization in epilepsy surgery was based entirely on the determination of the symptomatogenic zone. 'William Macewen,[2] Alexander Hughes Bennett and Rickman Godlee,[3] J. R. Green,[4] and Victor Horsley[5] performed the first operations for the treatment of epilepsy, basing the presurgical localization of the tissue to be resected mainly on seizure symptomatology. Bancaud and Talairach also regarded as crucial the order and sequence of semiological elements to extrapolate the anatomical origin of the seizure discharge. A methodical description of signs and symptoms, with an analysis of their sequential occurrence, led to the definition of seizure patterns that became the topic of the majority of Bancaud's publications.[6–13]

A good analysis of the ictal symptomatology requires in the first place a detailed clinical history. However, the patient's and family's seizure reports are often inaccurate. In addition, experience with patients who have undergone successful resective surgery has shown that some subtle ictal symptoms that may be overlooked are extremely helpful to lateralize or even localize the epileptogenic zone.[14–21] For these reasons, it is now widely accepted that an experienced epileptologist should personally review some of the patient's seizures recorded on video to define correctly the symptomatogenic zone.

Not all the ictal symptoms have the same value to localize the symptomatogenic zone, according to the principles of neurological localization. Some symptoms are highly likely to be produced by one well-defined cortical area; for example, an auditory aura lateralized to the left ear is likely to arise from the vicinity of Heschel's gyrus in the contralateral temporal

neocortex. Localized paresthesias affecting the right side of the face and right arm are probably due to epileptic discharges involving the left SI. Simple visual hallucinations (flashing lights or dots) in the left visual field are probably due to activation of primary visual cortex in the right occipital lobe. However, other ictal symptoms are less specific and less reliable to localize the symptomatogenic zone: Whole-body tingling, for example, can be seen in the context of epilepsy arising from different cortical areas.

It was assumed for a long time that, in patients with partial epilepsy, the symptomatogenic zone was the area from which the seizure was actually originating. However, it is important to stress that the sympomatogenic zone and the epileptogenic zone usually do not overlap. When the conditions of epileptic activation are reproduced experimentally with electrical cortical stimulation, it has been shown that most of the human cortex is 'silent' (it does not produce any symptoms) when it is stimulated. Even in 'eloquent' areas, the electrical stimulus must have certain features (in terms of intensity, duration, and frequency) to produce clinical symptoms. Different eloquent areas have also different thresholds to produce the corresponding symptoms.

This implies that discharges frequently arise from noneloquent areas in the brain, sometimes at a significant distance from eloquent cortex, and that they give rise to clinical symptoms only when they spread and activate an actual symptomatogenic zone. This explains why seizures arising from different locations may present with similar symptoms (and, by extension, with similar 'symptomatogenic zones'). For example, seizures arising from mesial occipital, mesial parietal, mesial frontal, and basal frontal regions may all manifest clinically with bilateral asymmetrical tonic seizures, caused by activation of the supplementary sensorimotor area (SSMA). Removing the SSMA would make seizure free only those patients in whom the seizures were really arising from this region in the mesial frontal lobe. Most likely, seizures would persist in patients with basal frontal, mesial parietal, or mesial occipital lobe epilepsies.

In spite of all these limitations (lack of precise correspondence between ictal symptoms and a clearly defined symptomatogenic zone, as well as lack of overlapping of sympomatogenic zones and epileptogenic zones), seizure semiology still remains an extremely valuable tool in the evaluation of epileptic patients. It has been shown that seizures can be accurately classified according to clinical semiology alone,[22,23] and that ictal symptoms need to be considered together with the electrophysiological and neuroimaging data to define correctly the epileptic syndrome.[22,23] Seizure semiology not infrequently can be used to support or discourage surgery. For example, a patient with seizures starting with a hypermotor phase (symptomatogenic zone probably corresponding to cingulate gyrus and adjacent structures) and then evolving into a dialeptic (quiet staring) phase most likely has frontal lobe epilepsy, even though the EEG may show interictal temporal spikes and a late temporal ictal pattern. A temporal lobectomy in this patient is likely to fail.

Irritative zone

The irritative zone is the area of cortex capable of generating interictal spikes on the EEG. The presence of interictal spikes strongly supports the diagnosis of epilepsy, although some epileptic patients do not exhibit any interictal epileptiform abnormalities even in prolonged recordings. We also know from extensive experience with routine EEGs that the spike location is a good indicator of the area of cortex from which seizures are originating. In general, isolated spikes, independent of whether they arise from silent or even eloquent cortex, do not produce any clinical symptoms. In order to produce symptoms, spikes usually have to give rise to afterdischarges (runs of epileptiform discharges that by tempotal summation have enough strength to activate a symptomatogenic zone when they generate in it or spread to it). There are several methods that can be used to register interictal spikes; all of them have limitations that will be discussed below.

Scalp electroencephalography

History

The greatest advance in EEG came in 1929, when Hans Berger published his first work on scalp recordings of human EEGs.[24,25] Berger developed the EEG to record human brain activity from the scalp, and his findings on interictal EEG activity were mentioned as early as 1933.[26] These were soon confirmed by other authors, including Adrian and Mathews[27] and Jasper and Carmichael.[28] The interictal spike as the hallmark of epilepsy was first described in 1934 by Fischer and Lowenbach.[25,29] Wilder Penfield, who founded the Montreal Neurologic Institute in 1934, soon recognized the great potential of the EEG to define better the epileptogenic zone. The laboratory of EEG and neurophysiology run by Herbert Jasper was the first of its kind to be dedicated to selecting epilepsy patients for surgery and providing the techniques for intraoperative recordings.[30] Jasper published one of the first reviews on the application of EEG to epilepsy and epilepsy surgery in Penfield and Erickson's book titled *Epilepsy and Cerebral Localization*.[31] In 1951, Bailey and Gibbs reported a series of 25 patients who underwent temporal lobectomy based solely on EEG criteria.[32] Their results were encouraging and helped establish the EEG as the primary modality of seizure localization in the workup of patients for surgical resection.

Scalp electroencephalography to determine the irritative zone

Scalp EEG is a convenient technique to give a good overview of the general distribution of the epileptiform activity, especially if it is performed with closely spaced electrodes and special electrodes if needed (sphenoidal or nasopharyngeal electrodes). It can sample extensive areas of the brain, and has no known serious complications because of its noninvasive nature; in addition, there is extensive experience in the identification of spikes in the scalp EEG. Because of these reasons, it continues to be the initial (and at times the only) indispensable step in the evaluation of the irritative zone.

Scalp EEG has, however, some technical limitations:

- The electrical activity recorded by scalp EEG is significantly distorted by high-resistance materials lying between the cortex and the recording electrodes (bone, meninges).
- To be detected, epileptiform discharges must involve synchronized activity of a significant extension of cortex

(around 6 cm^2).[33] Interictal spikes generated by a smaller cortical surface do not show up in scalp recordings.
- Interictal activity arising from deep or midline structures is usually not reflected on scalp EEG.
- Precise localization and determination of the extent of the cortical area that is giving rise to an interictal spike is impossible. From the surface distribution of the epileptiform discharge we can only estimate where the maximum is, and get a rough estimate of the approximate extent of the irritative zone.
- There are a number of factors that may influence frequency and morphology of interictal spikes. Spikes are more frequent and widespread during deep stages of sleep than during wakefulness and rapid eye movement sleep,[34] and there are reports suggesting that spikes also increase in frequency after seizures.[35,36] Levels of antiepileptic medications during the recording may also affect the frequency of interictal spiking, although this issue remains controversial.[35] All these factors, and particularly the duration of the EEG recording, will greatly influence the location and extent of the irritative zone we measure.

Invasive recording methods

History

Direct recording from the brain surface was attempted initially during surgery using the technique of electrocorticography (ECoG). However, chronic intracranial recordings were not reported until 1954, when Penfield used epidural strips of wires[37] The use of depth electrodes was developed and popularized by Bancaud and Talairach during the 1960s; their method, stereoelectroencephalography (SEEG), used a stereotactic technique to place accurately the electrodes and allowed recording of electrical activity of structures involved at different times during the course of a seizure.[38] Evaluation with depth electrodes soon became an essential step in the evaluation of surgical candidates in epilepsy surgery centers in Europe. Depth electrodes were introduced in North American by the Montreal Neurological Institute, and they soon became part of the standard evaluation of epilepsy surgery candidates.[39]

Invasive Recordings for Evaluation of the Irritative Zone

Direct recording from the brain surface by epidural, subdural, or depth electrodes should detect all interictal epileptiform discharges (even the ones generated by a small cortical area) without the distortion introduced by the high-resistance materials interposed between cortex and scalp. It should also permit a more accurate delineation of the boundaries of the irritative zone. However, invasive recordings have also some significant disadvantages:

- They are invasive techniques that may be associated with a number of complications, including infection, hemorrhage, and increase of intracranial pressure.
- Because of their invasive nature, they can be used to cover only a limited amount of cortical surface. An adequate coverage should be carefully planned based on the scalp EEG and neuroimaging data; however, once the electrodes have been implanted, information will be limited to the cortex that is being sampled. Potentially important information from other areas may be missed, making exact assessment of the boundaries of the irritative zone impossible.
- Experience with invasive recordings is much more limited than with scalp EEG, and there have been no recordings of normal activity in nonepileptic patients. For this reason the degree of abnormality of the recorded activities is subject to personal interpretations and also to error.
- It is unclear if the special conditions imposed by chronic invasive recordings may artificially enhance or decrease the epileptiform activity over the underlying cortex.

Electrocorticography (ECoG)

Interictal epileptiform activity can also be recorded directly from the cerebral cortex during surgery. The first report of direct electrical activity measurement from the human cerebral cortex during surgery was published in 1935 by Foerster and Altenburger.[40] By the early 1950s, it was extensively used and considered an indispensable technique in the evaluation of surgical candidates to define the irritative zone.[37] However, some studies pointed out similar outcomes in patients with total or partial removal of the irritative zone as defined by ECoG.[41,42] For this reason, ECoG was abandoned in some centers, but continues to be performed in others, as an adjunctive technique in the definition of the irritative zone.

ECoG is a safe technique, and possible complications derive from the craniotomy and surgery themselves, not from the recording. However, it has a number of inconvenient aspects: the area that can be sampled is limited by the exposure during surgery, and some regions, such as the mesial temporal structures or the medial surface of the brain, are difficult to reach (intraoperative recording from depth electrodes may solve this issue). ECoG prolongs the time of the intervention and requires immediate decision making. In addition, the particular circumstances of the recording during surgery (surgical trauma to brain surface, anesthetic agents that reduce or enhance spikes) may alter the amount and location of the epileptiform abnormalities. As with subdural or depth recordings, the experience with ECoG is limited and, once again, the degree of abnormality is subject to personal interpretations (Penfield had already described 'red and green' spikes with different epileptogenic potential). However, ECoG may still contribute to a better delineation of the irritative zone in selected cases, particularly in patients who have not been evaluated with chronic invasive recordings.

Magnetoencephalography

Magnetoencephalography (MEG) detects magnetic fields induced by epileptic discharges and has recently been introduced as an aid in the identification of the irritative zone. The advantages over scalp EEG are the lack of distortion of the magnetic signal by meninges or skull, and the optimal detection of dipoles oriented parallel to the cortical surface. However, limitations include a small signal-to-noise ratio due to the low amplitude of the magnetic signal generated by electric brain activity, rapid magnetic field falloff with distance, and an inconvenient recording device that limits the patient's mobility and therefore the possibility of performing

prolonged recordings. Some studies have shown that MEG has an accuracy in source location similar to that of scalp EEG.[43] Both techniques can complement each other in defining the extent and location of the epileptogenic zone.

Relationship of the irritative zone with the epileptogenic zone

The main goal of defining the location and boundaries of the irritative zone is trying to delineate the epileptogenic zone. However, we know that the irritative zone is not a fixed and static region; rather, its boundaries are subject to change.

- Different recording methods yield different irritative zones; scalp recordings and MEG only permit vague definition of the extent of the irritative zone. Invasive recordings are significantly more sensitive, detecting irritative cortex invisible to scalp electrodes or MEG, However, as mentioned above, only a very limited amount of cortex can be investigated with invasive electrodes. Besides, because of the possible complications and the conceptual limitations of the invasive recordings used to define the irritative zone (see above), it does not seem reasonable to use them routinely in every patient.
- The irritative zone also varies depending on the sampling period, the number of seizures, the state of wakefulness, and the level of antiepileptic medications.

We also know that the irritative zone and the epileptogenic zone often do not overlap. This variable topographical relationship was already demonstrated by Talairach and Bancaud.[44] The irritative zone usually is more extensive than the epileptogenic zone. For example, patients with temporal lobe tumors often have interictal spikes in both temporal regions; however, no seizures (or spikes) occur when the tumor is removed.[45] Some patients with tuberous sclerosis, infantile spasms, and multiregional spikes may be seizure free after focal resections.[46–48] Some patients in whom it is not possible to remove the entire irritative zone because it involves eloquent cortex may also become seizure free after partial resections. On the other hand, the opposite situation may also hold true in some patients, with the epileptogenic area being more extensive than the irritative zone. For example, we know that some patients with documented seizures display no interictal epileptiform abnormalities even during prolonged recordings in monitoring units.

Ictal onset zone

The ictal onset zone is the cortical region from which we can objectively demonstrate that seizures are arising. Some authors, such as Bancaud and Talairach, soon understood the limitations of interictal recording techniques to define the epileptogenic zone. At that time scalp EEG and ECoG were the main presurgical evaluation techniques. Scalp EEG, however, was used mainly in the interictal period, and corticography was also an interictal investigation requiring decision making in the setting of the operating room. Bancaud and Talairach's method of SEEG allowed epileptologists for the first time to perform long-term recordings and record seizures directly from the brain structures involved in their generation. They expected that a better knowledge of the spatial and temporal dynamics of seizure discharges should provide a better estimate of the epileptogenic zone. Besides, SEEG gave investigators enough time to analyze the recordings and decide on a surgical technique.

Methods to determine the ictal onset zone

We have two different ways to objectively demonstrate which is the cortical area from which the seizures are arising: EEG recordings and ictal single-photon emission computerized tomography (SPECT).

Determination of the ictal onset zone by electroencephalographic recordings

The ictal onset zone determined by EEG is usually a subset of the irritative zone: It includes not all the regions capable of generating spikes, but only those whose spikes are able to generate 'spontaneous' afterdischarges (runs of epileptiform discharges that have sufficient 'strength' to induce symptoms when they invade a sympomatogenic zone). The EEG recordings to demonstrate seizure onset may be obtained from all the methods describe above for the irritative zone, except for MEG and ECoG, which, with few exceptions, are used as interictal diagnostic tests.

Scalp EEG

Widespread use of long-term EEG monitoring has allowed direct recording of seizures in the setting of epilepsy monitoring units. Closely spaced electrodes and semi-invasive techniques such as sphenoidal, foramen ovale, or nasopharyngeal electrodes provide a better estimation of the cortical area involved in seizure generation. However, scalp EEG still has important limitations:

- Seizure activity is recorded by scalp electrodes only when a threshold amount of cortex is involved by the seizure discharge. That means that the EEG-recorded seizures almost invariably must spread to a significant degree before they can be detected with scalp EEG. Simultaneous scalp and invasive recordings demonstrate that the scalp recordings are usually silent at seizure onset and that the surface distribution of the EEG-recorded seizure is not infrequently misleading since it only represents a spread pattern.
- The ictal onset cortical area can be estimated only roughly by scalp EEG. There is extensive experience with this technique, and many patterns have now been closely linked to certain epileptogenic zones (as confirmed by results of surgical interventions). However, there are still some ictal patterns of unclear localizing value (rhythmical slowing in the delta range located in the temporal chain, for example, may represent mesial temporal or lateral neocortical temporal onset), and some seizures on scalp EEG may mislocalize or even mislateralize the epileptogenic focus, especially in extratemporal epilepsies.
- Seizures arising from certain areas may be difficult to record, or their ictal pattern may be nonlocalizable. For example, mesial frontal seizures usually have subtle and diffuse EEG changes (background attenuation, diffuse fast activity in the midline) or no EEG change at all.

- Seizures recorded in the monitoring unit may not be the best representation of the patient's habitual seizures as they are recorded after medication withdrawal.

Invasive recordings

As we explained above, invasive methods of EEG recording may have serious complications. In addition, an accurate delineation of the seizure onset zone is limited by the same factors that limited the accurate localization of the irritative zone:

- Only seizures arising from areas adequately sampled by the invasive electrodes can be recorded. Unfortunately, it is unusual that the entire seizure onset zone is covered due to difficulties in placing electrodes over extensive cortical areas. The experience with invasive recording methods has shown that, if the seizure onset zone is adequately covered, we should see ictal activity (paroxysmal fast frequencies, relative electrodecrement, repetitive spikes, etc.) arising from a small number of electrodes, and it should spread in a logical fashion to adjacent areas (e.g., paroxysmal fast frequencies in the mesial temporal electrodes spreading to more lateral temporal and frontal contacts). The seizure onset on EEG should also precede in time any clinical symptoms. If a large number of electrodes are involved by the discharge from the beginning of the EEG seizure (e.g., all the mesial and lateral contacts of depth electrodes situated in the temporal lobe), it is assumed that this corresponds to a spread pattern and the seizure originated in an area outside the recording electrodes.
- Even with a clear ictal pattern arising from a small number of electrodes, it is usually not possible to delineate the extent of the ictal onset zone. It is generally assumed that those regions invoved by the discharges early in the seizure are a part of the ictal onset zone and should be removed during resective epilepsy surgery. However, this has not been studied in depth, and the interpretation of what is meant by 'early spread' (how many seconds) certainly varies greatly among different epileptologists.
- As we mentioned before when we talked about the irritative zone, several factors (no antiepileptic medications, abnormal pressure over cortical surface, etc.) may alter the ictal patterns during invasive recordings.

Determination of ictal onset zone by ictal single-photon emission computerized tomography

SPECT measures blow flood, and, comparing interictal and ictal SPECT studies, we can evaluate the relative increase in blood flow of certain cerebral regions during the ictal phase with respect to the interictal period. Presumably, the neurons located in these areas are hyperactive due to epileptic activation and the increase in blood flow is an autoregulatory response. This technique can evaluate all brain areas with similar accuracy, including deep regions of gray matter that are difficult to monitor with scalp and even with invasive EEG.[49,50] However, determination of ictal onset zone by ictal SPECT has some practical limitations:

- The scan shows only the areas that have been activated at the time the isotope reaches that brain region. Therefore, invariably ictal SPECT will only provide information about areas to which the seizure has spread, which do not necessarily overlap with areas from which the seizure originated. In the monitoring units, specialized personnel are trained to perform the injection during the first seconds of the seizure. However, because of technical difficulties, this does not always occur. Besides, it will take approximately 20 seconds for the agent to reach the brain region of interest after the injection of the radioactive agent. Moreover, we know from invasive recordings that the EEG-recorded seizures usually start long (seconds and occasionally even minutes) before the patient experiences the first clinical signs. Therefore, in general the dye reaches the brain at least 1 minute after seizure onset, a time at which significant seizure spread has already occurred.
- The spatial resolution of the images is low compared to other anatomical neuroimaging techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET).
- The global sensitivity of ictal SPECT to detect increase in cerebral blood flow may be similar to or slightly lower than scalp EEG (e.g., epileptic auras that occasionally have an EEG correlate consistently do not show any changes in ictal SPECT). However, it is clearly inferior to the invasive EEG recordings, which always show seizure onset if adequate coverage is provided. Moreover, the 'time constant' of ictal SPECT (which is an expression of compensatory increased blood flow in response to a metabolic activation of cortex) is significantly larger (5 to 10 seconds) than the time constant of EEG, which is measured in milliseconds.

In summary, ictal SPECT, as ictal EEG, can only define approximately the location and extent of the ictal onset zone. Presently, ictal SPECT is only used to provide complementary information to the EEG data with respect to ictal onset zone.

We want to mention also that functional MRI is currently being explored as a possible future way to determine the ictal onset zone. However, it is still not used in routine presurgical evaluations.

Relationship of the ictal onset zone and the epileptogenic zone

The ictal onset zone and the epileptogenic zone do not necessarily overlap. Even if we could accurately delineate the extension of the ictal onset zone, the epileptogenic zone may be more or less extensive. We know from clinical experience that some patients become seizure free even though the ictal onset zone is not entirely removed during resective surgery; for example, some patients with benign mesial temporal tumors and documented seizures arising from both sides may become seizure free after resection of the tumor.[45] That means that the remaining seizure onset zone becomes inactive after surgery (it was dependent on the other ictal onset zone to generate seizures).

On the other hand, some patients continue to have seizures in spite of complete removal of the ictal onset zone as evidence by EEG recordings. In some cases, the failure can be explained because the EEG recording techniques were inadequate to define properly the location or extent of the actual ictal onset zone. In other cases, however, the epileptogenic zone may be

more extensive than the actual ictal onset zone, including regions that remain silent as long as another active, lower threshold area generates the seizures. When the actual seizure onset zone is removed, however, the other 'potentially epileptogenic' regions become clinically apparent.

From a practical point of view, it is impossible to overcome these limitations. In other words, at present we cannot identify the patients whose epileptogenic area is more extensive or more limited than the actual ictal onset zone that can be defined by EEG or SPECT recordings.

Epileptogenic lesion

The epileptogenic lesion is a structural lesion visible by neuroimaging techniques that is responsible for generation of seizures. Before the computerized tomography (CT) scan era, a 'lesional zone' was defined by Bancaud and Talairach as the cortical space occupied by abnormal slow-wave activity as defined by its frequency, reactivity, and waveform.[51] Talairach and Bancaud, using SEEG, mapped the exact extent of such tumors as astrocytomas or oligodendrogliomas and their relationships with stererotactically defined cortical areas. Their use of the term *lesional zone* presumed macroscopic alteration of neural tissue, which has since been demonstrated radiologically by neuroimaging techniques. The 'epileptogenic lesion' era in epilepsy surgery began with the introduction of the CT scan as a clinical tool. However, the real impact of anatomical neuroimaging was the development of MRI. It became routinely available for clinical use (including the evaluation of epilepsy patients) by the early 1980s.[52,53] High-resolution MRI, which became available in the mid-1980s, had the highest impact on the evaluation of lesions that cause seizure disorders, turning a significant proportion of formerly 'nonlesional' cases into 'lesional' epilepsies. High-resolution MRI made visualization of mesial temporal sclerosis possible, and it was recognized that malformation of cortical development was a frequent cause for intractable epilepsies.

However, not all the lesions evidenced by MRI in epileptic patients are epileptogenic. In other words, the patient's seizures may be unrelated to the lesion. In other cases, two or more lesions are seen on MRI, and it is difficult to establish which one is responsible for the patient's seizures. To solve this problem, video-EEG monitoring is routinely used as part of the presurgical evaluation, even in patients in whom the location of the lesion and the seizure semiology are congruent. The goal is to have neurophysiological confirmation of seizure origin in the area occupied by the lesion. In cases of dual (e.g., a cavernous angioma located in the posterior left temporal lobe that coexists with a sclerotic hippocampus in the same side) or multiple (e.g., multiple tubers) pathology with lesions located close to each other, it may be difficult to establish with scalp EEG which one is generating the patient's seizures. Invasive EEG recordings may be necessary in these cases.

Relationship of epileptogenic lesion with epioleptogenic zone

It was soon evident from studies by Bancaud and Talairach on cerebral tumors that the relationship between the lesional and the epileptogenic zone may be complex. We have already mentioned that a lesion visible on MRI may be unrelated to the patient's seizures; if lesions are multiple, one or many may be responsible for the patient's seizures. These issues can be generally solved by noninvasive or invasive recordings.

But even in the presence of a unique lesion that seems to be causing the seizures, its complete resection does not always guarantee seizure freedom. Seizure freedom associated with complete removal of the radiographic epileptogenic lesion is usually seen in cases of well-circumscribed lesions such as benign tumors, discrete vascular malformations such as cavernous angiomas, or sclerotic hippocampi. Other types of epileptogenic lesions, such as malformations of cortical development or gliotic scars seen in the context of posttraumatic epilepsy, are more often associated with persistent seizures after surgery, for two reasons. First, their boundaries are more difficult to establish radiologically and also macroscopically during intervention. Some malformations of cortical development are seen just as subtle blurring of the gray-white matter junction with poorly defined limits. The area around this lesion may be radiographically normal, but abnormal at a microscopic level; we have been able to demonstrate that, in certain types of malformations of cortical development, this area surrounding the radiographic abnormality is significantly more epileptogenic (as evidenced by intraoperative ECoG) than the lesion itself. When that is the case, this region has to be resected in order to make the patient seizure free. Failure to do so results in persistent seizures, and this is one of the explanations for the relatively high frequency of surgical failure in patients with neocortical dysplasia.

Second, it is also true that at times incomplete lesion removal may be associated with seizure freedom. For example, some patients with congenital hemiplegia, automotor seizures, and extensive porencephaly on MRI benefit from a standard anterior temporal lobectomy.[54]

At present we have no definite way to predict if the lesion seen on MRI overlaps completely with the epileptogenic zone, in spite of electrographic confirmation of seizure onset in the vicinity of the lesion. Extent of resection must be guided by clinical experience (as outlined above), including ECoG if possible in malformations of cortical development.

Functional deficit zone

The functional deficit zone is the area that shows abnormal functioning in the interictal period. This may be the result of a lesion with a destructive effect, or of abnormal synaptic transmission due to aberrant connections or imbalanced neurotransmitters in the area.

There are a number of ways to define the location and extent of the functional deficit zone. The first one is a *detailed neurological examination.* Using the principles of localization in neurology, the area responsible for certain deficits (e.g., hemiparesis, homonimous hemianopsia, or cortical sensory deficit) can be estimated. As early as the mid-nineteenth century, the standard neurological exam was understood well enough to allow localization of functional deficits if they were severe and affected some of the highly eloquent areas of the brain. These deficits, however, are present only in a minority of surgical candidates. Many cortical regions may be dysfunctional and clinically silent (e.g., slow-growing frontal lobe

tumors, which can go unnoticed for a long time before they result in clinical symptoms).

Detailed neuropsychological evaluation can provide some information about lateralized or even localized deficits[55] in patients without major focal findings in the general neurological examination. Brenda Milner and her group first applied this modality for localization of the epileptogenic zone in patients who were candidates for epilepsy surgery.[56] Because of the availability of more powerful tests to evaluate the cortical zones with functional deficit, the neuropsychological evaluation no longer has a major role regarding localization of the epileptogenic zone, but remains an indispensable tool for prognosis of neuropsychological deficits after surgery,[57] and it may significantly influence the final decision about surgery.

The *intracarotid amobarbital procedure* (Wada test) can provide some additional information about lateralized memory deficits that may help localize the epileptogenic zone and predict if the contralateral hemisphere is able to adequately support memory when focal resections are being planned, especially in temporal lobe cases.[58,59] However, the protocols used by the different centers are highly variable, and the results are occasionally discordant with the neuropsychological evaluation; overall, the information provided by the test regarding the functional deficit zone is considered only supportive and complementary of other tests' results.

It was the development of *functional neuroimaging techniques* (PET and interictal SPECT) that has had the greatest impact on the study of the functional deficit zone of patients with intractable epilepsy. In many epilepsy centers, PET scan has now become a routine test in the presurgical evaluation of patients with intractable epilepsy.

Interictal PET with 2-[^{18}F]-fluoro-2-deoxyglucose (FDG) has proven to be a reliable test for identifying dysfunctional cortex with hypometabolism. The first report of the use of FDG PET to help localize seizures was published in 1980.[60] Engel, Kuhn, and colleagues then showed that areas of interictal cortical hypometabolism imaged by FDG PET in patients with temporal lobe epilepsy correlated extremely well with the presumed lateralization of the epileptogenic zone as defined by depth electrodes.[61–63] A number of investigators have demonstrated the value of FDG PET in the lateralization and even localization of extratemporal lobe epilepsies.[64,65]

Interictal SPECT is another technique that provides information about dysfunctional cortex (with decreased blood perfusion in this case). However, interictal SPECT is less reliable than PET and currently is mainly used as a baseline exam for comparison with the scans obtained during the ictal phase.

^{1}H magnetic resonance spectroscopy (^{1}H MRS) is another technique that has been developed to evaluate *in vivo* the metabolic composition of the brain. Different compounds, including *N*-acetylaspartate (NAA), choline, creatine, and lactate, can be measured over the region of interest. Pathological cortex displays abnormal concentrations of these metabolites, and decreased NAA-containing ratios are found over the epileptogenic side in temporal and extratemporal epilepsies[66–6]; ^{1}H MRS abnormalities may help lateralize and predict seizure outcome after resective surgery.[69,70] The abnormal ratios seem to be the result of a metabolic more than an anatomical dysfunction; they have been shown to return to normal values after successful surgery.[71]

This technique still has, however, some limitations in clinical practice. Due to technical issues, it is not possible to scan extensive brain regions, and the region of interest has to be defined based on the results of other tests (MRI, EEG recordings, FDG PET, etc). At times, an accurate sampling of the region of interest is technically challenging (especially in extratemporal epilepsies) and the spectra obtained are of poor quality. Different centers currently use different imaging modalities (e.g., multivoxel versus single-voxel techniques), making the available data difficult to compare.

The information provided by ^{1}H MRS is at present considered only adjunctive to the data from EEG monitoring and anatomical neuroimaging during presurgical evaluation. However, it is likely that in the near future it may occupy a more important role in the presurgical evaluation of intractable epilepsy, when technical difficulties are solved and we are able to fully understand the meaning of the metabolic derangement.

Relationship of the functional deficit zone with the epileptogenic zone

The relationship between the functional deficit zone and the epileptogenic zone is complex and difficult to define even in individual cases. To start with, the functional deficit zone often varies in extension and boundaries depending on the technique (e.g., the areas that show hypometabolism in FDG PET may not overlap completely with the ones that show decreased blood flow in the interictal SPECT). As we have already mentioned, at times the information concerning memory is discrepant between the Wada test and neuropsychological evaluation tests.

The currently available techniques to define the functional deficit zone only measure global brain function (neurological exam, neuropsychological evaluation, Wada test to estimate memory), physiology (glucose uptake on FDG PET or blood flow on SPECT), or metabolic composition (^{1}H MRS); there are no tests available that estimate dysfunction directly related to epileptogenicity. As a result, the functional deficit zone is usually more extensive than the epileptogenic zone, and includes at times lesions not related to seizure generation or areas located at a significant distance from the seizure focus (diaschisis phenomenon). For example in patients with mesial temporal lobe epilepsy who become seizure free after selective resection of mesial structures, the presurgical PET usually shows an extensive area of hypometabolism involving also the lateral cortex. In patients with congenital hemiplegia and porencephaly on MRI, PET often shows extensive hypometabolism, even though some of these patients may become seizure free after limited resections, indicating that the epileptogenic zone is indeed more limited. In patients with tuberous sclerosis and infantile spasms, PET shows multiple patched areas of hypometabolism corresponding with the different cortical tubers; at times, these patients benefit from resection of individual tubers that correspond with the epileptogenic area. In addition, the spatial resolution of these functional neuroimaging techniques is poor compared to that of anatomical neuroimaging techniques such as high-resolution MRI.

At present, new techiques aimed at measuring cortical dysfunction more closely related to epileptogenicity are being developed. Some new functional neuroimaging techniques are able to

assess the distribution of certain neurotransmitters' receptors, which may be abnormal in the epileptogenic region. An example of these tests is the [^{11}C]-flumazenil PET study.[72–78]

Epileptogenic zone

The epileptogenic zone is the cortical area that is able to generate seizures, and whose complete removal is indispensable to make the patient seizure free. Of course, precise definition of the epileptogenic zone (location and boundaries) is essential for successful surgery of epilepsy. However, there is not a technique that precisely localizes the epileptogenic zone; we can only make an estimate through the information provided by the other five zones (symptomatogenic, irritative, ictal onset, functional deficit, and epileptogenic lesion), that are more or less precisely defined by the tests we have described above.

The evidence that the epileptogenic zone is a theoretical more than a practical concept is given by two facts:

1. The five areas described above never show complete overlap. The discrepancies are important in some patients and minor in others. If the discrepancies are significant and there is no plausible explanation for them, the patient is likely to have persistent seizures after surgery, and resection should be deferred until more precise testing (e.g., invasive EEG recording) is done. Another option is to consider the patient for alternative forms of treatment such as vagal nerve or deep brain stimulation. On the other hand, if the different zones show only minor discrepancies, it is generally assumed that the patient is an optimum surgical candidate and has good chances of becoming seizure free after removal of the area to which the different tests are pointing.
2. Even in the cases in which the different zones are similar, it is impossible to rule out the existence of a 'potential epileptogenic zone,' which remains silent in the presence of an epileptogenic zone with a lower threshold for seizure generation. However, this zone may become epileptogenic and generate seizures after the original epileptogenic zone is removed. This explains the occurrence of new seizure types in patients who have failed focal resections, suggesting different seizure origin and/or propagation pathways. At present it is impossible to localize this 'potential epileptogenic zone' that may be an important issue in some patients, especially those with extensive lesions and widespread epileptogenicity.

In view of all these limitations, it is obvious that we need to develop additional tests to define more directly the epileptogenic region. It is possible that tests that provide information about neurotransmitters directly involved in seizure generation may map the epileptogenic region more directly. Optimally, these tests should also be able to locate those regions with subtle abnormalities, corresponding to the 'potential epileptogenic zone.' Even when in these cases a complete resection involving the actual and potential epileptogenic zone is not possible, precise definition of the epileptogenic zone would permit a more accurate prognosis regarding seizure outcome after surgery. In addition, it is likely that the currently available techniques will significantly improve in sensitivity and specificity during the coming years, making determination of the different zones more precise and reliable. Simultaneous analysis of the information provided by the different tests will also increase their yield to estimate the epileptogenic region (e.g., computerized analysis of the superimposed MRI, ictal SPECT, and FDG PET images).[79, 80]

Case report

The case report presented below illustrates how we define the location and extent of the zones described above during the presurgical evaluation of a patient with intractable epilepsy. It also shows the complex relationship of the different zones with each other and with the epileptogenic zone.

I. G. is a 25-year-old right-handed woman who was the product of a normal pregnancy and delivery. She reached developmental milestones at appropriate intervals, finished high school, and attended college, although she did not complete a degree. She does not have any conventional risk factors for epilepsy (no history of febrile convulsions, central nervous system infections, or significant head trauma).

Her seizures started at the age of 10. They are described as involuntary contraction of the left side of her face that progresses to clonic activity of the left hand. At times this left face tonic phase may be preceded by ill-defined loss of sensation in the left leg or a sound similar to a helicopter in her head. Consciousness may or may not be affected during the seizures. Her seizures only occurred at night until she was 18, when they started to occur during the day also. Seizures happened around once or twice a month. The patient never had a generalized convulsion until her first noninvasive video-EEG monitoring, when medications were discontinued. The patient had failed a number of medications in the past, including phenytoin, valproate, phenobarbital, clonazepam, gabapentin, and lamotrigine.

Epileptogenic lesion (Figures 47.1 and 47.4D)

An MRI of the brain showed right frontoparietal atrophy. Volume loss was noticed along the right gyrus rectus, the adjacent orbital frontal gyri, the right superior frontal gyrus, the right insular cortex, the frontal operculum, and also, although to a lesser extent, the parietal operculum. The cerebral abnormality underlied a strip of focal atrophic scleroderma-like skin extending from the medial aspect of the right eyebrow to the vertex. The skin atrophy developed progressively at the age of 12 years, but had been stable approximately since the age of 22 years.

The patient had noninvasive video-EEG monitoring that showed continuous slowing in the right frontotemporal region with interictal sharp waves maximal at the F4 electrode. A single seizure was recorded; the clinical semiology was consistent with the history as described above. The EEG seizure arose from the right frontocentral region (max F4).

At this point, the family opted to proceed with medical therapy using a different drug regimen. However, seizures significantly increased in frequency over the next months, and the patient started to have one or two seizures a week. After the seizures the patient felt extremely tired and stayed in bed for one day. Seizures prevented the patient from participating in

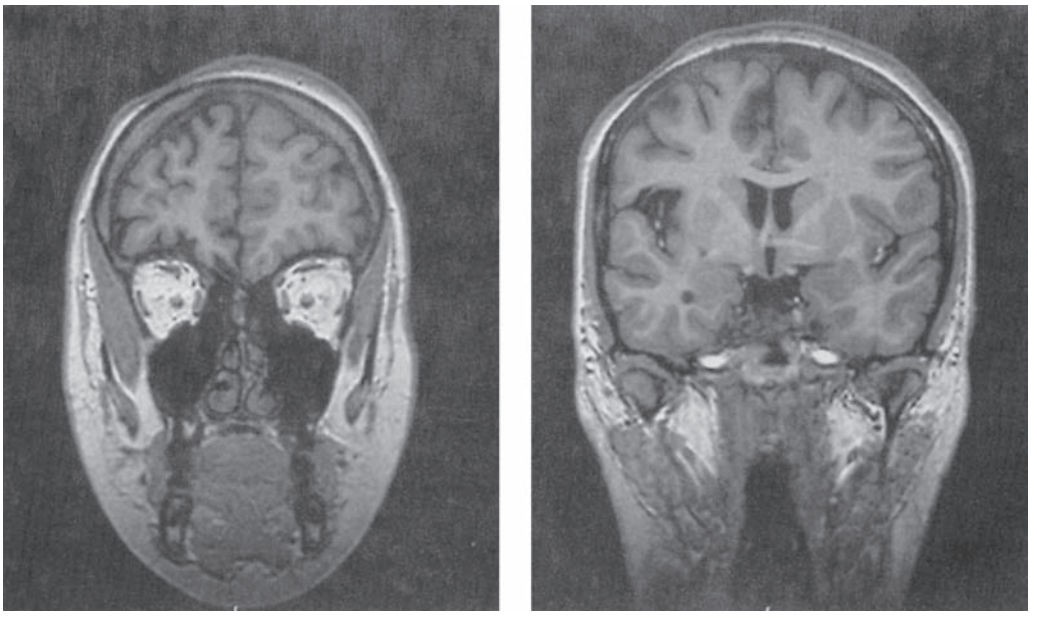


Figure 47.1 Preoperative MRIs (T1-weighted images, coronal cuts) showing the volume loss involving the frontal and part of the parietal lobes.

normal educational or social activities. The patient and her family decided to explore further the surgical options, and it was decided to proceed with invasive video-EEG monitoring for better delineation of the ictal onset zone and for mapping of eloquent cortex.

Four subdural electrode grids were placed over the right hemisphere. An 8 × 8 electrode grid (A plate) was located over the right frontal convexity with the posterior edge behind the central sulcus (Figure 47.2). A 4 × 4 electrode grid (B plate) was located over the basal frontal region. A 4 × 4 grid (C plate) was placed overlying the lateral aspect of the right temporal lobe, and a 1 × 6 strip (D strip) was placed over the mesial aspect of the right frontal lobe.

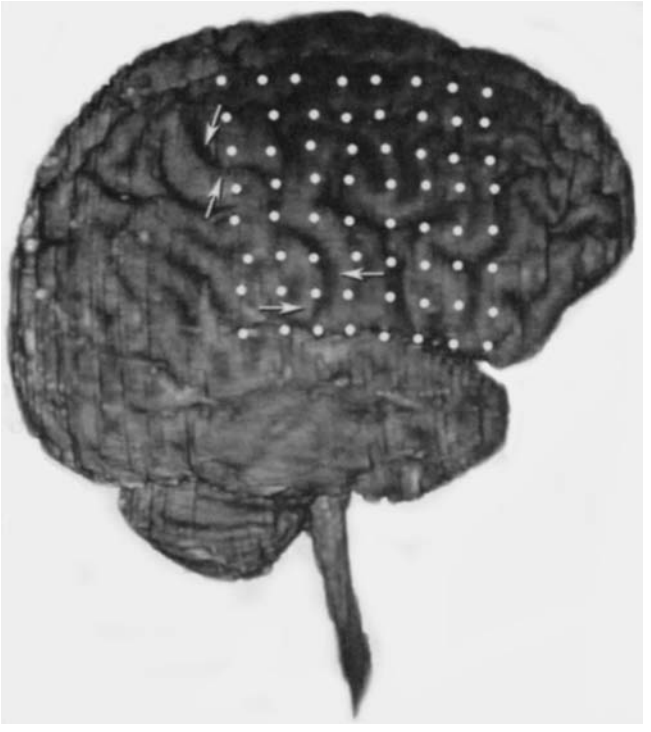


Figure 47.2 Three-dimensional MRI reconstruction showing the location of the A plate over the frontoparietal convexity. *Arrows* indicate central sulcus.

Symptomatogenic zone

The patient's seizures can be classified as aura→left face tonic →left arm clonic→generalized tonic-clonic seizures. The aura the patient describes has little localizing value as it varies from seizure to seizure and does not point to a specific brain region. However, the consistent left face tonic phase suggests early-spread of the discharges to the face region in the primary motor cortex of the right hemisphere, with later involvement of the arm area (manifested as clonic movements of the left arm). The EEG-recorded seizures support this conclusion.

Irritative zone (Figures 47.3A and 47.4A)

Interictal EEG showed prominent spiking mainly from two distinct regions in the A plate: the adjacent electrodes SA44, SA45, and SA52, near the base of the plate, and the electrodes SA3, SA4, and SA10, near the superior edge of the plate. Interictal spikes were seen frequently also in the electrodes SB2, SB6, SB10, and SB11 of the basal frontal B plate.

Ictal onset zone (Figures 47.3B, 47.3C, and 47.4B)

Several clinical seizures were recorded. Clinically the seizures consisted of left face tonic activity, evolving to left body clonic jerking and secondary generalization in five seizures. The patient was unable to speak during the motor phase, although in some cases she could prove that she was aware of her surroundings by mimicry in answer to questions. At times, repetitive mouth movements were seen

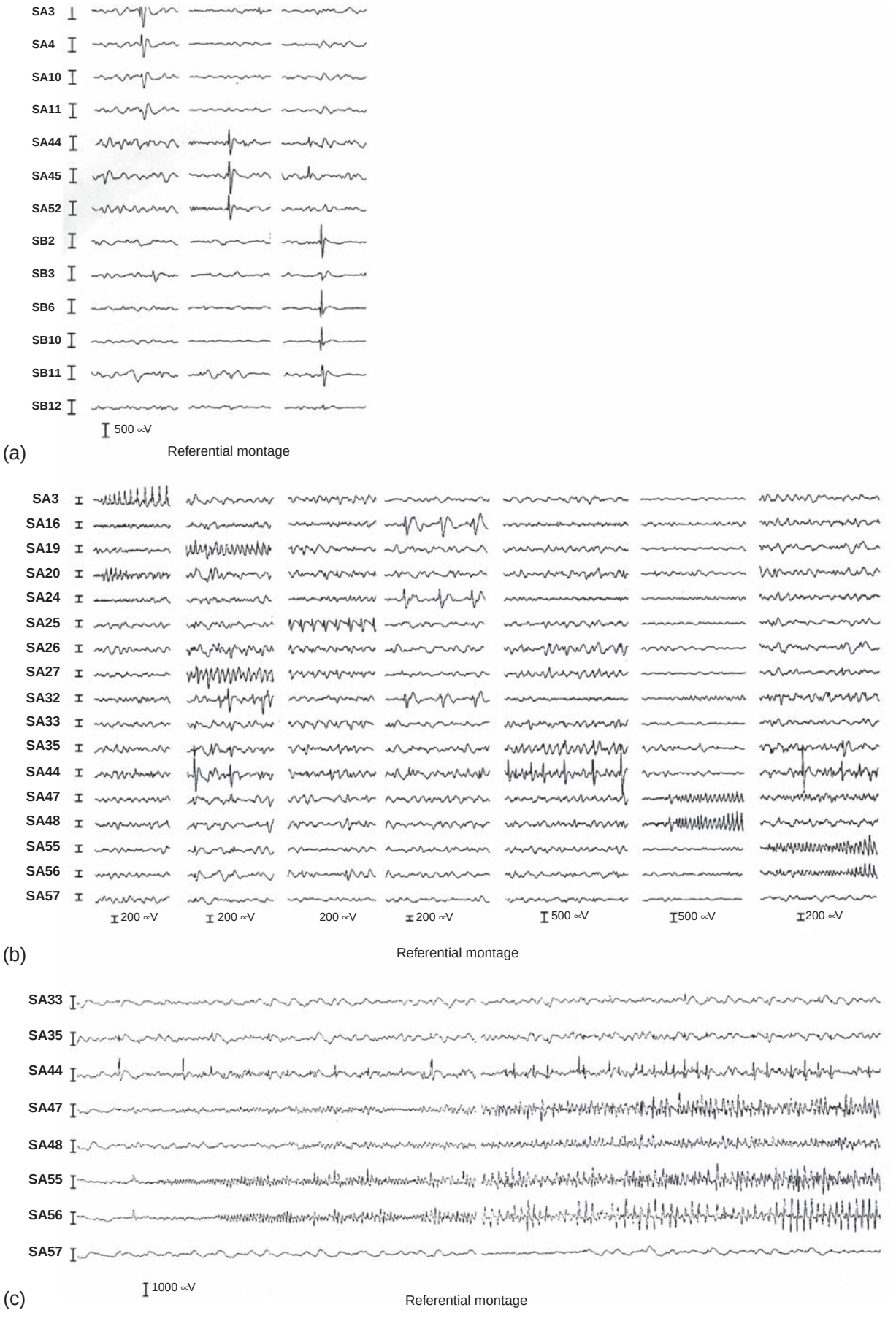


Figure 47.3 a: Diagram showing the different populations of interictal spikes. b: Diagram showing the different electrodes involved in seizure onset. c: Ictal recording showing a seizure arising from electrodes SA55 and SA56. The figure shows two noncontiguous 10-second pages.

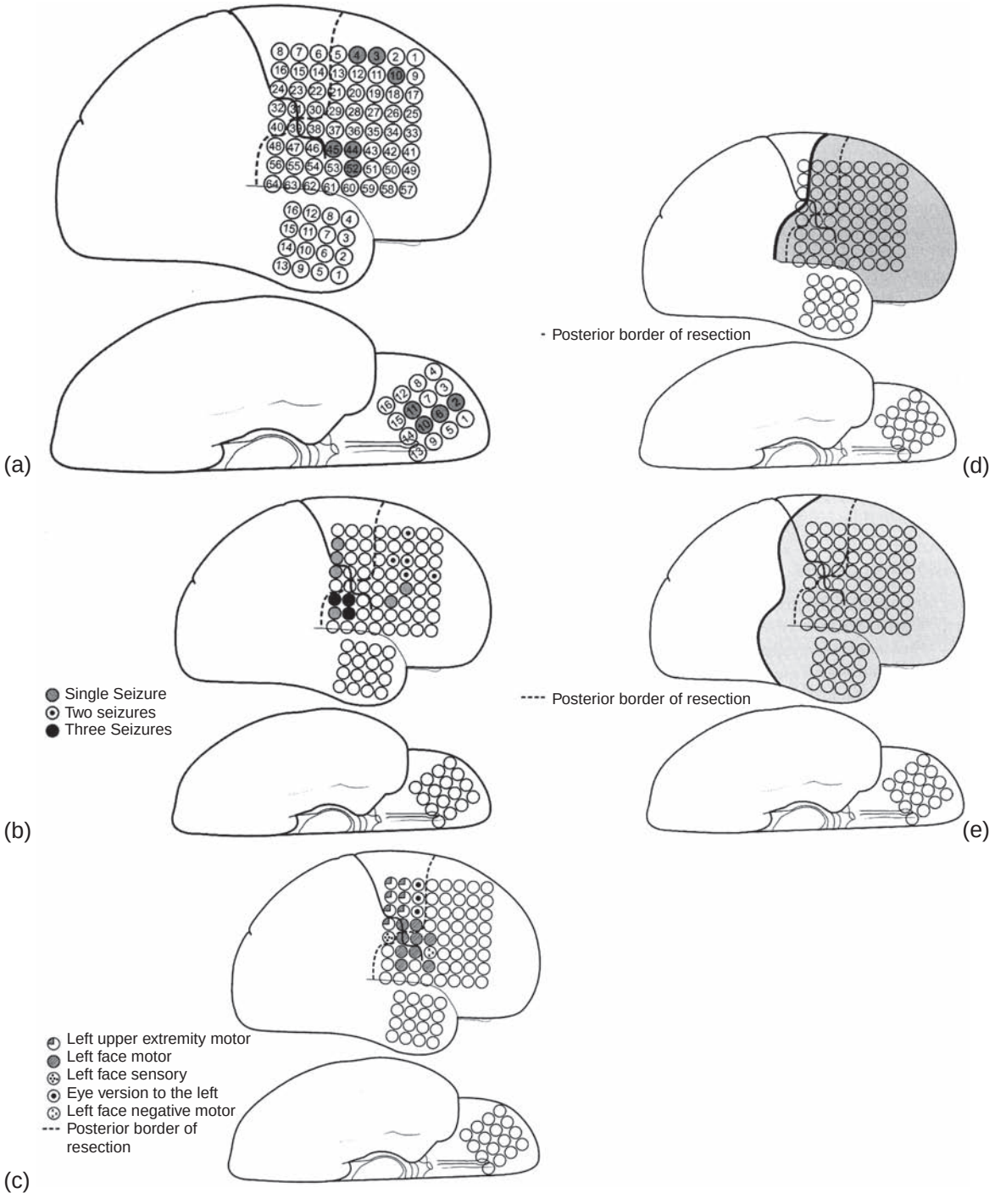


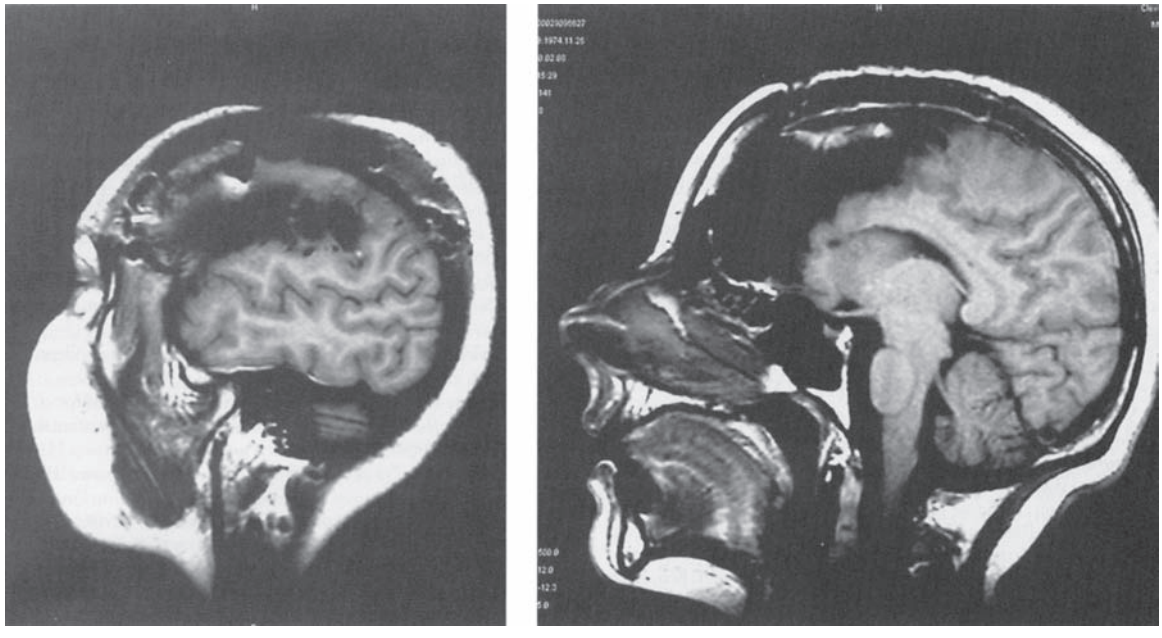
Figure 47.4 a: Irritative zone. The *dashed line* represents the posterior border of resection. b: Ictal onset zone. The *dashed line* represents the posterior border of resection. c: Map of cortical function as evidenced by cortical stimulation. d: Epileptogenic lesion. The area *shaded in gray* represents the region involved by the volume loss. e: Functional deficit zone. The area *shaded in gray* represents the region that showed decreased metabolism on FDG PET scan.

during the seizure. Three seizures came from a group of electrodes adjacent on the A plate (SA47, SA48, and SA55), located inferior to the central sulcus. One seizure arose from the electrodes SA16, SA24, and SA32, on the posterior edge of the plate, and one arose from the adjacent electrodes SA35 and SA44, in the inferior quadrant of the plate. In addition, several subclinical seizures, were recorded, arising at times from the same areas as the clinical seizures but also from the electrodes SA3 and SA20, SA19 and SA27, and finally SA25.

After video-EEG monitoring was completed, cortical stimulation was performed to map sensory and motor function. The results of the stimulation are shown in Figure 47.4C.

Functional deficit zone (Figure 47.4E)

A FDG PET scan showed moderate hypometabolism involving the right frontal lobe, specially pronounced at the junction of the anterior and middle thirds, and mild to moderate hypometabolism involving the right temporal cortex.



(a) (b)

Figure 47.5 Postoperative MRIs showing the extent of the resection (T1-weighted images, coronal cuts).

On the basis of the evaluation, it was decided to proceed with partial resection of the estimated epileptogenic zone in the frontal lobe and parietal operculum, including the primary face motor area but sparing the hand motor area (Figure 47.5). The extent of resection was further delineated by intraoperative cortical stimulation with the patient awake.

Functional outcome

After surgery, the patient had some weakness over the left extremities and difficulty in looking voluntarily to the left side. These deficits progressively resolved over a period of 10 days. A left facial droop was still present when the patient left the hospital 15 days after surgery. No sensory deficit over the left extremities was seen. Sensation over the left side of the face was also normal.

Seizure outcome

The patient remained seizure free for 20 days after the operation, and on day 21 she had a seizure consisting of clonic jerking of the left arm. This seizure most probably arose from the primary motor area of the hand, which was shown to be a part of the ictal onset zone but was not included in the resection to avoid the motor deficit.

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SECTION 5

The symptomatogenic zone

48 The symptomatogenic zone – general principles

C Kellinghaus and HO Lüders

Introduction

The objective of the presurgical evaluation of patients with intractable focal epilepsy is to identify the epileptogenic zone, i.e., the cortical area(s) capable of generating epileptic seizures whose surgical removal or disconnection will result in seizure freedom. Unfortunately, there is no diagnostic method that is able to directly assess the exact location and extent of the epileptogenic zone. Even in patients who are seizure free after epilepsy surgery, we can only be certain that the epileptogenic zone was included in the resected area. However, it is impossible to know whether a smaller resection would have had the same result. Therefore, the location and extent of the epileptogenic zone has to be estimated using all available diagnostic methods that can help in this estimation. The different diagnostic methods are used to define several cortical zones (symptomatogenic zone, irritative zone, seizure onset zone, epileptogenic lesion, functional deficit zone), each of which helps us to estimate the location and extent of the epileptogenic zone.[1]

The symptomatogenic zone is defined as the cortical area generating the initial ictal symptomatology when activated by epileptic seizures. It is delineated by detailed analysis of the ictal signs and symptoms. It is essential to first obtain a thorough history of the seizures from the patient, caregivers, and witnesses to the seizures. These findings can be extended and verified by analysis of ictal video recordings using long-term video-EEG obtained in the setting of a diagnostic or presurgical epilepsy monitoring unit, during routine EEG or other recordings, or even using material recorded at home by family members. In this analysis, the emphasis should be placed on the initial symptoms of the seizures because they are generated by the cortex in close proximity to the epileptogenic zone.

Historical overview

Before the advent of EEG in the late 1920s, trying to locate the symptomatogenic zone and the functional deficit zone by examining the patient and analysing seizure symptoms were the only methods available to determine the epileptogenic zone. With his work in the mid 19th century, Hughlings Jackson pioneered the concept that the symptomatogenic zone is a useful approximation of the epileptogenic zone. Initially he believed that the generators of focal motor seizures were located in the basal ganglia.[2] In 1863, however, he published a case of a patient with syphilis and focal motor seizures stating that in many patients with convulsions of one side of the body, autopsy reveals brain pathology on the opposite side of the brain, 'frequently on the surface of the hemisphere'.[3] In the following years he discovered further clinical evidence supporting his view that the motor cortex plays an important role in motor function as well as epileptic seizures. Experimental studies by Fritsch and Hitzig confirmed Jackson's clinical view showing that electrical stimulation of a dog's frontal cortex could cause movement of contralateral body parts.[4] In 1873, Jackson put forward his definition of epilepsy that is still valid: 'Epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of gray matter'.[5]

The work of Jackson and other pioneers of modern neuroscience like Gowers, Horsley and Ferrier led to the view that certain functions (e.g., motor control, sensation, language) were located in specific cortical brain areas. Using these principles for localisation of disease processes, they were able to correctly localize the epileptogenic zone and remove tumors or other lesions causing epilepsy.[6] One of the first cases of epilepsy surgery was published in 1879 by the Scottish neurosurgeon William MacEwen who successfully resected a frontal meningeoma rendering the patient seizure free and without deficits.[7] In 1884, Hughes Bennet and Rickman Godlee removed a cerebral tumor from the right frontal convexity near the primary motor area that had caused frequent focal and generalized motor seizures. While the operation stopped the seizures, the surgeons also documented well-known side-effects of epilepsy surgery like transient (worsening of the) hemiparesis and wound healing problems.[8]

Conditions necessary to produce ictal activation of cortical areas

Activation of cortical areas, either by ictal discharges or by electrical stimulation, is not an all-or-none phenomenon. This was elucidated by studying the effects of direct electrical stimulation using subdural or intracranial electrodes that closely resembles the effect of ictal activation.[9] There are several factors that determine whether a stimulus will be able to cause a clinical symptom.

Intensity, duration and polarity of the individual stimulation impulse

The response of neurons to an electrical field is related to the electrical potential distribution along each cell process.[10] Thus, the effect of an electrical impulse on neuronal tissue is strongly dependent of the amount of electrical charge (i.e., intensity multiplied with pulse duration) as well as the polarity of the impulse. Usually 'balanced-charge' bipolar square wave pulse forms are used.[11] Pulse duration usually is below 1 ms,[12,13] but longer pulses (up to 2.5 ms) have been used successfully.[14,15] Given a specific electrode geometry, electrode localization and pulse duration, the amount of electrical discharge applied to the cortex usually is modified by the chosen stimulus intensity (measured in voltage or amperage).

Stimulation frequency

It has turned out that the frequency that produces clinical effect with the lowest possible effective stimulus intensity is of approximately 20–80 Hz.[16] Most likely this is related to the duration of a single excitatory postsynaptic potential (15–50 ms), i.e., to achieve clinical signs the stimulus frequency should be high enough to produce temporal summation. Single stimuli, even when applied to eloquent cortex, are usually ineffective unless a very high intensity is used.

Duration of the stimulus train

In general, only trains of stimuli which permit temporal summation, are effective in eliciting clinical symptoms. Usually, train durations of 5–8 seconds are used,[12,16,17] and the symptoms tend to start after a delay of 1–3 seconds. In addition, the symptom or sign severity frequently increases during the stimulus train.[16]

Correlation of ictal cortical activation and the generation of ictal symptoms

Assuming that activation by ictal discharges follows the same basic neurophysiological principles as electrical stimulation, one can explain the not uncommon observation that epileptiform activity over eloquent cortical areas does not produce any symptoms. One of the best known examples is the absence of motor symptoms in patients with generalized spike-wave discharges in typical childhood absence epilepsy. Although the EEG clearly shows repetitive discharges over the primary motor area, no clonic motor activity may be seen. This is most probably because intensity or frequency (or both) of the discharge stimuli are not sufficient to elicit clinical symptoms. Therefore, the fact that ictal activation of a given cortical area does not produce any symptoms does not necessarily mean that this area is noneloquent. It may well be that the stimulus intensity, frequency and/or duration were not sufficient to elicit symptoms. These observations explain why studies trying to deduct the location and extent of the symptomatogenic zone solely by invasive ictal recordings are unreliable.

Spatial relationship of the symptomatogenic zone with the epileptogenic zone

The symptomatogenic zone and the epileptogenic zone frequently do not overlap. As stated above, the clinical effect of electrical stimulation is determined by multiple factors. However, even if we have epileptiform discharges of strength sufficient to activate eloquent cortex, very frequently the epileptiform discharge is not going to elicit symptoms or signs until it has spread outside the epileptogenic zone, i.e., in general, the epileptogenic and symptomatogenic zone does not overlap.[12] This has been demonstrated repeatedly during cortical stimulation when clinical symptoms only occurred when there were 'afterdischarges' (i.e., spontaneously ongoing and/or spreading epileptiform discharges after electrical cortical stimulation).[16] These symptoms, even if they resemble typical auras of the patient, frequently are elicited in proximity but not necessarily in the core of the epileptogenic zone, and they do not have additional value for defining resection boundaries.[18]

In addition, several symptomatogenic zones may be active at the same time, with one dominant symptom overshadowing others (e.g., focal clonic motor activity overshadowing focal sensory auras, loss of consciousness overshadowing auras.)[19] Thus, identification of the symptomatogenic area suggests that the epileptogenic zone is in the general neighbourhood, but it does not allow us to pinpoint the epileptogenic focus to a precise anatomic region.

Presurgical assessment of the symptomatogenic zone

Interview with the patient and family members

The first essential step in the assessment of the symptomatogenic zone is a careful interview of the patient, his family members or other witnesses about the seizure symptoms. The time course of the seizure symptomatology should be analysed placing special emphasis on the beginning. Some auras are generated by activation of a well-defined cortical area with relatively high degree of certainty. In these cases, the epileptogenic zone is usually also located in close proximity to the symptomatogenic zone responsible for the aura. This includes localized paresthesias in relatively restricted dermatomal distribution that are almost always generated by excitation of the primary somatosensory area of the contralateral hemisphere,[20] and visual auras with simple visual hallucinations that are usually the expression of activation of the primary visual cortex.[21] In both these cases, the epileptogenic zone tends to be in close proximity of the primary somatosensory area and the primary visual area, respectively. On the other hand, multisensorial hallucinations can be elicited by activation of several different cortical regions.[22] During the interview, particular care should be taken to be nonsuggestive, to use open questions where possible, or at least to give the patient several alternatives when focussing on a specific sign or symptom. This helps avoiding unnecessary bias and increases specifity and reliability of the data. Ideally, the

interviewer should have experience with a wide variety of different seizures and seizure symptoms.

Ictal video recordings

Although the first attempts to synchronously record EEG and epileptic seizures date back to the late 1930s,[23] ictal video recordings did not become widely available until the advent of modern communication and computing technology in the late 1970s.[24,25] Until then, analysis of ictal symptomatology was restricted to careful history-taking as well as systematic observation of seizures in epilepsy patients admitted to hospitals.

The introduction of closed-circuit video-EEG monitoring in dedicated wards has advanced our understanding of the relationship between the symptomatogenic zone and the epileptogenic zone considerably. Now it became possible to analyse and re-analyse the patient's seizures 'off-line' and without time constraints. In addition, the observer can now be blinded to other information relevant to the case, and different observers can analyze the same seizure independently. Thus, subtle but important signs can be noticed and evaluated regarding their localizing or lateralizing value. Video analysis alone, on the other hand, has some caveats. Ictal and postictal symptoms are not always easily distinguishable by semiology alone.[26] Conversely, the clinical onset of a seizure may become difficult to distinguish from normal nonictal behavior like daydreaming or fluctuation of attention. In addition, nonepileptic seizures may be only discerned from epileptic seizures by the concomitant EEG. As a consequence, video analysis of seizures has to be complemented by EEG recordings to determine the beginning and the end of a seizure as well as for ascertaining of the epileptic nature of the event.

Identification of established localizing and lateralizing signs

In patients in which postoperative seizure freedom indicates that the epileptogenic zone was at least included in the resected cortical area, the analysis of seizure symptoms can establish a correlation between a given symptom or evolution of symptoms and the location or laterality of the epileptogenic zone. In addition, the frequency of a symptom within a specific patient population, the predictive value for seizure freedom, the specifity for the hemisphere, lobe, or intralobar location of the epileptogenic zone, and the interrater reliability can be calculated.

Using these methods, several ictal symptoms and signs have been identified in the last decades that have a close correlation to the lateralisation of the epileptogenic zone[1,27] (see Table 48.1).

In addition, the localizing value of several symptoms has been established. For example, auditory and visual auras followed by immediate loss of consciousness seem to be typical for neocortical temporal epilepsy.[28] Early head version predicts extratemporal epilepsy,[29] and tonic posturing and cycling leg movements seems to be relatively specific for frontal lobe epilepsy.[30] The localizing value of auras arising from primary cortical areas (e.g., localized somatosensory or visual auras) has long been recognized (see above). Even in infants who cannot report auras, some of the main seizure symptoms occurring in this age group have important value in establishing the location of the epileptogenic zone: focal motor seizures and versive seizures indicate seizure onset in the contralateral hemisphere,[31] seizures featuring mainly behavioral arrest (hypomotor seizures) frequently are related to seizure onset in the posterior temporal regions.[32]

Electrical cortical stimulation

In a number of patients, particularly those who have no clear lesion in structural imaging studies, it becomes necessary to further delineate the seizure onset zone by electrocorticography, either intraoperatively or using chronically implanted subdural electrodes. In other patients, presurgical noninvasive studies permit relatively precise definition of the location and extent of the epileptogenic zone, but electrical cortical stimulation becomes necessary to determine its relationship to important adjacent eloquent cortical areas (Table 48.2).

Intraoperative stimulation, the method of choice for more than 100 years, because of its limitation, (anesthesia, time constraints), has been substituted by extraoperative stimulation in chronically implanted patients. Although the chronic implantation of intracranial and subdural electrodes carries the risk of complications like infection, bleeding or infarction, strict antiseptic precautions and restriction of the number of implanted electrodes to the necessary minimum can considerably lower the risk.[33,34]

The advances of the last decades relying mainly on detailed cortical stimulation using subdural grid electrodes in wake patients have resulted in the reliable definition of several different symptomatogenic zones (for details see the following chapters). These zones usually can be reproduced in any given patient. However, the interpretation of the results demands experience and care. Afterdischarges (i.e., epileptic discharges elicited by the stimulus) have to be taken into account. These discharges tend to spread to adjacent cortical areas and, therefore, elicit symptoms due to activation of extensive cortical areas located at a distance from the stimulated cortex. On the other hand, stimulation has to be strong enough to actually elicit the symptom corresponding to the region. Therefore, the best method to achieve reliable and valid results is to stimulate each electrode with stepwise increasing stimulus intensities until either symptoms are elicited, or afterdischarges are produced.[16,17,34] Moreover, individual activation thresholds vary over time[12] and depend on factors like anticonvulsant levels. To avoid false negative or false positive results, only those symptoms should be taken into account that are not associated with afterdischarges, and that are reproduced at different times.

Conclusion

Identifcation of symptomatogenic zones activated by the initial epileptic discharges is the oldest method used for determining the epileptogenic zone as well as the resection borders in epilepsy surgery. Although there is usually a stable and close spatial relationship between the symptomatogenic zone and the epileptogenic zone, frequently the two areas do not overlap. Careful analysis of the seizure symptoms using

Table 48.1 Lateralizing ictal and postictal symptoms with a specifity ≥ 75% (adapted from ref 1)

Symptom	Hemisphere of the epileptogenic zone	Specifity	Frequency	References
Localized somatosensory aura	Contralateral	89%	1–10% (epilepsy patients)	35,36
Hemifield visual aura	Contralateral	100%	29% occipital lobe epilepsy	37
Focal tonic/clonic activity	Contralateral	90%	45% frontal lobe epilepsy	38,39
Forced head version <10 sec before secondary generalization	Contralateral	>90%	35% temporal lobe epilepsy 45% extratemporal lobe epilepsy	29,38,39
'Figure-of-four' sign	Contralateral	90%	15% temporal lobe epilepsy 15% extratemporal lobe epilepsy	29,40
Unilateral dystonic posturing of the hand	Contralateral	>99%	45% temporal lobe epilepsy	41,42
Ictal automatisms with preserved consciousness	Nondominant	>99%	5% temporal lobe epilepsy	43,44
Ictal speech	Nondominant	80%	35% (epilepsy monitoring patients)	45
Ictal dysphasia and aphasia	Dominant	>99%	35% (epilepsy monitoring patients)	45
Ictal vomiting	Nondominant	80%	2% (epilepsy monitoring patients)	46
Ictal spitting	Nondominant	75%	0.5% (epilepsy monitoring patients)	47
Postictal palsy	Contralateral	>99%	0.5–15% (epilepsy monitoring patients, depends on testing)	48,49
Postictal dysphasia and aphasia	Dominant	80%	35% temporal lobe epilepsy	50
Postictal nosewiping	Ipsilateral	90%	55% temporal lobe epilepsy	51
Unilateral last clonic movement in secondary generalized seizure	Ipsilateral	80%	45–65% temporal lobe epilepsy	52,53

Table 48.2 Symptomatogenic zones as described by electrical cortical stimulation

Cortical area	Localization	Symptom
Primary motor area	Precentral gyrus	Tonic and/or clonic movement of a contralateral body part
Frontal eye field	Posterior and lateral part of superior frontal gyrus	Eye version to the contralateral side
Supplemental sensorimotor area (SSMA)	Medial aspect of the superior frontal gyrus, paracentral lobule, cingulated gyrus	Ipsilateral, contralateral or bilateral tonic and/or clonic movements, sensations
Negative motor area(s)	Inferior frontal gyrus, immediately in front of the primary motor area (1), mesial portion of the superior frontal gyrus (2)	Inability to move (ipsilateral and/or contralateral)
Anterior (Broca's) language area	Pars opercularis of the inferior frontal gyrus	Speech arrest, (motor) aphasia
Posterior (Wernicke's) language area	Posterior part of the first and second temporal gyri, supramarginal gyrus, angular gyrus	Comprehension deficits
Inferior temporal language area	Fusiform gyrus, inferior temporal gyrus, parahippocampal gyrus	Comprehension deficits, paraphasias
Visual areas	Occipital lobe (calcarine fissure)	Flashing lights, phosphenes (simple responses), geometric shapes (intermediate responses), images (complex responses)
Primary sensory area	Postcentral gyrus	Sensations (tingling etc.) of a contralateral bodypart
Secondary sensory area	Parietal operculum	Ipsilateral, contralateral or bilateral sensations
Auditory areas	Superior temporal gyrus (Heschl's transverse gyrus, planum temporale, middle and anterior part)	Simple (particularly Heschl's gyrus) or complex hallucinations
Olfactory areas	Insula, amygdala	Smells (frequently unpleasant)
Gustatory areas	Frontoparietal operculum, insula	Tastes

video-EEG reveal important information for the presurgical assessment of an epilepsy patient. This information can be used as an independent diagnostic tool to corroborate or refute hypotheses of the location of the epileptogenic zone generated on the basis of other diagnostic methods like imaging or EEG.

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49 Auras: localizing and lateralizing value

S Rona

Introduction

Epileptic auras are seizures characterized by subjective sensations experienced by the patient, unaccompanied by any objective clinical manifestations. They are usually brief and often evolve into other seizure types. On occasion they may be prolonged, constituting a form of status epilepticus.

Auras can be characterized by positive or, more rarely, negative sensory phenomena. Paresthesias, visual or auditory hallucinations, a sensation of fear or a feeling of movement when none is occurring are positive phenomena. Numbness of a body part, blindness, deafness or a feeling of inability to move are negative phenomena. It is now widely accepted that negative as well as positive ictal phenomena are expression of an active seizure discharge.

John Hughlings Jackson[1] first established a correlation between ictal manifestations and the location of a structural lesion. Before the advent of modern imaging techniques, epilepsy surgeons had to rely on ictal symptomatology to deduce localizing information which could guide the surgical procedure,[2] and it became clear that the aura as the first symptom at the beginning of a seizure was an important localizing element. Initially, surgeons applied information obtained through cortical stimulation in animals to localize brain functions, but soon thereafter this was complemented by cortical maps obtained with intraoperative stimulation in humans. Based on pioneering work by Cushing[3] and Förster,[4] Penfield and his colleagues[5,6,7] provided a comprehensive account of signs and symptoms that could be evoked by electrical stimulation of different brain regions during epilepsy surgery.

The aura as expression of activation of the symptomatogenic zone

Already Penfield and Jasper[5] recognized that the aura was produced by an epileptic discharge in neuronal circuits devoted to the cerebral representation of the sensation the patient is experiencing. However, when attempting to localize seizures based on their semiology, it is important to bear in mind that this, is in most cases, not the region where the seizure originates. By definition, ictal discharges are generated in the epileptogenic zone.[8] Theoretically, this can be any cortical region, but seizures often originate in so-called silent areas of the cortex and only become clinically manifest when they spread into areas that are able to produce symptoms. Accordingly, these are called 'symptomatogenic zones' (for a more in-depth discussion of this concept see Chapter 48).

Since auras are partial seizures without impairment of consciousness and patients have to be awake and not amnesic in order to report them, it might be presumed that the epileptogenic zone and the symptomatogenic zone are not far apart. This is not necessarily true – within fractions of a second, seizure discharges can travel quite far across the brain. However, they tend to follow preferential pathways which have been described extensively in the literature, so knowledge of the usual propagation pathways can help to identify potential regions of origin. Depending on the road they take, ictal discharges can involve, sequentially or simultaneously, several potentially symptomatogenic areas. Therefore, additional localizing information can be derived from the clinical evolution of the aura and eventual associated symptoms. However, it has to be kept in mind that some symptoms may overshadow others, so the fact that the patient experiences only one symptom does not mean that only one symptomatogenic area is activated by the ictal discharge.

Another potential source of inaccuracy is related to the patient him- or herself. Since auras are subjective by definition, the localizing value of the reported symptoms critically relies on the ability and willingness of the patient to describe them, which again depends on the age, intellectual level, mood and mental state of the patient.

Identification of the symptomatogenic zone

Provided the symptomatogenic zone activated during the aura is accepted as useful for the definition of the epileptogenic zone, how can it be identified? Essentially there are two possible ways to accomplish this: either the spontaneously occurring symptom and the corresponding electrical discharge can be recorded with closed-circuit video-EEG, preferably with invasive electrodes, or the symptom can be elicited by electrical stimulation. Both methods have inherent limitations.

Partial seizures are characterized by alteration of function in a relatively limited cerebral area. What makes localization of spontaneous discharges recorde with scalp electrodes more difficult is the fact that surface EEG recordings detect only a portion of the underlying electrical brain activity.[9,10] Due to their limited extension, only 30–70% of simple partial seizures are accompanied by a discernible ictal discharge in surface recordings.[11,12] One possible solution is to implant electrodes directly into the brain in order to be closer to the discharging focus, but the positioning of the electrodes itself creates a selection bias: even with densely spaced depth or grid electrodes, only a limited area can be electrically observed, and

brain sites at a distance which can contribute to the ictal symptoms may not be covered.

Despite the advent of functional imaging, which has replaced invasive studies in many fields, electrical stimulation remains the 'gold standard' for the reproduction of the effect of cortical activation by an epileptiform discharge, and consistent reproduction of an ictal sign or symptom by stimulation of a given cortical area can provide reliable evidence of the location of a symptomatogenic zone.[13] However, the validity of the information obtained by electrical stimulation is influenced by a number of variables. In order to have an unequivocal reponse, it is important that the stimulus does not produce an afterdischarge activating additional areas, which may also be located at a distance and thereby escape observation. On the other hand, it has to be sufficiently intense to effectively produce a response. The effective stimulus intensity depends on the degree of cortical excitability at the moment of stimulation and may vary over time; it may also be different at different sites that can produce the same symptom.

Even when properly performed, cortical stimulation may activate not only the cortex underlying the stimulated electrodes, but eventually a whole neuronal network contributing to the elicited symptom. The more complex the symptom (or aura), usually the more complicated the network that needs to be activated for its expression. Fish and colleagues, reviewing the Montreal experience with electrical stimulation,[14] observed that a particular clinical phenomenon could often be elicited in the same individual from more than one area. These areas could be clustering in adjacent sites or involve widespread noncontiguous sites affecting one or more lobes, sometimes in both hemispheres, with a distribution specific for any one patient. Gloor[15] proposed that such responses, especially in the case of complex experiential phenomena, reflect the activation of a matrix of excitation in a widely distributed population of neurons, resulting from synaptic plastic changes in networks whose precise configuration is specific for a given experience. This concept has been elaborated in detail in more recent network models of cortical representation.[16,17]

Schulz and colleagues, in a recent study of 16 patients with stimulation-induced auras recorded with subdural grid electrodes,[18] also noticed that the area from which auras could be elicited by stimulation was larger than expected for a normal cortical representation and suggested that epileptogenicity may lead to abnormal facilitation of cortical pathways, resulting in the expansion of symptomatogenic cortical areas. The authors postulate that stimulation-induced auras are likely to result from facilitated pathways between the epileptogenic zone around the lesion, the stimulated cortex and the symptomatogenic zone.

Localizing value of spontaneous and stimulation-induced auras

When a typical aura happens to be elicited by electrical stimulation, how does its localization compare to the onset zone of spontaneous seizures? Bernier and colleagues[19] found a greater than 90% concordance between spontaneous and induced auras or seizures in patients with single unilateral foci but less with multiple foci. In their series of 126 patients, stimulation data reliably predicted the resection area in unilateral and bilateral temporal foci but less in other locations. Wieser and coworkers[20] reported a 77% concordance rate in patients with temporal lobe seizures. Schulz and colleagues[18] assessed the value of stimulation-induced auras (SIA) for defining the extent of the epileptogenic zone during epilepsy surgery. The SIA zone overlapped with the lesion in 75%, with the EEG seizure onset zone in 75% and with the irritative zone (or area of interictal spiking) in 50% of the patients. However, analysis of surgical outcome showed a significant correlation only with total removal of the epileptogenic lesion. Therefore, these numbers may be different in patients without a visible lesion.

With due consideration of the above-mentioned limitations, aura semiology can still be considered to provide essential clues for the localization and, to a certain extent, lateralization of epileptic seizures, as well as the prediction of surgical success. Palmini and Gloor[21] found that the localizing value of auras in indicating the most likely lobar origin of seizures was as good as EEG and modern imaging procedures, whereas Boesebeck and colleagues,[22] examining patients with epilepsy surgery in the posterior cortex, reported that patients with lateralizing auras had a significantly better outcome compared to those without lateralizing features.

In the following section, the localizing and lateralizing value of different aura types will be examined more closely. Auras are classified in accordance with the Semiological Seizure Classification),[23] developed at the Cleveland Clinic and used in major epilepsy centers around the world.

Aura types

Somatosensory auras

Somatosensory auras consist of abnormal sensations, involving one or more body parts. Just like focal motor seizures, they may migrate from one region to the next, following a somatotopic pattern ('Jacksonian march').[1] The most common epileptic somatosensory perceptions are paresthesias ('tingling'), pain and thermal sensations are less frequent.[24,25] Sensations referred to the viscera, for example the abdominal aura, and sensations involving the entire body are not classified as somatosensory auras.

The following cortical areas are involved in the generation of somatosensory phenomena:

Primary somatosensory area (SI)

The primary somatosensory area is located in the postcentral gyrus (Brodmann areas 1, 2, and especially 3b)[26] and contains a topographic representation of the different body parts, supramedially for the foot and leg and more laterally on the convexity for the arm, hand, and face.[4,5,27] However, recent studies[27,28] have indicated that the functional anatomy in this region can vary in individual patients, and that sensory function can also be represented anterior to the central sulcus (Brodmann area 4). This is especially true for patients with lesions in this area. The majority of the sensations elicited from SI affect the face, mouth, and hands, less frequently the feet, and they are usually limited to a relatively restricted distribution. Penfield and Jasper[5] were also able to elicit sensations in the head region between the arm and leg area. During stimulation of the

postcentral gyrus, Förster[4] occasionally observed sensations at ipsilateral homologous body parts. These were elicited most often in the areas of the face and mouth, bladder, colon and genitals, but never occurred when arm or leg areas were stimulated. Mazzola *et al*[29] also found that evoked responses affecting limbs were exclusively contralateral to stimulation in SI.

Second sensory area (SII) and insula

The second sensory area is located on the superior bank of the sylvian fissure, and has a representation of both sides of the body.[5] Lüders and co-workers[30] localized the second sensory area in the inferior frontal gyrus immediately anterior to the primary face and mouth motor area by both electrical stimulation and evoked cortical potentials in one patient. According to Penfield and Jasper,[5] the character of the sensory aura originating in the second sensory area does not differ from the primary sensory region, although they noticed that some patients described a cold sensation. Somatosensory and pain responses to direct intracerebral stimulations of somatosensory areas were obtained by Mazzola *et al.*[29] in 14 patients referred for epilepsy surgery. Stimulations were delivered using transopercular electrodes exploring the suprasylvian parietal cortex (SI area), the parietal opercular cortex (SII area), and the insular cortex. In all three areas, all types of somatosensory responses, including paresthesias, temperature and pain sensations could be elicited. The authors found distinct somatosensory maps in the suprasylvian, opercular and insular regions and separate pain representations in SII and insular cortex, with a spatial resolution of the somatotopic map in SII intermediate between those found in SI and insula. The sensations obtained through insular stimulation by Penfield and colleagues[5,6] most often involved the mouth or the upper extremities. Responses were primarily contralateral but sometimes ipsilateral or bilateral. In the study of Mazzola and colleagues,[29] the highest percentage of ipsilateral or bilateral responses was observed after SII stimulation. When the evoked sensations involved the midline part of the body (face or trunk), they were mostly bilateral regardless of the stimulated region. Response lateralization was similar for left and right stimulation. Various types of nonsomatosensory responses (auditory, vegetative, vestibular, olfacto-gustatory, etc.) could only be evoked by insular stimulation,[6,29] confirming that SII is mostly devoted to the processing of somatosensory inputs while the insular cortex is a polymodal area.

Supplementary sensorimotor area (SSMA)

Sensations produced by activation of the SSMA tend to be poorly localized and usually affect more proximal body parts. They are often bilateral and sometimes described by patients as a whole body aura.[5] Lim *et al.*,[31] with cortical stimulation through subdural electrodes, were able to elicit subjective sensory symptoms in the contralateral upper or lower extremities, bilateral lower extremities, or the head. Stimulation sites were the mesial aspect of the superior frontal gyrus, the cingulate gyrus and the precuneus.

Localizing value of somatosensory auras

In patients with somatotopically well-localized somatosensory auras, the epileptogenic zone frequently is in the perirolandic region, close to the location of the symptomatogenic zone. Since somatosensory auras rarely appear in isolation, the combination with other sensory or motor features and the evolution of subsequent motor patterns can be of help in localization. In a prospective analysis of clinical seizure patterns and their predictive localizing value in frontal and temporal lobe epilepsies, Manford and co-workers[32] performed a cluster analysis of 14 distinct clinical symptom groups, showing that sensorimotor symptoms correlated consistently with pathologic findings in the perirolandic area. Salanova *et al.*,[33] reviewing patients with parietal lobe epilepsy who underwent surgery, found that somatosensory auras were contralateral in 51 of 52 patients and bilateral in one. This confirms a previous study by Ajmone-Marsan and Goldhammer,[24] where contralateral somatosensory auras were found to be highly localizing in 96% of patients with central parietal lesional epilepsy. According to these authors, the presence of a Jacksonian march did not add localizing value.

Blume and colleagues[34] described five patients with seizures involving secondary sensory areas. Four of their patients experienced ictal numbness or tingling bilaterally and/or axially, the fifth patient experienced bilateral ictal pain. Associated ictal symptoms implicating adjacent regions appeared in all patients. The close proximity of second sensory area, insula and temporal lobe explains that sensations produced by activation of these areas are often associated and then progress to motor phenomena of the face or mouth produced by spread into the lower rolandic cortex. According to Isnard and colleagues,[35] the association of a sensation of laryngeal constriction with paresthesias affecting large cutaneous territories, eventually followed by dysarthric speech and focal motor symptoms, is highly suggestive of an insular seizure origin. Of note, in 10% of patients studied by Mazzola *et al.*,[29] SII stimulation directly produced an unpleasant pharyngo-laryngeal strangling sensation.

Somatosensory auras can also occur in temporal lobe epilepsy. In their series of 72 patients with somatosensory auras, Tuxhorn and colleagues[36] noted that four patients whose aura was ipsilateral to the lesion had temporal lobe epilepsy associated with hippocampal sclerosis. Erickson *et al.*[37] also reported nine patients with temporal lobe epilepsy and somatosensory auras. The most common manifestation was tingling, but sensory loss and pain also occurred. In their series, seizure origin was in the contralateral temporal lobe in four of five patients with unilateral somatosensory symptoms, including all patients with unilateral auras affecting a limb. In all except one patient, the symptoms could be explained by spread to the primary or second sensory area. However, somatosensory symptoms can also be produced by stimulation of different areas in the temporal lobe. Fish and co-workers[14] were able to elicit ipsilateral, contralateral and bilateral vague somatosensory feelings affecting one or more limbs from stimulation of amygdala, hippocampus or temporal isocortex. Interestingly, already Penfield and Jasper[5] pointed out that sensory phenomena could be elicited in regions of cortex that did not represent somatic sensory cortex. This may be due to abnormal facilitation of networks involving sensory symptomatogenic areas as suggested by a more recent study.[18]

Subtypes of somatosensory auras

Painful auras

In the series of Maugiere *et al.*,[25] pain was the second most common ictal sensation, occurring in 24% of patients with

somatosensory seizures. The nature of the pain was often described as unnatural, stabbing or cramp-like and overall quite severe. Several studies have shown that neurons in the primary somatosensory cortex can respond to painful stimuli.[29,36,38] Mazzola and colleagues,[29] stimulating somatosensory areas through depth electrodes, have demonstrated that painful sensations can also be elicited from SII and the insula. Out of 858 epileptic patients reviewed by Young and Blume,[39] ten had seizures characterized by unilateral pain in the face, arm, leg or trunk. Unilateral pain consistently implicated ictal involvement of the contralateral rolandic region. Siegel *et al.*[40] reported eight patients with painful auras involving head, face, limbs or abdomen (often in sequential order in the same patient), all originating from the parietal lobe. When the painful symptoms were lateralized, they were contralateral to the side of seizure origin. In the series of Nair and colleagues,[38] painful auras were contralateral to the epileptogenic zone in patients with perirolandic epilepsy. Lateralization was inconsistent in patients with temporal lobe epilepsy.

Thermal auras

Mauguière *et al.*[25] found a sensation of warmth or coldness in 11% of patients with somatosensory auras, and the thermal perception was always associated with either elemental paresthesias or pain. It was mostly described as unpleasant, often spreading from the initial site to involve a whole arm or leg or the ipsilateral face. Rarely, bilateral spread could occur. Electrical stimulation studies have demonstrated that most thermal sensations are obtained from the perisylvian region.[5,29] They do not provide reliable lateralizing information.

Somatosensory illusions

Somatosensory illusions, such as a sensation of swelling or shrinking of a body part, or a kinesthetic illusion (sensation of movement) have been found to occur in about 10% of patients with somatosensory epilepsy.[25,33] Similar to other disturbances of body image, somatosensory illusions can be obtained by stimulation of the postcentral gyrus, the inferior parietal lobule or the temporo-parieto-occipital junction, more often of the nondominant hemisphere.[41,42] Penfield and Jasper[5] were able to produce a sensation of movement of a body part by electrical stimulation anterior to the central fissure. Sensations of ocular movement without any objective evidence of movement have been observed in seizures of occipital lobe origin.[43]

Penfield and Jasper also described the feeling of inability to move a body part and attributed it to activation of precentral negative motor areas. Likewise, the feeling of inability to move has been related to discharges in the parietal lobe and around the sylvian fissure, involving the second sensory area.[41] These seizures have been reported to occur ipsi- and contralaterally to the discharging focus as well as bilaterally,[44] and therefore do not have lateralizing value.

Visual auras

Visual auras can manifest as simple hallucinations of static, flashing or moving lights in different shapes and colors, complex hallucinations of persons, scenes or objects, and illusions in the form of distortion of existing objects. They can involve the entire visual field or only a part, typically half. Negative phenomena (transient loss of vision, scotomata or visual agnosia) are also possible. Complex visual manifestations that are not the predominant symptom or accompanied by other alterations of perception are better classified as 'psychic'.

With electrical stimulation, most visual responses can be elicited from the visual areas in the occipital lobe and adjacent border zones with the parietal and temporal lobes. Simple visual hallucinations (flashes or static lights) are often produced by activation of the primary visual area (Brodmann area 17), which is located on the mesial surface of the occipital lobe and has a topographic representation of the visual fields. The surrounding visual association areas (Brodmann areas 18 and 19) are involved in the perception of color, movement and other more complex aspects of vision, including the integration with other sensory modalities.[5,45] Richer and colleagues,[46] stimulating the extrastriate mesial parieto-occipital cortex through intracerebral depth electrodes in 30 patients, found static visual hallucinations (white or colored flashes) at the cuneus near the calcarine fissure, and blurring of vision at the posterior cingulate and inferior precuneus. Visual motion perception was evoked in four patients, arising from the mesial parieto-occipital fissure in three and posterior cingulate in one patient. Laff and colleagues[47] report a patient in whom subdural EEG recordings of illusory motion perception revealed seizure onset in the right temporo-parieto-occipital junction.

However, this subdivision is not exclusive and visual responses can be obtained from many sites along the visual pathways.[48] In a few instances, visual hallucinations have even been evoked by stimulation of the frontal lobe. Blanke *et al.*[49] report two patients with complex visual hallucinations produced by stimulation of the left prefrontal cortex with different spatial organization: while visual hallucinations produced by stimulation of the inferior frontal gyrus were perceived in the whole visual field, complex visual responses evoked by stimulation of the middle frontal gyrus appeared in the contralateral hemifield. Beauvais and colleagues,[50] in a study with stereo-EEG recordings, were able to record spontaneous visual hallucinations originating from the superior frontal sulcus.

Blume and co-workers[51] assessed the localizing value of different semiological elements, including visual hallucinations, in 41 patients with occipital lobe epilepsy studied with invasive electrodes. Upon statistical analysis, no aspect of semiology distinguished lateral from mesial occipital seizures. Bien and colleagues[52] report 20 patients experiencing visual auras from a series of surgically treated patients with intractable focal seizures. Elementary visual hallucinations, illusions and visual loss were reported by patients with occipital lobe epilepsy, as well as by patients with occipitotemporal and anteromesial temporal seizure onset. Complex hallucinations and concentric restriction of the visual field (tunnel vision) occurred only in temporal or occipitotemporal seizures.

Simple visual hallucinations, when they are lateralized, always point to an origin in the contralateral hemisphere. To a certain extent, an origin above or below the calcarine fissure can be predicted in the case of hallucinations localized in the lower or upper quadrant of the contralateral visual field. Complex visual auras arising from the temporo-occipital junction or the basal temporal cortex have been reported to lateralize to the right hemisphere,[22,53] but not all authors have made this observation.

Subtypes of visual auras

Amaurosis

Ictal amaurosis has been observed in conjunction with unilateral or bilateral occipital lobe[41] or occipitotemporal[52] discharges. In post-traumatic epilepsy, it has been shown to occur more often with injury to visual association areas than to the calcarine cortex itself.[54] Lateralized visual loss is indicative of an ictal event in the contralateral hemisphere.

Visual illusions

Visual illusions are defined as misperceptions of real visual stimuli, such as changes of dimensions, perceptual intensity, motion, or speed. Visual distortions like macropsia, micropsia, and metamorphopsia most often occur with ictal discharges close to the geniculostriate radiation, such as the basal temporal cortex, or visual association areas.[52,54] There is some evidence that each hemisphere is involved in size processing for contralateral stimuli.[55] Another rare type of visual illusion is called palinopsia, defined as the persistence or recurrence of images in the visual field when the stimulus is no longer present. It has also been reported as an ictal manifestation, associated with an occipital seizure discharge.[56] When the phenomenon is lateralized, the eventual brain lesion is always contralateral to the perseveration and usually located in the occipital, parieto-occipital or temporo-occipital region of the right hemisphere.[56,57]

Auditory auras

Auditory auras can manifest as elementary hallucinations of simple sounds ('ringing', 'buzzing'), complex hallucinations like voices or melodies, or auditory illusions in the form of distortion of environmental sounds. Ictal deafness may also occur.[13] Complex auditory manifestations accompanied by other alterations of perception are better classified as 'psychic'.

Auditory phenomena can be produced by stimulation of the primary (Brodmann area 41) and association auditory cortices (Brodmann areas 42 and 22) within the temporal lobe. In the experience of Penfield and colleagues,[7,58] elementary auditory hallucinations could be evoked mainly by electrical stimulation of Heschl's transverse gyri in the first temporal convolution bordering the posterior third of the sylvian fissure. When stimulating the lateral and superior surface of the superior temporal gyrus, complex hallucinations were elicited. Stimulation of the superior temporal gyrus outside Heschl's gyri and the adjacent temporo-occipital neocortex (Brodmann areas 42 and 22) produced auditory illusions. According to evoked potential studies,[59] each cerebral hemisphere receives input from both ears, although stimulation from the contralateral ear appears to be better represented within the auditory cortex. This has also been confirmed by electrical stimulation. De Graaf and colleagues[60] studied 65 patients with intracranial depth electrodes placed at different sites of the superior temporal gyrus. Patients reported auditory hallucinations as well as illusions in response to electrical stimulation. Hallucinations could be contralaterally or binaurally perceived, but could also be very clearly located in extrapersonal space. This latter perception mostly occurred with intense noises and was often accompanied by a feeling of fear or unpleasantness. In the planum temporale, auditory illusions and hallucinations were observed with equal frequency. Stimulation of Brodmann's area 22 also provoked hallucinations as well as illusions. Hallucinations were mainly perceived binaurally, whereas illusions were more often contralateral. Therefore, it can be assumed that auditory auras, when they are lateralized, are indicative of a contralateral seizure origin.

In a series of surgical patients with auditory auras,[61] the epileptogenic zone was located in the temporal lobe (15 patients), frontal lobe (two patients) or the fronto-temporal region (one patient). Of the patients with temporal lobe seizures, five had mesial temporal and ten neocortical temporal lobe epilepsy as defined by EEG. In addition to auditory symptoms, half of the patients described other auras, including psychic, somatosensory, visual, abdominal, and gustatory phenomena.

Vertiginous auras

A variety of symptoms reflecting disturbance of vestibular function (sensation of rotation, sensation of movement in all planes) may occur during epileptic seizures. Typically, they are not accompanied by nystagmus. In a survey of 120 patients with epileptic vertiginous sensations, Smith[62] observed a strong association with visual and auditory symptoms, supporting the idea of a symptomatogenic zone close to visual and auditory association areas. In a functional MRI study with galvanic stimulation, Lobel and co-workers[63] found activation in the region of the temporo-parietal junction, the central sulcus and the intraparietal sulcus, in addition to frontal areas, presumably expression of a network subserving vestibular sensations. Kahane and colleagues[64] studied cortical areas with vestibular input by electrical stimulation through implanted depth electrodes in 28 patients from a larger surgical series. Most vestibular sites were located in the temporal or parietal lobe, but some also in the frontal, occipital, and insular region. The authors identified a lateral cortical temporoparietal area from which vestibular symptoms, and above all rotatory sensations, were particularly easily elicited. This area extended above and below the sylvian fissure, mainly inside Brodmann areas 40, 21, and 22.

Vestibular cortical areas have been said to exhibit a right-hemispheric dominance[65]; however, in the study of Kahane *et al.*,[64] almost 20% of vertiginous responses occurred after stimulation of left hemispheric sites. Kluge and colleagues[66] reported one patient with episodes of epileptic rotational vertigo accompanied by a left fronto-central seizure discharge, whose seizures were abolished by lesionectomy of a small tumor in the left middle frontal gyrus, providing additional evidence of the involvement of the (left) frontal lobe in the processing of vestibular sensations.

Olfactory auras

Olfactory epileptic auras are rare, constituting about 1% of all auras, and are typically described as unpleasant.[67] They are often associated with other sensory phenomena, such as olfactory, psychic, complex visual, abdominal or auditory auras, and patients sometimes find it difficult to distinguish between olfactory and gustatory auras. Tumors in the mesial temporal region are the most frequent cause of olfactory auras,[67] but they have been reported to occur also with hippocampal

sclerosis.[68] Manford and co-workers[32] found two patients with frontal lesions (one medial and one lateral prefrontal/premotor) with seizures characterized by a mixture of fear and olfactory and gustatory auras.

Olfactory sensations can be obtained through electrical stimulation, but only isolated cases have been reported in the literature. The most consistent location where they could be elicited is the amygdala.[5,69] Penfield and Jasper[5] were able to produce an olfactory sensation also after direct stimulation of the olfactory bulb in one patient, Jasper and Rasmussen[69] through stimulation of an insular site. In their review of patients with frontal lobe epilepsy studied stereo-electroencephalographically, Bancaud and Talairach[70] postulated an involvement of the posterior part of the orbitofrontal region in the production of olfactory illusions and hallucinations. However, is not clear whether the orbitofrontal region can be regarded as the symptomatogenic zone or whether seizure activity has to spread to mesial temporal areas or the insula before an olfactory or gustatory sensation appears. Munari and colleagues,[71] studying 105 patients with depth electrodes in the orbitofrontal region, found that discharges beginning in the orbital cortex became clearly symptomatic only when they spread to extraorbital regions.

Greenberg[72] suspects that an interaction of several areas is necessary to generate false perceptions of smell, but the precise mechanism by which this is achieved still remains unknown. The high frequency of gustatory and psychic auras and low frequency of abdominal auras in the series of Acharya and colleagues[67] suggests different pathways for the generation of olfactory, gustatory and psychic auras, probably more related to the amygdala, and abdominal auras, which appear to be more related to the hippocampus. Olfactory auras have no lateralizing value.

Gustatory auras

Although olfactory and gustatory auras are often associated, anatomic and physiologic data indicate a distinct cerebral representation of taste. Electrical stimulation studies have produced gustatory hallucinations mainly in two areas: the parietal operculum and the anterior mesiobasal part of the temporal lobe.[5,72] In a group of 20 patients with gustatory auras investigated with depth electrodes, Hausser-Hauw and Bancaud[73] were able to elicit gustatory hallucinations from either the parietal or rolandic operculum, in one patient each from the medial aspect of the right superior temporal gyrus and the anterior part of the right middle temporal gyrus. In addition, they electrically induced seizures with gustatory hallucinations by stimulation of the hippocampus and amygdala. Spontaneous seizures with gustatory hallucinations were arising from the temporal, parietal or parietotemporal region. The authors conclude that representation of taste is located in the frontoparietal operculum since gustatory sensations alone could be elicited only when this area was stimulated. Gustatory auras are usually not lateralized, but in the single case of Hausser-Hauw and Bancaud with a lateralized ictal taste sensation,[73] the discharge involved the contralateral hemisphere.

Autonomic auras

The term 'autonomic aura' refers to sensations suggesting an ictal activation of the autonomic nervous system (e.g., palpitations, difficulty breathing, urinary urge, feeling hot or cold) without objective evidence of altered nervous system function. The abdominal aura, which likely represents a subtype of autonomic aura, is classified separately because it is one of the most frequent types of aura and often associated with temporal lobe epilepsy.

Autonomic symptoms can be elicited by electrical stimulation of a number of cortical areas, namely the insula,[5,6,29,70] the anterior portion of the cingulate gyrus,[74] and the SSMA.[5] Structures within the mesial temporal lobe, in particular the amygdala, are also thought to be involved in autonomic function.[14] Van Buren and Ajmone-Marsan[75] have observed bradycardia, decreased skin resistance, increased esophageal peristalsis and apnea following amygdalar stimulation; thermoregulatory phenomena (feeling of warmth or coldness, shivering) have been elicited from the amygdala and the posterior hippocampus, as well as the mesial frontal region.[14,76] Already Penfield and Jasper[5] found that similar autonomic phenomena could be elicited from more than one area. One possible explanation is that autonomic responses originating from different cortical regions may be mediated through a common subcortical relay station such as the hypothalamus. Stimulation of the diencephalon has been shown to cause a variety of autonomic phenomena.[77]

Autonomic auras are frequently observed in seizures arising from the orbitofrontal region, most often due to seizure spread to the temporal lobe.[71] A sensation of laryngeal constriction has been reported to be typical for seizures arising from the insula,[35] especially if it is followed by diffuse and unpleasant paresthesias. Ictal SPECT obtained in two patients with ictal urinary urge[78] also showed a hyperperfusion of the insular cortex. Authors who studied this phenomenon agree that ictal urinary urge appears to be a lateralizing sign for non-dominant temporal lobe epilepsy.[78,79] Other types of autonomic auras do not provide lateralizing information.

Abdominal auras

Abdominal (or epigastric) auras are characterized by a sensation of nausea, pain or some kind of undescribable discomfort in the abdominal or periumbilical region. Most patients with ictal vomiting also experience a similar sensation. According to Van Buren,[80] this sensation is static in about half of the patients, in the other half it tends to rise from the epigastric region to the chest, throat or, more rarely, head or face. Discending abdominal auras have also been described.

Electrical stimulation studies suggest that the primary symptomatogenic zone for abdominal auras is located in the insula, even though other structures like the lower rolandic, the mesial temporal and the supplementary motor areas have been implicated.[5] While Penfield and Faulk[6] found gastrointestinal motility changes only with insular stimulation, Bartolomei and colleagues[81] induced viscero-sensitive phenomena including epigastric or throat sensations after either rhinal, amygdalar or hippocampal stimulation. Fish and coworkers[14] were also able to elicit an epigastric aura through mesial frontal stimulation. Stimulation-induced rising thoracic sensations were found to have the same anatomical distribution as static abdominal sensations.[5,6]

Abdominal auras are often thought to be characteristic for patients suffering from mesial temporal sclerosis, but several authors have reported abdominal auras as a manifestation of

seizures originating from other brain regions. In Van Buren's series,[80] only 69 of 100 patients with abdominal auras had temporal lobe epilepsy. Henkel *et al.*,[82] in a survey of 491 surgical patients, found that abdominal auras were more frequent in temporal than in extratemporal epilepsy, and more frequent in mesial than in neocortical temporal lobe epilepsy. According to these authors, an abdominal aura is associated with temporal lobe epilepsy with a probability of 74%, and the evolution of an abdominal aura into an automotor seizure increases the probability of temporal lobe origin to 98%. Most patients with extratemporal epilepsies had seizures arising from the frontal lobe. Three patients with parieto-occipital lobe epilepsy had abdominal auras associated with visual symptoms, providing an additional clue for localization.

Painful abdominal auras have been observed in patients with temporal and frontal lobe epilepsies. In three patients described by Young and Blume,[39] abdominal ictal pain reflected temporal lobe epileptic activity. Nair *et al.*[38] also found that the number of painful abdominal auras was highest in temporal lobe epilepsy. However, the relative frequency of painful abdominal auras was higher in patients with frontal lobe than in those with temporal lobe seizures.

There is no consensus with regard to lateralization of the abdominal aura. In Henkel's study,[82] no prevalence of one side existed. However, cluster analysis in another study of 31 surgically treated patients with temporal lobe epilepsy,[83] suggested that an abdominal aura combined with ictal vomiting lateralizes to the right hemisphere.

Psychic auras

Psychic auras include a variety of symptoms which can be generated by activation (and interaction) of different symptomatogenic areas, mostly located in the temporal lobe. In the past, psychic auras have also been labelled, 'experiential', since they often consist of multisensorial hallucinations or illusions reproducing an experience. For practical purposes they can be subdivided into three broad categories, although symptoms often overlap: emotional or affective manifestations (fear, anxiety or elation), distortions of familiarity such as the 'déjà vu' (i.e., the sensation of having previously lived through the same experience) or the 'jamais vu' phenomenon, and multisensorial hallucinations including the revocation of complex memories.

Penfield[5] found that most experiential reponses were elicited from the lateral temporal isocortex, or by mesial limbic stimulation in the region of the uncus. In later stereotactic investigations by the Montreal group,[15] virtually all psychic reponses were elicited by stimulations of the limbic structures of the temporal lobe. Halgren and co-workers,[76] in line with observations made by other authors, pointed out that mental phenomena evoked by mesial temporal lobe stimulation were variable and highly individual, related to the personality of the patient stimulated.

Forced thoughts, on the other hand, have been attributed to the frontal lobe. Mendez *et al.*[84] report three patients with left frontal lesions with auras consisting of forced thinking associated with speech arrest. The authors hypothesize that forced thinking is a manifestation of expressive language, distinct from experiential phenomena arising from the temporolimbic region.

Most psychic auras do not provide reliable lateralizing information. In Fish's series of patients with frontal and temporal lobe epilepsies studied with intracranial stimulation,[14] there was no consistent lateralization of psychic phenomena, with the exception of the déjà-vu illusion (see below).

Subtypes of psychic auras

Fear

The sensation of fear is said to be characteristic of activation of the amygdala. In Fish's series,[14] fear was indeed elicited most often from the amygdala, but also from the hippocampus, the temporal isocortex and, in two cases, by mesial frontal stimulation. Affective phenomena other than fear were also elicited mostly from the amygdala, in one case each from the hippocampus and the frontal lobe.

Pleasant auras

The localizing value of pleasant ictal sensations such as harmony, satisfaction, euphoria, or orgasm-like sensations, has been investigated by Stefan and colleagues.[85] In some patients, the happy feeling was associated with other sensory phenomena like an unpleasant smell, an epigastric or déjà-vu sensation or visual hallucinations; in one patient, the sensation could be triggered by eating spicy food. In eight of eleven patients, ictal happiness was associated with a discharge in temporal mesiobasal areas. Lateralization in this series was inconclusive. Janszky *et al.*[86] reported seven patients who experienced an orgasmic aura at the start of their seizures. All had temporal lobe epilepsy, and findings suggested a right-sided focus in six of these patients.

Distortions of familiarity

Distortions of familiarity like a feeling that a certain experience has occurred before ('déjà vu') or that a familiar context appears completely new ('jamais vu'), or a mixture of both, can also be generated by activation of the basal temporal region. In the series of Bartolomei and colleagues,[81] these phenomena were evoked much more frequently by stimulation of the rhinal cortex than by stimulation of other mesial temporal areas. In particular, déjà vu was associated with stimulation of the entorhinal cortex and reminiscence of memories with perirhinal stimulation. Some evidence suggests that déjà-vu sensations occur (or are reported) more commonly in seizures originating from the nondominant hemisphere. In Fish's series,[14] the déjà-vu illusion was elicited on the right side in four of five patients. A similar observation has been made by Weinand *et al.*,[87] who reported eight patients where déjà-vu auras lateralized to the nondominant hemisphere.

Multisensorial hallucinations and out-of-body experience

It is likely that the revocation of complex multisensorial experiences necessitates activation of a larger cortical network, important parts of which are the mesiobasal limbic cortex, the lateral temporal neocortex and the temporo-parieto-occipital junction.[15,16,17] The prevalent symptom of these hallucinations may provide some localizing information: Penfield and Perot[7] noted some degree of topographical segregation between auditory and visual experiential reponses on the lateral surface of the temporal lobe; while auditory reponses were clustered along the

first temporal convolution, visual reponses were evoked from more widespread regions of the temporal isocortex. Bancaud and co-workers[88] were able to elicit complex psychic symptoms ('dreamy states') by stimulation of either the amygdala, the anterior hippocampus or the lateral temporal neocortex (mainly the superior temporal gyrus). However, they found that spontaneous 'dreamy states' were always accompanied by simultaneous activation of all three structures.

Rare types of complex hallucinatory events which can be associated with vestibular sensations and other disturbances of body image are autoscopy and out-of-body experience. The electroclinical correlates of these phenomena were studied by Blanke and colleagues[89] in six patients, two of whom were investigated with subdural electrodes. In one patient, an out-of-body experience was induced through stimulation of the right parieto-temporal junction. At the same electrode site, vestibular sensations and visual body part illusions were produced. Overlap analysis found the angular gyrus to be involved in five patients in whom lesion analysis could be performed. The recorded seizures could originate from either hemisphere. The authors hypothesize that the experience of seeing one's body in a position that does not coincide with its felt position is due to faulty integration of input from proprioceptive tactile, visual and vestibular information systems with sensory information of extrapersonal space.

Nonspecific auras

This term refers to a variety of vague feelings that cannot be readily attributed to one of the previously described aura categories. Reasons why some auras appear nonspecific may be related to the varying ability of patients to describe their symptoms, their highly individual character which defies classification or further study, or their nondistinct localization.

Two subtypes of nonspecific auras, cephalic and whole-body auras, have been investigated more in detail:

Cephalic auras

Cephalic auras include sensations such as nonvertiginous 'dizziness', 'lightheadedness', an 'electric shock-like' feeling, 'numbness' or 'pressure'. Nair and Lüders[90] performed a retrospective review of video-EEG monitoring reports of 446 patients, about half of whom had temporal lobe epilepsies. In their series, cephalic auras were seen in patients with seizures originating from all lobes, but more commonly in lateral temporal lobe epilepsies. Palmini and Gloor[21] found that they occurred more often in patients with frontal lobe epilepsy.

Accordingly, different symptomatogenic areas for cephalic auras have been identified with intracranial recordings. Jobst *et al.*[91] found a cephalic aura in 24% of a series of 26 patients with frontal lobe epilepsy, 24 of whom were recorded with intracranial electrodes. Fish and co-authors,[14] using electrical stimulation of the temporal and frontal lobes, predominantly produced cephalic auras following amygdalar stimulation. In the series of Bartolomei and colleagues,[81] responses from rhinal stimulation also included headache and vague sensations of 'something happening in the head'. Penfield and Jasper[5] elicited cephalic auras from several noncontiguous areas of the temporal lobe, including the lateral temporal neocortex.

Some patients also report painful cephalic auras. Young and Blume[39] described 11 patients with ictal pain restricted to the head. Cephalic pain did not localize the site of seizure origin and was thought to reflect a vascular mechanism. In two patients with ictal headache recorded with depth electrodes, the epileptogenic focus was found in the right limbic system, and temporal lobectomy relieved the symptoms.[92] In the series of Nair *et al.*,[38] painful cephalic auras could be seen in patients with seizures originating from any lobe except the perirolandic region. In two patients with temporal lobe epilepsy where the cephalic pain was lateralized to one side, it was ipsilateral to the epileptogenic hemisphere. Bernasconi *et al.*,[93] reporting on 47 patients with periictal headache, also noted that the headache was more likely to be ipsilateral to the seizure onset focus in temporal lobe epilepsy (90% of cases), whereas headache in nontemporal lobe epilepsy was not lateralizing.

Whole-body auras

Penfield and Jasper[5] were able to elicit generalized body sensations from the second sensory area as well as the supplementary sensorimotor area. In the series of Nair and Lüders,[90] whole-body auras occurred in patients with frontal, temporal and multifocal epilepsies; the highest percentage (39%) was found in patients with seizures originating from the posterior temporal lobe. In these patients, the symptomatogenic area may have been the second somatosensory cortex. Whole body auras have no known lateralizing features.

Summary and conclusions

Since it is usually the first symptom to appear in the course of a seizure, the aura is still the best available clinical indicator of the possible location of an epileptogenic zone. However, when attempting to derive localizing information from aura semiology during the presurgical evaluation, it has to be kept in mind that the aura (like any other clinical symptom) is not produced by the epileptogenic zone itself, but is expression of activation of one or more symptomatogenic zones, which are not identical with but may actually lie at a distance from the epileptogenic zone.

The best experimental model to define the localization of the different symptomatogenic areas is to simulate the effect of a seizure discharge with electrical cortical stimulation. Over the years, extensive cortical maps of different brain functions have been developed which are widely used and reproduced yet present inherent limitations. For example, electrical discharges below an effective stimulus intensity do not produce symptoms. Also, identical symptoms can be elicited from several different areas which may not even be consistent in any one patient, and virtually no symptom can be considered pathognomonic for a specific brain region. In recent years, the modular approach to the localization of brain function has given way more and more to an integrated network approach that explains why symptoms due to activation of a network may be elicited at different points of the same circuit. Different symptomatogenic zones may therefore form symptomatogenic systems, just like the epileptogenic zone may actually be an epileptogenic system, different parts of which have different activation thresholds.

Nonetheless, there are different probabilities with which any given symptom can be elicited at different cortical sites,[94]

which can be used for localization. Known localizing and lateralizing features of different aura types are summarized in Table 49.1. In addition, auras are often associated with other symptoms forming symptom clusters which, in their unique association, can provide localizational clues or trace the propagation pathway the seizure takes in the brain. In the end, the localization of a presumed epileptogenic zone can only be accomplished through a combination of several semiological, morphological and electrographic pieces of information, of which aura semiology is just one, albeit important element.

Table 49.1 Localization and lateralization of epileptic auras

Aura type	Symptomatogenic zone (electrical stimulation)	Epileptogenic zone (lobe)	Lateralization
Somatosensory			
Pain, thermal sensations	SSI, SSII, insula	Parietal, temporal	Contralateral if from SS I; may be ipsilateral from SS II, insula, SSMA
Paresthesias	SS I/II, SSMA, insula, temporal	All lobes, more often parietal or temporal	
Limbs			
Head, trunk, genitals			No
Somatosensory illusions	SS I, inferior parietal lobule, TPO junction	Parietal, temporal	More often ND
Sensation of movement	SS I, SSMA, primary motor	Frontal, parietal	No
Eyes	Occipital lobe	Occipital	No
Visual			
Amaurosis	Occipital, temporo-occipital	Occipital, temporal	If lateralized, contralateral
Blurring of vision	Posterior cingulate, mesial > lateral parieto-occipital	Occipital, parietal, posterior temporal	
Simple and complex hallucinations	More likely occipital or temporal, but all lobes possible	All lobes	More often ND
Illusions	Basal temporal, TPO junction	Temporal, parietal, occipital	No
Tunnel vision	Basal temporal, occipito-temporal		
Auditory			
Simple hallucinations	More likely Heschl's gyrus	Temporal	If lateralized, contralateral
Complex hallucinations, illusions	More likely auditory association cortex	Frontal, temporal Temporal	
Vertiginous	All lobes, more frequently temporo-parietal	Parietal, temporal, frontal	More often ND
Olfactory	Amygdala, insula	Frontal, insular, mesial temporal	No
Gustatory	Insula, mesial temporal	Temporal, insular	If lateralized contralateral
Autonomic			
Throat constriction	Insula	Insular	No
Breathing difficulty, palpitations, thermodysregulation	Insula, anterior cingulate, SSMA, amygdala, hippocampus, hypothalamus	Temporal, (orbito-) frontal, insular	No
Urinary urge	Insula	Temporal, insular	More often ND
Abdominal epigastric	Insula, mesial temporal, mesial frontal	All lobes, most often temporal	Right, if associated with vomiting
Psychic			
Fear	Amygdala, hippocampus, mesial frontal	(Mesial) temporal or frontal	No
Happiness, ecstasy	Temporal	Temporal	More often ND
Déjàvu/jamaisvu	Mesial > lateral temporal	Temporal	More often ND
Multisensorial exp.	Lateral temporal, TPO junction	Temporal, parietal	No
Out-of-body experience	TPO junction	Temporal, parietal	No
Nonspecific			
Cephalic	More often frontal or temporal, but all lobes possible	All lobes	No
Whole-body	SS II, SSMA	More often mesial frontal or post. temp.	No

Abbreviations: SS I: primary somatosensory area, SS II: second somatosensory area, SSMA: supplementary sensorimotor area, TPO: temporo-parieto-occipital, ND: nondominant hemisphere

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50 Autonomic seizures: localizing and lateralizing value

V Nagaraddi and HO Lüders

Summary

Autonomic symptoms are common during epileptic seizures, mainly in conjunction with other more prominent symptoms. However, in selected cases autonomic symptoms may also constitute the predominant ictal manifestation. Autonomic seizures are actually mediated by activation of the central autonomic network and are not an adjunct to motor and other manifestations of seizures. Autonomic seizures have been divided into cardiovascular, respiratory, gastrointestinal, cutaneous, papillary, and urogenital, depending upon the symptoms.[1]

Certain autonomic symptoms provide lateralizing and/or localizing information about the ictal onset zone, due to specific representation of the central autonomic network in the cortex. Autonomic symptoms range from subtle changes, which are apparent only with video-EEG monitoring, to severe, sometimes life-threatening events. When autonomic symptoms are the sole seizure manifestation, they can be difficult to differentiate from psychogenic non-epileptic seizures. Finally, autonomic symptoms during seizures provide a unique opportunity to study the functional organization of the central autonomic network.[1]

Introduction

Autonomic symptoms occurring during seizures have been recognized for more than 100 years. Changes in heart rate and respiration during a generalized tonic–clonic seizure are predictable and are obvious to an observer. Autonomic symptoms during focal seizures have long been observed as well, including goose bumps, flushing, pallor, sweating, sexual sensations, and pupillary changes.[2]

In 1981, the commission on classification and terminology of the International League against Epilepsy included autonomic seizures as a subdivision of simple partial seizures in the revised seizure classification. This subdivision included among others, epigastric sensations, pallor, sweating, flushing, piloerection and pupillary dilation.[3]

Autonomic symptoms can occur either during the ictus or postictally. They may also play a role in some interictal epileptic behaviors. Autonomic symptoms are being recognized with increasing frequency. Nevertheless, autonomic seizures are still frequently under- or misdiagnosed, resulting in expensive investigations and inappropriate therapies, leaving incapacitating and potentially fatal symptoms untreated.[4]

Both focal and generalized seizures alter the central autonomic functioning during ictal, postictal, and interictal states. All aspects of autonomic function can be affected, including the parasympathetic, sympathetic, and adrenal medullary systems. Focal and generalized seizures typically activate the sympathetic nervous system, increasing the heart rate and blood pressure, although parasympathetic activation or sympathetic inhibition may predominate during some focal seizures.[5]

Neuroanatomy of the autonomic system

The preganglionic sympathetic and parasympathetic efferent pathways are regulated by reciprocally interconnected cortical, subcortical, and brainstem regions. The components of the central autonomic network have been established by experimental methods, and include the insular cortex, the medial prefrontal cortex, the central nucleus of the amygdala, the nucleus of the stria terminalis, the hypothalamus, the midbrain periaqueductal gray matter, the pontine parabrachial region, the nucleus of the solitary tract and the intermediate reticular zone of the medulla.[6]

Anatomic and physiologic studies have defined a topographically organized visceral map in the insula, supporting the concept of the insula as a 'visceral sensory cortex', with localization of gustatory responsive neurons to the rostral agranular region and gastric mechanical responsive neurons to the caudal granular region. Electrical stimulation studies of the insular cortex have demonstrated heart rate, blood pressure, respiratory, piloerector, pupillary, gastrointestinal, salivatory, and adrenal responses. Intraoperative stimulation studies of the human insular cortex have suggested that tachycardia and pressor responses occur more commonly with right anterior insula stimulation, whereas bradycardia and depressor responses are more common with left anterior insular stimulation.[7,8]

Stimulation of the medial prefrontal cortex produces profound changes in blood pressure, heart rate, and gastrointestinal motility. A viscerotopic map of this region, which includes the anterior cingulate gyrus and the inferior and prelimbic cortices, supports the concept of the medial prefrontal cortex as a 'visceral motor cortex.' Intraoperative human stimulation studies of the cingulate gyrus have demonstrated changes in heart rate and blood pressure.[4,9]

Definition of autonomic seizures

Autonomic seizures have a measurable or visible autonomic symptom or manifestation, for example change in the heart rate or piloerection, which is also a prominent or predominant feature of the seizure. The symptom is usually verifiable by an observer, reproducible over several seizures and can be documented quantitatively or qualitatively. This is important in distinguishing autonomic seizures from autonomic auras, which are symptoms perceived by the patient, such as feeling hot, or cold and clammy etc., but there is no change that can be verified by observation or measurement, such as the temperature being assessed by touch or measured by a thermometer and sweating documented by either touch or observation. The limitation is that many of the autonomic symptoms in question, are not quantifiable in most routine settings, because there is no simple, practical means of measuring it, for example peristalsis, pupillary changes etc.

It should also be noted that almost all epileptic seizures have some autonomic symptoms, especially cardiac and respiratory changes. Most focal and generalized tonic-clonic seizures have changes in heart rate, as measured by the EKG. In most of these cases, there is sinus tachycardia at the onset of seizure and to a lesser extent sinus bradycardia. Similarly, there are changes in the respiratory pattern and rate, which could be either due to modulation of the respiratory centers in the cortex and brainstem due to the spread of the seizure or as a result of the tonic contraction and spasms of the diaphragm and intercostal muscles. In these seizures, the predominant feature is either the alteration in consciousness and or the motor manifestations accompanying it and therefore they are not classified as true 'autonomic seizures'.[4,5]

Cardiac manifestations

Cardiac manifestations are the most studied autonomic alterations, partly because of trying to elucidate the pathophysiology of SUDEP and also because most EEG recordings have an EKG channel that can be easily analyzed.

Ictal tachycardia

An increase in the heart rate is seen in the vast majority of all epileptic seizures, including subclinical electrographic seizures.[10–13] Depending upon the definition of tachycardia, usually >100 beats per minute, the incidence of ictal tachycardia varied from 33–87%.[14–18] Furthermore, there is a significant preponderance of ictal tachycardia in temporal lobe epilepsy versus extratemporal lobe epilepsy (62% versus 11%, $p < 0.0018$)[19] and in one study ictal tachycardia was seen in 98% of temporal lobe seizures.[16,20,21] Within the temporal lobe, ictal tachycardia was found to be more prevalent in seizures arising from the mesial temporal lobe.[15,21] The onset of tachycardia tended to precede the EEG seizure onset, more so in temporal lobe versus extratemporal lobe seizures and mesial temporal lobe versus lateral temporal lobe seizures.[13,17,21] Finally, ictal tachycardia has been lateralized to the right hemisphere in several studies.[17,22] This suggests that early and significant tachycardia was primarily associated with right mesial temporal lobe seizures.[20]

Ictal bradycardia

A decrease in the heart rate is a lot less common and varied from 0-5% of seizures reported in several studies.[14,16,17,20] There are mixed results to the localization and lateralization of ictal bradycardia. Most of the prior reports had shown a predilection of ictal bradycardia in left temporal lobe seizures.[23–25] However, a recent study and other reports dispute this finding and suggest that there is usually bilateral involvement in seizures causing ictal bradycardia.[24,26] The reason may be due to the fact that ictal bradycardia is relatively uncommon and the number of seizures with ictal bradycardia in all of the studies were small, which included several case reports.

Ictal asystole

The incidence of ictal asystole is extremely rare,[27,28] though it may be higher than previously estimated especially in focal intractable epilepsy.[29–31] It has been implicated as one of the causes of SUDEP. There are several anecdotal case reports of ictal asystole following ictal bradycardia in left hemispheric seizures, mainly left temporal and frontal lobe seizures.[28,32–35] Single cases of ictal asystole in seizures arising from the left cingulate gyrus[36] and right frontal lobe[37]have also been reported.

Ictal arrhythmia

High-risk or fatal cardiac arrhythmias during epileptic seizures are thought to be uncommon,[38,39] however the incidence of ictal arrhythmias appears to be more common in intractable and generalized seizures.[40] Various cardiac arrhythmias that have been reported during epileptic seizures include atrial fibrillation (AF), supraventricular tachycardia (SVT), premature ventricular contraction (PVC), premature atrial contraction (PAC), bundle branch block (BBB), ST depression and T-wave inversion.[39,40] None of these ictal cardiac arrhythmias seem to have any localizing or lateralizing value.

Respiratory manifestations

Respiratory manifestations are not as common as cardiac manifestations but is probably the second most common manifestation of autonomic seizures. Most of the studies have been done in pediatric patients as they appear to be more common in children

Ictal hyperventilation

Ictal hyperventilation, defined as a 10% increase in the respiratory rate from the pre-ictal baseline, was seen in 56% of focal seizures recorded from 37 children.[41] In another study, hyperventilation was seen in 18% of children with autonomic seizures and was more common in temporal lobe epilepsy compared to extra temporal lobe epilepsy, but this was not statistically significant.[42] A study in adults found hyperventilation in both temporal and frontal lobe epilepsies, but occurred more in mesial compared to lateral temporal lobe epilepsy.[43]

Ictal apnea

Ictal apnea is most commonly reported in neonates and infants, typically lasting 1–2 minutes.[44–51] It was seen in 20% of children,[42] 58% of adults[52] and 30% of focal epilepsies.[41] When localized, it was mostly seen in temporal lobe epilepsies,[44–48,51,53] with cases lateralizing to both the left[53] and right[47,51] temporal regions.

Ictal dyspnea and stridor

This is not a well defined entity in the available literature. It was seen in 15% of children and two-third were associated with the tonic phase of epileptic seizures.[42] A case report describes stereotypical episodes of dyspnea over 4 months which turned out to be due to a right mesial temporal lobe epilepsy.[54]

Postictal nose wiping/postictal coughing

These two manifestations are thought to be due to same mechanism, which is increased parasympathetic activity, resulting in increased nasal and/or pharyngeal secretions, which then cause the patient either to wipe the nose or induce coughing. These reflexive maneuvers are usually seen postictally because during the ictus, both reflexive maneuvers are inhibited. Postictal coughing is most commonly seen in temporal lobe epilepsies, but has not been consistently lateralized to either the right or left hemisphere.[42,55,56] However, the hand used in postictal nose wiping seems to lateralize and or localize to the ipsilateral temporal lobe.[57–60]

Gastrointestinal manifestations

Gastrointestinal manifestations are the earliest autonomic symptoms to be described and studied. These symptoms generally have good lateralizing and localizing value except for ictal defecation because it is relatively rare and probably under reported. Abdominal epilepsy has been included here, even though it actually constitutes several different autonomic symptoms, but they are primarily gastrointestinal manifestations.

Epigastric aura

Epigastric aura is the earliest autonomic manifestation to be described[61]and the most commonly reported aura,[62] it has significant localizing value, arising from the mesial temporal lobe structures and the insula primarily.[63,64] In terms of lateralizing value, some authors claim that it is more common in non-dominant hemispheric epilepsy,[65,66] but it has not been confirmed by others.[67–69]

Abdominal epilepsy

Abdominal epilepsy is the earliest autonomic seizure to be described, and was previously called visceral seizures.[9,70] It is more common in children[71,72] than adults.[73,74] It is characterized by recurrent paroxysmal abdominal pain, usually associated with nausea, vomiting, lethargy and confusion.[75–78] Abdominal epilepsy has not been consistently lateralized[73] but has been localized to the temporal lobe in several reports.[42,79–82] Most patients reported as abdominal epilepsy had paroxysmal autonomic symptoms but no objective proof that these symptoms actually were an expression of epileptic seizures.

Ictal vomiting (Ictus emeticus)

In contrast to abdominal epilepsy, in which vomiting usually accompanies the abdominal pain and the patient is aware of it, vomiting in ictus emeticus occurs as the sole manifestation[83,84] or may be associated with other symptomatology of temporal lobe seizures, but the patient is usually amnesic of the vomiting.[85–87] Ictal vomiting is a relatively rare manifestation of temporal lobe seizures in adults.[84,88] It has been postulated to arise mostly from the non-dominant temporal lobe[70,86–90] however there have been several reports of ictal vomiting with dominant temporal lobe epilepsy.[42,91–95] On the other hand, ictal vomiting is the predominant manifestation of the early onset benign childhood occipital lobe epilepsy, which affects 13% of children aged 3-6 years.[96–101] Ictal vomiting is also seen in extraoccipital benign childhood epilepsies and carries the same prognosis.[102,103] Ictal vomiting is thought to occur when the epileptic discharges involve the medial and lateral aspects of the temporal lobe and the adjacent insular cortex.[85–87,104,105] Even in extra-temporal lobe epilepsies, it has been shown that ictal vomiting occurs when the ictal discharge spreads to the temporal lobe from the extratemporal focus, which in most cases is the occipital lobe.[104,106]

Ictal spitting (Ictus exporatus)

Ictal spitting is a rare manifestation of epileptic seizures, with an incidence of 0.2 to 2.2% of patients in epilepsy monitoring units.[107–109] It has been lateralized and localized to the non-dominant temporal lobe in most of the studies,[42,108–112] but has been reported in dominant temporal lobe in a couple of studies.[107,113] Ictal spitting is also thought to arise from the insular cortex.[109]

Ictal defecation

Ictal defecation is the urge to defecate, associated with the onset of a focal seizure, which has been reported anecdotally by several authors.[64,70,114,115] A.L. Reeves mentioned several cases in a review article, of patients with the urge to defecate at the onset of a seizure. A recent case report describes a 47 year old right handed woman with the urge to defecate at the onset of a seizure and the EEG was lateralized to the right hemisphere during the seizure.[116]

Cutaneous manifestations

Cutaneous manifestations are rare autonomic expressions of focal epilepsy, that were first described by Penfield,[114] Mulder[70], Daly[115] and Van Buren.[64,64,64] They usually occur in conjunction with one another, in addition to other common manifestations of focal epilepsy. Other cutaneous manifestations, which have been cited in the literature include sweating, cyanosis and purpura, but will not be covered here because there have been no reported localizing or lateralizing value to any of these manifestations and most of these studies were case-reports.

Ictal piloerection (goose bumps)

Ictal piloerection was identified in only 0.4% of 3500 patients undergoing video-EEG monitoring in a single epilepsy center over a 7 year period.[117] It has been localized to the temporal lobe in the majority of the patients reported in the literature,[117–119] including confirmation with cortical stimulation.[117,120] The piloerection mostly tended to occur unilaterally and often had a 'Jacksonian march' and in most of the cases, it was ipsilateral to the onset of the focal epilepsy.[117–119,121] The etiology was diverse, and included tumors,[121,122] hippocampal sclerosis,[120,121,123,124] limbic encephalitis,[125] hyperosmolor non-ketotic hyperglycemia,[126] post-traumatic[127] and cryptogenic.[118,124] However, it has not been consistently lateralized to either hemisphere and with several case reports of left[118–120,124,128] and right[122,123,127,129] hemispheric onsets.

Ictal pallor

The only comprehensive study of ictal pallor was a recent study in 100 children, in whom 11 were found to have ictal pallor. In this study 11 children had left temporal lobe epilepsy.[130] This has not been replicated in adults with only a handful of reports and in most of these reports, ictal pallor was usually concomitantly associated with other cutaneous manifestation.

Ictal flushing

In contrast to ictal pallor, ictal flushing was observed in 19 out of 100 children undergoing video-EEG monitoring. Ictal flushing showed neither lateralizing nor localizing value. Flushing was mostly facial and happened not only during simple partial (motor) seizures but also during complex partial (temporal lobe) seizures, which suggests that flushing is due to both skin hyperperfusion during motor activities but also due to central autonomic involvement.[42]

Pupillary manifestations

Pupillary manifestations are rare autonomic manifestations, with only a handful of case reports in the literature and hence have limited localizing and lateralizing value.

Ictal mydriasis

Bilateral mydriasis is a common concomitant of generalized convulsive seizures, both primary and secondarily generalized, most probably due to the diffuse spread of the epileptic discharges, thus activating widespread subcortical midline structures and the central sympathetic nervous system.[1,4] Unilateral mydriasis is far less common and has been reported to be ipsilateral in focal occipito-temporal seizures[131] and contralateral in a young boy with a ' benign left frontal epileptic focus'.[132]

Ictal miosis

Bilateral miosis has been described in a case of generalized photosensitive epilepsy along with bilateral adduction as part of a near reflex accommodation spasm.[133] Bilateral miosis has also been described with bilateral internal ophthalmoplegia in a patient with left temporo-occipital epilepsy[134] and without internal ophthalmoplegia in a 3-year-old girl with right-sided mesiotemporal ganglioglioma.[42] Unilateral miosis associated with ptosis has been reported in two patients with temporal lobe epilepsy, with one case presumed to be ipsilateral and the other contralateral to the unilateral miosis.[135] Left miosis associated with left homonymous hemianopia and visual hallucinations has also been reported in a patient with right occipital lobe epilepsy due to a small cavernous hemangioma.[136]

Urogenital manifestations

Urine incontinence is the most common urogenital manifestation and is a common feature of generalized tonic-clonic seizures and usually occurs after the clonic jerking stops. It is not due to increased intravesicular pressure during the seizure, but rather depends on relaxation of the vesical sphincter during the phase of muscular recovery and occurs only if the bladder is full at the time of the attack. However, urine incontinence does not have any localizing or lateralizing value.

Ictal urinary urge

The aura of urinary urgency during seizures has been shown to be a lateralizing sign for non-dominant temporal lobe in two studies with a total of 12 adults undergoing video-EEG monitoring.[137,138] A single case of ictal urinary urge associated with confusion, oral and genital automatism has been reported in a 6-year-old boy with a left temporal lobe seizure.[139]

Sexual/orgasmic aura

Sexual auras refer to seizures that include erotic thoughts and feelings, sexual arousal, and orgasm. They may be accompanied by genital viscerosensory phenomena, vulvovaginal secretory activity, and olfactory hallucinations. Sexual auras are reported more frequently by women and may be associated more commonly with right temporal lobe epilepsy.[140–142] Orgasmic auras, a subset of sexual auras, have been lateralized to the right hemisphere in the majority of the cases reported in the literature.[143] In a case series of seven patients experiencing an orgasmic aura, six had right temporal lobe epilepsy confirmed by EEG, MRI, and ictal SPECT and the remaining patient who was left hemisphere dominant as confirmed by WADA, had left temporal lobe epilepsy.[144] There are, however, also isolated reports of orgasmic auras with seizures from the left hemisphere, as determined by EEG.[145]

Genital aura

Genital auras are characterized by unpleasant, sometimes painful, frightening, or emotionally neutral somatosensory sensations in the genitals and can be accompanied by ictal orgasm. Genital auras are localized to the parasagittal postcentral gyrus, where genital sensations are represented.

When these sensations are bilateral, then the secondary somatosensory area is also thought to be involved.[145–147]

Sexual automatisms

Sexual automatisms, characterized by hypermotor movements consisting of writhing, thrusting, and rhythmic movements of the pelvis, arms, and legs, sometimes associated with picking and rhythmic manipulation of the groin or genitalia, exhibitionism, and masturbation, are localized to seizures from the frontal lobe. In addition, sexual automatisms were seen from different subcompartments of the frontal lobe, including the frontal convexity, the orbitofrontal region, and the supplementary sensorimotor area.[148–151]

Genital automatisms

Genital automatisms, characterized by discrete genital automatisms such as grabbing or fondling the genitals, which can be accompanied by masturbatory activity and exhibitionistic behavior, were generally associated with temporal lobe seizures, but could not be lateralized.[141,142,152–154] Several recent studies in both adults and children have not shown any localizing or lateralizing value to genital automatisms. However, genital automatisms did localize to the temporal lobe when associated with ictal urinary urge or unilateral hand automatisms in adults. In children, the hand used for genital automatisms was more frequently ipsilateral to the seizure onset zone.[155,156]

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51 Simple motor seizures: localizing and lateralizing value

S Noachtar and S Arnold

Definition of simple motor seizures

Simple motor seizures are characterized by unnatural, relatively simple movements that can be reproduced by electrical stimulation of the primary and supplementary sensorimotor areas.[1] Simple motor seizures can be divided into the following subtypes depending on the duration of the muscle contraction, the rhythmicity of movement repetition, and the muscles involved: myoclonic seizures (negative myoclonic seizure), clonic seizures, tonic seizures, epileptic spasms, versive seizures, and tonic-clonic seizures.[1–3]

In contrast to simple motor seizures, during complex motor seizures the patients perform movements that imitate natural movements, are relatively complex, and tend to involve different body segments moving in different planes. These movements have also been labeled automatisms.

If a given seizure cannot be classified into the following categories based on the available information the term simple motor seizure is recommended.[1–3]

Myoclonic seizures

Myoclonic seizures consist of sudden muscle jerks of short duration (less than 400 ms), which do not recur in a rhythmical fashion. They can be either bilateral (generalized) or unilateral (Figure 51.1–51.2). Generalized myoclonic seizures, which predominantly affect the shoulders and proximal arms, are typical for patients with juvenile myoclonic epilepsy[4] and have already been recognized in the mid-19th century.[5] Generalized myoclonic seizures are also frequently seen in patients with Lennox-Gastaut syndrome[6] and the rare MERRF syndrome (myopathy, encephalopathy, ragged red fibers) (Figure 51.1) or Unverricht-Lundborg-syndrome. Electroencephalographically, generalized myoclonic seizures are frequently associated with generalized polyspikes that have a fronto-central maximum. Bilateral myoclonic seizures are rarely observed in patients with focal epilepsies (Figure 51.2). The primary motor cortex or premotor areas are most likely involved in the generation of this seizure type.

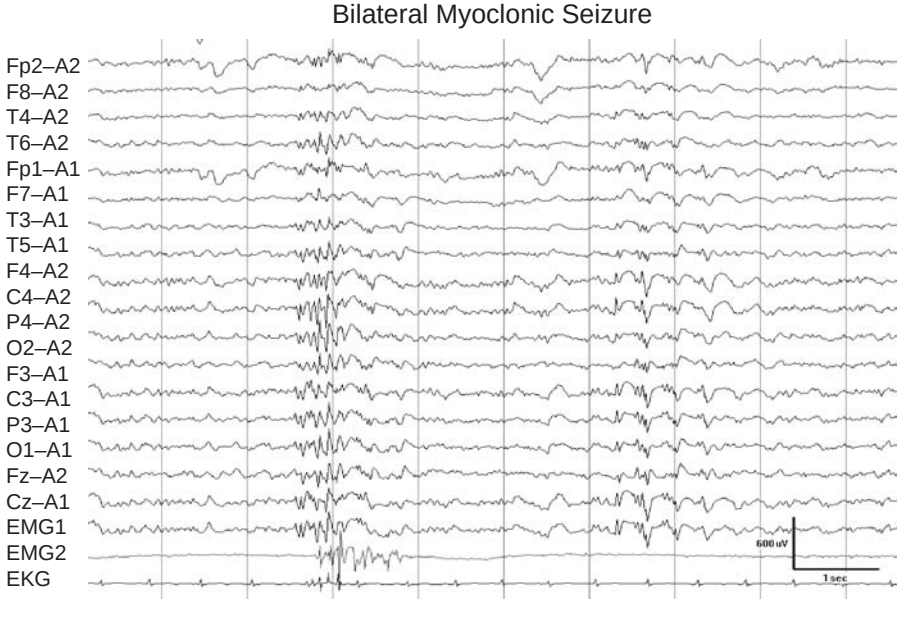

Figure 51.1. The generalized polyspikes in this 28-year old patient with MERFF syndrome are consistently associated with generalized myoclonic jerks of the trunk and proximal limbs, whereas single spikes, spike-wave complexes and less dense polyspikes were not. Longitudinal bipolar montage including EMG of both legs (EMG1=left anterior tibial muscle; EMG2= right anterior tibial muscle).

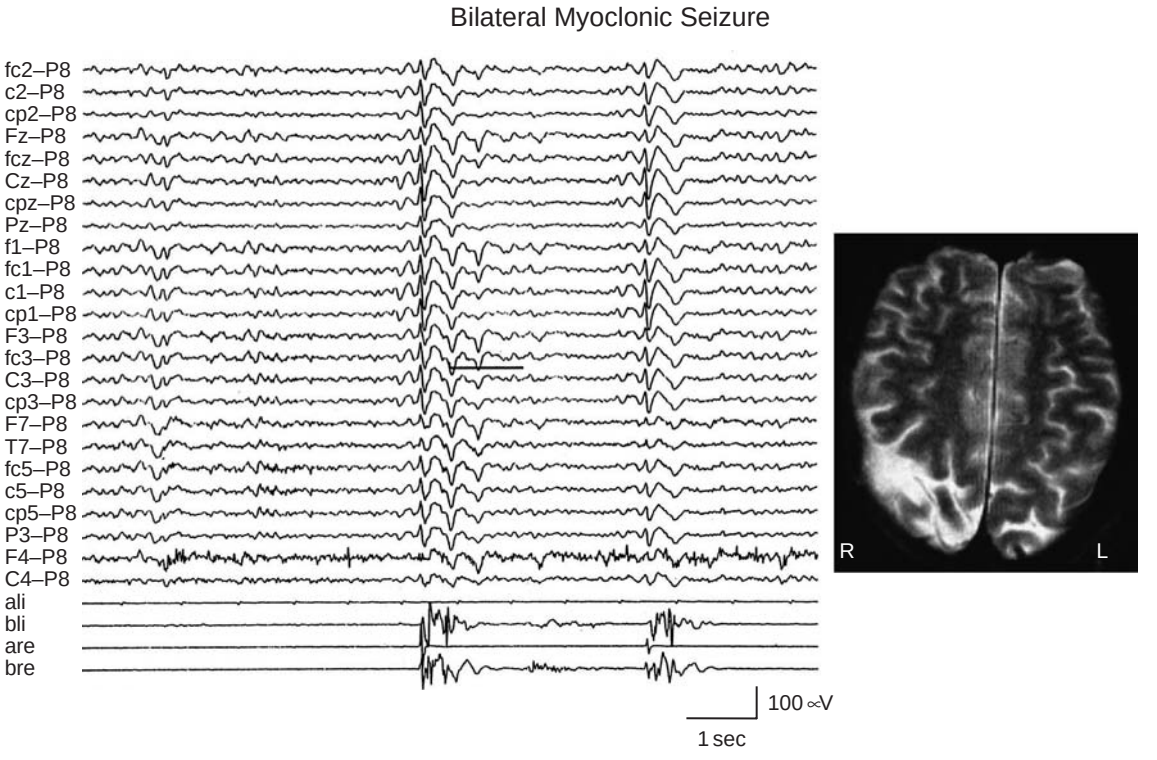

Figure 51.2. This 53-year-old patient has myoclonic seizures of both legs with a right zentral perinatal lesion. EEG is referenced to the electrode P8. ali= left brachioradial muscle EMG; bli=left anterior tibial muscle EMG; are=right brachioradial muscle EMG; bre=right anterior tibial muscle EMG.

Unilateral myoclonic seizures are very rare and occur contralateral or predominantly contralateral to the epileptogenic zone. Figure 51.2 shows the rare occasion that left central polyspikes in the EEG were consistently associated with myoclonic jerks of the both legs in a patient with a left central perinatal lesion. Some patients with juvenile myoclonic epilepsy report unilateral myoclonic jerks although video recording usually establishes the bilateral character of the myoclonic jerks. These patients typically favor the dominant arm.[7]

Negative myoclonic seizures

Negative myoclonus is a rare epileptic seizure type which is characterized by brief periods (20–400 ms) muscle atonia (Figure 51.3).[8] Negative myoclonus occurs only if muscle activity is exerted and the sujdden muscle atonia leads to the drop of the limb. Polygraphic recordings are helpful to document muscle atonia in the EMG associated with negative myoclonic seizures and epileptiform discharges in the EEG

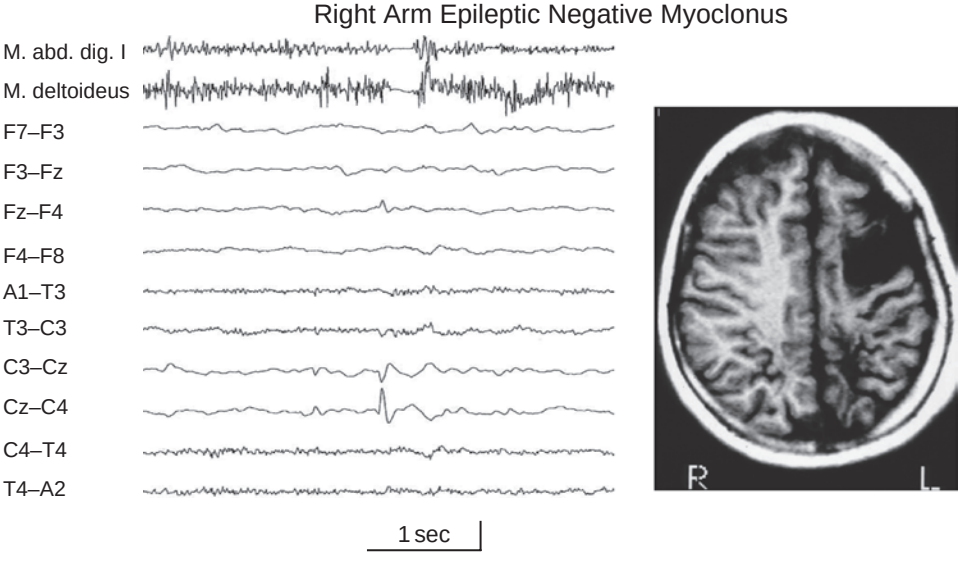

Figure 51.3. The transverse bipolar EEG montage shows that the left central sharp wave elicited a atonia of muscle activity in the right abductor digiti minimi and the right delta muscle, which documents an epileptic negative myoclonus. The MRI of this patient showed diffuse left hemisphere perinatal lesion and atrophy.

and distinguish negative myoclonus from myoclonic seizures, which may be difficult visually (Figure 51.3). Negative epileptic myoclonus has been described in patients with frontal and paracentral epilepsies.[9,10] Bilateral negative myoclonus also occurs in different encephalopathies.[8] In unilateral negative myoclonus, the epileptogenic region is contralateral to the affected limb. The central primary somatosensory cortex is considered responsible for the generation of negative myoclonus but there is very little data available.[11] The cortex in the postcentral gyrus has been shown to generate contralateral negative myoclonus.[10]

Clonic seizures

Clonic seizures consist of repeated, short contractions of various muscle groups (agonists and antagonists) usually characterized by jerking or twitching movements recurring at a regular interval between 0.2 and 5 per second (Figure 51.4). The jerks seen with myoclonic and clonic seizures are the same except that myoclonic seizures consist of single jerks which repeat in an irregular fashion whereas with clonic seizures the jerks have a regular rate. In other words, clonic seizures consist of 'myoclonic jerks' recurring at a regular repetition rate. The movements may affect any part of the body. Generally they are an expression of epileptic activation of the primary motor or the premotor areas.[12] Focal clonic seizures mostly affect the distal segments of the extremities, e.g., the hand or the face. Clonic activity may show a 'march' from the distal to the proximal parts of the extremities, reflecting the spreading activation of the primary motor cortex. Electrical stimulation of the supplementary sensorimotor area can elicit distal clonic movements, but only very rarely.[13] Typically clonic seizures start with a tonic phase, which frequently is not clinically detected unless polygraphic recordings reveal that the frequency of muscle contraction is higher in the beginning of the seizure and gets gradually slower, thus leading to recognizable clonic jerks.[14] Unilateral clonic seizures typically involve the face or hand area and less frequently the leg or trunk[15–17].

Clonic seizures were first systematically described in 1827 by Bravais[18] who distinguished facial, brachial, and crural onset clonic seizures and described the typical unilateral march of the convulsion which was later associated with Hughlings Jackson's name. In a large series of 8938 epileptic patients clonic seizures have been found to be rare occurring in only 2.2% of the patients.[19] However, clonic seizures were relatively frequent in those 127 patients who had somatosensory auras. One third (34.3%) of these patients had clonic seizures.[19] Of 52 patients reported by Hallen in 1952, clonic seizures started in the hand in 16, in the face in 14, in the foot in ten, in the shoulder in four, in the leg in four, in the head in two, in the thorax in one and in the neck in another patient.

The seizures types preceding and following clonic seizures are very variable. We analyzed all patients in whom clonic seizures were recorded at the Epilepsy Monitoring Units of the Bethel Epilepsy Center from 1991–1994 and the University of Munich Epilepsy Program from 1994–1995. We identified 127 patients with clonic seizures occurring in 162 different seizure evolutions from the data bases (Figure 51.5). Thus, some patients had more than one seizure evolution. Clonic seizures were the initial seizures in 33 patients. In the remaining 129 seizure sequences usually automotor (n=45) and tonic (n=45) seizures preceded the clonic seizures. The different seizure types preceding clonic seizures are listed in Figure 51.5. The clonic seizures evolved typically into generalized tonic-clonic seizures (n=58) and less frequently into other seizure types such as tonic or versive seizures (Figure 51.5). No following seizure types were observed in 42 patients.

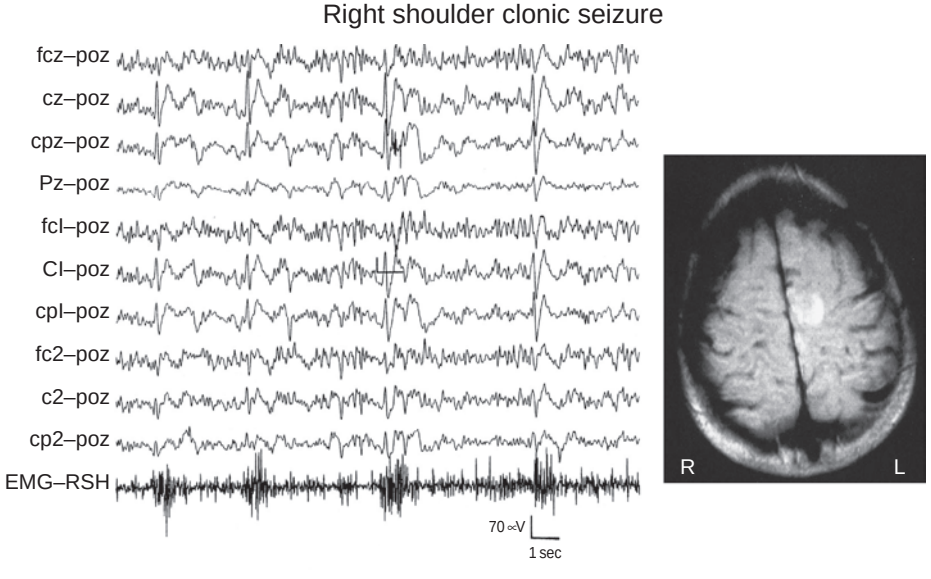

Figure 51.4. This 14-year-old boy had clonic seizures of the right shoulder secondary to a low-grade glioma, which were consistently associated with left central spikes in the surface EEG. Selection of ten EEG channels in a referential montage to the electrode POZ. EMG-RSH=EMG of the left delta muscle.

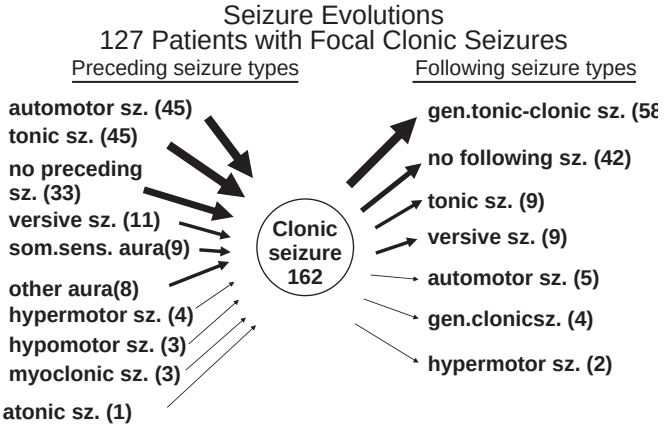

Figure 51.5. Seizure types preceding and following clonic seizures in 162 seizure evolutions of 127 patients who underwent EEG-video monitoring. Clonic seizures were the initial seizure manifestation in 33 seizure evolutions. The frequency of preceding and following seizure types are given in parenthesis. Clonic seizures were preceded by other seizure types in 129 seizure evolutions.

Clonic seizures may represent the initial seizure symptomatology but may be preceded by other seizure types such as auras, automotor or tonic seizures (Figure 51.5). Clonic seizures can evolve into other seizure types most commonly into generalized tonic clonic seizures (Figure 51.5–6). Unilateral clonic seizures are present in several focal epilepsies. In patients with frontal lobe epilepsy, clonic seizures tend to occur early in the seizure evolution and the patient is usually conscious at the time the clonic activity begins (Figure 51.6).[12,20] When clonic seizures are the result of spread of epileptiform activity into the frontal lobe from the occipital or temporal lobe, consciousness is usually altered at the onset of unilateral clonic seizures. Generalized clonic seizures only very rarely occur with preserved consciousness.[21]

Fincher and Dowman[22] reported on a series of 130 patients with 'Jacksonian' seizures. Eighty-four patients had 'purely motor' seizures. In 20 patients somatosensory auras were followed by motor seizures and in nine patients motor features immediately preceded sensory 'attacks'. In 17 instances there were sensory and motor 'attacks' occurring simultaneously. The authors mention two patients, in whom generalized jerkings were not associated with loss of consciousness. Consciousness is usually preserved if unilateral clonic activity is the initial seizure manifestation. If an automotor seizure precedes a clonic seizure, which we observed only in temporal lobe epilepsy and not in frontal lobe epilepsy consciousness will typically be disturbed during the clonic seizure.[23]

A series of 'pure' frontal lobe epilepsies of the Montreal Neurological Institute showed focal 'sensorimotor seizures' in 27% of the patients.[24] Automotor seizures were as common in this series (30%). Geier *et al.*[25] found 'clonic and/or tonic seizures' which were not further specified in 77.3% of 22 patients with frontal lobe epilepsies. Disturbance of consciousness (100%), deviation of head and eyes (86.4%), vocalisation (86.4%), and falling (81.8%) were more common in this study than clonic seizures. In a recent study of 252 patients with focal epilepsies 14 patients had clonic seizures.[20] In the 14 patients with clonic seizures a structural lesion could be demonstrated in the primary motor cortex in seven patients, in the premotor region in one patient and in the parietal cortex in another patient. Clonic seizures occurred both in temporal and frontal lobe epilepsies but the seizure evolution was different: if the clonic seizures occurred early in the seizure evolution there was a significant association with frontal lobe epilepsy.[20]

In a series of 40 patients with frontal lobe epilepsies who underwent selective epilepsy surgery of the parasagittal convexity of the frontal lobes (PSC) or anterolaterodorsal convexity (ALDC) and remained seizure free, seizure onset in the PSC (eight of ten patients) was more frequently associated

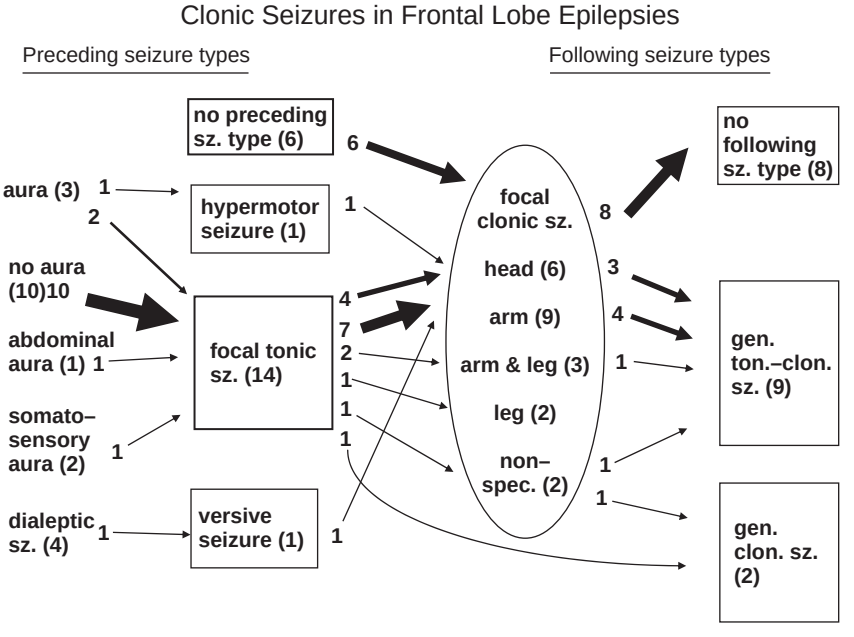

Figure 51.6. Seizure types preceding and following clonic seizures as documented by EEG-video monitoring in 19 patients with frontal lobe epilepsies. Clonic seizures were the initial seizure manifestation in seven seizure evolutions. Focal clonic seizures evolved further either into generalized tonic-clonic or generalized clonic seizures.

with focal motor seizures than seizure onset in the ALDC (15 of 30 patients).[26] In a later report of the same group 29% to 60% of the patients with 'dorsolateral frontal lobe epilepsies' had clonic seizures.[27] The authors concluded that clonic seizures occur in patients with epilepsy of different frontal compartments and are not a reliable indicator of seizure onset location.[27] A neuroimaging study using FDG-PET in patients with probable frontal lobe epilepsy reported clonic seizures in nine of 22 patients. In six patients clonic activity was the initial seizure symptom. Precentral seizure onset was assumed in three, premotor onset also in three, and mesial onset in another three patients.[28] A study of ten patients with medial frontal or orbitofrontal seizure onset did not describe clonic seizures.[29] These patients had seizures characterized by complex motor automatisms with kicking and trashing movements and a bizarre appearance frequently leading to erroneous diagnosis of non-epileptic psychogenic seizures.

Data about seizure evolution of focal clonic seizures is sparse. Thirty percent of 24 patients with frontal lobe epilepsy have been described to have clonic seizures.[30] In three of these patients the clonic seizures were preceded by conscious contralateral version. The clonic seizures were followed by tonic seizures consisting of tonic posturing of all extremities in three patients. Harvey *et al.*[31] reported clinical seizures characteristics in 22 children with frontal lobe epilepsies who underwent ictal SPECT studies. Ten children had clonic seizures. Seizure evolution commenced most frequently with behavioral arrest (n=13) or auras (n=6) which evolved into tonic seizures (n=11), hypermotor (n=6), or automotor seizures (n=2). The clonic seizures were preceded by tonic seizures in seven patients, by an aura in one patient, by behavioral arrest in one patient, and by an automotor seizure in another patient. Only one patient had clonic seizures as the inital seizure manifestation. In one child the clonic seizures further evolved into generalized tonic-clonic seizures.

We identified 19 patients of the above mentioned series of 129 patients with clonic seizures who had a frontal lobe epilepsy. The seizure evolutions in these cases are shown in Figure 51.6. Only in six patients the seizures started with clonic activity. More commonly, the clonic seizures were preceded by one or two other seizure types such as auras and tonic seizures.

In conclusion, the occurrence and frequency of clonic seizures in frontal lobe epilepsy varies considerably between studies. It seems that the occurrence of clonic seizures depends on different locations of seizure onset in the frontal lobe and individually different seizure spread patterns. In our series, tonic seizures typically preceded clonic seizures and only a minority of the patients had clonic seizures as the initial seizure type.

In temporal lobe epilepsy, complex motor activity like oral automatisms was seen most frequently (10%) whereas simple motor activity like facial and brachial twitching without Jacksonian march occurred 'less commonly' (4%).[32] Another study only mentions automatisms as the ictal symptomatology of seizures in patients with temporal lobe epilepsies.[33]

In a cluster analysis of 59 patients of 'primary psychomotor epilepsy' unilateral and bilateral tonic, clonic, and versive activity was described.[34] Most commonly the face area was involved unilaterally (about 30–50% of the seizures), followed by the hand (20%) and the leg (7%). In this report tonic, clonic, and versive seizures were all lumped together.[34]

A recent study of seizures in 31 patients with temporal lobe epilepsy who underwent epilepsy surgery and were seizure free reported unilateral clonic activity in the face in eight and in the arm in three patients.[35] Bilateral clonic activity of the arms was observed in 14 patients and of the legs in one patient.[35] These findings are in agreement with the study of Abou-Khalil *et al.*[36] who observed focal clonic activity in eight of their 32 patients with unilateral temporal lobe epilepsies documented by EEG-video recordings. In three of these patients the clonic activity was concomitant with head turning to one side. However, the study did not distinguish between head turning that looks like a normal movement and the forceful 'version' frequently associated with unilateral clonic movements which is almost pathognomonic of regional contralateral epilepsy.[37] The study of Manford *et al.*[20] reported on clonic movements in 17 of 58 'temporal seizures' in 42 patients with temporal lobe lesions. Clonic movements were observed more frequently in patients with frontal lobe lesions (35 of 61 seizures of 49 patients). However, clonic movements are only suggestive of frontal lobe epilepsy when they occur early in the evolution of a seizure.[20]

We evaluated the seizure sequences in our series of 24 patients with temporal lobe epilepsies who demonstrated clonic seizures during EEG-video recordings (Figure 51.7). All 24 patients had automotor seizure preceding the clonic seizures and in no case did the clonic seizures involve primarily the leg. In three patients, automotor seizures first evolved into versive seizures and then eventually into clonic seizures. All patients had generalized tonic-clonic seizures following the clonic seizures. We recently found statistically significant differences in the seizure evolutions of mesial and neocortical temporal lobe epilepsy.[38] Abdominal auras and contralateral dystonic posturing were more frequent in patients with mesial temporal lobe epilepsy whereas early clonic seizures occurred more frequently in patients with neocortical temporal lobe epilepsy. This might reflect different cortical spread of seizure activity.[38]

In conclusion, clonic seizures are usually preceded by automotor and followed by generalized tonic-clonic seizures in temporal lobe epilepsy. Thus, the seizure sequences of clonic seizures in temporal lobe epilepsy is clearly different from the seizure sequences in frontal lobe epilepsy (Figure 51.6–7).

It is well known that tumors in the paracentral (perirolandic) region are frequently associated with epilepsy.[39] Most studies about focal epilepsy syndromes distinguish frontal and parietal lobe epilepsies. However, in a considerable number of patients the seizure anatomically involves both, the frontal and the parietal lobe. The observation that seizures arising from the frontal and parietal lobes outside the perirolandic region behave differently both, clinically and pathophysiologically to seizures arising from the perirolandic (paracentral) region has been recognized for decades and is reflected in the studies of the Montreal school.[30, 40]

About one third (34.3%) of 127 patients who had somatosensory auras had also had clonic seizures.[19] Fifty percent of the lesions of these patients were located in the contralateral central region.[19] In a series of 28 patients in whom extratemporal seizure onset had been documented by means of invasive EEG recordings, nine patients had clonic seizures and two of them had epilepsia partialis continua.[41] The seizure onset

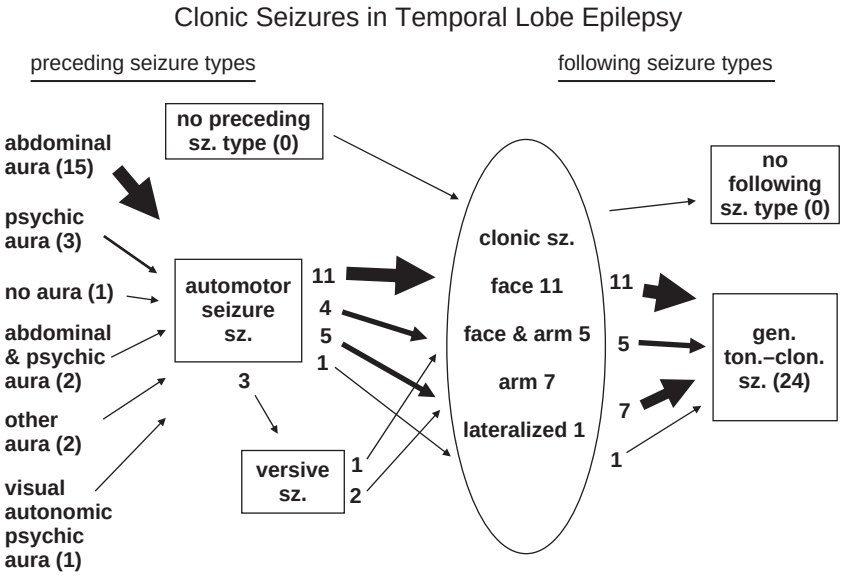

Figure 51.7. Seizure types preceding and following clonic seizures as documented by EEG-video monitoring in 24 patients with temporal lobe epilepsies. All clonic seizures of this series were preceded by other seizure types. Most commonly clonic seizures involved the face and were preceded by automotor seizures. All patients showed an evolution to generalized tonic-clonic seizures.

was perirolandic in six of these nine cases and six patients had auras preceding the clonic seizures. Of 34 patients with parietal lobe tumors who underwent surgical resection at the Montreal Neurological Institute between 1934 and 1988, 82% had focal clonic activity in the course of their seizures.[42] In a greater series of 82 patients with parietal lobe epilepsy of the same institution 57% had clonic seizures.[40] However, as mentioned above, in the MNI series parietal lobe epilepsy usually refers to the parietal lobe posterior to the postcentral sulcus and does not include the postcentral gyrus.[40] In another series, clonic seizures occurred in three of ten patients with lesions in the parietal lobe (including the postcentral gyrus).[43] One patient had 'focal motor seizures' which were preceded by a somatosensory aura of the right hand. In two patients somatosensory auras preceded the clonic seizures, in one patient clonic seizures were the initial seizure manifestation. In another study of 11 patients with parietal lesions most probably also involving the postcentral gyrus, clonic seizures were reported in 4 patients.[44] Somatosensory auras were present in 7 patients of this series.

In a recent report of 11 patients with seizures involving the supplementary sensorimotor area, all patients showed clonic movements present in one or more extremities following tonic posturing which usually lasted 10–30 seconds.[45] The clonic movements and the tonic posturing are usually bilateral, but unilateral clonic activity is an excellent lateralizing sign.[26,46] Seizures involving the supplementary sensorimotor area are typically either tonic or less frequently hypermotor seizures,[23] e.g., consisting of bizarre and violent movements predominantly of the trunk and the proximal extremities.[45,47–49]

Tonic and clonic seizures have been described in patients with occipital lobe epilepsy.[50,51] The initial seizure symptomatology most frequently includes visual auras and other signs such as eye blinking or eye deviation. Spread to the frontal lobes is usually associated with tonic and/or clonic activity. This has been reported in three of 25 patients as the only spread pattern. In another 11 patients of this series, a combination of 'frontal' and 'temporal lobe type' seizure was observed.[51] However, no data were available in this study regarding the exact seizure semiology and frequency of tonic or clonic seizures.[51] In another study of eight patients in whom occipitotemporal seizure onset was documented by invasive EEG studies, no patient had clonic seizures of the extremities.[52] One patient had jerking eye movements to the right. In the series of 42 patients with occipital lobe epilepsies of the MNI treated between 1930 and 1991, 13 patients had unilateral clonic seizures of the arm or face.[50] In ten patients versive head and/or eye deviation preceded the clonic seizures.[50] The detailed evolution of the clonic seizures is not mentioned.

Since the early reports it has been recognized that children with benign focal epilepsy of childhood frequently have clonic seizures.[53] Characteristic seizures consist of tonic, tonic-clonic, or clonic seizures involving the face area. Usually this is preceded by an unilateral somatosensory aura of the face.[54] Spreading of the clonic activity to the ipsilateral hand or arm ('Jacksonian march') occurs only infrequently. Usually the seizures occur during sleep and evolve into generalized tonic-clonic seizures. In these cases a focal seizure onset may be overlooked.

Rasmussen's encephalitis almost invariably is associated with clonic status which usually is restricted to the arm and less frequently to the face and leg of one side.[55] Clonic status usually occurs with the progression of this syndrome which typically includes hemiparesis of the affected limbs (Figure 51.8).

Generalized clonic seizures are frequently seen following generalized tonic seizures in grand mal epilepsy. This type of seizures (generalized tonic-clonic seizures) will be discussed in detail in another chapter. Isolated generalized clonic seizures are rare in adults but may, for instance, occur in patients with progressive myoclonic epilepsies.[7] These patients typically have generalized myoclonic seizures which are not as repetitive and rhythmic as clonic seizures. In newborns, generalized clonic seizures are more frequently observed but may still have a focal seizure onset in the EEG.[56] We identified two patients who had generalized clonic seizures in our series of frontal

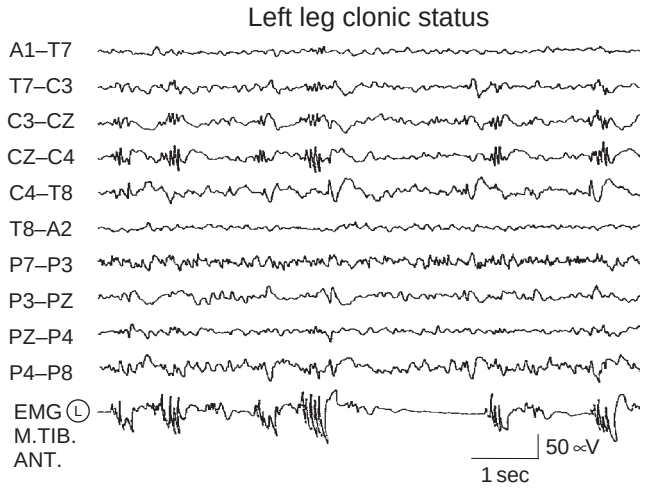

Figure 51.8. Sixty-nine-year old man with continual jerking of the left foot and leg for several weeks, without loss of consciousness. Electromyography from the left anterior tibial muscle showed that jerks occurred synchronously with each burst of polyspikes on EEG. Polyspikes were maximum at left vertex electrodes, presumably as a result of paradoxical lateralization of the discharge from the right interhemispheric region.

lobe epilepsies. Both patients had focal tonic seizures preceding the generalized clonic seizures.

Jackson's clinico-pathological observations showed that motor seizures are associated with lesions of the motor cortex.[57] Electrical stimulation of the primary motor area (Brodmann's area 4) or the premotor areas (area 6) can elicit clonic movements.[58–60] It is therefore reasonable to conclude that clonic seizures are an expression of epileptic activation of the motor cortex. Electrical stimulation of the supplementary sensorimotor area can elicit clonic movements, but this occurs only very rarely and typically not at seizure onset but later in the seizure evolution.[13,62]

The fact that the hand and face area are most commonly involved in clonic seizures is usually attributed to the large cortical representation of these parts of the body. In contrast, the rare occurrence of clonic seizures limited to the trunk reflects its small cortical representation.[17] Spread of clonic seizures may reflect the cortical representation of the body in the motor cortex. It has been speculated that the variability of the observed spread patterns may reflect interindividual variability of the cortical representation.[15] It is important to remember also that clonic seizures can only be elicited when the epileptic discharge is strong enough to produce suprathreshold activation of a given region of motor cortex. Experimental studies have shown that different regions of the motor cortex have also different thresholds to electrical stimulation.[63]

It is important to point out that high-frequency electrical stimulation (50–60 Hz) of the primary motor area in wake humans ictally causes tonic contractions, which evolve into clonic twitching of the affected muscles at a frequency of ca. 1–2 Hz.[14] The epileptic clonus consists of simultaneous contractions of agonistic and antagonistic muscles at regular intervals and is separated by periods of complete muscle relaxation. Epileptic clonic muscle contractions are generated by localized polyspike-wave activity in cortical primary motor areas. The periods of muscle relaxation occur during the EEG slow waves. The study of Hamer *et al.*[14] suggests that focal clonic seizures are focal tonic-clonic seizures. It is known that single or short series of electrical stimuli only elicit muscle responses if relatively high intensities are used.[60,64] Temporal and spatial summation of the stimuli were needed for clonus generation.[65] This principle is illustrated in the patient with the left calf clonic status shown in Figure 51.8. This explains why single spikes or slow, repetitive spikes frequently do not elicit muscle twitching, whereas polyspikes or runs of paroxysmal fast activity are usually associated with muscle responses. Most probably temporal facilitation elicited by repetitive stimulation is necessary to exceed the threshold of the motor cortex. Jerking of the left calf was always accompanied by polyspikes in the EEG (Figure 51.8), whose potential field extended from the vertex to the left central region. Conversely, individual spikes that did not correlate with jerking of the foot had a slightly different potential field extending to the right centroparietal area. The polyspikes in this case have a maximum ipsilateral to the affected leg. This is an example of paradoxical lateralization.[66–68]

The EEG of generalized clonic seizures shows generalized epileptiform discharges. There is typically a 1:1 relationship between muscle twitch and epileptic discharge, and the background activity between the discharges is generally suppressed. Generalized fast activity usually leads to tonic 'posturing seizures' and only exceptionally to clonic movements. Generalized clonic seizures are assumed to be the result of intermittent generalized epileptic activation of the motor region of the cortex (Brodman areas 4 and 6). We have also observed cases in which epileptic seizures originating in the supplementary sensorimotor area led to bilateral clonic movements of the upper extremities without any clouding of consciousness. In these cases no generalized spike-and-wave discharges occurred. It is quite probable that the generalized clonic seizures in these cases are caused by restricted activation of one or both of the supplementary sensorimotor areas.

Tonic seizures

Tonic seizures consist of a sustained contraction of one or more muscle groups usually lasting at least 3 sec leading to posturing of the limbs or whole body.[3,23,69] Tonic seizures in patients with focal epilepsy preferentially affect proximal muscle groups on both sides of the body. However, they predominate most often in the contralateral body, leading to an asymmetric posture.[70] In most patients with focal epilepsy, consciousness is unclouded, at least at the onset of such unilateral or asymmetric seizures.[25,71,72] If clearly unilateral, tonic seizures have a high lateralizing significance, pointing to a contralateral seizure onset. Ictal EEG in frontal epilepsies shows a low-amplitude high-frequency pattern ('recruitment pattern') (Figure 51.9). Consciousness is disturbed from the beginning of generalized tonic seizures, which are common in patients with Lennox-Gastaut syndrome.[6] Generalized tonic seizures usually last from 3–10 sec. The ictal EEG of generalized tonic seizures in patients with Lennox-Gastaut syndrome is similar to the ictal EEG in frontal lobe epilepsies showing a diffuse low-amplitude high-frequency recruiment pattern (Figure 51.9). Tonic seizures in focal epilepsies are more commonly bilateral (76%) than unilateral (24%).[73] The majority of bilateral tonic seizures involve the whole body (both arms

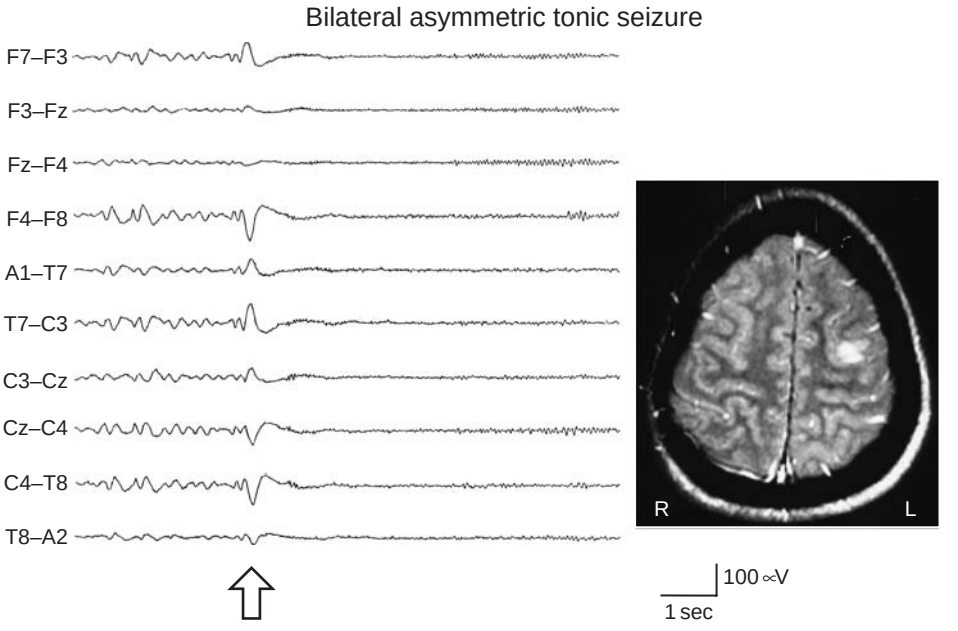

Figure 51.9. This transverse bipolar EEG montage of a 17-year old female with a low grade glioma in the medium frontal gyrus shows a typical EEG seizure pattern during a bilateral asymmetrical tonic seizure. After a high amplitude midline sharp wave the EEG shows low amplitude high frequency activity with a midline frontocentral maximum (recruitment pattern). The arrow marks the clinical seizure onset.

and legs and trunk).[73] Unilateral tonic seizures affected most commonly one arm (56%) or one side of the body (20%).[73]

Tonic seizures occur most commonly in frontal lobe epilepsy (62.2%) and very rarely in temporal lobe epilepsy (1.7%). In the latter only unilateral tonic seizures occurred, whereas 32% of the tonic seizures in frontal lobe epilepsies were bilateral.[73]

Focal tonic seizures most probably originate in the cortical motor areas, i.e., the primary motor and the supplementary sensorimotor areas. However, the reticular formation of the brain stem and the thalamus were reported to be involved in the generation of tonic seizures in patients with Lennox-Gastaut syndrome.[74]

Phonatory seizures could be considered tonic seizures of the phonatory muscle system. They result from activation by the ictal discharge of the primary motor cortex or the SMA.[75] Phonatory movements have been elicited on stimulation of the SMA or the primary motor cortex below the tongue or lip area. Vocalization in SMA seizures is more often sustained than interrupted, whereas seizures involving the primary motor area tend to produce interrupted sounds.

Paroxysmal dystonia resulting from subcortical pathology such as brainstem dysfunction or multiple sclerosis has to be considered in the differentialdiagnosis of focal tonic seizures.

Epileptic spasms

Epileptic spasms typically occur between 3–12 months of age. They are a frequent seizure type in children with West syndrome and in this context have also been called 'infantile spasms'.[76] Epileptic spasms consist of relatively symmetric tonic and myoclonic features, which may vary in the same patient from one seizure to another. The muscle contractions predominantly affect the proximal and axial muscles and typically lead to flexion of the neck (and legs) and abduction of both arms. Less frequently myoclonic or tonic extension may lead to an opisthotonic posture. Epileptic spasms usually last 2–10 seconds and frequently occur in clusters. Short myoclonic contractions may mix with tonic contractions in one cluster. The ictal EEG of patients with West syndrome during epileptic spasms typically shows an attenuation of the background activity and depending on the resolution of the EEG system a low-amplitude high-frequency pattern (Figure 51.10).

This seizure type is age specific and also occurs in focal epilepsies with different epileptogenic zones. Well established examples have been published like for instance an 11-month-old with epileptic spasms secondary to a right temporal hamartoma which was seizure free postoperatively.[23] Consequently,

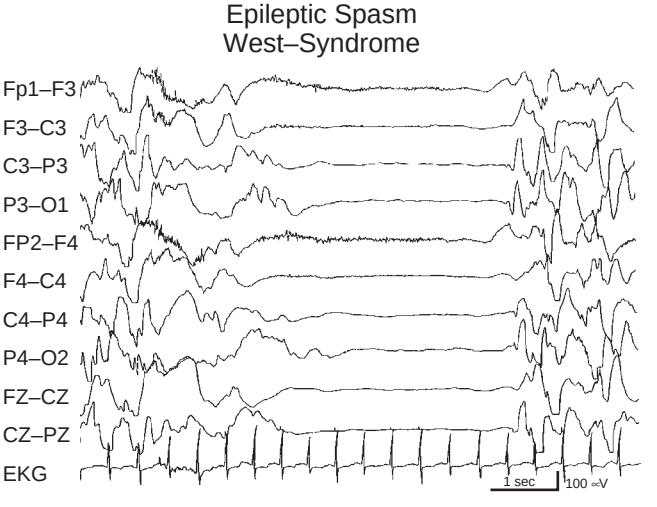

Figure 51.10. The epileptic spasm of this 8-month-old child with West syndrome is electroencephalographically associated with a diffuse attenuation of the hypsarrhythmia during the seizure.

epileptic spasms do not allow localization. Children with epileptic spasms typically develop other seizure types after the age of 3–5 years[77] as in the above-mentioned case, in whom at the age of 2 1/2 years mild automatisms occurred.[23]

Versive seizures

Versive seizures consist of a sustained, unnatural turning of the eyes and head to one side.[37] The version usually consists of a smooth, tonic lateral deviation of the eyes with, not infrequently, a clonic superimposed component. Often the angle of the mouth is also deviated to the same side and the neck is extended. These seizures are the expression of epileptic activation of the frontal eye field (inferior/medial frontal gyrus) that is contralateral to the side to which the eyes turn.[60,78] Epileptic activation from the temporal lobe or other structures distant from the frontal eye fields may spread into the frontal eye field, giving rise to versive seizures.[37] In temporal lobe epilepsy, version occurs when the patient has already lost consciousness and the version is frequently preceded by oral and maunal automatisms (automotor seizure). A study of patients with extratemporal and temporal epilepsies showed that version occurred earlier than 18 seconds in seizures with an extratemporal onset and later than 18 seconds in the vast majority of temporal lobe epilepsies,[79] which reflects faster spread to the frontal eye fields from extratemporal particularly frontal lobe regions than from the temporal lobes. Patients may be unconscious (n=16) or conscious (n=7) depending from which region of the cortex the seizures originated in 222 patients considered for epilepsy surgery at the Montreal Neurological Institute.[80]

The early 1980s witnessed a controversy surrounding the lateralizing value of versive seizures in temporal epilepsy.[81,82] Then Wyllie *et al.* defined version as a forced, sustained, and unnatural movement. On the basis of this definition, versive seizures have a high lateralizing significance to seizure onset in the contralateral hemisphere, particularly when they occur immediately before a generalized tonic-clonic seizure.[46] The mechanisms involved in the contralateral head version is not well understood considering that for a version of the head to the contralateral side the ipsilateral sternocleidomastoid muscle needs to be activated.[83] Quantitative movement analysis was able to demonstrate that in temporal lobe epilepsy there is a initial ipsilateral head turning followed by a contralateral head version which last longer and occurs prior to secondary generalization.[78]

Tonic-clonic seizures

Tonic-clonic seizures are characterized by a typical sequence of a generalized tonic contraction followed by clonic contractions. Grand mal (= 'the great evil') is a synonym for generalized

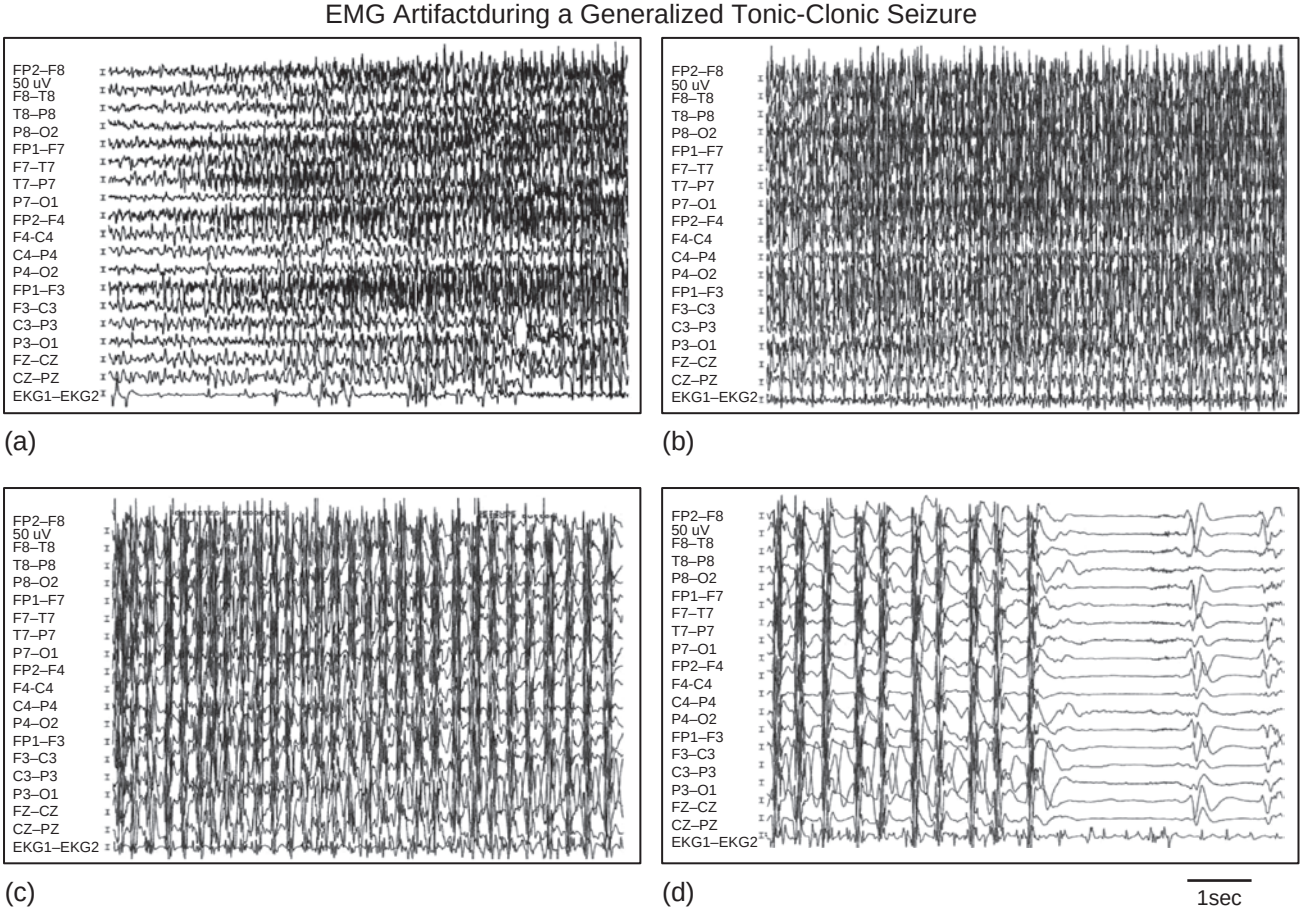

Figure 51.11. Typical EMG artifact illustrating the course of a generalized tonic-clonic seizure. Initially the tonic activity increases in amplitude (a–b) followed by gradually increasing clonic activity with periods of reduced EMG artifact (c–d). The duration of the pauses inbetween the clonic activity increases towards the end of the clonic activity. This EMG artifact is very typical for generalized tonic-clonic seizures and may even help to distinguish them from non-epileptic pseudoseizures.

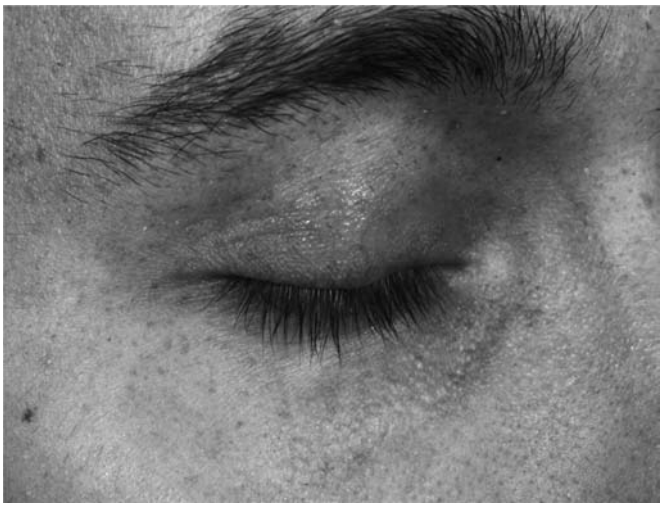

Figure 51.12. The increased intrathoracal pressure during the tonic phase may lead to subcutan petechial bleeding, which can be seen in the periorbital region of this 16-year-old male. He had his first generalized tonic-clonic seizure the day before. This phenomenon is typical for generalized tonic-clonic seizures.

tonic-clonic seizure, which is the only seizure type in grand mal epilepsies (Epilepsy with grand mal [generalized tonic-clonic] seizures on awakening) (Commission on Classification and Terminology of the International League Against Epilepsy.[84] The seizures have a typical evolution, initially occurring with tonic posturing, adduction with extension of all four extremities, and flexion of the wrist and fingers. This phase lasts for approximately 5 (to 12) seconds and then evolves into a 'tremor-like' twitching.[85] The ictal EEG shows a typical EMG artifact (Figure 51.11). The repetition rate of the twitches gradually becomes slower and the amplitude increases, giving rise to the clonic phase (Figure 51.12). The clonic phase consists predominantly of flexion myoclonic jerks of the elbow, hip, and knee. The duration of the tonic-clonic seizures varies between 1–2 minutes.[85]

Consciousness is always disturbed with the beginning of the tonic phase. Generalized tonic-clonic seizures are followed by a prolonged postictal coma and confusion. During the tonic phase increased intrathoracal pressure may lead to petechial subcutan bleeding in the periorbital region (Figure 51.12).

Generalized tonic-clonic seizures may occur in generalized and focal epilepsy syndromes. Occasionally other generalized seizure types may evolve into generalized tonic-clonic seizures (i.e., generalized myoclonic seizure → generalized tonic-clonic seizure or dialeptic seizure → generalized tonic-clonic seizure). The evolution of generalized myoclonic seizures into generalized tonic-clonic seizures is typical for juvenile myoclonic epilepsy. In focal epilepsies, generalized tonic-clonic seizures usually constitute the end of a seizure evolution. The focal seizure types preceding a generalized tonic-clonic seizure depend on the cortical region, which gives rise to the seizure.

Secondarily generalized tonic-clonic seizures may infrequently evolve into a short (2–10 sec) focal motor seizure that may be generated by persisting epileptiform discharges in the hemisphere of origin or may involve the contralateral hemsiphere (paradoxical version).[86,87] The clonic phase of generalized tonic-clonic seizures may end asymmetrically, showing clonic jerks persisting in the limbs ipislateral to the hemisphere of seizure onset.[85] It is speculated that this seizure evolution reflects earlier seizure cessation in the hemisphere of seizure onset, whereas the contralateral hemisphere still continues to seize. Patients with juvenile myoclonic epilepsy may have generalized myoclonic seizure preceding the generalized tonic-clonic seizures, particularly after sleep deprivation. Clinical experience shows that there are some patients with clonic-tonic-clonic seizures but there are only anecdotal reports on this observation.[7]

The pathophysiological considerations on the origin of generalized tonic-clonic seizures are the same as discussed above for generalized tonic and generalized clonic seizures.

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52 Complex motor seizures: localizing and lateralizing value

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Introduction

Clinical signs and symptoms expressed during epileptic seizures are thought to be generated by widespread neuronal matrices, linked together by anatomic connections, and further strengthened through repeated use.[1–4] Although presenting great interindividual variability such neural networks share similarities among different patients, permitting the expression of stereotyped ictal behaviors that might indicate the underlying neural substrates. When motor networks are activated during seizures, patients may exhibit motor behaviors that can be classified as simple motor seizures (reproducible by direct stimulation of the primary motor cortex) or complex motor seizures.[5,6] Classifying seizures according to semiological ictal findings, and particularly according to motor behavior is especially useful during presurgical video-EEG evaluations. This semiological-oriented classification was first proposed by Lüders and colleagues as an alternative classification to that of ILAE.[5,6] Semiologic Seizure Classification (SSC) might provide a more comprehensive picture of epileptic seizures, notably in patients with focal epilepsy, being very useful for both, everyday clinical practice and more specialized evaluations in epilepsy centers.[7–9] The relevance of this semiological-based approach is well demonstrated by Chee and colleagues[10] who reported that the epileptogenic region can be correctly lateralized by semiological analysis in 78% of patients, with positive predictive value of 94%, and very good interobserver reliability. When combined with video-EEG analysis, semiological findings might allow lateralization and/or localization of epileptogenic and symptomatogenic zone in most patients.[11–13]

According to the SSC complex motor seizures encompass three main seizure types: (1) automotor seizures; (2) hipermotor seizures; and (3) gelastic seizures. Automotor and hypermotor seizures are more frequently associated to temporal or frontal lobe epilepsies, respectively,[5] while gelastic seizures are usually related to hypothalamic hamartoma.[5,14] Complex motor behaviors may also be observed in the late course of posterior cortex seizures, once these might propagate to more anterior regions.[15–18]

The reader must observe four important points regarding this classification. First, the complex motor behaviors observed during seizures are usually similar to complex movements executed during common life diary activities (e.g., coughing, swallowing, lip smacking, clapping hands, among many others), or alternatively, can resemble motor behaviors observed in movement disorders (e.g., limb dystonic posturing), suggesting they share common functional anatomic substrates.[5] Second, the ictal motor behavior can be qualified as ipsi- or contralateral, according to the lateralization of the epileptogenic zone. Third, distinct from ILAE's classification,[19] in the SSC the term 'complex' refers to the complexity of the movement, and not to the patients' state of consciousness.[5] Forth, classifying seizures according to ictal motor behavior is a purely semiological concept, and therefore, based exclusively on clinical manifestations observed during seizures.[5] When these ictal signs and symptoms are sequentially considered, they may additionally indicate specific propagation patterns and reflect the anatomical sites involved during seizure propagation, the sequences of these involvements, and some mechanisms of ictal spreading. The assessment of symptomatogenic motor regions and networks through ictal semiology is of paramount importance for the process of epileptogenic and symptomatogenic zone localization. In addition, ictal semiology might also hold postsurgical prognostic significance.

In this chapter we will address the complex motor seizures, mainly emphasizing motor components and localizing and/or lateralizing features. Periictal complex motor phenomena, when common, stereotyped, and consistently associated with complex motor seizures will also be described, since they might also carry valuable localizing and lateralizing information. In addition, we will briefly review the existing evidences on the mechanisms and anatomic areas possibly involved in the production of complex motor seizures and associated common behaviors. Table 52.1 summarizes existing data on complex motor seizures. Preliminarily, however, a brief consideration about auras will be presented, once auras antecede complex motor behaviors in most patients.

Auras

Auras are reported by most patients with automotor or hypermotor seizures. Automotor seizures are more frequently associated to temporal lobe epilepsy, and by far epigastric aura with raising sensation is the most common type of aura anteceding these seizures. Epigastric aura might also occur in association with frontal lobe epilepsy, although much less frequently.[20–26] Also common in automotor seizures are auras of fear, anxiety, or other related symptoms.[20,24–26] Other types of auras common to automotor seizures but less frequently

Table 52.1 Selected motor behaviors observed in association with complex motor seizures

Motor characteristics findings	Frequency	Lateralizing value	Epileptogenic zone	Simptomatogenic zone	Observation
Limb automatisms	Most patients.	Usually ipsilateral in MTLE, contralateral in NTLE, and nonlateralizing in frontal lobe seizures.	Highly suggestive of MTLE when associated with contralateral dystonic posturing.	Variable. Frontal or temporal activation. May correspond to releasing phenomena.	When automotor and associated with preserved responsiveness suggest nondominant temporal lobe (6% of TLE).
Oral automatism	Very common.	Nonlateralizing.	Suggests temporal lobe. May be observed in seizures originating in frontal lobe.	Limbic system.	Positive ictal activation or releasing phenomena.
Genital and sexual automatisms	10% of patients with FLE or TLE.	Poor. Lateralizatory value on depending other signs.	Frontal or temporal.	Unknown.	In hypermotor seizures, suggest frontal lobe. In automotor seizures, suggest temporal lobe.
Unilateral dystonic limb posturing	15–70% of patients with TLE or FLE.	Contralateral in more than 90% of patients.	Temporal or frontal.	Temporal, frontal, parietal and basal ganglia (Putamen).	When associated with unilateral automatisms suggests mesial temporal epilepsy.
Unilateral tonic posturing	50% of FLE patients. 15–20% of TLE patients.	Contralateral in 40–90% of patients.	Temporal or frontal.	Supplementary motor area, basal ganglia, other frontal areas cannot be excluded.	May be differentiated from dystonic posturing by absence of rotational components.
Unilateral immobile limb	5–28% of patients with TLE.	Contralateral in most patients with automotor seizures.	Temporal.	Contralateral frontal lobe.	Probably a negative motor phenomenon.
Postictal palsy	Less than 1% of patients.	Contralateral in all patients.	Frontal or temporal.	Possible exhaustion or inhibition of Brodmann area 4 and 6.	Should be differentiated from ictal unilateral immobile limb.
Pelvic thrusting	24% of FLE patients. 6% of TLE patients.	None.	Usually frontal, may be temporal.	Unknown.	May be observed in pseudoseizures (17% of patients).
Non-versive head turning	75% of TLE patients. 50% of FLE patients.	Usually ipsilateral (see text for details).	Not determined. Basal ganglia (striatum) might be involved.	Unknown.	Lateralizatory value is controversial.
Head version	35% of TLE patients. 20–60% of FLE patients.	Contralateral in more than 90% of patients.	Frontal or temporal.	Broadmann's area 6 and 8.	Associated with conjugate eye versions to the same side and preceding (10 seconds or less) secondary generalizations.
Head and eye ipsiversion at the end of generalized seizure	15–20% of secondary generalized seizures.	Ipsilateral if initial head version vanish during generalization.	Frontal or temporal.	Cotralateral Boardman's area 6 and 8.	If initial head version is maintained during seizure, late head version still contralateral to epileptogenic zone.
Unilateral eye blinking	0.8–1.5% of patients.	Ipsialateral in 80% of patients.	Mostly temporal in automotor seizures.	Not determined.	Involvement of inferior post-central area has been suggested.

Continued

Table 52.1 cont'd

Motor characteristics findings	Frequency	Lateralizing value	Epileptogenic zone	Simptomatogenic zone	Observation
Nosewiping	50–85% of MTLE patients. 10–33% of extratempor al patients.	Ipsilateral to temporal lobe epileptogenic zone in 70–90%. Nonlateralizing in frontal lobe seizures.	Suggest mesial temporal epileptogenic zone. Might be extratemporal.	Unknow. Might reflect olfactory hallucinations, nasal secretion or abnormal amygdalar network functioning.	May reflect contralateral postictal movement abnormalities or neglect.
Ictal vomiting	2% of TLE patients.	Suggests nondominant epileptogenic zone.	Suggests nondominant temporal lobe.	Activation of limbic structures, insula, and mesial frontal regions.	Unknown mechanisms.
Ictal spitting	Less then 1% of patients.	Suggests nondominant epileptogenic zone.	Suggests nondominant temporal lobe or hemisphere.	Cortical activation or releasing phenomena of unknown networks.	It is not due to bad mouth sensation, excessive salivation, or drooling.
Ictal urinary urge	2.5% of TLE patients. are in other Epilepsies.	Suggests nondominat epileptogenic zone.	Suggests nondominant temporal lobe.	Insular cortex, mesial frontal region, medial temporal gyrus, and operculum.	Suggests activation of specific nondominant hemispheric bladder control centers.
Periictal water drinking	15% of TLE patients.	Suggest nondominant epileptogenic zone.	Suggests nondominant temporal lobe.	Amigdala, hippocampus, and parahippocampal gyrus. Hypothalamus?	Unknow. Propagation of ictal activity to hypothalamus has been suggested.
Periictal cough	9–40% of patients.	Nonlateralizing.	Suggests temporal lobe.	Unknown. Might be due to activation of central autonomic pathway.	Multiple mechanisms. Increased respiratory secretion might have a role.
Unilateral ear-plugging	Rare.	Suggests contralateral epileptogeni c zone.	Suggests neocortical temporal cortex.	Auditory cortex, on superior temporal gyrus.	Probably a stereotyped response to annoying auditory phenomena.
Complex hypermotor ictal behaviors	More then 50% of FLE patients. 2–3% of TLE patients.	Nonlateralizing.	Highly suggestive of frontal lobe. Might be observed in seizures from other regions due to ictal propagation.	Frontal lobe.	There is no consensus on the specific localization of epileptogenic or symptomatogenic zones in frontal lobes.
Gelastic seizures	Rare	Nonlateralizing.	Highly suggesive of hypothalamic hamartomas. Other lesions also possible, mostly frontal or temporal.	Anterior cingulated regions inolved in motor aspects of laughter. Temporal lobes involved in mirth.	Mirth is only possible with conscience preservation during at least part of the seizure.

Observations: Data regarding adult patients. Motor symptoms might be observed in posterior cortex epilepsy due to seizure propagation. The general predominance of central autonomic networks in nondominant or right hemisphere might account for nondominant (right) periictal-related behaviors. Frequencies are taken from reports on different series of video-EEG monitoring. For references, consult text. Ipsilateral or contralateral refers to the epileptogenic zone.
Legends: FLE = frontal lobe epilepsy; **TLE** = temporal lobe epilepsy, **MTLE** = mesial temporal lobe epilepsy; **NTLE** = neocortical temporal lobe epilepsy. **ETLE** = extra-temporal lobe epilepsy.

observed are *déjà vu, jamais vu*, olfactory auras, feelings of depersonalization.[20,24] Some auras preceding automotor seizures are difficult to be characterized by patients and neurologists because they consist of complex subjective symptoms exclusively felt during seizures, and not usually experienced in other contexts. It is not uncommon that patients with automotor seizures and mesial temporal lobe epilepsy have history of auras in the past that no longer exist. This should be specifically asked to patients, once past or present history of auras is an important aspect of automotor seizures.

Depending on the series, 15–69% of patients have auras preceding complex motor seizures of frontal lobe origin, a region more often associated with hypermotor seizures. [21,23,27–29] These auras consist of feelings of tightness or tingling of certain body parts, auras of whole body sensation, cephalic sensation, and other nonspecific feelings.[21,23,27–31] Palpitations, fear, anxiety, and even panic have also been reported, although much less frequently.[21,23,27–29,32,33] When comparing seizures of temporal lobe origin with those emanating from frontal lobes, psychic, gustatory, olfactory, fear, auditory, visual, or experiential auras suggest temporal lobe seizure onset and therefore are more frequently associated with automotor seizures.[24] A nonspecific general body sensation is much more suggestive of frontal lobe epilepsy, frequently preceding hypermotor seizures.[23,33] Cephalic sensations or other vague complaints are nonspecific and might occur in both, automotor and hypermotor seizures. Because auras are among the first clinical seizure symptoms, they might reflect initial and more circumscribe regional alterations, having diagnostic and prognostic significances.[31,34] For these reasons, detailed evaluation of auras should not be forgotten during complex motor seizures evaluations. The reader should review the chapter about auras for a more detailed discussion.

Automotor seizures

Automotor seizures (SSC) or complex partial seizures (ILAE's classification) are by far the commonest type of complex motor seizures observed in video-EEG units. Automotor seizures are more commonly observed in association with temporal lobe epilepsy. These seizures are usually preceded by auras and their most remarkable characteristics are the impairment of consciousness and the presence of automatisms (e.g., oral automatisms, and limb automatism) and/or stereotyped motor behaviors (e.g., dystonic posturing), involving mainly hands, mouth, or tongue.[5] The lateralizing and localizing semiological findings in automotor seizures are rich, especially when observed in association with temporal lobe epilepsy, where the number of clinical symptoms per seizures and duration of the seizures are usually higher than in other complex motor seizures.[23] Consciousness is affected, but can be preserved in variable degrees, especially when seizures originate and remain restricted to the nondominant hemisphere.[10,12,35–37] In the following sections we will review in detail these automatisms and most common associated periictal motor behaviors. A short discussion about mechanisms of all these ictal or periictal motor behaviors is also presented.

Automatisms

Oral or alimentary automatisms and automatisms of limbs usually more exuberant in the upper limbs are commonly observed in automotor seizures. These automatisms are significantly more observed in temporal lobe epilepsy but can be also seen in extratemporal seizures.[16,23,33,38,39] Typical automatisms observed in automotor seizures can be discrete, consisting of repetitive and stereotyped involuntary actions as is the case of oral automatisms,[10,40,41] or more complex, characterized by involuntary, learned and semipurposeful complex motor acts, like fumbling, picking, or gesticulating movements.[24,40,42–45] By comparing automatisms between patients with 'pure culture' of temporal and frontal lobe epilepsies, Kotagal and colleagues[23] observed that alimentary automatisms, repetitive upper limb automatisms, perseverative automatisms, looking around and complex gestures were much more commonly seen in temporal lobe epilepsy, while hypermotor seizures were much more frequent in frontal lobe epilepsy. Indeed, although in surgical series of frontal lobe epilepsies up to 77% of patients might present some type of automatism during seizures, they are usually hyperkinetic and qualitatively distinct from automotor automatisms. These aspects will be discussed further in hypermotor seizures.[21,23]

Automatisms in automotor seizures may be interpreted as release phenomenon and/or the result of activation or disruptions caused by seizure propagation to limbic system, subcortical structures, and/or other cortical regions.[40,45–47] In the following sections we will better characterize the most common types of automatisms associated with automotor seizures, namely, oral and gestural automatisms, and discuss their underlying mechanisms.

Oral automatisms

Automatisms involving the oral region including masticator movements, swallowing, lip smacking, kissing or other tongue movements are classically observed in automotor seizures from temporal lobe origin.[33,40,48] However, they can also occur in extratemporal seizures, especially when ictal discharges spread and secondarily involve the temporal lobes.[16,18,21,38,39,49,50] When occurring in frontal lobe epilepsy, these automatisms are more common in association with orbito-frontal seizures.[21] Precise mechanisms of oral automatisms are still poorly elucidated. They may represent release phenomenon or positive activation of the limbic system.[40] Electrical stimulation of limbic structures, and particularly of amygdala, can induce oral automatisms, but only when associated to clinical seizures or widespread afterdischarges.[2] In line with this observation, Maillard and colleagues[45] observed that oral automatisms occur relatively early during seizures initiated in medial-lateral temporal structures, but only late in medial temporal seizures, suggesting that oral automatisms require widespread dysfunction of medial and neocortical temporal lobe structures for their expression.[45,51]

Gestural automatisms

Gestural automatisms observed in automotor seizures are far more prominent in upper limbs and face. Lower limb automatisms although less frequent and more discrete share similar mechanisms and significances.[52] In unilateral temporal lobe automotor seizures, while the contralateral limb is usually tonic, dystonic, or immobile, the ipsilateral limb may present

several different patterns of gestural automatisms.[10,40,41,53–57] Depending on the series, limb automatisms are reported in more than 80% of temporal lobe epilepsy patients,[10,57,58] being exclusively unilateral in more than 50% of the patients.[58] Gestural automatisms are usually observed after the initial instants of the seizure, which seems to be the time necessary for the ictal spread to limbic-neocortical structures.[45] During video-EEG it is useful to observe that limb automatisms are predominantly ipsilateral to the epileptogenic zone in patients with mesial temporal lobe epilepsy, but contralateral in patients with neocortical temporal lobe epilepsy.[57,59] In mesial temporal lobe epilepsy, automatisms occur just before or simultaneously to dystonic posturing. This pattern suggests that ictal activity spreads from mesial temporal lobe structures sequentially to medial frontal cortex and then to striatopallidal complex, or that it spreads to medial frontal cortex and basal ganglia simultaneously.[57] Unilateral ictal automatisms associated with contralateral dystonic posturing are highly suggestive of mesial temporal lobe epilepsy.[58,60] However, the lateralizing value of unilateral automatisms not associated with dystonic posture has limited lateralizing value.[58] When occurring isolated and left-sided, they might indicate ipsilateral epileptogenic zone. When observed right-sided, without contralateral dystonia, they have no lateralizing value.[58] It is interesting to note that unilateral automatisms in automotor seizures of mesial temporal lobe origin might correspond in fact to bilateral automatisms, being the automatisms contralateral to the epileptogenic zone overridden by dystonic or tonic posture, or by ictal paresis.[58,60] With very rare exceptions, automatisms observed in automotor seizures with preserved responsiveness are characteristic of epileptogenic zone in the nondominant temporal lobe.[35–37,61] Gestural automatisms have complex mechanisms, most of them not elucidated yet. By stimulating the anterior gyrus cinguli and mesiotemporal structures, oral and hand automatisms can be evoked,[62–64] thus suggesting that these automatisms can be caused by ictal spreading activity. However, other authors have suggested also that at least some automatisms may correspond to releasing phenomenon, not being caused by direct ictal activation.[35,58,65]

Genital and sexual automatisms

Genital automatisms are defined as repeated ictal fondling, grabbing, scratching or other genital manipulations. They must be differentiated from other genital or seizure manifestations, like sexual or orgasmic auras, genital sensory phenomena, or hypermotor sexual automatisms.[66–70] Genital and sexual automatisms are observed in about 10% of the patients referred for epilepsy surgery.[71] While orgasmic auras originate from the nondominant temporal lobe,[70,72,73] genital and sexual automatisms are essentially nonlateralizing, and may be seen in seizures originating from frontal as well as temporal lobes.[69,71,72,74–76] According to Leutmezer and colleagues,[76] the term 'sexual' refers to symptoms or signs with erotic components while the term 'genital' refers to symptoms or signs involving the genitalia but without erotic components. The quality of genital or sexual automatisms might indicate the lobe of seizure origin. Aggressive sexual pelvic or truncal movements are usually automatisms appearing in the context of hypermotor seizures associated with frontal lobe epilepsy,[71,75,76] while subtle genital automatisms like fondling or grabbing the genitals are more commonly observed in temporal lobe seizures.[69,71,76] The latter occur more frequently in men and may localize the seizure onset to the ipsilateral temporal lobe only when associated to unilateral hand automatisms (70% of patients), or to the nondominant temporal lobe when associated with periictal urinary urge (in 22% of patients).[69]

Pelvic thrusting is a complex motor behavior that needs some consideration because it might be observed in a moderate number of patients, with different meanings. Geyer and colleagues reported that pelvic thrusting is more commonly observed in frontal lobe seizures (24% of the patients) or in pseudoseizures (17% of the patients),[77] but it can be also observed in temporal lobe seizures, in a smaller percentage of cases (6% of the patients). It does not have any lateralizing value.[77]

The mechanisms underlying sexual and genital automatisms are also not well understood. A transitory Klüver and Bucy syndrome-like phenomenon caused by bi-temporal lobe dysfunction, a nonspecific behavioral pattern, or even a specific behavior related to limbic activation, or a reaction to other internal stimuli were all hypothesized mechanisms, but so far not corroborated by electro-clinical supportive data.[69,78]

Stereotyped ictal or periictal motor behaviors

Prominent stereotyped motor behaviors are integrant components of complex motor seizures, mainly automotor seizures. The assessment of their semiological characteristics is of diagnostic importance since they frequently carry useful and reliable information for the localization of the epileptogenic zone. The main clinical features of the most common types of ictal stereotyped motor behaviors are described in the following sections.

Dystonic limb posturing

Dystonic limb posturing consists of a sustained limb posturing similar to that observed in movement disorders, very often occurring in the course of automotor seizures. Unilateral or predominantly unilateral dystonic posturing of the upper limb is perhaps the most reliable lateralizing sign in temporal lobe automotor seizures.[10,54,55,57,79–84] Although less frequently it can also occur in frontal lobe epilepsy, where it might be observed latter in the course of the seizures. Depending on the series and on the clinical criteria of inclusion, dystonic posturing can be observed in 15–70% of the patients.[10,40,55,57,81,82,84–86] When present, unilateral dystonic posturing is usually observed several seconds after seizure onset, suggesting that seizure propagation is necessary for producing it.[87] Dystonic posturing occurs contralateral to the epileptogenic zone in more than 90% of the patients with temporal or extratemporal seizures.[54,82,84,88] Contralateral dystonic posturing associated with head turning and automatisms ipsilateral to the epileptogenic zone are findings highly suggestive of mesial temporal lobe epilepsy.[55,57,79,81,89] Rusu and colleagues also associated dystonic posturing with hypersalivation, somatomotor manifestations, secondary generalization, profound clouding of conscience, and prolongued postictal confusion to mesial temporal lobe epilepsy.[84] Dystonic posturing may occur in different degrees of complexity and duration, and has been correlated with different seizure patterns of propagation to temporal, frontal, and parietal lobes.[84,87,90,91] However, most

authors agree that direct or indirect basal ganglia activation,[87,90,91] and more specifically, the putamen seems to be necessary for ictal dystonic posturing.[87,92,93] PET and SPECT findings are in line with these evidences,[94] and additionally revealed alterations in insula, inferior and superior frontal gyri, cingulated gyri, as well as in parietal areas.[84,94] Taken together, these findings suggest that dystonic posturing results from widespread subcortical and cortical involvement of different neural networks. This observation agrees with those suggesting that dystonic posturing might be a negative predictor for good surgical outcome in mesial temporal lobe epilepsy,[84,95] once broad spread of ictal activity has been previously reported to be accompanied by worse post-surgical outcome.[96]

Unilateral tonic posturing

Contralateral tonic limb posturing, although less frequent and less specific, is also considered an important lateralizing sign in temporal lobe automotor seizures. It is observed in about 17% of temporal lobe epilepsy patients, being contralateral to the epileptogenic zone in 40 to 86% of them.[54,82] Unilateral tonic limb posturing may be also observed in up to 15% of extratemporal seizures,[54] being contralateral to the seizure focus in 67–89% of these patients.[54,85] Tonic posturing has been differentiated from dystonic posturing by the absence of rotational or torsion components. However, it can be observed co-occurring with dystonic posturing and it has been considered as a muted expression of more classical dystonic posturing by some authors.[54,84] Unilateral tonic posturing are most likely due to the activation of the supplementary motor area (SMA), although basal ganglia, cingulate gyrus, and primary motor area cannot be ruled out in the generation of tonic posturing.[65,97]

Unilateral immobile limb

Unilateral immobile limb or unilateral ictal akinesia was initially described as 'ictal paresis' or 'ictal paralysis' and can be defined as a sudden loss of tone in one upper limb while the opposite side expresses automatisms. It is often observed during temporal lobe seizures, being considered as highly specific for lateralizing the epileptogenic zone.[54] Ictal immobile limb is reported in about 5–28% of the patients, being contralateral to the epileptic focus in virtually all patients.[54,98,99] It is frequently associated to ipsilateral limb automatisms, usually occurring immediately after the initial symptoms.[99] In some seizures it occurs after patients had already initiated bilateral automatisms, while in others it may appear concomitantly with the onset of the ipsilateral automatisms. In about 70% of the seizures, unilateral immobile limb may precede typical ictal dystonia. In the other 30%, it may be followed by more complex automatisms, other signs of frontal lobe involvement, or secondary generalization. Authors have excluded tonic posturing as cause of upper limb immobility, despite the fact that muscle tonus had been tested in only few patients.[98] Ictal paresis should be differentiated from postictal paresis or Todd's palsy, a transient focal motor deficit that might occur after a seizure in 0.5–13.4% of the patients, depending on the series.[100,101] It lasts about 3 minutes, ranging from 11 seconds to 22 minutes, usually being unilateral and contralateral to the seizure focus.[101] Bilateral postictal paresis has also been described.[101,102] Postictal limb paresis might be associated with ictal unilateral clonic activity (55.6% of seizures), dystonic posturing (47.9% of seizures), and ictal limb paresis (24.6% of seizures).[100] The mechanisms underlying ictal unilateral immobile limb are not completely elucidated, corresponding probably to a negative motor sign. Ictal invasive recordings performed in few patients suggested epileptic activation of the contralateral premotor cortex, prefrontal cortex, anterior cingulate gyrus and orbitofrontal cortex as the neural substrates involved in this motor behavior.[99] Congruent with these findings, negative motor responses can be elicited by stimulation of mesial and lateral frontal lobe regions.[103–105]

Eyes motor behaviors

Conjugated and sustained tonic versive eye movement occurring shortly before generalization is the most reliable ocular sign for seizure lateralization. It usually occurs associated to head version. Both, head and eyes version, frequently appear contralaterally to the epileptogenic zone,[106,106,107] due to seizure propagation to Broadman's area 8. Although they are simple motor phenomena, they were included here because head and eyes version may be observed in the context of complex motor seizures. Unilateral eye blinking is rare and may be observed in about 0.8 to 1.5% of seizures from patients referred to video-EEG, being ipsilateral to the epileptogenic area in about 80% of the patients.[65,108,109] The mechanisms underlying ipsilateral ictal eye blinking are still unclear.

Nistagmus is another eye motor sign, observed in less then 1% of patients during video-EEG and reviewed here because it is a motor sign with lateralizing properties. Nistagmus is usually observed in association with posterior cortex epilepsy, the fast phase being contralateral to the epileptogenic zone in all well-documented cases.[110–117] Mechanisms of ictal nistagmus are complex and still not elucidated. Intermitent, but periodic activation of cortical saccade areas by ictal activity, activation of slow ipsiversive smooth pursuit region, or even activation of cortical optokinetic regions and subsequently subcortical structures were all mechanism hypothesized.[117]

Head turning and head version

Versive and nonversive head turnings are common signs of automotor seizures. Version classically defines a tonic, unnatural, and forced lateral gyratory movement while head deviation or head turning refers to other head gyratory movements with more natural and unforced components. While some controversy exists about the significance and reliability of ictal nonversive head turning as a lateralizing sign, authors agree that forced versive head movements are contralateral to the epileptogenic zone in more then 90% of cases, especially when associated to conjugated eyes version and occurring shortly (usually 10 seconds or less) before secondary generalization.[10,21,43,81,85,106,107,118–121] When contralateral to epileptogenic zone, head versions are sometimes referred as adversion or contraversion. Depending on the series, head version is observed in approximately 35% of patients with temporal lobe epilepsy and in 20–60% of patients with extratemporal epilepsies, mainly frontal lobe epilepsies.[10,21,43,81,85,106,107,118–121]

Nonversive head turning occurs in up to 73% of the temporal lobe seizures, but its value as a lateralizing sign has been controversial.[120] In focal seizures without generalization, when a single head turning occur, it is ipsilateral to the epileptogenic

focus in up to 94% of the seizures.[120] When two head turnings occur to the same direction (19% of the seizures), they are usually ipsilateral to the seizure focus. However, in focal seizures with secondary generalization, when two head turnings occur, the first is usually ipsilateral to the seizure onset and the second is contralateral to the epileptogenic zone, usually appearing shortly before generalization.[81,120] Head turning or deviation can be observed in about 50% of patients with frontal lobe seizures, being also ipsilateral to the epileptogenic zone in most cases. When patients show both sides head gyratory movements, ipsilateral head turning usually occurs earlier and precedes contralateral head turning.

Late ipsiversion of head and eye at the end of a generalized tonic-clonic seizure might be observed in 15–20% of patients. When initial contraversion persists during the generalization phase, late head deviation is usually contralateral. When initial contraversion vanish during the generalized phase, late version is usually ipsilateral.[10,106] Head version can be elicted by direct electric stimulation of the premotor areas (Broadman's areas 6 and 8). Thus, propagation of seizures to these areas might underlie this behavior shortly before generalization. This seems to be also the mechanism of late ipsiversion, when activation of contralateral nonepileptogenic hemisphere predominates, after the initial ictal activity in the epileptogenic hemisphere is already exhausted or inhibited.[10,106,117] The mechanisms of other nonversive head turning are less well understood. The association of ipsilateral head turning with contralateral dystonic limb posturing has led some authors to associate ipsilateral head turning with seizure spreading to the basal ganglia, and more specifically to the striatum.[81,120,121] However, other authors have suggested neglect of the contralateral space as the possible mechanism involved in ipsilateral head turning.[107,121]

Facial alterations

Facial expression changes occur in virtually all types of complex motor seizures. In automotor seizures, most patients exhibit neutral facial expression and staring, but emotional facial changes (e.g., disgust, happiness, and sadness) may also be observed.[122–124] Expressions of anger, surprise, or fear are not commonly seen in automotor seizures, but frequently occur in hypermotor seizures.[122,124–126] Although emotional facial asymmetry is not a specific ictal motor abnormality, it deserves a brief mention here because it might help in lateralizing the epileptogenic zone. Observed in about 70% of temporal lobe epilepsy patients, inferior facial weakness is usually, but not always, contralateral to the epileptogenic zone.[127–130] Ictal smile was reported in children, occurring in 11% of frontal lobe seizures, in 3% of temporal lobe seizures, and in 26% of posterior cortex seizures, where it is significantly more common. This finding might lateralize the epileptogenic zone to the nondominant hemisphere.[131] Rarely, ictal cry may be observed in patients with temporal or medial frontal lobe epilepsy.[132,133]

Mechanisms involved in ictal facial expression changes are multiple and complex. Facial alterations might be caused by direct seizure activation or disconnections of cortical or subcortical motor areas involved in facial muscle control,[122,134–139] or be provoked by ictal alterations in emotion-regulation networks. Seizures originating from or involving limbic and related structures may also activate or disrupt regions involved in the modulation of emotional responses, provoking emotional facial alterations that can appear associated to complex motor behaviors, like fear or anger, sometimes being quite dramatic and resembling panic attacks.[124,126,140] Associated emotional behavior may be observed in temporal lobe epilepsy, but extreme emotional ictal behaviors (usually intense agitation, screaming, facial expression of rage, fear, or anger) are more commonly observed in frontal lobe seizures.[125,126] The analysis of the neural substrates underlying emotional responses is particularly complex, once emotions and related behaviors are difficult to be reproduced and studied under controlled situations. Nevertheless, an increasing body of evidence has pointed amygdala, prefrontal cortex, hypothalamus, cingulate cortex, orbitofrontal cortex, insular cortex, and the ventral striatum as components of a complex neural emotional network.[141–144] More complex emotional motor behaviors might be related to seizure propagation to rostral cingulate (M3) or caudal cingulate areas (M4), regions that might be responsible for 'emotional facial movements'.[46,136,139]

Nosewiping or nose-rubbing

Many epileptic patients wipe or rub their nose during or shortly after ictal period (less then 60 secounds) and this motor behavior appears to have localizatory and lateralizing value.[117,145,146] Nosewiping is significantly more frequent in mesial temporal lobe seizures than in other temporal lobe or extratemporal lobe seizures.[147,148] In temporal lobe epilepsy, ictal or postictal nosewiping might be observed in 50–85% of the patients and in 43% of the seizures, while it might be observed in only 10–33% of all patients with extratemporal epilepsy.[145,148,149] In automotor temporal lobe seizures, nosewiping has lateralizing properties, being performed with the hand ipsilateral to the epileptogenic zone in about 75–90% of patients.[145,146,148,149] In extratemporal epilepsies nosewiping might be observed in about 50% of the patients.[149] Nosewiping is uncommon in patients with generalized epilepsy, after secoundarily generalized seizures or during nonepileptic events.[146] Nose wiping is hardly lateralizatory in frontal lobe epilepsy.[150]

The pathophysiology of ictal and postictal nose wiping remains uncertain but it might reflect ictal olfactory hallucinations or increased nasal secretions.[148] Earlier ictal amygdala involvement is more common in nosewiping. This finding together with observations that amygdala has a particular role in the olfactory system[2,148] might suggest that direct amygdala ictal activation or disorganization of amygdale-related neural network might play an important role in the genesis of ictal or postictal nosewiping.[2,148] The use of the ipsilateral hand may be related to contralateral postictal movement abnormalities or neglect.[151–153]

Other stereotyped motor behaviors

Some ictal or periictal complex motor behaviors may be determined by special and well-characterized physiological states that can cause stereotyped and well-defined clinical situations such as cough, urinary urgency, thirst, vomiting, spitting, orgasmic related behaviors, among others. These periictal complex motor behaviors possibly have some common points that might allow them to be grouped together. In this venue, it is interesting to note that many of these behaviors are more

commonly observed in patients with nondominant temporal lobe epilepsy. Although several mechanisms could be involved, it is tempting to hypothesize that some of these abnormal behaviors can only be observed because patients keep some degree of awareness about their own feelings, about themselves, and about the surrounding ambient during seizures. Moreover, some of these behaviors correspond to autonomic responses, and the predominance of autonomic functions in the nondominant temporal lobe has also been advocated.[154]

Ictal vomiting

Ictal vomiting is an unusual manifestation, observed in about 2% of patients submitted to video-EEG.[89,155,156] Frequently associated with nondominant temporal lobe epilepsy, it might be also observed in language-dominant temporal lobe epilepsy.[155,157–163] The mechanisms of ictal vomiting are not yet completely elucidated. However, seizure activity in mesial temporal structures, other limbic structures, insula, and mesial frontal regions seems to be necessary. This association is supported by several clinical-electrografic correlations,[155,158–163] direct electrical stimulation[157] and evidences obtained from SPECT studies.[159]

Ictal spitting

Ictal spitting is another uncommon ictal behavior, occurring in less than 1% of the patients referred for video-EEG monitoring.[164,165] It is usually observed in seizures involving nondominant temporal lobe epilepsy,[164,165] but seizures of language-dominant temporal lobe and extratemporal lobes were also reported.[166] The mechanisms underlying ictal spitting remain largely unknown. Increased salivation, a rare finding also associated with nondominant temporal lobe epilepsy has not been associated with spitting in most patients.[167] It appears that spitting corresponds to complex automatisms similar to other oroalimentary automatisms. The association of ictal spitting with nondominant hemisphere further suggests involvement of autonomic mechanisms. However, ictal spiting is hardly explained by bad mouth sensations, excessive salivation or drooling, as one could intuitively suppose.[166,167]

Ictal urinary urge

Ictal urinary urge provokes characteristic motor behavior in association with seizures,[168,169] usually with epileptic focus located in the nondominant hemisphere.[168,169] It might be observed in 0.2–2.5% of patients during video-EEG, being more common in temporal lobe epilepsy.[65,168,169] The lateralizing significance of this sign can be explained by a hemispheric specific representation of central bladder control. PET studies on brain activation during micturition in normal subjects suggested a predominance of the right hemisphere in central bladder control.[170,171] The symptomatogenic zone probably involves the insular cortex, mesial frontal region or the medial temporal gyrus and operculum.[168–172]

Periictal water drinking

Water drinking is also a characteristic behavior occasionally observed during or up to 2 minutes after an automotor seizure.[154,173,174] It occurs in about 15% of patients and it is usually associated with nondominant temporal lobe epileptogenic zone. Depth electrodes recordings have evidenced seizures starting in the amygdala, hippocampus, and parahippocampal gyrus.[153,154,174] Propagation of seizures from these structures to hypothalamus was suggested as the cause for water drinking.[154] As in other nondominant temporal lobe seizures, the general predominance of central autonomic networks functioning in the nondominant hemisphere has been also advocated,[154] but more specific mechanisms remain uncertain.

Ictal or periictal cough

Cough is a relatively common ictal or periictal finding in epilepsy, being observed in 9–40% of patients during video-EEG.[175–177] Coughing may be observed in temporal lobe seizures as well as in extratemporal seizures, but it is rare in pseudoseizures. Some authors have suggested that periictal coughing is more often observed in temporal lobe epilepsy, although without lateralising properties.[175–177] Mechanisms of periictal cough are complex and might differ between temporal and extratemporal lobe seizures.[176,177] Nevertheless, pericital coughing is thought to be consequence of increased respiratory secretion or provoked by direct activation of the central autonomic pathways.[177]

Unilateral ear plugging

Ear plugging may be observed in some epileptic patients, probably representing a stereotyped response to an annoying auditory phenomenon. It is usually observed in children with epilepsy and learning disabilities or poor communication skills.[178] Similar to nose rubbing, ear plugging is not a primary motor seizure, but a motor behavior probably performed in response to an auditory hallucination provoked by seizures involving the contralateral superior temporal gyrus.[178] Thus, this behavior may occasionally be helpful in indicating the localization of the epileptogenic zone in the contralateral auditory cortex, on the superior temporal gyrus.[178]

Hypermotor seizures

Hypermotor (Semiological Classification) or hyperkinetic seizures (ILAE Classification) were first defined as hypermotoric turning movements and postures,[42] and further detailed by Lüders and colleagues as seizures in which the main clinical manifestations consist of complex movements involving the proximal segments of limbs and trunk. These characteristics result in large movements that might appear violent when occurring in high speed.[5] These seizures are commonly refereed as complex gestural automatisms, gestural motor symptoms, hyperkinetic or hypermotoric behavior.[166] Motor activity includes axial motor components like trashing, jumping, or body rocking. It might involve lower or upper extremities like thrashing of the extremities, bicycling leg movements, stepping, pedaling, hand flapping, clapping, slamming, pounding, fist clenching, grasping, shaking or playing with objects. Sexual automatisms are common and characterized mainly by pelvic thrusting and aggressive genital manipulations. Vocalization, laughing, shouting, or crying are frequently associated, but considered not specific findings of hypermotor seizures.[21,23,32,75,179–181] Not only the pattern of motor behavior, but also its quality, i.e., agitated, frenetic, and hyperkinetic, characterizes seizures as hypermotor seizures.

Although movements might seems violent, emotional or affective signs are reported as minimal and rare.[126,182] Nevertheless some patients might exhibit emotional components associated with hypermotor seizures,[126] but these aspects cannot be easily characterized and as a consequence, they are far less studied. The combination of all these components results in the large clinical variability of hypermotor seizures and unique and very bizarre-appearing seizures, sometimes suggesting pseudoseizures for those not habituated with video-EEG. For those habituated, hypermotor seizures are perhaps too bizarre for pseudoseizures.[181,183] Hypermotor seizures usually originate in the frontal lobes,[42,184] but it may also begin in the temporal lobes, posterior cortex, and insula.[18,39,185,186] In the next sessions we discuss hypermotor seizures and other complex motor ictal behaviors related with frontal, temporal, and insular regions, pointing some important clinical differences of these seizures.

Hypermotor seizures and frontal lobe

Frontal lobe seizures express one of its main function: triggering, organizing, and performing most diverse motor activity. Except for 'frontal lobe absences' where little or no motor activity is observed, some form of motor activity is observed in virtually all patients with frontal lobe epilepsy and more complex motor ictal behaviors are very common.[21–23,32,33,38,97,166,179,181,187–192] However, it is important to remember that these seizures are not exclusively characterized by motor activity. In fact, many patients may have auras preceding complex motor ictal behaviors of frontal lobe origin.[21,23,28,166,183,193] Moreover, in spite of being much less evident, motor behavior is preceded or followed by tonic muscle activity of limbs. Mainly due to the exuberance of the hypermotoric behaviors and short duration of episodes, auras and other periictal subtle muscle activities are usually underestimated, and specific efforts in their identification may be necessary. During hypermotor seizures, conscience may be preserved to some degree in many patients and this aspect, associated with the brevity of seizures might account for minimal postictal confusion.[179] Considering all types of automatisms observed in surgical series of frontal lobe epilepsy, hyperkinetic automatisms seems to be the most common type of automatisms, occurring in more than 50% of these patients.[21] They are usually observed early (first half) in the seizure.[184] When paroxysmal dystonic movements are observed in association with nocturnal hypermotor seizures, autosomal dominant nocturnal frontal lobe epilepsy should be suspected.[194–196]

When associated with hyperkinetic automatisms, some other clinical characteristics classically suggest seizures originating in frontal lobe. These findings are brief seizures, seizures of sudden onset and termination, early motor signs, minimal post ictal confusion, seizures that occur in cluster, seizures occurring during sleep, and seizure with tendency to rapid generalization, although not as frequent as previously suggested.[21,23,32,179–181] More recently, authors have been observing that some of these associations might be clinically nonelevant or even controversial.[21,181,184,197] Nevertheless, some of these characteristics seem to be a direct consequence of seizure spreading properties in the frontal lobe. Indeed, it is interesting to note that in spite of the intense interconnections of frontal lobes with other brain regions, ictal activity of complex motor seizures remains restricted to the frontal lobe where it originates. When propagating outside the frontal lobe of origin, it usually spreads to the contralateral frontal lobe. Because of the limited ictal spreading for an appreciable period of time, some authors were able to lateralize clinical seizure findings in up to 75% of patients with frontal lobe epilepsy.[198,199] However, it is also interesting to note that the variable and often bilateral limb motor phenomena observed in hypermotor seizures of frontal lobe origin may reflect prominent multiple target corticofugal projections from the epileptogenic zone and significant projections to proximal limbs.[199,200] Thus, bilaterality of clinical expression of motor components observed in hypermotor seizures from frontal lobe origin does not necessarily reflect bilateral cortical spread. When seizures spread to other brain regions outside frontal lobes, ictal activity frequently invades the temporal lobes, leading to false impression of temporal lobe seizures.[181,192,201–203] Differences between complex ictal motor behaviors in frontal lobe epilepsy and temporal lobe epilepsy have been observed since Penfield and Jasper.[23] Even when limited to the frontal lobe of origin, hypermotor seizures are characterized by involvement of all limbs, being bilateral, like thrashing or hitting, and include the lower limbs in movements resembling running, kicking, crossing and uncrossing the legs, or pedaling movements. They might be frenetic and bizarre, and patient may vigorously rock to and from, pound the bed or other objects with their hands, and jump or scramble about. It might be associated with pelvic trust and aggressive genital manipulation.[23,75,180,204] It is not uncommon that patients yell, growl, shout expletives, bark, laugh, whistle, or hum. Head and eyes deviation are frequently observed during hypermotor seizures but are of lesser lateralizing or localizatory value, except when versive, sustained and occurring late in seizures, shortly before generalization, being in this case contralateral to the epileptogenic zone. These patients might have poor surgical prognostic.[21,85,205] Conscience might be preserved during episodes, in spite of patients not being able to cooperate with test performed during the ictal period. Depending on the authors, some complex motoric behaviors observed in frontal lobe epilepsy may be seen as adapted behaviors to the environment or active interactions with surrounding objects, an observation in line with findings of some conscience maintenance during hypermotor seizures.[179] When frontal lobe and temporal lobe ictal automatisms are compared, differences are indeed quite evident and should be stressed here. Perseverative automatisms and complex gestures occurring in more homogeneous and stereotyped clinical patterns are usually observed in association with temporal lobe seizures. Upper extremities automatism observed in MTLE involve the distal segments of the fingers and hands and are discrete, repetitive and stereotyped, characterizing automotor seizures.[184] By contrast, upper extremity automatisms observed in most frontal lobe seizures present great clinical variability, being coarse, irregular, complex, semi-purposive, and involving more proximal muscles of shoulder, elbows, as well the hands, characterizing hypermotor seizures.[184,206] Alimentary automatisms might occur in both type of epilepsy, but are more frequent and occur early in temporal lobe epilepsy.[33,184] When observed in frontal lobe seizures, 'automotor-type' automatisms have been associated with seizure origin in orbito-frontal regions and as stated before, it might

reflect seizure propagation from frontal to temporal lobe, leading to false localization of the epileptogenic zone localizing in the temporal lobe.[202,203,206] This situation might be particularly tricky in presurgical evaluation of patients with normal neuroimaging findings, where extra-caution is necessary. When multiple motor symptoms are considered together, complex motor seizures might be better characterized and understood. Differences between complex motor seizures of frontal and temporal lobe origin might be also better appreciated. In this venue, Kotagal and colleagues[23] demonstrated that complex motor seizures of frontal lobe origin are characterized by a cluster of repetitive proximal upper extremity movements, complex motor activity, and hypermotor activity. In contrast, complex motor seizures of temporal lobe origin are better characterized by a cluster of oroalimentar automatisms and repetitive distal upper extremity movements. Usually but not always, alteration of conscience is associated with both seizure patterns.[23] Although infrequent, mixed semiology might suggest propagation from one lobe to another. In these situations, a very careful analysis of initial symptoms and the sequence of appearance of ictal motor findings are particularly important. Such approach might indicate more precisely the initial symptomatogenic zone and the patterns of seizure propagation. When clustered together, some clinical seizure patterns may indicate the ictal activation of functionally and/or anatomically related areas, an observation that might help during clinical evaluation of patients, especially in those with normal neuroimaging findings.[23]

Origin of hypermotor seizures in frontal lobe

Although the association between hypermotor seizures and frontal lobes overall is well accepted, there is no consensus on the specific localization of the symptomatogenic zone responsible for complex motor behavior observed in frontal lobe seizures. This fact reflects mainly the relative few studies on 'pure culture' frontal lobe epilepsy and series with limited number of patients included. Also account for these difficulties, the intrinsic proprieties of frontal lobe, such as its large volume as well as the complexity of connections of its neural networks, leading to rapid seizure propagation in variable spreading patterns within the frontal lobes.

According to Bancaud and Tailarach, there are five different frontal regions from which complex motor seizures might originate: anterior cingulated gyrus, frontopolar cortex, orbito-frontal cortex, opercular-insular cortex, and medial-intermediate region.[207] More recently, hypermotor seizures have been associated with seizures originating from medial or orbitofrontal regions,[206] an association further confirmed by SPECT findings in few patients.[208,209] Also in hypermotor seizures, PET revealed interictal hypometabolism involving frontomesial, anterior cingulate, perirolandic, and anterior insular/frontal opercular areas.[210] However, none of ictal complex motor behavioral patterns were observed to be exclusive from these regions, once there are well-documented examples of such seizures initiating in other frontal lobe regions as well.[21,181,188,208] Other authors have further differentiating prefrontal seizures in ventro-medial prefrontal seizures or dorsolateral prefrontal seizures. Seizures arising from ventral or ventro-medial regions appear to correspond to those initially described as 'complex partial seizures of frontal origin'. [179,180] Some of these patients exhibit hypermotor seizures resembling intense and dramatic behavioral reaction to fear, with semi-purposeful gesticulation, like kicking or punching, bipedal cycling movements or attempts to escape. On its turns, seizure originating in dorso-lateral prefrontal regions might be characterized by tonic eye deviation preceding head version and complex semi-purposeful gestural automatisms that might be directed toward the same location as the gaze.[179] However, as stated before, the origin of hypermotor complex behaviors within the frontal lobe is a matter of ongoing research. In spite of some seizure patterns being associated with specific frontal lobe regions by some authors, others could not observe such associations. On the contrary, they simply concluded that hyperactive seizures with frenetic automatisms, characteristic of hypermotor frontal lobe epilepsy, do not seem to be associated with any specific sublobar region within the frontal lobes.[181,206] In line with this last hypothesis, a mechanism proposed for complex ictal motor behaviors observed in frontal lobe epilepsy is that epileptic activity may simply disrupt the control normally exerted by higher brain centers over other regions, allowing release phenomena or disinhibition of more primitive and stereotyped behaviors.[179] It is possible that frontal lobe seizures might leads to an imbalance between internally generated control of movement and response to environmental cues.[179] This phenomenon would be the basis of the complex motor behaviors observed in frontal lobe epilepsy. Nevertheless, frontal lobe epilepsy remains the next frontier.[191] Whether hypermotor seizure or complex ictal motor phenomena have origin in specific subregions within the frontal lobe or not is still unknown. Studies with larger groups of patients with pure frontal lobe epilepsy, evaluated with modern neuroimaging appropriately combined with electrophysiological techniques and proven seizure free after surgery, are necessary to solve this problem.

Hypermotor seizures in temporal lobe epilepsy

Much less frequently, hypermotor seizures are observed in seizures originating in the temporal lobes, even if sleep-related.[185,197] This should not be a surprise if one considers that temporal and frontal structures are highly interconnected and under certain aspects, some of these regions might be considered as a physiological continuum, as is the case of limbic and para-limbic structures. In this venue, Carreno and colleagues,[185] analyzing a series of 502 patients with temporal lobe epilepsy identified only 12 individuals (2.4%) with seizures originating from mesial or neocortical temporal lobes, who exhibited complex motor behaviors similar to those observed during frontal lobe seizures. Large amplitude movements mainly involving the proximal segments of the limbs were observed in six of these patients, four other patients presented unilateral hemiballismus-like movements and the remaining two had movements affecting all four members, resembling rowing or bicycling (one patient) and violent and disorganized thrashing (the other patient). As observed by those authors, these patients might present 'temporal lobe' auras preceding the hypermotor phase, a finding that although far from being specific, might help differentiate hypermotor temporal lobe seizures from frontal lobe seizures. It is also possible that careful evaluation of the very early symptoms in these patients might provide additional clues for temporal lobe seizure onset, with rapid, but latter propagation

to frontal lobes. Indeed, although the epileptogenic zone in those cases is located in the temporal lobe, there are growing evidences suggesting that the symptomatogenic zones are in fact located in the anterior cingulated cortex and/or the orbitofrontal cortex.[125,126,211] This pattern of propagation with ictal discharges spreading to frontal lobe structures would explain the frontal-like symptomatology presented by this particular group of temporal lobe epilepsy patients. Surgical results in these patients are mainly dependent on the etiology of the epilepsy (mesial temporal sclerosis, malformations of cortical development, tumors, among others), being similar to those observed in patients with typical temporal lobe seizure semiology.[185]

Hypermotor seizures in insular lobe

Ryvlin and colleges[186] recently reported on three patients with medically intractable nocturnal hypermotor seizures whose depth electrodes investigation had demonstrated non-equivocal insular origin, more specifically in its anterosuperior portion. This observation was further corroborated by additional findings, with patient's habitual seizures being triggered by electrical stimulation in one patient, and interictal spikes over the insular region in the other two patients (suggesting its involvement in the origin of the hypermotor seizures). Thus, as in the case of seizures emanating from temporal lobes, seizures originating in insular regions might be associated with hypermotor behaviors as well.

Epileptogenic zone in bimanual-bipedal automatisms

Bimanual-bipedal automatisms are one of many automatisms observed during hypermotor seizures. However, because it is frequent, better characterized in literature, stereotyped, and easily recognizable during video-EEG, it deserves additional comments. Although usually seen as a frontal lobe clinical finding, it might be observed in few patients with seizures originating in temporal lobes as well.[212,213] Swartz[212] reported that bimanual-bipedal automatisms occur in 27% of patients with frontal lobe seizure onset and in 7% of patients with temporal lobe epilepsy. Disputing this, other authors report these behaviors as being exclusive of frontal lobe epilepsy semiology.[23] According to Swartz mesio and/or latero-temporal plus orbital areas seem to be activated in seizures originating from temporal lobes, while dorsolateral and mesiofrontal areas were more commonly activated in seizures originating from the frontal lobes.[212] Thus, although symptomatic areas of bipedal-bimanual automatisms are frontal lobes, epileptogenic areas might be frontal or temporal.

Gyratory ictal behavior

Gyratory ictal behavior, commonly refereed as gyratory seizures, is characterized by ictal rotation usually around the body axis for at least 180 degrees.[214] It was included here because gyratory ictal behaviors might be observed as integrant components of complex motor seizures. It is a non usual ictal clinical finding, observed in about 4% of patients referred to epilepsy surgery and hardly observed in pseudoseizures.[183] Gyratory ictal behaviors are more commonly observed in seizures originating from frontal lobes, but it might be also observed in seizures originating from the temporal lobes.[214] Gyratory ictal behaviors might have localizatory and lateralizing value. When following a forced head version, the rotation side is usually contralateral to the epileptogenic zone. Conversely, when not preceded by a forced head version, the direction of rotation is usually toward the side of seizure onset.[214] The mechanisms involved in the genesis of these behaviors are unknown.

Gelastic seizures

Gelastic seizures are seizures whose main characteristics are brief periods of laughter or grimaces, accompanied or not by subjective feelings of mirth. The term 'gelastic' is originated from the Greek word *gelos* which means joy, an expression referring to the observation of laughter during seizures.[14,215–219] Gelastic seizures are uncommon type of seizures, better classified apart from other complex motor seizures due to their peculiar characteristics. Although this semiological finding strongly suggests hypothalamic hamartoma as the cause of the seizures, rare patients might experience gelastic seizures due to other types of brain lesions, located in diverse brain areas.[14,14,215–224]

Hypothalamic hamartomas are rare but well-recognized developmental malformations of the tuber cinereum, associated with precocious puberty and gelastic seizures. Although there is a spectrum of epilepsy severity associated with hypothalamic hamartomas, patients with hypothalamic hamartomas who present the classical form of the disease develop gelastic seizures during infancy or early childhood, followed by appearance of generalized seizures associated with broad cognitive and behavioral deterioration. Endocrine disorders are also observed, leading to precocious puberty.[14,14,215–219] Rare patients might experience milder forms of the disease, with seizures only characterized by pressure to laugh.[225] Typically, gelastic seizures might be difficult to recognize as epileptic events until an average of 4 years. These patients are poorly responsive to pharmachological treatments. Alternatives therapies, such as vagal nerve stimulation and the ketogenic diet have not shown clear benefits. However, because gelastic seizures originate and propagate from hypothalamic hamartomas, surgical seizure control is possible. Advances in surgical techniques have allowed safe resections of hypothalamic hamartomas, leading to drastic improvements in seizure control.[14,220–223,226–231] Surgical treatment is also possible in refractory cases associated with lesions other than hypothalamic hamartoma.[215,217,224,232–235] In these cases the prognosis is mainly dependent on the local and extension of the lesion. As is the rule in epilepsy surgery, small epileptogenic lesions located outside the eloquent cortical areas, and whose epileptogenic zone can be completely excised, carry good surgical prognosis.

The pathophysiology of gelastic seizures remains undefined but it is mainly dependent on the lesion from where seizures emanate. In the case of hypothalamic hamartomas, investigations involving ictal recordings from implanted electrodes, including electrode contacts placed directly into the hypothalamic hamartoma, suggested that gelastic seizures arise directly form these lesions.[14,236] Recently, Wu and collegues[237]

have demonstrated that hypothalamic hamartoma cells exhibit intrinsic pacemaker-like activity, a finding suggesting these cells might underlay the genesis of epileptic activity. Although this finding might provide evidences for seizure generation, less is known about the microcellular network associated with these cells or the hypothalamic hamartoma neural network involved in seizure spreading.[237–244] Although seizures seem to originate in the hypothalamic hamartoma itself, the neural networks and pathways which are activated during seizure propagation seem to be directly responsible for promoting the laughter or joy and different patterns of propagation might account for some clinical variability of gelastic seizures. These circuits are still not completely defined. Circuits involved in physiological laughter and/or mirth seem to be activated during seizure propagation in these patients, resulting in the gelastic seizures. The same brain networks might be activated during gelastic seizures originated from other brain lesions that not hypothalamic hamartomas. Although various anatomical regions may elicit laughter, it seems that the anterior cingulate regions are involved in the motor aspects of laughter, while temporal lobes, and particularly its basal regions, seem to be mainly involved in the processing of mirth.[217,233,238,245] Although laughter is quite evident in these patients, mirth is a subjective sensation and patients need to keep some degree of awareness of the seizures in order to be able to report it.

Complex motor seizures in children

Clinical features of complex motor seizures are distinct in children. Not only the etiological profile and associated pathologies are diverse[246–249] but differences in brain maturation also seem to influence seizure semiology.[41,42,246–248,250–256] Adapting Gloor's concepts,[1] it is probably appropriate to consider that clinical phenomenology of seizures in children is generated by widespread immature neuronal matrices, not fully specialized, linked together by still in-development anatomical connections that are just beginning to become strengthened through repeated use.[1,2] Indeed, it is during brain maturation that neuronal matrices are formed and wired together, creating the organized and specific neuronal networks characteristic of adult life. In immature neural matrices, the epileptic electrical activity seems to evolve according to patterns of propagation distinct from those observed during adulthood.[251,257] Differences in propagation patterns seem to be influential to the clinical course of complex motor seizures in children. These theoretical considerations are important once they might help to explain the occurrence of a certain gradient of motor findings between childhood and adulthood, evolving from more simple, prominent and broader, to more elaborate, discrete, and focal complex motor patterns.

In children under 3–4 years old with temporal lobe epilepsy, seizures tend to manifest with prominent tonic, clonic, or myoclonic patterns that are sometimes bilateral and symmetrical, with ictal characteristics closer to seizures from generalized epilepsy syndromes. Although lateralising signs might be observed with very good interobserver agreement in up to 75% of children under 13 years old, the lack of specific clinical lateralizing signs, especially unilateral automatisms, dystonic posturing, version, postictal dysphasia, and postictal facial wiping is not unusual in young children.[256] Postictal nose wiping, unilateral tonic seizures, Todd's paralysis, unilateral clonic seizures, and ictal nistagmus are among lateralising signs observed earlier.[42,246,248,251,258–262] When automatisms are observed, they tend to be less elaborated and are usually restricted to oroalimentar automatisms.[251] These features may be also seen in focal epilepsies originating in other brain areas.[249,258–261] As the child grows, the motor manifestations become more elaborated. These modifications seem to become clinically evident after 3.5–4 years of life, probably coinciding with more advanced stages of brain maturation.[251] At these later stages, motor signs become progressively less prominent, giving room to more complex automatisms that increases in complexity as the child grows. At this age, many children might also show dystonic posture or versive movements.[42,246] After six years of age, motor phenomenology of temporal lobe seizures become similar to that observed in adults.[42,246,248,256]

As can be concluded from above, complex motor seizure analysis is particularly challenging in young children, once they present less frequently lateralizing and localizing signs, and they are usually unable to give reliable information about auras or other subjective symptoms. Oller-Daurella and Oller,[263] studying focal seizures in 154 children during the first 3 years of life observed that only 23% of them had focal ictal signs suggestive of focal pathologies. All the others had nonfocal seizures. In a postsurgical retrospective analysis, Loddenkemper and colleges[262] studied ictal lateralizing findings in infants from 1 to 32 months of age with focal epilepsy. They observed reliable lateralizing motor signs in only 58% of the seizures, in 63% of the children, mostly consisting of lateralized simple motor seizures. Complex motor behaviors were not observed or were not reliable for focus localization.[262] Head and eye version were common, but shifted laterality, consequently being nonreliable as lateralizing signs.[262]

In young children, temporal, temporo-parietal, or occipital lobe seizures are more commonly characterized by impaired responsiveness and awareness (difficult to evaluate in very young children) and decreased motor activity. This pattern is usually referred as hypomotor seizures. Hypermotor seizures might occur, but it is sporadic.[56,252,264] These seizures are clearly distinct from seizures initiating in frontal, central, fronto-central or fronto-parietal regions, that are characterized by motor alterations consisting of tonic, atonic, or clonic movements.[56,264] Pediatric frontal lobe epilepsy might be especially challenging for epilepsy surgery. When compared with those children with temporal lobe epilepsy, children with frontal lobe epilepsy had more frequent seizures, seizures of brief duration, and seizures occurring more often during sleep. Other characteristics of pediatric frontal lobe epilepsy are seizures of explosive onset with scream or cry, marked agitation during seizures, stiffening, kicking, or bicycling of legs, incontinence, and rapid recovery, with only brief postictal phase.[265,266] In older children, seizures assume patters of adulthood epilepsy. In mesial temporal lobe epilepsy seizures are usually of automotor type while in patients with frontal lobe epilepsy seizures might be complex hypermotor seizures or simple motor seizures, like asymmetric tonic seizures or focal clonic signs.[265] Epileptic spasms are nonspecific findings

regarding lateralization, once it can be observed in association with focal lesions in all regions cited above.[264]

Final comments

The reader must keep in mind that, although several aspects of complex motor seizures might help in localize and lateralize the seizure onset zone, semiological findings cannot be 100% accurate. Some discrepancy should always be expected between the epileptogenic and symptomatogenic zone once these zones are conceptually distinct, and although overlapping is common, there exist considerable intra- and interpatient variability. Also because of this variability, exceptions in the lateralizing and localizatory value of many signs may be expected. Nevertheless, careful descriptions of the complex motor findings observed during ictal periods are accurate enough for correct semiological seizure classification, frequently providing useful evidences supporting surgical decisions.[7–9] In this venue, besides studying isolated clinical signs and describing them in detail, epileptologists should also concentrate research efforts in specifying common patterns of composed motor behaviors, as well as in the establishment of common patterns of temporal and sequential evolution of these behaviors. Although not practical during actual routine presurgical evaluation, it is however possible that such analysis might be particularly relevant in near future. For example, combining two motor signs might improve the diagnostic power of the epileptogenic zone, as is the case of ipsilateral automatism associated with contralateral dystonic posturing in automotor seizures. Also, some patterns might have prognostic significances, as is the case of patients that evolve to generalization during ictal spreading of mesial temporal lobe seizures.[95] For these matters, cluster analysis,[184,267] neuroetholgy,[268] or other techniques developed in order to group common events together and establish time-related sequences of behaviors might add further insights to clinical analysis of isolated signs. We believe such approaches might help planning more tailored surgical resections in future.

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53 Dialeptic seizures: localizing and lateralizing value

S Noachtar

Definition

Definition of dialeptic seizure

The term dialeptic seizure has been introduced by us to allow for a seizure classification which is purely based on ictal seizure semiology.[1,2] Dialeptic seizure refers to a seizure whose predominant ictal features are alteration of consciousness, staring and loss, or minimal motor activity. The term absence seizures, on the other hand, describes a subgroup of dialeptic seizures but also includes EEG findings in the seizure classification.[3] It was the pioneering work of Gibbs and co-workers who demonstrated that in patients with absence epilepsies dialeptic seizures were associated with generalized 3 Hz spike-wave complexes in the EEG.[4] Ever since the term absence has been defined as an electroclinical syndrome consisting of loss of consciousness, arrest of activity *and* an EEG showing generalized spike-wave complexes. It seems therefore appropriate to introduce a new term which describes the ictal loss of consciousness and the arrest of motor activity emphazising a purely clinical seizure classification independent of associated EEG findings. The verb διαλειπειν is old Greek and means to interrupt, stand still, or pass out.

Definitions of consciousness are subject to controversy.[5,6] A clinically applicable definition of consciousness has to be restricted to awareness and responsiveness which is actually included in the proposal of the International Classification of Epileptic Seizures (ICES).[3] However, there are not infrequently limitations and exceptions to this concept. Patients may not infrequently recall the command to push a button during a seizure but may have been unable to do so.[7,8] Awareness and responsiveness may be disturbed differently. It has been shown recently, that patients may be fully responsive during focal seizures associated with automatisms and yet not be able to recall the events during the seizure. We could observe this phenomenon prospectively in 10% of the patients with right temporal lobe epilepsies.[9] Even with simultaneous Video-EEG recordings it may be impossible to exclude that the patients failure to respond was not caused by an arrest of activity due to epileptic activation of the speech areas. Thus, assessment of consciousness during an epileptic seizure may well not be trivial and remains conceptually difficult.[5]

For the purpose of the present chapter we will consider that an impairment of consciousness occurred during a dialeptic seizure if either responsiveness or recall were disturbed. Clinically, dialeptic seizures frequently are associated with minimal motor activity such as eyelid myoclonia and upward eye movements. To classify seizures in children or mentally retarded adults in whom it is sometimes impossible to assess ictal consciousness the term hypomotor seizure has been introduced.[10,11] Loss of voluntary tonic motor activity may be present during dialeptic seizures and is clearly distinct from atonia of postural tone leading to drop or fall. If the predominant feature of a seizure is an inability to follow a motor command such as pressing a button with full recall of the event, the seizure should be classified as an akinetic seizure (see Chapter 54a). If motor activity is present during a dialeptic seizure it is usually restricted to some minor motor movements like eye blinking. If motor activity predominates the seizure semiology the seizure will be classified according to the specific motor activity (e.g., automotor seizure, if automatisms occur or clonic seizure left arm, if the left arm is jerking).

Subgroups of dialeptic seizures

A subclassification of dialeptic seizures seems justified since the above mentioned definition is quite broad. Some patients have very brief dialeptic seizures characterized by an abrupt onset and offset. These seizures when associated with bursts of generalized 3 Hz spike-wave complexes have been classified as typical absences and are usually seen in patients with absence epilepsies.[3] On the other hand, the ICES identifies as atypical absences dialeptic seizures in which changes in muscle tone are more pronounced and which usually do not begin and end abruptly and are accompanied by generalized irregular slow spike-wave complexes with a repetition rate of 2.5 Hz or less.[3] It has also been proposed to distinguish between 'simple' absences and 'complex' absences basically depending on the degree of motor activity associated.[12,13] Clinically, this subclassification overlaps somewhat with the distinction between 'typical' and 'atypical' absences which has been proposed by the ICES.[3] However, there is evidence to suggest that the distinction between typical and atypical absences depends mainly on the EEG abnormalities associated with the dialeptic seizures.[14] Holmes *et al.*[14] analyzed a total of 926 dialeptic seizures in 54 patients with generalized epilepsies and found automatisms more frequently in 'typical absences' and more loss of muscle tone in 'atypical absences'. Both subtypes of dialeptic seizures usually had a sudden onset and end. The authors concluded that typical and atypical 'absence' seizures are not discrete entities but rather form a continuum.[14] Based on the associated motor or automotor activity dialeptic seizures occurring in patients with generalized epilepsies

(absences) have been subdivided in six subtypes by Penry and co-workers.[15] Only about 10% of all absence seizures are characterized by lapse of consciousness usually associated with a change in facial expression (staring) and cessation of motor activity, according to Penry *et al.*[15]

Of the patients with absence seizures, 71% showed at least some clonic components.[15] Dialeptic seizures with tonic components are rare (3%),[15] and show an increase of muscle tone which may cause a backward movement of the head and trunk ('retropulsiv petit mal').[16] The tonic postural movements usually include both flexor and extensor muscles of the trunk or head, but extensors typically dominate. They can be asymmetric, leading to brief versive movements. Atonic components during dialeptic seizures are usually gradual causing the head to drop slightly or objects fall of the hands. An asymmetry of the decrease of muscle tone may occur. Myoclonic jerks may intermix leading to a rhythmic appearance of a head drop. Rarely the atonia is as severe and lasts long enough to cause the patient fall. Seizures in which the loss of tone is the predominant feature should be classified as atonic seizures or astatic seizures when the patients actually falls. An atonic component occurred in about half of the patients in at least one absence seizure.[15]

Most patients with dialeptic seizures present some mild automatisms in at least some of their seizures. The automatisms may reflect a continuation of what the patient was doing prior to the seizure onset. The patient may, for instance, continue moving the fork or spoon or chewing if a seizure occurs while eating or continue to walk if a seizure commences while walking. However, the movements will usually be slower and not as elaborate. De novo automatisms typically include simple movements such as lip licking, grimacing, yawning, swallowing, scratching or fumbling. About 88% of the patients of Penry *et al.* showed some kind of automatisms during their dialeptic seizures,[15] and 28% of all dialeptic seizures were subclassified as dialeptic seizures with automatisms. The occurrence of automatisms increases with seizure duration and usually oral automatisms occur first followed by manual automatisms.[17] At a seizure duration of 3 seconds in 22% of the seizures automatisms were present, whereas at a seizure duration of 18 seconds in 95% of the seizures automatisms occurred.[15] Seizures in which the automatisms constitute a prominent part of the seizure should be classified as automotor seizures. Some dialeptic seizures are accompanied with autonomic components such as pallor of the face, flushing, mydriasis, salivation, tachycardia, piloerection and rarely urinary incontinence.

It is important to notice that in 40% of the dialeptic seizures of patients with generalized epilepsies several of the above-mentioned features occurred.[15] There was a considerable overlap of the subtypes from one seizure to another in the same individual.[15] Fifty percent of the patients evaluated have had only one of the above-mentioned subtypes of absence seizures.[15]

There are reports which will be discussed later that describe dialeptic seizures in patients with focal epilepsies. However, subtypes of dialeptic seizures are not systematically studied in these patients.[18–21] Further studies are currently being undertaken to gain more insight into the semiology of dialeptic seizures in focal epilepsies.[22]

Relationship of dialeptic seizures with 'absence seizures' and 'complex-partial' seizures

As mentioned above the term dialeptic seizure exclusively refers to an ictal seizure semiology. The ICES, however, is based on both, clinical symptomatology and EEG.[3] Therefore, a seizure consisting of lapse of consciousness and minimum of motor activity, i.e., would be classified as 'complex-partial' seizure according to the ICES if the EEG reveals focal epileptiform activity.[23–24] A seizure with essentially identical seizure semiology would be classified as an absence seizure in ICES, if the EEG showed generalized spike-wave complexes. Thus, absence seizures define an electroclinical syndrome consisting of dialeptic seizures, and less frequently other semiological seizure types like automotor seizures or akinetic seizures, occurring in association with generalized spike-wave-complexes. Complex partial seizures of the ICES define any seizure occurring in association with an alteration of consciousness and focal epileptiform EEG discharges (or normal EEG) and clinical or imaging features suggesting a focal epilepsy. Dialeptic seizures associated with a focal EEG pattern are actually one type of complex partial seizures of the ICES. The main difference between these terms is that dialeptic seizures refer exclusively to the clinical semiology of the seizures whereas absence seizures and complex partial seizures define electroclinical complexes, i.e., the definition of the terms includes clinical semiology and a specific EEG seizure pattern.

In this chapter we will use the above-mentioned clinical definition of dialeptic seizures. This will allow us to use the term dialeptic seizure independently of the EEG. Such an approach may enable us to better assess the mode of appearance and frequency of dialeptic seizures in different epilepsy syndromes and allow us to better investigate the evolution and spread of epileptic seizures.[24]

Relationship of dialeptic seizures with epilepsy syndromes

Dialeptic seizures can occur in different epilepsy syndromes (Figure 53.1). Most patients with dialeptic seizures have generalized epilepsies such as absence epilepsy and Lennox-Gastaut syndrome. Dialeptic seizures also occur even if less frequently in other generalized epilepsies such as generalized myoclonic epilepsy and probably even less frequently in focal epilepsies.[18,25–28] We recently reviewed the electronic data files of the Epilepsy Program of the Cleveland Clinic Foundation and identified 34 patients with unequivocal EEG-video documented dialeptic seizures in patients with focal epilepsies (Figure 53. 2).

Clinical characteristics of dialeptic seizures

Clinical symptomatology

Dialeptic seizures are seen in different epileptic syndromes and tend to vary considerably in their clinical semiology. In the literature there is no good semiological study studying systematically the differences of dialeptic seizures in different epileptic syndromes. Particularly, there is little data on dialeptic seizures in focal epilepsies. Because of this limitation it is necessary to describe the characteristics of dialeptic seizures independently for each epileptic syndrome.

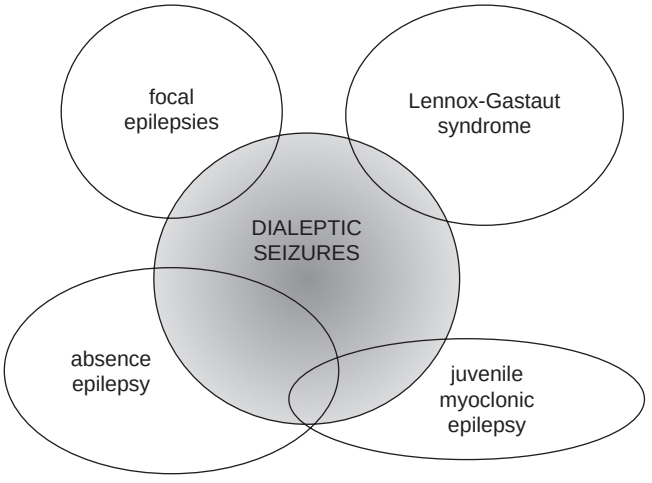

Figure 53.1 Dialeptic seizures occur in absence epilepsy, juvenile myoclonic epilepsy, Lennox-Gastaut syndrome and in focal epilepsies.

Dialeptic seizures in patients with absence epilepsy

The hallmark of dialeptic seizures in these patients is a sudden lapse of consciousness with amnesia and an arrest of volitional movements. Usually the seizures are brief, lasting about 4–10 seconds.[29] Rarely (3%), dialeptic seizures last up to one minute.[15–17,30] The seizures may be subtle and go unnoticed by the surrounding. The patient will typically show an arrest of whatever they were doing at the onset of the seizure. A pre-existing movement like walking may however sometimes be continued for some time. If a dialeptic seizure occurs while talking, the patient may realize an interruption of the conversation but may otherwise be unaware of having had a seizure. During an dialeptic seizure the patient is unresponsive, but may grunt in reply to a question or verbal commands. Reactivity is frequently disturbed at the beginning of the seizure and is less pronounced after a few seconds.[7] Browne *et al.*[7] could demonstrate, that 4 seconds after onset of the spike-wave discharges, 52% of their patients with generalized epilepsies had normal reaction time. This can be nicely documented when asking the patient to press a button using the 'clicker test'. The patients are usually unable to follow the command to press the button but some may recall the command later[8].

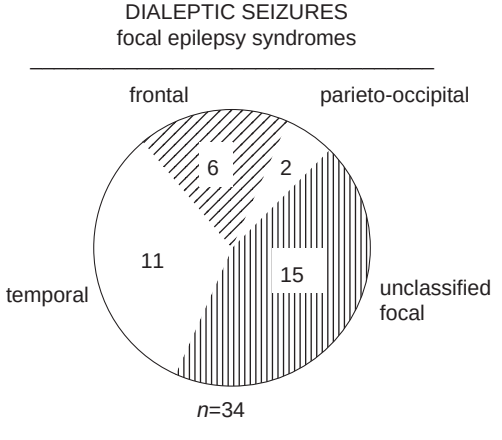

Figure 53.2 Focal epilepsies in which video-EEG documented dialeptic seizures were seen in 34 patients recorded at the Cleveland Clinic Foundation.

During a dialeptic seizure motor activity is normally reduced to a minimum, although some minor movements may be present the longer the seizure lasts.[17] These typically include clonic or versive upward eye movements, blinking or mild clonic jerks of the face or the extremities. The muscle tone may change during such attacks either presenting an increase of tone such as in a 'retropulsiv' movement of the trunk [16] or rarely a decrease of tone leading to dropping of the head or slumping of the trunk. The face usually gives the impression of atonic stare. The eyes become vacant giving a trance like expression. Subtle automatisms like lip smacking, swallowing, or fumbling may also occur but should not predominate otherwise the seizure would be classified as automotor seizure. Polygraphic video-EEG studies have shown that 1.2 seconds after onset ocular movements occur followed by oral automatisms about 4 seconds later and 1 second later manual automatisms develop.[17] Dialeptic seizures usually end abruptly, and the patient may commence his previous activities being amnestic for the time of the seizure. Detailed video-EEG analysis supported the clinical experience that most patients demonstrate some mild motor activity during their dialeptic seizures and only rarely lapse of consciousness and arrest of motor activity are the only ictal features.[15–17]

Dialeptic seizure is the predominant seizure type in absence epilepsies and best described in this epilepsy syndrome. These patients account for 10–15% of epilepsy patients in the pediatric age range.[31] The dialeptic seizures in these patients usually last 3 to 10 seconds, occur daily and very frequently ('pyknolepsy').[32] The age of onset ranges from 3 to 12 years of age and girls account for approximately two-thirds of the affected.[16,30] Later in life, patients with absence epilepsies frequently suffer also from generalized tonic-clonic seizures.[16,29,33]

In long-term follow-up studies, the proportion of patients entering remission varied between 19% to 90%.[34–42] Favorable prognostic factors include normal intelligence, lack of additional generalized tonic-clonic seizures, typical 3 Hz Spike-wave-complexes and initial response to medical treatment. Generalized tonic-clonic seizures occur in 35–60% of these patients.[35,37,38,41]

The longer the follow-up period, the poorer seems the remission rate. However, even if the dialeptic seizures have a good prognosis, generalized tonic-clonic seizures may ensue in adulthood.[43] In a long-term follow-up study over 20 to 37 years, 92% of the patients, in whom the dialeptic seizures persisted beyond the age of 30 to 61 years, eventually developed generalized tonic-clonic seizures.[44]

Some authors subdivide absence epilepsies into childhood absence epilepsy and juvenile absence epilepsy according to the age of onset and clinical course.[16,45] The patients with juvenile absence epilepsy are reported to have less frequent dialeptic seizures ('spanioleptic'), generalized tonic-clonic seizures may precede the dialeptic seizures more frequently and the EEG shows more irregular and fast spike-wave-complexes and a higher rate of photoparoxysmal responses [46] as compared to the childhood absence epilepsy group. These differences are considered to reflect genetically different traits.[47] Others have questioned the clinical significance of this subdivision of absence epilepsies and propose a continuum of idiopathic generalized epilepsies with a great deal of overlap.[48–51] The issue is at present not resolved, but subclassification of the absence epilepsies may be justified in the light of further

genetic studies[47] and possible different prognosis.[42,51] Childhood absence epilepsy showed less seizure relapse after discontinuation of antiepileptic medication (19%) than juvenile absence epilepsy (33%),[42] but this observation was not supported by others.[51]

The ictal EEG usually reveals regular spike-wave-complexes which show a repetition rate of 3 Hz. The spikes may be more blunt and the repetition rate will drop the longer the dialeptic seizures last.

Patients with absence epilepsies are particularly sensitive to hyperventilation and/or photic stimulation.[34,52–54] Of the 374 dialeptic seizures in the 48 patients evaluated by Penry *et al.*, 29% occurred spontaneously. Hyperventilation which is the most potent activator in these patients, provoked 53% and photic stimulation another 18% of the dialeptic seizures.[15] Both methods also activate interictal generalized spike-wave-complexes in the EEG.

The evolution of dialeptic seizures depends on the epilepsy syndrome. In generalized epilepsy syndromes the typical evolution of an dialeptic seizure is into a generalized tonic-clonic seizure.[16,24]

Dialeptic seizures in patients with Lennox-Gastaut syndrome

It was already noticed in the early days of EEG that a slow repetition rate of generalized spike-wave-complexes at 2 Hz ('petit mal variant') correlates with a milder impairment of consciousness during dialeptic seizures as compared to the 3 Hz spike-wave pattern.[54–55] The syndrome has been delineated later referring to patients with frequent tonic-, atonic-, myoclonic- and dialeptic seizures commencing early in childhood and being poorly responsive to medication. The patients usually have or develop mental impairment.[56,57] The ICES lists these dialeptic seizures as 'atypical' absences (see above).[3] In a pediatric age group Lennox-Gastaut syndrome accounted for 1–2%, whereas childhood absence epilepsy for 10–15% and juvenile absence epilepsy for 5%.[31] In patients with Lennox-Gastaut syndrome the onset and end of dialeptic seizures was reported to be more gradual and not as abrupt as in the absence epilepsy patients and the attacks usually last longer. However, the video-EEG study of Holmes *et al.*,[14] on 926 dialeptic seizures in 54 patients did not show any significant difference in the seizure onset and end between typical and atypical absence seizures. Some tonic, atonic and/or clonic movements particularly concerning the eyes and the perioral muscles and automatisms may occur.

Dialeptic seizures in these patients are not precipitated by hyperventilation and photic stimulation. Hyperventilation rarely facilitates the occurrence of slow-spikes-wave complexes and photic stimulation does not have any effect.[58]

The evolution of dialeptic seizures in these patients has not yet been systematically evaluated but they can also evolve into generalized tonic-clonic seizures.

Dialeptic seizures in patients with other generalized epilepsies

Dialeptic seizures are not infrequently seen in patients with other generalized epilepsies.[16,59] Juvenile myoclonic epilepsy occurs in 5% of a pediatric population.[31] The frequency of dialeptic seizures in patients with juvenile myoclonic epilepsy varies between 15–40% of the patients in different studies.[16,61–63] Clinically, the dialeptic seizures in this patients group do not differ from those seen in patients with absence epilepsies. However, the ictal EEG in this older age group is not as regular as in the children with absence epilepsies and shows typically irregular spike-wave complexes with a repetition rate faster than 3 Hz.

Photic stimulation seems to be particularly useful in patients with juvenile myoclonic epilepsy and elicits epileptiform activity in the EEG of 30% of these patients,[46] although dialeptic are rarely provoked. Rarely, other mechanisms such as reading-induced or video-game-induced dialeptic seizures have been reported.[64,65]

Some authors proposed the classification of an 'epilepsy with myoclonic absences' describing an epilepsy syndrome with patients who they felt are inbetween the idiopathic absence epilepsies and the Lennox-Gastaut syndrome.[35,66–68] 'Myoclonic absence seizures' represent the only or predominant seizure type in these sometimes mentally retarded patients and the myoclonic components are described to be massive as compared to the mild clonic movements recognized in typical dialeptic seizures. These seizures are refractory to medication in about 50% of these patients. This syndrome has been included in the International Classification of Epileptic Syndromes.[69] However, a distinction by seizure type alone appears unjustified.

Patients with neurological diseases such as Batten disease, Lafora disease, or subacute sclerotic panencephalitis are rarely reported to suffer from dialeptic seizures.[70–72]

Dialeptic seizures in focal epilepsies

Janz[73] already pointed out that dialeptic seizures consisting of pure brief lapse of consciousness may occur in epilepsy syndromes other than generalized epilepsies as well and therefore proposed the term 'pyknoleptic petit mal' for dialeptic seizures in patients with childhood absence epilepsy. Although several textbooks on epilepsy mention that dialeptic seizures may also occur in focal epilepsies, our knowledge at present is very limited.[16,73] Only few data and scattered reports are available which mainly deal, although not exclusively, with patients with frontal lobe epilepsies.[25,28]

An abrupt ictal onset and end which is a typical feature of dialeptic seizures in childhood absence epilepsies seems also to occur in patients with frontal lobe epilepsies. This observation prompted the French school to coin the term 'frontal absence'.[27,74] Fronto-mesial and fronto-orbital seizure onset has been associated with this kind of seizure.[27,74] 'Complex partial seizures' including dialeptic seizures (frontal absences) have been reported to occur in 161 seizures of medial intermediate frontal onset of 39 patients.[27,74] However, the relative frequency of dialeptic seizures (frontal absences) was not specified. The symptoms observed during these 'frontal absences' include disturbance of consciousness (loss of contact), speech arrest, arrest of movements, simple gestures (automatisms), conjugate deviation of the eyes and head, and immediate recovery of consciousness.[27,74]

Patients with temporal lobe epilepsies not infrequently also have seizures consisting of an arrest of movement and lapse of consciousness without automatisms or other

motor movements.[21,78] Because these seizures resemble the dialeptic seizures ('absences') seen in patients with generalized epilepsies the term 'pseudoabsence' has been proposed.[26,78,79] Karbowski *et al.* described this phenomenon in 5 of 12 children evaluated.[80] Wieser *et al.* reported that 'pseudoabsence' seizures have been the predominant seizure type in 2 out of 25 patients evaluated.[79] Shimizu *et al.* reported that the interictal PET regional hypometabolism was identical in 18 temporal lobe patients regardless whether they had seizures characterized by automatisms ('automotor seizure') or motionless staring ('dialeptic seizures').[81] Wieser subclassified focal seizures arising from frontal and temporal lobe according to seizure onset as documented by depth recordings.[82] However, no clear clinical distinction was made with regard to dialeptic seizures. Recently, a study using cluster analysis in seizures of patients with frontal and temporal lobe epilepsies concluded that dialeptic seizures may occur in both syndromes and cannot be distinguished on clinical grounds only.

The distinction of dialeptic seizures consisting of an arrest of movement and lapse of consciousness arising from the temporal lobes and dialeptic seizures particularly in patients with Lennox-Gastaut syndrome ('atypical' absences) is sometimes impossible based on clinical semiology.[83]

We reviewed the database at the Epilepsy Monitoring Unit of the Cleveland Clinic Foundation from 1991 to 1995 looking for patients who underwent prolonged video-EEG Monitoring and in whom at least one unequivocal dialeptic seizure was recorded. Dialeptic seizures were defined purely on clinical grounds as seizures in which arrest of activity and lapse of consciousness were the predominant ictal features, and other features such as automatisms are not as prominent. We identified 34 patients with focal epilepsies in whom dialeptic seizures were documented by EEG and video. Fifteen of these 34 patients had focal epilepsies of one hemisphere but the epileptogenic zone could not be localized further. Eleven patients had temporal, six patients frontal and another two had parieto-occipital lobe epilepsies (Figure 53.2). The proportion of patients with temporal lobe epilepsy may be biased because these patients tend to be over-represented in epilepsy surgery centers.

In focal epilepsies hyperventilation may provoke focal epileptiform discharges in up to 10% of the patients, but it is not known whether this activates dialeptic seizures. Photic stimulation is not an activator of focal seizures except rarely in parieto-occipital epilepsies. It is not known if dialeptic seizures can be triggered by photic stimulation.

The semiology of the dialeptic seizures was similar independent of the lobe of seizure origin. Thus, analysis of the dialeptic seizure itself did not allow differentiation of the epileptogenic zone. However, the evolution of dialeptic seizures may provide lateralizing or localizing information (see below). Dialeptic seizures may be preceded by other seizure types such as auras[24,25] (see below). In focal epilepsies the evolutions are more variable: an aura may precede a dialeptic seizure and the dialeptic seizure itself may evolve into other focal seizures such as for instance into a versive seizure. At present no representative data is available as to the evolution of dialeptic seizures. There are two main reasons for this: the term 'absence' is by definition of ICES a generalized seizure, and ICES does not allow for classification of seizure evolution in generalized epilepsies. Recently, a study analyzed seizure patterns in patients with frontal and temporal lobe epilepsies and used a purely clinically-based definition of the seizure types.[84] Most dialeptic seizures (identified as 'absence' seizures in this study) commenced without warning, but in 13 of 57 cases auras preceded the dialeptic seizures and further evolved into versive or automotor seizures.[84]

Pathophysiology

Generalized epilepsies

The advent of electroencephalography proved the epileptic origin of dialeptic seizures in generalized epilepsies. Gibbs *et al.* described first that 'absence' seizures are associated with a generalized 3 Hz spike-wave pattern in the EEG.[4] Since several experimental animal models have been established which served for both the search of the underlying mechanisms of the absence epilepsies and the development of drugs against human dialeptic seizures. Examples include, amongst others, the systemic pentylenetetrazol model,[85] the feline generalized penicillin model,[86] the rat ICV enkephaline model,[87] the systemic gamma-hydroxybutyrate model,[88] the tetrahydroxyisoxosolopyridine (THIP) model,[89] and genetic models such as the photosensitive Senegalese baboon (papio papio)[90] or the tottering mouse.[91]

The concepts proposed for the generation of dialeptic seizures occurring in generalized epilepsies have been subject to much controversy. Two contrary hypotheses have been debated for decades.[92] The centrencephalic theory (Montreal school) proposed that a thalamocortical mechanisms capable of inducing spindles and recruiting responses were involved in the production of generalized spike-wave discharges and typical dialeptic seizures.[93,94] It has been postulated that brain stem structures as also the thalamus may play an essential role in the pathogenesis of dialeptic seizures. A recent study using functional MRI supported this view and showed that, during absence seizures of a patient with absence epilepsy, the BOLD effect in the frontal cortex was reduced whereas it was increased in the thalamus.[95] In contrast to this concept it has been stated that generalized spike-wave discharges are a cortical phenomenon.[96,97] Both concepts were based on the results of experimental studies in animals. In an attempt to reconcile these apparently conflicting views, the corticoreticular hypothesis has been put forward. It postulated that generalized spike-wave discharges result from an abnormal interaction of cortical and diffusely projecting subcortical thalamic and midbrain reticular mechanisms.[98,99] Based on this theory, the cortex is the primary generator of spike-wave discharges.[100] It could be demonstrated that electrical stimulation of the thalamus which elicited spindles and recruiting responses in control animals elicited spike-wave complexes in cats given penicillin intramuscularly.[101] On the other hand, injection of penicillin in the thalamus did not elicit spike-wave discharges, whereas diffuse application on the cortex did. Additional studies could also demonstrate a facilitating effect on spike-wave discharges through a depression of desynchronizing effects of the reticular formation.[102]

Several further mechanisms, such as altered properties of T-type calcium channels, increased numbers of GABA-B receptors, and changes in the subunit composition of GABA-A receptors have been postulated to be involved in the generation of dialeptic seizures in generalized epilepsies.[103] Since the

predominant clinical feature of dialeptic seizures is an inhibition of motor and cognitive function, it has been suggested that the underlying mechanisms may involve synaptic inhibition.[104] It could be demonstrated in the feline generalized penicillin model, that the slow-waves of the spike-wave complexes are associated with GABA-mediated chloride-sensitive IPSPs in cortical neurons.[105] Furthermore, GABA agonists like THIP can elicit 'absence like seizures' suggesting an effect of synaptic inhibition.[89]

Focal epilepsies

The term 'frontal absence' has been coined by the French school referring to brief seizures which are clinically not distinguishable from dialeptic seizures of the generalized epilepsies. Invasive EEG recordings in these patients frequently revealed a frontal seizure onset.[13,106,107] It has been suggested that epileptic discharges arising from several areas of the frontal lobe, such as intermediate frontal region, orbitofrontal region, and cingulate gyrus may elicit dialeptic seizures.[20,74,79,108,109] It is intriguing that a seizure symptomatology which conceptually is so strongly associated with generalized epilepsy can have a focal seizure onset. The concept of 'frontal absence' was further supported by studies showing that electrical stimulation of the mesial frontal lobe can give rise to dialeptic seizures as well as to generalized spike-wave discharges at the scalp.[18,26] This finding is in correspondence with the EEG observation of secondary bilateral synchrony arising from the mesial frontal lobe.[28] Systematic electrical stimulation of the frontal lobe disclosed regions from which an arrest of motor activity could be elicited.[110–112] Close connections between the prefrontal cortex and the nonspecific thalamic nucleus and the midline region of the intralaminar thalamic complex are known to exist.[113] Seizures may arise from prefrontal cortex rapidly spread to the reticular formation causing an alteration of consciousness and generalization. Epileptic activation of the negative motor regions or the disturbance of consciousness itself may lead to an arrest of motor activity. It is not yet clear whether the frontal cortex or subcortical structures are the pacemaker of these ictal discharges, which usually involves both of them during the course of a seizure.[74]

Arrest of motor activity and blank staring with loss of consciousness have also been described in patients with temporal lobe epilepsies,[19,80] which makes it most unlikely to be specific to a particular cortex region. Epileptic activation of limbic structures has been proposed as the pathogenesis for these dialeptic seizures but this has not yet been proven.[73] Invasive recordings have shown that ictal discharges in the mesial temporal lobes may be associated with this symptomatology.[82] Ictal SPECT studies in patients with temporal lobe epilepsies have shown that loss of consciousness was associated with hyperperfusion of brainstem structures as a result of spread of epileptic activity.[114] Although some invasive recordings can reveal highly localized seizure onset zones, it has to be kept in mind that invasive studies only record from a very limited region of the brain.

Theoretically, the degree of arrest of motor activity and loss of consciousness may be a reflection of the volume of cortex involved in the seizure discharge. It is conceivable that motor activity may be inhibited either by epileptic activity excerting an interference on the function of primary motor cortex or epileptic activation of negative motor areas which both lie within the frontal lobe. Source analysis of generalized spike-wave complexes seen with dialeptic seizures in patients with generalized epilepsies points to the frontal lobes.[115] Alternatively, arrest of motor activity could be an expression of the loss of consciousness. However, as mentioned before, preserved perception associated with inhibited motor activity has been documented.[116] On the other hand disturbed perception with preservation of some automatic motor activity has also been observed. It therefore seems unlikely that consciousness and motor activity are disturbed by the same mechanisms.

Illustrative patient

This 16-year-old girl has had epilepsy since the age of 14 years. The seizures were characterized by loss of responsiveness and arrest of behavior. Sometimes, her dialeptic seizures were heralded by an aura sensation of vague strangeness or familiarity (psychic aura). Postictally, she had difficulty naming objects but she could describe the use of the objects. The postictal aphasia points to seizure onset in the dominant hemisphere. Ictal EEG showed left temporal seizure pattern. Interictally, the EEG showed spikes and continuous slowing in the left temporal region. MRI showed a low grade astrocytoma in the anterior part of the left inferior temporal gyrus and ipsilateral mesial temporal sclerosis. The patient underwent a left anterior temporal resection including the tumor and remained seizure free for 5 years' follow-up.

Localizing and lateralizing significance

The above-mentioned semiological features of dialeptic seizures allow to some extent to identify the epilepsy syndrome and thus the epileptogenic zone. The semiology of dialeptic seizures may provide some clues as to the epilepsy syndrome: shorter duration (< 20 s) is more likely to occur in generalized epilepsy as compared to focal epilepsy.[22] Typically additional clinical factors are helpful like for instance the pyknoleptic occurrence of brief dialeptic seizures in a neurological normal child of school age which is highly suggestive of absence epilepsy. Pyknoleptic appearance was extremely rare in focal epilepsy.[22] Since, by definition, little additional clinical features are associated with dialeptic seizure it is not surprising that the analysis of these phenomena provides few criteria for differentiation between different epilepsy syndromes. Blinking seems to be significantly more frequent in generalized epilepsy than focal epilepsy.[22] The evolution of dialeptic seizures is important for localization and lateralization. If dialeptic seizures are preceded by an aura this fact clearly points to a focal epilepsy and the characteristics of the aura are crucial for further localization. There is scant data on which and how often lateralizing features occur during dialeptic seizures. Somatosensory auras would favor a seizure onset in the paracentral region, or abdominal auras a temporal seizure onset.[117] Unilateral clonic seizures which evolved into dialeptic seizure have been reported, but the epileptogenic zone in this patient was most likely rather diffuse as documented by EEG and multiple other seizure types.[24]

The seizure evolution following a dialeptic seizure is also important: dialeptic seizures which evolve into hypermotor or tonic seizures are highly suggestive of a frontal seizure onset. Automotor seizures of patients with temporal lobe epilepsy frequently show some motionless stare at seizure onset.[21] This evolution is typical for automotor seizures and should not be classified as dialeptic seizure→ automotor.[2,118]

Postictal phenomena, such as postictal aphasia, point to a seizure onset in the dominant hemisphere as shown in the illustrative patient. We observed a few versive seizures following dialeptic seizures which arose contralateral to the direction of the version.[119] Other lateralizing phenomena, such as postictal coughing,[120] ipsilateral nose wiping,[121] sign of four,[122] ictal vomiting,[123] and unilateral blinking [124,125] occur probably rarely, if at all, during dialeptic seizures but no data is available of the frequency and lateralizing significance in the setting of dialeptic seizures.

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54a Special seizures: localizing and lateralizing value

SR Benbadis

Introduction

'Special seizures' are, in the semiologic seizure classification, those that cannot be classified in any of the other broad categories[1] (see Chapter 34 in this volume). Thus, by definition, these seizures do not meet criteria for *auras*, *autonomic seizures*, *dialeptic seizures*, or *motor seizures*. In general, special seizures represent *negative* phenomena, which makes them unusual or 'special' among epileptic seizures. Special seizures include atonic seizures, astatic seizures, hypomotor seizures, akinetic seizures, negative myoclonic seizures, and aphasic seizures (see Chapter 32 in this book).

Astatic and hypomotor seizures

These two categories of special seizures, like others in the semiologic classification, are defined by the predominant phenomenology. What they have in common is that they are also defined by the *inability to characterize the mechanism of the symptoms due to lack of information*. Thus, they do not represent unique or specific seizure types and do not have a clear localizing value.

- *Astatic seizures* are seizures whose salient feature is a fall, but in which the mechanism of the fall cannot be further categorized. Thus, this category is most useful when there are incomplete data, e.g., history only or infants. If the predominant historical feature is a fall and there is no further useful information, this category (astatic seizure) is used. When more data are available, especially video-EEG recordings, more a specific seizure type should be identified in most cases. Seizure types that can result in a fall include tonic, atonic, GTC, and (more rarely) myoclonic seizures. Again, these are usually relatively easily identified with video-EEG monitoring. In occasional situations where the seizure cannot be more precisely classified even on video-EEG it is usually because they represent a 'mixture' of myoclonic, tonic, and atonic features[2]. These are usually seen in patients with symptomatic generalized epilepsies of the Lennox-Gastaut type (see tonic seizures in Chapter 53 and atonic seizures below), and in myoclonic astatic epilepsy of early childhood (Doose syndrome).[2]
- *Hypomotor seizures* are those whose salient feature is immobility or a reduction in movements. As for astatic seizures, this category is most useful when there is incomplete data, e.g., history only. If the predominant historical feature is immobility and there is no further useful information, this category (hypomotor seizure) is used. More specific seizure types that can result in a hypomotor behavior include auras (by way of distress or distractibility), dialeptic seizures (where the predominant manifestation is an alteration of consciousness), and negative myoclonic or akinetic seizures (see below), and these can be identified more precisely with video-EEG recordings. Probably the common justified use of this category is in infants and young children where consciousness cannot be assessed. In fact, in this age group hypomotor seizures are likely a bland form of 'complex partial' seizures with no or minimal automatisms.[3]

Atonic seizures

Atonic seizures are defined by loss of postural tone. This is usually abrupt and results in a fall, complete or incomplete depending on severity and the patient's position. They frequently result in injuries.

Atonic seizures are seen almost exclusively in patients with symptomatic generalized epilepsies of the Lennox-Gastaut type, so their 'localizating value' is that they are usually... generalized. Atonic seizures are, in fact, a type of generalized seizures in the ILAE seizure classification,[4] and are typically accompanied, ictally, by generalized seizure patterns such as electrodecrement, paroxysmal fast activity, or spike-wave complexes. There is some evidence for a symptomatogenic zone in deep (nonrespectable) structures such as the brainstem reticular formation[5,6] or the thalamus.[7] Atonic seizures are considered relatively common in the symptomatic generalized epilepsies of the Lennox-Gastaut type because seizures that cause falls are often assumed to be atonic. However, careful video analysis shows that the majority of epileptic falls are tonic rather than atonic.[6, 8] Often it is not completely clear that it is 'atonia' that is causing the fall, and it is instead a mixture (or sequence) of myoclonic, tonic and atonic phenomena.

Atonic seizures can, rarely, be seen in focal epilepsy but this has not been clearly documented.[9] However, even in patients with focal epilepsy (e.g., secondary to a focal cortical dysplasia), ictal SPECT recordings point to a strong inhibition in the *bilateral* motor cortexes.[10] From a practical point of view,

atonic seizures do not a have a reliable localizing value for purposes of resective surgery, and their presence should, generally, argue against pursuing resective surgery.

Akinetic seizures and negative myoclonic seizures (epileptic negative myoclonus)

That electrical stimulation of the cortex can inhibit movements has been known since the seminal work of Penfield and Jasper.[11] More recent studies showed that electrical stimulation of two regions in the frontal lobe elicit inability to initiate or maintain voluntary movements.[12–15] The *primary negative motor area* lies in the inferior frontal gyrus, immediately anterior to the motor face area, close to (and often overlapping with) Broca's area on the dominant side. The *supplementary negative motor area* is anterior to the face region of the supplementary sensorimotor area. Electrical activation of these negative motor areas may produce focal as well as bilateral inability to perform voluntary movements.[12,13] The fact that responses to electrical stimulation are often bilateral makes these seizures difficult to lateralize on clinical (semiologic) grounds. Studies in primates support observations documenting two similar negative motor areas in the frontal lobe.[12] Premotor and primary somatosensory cortex xan also produce (contralateral) negative motor responses.[16,17] Epileptic myoclonus is referred to as 'pure' when it is not immediately preceded by positive myoclonus, enhancement of EMG, or a motor evoked potential.[16] There is good evidence that the presence or absence of an antecedent positive motor phenomenon depends partly on stimulus intensity, except for the SMA where pure silent periods are obtained regardless of stimulus intensity.[16]

Akinetic seizures

Akinetic seizures are defined, in the semiologic classification, by the inability to perform voluntary movements, not due to loss of consciousness (which would make it a dialeptic seizure), or loss of muscle tone (which would make it an atonic seizure). It should be pointed out that the term 'akinetic seizures' has different meanings outside of the semiologic classification. A longer duration (several seconds) differentiates it from negative myoclonic seizures, which are much briefer (see below). Akinetic seizures have been reported under other names such as ictal paresis[18] and hemiparetic seizures.[19]

The symptomatogenic zone for akinetic seizures is most likely the primary or supplementary negative motor areas, as can be demonstrated by video-EEG recordings[20] and confirmed by electrical cortical stimulation.[12–15] Akinetic seizures most often affect distal (hand) muscles. Because of their proximity, the primary motor area are often simultaneously activated, producing clonic jerking of the face or tongue at the same time.

Negative myoclonic seizures (epileptic negative myoclonus)

Negative myoclonic seizures are *brief* (often 30–50 msec but by definition < 500 msec) episodes of muscle atonia, and can be viewed as the brief (sporadic) version of akinetic seizures. They can in fact be elicited by electrical stimulation using single or low frequency (1 Hz) stimulation.[16] This is analogous, on the 'positive' side, to myoclonic seizures being the brief (sporadic) version of clonic seizures. They are only clinically apparent if the muscles in question are tonically used at the time (for example, outstretched hands). The muscle atonia can be documented by a silent period on EMG, which is identical whether the negative myoclonus is epileptic or nonepileptic such as asterixis.

The epileptic nature of a negative myoclonus, and its symptomatogenic zone, can be documented by its time-locked association to an epileptiform EEG discharge (spike or sharp wave), which typically occurs 15–50 msec prior to the EMG inhibition.[21–25] Since negative myoclonic seizures are essentially the brief (sporadic) version of akinetic seizures, their localizing value (or lack thereof) is similar, pointing to the negative motor areas mentioned above: premotor cortex[16] post-central primary somatosensory,[16] primary[2,23] and supplementary negative motor area (dorsolateral frontal).[26,27] In keeping with this, when epileptic negative myoclonus is seen in association with clear surface EEG abnormalities, the phenotype resembles benign childhood epilepsy with Rolandic spikes.[28]

Aphasic seizures

Various speech disturbances can occur during seizures.[29–31] Ictal aphasia (or dysphasia) is found in about 30% of patients with temporal lobe epilepsy.[29,32] However, the term 'aphasic seizures' should be reserved for seizures in which aphasia is the *predominant* ictal symptom, and such seizures are relatively rare (the vast majority of aphasias are caused by head injury, stroke and dementia). In the International Classification of Epileptic Seizures, 'dysphasic seizures' are found under 'simple partial' seizures (with psychic symptoms), which is appropriate, since by definition aphasia requires intact consciousness. Confusingly, however, it is also stated that these seizures more commonly occur as 'complex partial' seizures.[4]

Studies of electrical cortical stimulation have identified four language areas: Broca's, Wernicke's and supplementary motor areas have been known since the work of Penfield and associates,[33,11] while the basal temporal language area was described more recently.[34–36] Identifying a language disturbance during electrical cortical stimulation requires a meticulous methodology to exclude speech impairment caused by nonspecific motor phenomena (positive, negative or apraxic).[34,35] Identifying aphasia during seizures is fraught with the same difficulties, as it requires a *selective* impairment of language. Consciousness and awareness should be intact. If a patient has a more global impairment or is mute, aphasia may well be present but cannot be identified. As pointed out above, ictal aphasia may be difficult to elicit and diagnose in typical short-lived seizures. Thus, while some reports on ictal aphasia include cases of sporadic seizures,[37–42] the majority describe cases of status epilepticus.[43–51]

Types of aphasia include Wernicke, conduction, anomic, and isolation (transcortical) aphasia.[52] However, due to short seizure duration and concomitant symptoms, such complex classification is not possible for ictal aphasia. From a practical

point of view, ascertaining the presence of a true language disturbances, rather than a nonspecific motor phenomenon (e.g., speech arrest) or a more global alteration in consciousness, is the crucial step. The basic dichotomy (i.e., anterior/Broca/expressive/nonfluent vs. posterior/Wernicke/receptive/fluent) is realistically practical for seizures, and consistent with the early reports of ictal dysphasia.[32] The easiest type to identify ictally is the anterior type (Broca, nonfluent, expressive,). The posterior type (Wernicke, receptive, fluent) is more difficult to distinguish from less specific alteration of awareness. Further subtypes cannot realistically be identified ictally, which is unimportant since the type of aphasia does not reliably predict the lobe or region of seizure onset.[30] The fact that *subtypes* of aphasia have no specific localizing value is quite consistent with the findings of cortical stimulations, where the type of aphasia may change with the stimulus intensity, and where stimulation of Broca, Wernicke, and basal temporal language areas produces relatively similar deficits.[35]

Localizing value

Most patients with documented aphasic seizures have temporal lobe epilepsy, but this most likely reflects the predominance of such patients in monitoring units. In the only sizeable series of patients with ictal aphasia,[32] 30 of 34 patients (88%) had left temporal lobe epilepsy (defined preoperatively). Of 17 patients with definite localization (i.e., became seizurefree after temporal lobectomy) and ictal aphasia, 16 (94%) had left temporal lobe seizures. Ictal aphasia can occur in seizures arising from almost any lobe, including frontal, fronto-temporal, centro-parietal, parietal, temporo-parietal, posterior lateral temporal, and temporo-occipital.[37,40,45,47,50,51,49,53,55] This is not surprising if one considers the four language areas defined by electrical stimulations. Furthermore, the presence of ictal aphasia in seizures of various origin is also in keeping with the important concept that distinguishes between epileptogenic zone and symptomatogenic zone[56]; in brief, epileptogenic zones in various locations may be in silent cortex but produce discharges which spread to one or more language areas. In additional to the 'classical' language areas, there is also convincing evidence incriminating the basal temporal language area.[30,37,38,43]

Ictal aphasia as a lateralizing sign

By contrast, regardless of the lobe, the *lateralizing* value of ictal aphasia is excellent, with nondominant seizures being exceptional. Ictal aphasia was seen in two seizures arising from the nondominant hemisphere (in one patient) in the series of Gabr *et al.*,[29] and in that patient aphasia was limited to paraphasia. One similar exception was reported in the series by Serafetinides and Falconer[32]; although the patient had ictal aphasia and proven right temporal lobe epilepsy (by seizure-freedom after temporal lobectomy), language dominance had not been determined by Wada testing, and the patient may have been right-hemisphere dominant. Thus, when present, the lateralizing value of ictal aphasia is high, and seems to be comparable to that of postictal aphasia, which is 92–100%.[29,57]

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54b Secondary generalized tonic-clonic seizures

SD Lhatoo and HO Lüders

Introduction

Secondary generalized tonic-clonic seizures (SGTCS) are a common occurrence in the video-monitoring phase of the presurgical assessment of focal epilepsies, although in contrast to primary generalized tonic clonic seizures (PGTCS), the rather scanty literature available on their semiology and pathophysiology belies this. To date, the most authoritative work on generalized tonic clonic seizures (GTCS) has been the description provided by Gastaut and Broughton in their influential monograph *Epileptic Seizures: Clinical and Electrographic Features, Diagnosis and Treatment*. Modern epilepsy semiology literature is reliant on their observations and the few contemporary analyses that exist use their description as a benchmark. Gastaut and Broughton acknowledged the difficulty in distinguishing PGTCS from SGTCS when seizures were clinically generalized at onset, a conundrum that has not completely diminished since then, and thus their classical account of the generalized tonic-clonic seizure appears to present a composite of mainly 'grand mal' primary but also secondary generalized tonic-clonic seizures. However, certain semiological features often differ and may be of critical value in the distinction of one from another. Furthermore, these features may have a lateralizing value that complements the other facets of presurgical assessment.

Semiology of the SGTCS

Gastaut and Broughton's work provides exquisite detail on the semiology and pathophysiology of GTCS with detailed descriptions of electroencephalography, electrocardiography, electrodermography, sphygmomanometry, pupillary measurement, intravesical pressure measurements, and audiometry and spirometry. They divided the various phases of the GTCS into:

1. preictal manifestations
2. the ictal phase
   a. the tonic phase (including an 'intermediate vibratory period')
   b. the clonic phase
   c. (concurrent) Autonomic changes
3. immediate postictal features
4. late postictal features

It is the first two phases–the preictal phase and the ictal phase, that are of greatest semiological interest, mainly because of the clinical information that they provide as an aid to seizure localization and lateralization. The later phases of the SGTCS are less likely to yield significant information.

The preictal 'myoclonic' phase (such as occurs in juvenile myoclonic epilepsy (JME)) was thought to occur in the majority and constituted a 'succession of brief, bilateral and massive muscle contractions which usually last a total of several seconds ... frequently accompanied by a spasmodic cry'. The tonic phase, accompanied by loss of consciousness, was characterized by a brief phase in flexion followed by a longer one in extension, in all lasting ten to twenty seconds. A typical flexion was described as one similar to the response to the command 'Put up your hands!' with shoulder elevation, arm elevation and the elbow semiflexion. The lower limbs were described as being less involved but often with flexion, abduction and external rotation of the thighs and legs, completing an emprosthotonic posture (Figure 54b.1).

This tonic flexion was followed by tonic extension into an opisthotonic position (Figure 54b.2). Contraction of the thoraco-abdominal musculature produced the 'tonic epileptic cry'. The arms became semiflexed in front of the chest but also at times became extended, with forearm pronation and either wrist flexion and finger extension or wrist extension and fist clenching. The legs went into forced extension, adduction and external rotation along with extension of the feet and toes into a Babinski-like posture. This 'tetanic' phase subsequently became less complete and the rigidity was replaced by a fine tremor that grew in amplitude and slowed in frequency from 8 per second to 4 per second because of recurrent decreases in muscle tone–a so-called 'intermediate vibratory period'.

The clonic phase lasted about 30 seconds and was said to occur when each of the recurrent muscular contractions responsible for the vibratory phase became sufficiently prolonged to completely interrupt the tonic contraction, the resultant flexor spasms of the entire body appearing to resemble an 'an epileptic form of bilateral myoclonus'. This myoclonus progressively slowed until seizure cessation. Variations to this entire theme were considered occasional and unusual. Asynchrony between two sides during the tonic or clonic phases was one such deviation. This asynchrony could be clinical or only evident on EMG recordings when clinically unnoticed.

Lateralization in the initial phase of the SGTCS

Two important studies have addressed the issue of the importance of two semiological features at the onset of secondary

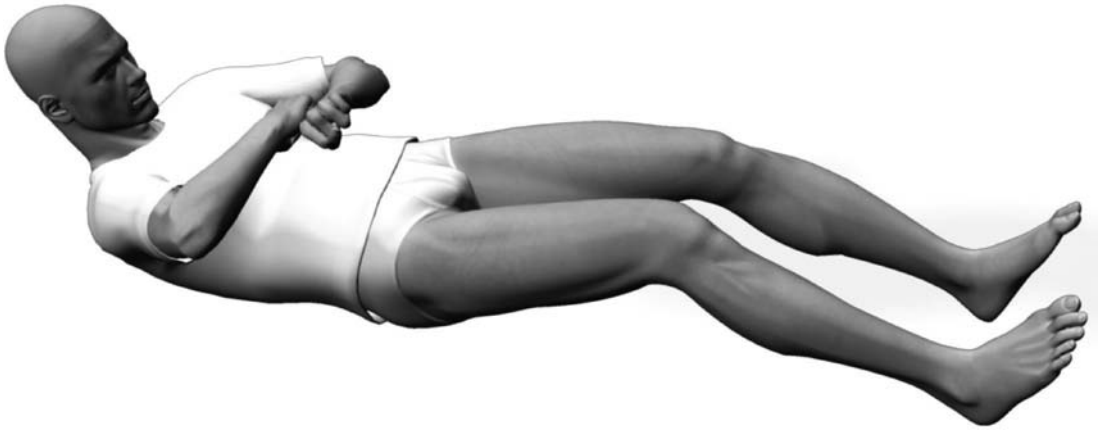

Figure 54b.1 The flexion or 'emprosthotonic' posture.

generalization in focal epilepsies that can be an invaluable aid to lateralization. Wyllie *et al.*[2] studied head version in 61 seizures in 27 patients and reported that this occurred contralateral to the hemisphere of seizure onset in all patients. It is important to emphasize here that the definition of head version is crucial to correct lateralization. Only forced and prolonged head turning, usually in a clonic motion with the chin pointing upwards, with eye version to the same side as head version allows precise lateralization (Figure 54b.3). Very frequently, such a version is also accompanied by pulling of the face towards the contralateral, clonic, twitching side.

Kotagal *et al.*[3] reported the 'sign of 4' or the 'figure 4 sign' where the elbow contralateral to the hemisphere of seizure onset extends and the ipsilateral elbow flexes over the chest to produce an upper limbs posture that resembles a figure 4. (Figure 54b.1). In a study that looked at 39 patients with focal epilepsy, correct lateralization with this sign was seen in 90%. Other studies have subsequently confirmed the clinical utility of this sign.

However, both head version and the sign of 4 are unreliable signs once the seizure is well established and their main value is derived at the onset of generalization when they are less likely to represent symptomatology remote from the ictal onset zone.

Lateralization in the SGTCS and seizure progression

A few studies have since examined the progression of the SGTCS (Table 54b.1). A study from Bethesda, Maryland in 1994[4] presented a videotape analysis of 120 SGTCS in 47 patients with focal epilepsy with an age range between 11 and 56 years. Seizure semiology analysis was carried out jointly by three observers and the generalized phase was divided into five phases that constituted onset of generalization, pretonic clonic, tonic, tremulousness and clonic phases. Eighty-four percent of the seizures had the 'onset' phase characterized by vocalization, head version or some form of movement, 48% had a pretonic clonic phase where patients had irregular and asymmetric jerking, 95% a tonic phase and 98% a clonic phase. Only 27% of these seizures exhibited all five phases. The authors noted that generalization was not uniform or symmetric and noted the marked heterogeneity in GTCS phenomenology. Another study that examined SGTCS progression in temporal lobe epilepsy patients in 2001[5] found the classically described sequence of progression in only half their patients and in a third, a clonic phase preceded the tonic and in a quarter, the progression was one of tonic to clonic to tonic. Asynchrony in the clonic phase was noted in only two patients.

An unblinded videotape analysis from Nashville, Tennessee in 1999[6] compared ten GTCS in nine patients with idiopathic generalized epilepsy and ten GTCS in ten patients with temporal lobe epilepsy. Interestingly, (and this has been noted by subsequent studies), focal features were seen before generalization in seven idiopathic generalized seizures, most commonly comprising head turning, in one patient occurring in different directions in two different seizures. The authors noted that the tonic phase was always symmetric but that in the last generalized

Figure 54b.2 The extension or (opisthotonic) posture.

Figure 54b.3 The sign of 4 with right elbow extension indicating left hemisphere seizure onset. Also notice version of the head to the right.

clonic phase, asymmetry or asynchrony of motor activity was seen transiently in three seizures. In contrast, in the temporal lobe epilepsy patients, focal tonic activity occurred in four seizures, with variable lateralization and there was asymmetric or asynchronous activity in the clonic phase in eight seizures. Seizure progression in these patients was tonic to clonic in eight, clonic to tonic to clonic in one and only clonic in one.

A 2003 study from Calgary[7] attempted to distinguish primary from SGTCS in children aged 18 months to 17 years by examining 64 GTCS in 13 children with medically refractory epilepsy. The study highlighted mouth movements and motor activity following clinical and EEG seizure end as distinctive features of the SGTCS, although these conclusions and their value in clinical practice is debatable. However, these authors also noted the asymmetry in arm movements in seven out of 12 children and in leg movements in nine out of 12 children during secondary generalization. In five patients, seizure activity continued on one side, with varying lateralization.

Thus, no reliable clinical features appear to lateralize the hemisphere of seizure onset once the seizure is well under way. This is not surprising, given that the seizure has propagated to areas distant from the ictal onset zone.

Lateralization in the latter phase of the SGTCS

Two studies have examined lateralization during seizure termination in temporal lobe epilepsy. They found that in 80–83% of seizures that ended in an asynchronous fashion, the final clonic movements occurred on the side ipsilateral to the hemisphere of seizure onset.[8,9] This may reflect on earlier seizure cessation in the hemisphere of seizure onset due to factors such as neuronal fatigue, an exhaustion of excitatory processes, or a predominance of inhibitory processes. The marked slowing usually seen on scalp-EEG during this phase in the hemisphere ipsilateral to the paradoxical movements lends support to this. Paradoxical movements are most likely to be generated in the contralateral cortex and propagated by the pyramidal tract, rather than originating in the brainstem, not least because there is a clear relationship between ipsilateral cortical discharges and strictly contralateral clonic signs. There appears to be some lateralizing value to this sign although it is important to emphasize that the seizure should always be viewed in its entirety and the value of lateralizing signs at seizure onset outweigh the importance of phenomena that occur during or towards the end of seizures.

Two common themes emerge from these studies. Firstly, that there is considerable heterogeneity in seizure progression during the phase of secondary generalization as compared to Gastaut's classical description and secondly, there is asynchrony (disparity of rhythm between the two sides) and/or asymmetry (disparity in amplitude of limb movement between the two sides) during the seizure in a substantial proportion of patients. Contrary to the caution required in interpreting late ictal phenomena, forced head version immediately prior to the onset of secondary generalization and the asymmetric 'sign of 4' tonic posturing at the onset of the SGTCS are known to be useful lateralizing features where head version or elbow extension in the sign of 4 occur contralateral to the hemisphere of seizure onset.[3] However, there is literature to suggest that focal features also arise in the GTCS of idiopathic generalized epilepsy, although definitions of head version for example, may differ in their interpretation.[10]

The Cleveland Clinic experience

In our own semiological analysis of 24 SGTCS in 14 patients (12 male, two female) aged 9–39 years who underwent

Table 54b.1 Studies of seizure semiology in secondary generalized tonic-clonic seizures

		Seizure progression – % of patients[b]				Asynchrony[c]
Study	**No of seizures[a]**	***T*→*C***	***C*→*T*→*C***	***T*→*C*→*T***	***C***	**yes/no – %**
Theodore 1994	120		48			
Niaz 1999	10	80	10		10	Yes (80)
Jobst 2001	286	52	31	28		Yes
Trinka 2002	39					Yes (60)
Leutmezer 2002	74					Yes (43)
Kirton 2003	64					Yes (38.5)

[a] Number of seizures specified rather than number of patients because of seizure heterogeneity in the same patient
[b] T = tonic, C = clonic
[c] Asynchrony is used synonymously with asymmetry

Table 54b.2 Clinical characteristics of patients with secondary generalized tonic-clonic seizures

Patient	Sex	Age	Duration of ep.	Diagnosis	Pathology
1.	F	26	12	Left temporal lobe epilepsy	Temporal hamartoma
2.	M	27	15	Right temporo-parieto-occipital epilepsy	Bihemispheric MCD
3.	M	18	13	Right mesial frontal lobe epilepsy	Remote infarct
4.	M	25	21	Left basal temporal lobe epilepsy	Focal subpial gliosis
5.	M	19	10	Left lateral temporal lobe epilepsy	Focal subpial gliosis
6.	M	14	9	Right temporo-parietal epilepsy	Focal cortical dysplasia
7.	F	35	19	Right hemispheric epilepsy	Bihemispheric MCD
8.	M	25	15	Left hemispheric epilepsy	Unknown
9.	M	18	15	Right mesial frontal lobe epilepsy	Remote infarct/contusion
10.	M	20	9	Right parieto-occipital epilepsy	Focal cortical dysplasia
11.	M	39	22	Right temporo-occipital epilepsy	Bihemispheric MCD
12.	M	23	20	Left lateral frontal lobe epilepsy	Focal subpial gliosis
13.	M	9	7	Right lateral temporal lobe epilepsy	Unknown
14.	M	13	1	Right temporo-occipital epilepsy	DNET

MCD – malformation of clinical development; DNET – dysembryoplastic neuroepithelial tumor.

video-EEG monitoring as part of their presurgical investigation for medically refractory focal epilepsy, we found confirmation of some of the clinical features described in the literature. All 14 patients had invasive evaluations with subdural grid electrodes and/or depth electrodes. The duration of epilepsy ranged from 1–22 years. Clinical details are provided in Table 54b.2. In each case, the epilepsy diagnosis was made with on the basis of semiology, MR as well as functional imaging, interictal and ictal EEG findings.

Seizure semiology was studied from the point of onset of secondary generalization. We employed a practical definition for generalization as that clinical stage where there was clear evidence of bilateral motor arm and/or leg involvement along with complete loss of consciousness. Thus, we did not include head or eye version in this definition. Mode of onset, progression of generalization, duration of various motor stages, symmetry of seizures, synchrony of the clonic phase, and the presence or absence of paradoxical lateralization were all studied. Asymmetry was defined as a greater than 50% difference in amplitude of movement between the two sides of the body. Asynchrony was defined as a clear difference in the rhythm of movement between the two sides of the body. Table 54b.3 summarizes these findings.

Table 54b.3 Characteristics of Secondary Generalization in SGTCS

Pt.	Onset	Tonic phase	Vibratory phase	Clonic phase	Asynchrony	Paradoxical lat.
1.	ST	S	S	S	No	No
2.	AST	A	S	S	Yes	No
3.	Sign of 4 – rt arm	S	S	S	No	No
4.	Bilat. arm clonic	S	S	A	No	No
5a.	ST	S	S	A	Yes	No
5b.	ST	S	No	S	No	No
5c.	Sign of 4 – rt arm	S	No	S	Yes	Yes
5d.	ST	A	No	S	Yes	Yes
6.	Bilat. leg clonic	No	No	A	Yes	Yes
7.	AST	A	No	S	No	No
8.	Sign of 4 – rt arm	S	No	A	No	No
9a.	AST	S	S	S	No	No
9b.	AST	S	A	A	Yes	No
9c.	Sign of 4 – lt arm	A	S	A	Yes	No
9d.	Sign of 4 – lt arm	A	A	A	Yes	No
10a.	ST	S	No	S	Yes	No
10b.	ST	S	S	A	Yes	No
10c.	Sign of 4 – lt arm	S	S	S	Yes	No
10d.	Bilat. arm clonic	A	S	A	Yes	No
11.	Sign of 4 – lt arm	A	No	A	Yes	No
12a.	Sign of 4 – rt arm	S	No	S	No	No
12b.	Bilat. arm clonic	A	S	S	Yes	Yes
13.	AST	A	No	A	Yes	No
14.	AST	A	No	A	Yes	Yes

AST – asymmetric tonic; ST – symmetric tonic; S – symmetric; A – asymmetric.

Seizure onset

The sign of 4 was seen in eight (seven patients) of 24 (33%) seizures. In seven of these seizures (87.5%), it predicted the side of seizure onset correctly, with arm extension contralateral to the side of seizure onset. In one patient, two further seizures occurred without a sign of 4, suggesting that this does not consistently occur in all seizures in the same patients. In 6/24 (25%) seizures, there was an asymmetric tonic onset to the seizures that did not amount to a sign of 4. In 6/24 (25%), there was a symmetric tonic onset to the generalization. In 4/24 (17%) there was a clonic onset that was asymmetric in all.

Seizure progression

Progression of generalization through various phases also varied. In 13/24 seizures (54%), there was a tonic phase followed by the vibratory phase, followed by a clonic phase. In 6/24 seizures (25%), there was no intervening vibratory phase. In one patient, there was progression from a tonic to a focal arm clonic phase. The clonic to tonic to clonic progression noted by Gastaut was seen in only 3/24 (13%) of seizures and in one patient, the seizure remained clonic throughout. All seizures had a clonic phase.

The tonic phase

During the tonic phase, the dominant posture varied with different patients and with different seizures in the same patients. These postures could be categorized into the following types:

1. Type 1 (35%) The upper limbs were held in a position of shoulder adduction, elbow flexion, wrist flexion and finger flexion or extension. The lower limbs were held extended with plantar flexion. The neck was flexed (Figure 54b.4a).
2. Type 2 (26%) The body was held in the same position as in Type 1 but with persistent elbow extension rather than flexion (Figure 54b.4b).
3. Type 3 (9%) The body was held in the same position as in Type 1 but with hip and knee flexion rather than extension (Figure 54b.4c).
4. Type 4 (30%) The body was held in a position of bilateral asymmetric tonicity with upper and/or lower limb flexion on one side and upper and/or lower limb extension on the other (Figure 54b.4d).

The clonic phase and paradoxical lateralization

During the clonic phase, there were asymmetric movements in 13/24 seizures (54%) and asynchrony of limb movements in 15/24 of seizures (62%) (Video.1). During both the tonic phase as well as the clonic phase, asymmetry and/or asynchrony had no lateralizing value.

Focal clonic limb movements occurred at the end of the bilateral motor seizure in 8/24 seizures (33%) in seven patients. These comprised strictly unilateral arm clonic movements in seven and clonic movements of the face, arm and leg in one patient. In six (75%), these lateralizing movements occurred paradoxically ipsilateral to the side of seizure onset, a figure that is keeping with similar observations made by previous studies that have examined seizure termination in temporal lobe epilepsy.[8,9]

Thus, asymmetry and asynchrony at any stage of the secondary GTCS seems a common phenomenon. This is at variance with the primary GTCS, where symmetry and synchrony are more often found.[6] However, there are an increasing number of studies that report clinical as well as electroencephalographic focality in patients with primary GTCS. Usui *et al*[11] reported 26 patients with JME, only two of whom had both JME and a focal epilepsy. Of these patients, 46% had focal semiological features that included focal

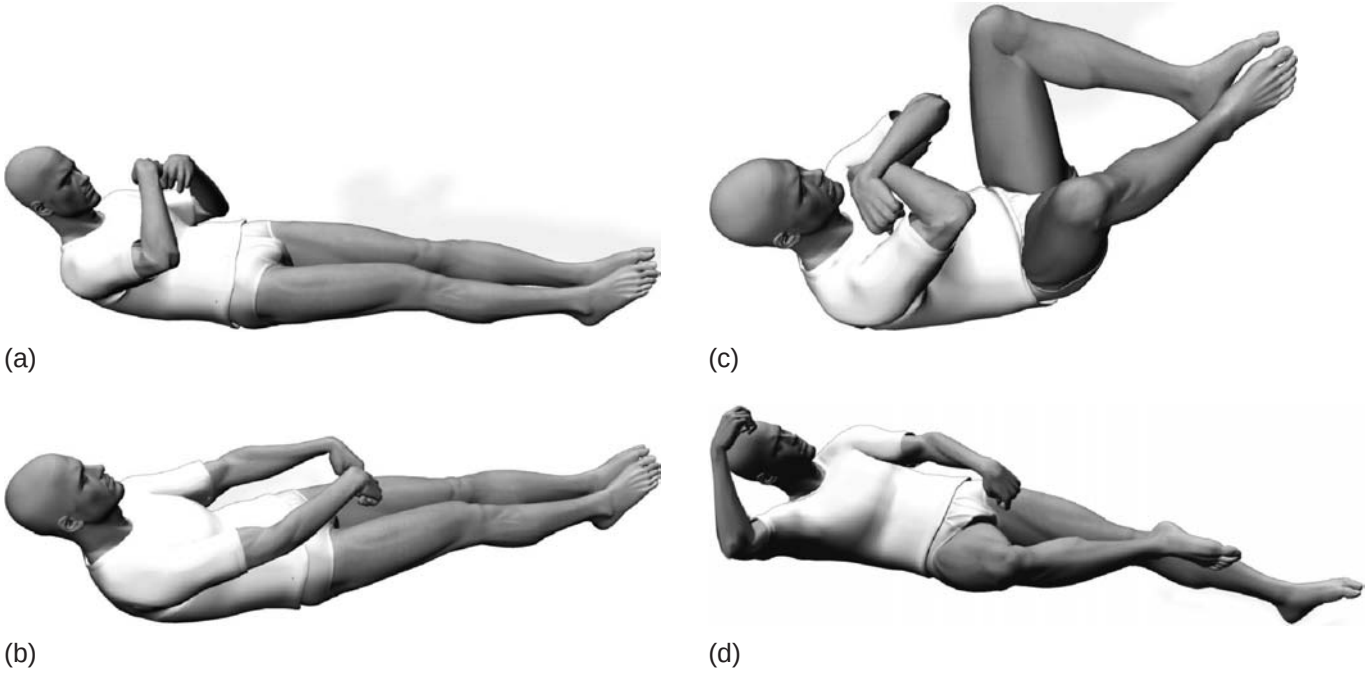

Figure 54b.4 (a–d) Dominant body postures during the tonic phase of the SGTCS.

myoclonus, sign of 4 tonic posturing, forced head version and left arm clonic movements. EEG seizures in these patients were all generalized at the onset, although in two patients with left head version at onset, the EEG lateralized to the right side during the seizure. It is likely, therefore, that primary and secondary GTCS represent a semiological spectrum where symmetry and synchrony are seen most often in primary GTCS, with increasing asymmetry and asynchrony across the continuum towards a typical secondary GTCS. (Figure 54b.5).

Pathophysiology of the secondary GTCS

Gastaut, commenting on asynchronous generalized seizures, speculated on the possibility of two independent unilateral seizures occurring, one in each hemisphere. The traditionally held view of ictal cortical activity during a generalized seizure is one of complete synchronization of widespread brain activity. Recently, there has been some debate whether this is true. Investigators have attempted to address these questions with human EEG analyses, both scalp as well as invasive, and with magnetoencephalography (MEG).[12–15]

Synchronization implies the agreement in time of a particular property of two dynamical systems, usually in the time and frequency domains, and biological synchronization (particularly phase synchronization) has been studied in various ways.[16] In the context of epilepsy, nearest-neighbor phase synchronization (NNPS) has been used in scalp EEGs as a means to more sensitive seizure detection.[15] Whilst synchronization of adjacent brain areas is a not a biologically counter-intuitive premise and the results are therefore not surprising, this method does not address the issue of distant brain synchronization during seizures. Furthermore, scalp EEG studies are subject to reference contamination and volume conduction artifacts, issues that may be particularly prominent during generalized seizures.

Le Van Quyen[13] used the Hilbert transform method and wavelet methods to analyze neural synchrony in a patient with mesial temporal lobe epilepsy undergoing a depth electrode evaluation. A contact each in the ipsilateral amygdala and hippocampus was used against an ear (scalp) electrode that was thought to be quiet. The raw data was digitized at 200 Hz and passed to a 32-channel amplifier system with band-pass filter settings of 0.5–99 Hz. Preseizure recordings showed phase relationship of neuronal activity in the 30–80 Hz range. At seizure onset, (presumably with a seizure that remained focal) there was a transition to synchrony in the 12–15 Hz and 3 Hz range. As the seizure progressed, there was synchrony in the 3 Hz range that persisted but there was strong desynchronization in the high frequency range. Following the seizure, there was synchrony again in the 30–80 Hz range. Thus, despite the relative proximity of the electrodes studied, there was some evidence of asynchrony. Another patient with orbitofrontal epilepsy was studied with subdural grids. Here, seizure onset was characterized by abrupt synchrony at 8–10 Hz followed by synchronies at 25–90 Hz. As the seizure progressed, there was a progressive decline in synchronization frequency. However, it is not clear if this patient had secondary generalization to the seizure and what precise electrodes, near or distant, showed asynchrony. Gotman in 1987[17] described interhemispheric interactions in focal seizures after examining the intracranial recordings of eight patients with epilepsy. They compared, where possible, homologous brain regions in each hemisphere and found that interhemispheric coherence or broadly, phase synchrony, was surprisingly low. However, sampling of brain areas was limited to a few depth electrodes and no data on the clinical semiology was presented. Other observers have made observations on pathological synchrony in epileptogenic brain in focal epilepsy through invasive recordings although again, conclusions are restricted by the limited areas covered by the electrode contacts.[14]

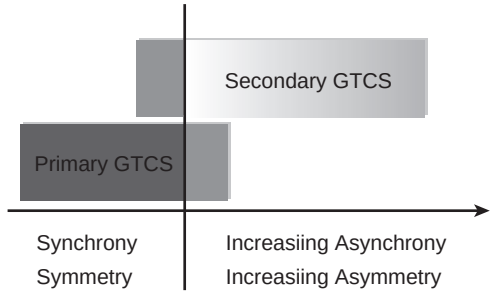

Figure 54b.5 The semiological spectrum of primary and secondary generalized tonic-clonic seizures.

A magneto-encephalographic study with scalp-EEG examined local and distant phase synchronization in generalized seizures.[12] Interestingly, distant synchronization was observed to be better in primary generalized absence seizures compared with secondarily generalized motor seizures in focal epilepsy, although in the latter, there was evidence of strong local synchrony in keeping with the scalp EEG data presented by van Putten.[15]

Thus, although it makes intuitive sense that there should be generalized synchrony in extended brain regions during generalized seizures, the true picture is less clear and there is evidence in the literature that significant asynchrony may occur in SGTCS. Patients undergoing invasive monitoring with subdural grids and/or depth electrodes provide an opportunity to examine these issues.

Brain synchrony in SGTCS and the concept of multiple simultaneous seizures

We analyzed the SGTCS of nine seizures in nine of the above patients who underwent an invasive presurgical evaluation for medically refractory epilepsy. Electrodes of seizure onset were screened and referenced to an uninvolved/artifact free intracranial electrode. Pre- and postoperative 3D MRI reconstruction was used with data from somatosensory evoked potentials and cortical electrical stimulation to determine the position of the central sulcus in order to locate electrodes over the motor strip. These were screened and referenced to an uninvolved/artifact free intracranial electrode. The seizure patterns at onset and during each phase of the secondary

GTCS were analyzed with particular emphasis on synchrony of EEG rhythms. Synchrony was not defined quantitatively but in practical terms as the consistent agreement in time and/or frequency between the electrical activities of one brain region with another.

Results of the analysis of synchrony are detailed in Table 54b.4. Synchrony between the motor strip and the brain region of seizure onset was seen only in three patients (33%), one during the tonic phase only and too during the clonic phase only. Thus, in the majority of patients, there was a clear asynchrony with very different seizure rhythms occurring in the two hemispheres or even within one hemisphere. This appeared to confirm Gastaut's suspicion that there is indeed more than one seizure occurring in the brain during a generalized seizure. In patient 1 for example (Figures 54b.6–8), where there is coverage of both motor strips as well as of the region of seizure onset. A clear difference in seizure rhythms can be visualized between the frontal lobes on either side and between the frontal lobe and temporal lobe in the hemisphere of seizure onset.

Thus, synchronization of brain regions does not appear to be necessary during SGTCS. Indeed, different seizures appear to occur simultaneously in different brain regions during the same clinical seizure.

Seizure generation and seizure modulation; the roles of cortex and brainstem

As is evident from discussions elsewhere in this book, there is robust animal evidence of brainstem seizure generation. However, it is far from clear that the same is true in humans. It appears likely however, that involvement of the cortex is critical to seizure generation. In all our patients, clinical seizure end always preceded EEG seizure end, suggesting that for the production of clinical seizure symptoms, a cortical discharge is always necessary, unlike the situation with brainstem seizure generation for example, where clinical symptoms could be expected to occur in the absence of cortical discharge. However, it is extremely likely that the brainstem plays an important part in the modulation of the secondary GTCS. Whilst it is easy to visualize the corticospinal tract as the main pathway for the clinical motor expression of the cortical seizure discharge, there are several other pathways that originate in the frontal cortex that relay in the human brainstem. These include projections to the brainstem reticular nuclei, the vestibular nuclei, the superior colliculus, the red nucleus, and the olivary nuclei, amongst others. There are interneuronal connections between these structures in the

Table 54b.4 Brain synchrony between different brain regions in secondary generalized tonic clonic seizures

	EEG synchrony between regions	
Patient diagnosis	**Tonic phase**	**Clonic Phase**
1. Lt Hemispheric E	–	–
2. Rt TLE	+	–
3. Rt TLE	–	–
4. Rt Mesial FLE	–	–
5. Lt Hemispheric E	–	–
6. Lt TLE	–	–
7. Rt TOE	–	+
8. Rt TPE	–	–
9. Rt POE	–	+

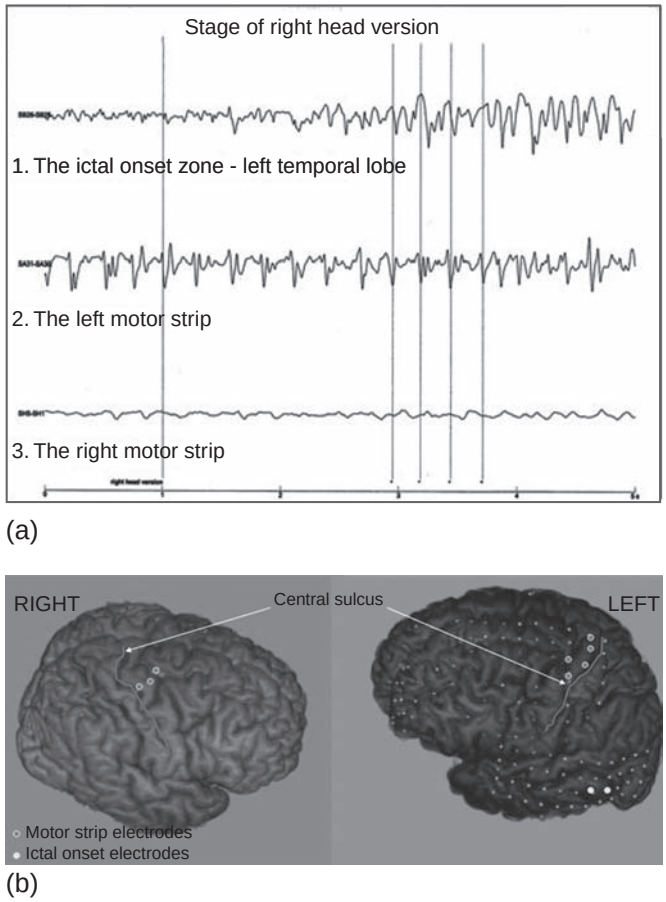

Figure 54b.6 Left hemisphere epilepsy – stage of right head version: (a) asynchrony between left temporal lobe and left motor strip. No activity in the right motor strip. (b) 3D MRI brain reconstruction showing the central sulcus and the sampled motor strip electrodes in relation to it.

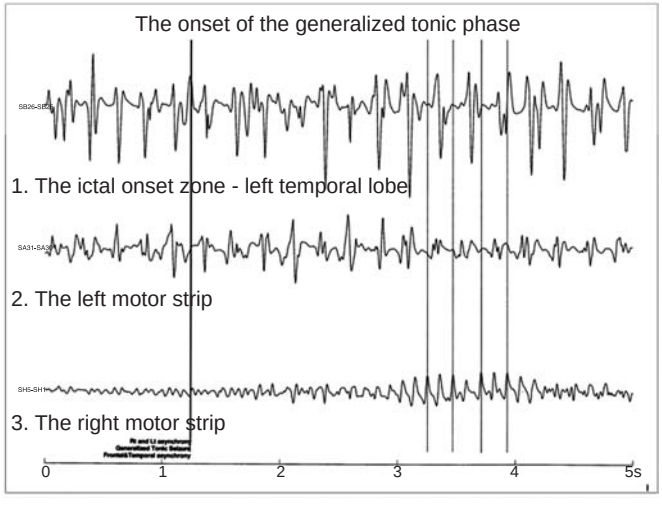

Figure 54b.7 Onset of the generalized tonic phase. EEG asynchrony between motor strips and between left temporal lobe and left motor strip in the presence of clinical synchrony.

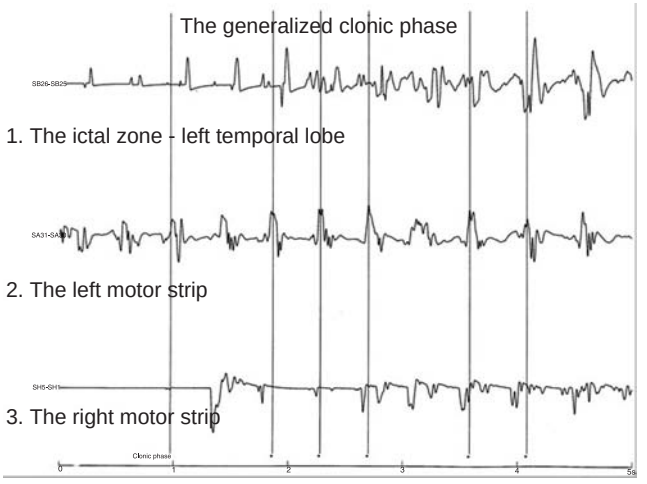

Figure 54b.8 The generalized clonic phase with persistent EEG asynchrony between motor strips, between the left temporal lobe and the left motor strip during apparent clinical synchrony.

brainstem that probably form networks as part of central pattern generators. From here, the vestibulospinal and reticulospinal tracts project downwards into the spinal cord and are likely candidates for the structures that subserve the variability in tonic posturing that is seen with the secondary GTCS. The vestibulospinal tract for example, produces upper limb flexion and lower limb extension whereas the reticulospinal tract produces the converse.

Patients who have undergone anatomical hemispherectomies may provide the best human evidence of brainstem seizure modulation. Video 2 demonstrates a generalized tonic-clonic seizure in a 3½-year-old posthemispherectomy patient who has no residual cortex on the right side. The patient first presented with infantile spasms from birth due to an extensive right hemispheric malformation of cortical development. A right functional hemispherectomy was carried out with removal of the pericentral and temporal cortices. Following this, the patient continued to have medically refractory seizures although these were now left arm tonic seizures evolving into bilateral asymmetric tonic seizures and generalized clonic seizures, indicating a right frontal lobe onset. An anatomical hemispherectomy was then carried out with complete removal of all cortical structures. Following this surgery, the patient continued to have seizures that now originated from the left frontal region as shown in Figure 54b.9.

As evidenced from the video, the tonic and clonic manifestations of the seizure are very symmetric in their expression, rendering it unlikely that the uncrossed ipsilateral corticospinal tract or the ipsilateral supplementary motor cortex have a role in their generation. Both these pathways have a clear predominance of contralateral projections and therefore tend to produce either strictly or predominantly contralateral motor seizures. Therefore, it is more probable that the ipsilateral cortical seizure discharge is being modulated in the brainstem to produce bilateral motor phenomena expressed through the vestibulospinal and/or reticulospinal tracts.

Conclusions

In summary, the semiology of the secondary GTCS is phenomenologically heterogeneous, with asynchrony and asymmetry displayed prominently in a substantial proportion of seizures, unlike the GTCS of primary generalized epilepsy where seizures are mostly synchronous and symmetric. Clinical asynchrony and asymmetry are accompanied by electrical asynchrony in the majority of patients as evidenced by the study of seizure rhythms in patients with secondary GTCS

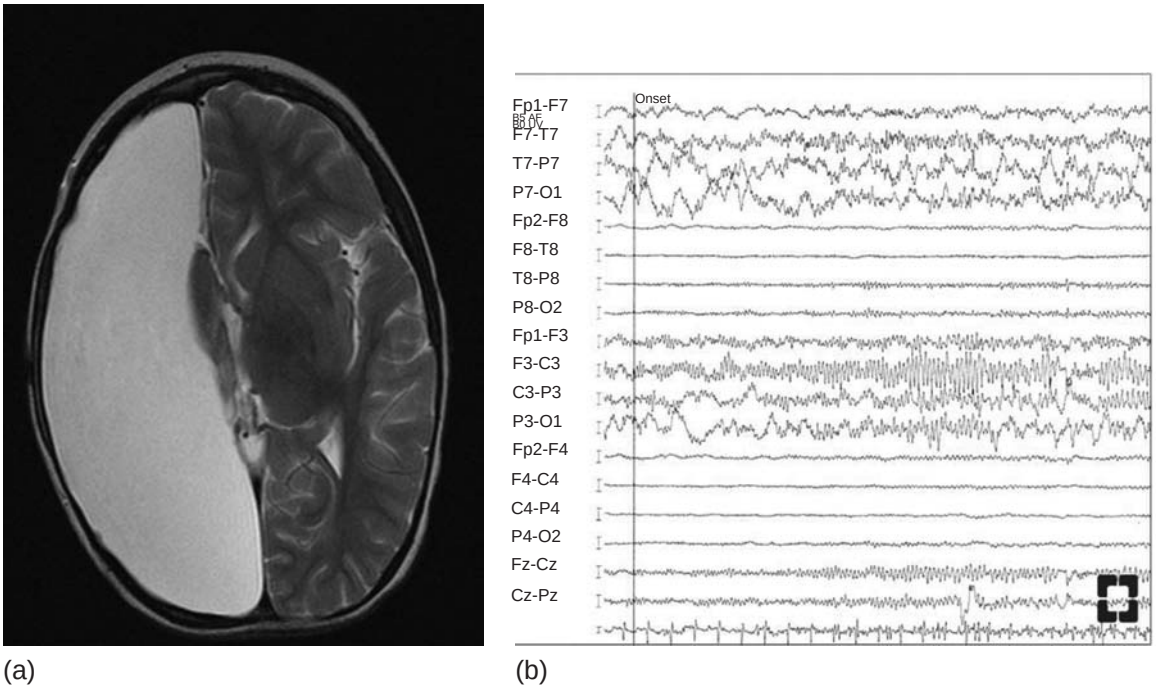

Figure 54b.9 MRI Brain image of patient with right anatomical hemispherectomy. EEG showing seizure onset in the left frontal region.

undergoing invasive evaluations. Electrical synchronization of brain activity does not appear necessary in secondary GTCS and indeed, there may be more than one seizure occurring in different brain regions at the same time. In humans, seizure generation is most likely to occur only in the cortex, although evidence from patients who have undergone anatomical hemispherectomies strongly suggests that significant seizure modulation takes place in the brainstem. Thus, both areas of the brain (cortex and brainstem) are important in the shaping of the semiology of the secondary GTCS.

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SECTION 6

The irritative zone

55 The irritative zone: general principles

M Eccher and D Nair

Introduction

There are various cortical zones in epilepsy that have been defined in order to service as tools to aid in the presurgical evaluation for epilepsy surgery. One of these zones is the irritative zone which has been defined as that region of cortex which generates interictal epileptiform discharges. The presence of interictal spikes is a hallmark of epilepsy and often used in corroborating the diagnosis.[1,2] In addition, the characteristics of the interictal epileptiform activity can also aid in defining the epilepsy syndrome, such as differentiating focal from generalized epilepsy. in some situations. The irritative zone can be measured by a variety of means: surface and invasive EEG with visual analysis or dipole source modeling of EEG, magnetoencephalography (MEG), and EEG spike triggered functional magnetic resonance imaging (fMRI). The reason to pursue accurate measurement of these cortical zones including the irritative zone is to define the epileptogenic zone in a particular patient. The epileptogenic zone is a theoretical concept but its estimation is a prerequisite in planning of successful resective epilepsy surgery.

Factors affecting the irritative zone

The irritative zones can be affected by a number of factors: the type epilepsy syndrome, the conscious state of the patient, changes in temperature, age, presence of anesthesia, and use of anticonvulsants etc. One of the clearest examples of the variance of epileptiform activity based on a change in the state in a pediatric patient is electrical status epilepticus during slow wave sleep[3] which demonstrates a dramatic change of spikes frequency from the awake to a sleep state. In many focal epilepsy syndromes NREM sleep may increase the frequency of interictal epileptiform activity in both adult as well as pediatric age groups. In some children with focal epilepsy there may be a presence of nearly continuous production of interictal epileptiform discharges during sleep. The mechanisms for this activation is not yet clear but may involve the activating and synchronizing properties of oscillations generated between cortical and thalamic structures which may lead to the development of paroxysmal synchronization. Focal cerebral cooling has been shown to reduce epileptiform activity in animals as well as reports of cold saline irrigation has been shown to result in transient or complete cessation of spiking.[4] There is also reports that dendate spike activity recorded in urethanized infant rats increase severalfold when cooled from 32–27° C.[5] This raises the possibility that variation of body temperature may have an effect on frequency of epileptiform spikes. How significant this effect is unclear and is not well studied in the human brain. The effect of anesthetics on interictal spikes has been discussed in some detail in the chapter on intraoperative cortical mapping and electrocorticography. The presence of interictal epileptiform activity can be influenced also by antiepileptic medications. Intravenous benzodiapezines results in both acute seizure control and suppression of interictal epileptiform activity. For epilepsies other than absence, antiepileptic medications given over a medium and long term range has no clear correlation between seizure control and frequency of interictal epileptiform activity.[6] In patients whose epilepsy is in remission the persistence of interictal epileptiform discharges has been associated with a higher risk for seizure recurrence upon discontinuation of antiepileptic medications.[8,9]

Special features influencing the irritative zone

There are some interesting features of the irritative zone that are of particular interest. One in particular is that around 10% of patients with epilepsy never show any interictal epileptiform discharges. This is in part due to several limitations inherent to EEG. One main problem is the difficulty with temporal sampling. This is particularly problematic with the short-time sampling that occurs during a routine EEG. Even with long-term monitoring in a video-EEG unit, the time restriction is limited to a few weeks at most. On the other hand, the presence of interictal epileptiform discharges does not always indicate the presence of epilepsy, as a small percentage of normal subjects who never develop epilepsy may still have interictal epileptiform discharges. Another issue affecting EEG interpretation is that the cortical generators of many normal as well as abnormal waveforms recorded on the EEG are not well known, particularly when looking with invasive EEG. This goes hand-in-hand with the notion that all spikes might not be similar. To begin with, the ability to record spikes at the scalp in patients with temporal lobe epilepsy usually involves synchronous or temporally overalapping activation of 10–20 cm^2 of gyral cortex.[10] So there are many spikes that are seen on intracranial-EEG and not seen at the scalp at all. The significance of these spikes is not known. Additionally, due to the limitations involved with intracranial-EEG, what constitutes an epileptiform spike from a nonepileptiform transient is not clear, as mentioned earlier.

There are a number of normal patterns that are sharply contoured seen on the scalp-EEG which have been shown to be normal variants due the ability to study healthy volunteers with scalp-EEG. Similar investigations of identifying normal patterns are not feasible for intracranial-EEG. Some spikes may have particular characteristics that make them perhaps more significant than other spikes. For example, there may be forms of interictal epileptiform activity seen with such frequency or regularity that they may represent a transitional state from interictal to ictal EEG activity. This was suggested in a study of cortical dysplasia in which continuous epileptiform discharges had a high intrinsic epileptogenic property, so much so that if regions harboring these spikes were left behind during epilepsy surgery those patients uniformly faired poorly from a standpoint of seizure freedom after surgery.[11] In contrast to this phenomenon, patients with mesial temporal lobe epilepsy can often have an irritative zone that extends to the opposite hemisphere, as with the case of bitemporal spikes. However, these patients have a very high success rate with unitemporal resection which leaves intact the opposite temporal structures.

In generalized epilepsy such as absence, the frequency of 3 Hz-spike and wave has a close correlation with the frequency of detected seizures. In focal epilepsy the correlation is substantially weaker. However, it has been shown in one study of nonlesional intractable temporal lobe epilepsy, patients with few or no interictal epileptiform activity had a later age of seizure onset, less frequent and less severe seizures, and a lower incidence of hippocampal atrophy to suggest that a rarity of spikes could reflect a disease state that is not less severe.[12] However, in most cases of focal epilepsy there is very little evidence to suggest that there is a direct correlation between spikes and seizures. Since there is no clear increase in the frequency of spikes before seizures or an increase in spike frequency with a decrease in antiepileptic medications, the mechanisms for interictal and ictal phenomenon may be different.[13]

The presence of spikes is not usually associated with any clinical manifestation as compared with epileptiform activity consisting of ictal epileptiform activity. However, if epileptiform spikes are of 'sufficient intensity' and are being generated in a region within the eloquent cortex, then they may result in symptoms. A clear example is focal myoclonic jerks associated with spikes in the primary motor cortex. This type of myoclonus can be of positive or negative motor activity (Figure 55.1). Some more sensitive measures of clinical observation such as continuous psychological testing can show brief episodes of impaired cognitive function at the time of epileptiform discharges. There also evidence that the localization of the interictal spike activity would predict the impairment seen with such testing.[14,15] There is some suggestion that suppression of interictal discharges with antiepileptic medications could improve psychosocial function.[16]

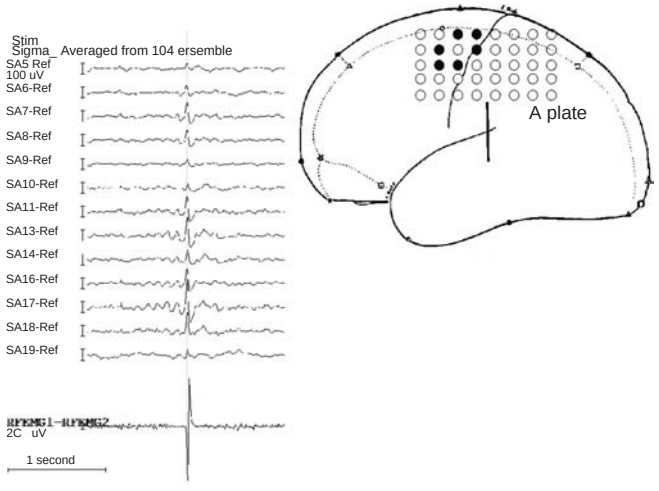


Figure 55.1 Patient with a history of medically intractable epilepsy who presents with positive and negative myoclonus undergoing an invasive evaluation for epilepsy surgery. Shown on the illustration is a map of the patient's 'A plate' subdural grid, in which spikes are shown maximum at electrodes 7, 8, 11, 13, 16, 17 (marked by the solid circles). Also shown is the EMG activity monitored during the patients spiking activity. The EEG shows 104 averaged spikes. Note the time display is shortened to show the relationship of the spike to the EMG activity. Just prior to the spike there is a marked decrease in EMG activity followed by a myoclonic jerk from the right finger that is time-locked to the interictal spike.

The relationship of the irritative zone to other cortical zones in epilepsy

The irritative zone stands in contrast to other defined zones of the epileptic brain (see Table 55.1). The delineation of these individual cortical zones is essential to the process of determining whether a patient with medically refractory focal epilepsy can be offered resection with reasonable chances of seizure freedom or substantial improvement without unacceptable postoperative deficits. It is our contention that the differentiations set forth in this set of definitions is implicit in any evaluation for epilepsy surgery; making them explicit allows for clarity in decision making, and must therefore optimize patient care. Complexities involved in studying these concepts include the current limitations in studying cortical

Table 55.1 Zone-wise definitions of the epileptic brain[32]

Epileptogenic zone	Region of cortex that can generate epileptic seizures, the total removal or disconnection of which is necessary and sufficient for seizure freedom
Irritative zone	Region of cortex that generates interictal epileptiform discharges in the EEG or MEG
Seizure-onset zone	Region of cortex from which clinical seizures originate
Ictal symptomatogenic zone	Region of cortex that generates the initial seizure symptomatology
Functional-deficit zone	Region of cortex that in the interictal period is functionally abnormal

neuronal function in health and pathology. There are various permutations that one can see with the relationship of various cortical zones of epilepsy based on different epilepsy syndromes. Two such examples are illustrated in Figure 55.2. However, the relationships can be even more complex in that even within an epilepsy syndrome such as temporal lobe epilepsy, the relationship of the different cortical zones can be slightly different. For example, in Figure 55.2A, which illustrates a case of temporal lobe epilepsy, bitemporal spikes are depicted. Other cases of temporal lobe epilepsy may have no interictal epileptiform discharges or may have a wider population of spikes. The ability to measure the functional deficit zone might be influenced by the frequency of spikes and/or seizures, so that regions of hypermetabolims may be depicted by a PET scan with an active epileptogenicity. The measurement of these different zones helps in the formulation of a hypothesis of the location of the epileptogenic zone in a particular patient. This concept is the crux of planning resective epilepsy surgery or planning an invasive evaluation for epilepsy surgery.

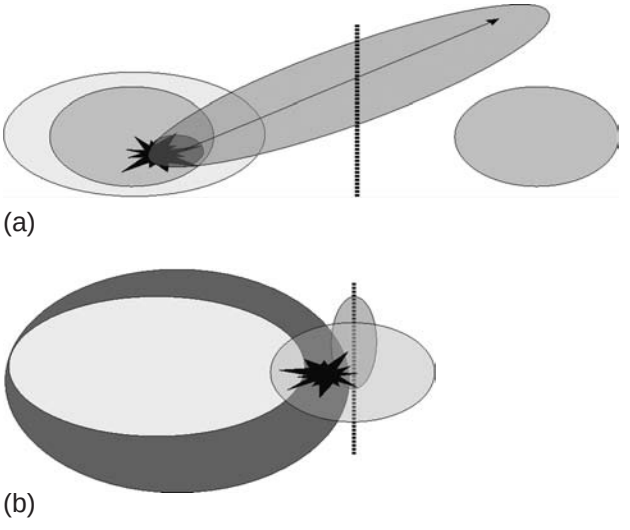


Figure 55.2 The relationship between the different cortical zones is graphically displayed in two examples. The yellow sphere represents the functional deficit zone; the light green sphere represents the irritative zone; the light orange sphere represents the symptomatogenic zone; the red sphere represents the ictal onset zone; and the black star represents the epileptogenic zone; the hashed line represents the division between the two hemispheres. Example a might represent a case of temporal lobe epilepsy in which there might be bitemporal spikes, unitemporal ictal onset, seizure semiology with lateralizing and localizing signs (direction of arrow indicates onset to progression of the semiological signs), and hypometabolism on a PET scan involving the temporal lobe ipsilateral to the ictal onset. In this example, seizure freedom could be achieved with a mesial temporal resection, and one can assume that the epileptogenic zone would have encompassed mesial temporal structures and perhaps the portions of the parahippocampal gyrus (extending just beyond the ictal onset perhaps recorded on depth electrodes as one example). Another situation is shown in Figure 55.2b which might represent a case of supplementary sensorimotor area epilepsy. In this case the irritative zone might be represented by spikes at the midline, ictal onset is lateralized to one hemisphere; there is PET hypometabolism of frontal and temporal lobes ipsilateral to the ictal onset, seizure semiology might imply SSMA onset. The epileptogenic zone is localized to a portion of the SSMA. (See Color plates.)

EEG recordings of the irritative zone

The first, and for decades the only, means by which to delineate brain regions giving rise to interictal paroxysmal activity was EEG. EEG enjoys several advantages over other means by which to define the irritative zone. It is of relative technological simplicity in the age of microcomputing, and can be utilized by a single clinician working alone or with the aid of a small number of well trained technologists. It is commonly available, well established in the clinical arena, and well studied in the scientific literature.

The irritative zone is localized on scalp-EEG by mapping of the potential differences recorded at the surface.[17] Epileptiform potentials are recognized as sharply contoured transients, nearly always of negative polarity, which disturb the background cerebral rhythms. When they are focal in nature, their localization is recognized in a referential montage as the electrode(s) of maximal voltage amplitude, and in a bipolar montage as the electrode(s) across which a phase reversal can be seen. The irritative zone is then concluded to reside in that region of the cerebral cortex underlying the electrodes at which these potentials are recorded.

The limitations of scalp EEG in the localization of the irritative zone include the region of cortex required to be recruited in the epileptiform activity before being seen at the scalp. At least 6 cm^3 of cortex,[18] possibly as much as 20 cm^2,[10] must be involved if a cortical transient potential is to propagate to the scalp surface. The cortical surface is highly convoluted and spatially complex, and the relationship of the scalp localization to the cortical area of origin is approximate at best

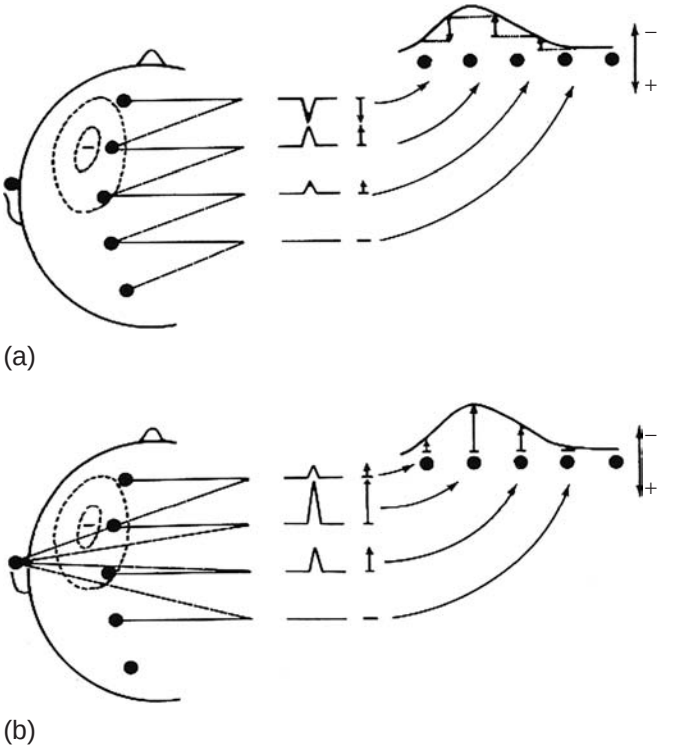


Figure 55.3 A schematic illustration of electrical potential analysis in clinical EEG. Using either bipolar (a) or referential (b) analysis, the voltage maximum of a transient recorded on clinical EEG can be plotted out; the generator is assumed to underlie the electrode at which the voltage maximum is recorded (used with permission from Fisch.)[49]

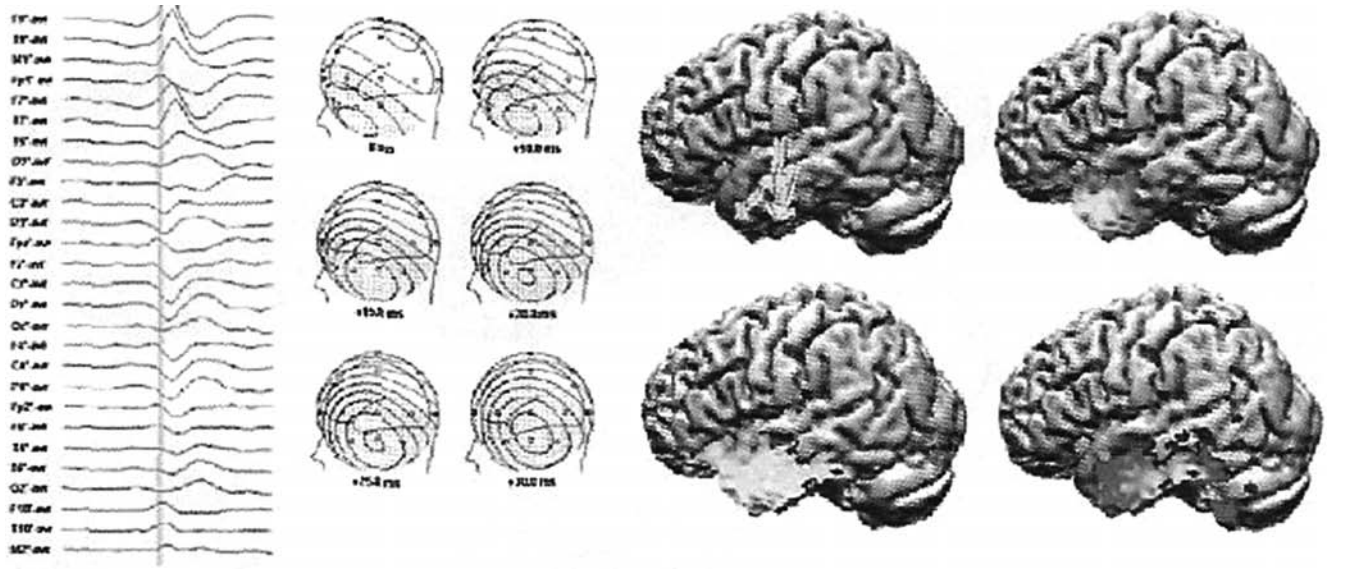


Figure 55.4 Dipole modeling from EEG. Raw EEG waveform on the left, with cursor at the point of initial deflection, defined as time 0 ms. In the middle, derived surface isopotential lines at 5 ms intervals from 5–30 ms. On the right, four brain models with superimposed dipole model solutions: on the upper left, three single dipole solutions at 0, 15, and 30 msec, and in the other three, current source density solutions, separately for each time point – 0ms upper right, 15 ms lower left, and 30 ms lower right. Single dipole solutions have less visual appeal, but less manipulation and abstraction. Current source density maps could be considered a representation of the irritative zone, but their abstraction from the original dipole must be borne in mind. (Used by permission from Ebersole.)[50]

and misleading at worst: potentials from the superficial midline cortex can appear to localize opposite the midline from their origin, and potentials from deep midline cortex, orbitofrontal cortex, insular cortex, supratentorial occipitotemporal cortex, and the mesial temporal structures may propagate to the surface poorly or not at all.[19]

The least invasive means of supplementing scalp-EEG is with the addition of sphenoidal electrodes. These can be performed when a mesial temporal focus is suspected. Placed by needle under the zygomatic arch and over the mandibular ramus, sphenoidal electrodes are intended to reside near the vicinity of the foramen ovale making them more effective in recording potentials of mesial temporal origin as compared with scalp electrodes.[20–22] They are generally well tolerated by patients, especially when placed under light sedation, and are of low morbidity in experienced hands. The chief arguments against their use are that they add insufficiently to the overall evaluation of such patients, when other sources of lateralizing information such as imaging and semiology are considered, to justify their modest risk and discomfort (Blume).[23]

Another, noninvasive, technique developed to augment the localizing potential of surface EEG is electrical dipole source modeling. This technique aims to solve the 'inverse problem' of clinical EEG and deduce the cerebral electrical potential giving rise to the electrical potential differences recorded on the surface. The laws of physics dictate that there are infinite possible solutions to any inverse problem, however, and the source can therefore only be modeled as an abstracted single dipole or set of dipoles. Optimizal accuracy requires modeling conductance of electrical signals through four 'spheres' of different physical properties–brain, cerebrospinal fluid, skull, and scalp.[24]

Recent studies indicate that dipole analysis has the potential to provide a reasonable spatial estimate of the source of surface EEG potentials. Comparison of surface recorded potentials to invasively recorded EEG has suggested that the modeled dipole sources are in fact within several millimeters of the cortex generating subdural EEG discharges. While initially studied in temporal lobe epilepsy, this modality appears to have potential applicability to all forms of localization-related epilepsy.[25]

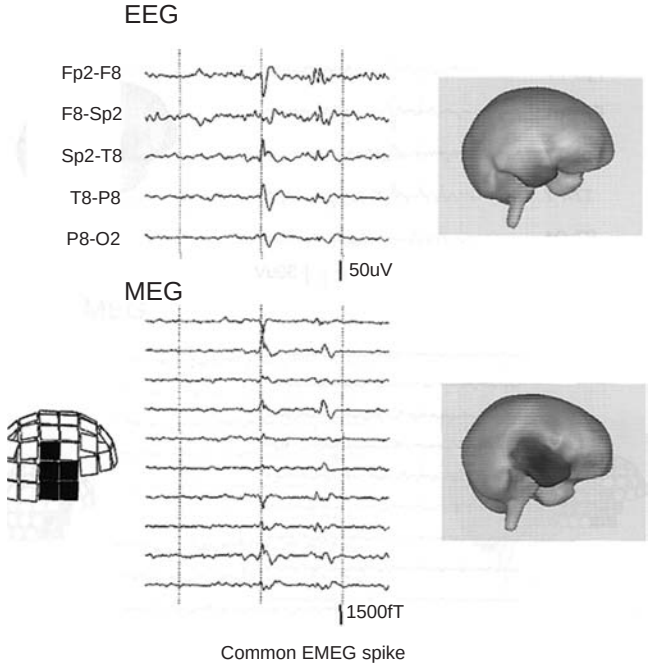
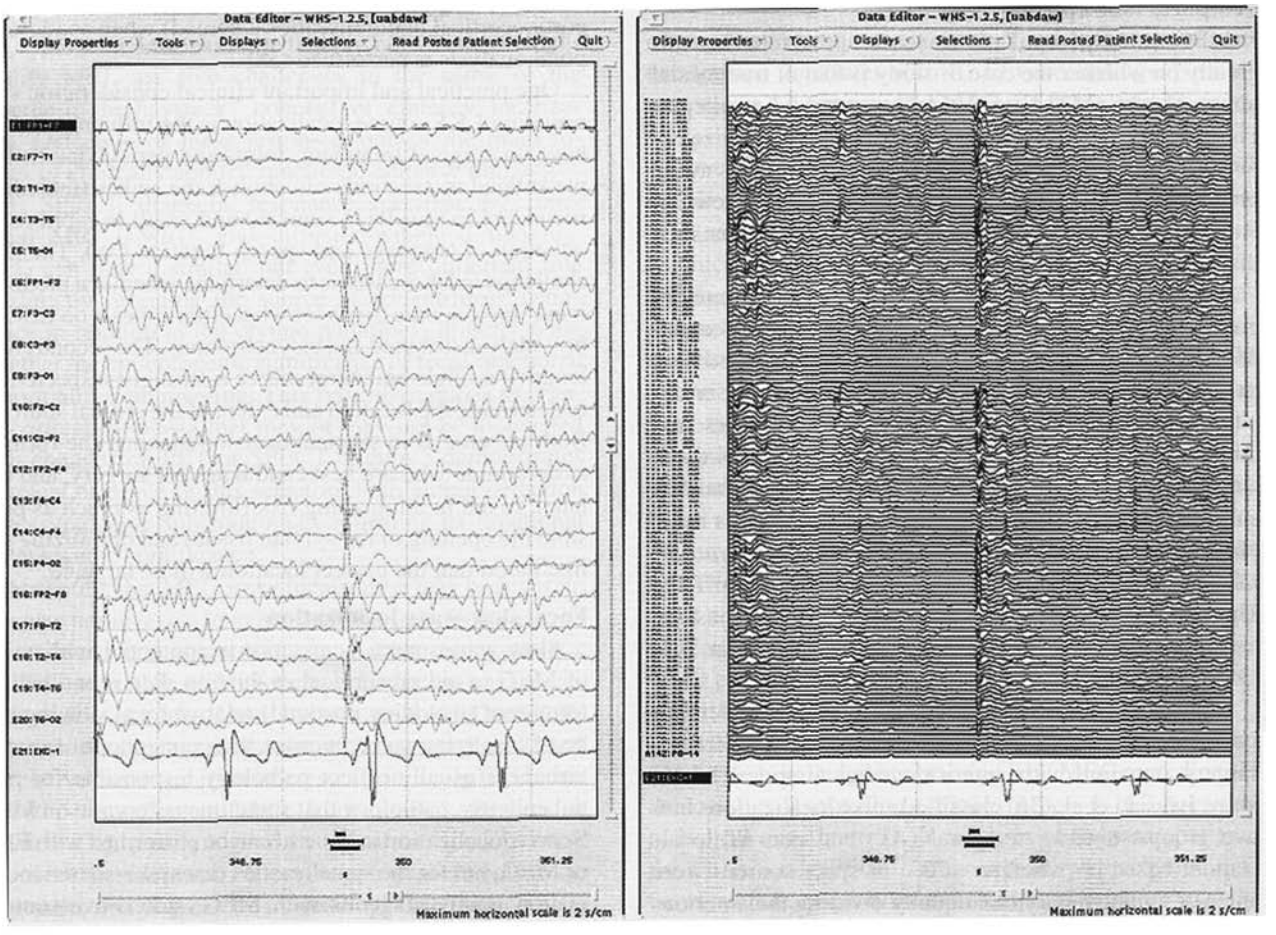


Figure 55.5 Dipole source modeling, with a current density representation, of the same epileptiform transient in simultaneously recorded EEG and MEG. (Used with permission from Iwasaki *et al.*)[51]



(a)

Figure 55.6a Left: 23-channel EEG of frontally maximal discharge with secondary bilateral synchrony. Right: 128-channel MEG of spike corresponding to that on EEG. (Modified with permission from Knowlton and Shih.)[52]

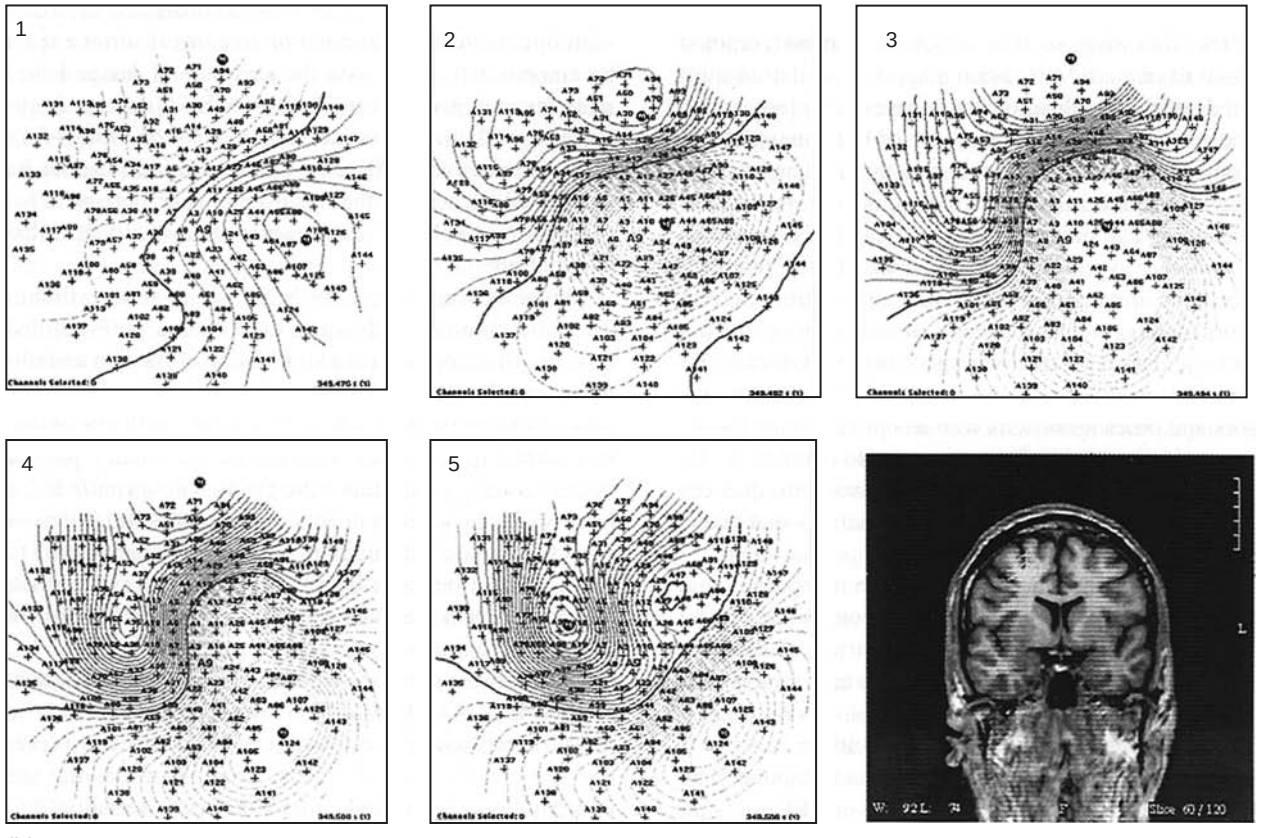
Dipole source analysis, until fairly recently an investigational tool, is now available as software extensions for many EEG systems, either commercially (e.g., BESA (www.besa.de) or Curry (www.neuroscan.com)) or as somewhat less comprehensive freeware (LORETA (www.unizh.ch/keyinst/ loreta.htm)). This approach can produce graphical representations of the spatial region putatively responsible for the observed surface potantials. These representations can be quite visually appealing, essentially appearing to highlight the area of cortex giving rise to a spike – in short, providing an outline of the irritative zone.

Current models, however, have weaknesses inherent in their structure. Optimal dipole modeling requires using not an average head model, but a 3D reconstruction of the patient's own head.[24] Which exact point of the interictal EEG spike is chosen for the model can produce substantial variation in the resulting modeled locus. The best available evidence suggests that the errors introduced by such issues are in the order of a few millimeters, but comparatively few patients have been formally studied versus the gold standard of invasively recorded EEG. In some, the error may approach a magnitude of centimeters.[25] Until there is greater confidence regarding in which patients dipole source modeling is essentially 100% accurate, this modality will not achieve replacement of intracranial-EEG. For the near future, it will likely represent merely a complement to such invasive recording, however, with accruing experience at major centers, such modeling stands poised to spare some patients this step.

Invasive EEG recordings of the irritative zone

Until recent years, direct EEG recording from the brain was the only neurophysiological means of characterizing the irritative zone more finely than could surface EEG, and experience with invasive EEG is vast. New utilizations of invasive monitoring have been devised in recent years.

Foramen ovale recording, which has fallen out of favor in the U.S. has never been abandoned in many centers, especially in Europe, and studies regarding its use continue.[26–28] Placed under fluoroscopy by an anterior approach through the cheek and then the foramen ovale into the subarachnoid space between the mesial temporal lobe and the pons, they are limited to evaluation of patients with mesial temporal lobe epilepsy. These electrodes do not require craniotomy, and can provide semi-invasive lateralization of interictal spikes and ictal onsets when that information is essential and sphenoidal electrode-supplemented surface EEG is insufficient. Foramen ovale electrodes cannot be utilized for functional stimulation mapping, unlike all other intracerebral electrodes, and they can only be utilized in relatively confirmed temporal lobe epilepsy



(b)

Figure 55.6b 1–5: Surface magnetic flux contour plots at 0 ms, 12 ms, 24 ms, 30 ms, and 36 ms of the MEG discharge in Figure 55.6a. Frames 2 and 3 show a lateralized contour pattern potentially attributable to a single dipole, modeled in the lower right; by frame 4, the singularity of the dipole is lost. (Modified with permission from Knowlton and Shih.)[52]

in which the only question is lateralization. Their proponents tout their high patient tolerability and the fact that they do not require general anesthesia and craniotomy. Whether they are safer than craniotomy and invasive electrode placement unfortunately has not been subjected to rigorous study.

Direct invasive EEG is the gold standard for delineation of the irritative zone. It was the first technique introduced for increasing the spatial resolution of surface EEG,[29–31] was the basis of the original definition of the irritative zone,[32] and remains the gold standard against which all other current techniques are compared (e.g., reference 10). Depth electrodes, subdural electrode strips or grids, or any combination of these can be utilized. Subdural electrodes record from the cortical surface. Depth electrodes have been used in years past to record from various subcortical structures; their most universally accepted use, particularly in the U.S., has been in recording from the amygdala and hippocampus.[33] In some centers, particularly in Europe, depth electrodes have been used to the relative exclusion of subdural electrodes in the evaluation of malformations of cortical development and other epileptogenic lesions,[34] including even in the sylvian fissure.[35] They are placed under fluoroscopic or stereotactic guidance to avoid pial vessels. This approach, termed stereoelectroencephalography, aims to place electrodes on all sides of, and within, the epileptogenic lesion and thereby localize the region of interictal spiking and ictal onset.[36]

In all approaches, the irritative zone is considered to comprise all tissue from which interictal spikes are recorded. This delineation of the irritative zone is conceptually straightforward, and does not required computational abstraction or processing. The clinical neurophysiologist evaluating a patient for epilepsy surgery need not have significant additional skills beyond those utilized in surface EEG. It is for these practical reasons, as well as historical ones, that invasive EEG remains the gold standard against which all other techniques are measured. Unfortunately, only tissue upon or into which electrodes have been placed can be evaluated. A firm presurgical hypothesis must have been developed on the basis of imaging, surface EEG, seizure semiology, and the other modalities discussed in this chapter, and invasive electrodes are placed in a specific locale on the basis of this hypothesis.[36] Unless electrodes are placed outside the hypothesized irritative zone, invasive EEG cannot provide evidence of a more widespread irritative zone than suspected – this is the chief limitation of invasive EEG in defining the irritative zone.

MEG recordings of the irritative zone

Previously an investigational modality, MEG is now making the transition to routine clinical use in some centers. Based on essentially the same physics as EEG, MEG records the magnetic fields generated by neuroglial ion shifts, instead of the electrical fields recorded by EEG. MEG requires superconducting detectors at 4 K (superconducting quantum interference devices, or SQUIDs) – a clinical MEG machine is comprised of several SQUIDs in a large flask of liquid helium. Brain signals are several orders of magnitude weaker than common modern environmental electronic noise, so a MEG machine must be

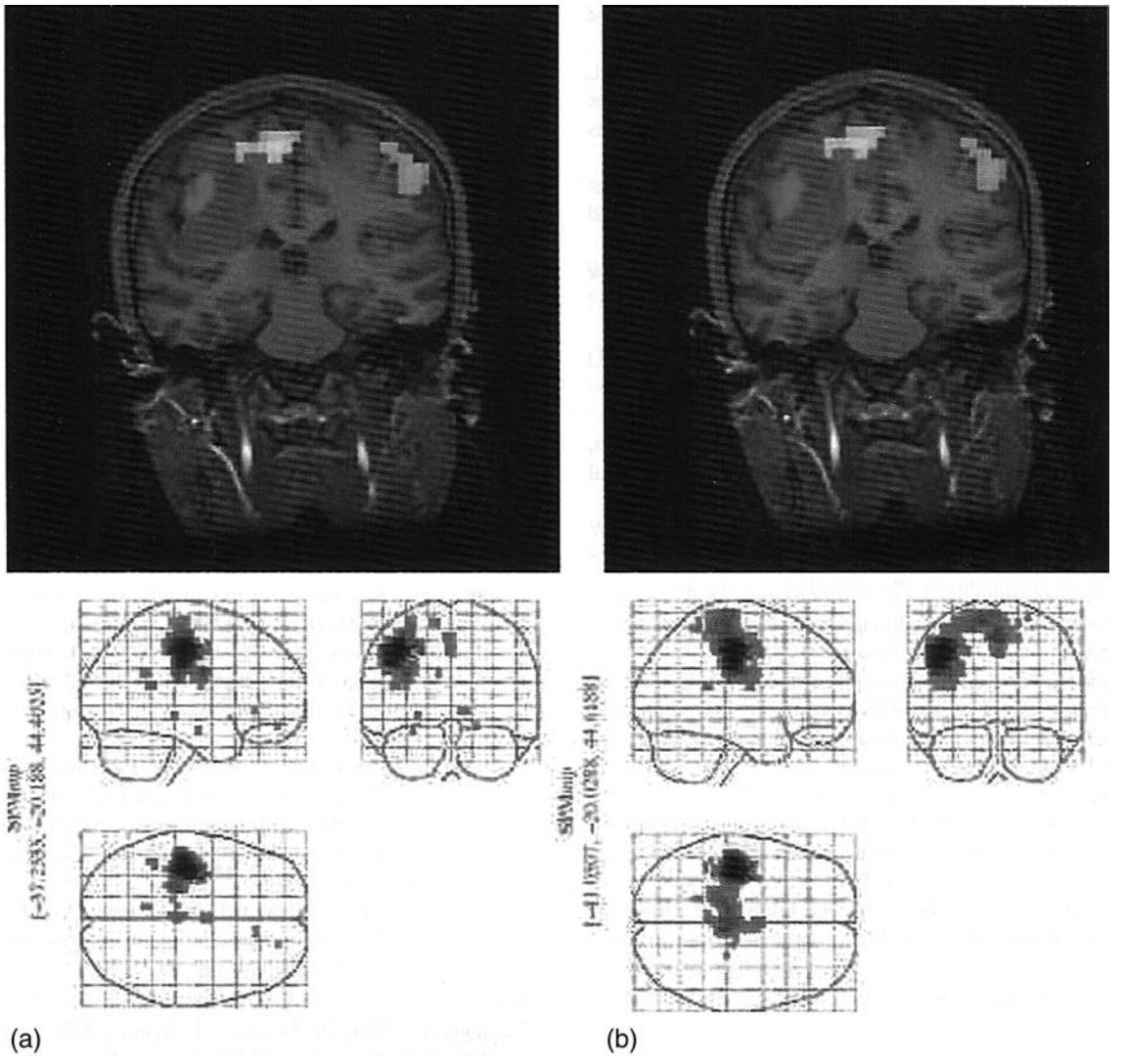


Figure 55.7 fMRI of a patient with right central malformation of cortical development and intractable epilepsy. On the left, activation associated with right finger-tapping in blue, left finger-tapping in yellow, and interictal surface EEG spikes in red; on the right, the same motor mapping tasks with activation associated with EEG spikes *and* slow waves in red. (Modified with permission from Diehl *et al.*)[53] (See Color plates.)

placed in a very carefully magnetically shielded (Faraday cage) room. Obviously, unlike EEG, MEG will remain limited to highly industrialized countries for some years to come.

The advantages of MEG over EEG are debated,[37–39] but potentially substantial. MEG assesses the strength and orientation of magnetic field, not electrical potential difference – it is therefore reference free, unlike EEG. The orientation of the magnetic field in the tissue is orthogonal to that of the electrical dipole – MEG therefore essentially records dipoles oriented parallel to the scalp, where EEG records those oriented perpendicular to it, so the two are theoretically complementary.[40] Without question, MEG can record spikes that are not apparent on EEG, and vice versa.[41] MEG therefore offers a complementary means of mapping the irritative zone by exactly the same two means as does EEG – visual analysis and dipole source modeling. Dipole modeling is much more straightforward than with EEG, because the magnetic permitivity of all layers of cerebral tissue, fluid and bone is identical, and the model therefore need not include multiple spheres. As with EEG dipole modeling, a highly visually appealing map of the interictal irritative zone can be produced (see, e.g., Ko *et al.*, Figure 2).[42] Unfortunately, to this point, the published case series comparing MEG to surface and invasive EEG are small. The relative value of the irritative zone map produced by MEG dipole modeling remains to be rigorously validated (the same could be justly said, however, for the irritative zone as mapped by invasive EEG). With further study, MEG stands to become a vitally useful tool in presurgical epilepsy evaluation.

MRI recordings of the irritative zone

Also now technically feasible, though less clearly poised to transition from investigation to clinical use, is functional magnetic resonance imaging (fMRI) of the irritative zone. The engineering hurdles associated with recording EEG in the inhospitable environment of the MRI machine have been successfully addressed.[43,44] Series are now available that demonstrate that an MRI signal can be acquired in the time window immediately following an interictal spike recorded on concurrent EEG. Contrast of the T2* image in this time window to the average acquired in the comparative resting state permits

identification of that region of tissue in which a blood–oxygen label-dependent (BOLD) change occurs. The tissue that has a detectable metabolic response concurrent with an EEG spike could be construed to be a better representation of that body of physiologically activated brain tissue than the volume across which the electrical potential is distributed. As with all fMRI assessments, the region of T2* change can be represented graphically, producing a visually appealing representation of, putatively, the irritative zone. There are conceptual problems with this leap, however. It is well known that the BOLD effect on which fMRI is based is spatially skewed towards draining cortical veins.[45,46] Also, inherent in the technique is the utilization of a mathematical model of the hemodynamic response; manipulations of the exact time-to-peak-response in the model can profoundly affect the volume of tissue concluded to be 'involved'.[47] Finally, as EEG-spike-triggered fMRI utilizes surface EEG, its resolution is limited to those interictal paroxysms that activate enough tissue that the dipole propagates to the surface. Clarification of the utility of the fMRI-mapped region of BOLD change concurrent with interictal surface EEG spikes must await future studies.

Conclusions

Clearly, multiple physiologically-based techniques are now available for evaluating the volume of brain tissue giving rise to paroxysmal bursts of activity between epileptic seizures. The role that delineation of this zone plays in the presurgical evaluation of each individual patient depends upon the patient's specific localization-related syndrome. As has long been appreciated,[48] the interictal irritative zone may not overlap well, or even at all, with the ictal onset zone, and the relationship of these two cortical areas to the epileptogenic zone as we define it is highly variable between syndromes. Much work remains to be done to clarify which of these techniques, or which combination of these techniques, will best permit us to offer curative surgeries to our patients.

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56 Noninvasive electroencephalography evaluation of the irritative zone

HM Hamer

General concepts

The main goal of the presurgical evaluation in patients with medically intractable epilepsy is the identification of the cortical area capable of generating seizures, and whose removal or disconnection will result in seizure freedom. This area is called the epileptogenic zone.[1] The irritative zone is the area of cortex capable of generating interictal epileptiform discharges (IED). It does not coincide but frequently overlaps with the usually smaller epileptogenic zone. Extensive experience with routine extracranial EEG shows that in general the location of IED is a good indicator of the area of cortex from which seizures are originating.[1,2] The methodology of many studies on this topic, however, is biased towards patients with medically refractory epilepsies.[3,4]

The term interictal epileptiform discharge (IED) comprises spikes and sharp waves which usually break background activity. Both, spikes with a duration of less than 70 ms and sharp waves with a duration of 70–200 ms, have a pointed peak and are of negative polarity in most cases because they are generated by depolarization of vertically oriented neurons.[3,5,6] Positive IED can be seen in electrocorticography and infrequently in patients with a breach rhythm, head trauma or cortical dysplasia.[3,7] Spikes and sharp waves convey an increased risk of epilepsy and must be differentiated from benign variants resembling IED.[2,3] Some reports suggest that spike suppression and not an increase of IED frequency heralds seizures which proposes that a strong after-inhibition produced by IED protects against the occurrence of ictal discharges by maintaining a low level of excitation in a general condition of hyperexcitability.[2,8] This finding, however, remains controversial.[9,10]

There is evidence that the interictal epileptiform discharges in focal and generalized epilepsies, though not accompanied by obvious clinical events, can induce brief episodes of impaired cognitive function if tested with sensitive methods.[11,12] In focal epilepsy, the type of deficit may depend on where in the cortex the IED arises.[13] Suppressing interictal discharges could improve behavior in children particularly with focal epilepsy.[14] Auditory reaction times was found normal before IED in absence epilepsy but decreased in many patients at the onset and after a delay of 0.5 seconds of IED.[12,15] Moreover, chronic and frequent IED on the left may induce a reorganization of speech lateralization.[16]

EEG recorded by scalp and sphenoidal electrodes compared to intracranial electrodes and Magnetoencephalography

In general, surface EEG provides a good overview because it samples from a large portion of the brain. However, several square centimeters of synchronously discharging cortex are necessary to be detected by overlying scalp electrodes.[17–19] Cerebral activity is attenuated by the impedance of the cerebrospinal fluid, meninges, skull and scalp. Therefore, scalp-EEG fails to show a great number of IED recorded by depth or subdural electrodes (Figure 56.1) and interictal activity arising from deep or midline structures is usually not reflected in surface EEG.[1] The distribution of IED on the scalp depends on the conductive properties of the surrounding tissue, the spatial characteristics of the generator, propagation pathways and on the spatial resolution of the surface EEG. Consequently, the distribution of interictal epileptic discharges in the scalp EEG can fail to localize or even mislocalize the region or hemisphere of seizure origin.[3] Patients with an epileptogenic zone in the frontal, occipital, insular-opercular and orbitofrontal regions may show falsely localizing temporal IED.[20–22] Closely spaced scalp electrodes can improve the yield of spike detection and localization over the standard 10–20 system.[23,24]

It remains controversial whether or not sphenoidal electrodes placed close to the foramen ovale increase the sensitivity of IED detection. While several studies found that in a minority of patients, especially with temporal lobe epilepsies sphenoidal electrodes can record epileptiform activity which does not appear in anterior temporal electrodes (Figure 56.2),[25–29] others could not verify this observation.[30] Sharp waves with the maximal amplitude at the sphenoidal electrodes can arise from the mesial or lateral temporal lobe or from an orbito-frontal focus.[27] Sphenoidal electrodes can register higher amplitudes of IED as compared to scalp electrodes.[3,31,32] However, sphenoidal electrodes still fail to detect a large proportion of IED recorded by foramen ovale electrodes (Figure 56.1).[30]

Multichannel whole-head MEG has a similar sensitivity to detect IED as compared to noninvasive EEG[19,33,34] and the combination of both provide complementary and confirmatory information for the localization IED which cannot be obtained with either technique alone. In a study on 70 surgical candidates, MEG identified IED in one-third of EEG negative patients, especially in cases of lateral neocortical epilepsies and epilepsies due to cortical dysplasia.[19,35] Conversely, IED were seen only in the EEG in a subset of patients with mesial frontal lobe epilepsy.[35]

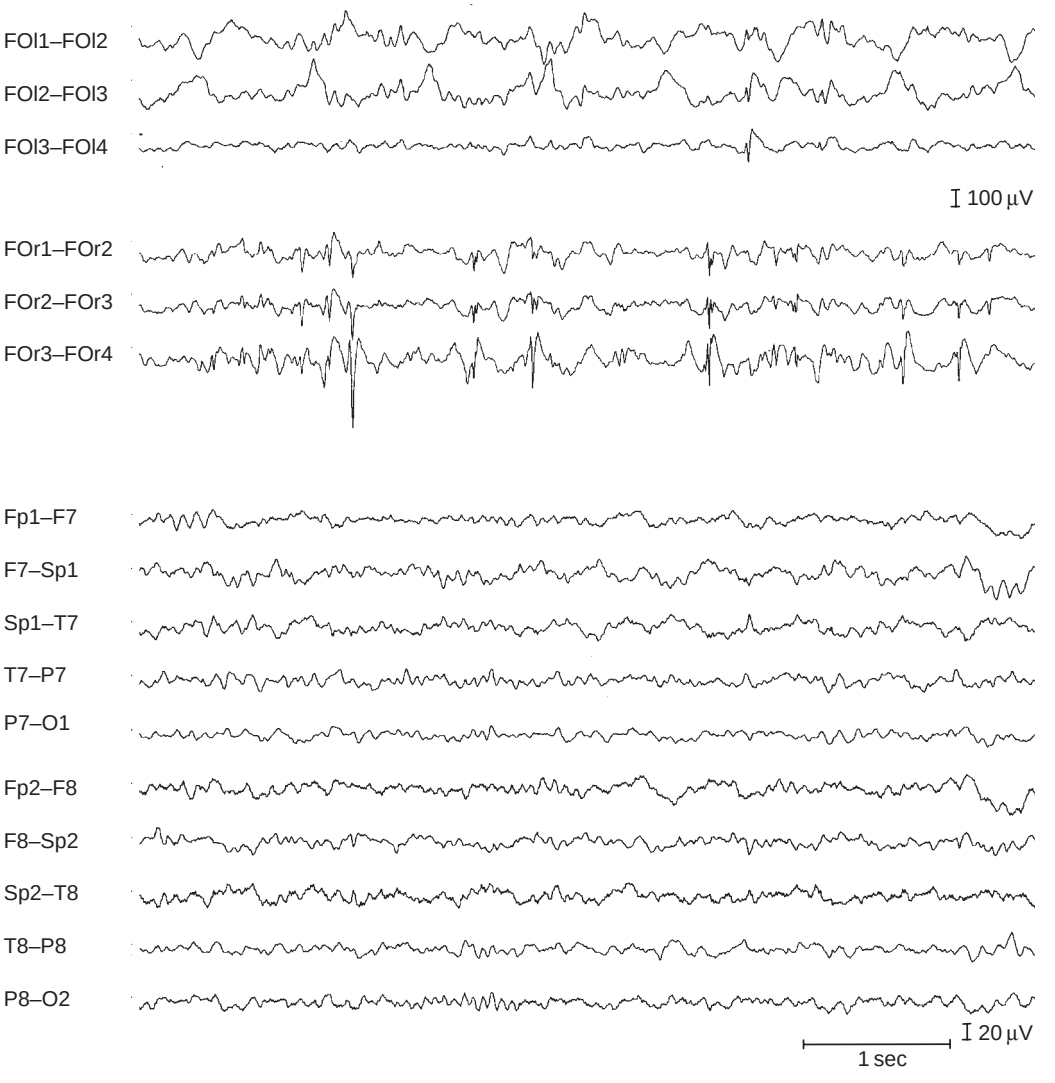

Figure 56.1 Invasive Video-EEG monitoring with bilateral foramen ovale electrodes of a 38-year-old patient with bitemporal epilepsy. In addition, scalp electrodes were attached according to the International 10–20 system and sphenoidal electrodes were bilaterally inserted. Note the interictal epileptiform discharges (IED) recorded maximally at the fourth contact of the right foramen ovale electrode while the scalp and sphenoidal electrodes fail to detect these IED. FOr1, FOr2, FOr3, FOr4: four contacts of the right foramen ovale electrode; FOl1, FOl2, FOl3, FOl4: four contacts of the left foramen ovale electrode; Sp1: left sphenoidal electrode; Sp2: right sphenoidal electrode.

Yield of scalp EEG

The first EEG will uncover IED in about 30–50% of the patients with epilepsy and the yield increases to 60–90% by the fourth EEG.[2,36–38] This contrasts with the frequency of IED in nonepileptic patients ranging from 0.5% in healthy young men[39] to 12% in a study including all age groups and patients with progressive cerebral disorders.[40] Specificity is probably lower and sensitivity higher in children as compared to adults, but reliable estimates are not available.[2] The frequency of IED in elderly patients with epilepsy is substantially lower than that reported in epileptic populations as a whole.[36,41] The majority of reports could not establish a correlation between the levels of anticonvulsants and the frequency of focal interictal spiking, although this issue remains controversial.[9,36,42–45] Overall, it can be expected that around 10% of the patients with epilepsy (more with extratemporal than with temporal epilepsy) will show no IED in scalp EEG during wakefulness or sleep in spite of prolonged or repeated recordings.[2,46,47] The yield from a single EEG is substantially increased in patients investigated within one or two days after a seizure, and is greater in patients with monthly seizures than in those who had been seizurefree for a year.[36,45,48] The duration of recording may also affect the detection rate of interictal spiking.[9]

Moreover, the yield can be significantly increased and new abnormalities found, if the EEG includes sleep recordings.[2,48,49] IED are seen more commonly during sleep, with the greatest activation during non-REM sleep.[1,50–53] Increased neuronal synchronization within thalamocortical projection neurons during non-REM sleep may contribute to the activation process in epileptic cortex.[46] The predictive accuracy in lateralization of epileptogenesis is improved during non-REM sleep in patients who showed bilateral or no discharges in wakefulness because unilateral discharges arising de novo in sleep were always correctly lateralizing.[46] In patients who had unilateral discharges in the awake state whether ipsilateral or contralateral to the epileptogenic zone, the findings were generally unchanged during sleep although sleep may alter IED morphology and distribution.[52] Spikes can be more

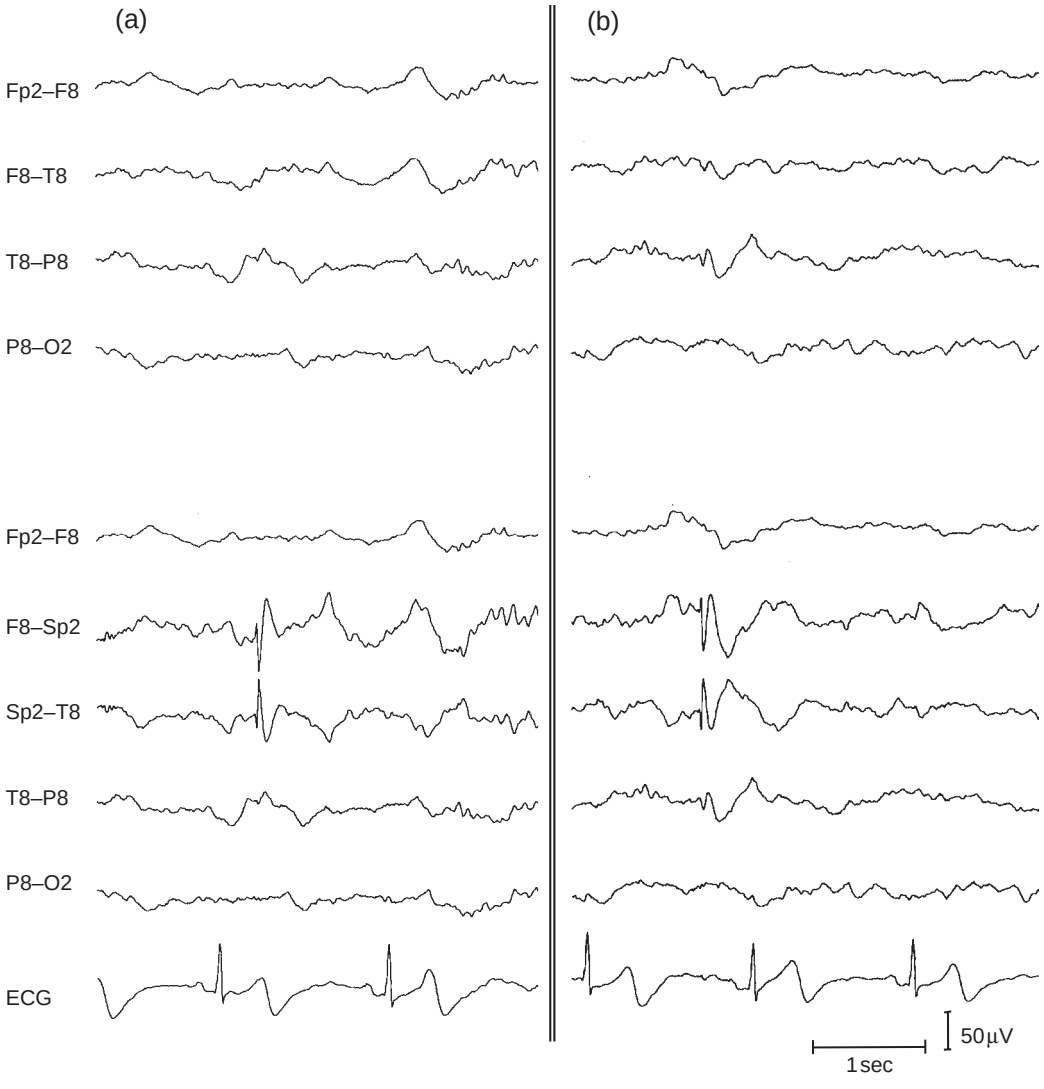

Figure 56.2 Two examples of interictal epileptiform discharges (IED) of a 39-year-old patient with right mesial temporal epilepsy due to hippocampal sclerosis. Scalp electrodes were attached according to the International 10–20 system and additional sphenoidal electrodes were bilaterally inserted (Sp2: right sphenoidal electrode). The first four channels represent a longitudinal bipolar montage of scalp electrodes over the right temporal area. In the following five channels, the right sphenoidal electrode is included between F8 and T8 in a bipolar fashion. Note the sharp waves recorded by the sphenoidal electrode and missed by the scalp electrodes. ECG: electrocardiogram.

widespread during non-REM sleep than during wakefulness or REM sleep suggesting that the localization of interictal discharges in REM sleep may be a better indicator of the epileptogenic zone than in non-REM sleep.[53] Hyperventilation or photic stimulation rarely activate IED in patients with focal epilepsies.[54,54–57]

Specificity of interictal scalp EEG

In general, the frequency, repetition rate, morphologic characteristics and state dependence of interictal epileptiform activity cannot be used to predict the etiology or severity of the disorder.[3] However, rhythmic spiking on a slow background activity and not associated with behavioral changes has been found to be characteristic for focal cortical dysplastic lesions.[58–60] Tumors tended to cause wider distributed IED as compared to developmental abnormalities or hippocampal sclerosis,[21,24,61] which was also true for seizure patterns.[62] This may be caused by local neuronal injury, edema, ischemia or other electrical and/or biochemical effects of the structural lesion on susceptible neighboring brain tissue or homologous contralateral areas.[63,64]

Prognostic relevance of postoperative IED

In both, temporal and extratemporal epilepsy, absence of IED in the 6-month or 1-year postoperative scalp-EEG was associated with good postoperative outcome.[65–69] The prognostic value of a 3-month postoperative EEG remains controversial.[25,70–72] The presence of IED in the early extracranial postoperative EEG (within 1 or 2 weeks) were not found to be of prognostic value in most of the studies.[71,73–76] There are conflicting results on the prognostic value of IED in the postresection electrocorticography (ECoG). Several studies found an association between postresection IED in this test and less favorable outcome [74,77–80] while others did not.[25,67,71,73,81–83] The lack of agreement of these studies may be due to differences in the patient populations (e.g. lesional versus nonlesional cases), the recording

techniques and in the anesthetic agents used during surgery. Even in the studies confirming the association of postresection IED and seizure continuation, the percentage of patients with postresection persistence of IED but still favorable outcome varied from 25–47%[69,74,78,79] which can make it difficult to estimate the prognosis in individual cases.

Temporal lobe epilepsy (TLE)

As mentioned above, several studies indicated that the majority of mesial and neocortical temporal IED fails to be recorded by surface electrodes.[4,18,84] The IED which are recorded in the extracranial EEG, however, may show a better correlation with the seizure origin as compared to IED recorded by depth electrodes.[85] This suggests that widely synchronous interictal spikes more likely rise from the epileptogenic area than spikes with smaller fields.

In addition to IED, temporal intermittent rhythmic delta activity (TIRDA) was also strongly correlated with a clinical diagnosis of TLE[85–87] (Figure 56.3). TIRDA was seen in 0.3% of all recordings obtained in a general EEG laboratory [88] but in as many as 28% of patients being evaluated for temporal lobe resection.[89] A significant association was found between a mesial temporal epileptogenic zone and TIRDA.[90] On the other hand, temporal intermittent polymorphic delta activity was recorded in patients with temporal and extratemporal epilepsies.[89]

Distribution of IED in TLE

In TLE, IED tend to produce a stereotyped pattern on the scalp with highest amplitudes at the anterior temporal electrodes. This may be due to the location of the neuronal generators within the temporal lobe and anatomical characteristics of the brain coverings, such as skull discontinuities.[17] Children may have a more widespread irritative zone which may be caused by a high frequency of dual pathology.[91] Most[78,82,92–95] but not all studies[47,96] confirmed the finding that IED confined to the anterior temporal region are predictive of good postoperative outcome after TLE surgery.

Lateralizing value of IED

The incidence of bilateral IED in TLE is estimated to lie between 20 and 44% and may be higher when investigated with invasive EEG.[4] The probability of bilateral IED was positively correlated with the duration of the EEG monitoring.[96,97] Bitemporal IED increase the likelihood that seizures are arising independently from both sides[98] and can reflect bilateral damage, dysfunction at a distance, or secondary epileptogenesis.[21,99,100]

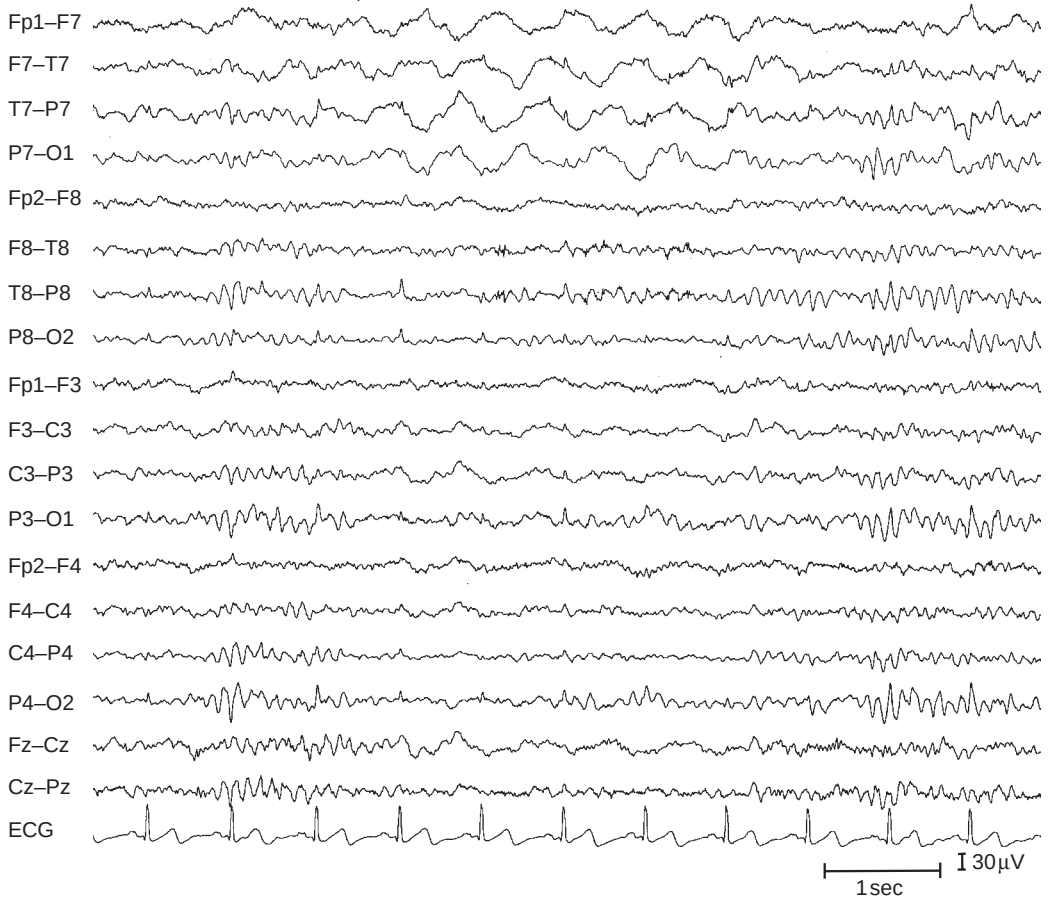

Figure 56.3 Interictal EEG of a 21-year-old patient with left temporal lobe epilepsy due to hippocampal sclerosis. Scalp electrodes are attached according to the International 10–20 system. Note the temporal intermittent rhythmic delta activity (TIRDA) in the left temporal region. ECG: electrocardiogram.

In extracranial EEG recordings, interictal discharges can have a more reliable lateralizing value than ictal changes in temporal lobe epilepsy,[100] and they almost always predict seizure origin in TLE and good postoperative outcome if they are exclusive or clearly preponderant on the side of surgery.[4,37,71,78,82,85,98,101–108] In a study of 59 candidates for temporal lobectomy, 92% of patents with >90% lateralization of the IEDs had a good surgical outcome, whereas only 50% with <90% had a favorable outcome.[47] Preoperative IED frequency was not associated with postoperative outcome.[109,110] In addition to IED, lateralization of delta activity also indicated the side of temporal seizure origin in a high proportion of patients.[58,85] These findings may not fully be applicable for tumor patients who can show a wide irritative zone[24] and whose postoperative seizure outcome was not affected by bilateral IED.[65]

Mesial temporal lobe epilepsy (mTLE)

The IED in hippocampal sclerosis (HS) have a very localized field which is frequently missed by scalp electrodes.[4] If IED are recorded in the extracranial EEG, they are highly restricted to anterior temporal electrodes.[24,111,112] Using three-dimensional multiple dipole modeling, two possible sources of interictal spikes in HS patients could be identified.[113] The first source involved the mesio-basal aspect of the temporal lobe (hippocampus and parahippocampal gyrus) and was followed within 40 msec by activation of the anterior temporal lobe neocortex. Extracranially recorded IED in mesial and not in lateral TLE frequently show a negative pole in the anterior temporal region or at the sphenoidal electrode and a widespread positive pole over the vertex.[114] As a rule, patients with HS have greater than 90% of their interictal epileptiform discharges in the anterior temporal region. Therefore, frequent posterior or extra-temporal sharp waves may decrease the certainty of the diagnosis of HS.[24] The rare occurrence of lateral temporal and frontal spikes/sharp waves in patients with HS may be due to spread of epileptic discharges to the temporal neocortex or to the (orbito-)frontal cortex via the limbic system.[114]

In patients with a history and ictal symptoms and signs suggestive of mTLE, interictal epileptiform discharges recorded during serial routine EEGs can reliably lateralize the seizure focus if they are consistently lateralized to one temporal lobe and are concordant with MRI-identified unilateral hippocampal atrophy.[96,102,104] This supports the view that seizure recordings may not be necessary in this situation.[115] In mTLE, concordance of structural MRI and interictal EEG was more closely associated with good surgical outcome than concordance of MRI and ictal EEG findings with nonlateralizing interictal EEG.[116] Although bilateral IED decrease substantially the chances of a favorable postoperative outcome,[117] subjects with bitemporal IED but MRI hippocampal abnormalities concordant with the ictal-onset region still can have a good to excellent surgical outcome.[24,94,103,112,118]

Frontal lobe epilepsy (FLE)

The value of noninvasive EEG is more limited in extratemporal epilepsy than in TLE. More than a third of patients with frontal lobe epilepsy may not show any IED in extracranial EEG[26,119] so that absence of interictal spikes with documented seizures suggests extratemporal epilepsy.[120] If IED are recorded in extratemporal epilepsy, especially in FLE, they tend to be less welllocalized, multifocal, generalized, or even mislateralized.[22,26,119,121–125] The poor localization of IED in FLE is due to the anatomy of the frontal lobe with inaccessibility of much of the frontal lobe to surface electrodes and the network of projection pathways that allow the rapid spread of epileptiform activity within and outside the frontal lobes. The rates of bilateral IED were significantly higher in patients with FLE than with TLE.[123,126,127] Mesial frontal lesions facilitate secondary bilateral synchrony (Figure 56.4)[128,129] which is the phenomenon of seemingly generalized IED which can be observed in up to 40% of these patients.[129,130] The presence of unilateral focal discharges that initiate the generalized IED and additional focal or at least lateralized epileptiform or nonepileptiform abnormalities seen strictly on the same side differentiate secondary bilateral synchrony from generalized IED observed in idiopathic generalized epilepsy.[131] Nonepileptiform EEG abnormalities, such as focal or lateralized slowing or an asymmetry of background activity, may give a clue to the abnormal side in the situation of independent bilateral IED. Patients whose seizures originated from the dorsolateral frontal convexity frequently had focal interictal epileptiform abnormalities that localized to the region of seizure onset while patients whose seizures began in the mesial frontal region had either no interictal epileptiform activity or had multifocal epileptiform discharges.[132,133]

Generalized IED in FLE were associated with poor postoperative outcome[134] while unifocal IED were highly predictive of successful outcome.[121]

Parietal lobe epilepsy (PLE)

The relative frequency of parietal lobe epilepsy is generally considered low and the data concerning this patient group are limited.[135] The majority of patients with PLE shows IED. The IED are usually widespread and multifocal and can be bilateral suggesting an extent of the irritative zone far beyond the epileptogenic zone.[62,135–138] Secondary bilateral synchrony can be recorded in up to 30% of the cases especially with parasagittal lesions.[62,137] In general, extracranial interictal EEG findings are an unreliable indicator of parietal lobe epilepsy.[138,139] Electrophysiologic studies should be carefully addressed if there is disagreement between scalp-recorded EEG and neuroimaging.

Occipital lobe epilepsy (OLE)

A great majority of patients with OLE have abnormal interictal or ictal EEG findings but scalp EEG may fail to detect epileptiform activity generated by an irritative zone on the inferior and mesial occipital surfaces. Nonepileptiform abnormalities, such as decreased alpha activity or focal slowing, may then help to detect occipital dysfunction. The most frequent IED in OLE are spikes and sharp waves in temporal or temporo-occipital regions with shifting maximums in some patients.[21,135,140,141] Widespread and bilateral IED are common and isolated epileptiform activity restricted to the occipital

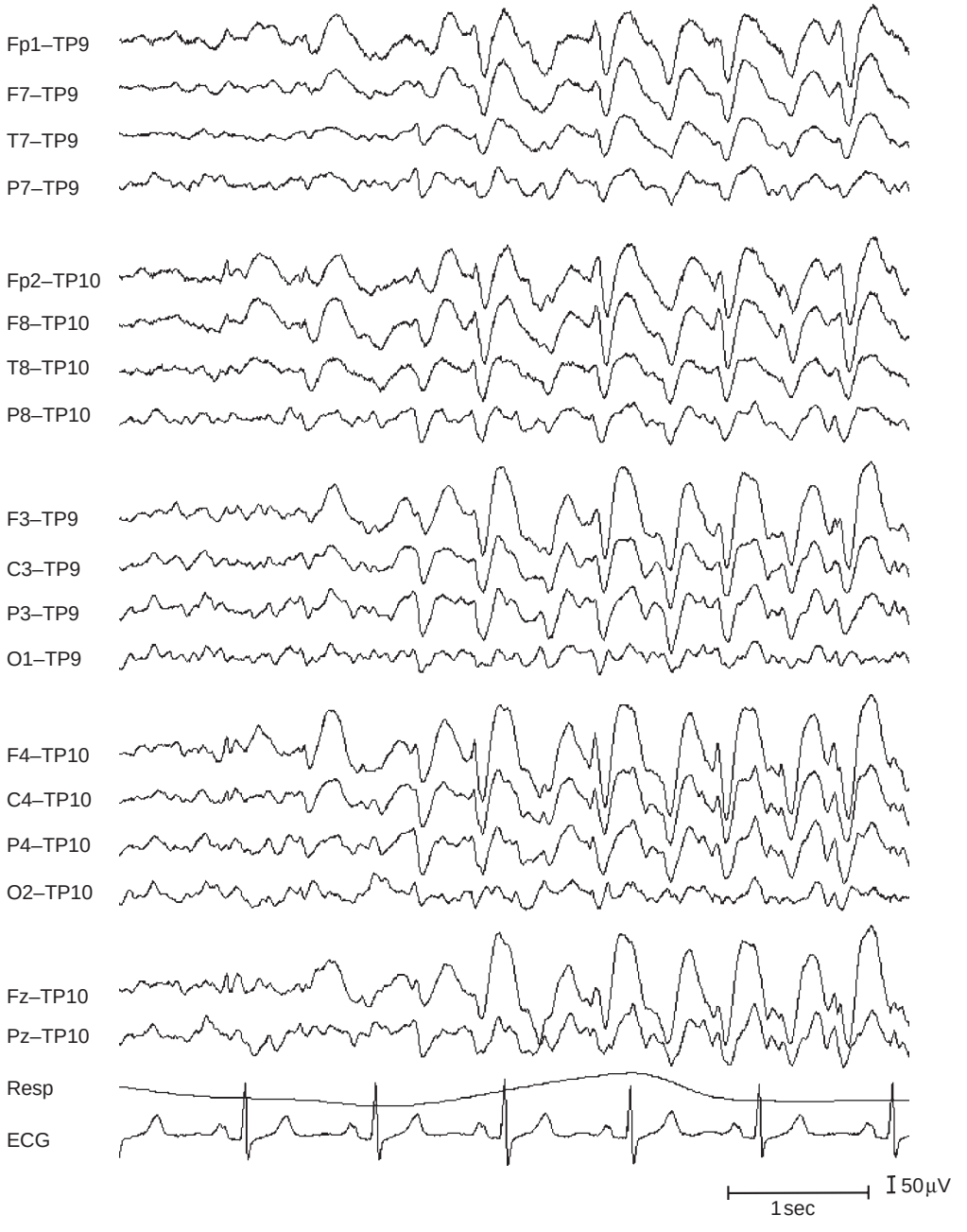

Figure 56.4 Interictal EEG of a 21-year-old patient with right frontal epilepsy. Referential montage with the ipsilateral TP9 (resp. TP10) electrode as reference electrode. Note the secondary bilateral synchrony consisting of generalized spike-wave-complexes preceded by right frontal discharges. ECG: electrocardiogram; Resp: respiration.

lobe is infrequent.[21,75,140,142] Rarely, IED can be recorded with highest amplitudes in the contralateral occipital region in the sense of a paradoxical lateralization if the dipole is oriented in such a way that contralateral occipital electrodes best detect it. This can be suspected if IED appear ipsilateral to more normal background activity.[143] A preponderance of focal IED may reflect the underlying pathology because the incidence of focal occipital IED was much higher in occipital epilepsies caused by malformations than in those due to tumors.[21] Patients with focal epilepsies generally have a low incidence of photosensitivity of 0.7–3.0%.[56,57,144] Among these patients, however, patients with OLE have the highest incidence ranging from 6–13%.[57,141,145]

In contrast to temporal lobe epilepsies, where the lack of contralateral IED is predictive for a seizure-free postoperative outcome,[117] this correlation could not be shown in posterior epilepsies.[62] Moreover, location of IED in any cortical region was not associated with the outcome in 42 surgical candidates suffering from occipital or parietal lobe epilepsy.[62] Similarly in another study of 35 patients who underwent surgery for intractable OLE, there was no relation between occipital and extraoccipital interictal surface EEG findings and seizure characteristics, postoperative outcome, or lesion location on MRI.[21]

Conclusions

Interictal EEG alone cannot exclude or establish the diagnosis of epilepsy and the amount of IED does not provide a guide to

seizure frequency. Negative findings from a single waking EEG are to be expected in many patients and contribute little to the diagnostic assessment, whereas the absence of IED in serial EEG both in waking and sleep significantly reduces the probability of epilepsy. The finding of epileptiform EEG activity plays an important role in classification of epilepsies and epilepsy syndromes especially in the absence of other evidence of cerebral disease. Tumorous epilepsies appear to generate wider irritative zones as compared to other etiologies.

The great value of IED in localizing temporal epileptogenesis and predicting postoperative outcome in TLE has been increasingly recognized in recent years although scalp EEG fails to detect most of the epileptiform activity recorded by intracranial electrodes. In the vast majority of patients with mesial temporal lobe epilepsy, interictal epileptiform activity is highly restricted to anterior temporal electrodes including sphenoidal electrodes. Bilateral IED can be generated by unilateral TLE but decrease the chances of postoperative seizure freedom.

The value of interictal epileptiform activity in the scalp-recorded EEG is more limited in extratemporal epilepsy as compared to temporal lobe epilepsy. Many of the patients with extratemporal epilepsy show either no or widespread and multifocal discharges. Mesial frontal and parietal lesions facilitate secondary bilateral synchrony. In contrast to temporal lobe epilepsy, no association could be found between poor postoperative outcome and preoperatively recorded multifocal or bilateral IED in occipital or parietal lobe epilepsies.In general, the absence of IED in the 6-month or 1-year postoperative scalp-EEG is associated with good postoperative outcome.

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57 The irritative zone evaluated with invasive recordings

A Palmini

Introduction

Epilepsy surgery offers the perspective for a definitive treatment, notably in those patients in whom antiepileptic drugs prove insufficient to control seizures. A treatment intended to eradicate epilepsy should aim at removing all relevant epileptogenic brain tissue, sparing eloquent cortex. Of course, an a priori step, and thus a major issue, is to determine what exactly means relevant epileptogenic brain tissue.

Prior to this era of major conceptual and practical advances in the identification of tissue that should be removed to control seizures surgically,[1,2] a great deal of attention was given to cortical regions displaying interictal spikes. Indeed, the identification of these regions via extra- or intra-operative electroencephalography was the cornerstone for the early development of epilepsy surgery.[3–6] Interestingly, the importance attached to interictal spikes have diminished in the last two decades, *pari pasu* with major developments in neuroimaging and the greater feasibility of ictal recordings. Furthermore, something close to a *coup de grace* on interictal spikes was perpetrated by a major conceptual advance, namely, the understanding of the role of structural lesions, ictal recordings, ictal semiology, and dysfunctional cortex in seizure generation.[1,2] In other words, different methodologies and more data have progressively taken the place of interictal spikes and have done so by refining (or 'redefining') the concept of epileptogenic brain tissue, replacing it by this more pragmatic concept of *relevant* epileptogenic brain tissue. Thus, in this introduction of a chapter where we review the methods and objectives of localizing interictal spikes by directly recording from the cortical tissue of epileptic patients, we need to acknowledge that such localization is currently not at the top of the hierarchical listing of the most useful tools to delineate the epileptogenic zone (EZ; ie, the 'relevant' epileptogenic brain tissue).

Nevertheless, as many have correctly said and I have stated recently,[7] experienced epileptologists would not dispense with a full analysis of the interictal spikes. If this holds true for the analysis of scalp recordings, let alone for the opportunity to analyze interictal spikes recorded directly from the brain. With these preliminary considerations in mind, this chapter will try to reconcile two truisms about interictal spikes: the fact that they may often not be a major player in the delineation of the EZ while, at the same time, and in specific circumstances, their careful analysis through invasive recordings may provide invaluable and *unique* data for such delineation.

We will start by reviewing the spatial relations between interictal spikes, ictal recordings, and structural lesions, as observed through distinct modes of invasive neurophysiological evaluation. We will then move on to those 'specific circumstances' where interictal spikes may be crucial in the delineation of the EZ.

The irritative zone localized by invasive recordings and the relevant epileptogenic brain tissue

How different methods of invasive recordings evaluate the irritative zone

Acute electrocorticography

Invasive recordings of interictal spikes are almost as old as scalp EEG itself. From the inception of electroencephalography, this method was applied to record directly from the brain surface. Indeed, Penfield and Jasper at the Montreal Neurological Institute (MNI) used acute intraoperative electrocorticography (ECoG) to advance the field of epilepsy surgery in the 1940s and 1950s.[3–5] The strong impact imparted by this and other traditional schools of thought in the epilepsy surgery field have led to the continued use of acute ECoG by many epilepsy Centers around the world.[8–11]

Like all recording methods, the use of acute ECoG to analyze the irritative zone has advantages and disadvantages. The risks, costs, and technology involved in acute ECoG recordings are much less impressive in comparison with other invasive methods. In addition, the surgeon and the neurophysiologist can explore various subregions within a given exposed cortical area, by freely moving the cortically-applied carbon ball or strips/grids electrodes. Furthermore, as will be reviewed below, there are some patterns in the acute ECoG that may be more or less specific for certain types of underlying pathologies and which may have a major impact in the final delineation of the EZ.[8–10]

Finally, there are two peculiar additional advantages of the use of acute ECoG, and both pertain to the possibility of additional recordings *after* tissue resection. One is that carbon ball electrodes can record from the depth of gyri, after an initial resection was performed (Figure 57.1). This is important because some epileptogenic pathologies, particularly focal cortical dysplasias (FCD), may extend to or involve only these deeper cortical areas (Figure 57.2).[12] Despite the high degree of epileptogenicity of these lesions, very active epileptogenic

activity originating in these deep seated lesions (or parts thereof) (Figures 57.1 and 57.2) may defy recordings purely from the cortical surface – such as the type of probing provided by subdural grid electrodes.

The other related advantage is that acute ECoG allows an 'electrical revision' of the exposed cortical surface after initial resection. Epileptogenic abnormalities encountered in these acute post resection recordings may or may not be relevant for prognosis or as an indication of the need for additional tissue resection. As will be reviewed below, such variability is related to the underlying pathology. In those scenarios where additional resection may have an impact on the final outcome, acute ECoG stands as the only method allowing such tailoring.

On the other hand, although it provides relative gains in the spatial domain, acute ECoG is potentially less effective than chronic invasive recordings in the time domain. In other words, while acute ECoG allows free movement of electrode contacts within a given area, the time allotted to record – and thus determine the irritative zone – is limited to something around 20–60 minutes. In contrast, other methods allow recordings for days or weeks. Another disadvantage of acute ECoG is that recording electrodes usually cover only a given surface of the cortex. Other methods may allow the implantation of electrode contacts in different regions of one, or even the two hemispheres, and thus the chronic recording is not only longer, but also may encompass more cortical regions. This may be an apparent paradox with what was mentioned above, about the spatial advantages of the acute ECoG. This apparent paradox is reconciled by the 'golf player' approach to the localization of the EZ, which is a metaphor for the sequential steps taken to progressively circumscribe the cortical area in which the EZ is contained, resembling the approach of a golf player to progressively approximate the ball to hole. The first shot usually approximates the ball, the second aims at better positioning the ball as close as possible to the hole, and the third shot will eventually try to succeed in putting the ball in. The approach to the localization of the EZ also begins with semiology and scalp EEG, both providing a first step toward localization, which is refined by further 'shots', such as structural and functional imaging and, occasionally, invasive EEG recordings. Before we are close enough to the EZ, the cortical coverage provided by acute ECoG is usually smaller than other methods of recording, which can sample (interictal and ictal activity) from different areas of both hemispheres. However, once the cortical region containing the EZ is fairly circumscribed within the limits of a craniotomy, then the acute ECoG recording electrodes provide a better and flexible coverage of all cortical regions exposed by the craniotomy. This resolves the spatial resolution paradox.

Chronic recording with subdural grids and strips

Interictal spikes can also be probed through chronic invasive recordings with subdural grids and strips. These subdural

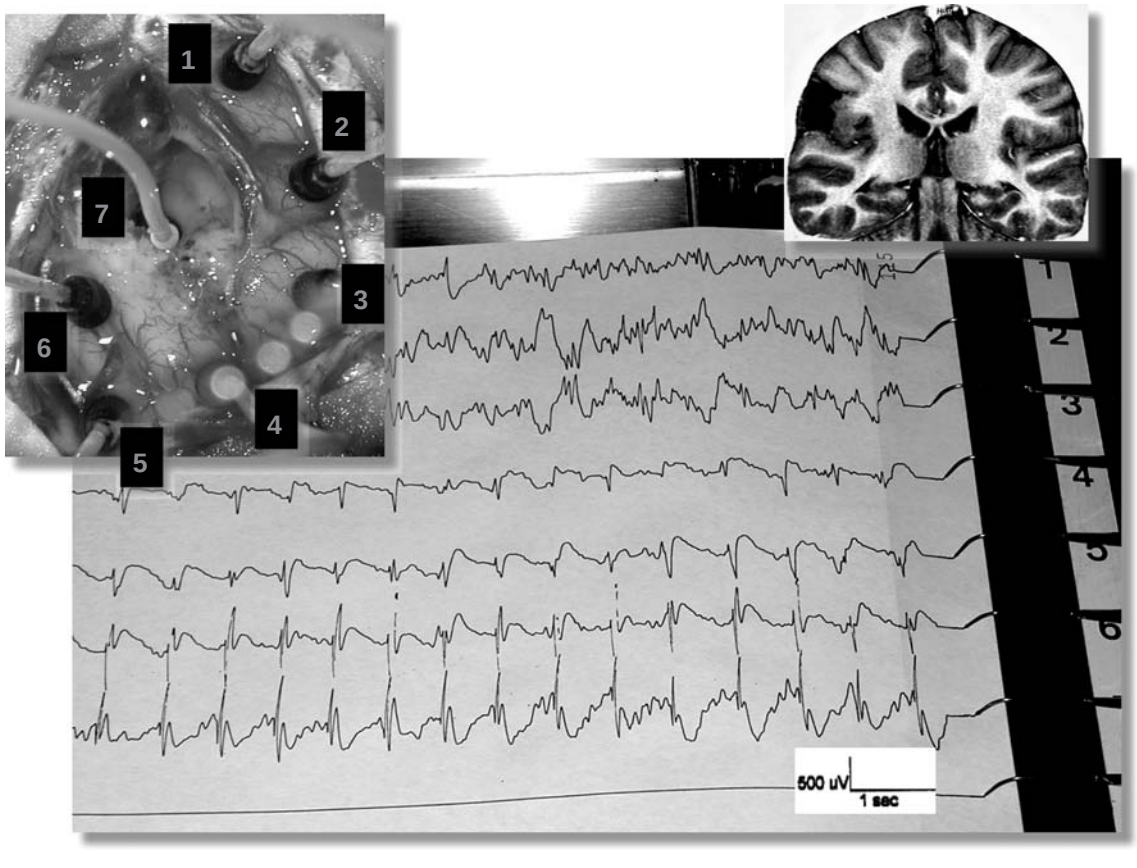

Figure 57.1 Composite picture of acute ECoG recording with carbon ball electrodes and histopathological H-E section showing type II focal cortical dysplasia. The recording was obtained during reoperation. Note that electrode 7 records from deeper regions on the bottom of the previous resection. The portion of the ECoG included in the picture is restricted to the recording of the electrodes shown on the left side. The ECoG montage is circular, starting with 1–2 and finishing with 7–1. Continuous, repetitive spikes very typical of type II focal cortical dysplasia are recorded phase-reversing at electrode position 7, with some adjacent volume conduction. The MRI picture of this patient is shown in Figure 57.2.

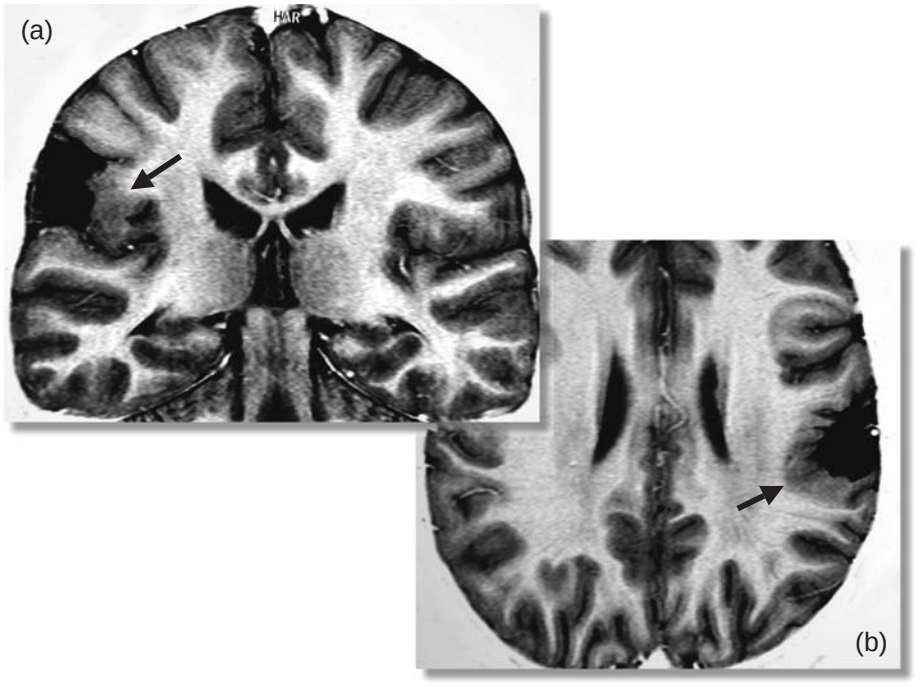

Figure 57.2 Postoperative coronal (a) and axial (b) MRI sections acquired on inversion recovery showing dysplastic tissue in the peri-insular 'deep' cortex (arrows). Previous resection was restricted to more superficial cortical regions and this deeper abnormality remained and led to seizure recurrence.

electrodes sample electrical activity from variable extensions of cortical tissue, within which the EZ is believed to be contained. The first main difference between chronic subdural recording versus acute ECoG is that whereas the latter specifically aims at interictal recording (that is, to pigeonhole the irritative zone as much as possible), the former is primarily intended to record seizures, that is, to localize the *ictal onset zone*. Theoretically, chronic subdural recordings with grids provide an almost ideal situation, in which both the ictal onset zone and the (more or less) adjacent irritative zone would be localized.[13] Several factors, however, mitigate against this very desirable scenario. First and foremost, is the need for a dedicated surgical procedure to implant the electrodes, with the attending risks of infection, edema, and hemorrhage.[14,15] In addition, grids cover only a portion of the exposed surface of the cortex, and it is not uncommon that parts of the irritative zone extend beyond (anterior, posterior, superior, or inferior to) the electrode coverage.[16] Because these electrodes are fixed, they cannot be moved after implantation. Another caveat, which chronic grids share with acute ECoG, is that both are incapable of recording fully (ECoG) or partially (grids) from inferior and medial surfaces of the cortex. Of course, grids can and often are implanted in areas inaccessible to carbon ball ECoG electrodes, such as the inferior temporal, the orbital, and the medial frontal cortices. However, the coverage is incomplete. Finally, one other important disadvantage of chronic subdural grids recording in comparison to acute ECoG is the fact that the latter can provide postresection recordings to verify the extent of resection of the part of the irritative zone exposed by the craniotomy. This often leads to tailoring of the extent of resection, which is important in many situations, particularly when the underlying pathology involves cortical regions in the deeper parts of the gyri (see above). Carbon ball electrodes can be used to probe from these deeper cortical regions after initial resection, which is not the case with grid and strip electrodes.

Intracerebral depth electrodes

The irritative zone can also be examined through intracranial EEG using stereotactically implanted depth electrodes. This is the only method allowing chronic recording of deeply situated cortical targets. At the outset it is important to mention that even more than the recording with subdural electrodes, the use of depth electrodes is fully intended to record ictal activity. Indeed, the very decision process of where to implant these electrodes is driven by the most likely ictal onset and early propagation regions, in what is known as the anatomofunctional 3D view of the EZ.[12,17] In other words, depth electrodes are implanted in the regions most likely to be involved at seizure onset and early propagation, providing a dynamic, electrical picture of seizure onset and progression.[18] The cortical volume sampled by depth electrode contacts is small, and thus a hypothesis-driven choice of targets is key to a successful investigation. Accordingly, this inherently limited sampling allows only an equally limited view of the irritative zone. However, the sampling provided, albeit limited, may be of relevance for the understanding of the relations between spikes, structural lesions, and ictal onset zones in selected cases. Examples include the interictal spikes recorded from within focal dysplastic lesions[12,19,20] adjacent from dysembryoplastic neuroepithelial tumors[21] and from mesial temporal regions[22] in patients with indication for bitemporal implantation. Nevertheless, it is to be understood that the indications for depth electrode implantation are virtually never related to the mapping of interictal spikes. In addition to the sampling limitations, depth electrode implantation is an invasive and costly

procedure whose indications – even to explore ictal onset zones – are often debatable.

The irritative zone (usually) contains the ictal onset zone: understanding the actual and potential relations

If the interictal spike is a signature of epileptogenicity, it is then to be expected that the region of seizure onset is to be found within the (usually larger) area from where spikes are recorded. Spikes can be generated by genuinely pathologic cortical regions but also by nonpathologic cortical areas whose epileptogenic threshold was lowered due to synaptic (or ephatic) connections with the primarily pathologic cortex. In other words, the irritative zone includes both pathologic and non pathologic tissue. Although the differentiation of where the former ends and latter begins is often blurred, it is accepted that the ictal onset zone is usually linked to pathologic tissue. This is an old concept, actually. In the 1940s, Penfield used the term 'epileptogenic lesion' to describe not necessarily a visible structural lesion, but rather a surrounding, partially damaged, cortical area in which a critical mass of preserved neuronal activity did generate spikes thought to be relevant for seizure generation.[4,5]

Taking from the discussion above, the identification of the irritative zone by whatever method is a 'first filtering' of electrical brain activity, useful to circumscribe the much valued ictal onset zone. This usefulness, of course, is constrained by the sampling issue. The more accurate the sampling, that is, the more accurate the determination of the irritative zone, the higher the chances of localizing the ictal onset zone. The use of invasive recordings in this regard is then to be critically appraised.

On the one hand, by recording directly from cortical generators, intracranial electrodes may refine the mapping of the irritative zone, adding dimensions unavailable or inconsistently available from scalp recordings, such as variable spike amplitude, sharpness, frequency, and rhythmicity. Within a larger cortical area, those regions displaying higher amplitude, sharper, very frequent and/or rhythmic spikes are usually closer to or colocalize with the ictal onset zone.[23] On the other hand, direct cortical recording by whatever invasive method often depicts a more extensive irritative zone than scalp recordings,[24,25] and this may be a confounding factor in the localization of the EZ. A notable example are the very frequent bitemporal independent spikes recorded through depth or subdural electrodes almost in every instance these electrodes probe both temporal lobes.[22] As shown in studies from the pre-MRI era, temporal lobes displaying frequent spiking in depth electrode recordings may *not* be associated with seizure generation in patients with temporal lobe epilepsy and bitemporal interictal spikes.[22] Thus, interpretation of the extent and significance of the irritative zone as recorded through invasive electrodes cannot be dissociated from the other findings obtained through semiology, imaging and scalp recordings.

In the section above I analyzed the different types of invasive methods which can be used in the presurgical evaluation and which can record the irritative zone. At this point it should be said that each method will provide somewhat different relations between the irritative and the ictal onset zone. For instance, acute ECoG usually does not allow a correlation between these two anatomo-functional zones, and thus will rely on the data derived from imaging, semiology, and scalp recordings as well as on spike morphology, frequency and rhythmicity to adequately interpret the relevance of acutely recorded spikes. In contrast, one of the major advantages of invasive recordings with subdural grid and strip electrodes is to allow a spatial relation between a larger cortical region displaying spikes and (usually) a more limited region involved at seizure onset. Nevertheless, as will be seen below, even with the advantage of ictal electrographic recordings it is often difficult to assign 'values' or 'weights' to regions more or less adjacent to the ictal onset zone which display interictal spikes. Not unexpectedly, therefore, some studies have shown that the best surgical results are obtained with resection of both the ictal onset and the irritative zones, at least the irritative zone within the recording limits of subdural grids.[26,27] How much these findings should impact on the very indication of grid implantation (versus, for instance, acute ECoG recording) is not known. As will be seen later, the type and extent of the associated structural lesion (when present) or the presumed underlying etiology will be important to decide on how much of the irritative zone should be included in the final resection (as part of the EZ or 'relevant' epileptogenic brain tissue).

An additional point of practical relevance concerns the not uncommon observation that seizures may recur despite apparently complete resection of the ictal onset zone. The logical way to approach this phenomenon is through the conceptual understandings that the (i) ictal onset zone is not synonymous with the EZ, and (ii) that despite the best possible localization of the actual EZ at one point in time, there may be latent cortical regions that may take over as a previously unsuspected epileptogenic zone in the future. This latter possibility was conceptually advanced by Rosenow and Ludders by coining the terminology 'potential epileptogenic zone'.[28] The reason I mention this here is that the irritative zone – or the correct appraisal of the significance of the different types of interictal epileptic activity – may prove useful to anticipate the possibility that some cortical region may eventually harbor a 'potential EZ'. Notwithstanding the elegant conceptualization recently proposed by Rosenow and Ludders, the idea of a potential EZ was already present in some of Penfield's writings, where he proposed that within an area of epileptogenic cortex identified by ECoG, seizures could originate in more than one subregion and propagate through facilitated pathways.[4,5] These pathways could thus be conceived as a common denominator for electrical seizures originating in different subregions of a larger area of epileptogenic cortex. This, in turn, would lead to similar semiology, irrespective of the exact subregion of seizure origin. These are scenarios in which the EZ (or the 'potential' EZ) is more extensive than the (any single) seizure onset zone, justifying the individualization of these concepts. It is to be expected that incomplete resections of this 'potential' EZ, with preservation of higher threshold seizure onset zones, may be associated with later seizure recurrence after resection of the lowest threshold ictal zone.[29] In summary, the analysis of historical observations recently advanced through modern concepts suggest that 'relevant' epileptogenic tissue may be present outside the boundaries of the actual ictal onset zone, and one of the keys to anticipate this possibility is through improvements in the analysis of the irritative zone.

Lesions and spikes: the various combinations between structural lesions and the irritative zone

Traditionally, the relationship between epileptogenic cortex and epileptogenic lesions has been a critical issue, particularly at a time when the extent of resection was determined intraoperatively on the basis of acute ECoG combined with visually identifiable cortical scars and other types of lesions.[7]

From the start, Penfield and Jasper demonstrated that spikes were to be expected in the cortex *surrounding* the structural lesions, particularly those lesions without neuronal components, such as glial tumors or cysts.[4] These surrounding regions – as well as atrophic cortical lesions – were thought to be 'injured areas of gray matter'. Thus, the early history of the relations between epileptogenic lesions and epileptogenic cortex was based on the concept of *abnormal gray matter within atrophic scars or surrounding foreign tissue lesions*, and particularly related to the fact that epileptiform discharges were to be expected in the structurally and functionally disturbed but still viable surrounding gray matter. These concepts were further supported by pathological examination of this surrounding tissue, which usually demonstrated some degree of gliosis.

Clearly, epileptiform spikes can be recorded from structurally normal cortex, as demonstrated in different epilepsy syndromes, from the benign rolandic epilepsy[30] to the mirror foci studied by Frank Morrell,[31] which represented epileptiform spikes recorded at a distance from a foreign tissue lesion, in regions synaptically connected with the area harboring the primary lesion. Demonstrations that not all epileptiform spikes indicate *structurally abnormal* cortex have actually been provided long ago by the Montreal Neurological Institute school, and prompted the terminology 'red' versus 'green' ECoG spikes, pointing respectively to epileptiform discharges recorded from abnormal cortical tissue – that could be related to seizure generation – and to discharges recorded from structurally normal underlying cortex.[32] The latter was regarded as not relevant for the production of seizures. Nevertheless, in a detailed follow up study published in the early 1960s, Jasper and colleagues demonstrated a significant (albeit not absolute) correlation between completeness of excision of the cortex displaying interictal spikes and surgical outcome, suggesting that cortically recorded spikes were, more often than not, relevant for the overall epileptogenic proneness.[6]

The advent of MRI has shown that the generation of interictal spikes in lesional epilepsies is distributed along a spectrum, one end of which being represented by those patients in whom discharges are restricted to the cortical area containing the lesion or its immediate surroundings, and the other end by patients whose interictal discharges are distributed over much larger regions of one or both hemispheres. One intermediate situation is that in which spikes are recorded from cortical regions which are more extensive than the 'surroundings' of a lesion, but are still contained, for instance, in a single lobe or 'quadrant' of the brain. A major challenge of the presurgical evaluation in patients with refractory lesional partial epilepsies is to synthesize the relationships between the structural lesion, the irritative zone and the seizure onset zone into a sound localizing hypothesis for the ultimate EZ.

Different types of irritative zone on invasive recordings and their contribution to the 'relevant' epileptogenic brain tissue

Not all spikes are the same

A major point in any discussion on the irritative zone, or the cortical region displaying 'interictal spikes', is the fact that such spikes may be generated from pathologic tissue or from tissue to which this is synaptically or ephatically connected. Thus, differentiating which spikes represent primary epileptogenic processes of abnormal tissue from those signaling nonpathologic low-threshold cortex is very important. This issue is even more important when related to invasive recordings because the direct cortical recordings enabled by such electrodes magnifies (in a spatiotemporal dimension) the recording of spikes. In other words, direct cortical sampling is often associated with the recording of spikes in regions where they were not seen in scalp EEG, as well as a higher frequency and a higher amplitude of discharges.[24,25] In this context, the attention to details is of utmost importance to correctly assess the irritative zone as determined through invasive recordings. What should one look at then?

First, whether spikes occur associated or not with background abnormalities. Spikes associated with regions of continuous (or frequent) slow wave activity[33] or with background attenuation[27] as recorded through any of the methods of invasive recordings are more significant as markers of 'relevant' epileptogenic brain tissue, than spikes recorded over a normal background.

Second, whether spikes are isolated, discontinuous, and infrequent or, alternatively, frequent, continuous or quasi-continuous, repetitive (that is, consistent in a given region), and with some hint of rhythmicity. Although I will discuss this further, it should be stated at this point that repetitive, continuous or almost continuous spikes tend to colocalize with pathologic cortex, most commonly in focal cortical dysplasias[8,12] (and, more rarely, on gliotic scars).[34] Frequent, but not continuous or rhythmic, spikes have also been shown to be correlated with underlying pathological epileptogenic cortex.[35]

Third, applying digital quantification tools to direct cortical recordings, some authors have shown that within a large cortical region displaying spikes, some subregions can be shown to lead the others. Apparently, these 'leading regions' tend to be more significant to the identification of 'relevant' epileptogenic brain tissue.[23,36] However, this kind of complex work has not been sufficiently replicated particularly in regard to the practical relevance of resecting these 'leading' regions in relation to surgical outcome.

In summary, as already dwelled upon above in the section on the relationships between lesions and spikes, it is yet to be fully determined which spikes are 'red' and which are 'green'. Association with abnormal background, consistency, continuity, rhythmicity, as well as high frequency and amplitude are all features that have been described as markers of 'relevant' epileptogenic brain tissue. Within this framework, the characterization of interictal spikes through invasive recordings may then provide useful clues to the delineation of the presently determined and potential EZ.

When the irritative zone largely defines the epileptogenic zone: histopathological relations

In some specific histopathological scenarios, the irritative zone may be crucial to *define* the extent of the EZ. This is the case with some types of neocortical pathology, most notably the focal cortical dysplasias and gangliogliomas.[8,12,19,35] In these contexts, the application of invasive recordings is of paramount importance to fully characterize the interictal features that have shown to be highly correlated with the extent of the EZ. Perhaps three examples will suffice to make this point. First, acute surface ECoG recordings of focal cortical dysplasias often show continuous, rhythmic or bursting spikes that tend to be exquisitely colocalized with the dysplastic lesion[8,37] (Figures 57.1 and 57.3a,b). In fact, this colocalization – and the pivotal role of such patterns as markers of the EZ – has been demonstrated by the highly significant correlation between persistence of cortical regions displaying such continuous spiking and poor surgical outcome. In a recent review of 41 patients with type II (Taylor-type) focal cortical dysplasia with extended follow-up, none of the 22 in whom cortical regions displaying continuous spiking remained in postresection ECoG recordings were seizure free after operation (Palmini *et al*, unpublished observation). Similar findings have been reported by the group at King's Hospital, in London.[9] Another example, with a different method of invasive recording, was provided by the group at Saint-Anne, in Paris. The authors report on the stereo-EEG findings in patients with type II focal cortical dysplasia and showed that rhythmic spike discharges were virtually always recorded intralesionally and that seizures virtually always started from the same electrode contacts which, interictally, displayed these rhythmic discharges.[12,19] These findings have been independently confirmed.[38] Finally, Rosenow and colleagues have reviewed interictal cortical findings recorded through chronic subdural grid implantation in patients with gangliogliomas and have also shown very frequent spikes in the regions surrounding these developmental tumors.[35]

Taken together, these interictal findings in focal cortical dysplasia and gangliogliomas are intimately linked to the ultimate delineation of the EZ. In a sense, one could say that coupled with the localization of the structural lesion, these interictal findings could suffice to determine the extent of tissue that should be resected to achieve seizure freedom. Of course, such statement would kindle the debate on the role of determining the ictal onset zone in patients with these *specific types* of lesion. If one accepts the concept of 'potential' EZ,[2,28] it may well be that more restricted resections based upon lesion location and the ictal onset zone may prove less successful in the long run than resections based on lesion location and the striking irritative findings uncovered by invasive recordings in focal cortical dysplasias and gangliogliomas.

How completely should the irritative zone defined through invasive recordings be resected: outcome relations

Evidence accumulated over the years suggests it to be wise to address the issue of the outcome relations of completeness of resection of the irritative zone according to topography and etiology of the epilepsy. In doing so, we will first discuss this issue in patients with the various etiologies of temporal lobe epilepsy, and then proceed with a similar approach to those with extratemporal epilepsies.

Outcome relations of completeness of resection of the irritative zone in temporal lobe epilepsies

It is now accepted that one should view temporal lobe epilepsies within a topographical/etiological framework. Broadly speaking, this approach leads to the identification of three topographical/etiological scenarios: TLE associated with hippocampal sclerosis, TLE associated with other focal lesions, and MRI-negative TLE. Even though it would be justifiable to further subdivide the TLE due to non-HS lesions according to the specific etiology and to mesial versus lateral topography, the three-tiered approach mentioned above probably fits best with the discussion on the relations between rsection of the irritative zone and surgical outcome.

When epilepsy is associated with a non-HS lesion or when no lesion is seen on the MRI in patients with otherwise clearcut TLE, there is evidence that resecting the lesion and the cortical regions displaying spikes is the best strategy.[39–41] On the other hand, there seems to be a convergence of data and authoritative opinion [42,43] that in patients with temporal lobe epilepsy due to mesial temporal sclerosis there is no benefit in resecting neocortical spikes beyond the planned margins of resection. This, of course, is corroborated by the equally high rates of seizure freedom in patients undergoing anterior temporal lobectomy (which resects neocortical tissue) and selective amygdalohippocampectomy (which does not).[44]

Outcome relations of completeness of resection of the irritative zone in extratemporal epilepsies

The decision-making process regarding the extent of resection in patients with extratemporal epilepsies is significantly more complex than that in TLE. Here, the two most relevant domains are *presence or absence* of a visible lesion, and also the *type of lesion*. Some studies have provided overall results across both domains, and other have focused in specific scenarios of lesional versus non-lesional epilepsies and on specific etiologies.

In general, studies with subdural grids and depth electrodes have suggested that complete resections of the irritative zone tended to correlate with a better surgical outcome. For instance, Bautista and colleagues from Yale [45] have shown that the persistence of interictal spikes recorded through invasive recordings was almost always predictive of surgical failure, even in patients in whom complete excision of the ictal onset zone was performed. Similar correlations between complete versus partial removal of the irritative zone and surgical outcome have been produced from Cleveland.[26] Of course, some considerations apply to these findings. For instance, in the Yale study, most of the patients in whom the irritative zone was multifocal and therefore not fully resected had non-lesional extrahippocampal epilepsies, usually due to microscopic dysplastic lesions. Other studies combining different types of pathologies showed somewhat different results. For instance, the series from Miami in children[27] and that from King's College Hospital[9] have both shown a lack of correlation between complete resection of the irritative zone and outcome. Interestingly, these two series have also to be analyzed in some detail, because in both the authors explicitly 'split' the irritative zone in two patterns, differentiating between very

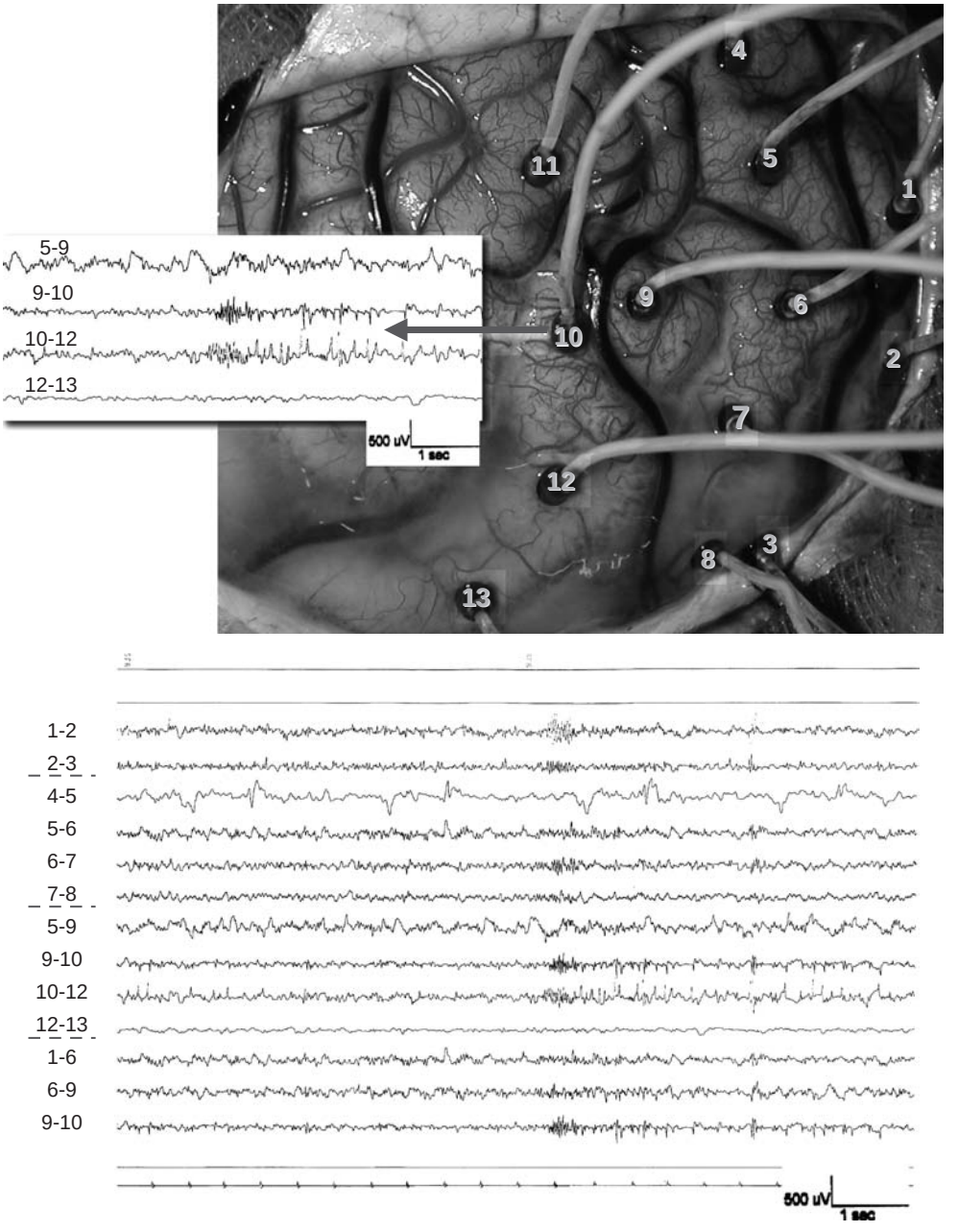

Figure 57.3 Top: Exposed craniotomy of the left frontocentroparietal regions. A 25-year-old man with refractory partial seizures beginning with a 'strange sensation' in the right forearm, then right hand, and rapidly followed by dystonic movement of the right arm and hand. Pathology showed focal cortical dysplasia. The frontal lobe is toward the right side of the picture. Thirteeen carbon-ball electrodes are shown overlying the exposed cortex. (The depicted electrode distribution followed several others fully exploring the exposed cortex; particulalrly, there were no epileptiform discharges in the 'non covered' posterior portion of the exposed cortex, in parietal the gyri beyond electrode 10). The arrow points to the ECoG recording and shows a paroxysmal burst of fast activity followed by repetitive spikes in the parietal lobe. Bottom: Acute ECoG showing a paroxysmal burst of fast spikes involving electrodes 2, 6, 9, and 10. Note that at electrode position 10 repetitive spikes follow the bursting discharge.

active, continuous or bursting spiking patterns – resection of which *did* correlate with outcome – and sporadic, infrequent, 'distant' spikes, resection of which *did not* correlate with surgical outcome.

From Montreal[46,47] additional data helps to shed light on the issue of the relevance of resecting the irritative zone. A review of the historical series of frontal lobe epilepsy surgeries in that institution showed that in patients with lesions, when acute ECoG spikes involved two or more gyri beyond the lesion, or when spikes persisted after the final resection, surgical outcome tended to be unfavorable. As expected, there was also a strong correlation between completeness of resection of the lesion and seizure control, which made it difficult to single out the specific role of the resection or persistence of ECoG spikes. The main positive message was the highly favorable outcome predicted by the combination of complete lesionectomy and complete resection of ECoG spikes, particularly when the latter were restricted to one or two gyri adjacent to the lesion. In patients with nonlesional frontal lobe epilepsy, both the extent of the irritative ECoG zone and post-resection data correlated with outcome: widespread spike distribution (involving more than two gyri) and persistence of spikes at some distance from the margins of excision correlated with unfavorable outcome. However, even in the context

of nonlesional frontal lobe epilepsies, complete resection of spiking cortex, particularly if spatially restricted, was occasionally associated with a good surgical outcome.

Finally, bringing pathology type to the forefront of this debate, the issue of the irritative zone in focal cortical dysplasias, particularly in type II (or Taylor-type) FCD[48] must be addressed. Several authors have independently confirmed the tendency of FCD to display two distinct types of interictal epileptiform discharges on acute ECoG.[8-10,49] The first type has a specificity of 75% for this pathological entity[9] and consists of a remarkable epileptiform pattern on acute ECoG manifesting as either continuous spiking, repetitive bursting of polyspikes, or recurrent electrographic seizures When cortical tissue displaying such continuous or bursting spikes are not included in the resection, seizures virtually always recur after operation.[8,9] Virtually identical findings have been recently reported from the Cleveland Clinic in a large series of patients with focal cortical dysplasia studied with subdural grids. Actually, the authors showed that the degree of resection of cortical regions displaying continuous or bursting spiking interictal patterns correlated with surgical outcome to the same extent as the resection of the ictal onset zone.[16]

The other type are the more usual *discontinuous* interictal spiking more or less adjacent to the dysplastic lesion. A recent reanalysis of our data in Porto Alegre shows that complete resection of these discontinuous spikes is also probably relevant to complete seizure control.[11] Caution, however, must be exercised in this conclusion, because more often than not patients had incomplete resections not only of the cortical tissue displaying these spikes, but also of the dysplastic lesion itself. The relevance of this discontinuous, sporadic, spikes recorded on acute ECoG in patients with FCD is still a matter of debate, because results have been conflicting. For instance, while our analysis from Porto Alegre and that from Montreal[11,47] suggests that cortical regions displaying these spikes should be included in the final resection, the series from King's College suggests that persistence of these spikes in post-resection ECoG do not correlate with surgical outcome.[9]

Taken as a whole, these findings on the outcome relations of completeness of resection of the irritative zone in extratemporal epilepsies inevitably transport us back in time to Rasmussen's concept of 'red' versus 'green' spikes. We believe the review presented in this chapter demonstrates that in the last 40 years or so we have been able to characterize some of the 'red' spikes. More work should be done to refine the separation between 'green' and 'red' isolated, sporadic spikes in different pathologies and also in MRI-negative scenarios. As a final word, we believe the results from different Centers[6,26,45] are indicative that it may be wise to step back and reappraise the relevance of the irritative zone in determining the 'relevant' epileptogenic brain tissue, and avoid giving so much more importance to the ictal onset zone. Even high class technology has not put to rest the importance of incorporating interictal epileptiform findings in the final planning of surgical resection.

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I would like to thank my colleague and friend Eliseu Paglioli for providing the surgical pictures included in this chapter.

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58 The significance of interictal fast ripples in the evaluation of the epileptogenic zone

A Bragin, RJ Staba, and J Engel, Jr

Introduction

Effective surgical treatment for focal epilepsy requires accurate delineation of the epileptogenic zone. The epileptogenic zone is defined as the area necessary and sufficient for spontaneous seizure generation, the removal or disconnection of which is necessary to achieve a seizure free outcome.[1] At the present time, the epileptogenic zone is a theoretical concept. Its location and extent are approximated by a presurgical evaluation designed to identify the irritative zone, which generates spontaneous EEG spikes; the ictal onset zone; the structural epileptogenic lesion; the symptomatic zone, which is responsible for initial ictal manifestations; and the functional deficit zone. There is, as yet, no diagnostic test that reliably and directly identifies the epileptogenic zone.

Interictal spikes are the electrographic hallmark of epilepsy, and are commonly used to diagnose epileptic conditions and to localize the area of epileptogenicity in patients who are candidates for surgical resection. The irritative zone, however, is often broader than the epileptogenic zone. Often, interictal spikes are recorded bilaterally even though seizures originate unilaterally. Intraoperative spike mapping is no longer used as the principal guide for determining the extent of tailored neocortical resections because it is well documented that interictal spikes are often falsely localizing. An approach that could discriminate between interictal spikes generated specifically within the epileptogenic zone and those that represent either propagation or transients initiated in irritable brain areas that are incapable of generating spontaneous seizures would make it possible to directly measure the epileptogenic zone, and would greatly facilitate presurgical evaluation. A unique electrographic epileptic abnormality, Fast Ripples (FR), offer an opportunity to develop a means to directly identify the epileptogenic zone.

FR are high frequency oscillations (150–500 Hz, in human (Figure 58.1) and 200–600 Hz in rats, (Figure 58.1) that occur in conjunction with interictal spikes, or occur independently of interictal spikes, but are strongly associated with brain tissue capable of generating spontaneous seizures.[2–4] To date, it is only possible to detect FR with wideband microelectrode recordings directly from hippocampus and other mesial temporal parahippocampal limbic structures. Although considerable work has now been done to characterize FR in mesial temporal lobe epilepsy, it is not known whether similar high frequency oscillations characterize the epileptogenic zone in neocortex. Also, in order for FR to become a useful diagnostic tool for determining the location and extent of the epileptogenic zone, it will be necessary to develop alternative methods to measure them noninvasively, preferably with neuroimaging that permits three-dimensional visualization of the entire brain. Even if noninvasive methodology for detecting FR is not developed, approaches that permit the direct brain recording of these phenomena with standard depth or grid electrodes would still greatly facilitate presurgical evaluation, because FR occur interictally and could be recorded intraoperatively, obviating the need for ictal recording.

Fast ripples as surrogate marker for delineating the epileptogenic zone

Fast ripples are epileptogenic events

In animals, high frequency oscillations in the range of 100–200 Hz, termed 'ripples,' occur in the normal hippocampus[5] and these normal electrical events can also be recorded from human hippocampus.[2,4,6,7] Ripples are believed to promote synchronization and information transfer across long distances.[8,9] Wideband microelectrode recording from epileptic hippocampus in patients with mesial temporal lobe epilepsy, and in the intrahippocampal kainic acid (KA) rat model of this disorder, revealed that normal ripples persist, but that much higher frequency oscillations FR can also be recorded in the epileptic hippocampus that are not typically present in the normal rat hippocampus, or contralateral to the hippocampus where seizures begin in the human.[3,4] These FR oscillations are similar to ripples in some ways. For example, both ripple and FR generation are state dependent. The rate of ripple and FR occurrence is higher during slow wave sleep compared to wakefulness.[6] However, during REM sleep, the rate of ripple occurrence decreases to a level even lower than that during the awake state, while the rate of FR occurrence during REM sleep remains higher than during wakefulness.[6]

Other distinctions can be made between ripples and FR. FR are common in the dentate gyrus where ripples never occur, and FR are generated by more localized neuronal networks than ripple oscillations (Figure 58.2).[7,10] The FR phase reversal in entorhinal cortex coincides with that of population

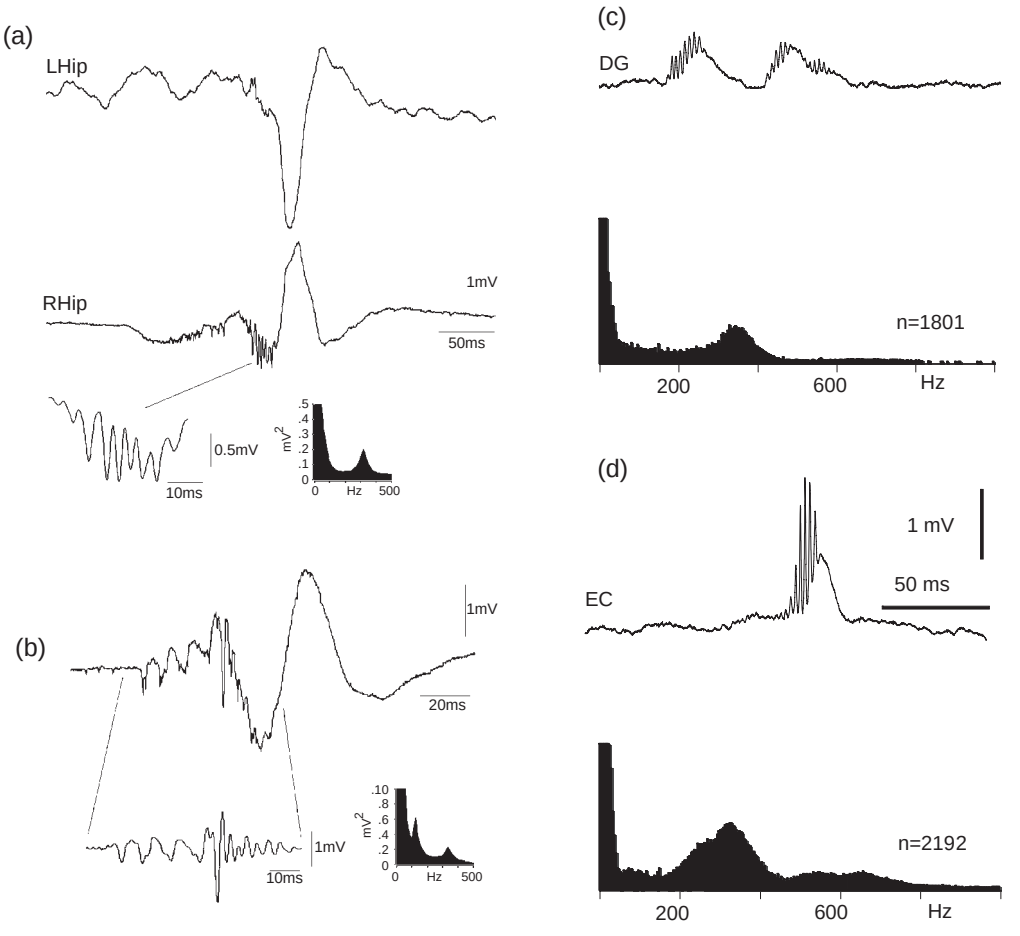

Figure 58.1 Wideband hippocampal electroencephalogram (EEG) recorded during a polysomnographically defined episode of nonrapid eye movement sleep. (a) EEG from left (LHip) and right hippocampus (RHip) recorded from a patient who had seizure starting in the RHip. Note the large amplitude EEG sharp wave detected in both LHip and RHip sites, whereas the small amplitude fast ripple (FR) oscillation was detected in only the RHip recording site. Power spectral analysis indicates a peak in power at approximately 320 Hz. Enlarged trace lowpass filtered 600 Hz. (From ref. 6 with permission). (b) Wideband EEG recorded from subicular complex shows FR immediately after a ripple oscillation. Enlarged trace below was bandpass filtered 80–500 Hz. The two peaks in the power spectra reflect the ripple (130 Hz) and FR (330 Hz). (c. Top) FR in the dentate gyrus of epileptic KA treated rat. (Bottom) Averaged power spectrogram of 1801 FR events. (d. Top) FR recorded in the entorhinal cortex of epileptic KA treated rat. (Bottom) Averaged power spectrogram of 2192 events (modified from ref. 10 with permission).

spikes evoked by electrical stimulation of hippocampus suggesting a common afferent input (Figure 58.2C).[7] Ripples appear to reflect summated synchronous inhibitory postsynaptic potentials,[11] whereas FR appear to represent summated action potentials from synchronously bursting neurons (i.e. bursts of population spikes),[3,10] The unique mechanisms generating ripples and FR are based on studies that show presumed granule cells discharge bursts of action potentials during FR oscillations recorded in the dentate gyrus,[3] and population spikes in this area reflect hypersynchronous discharges of granule cells.[12] In addition, voltage depth profiles of FR recorded in the dentate gyrus are similar to voltage depth profiles of population spikes evoked by electrical stimulation of the perforant path.[10]

Bursting neurons are known to be a characteristic of the epileptogenic region, and represent a large proportion of neurons in acute experimental foci, such as those induced by cortical penicillin.[13] The percentage of neurons that burst synchronously in chronic models of epilepsy, and in human epilepsy, however, are very small.[14] Whereas it can be extremely difficult to find synchronously bursting single units within epileptogenic regions of patients with epilepsy using microelectrode recordings,[15–17] a small number of synchronously bursting neurons can generate a field potential that is recordable over a much larger area. Recording FR, therefore, is an alternative and more sensitive approach to detect tissue that contains synchronously bursting neurons.

Fast ripples are unique to the epileptogenic zone

In experimental animal models of mesial temporal lobe epilepsy, FR can only be detected in the damaged hippocampal and parahippocampal structures involved in seizure generation.[2] They do not occur after kindling, for instance, because these animals do not generate spontaneous seizures. In patients with mesial temporal lobe epilepsy, FR are typically encountered in mesial temporal structures on the side where seizures originate, but occur much less frequently within contralateral homotopic structures (Figure 58.3).[4] Furthermore, rates of FR activity are higher in atrophic hippocampus compared to hippocampus that appears normal on MRI,[6] but FR are also present within parahippocampal structures and may occur most frequently in subiculum (Figure 58.4).[6]

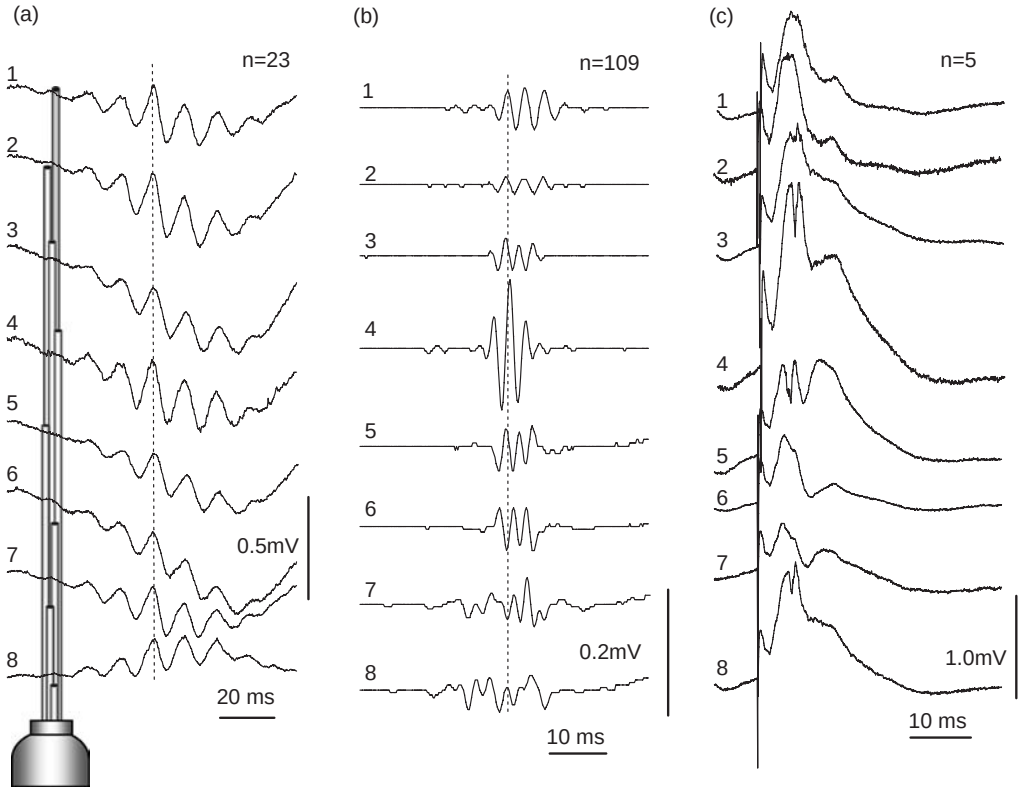

Figure 58.2 Comparison of voltage versus depth profiles of (a) ripples, (b) FR and (c) field potentials evoked in entorhinal cortex in response to hippocampal stimulation. Numbers on the left indicate microelectrode number in the bundle (shown in panel A), where microwire 1 is longest and was recording in the superficial layer of EC, while microwire 8 is shortest and was recording in the deepest layer of EC. The distance between microelectrode tips is 500 µm. Numbers on the top indicate number of events in each average. Notice that ripple oscillations do not show phase reversal at any of eight microelectrodes, while FR oscillations show phase reversal between microelectrodes 3–4 and 5–6. Maximum of evoked potential amplitude (c) is at microelectrodes 3 and 4 (from ref. 7 with permission).

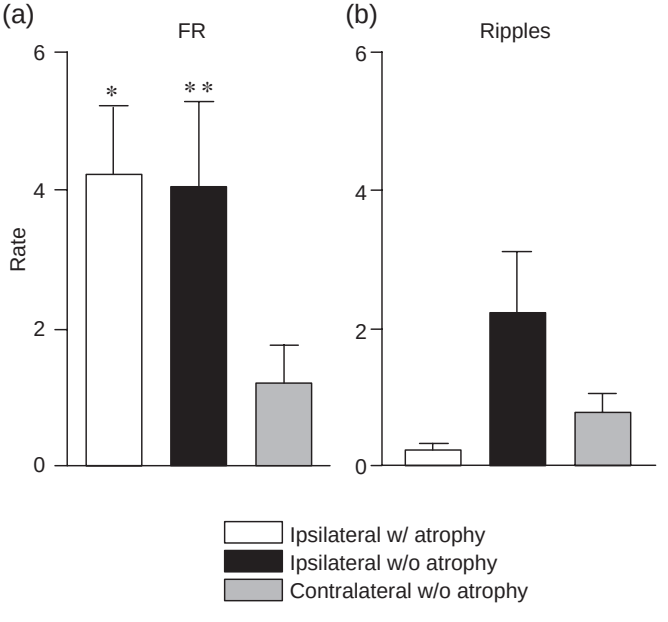

Figure 58.3 Rates of fast ripple (FR) and ripple occurrence in relation to epileptogenic zone. a. Mean (± SE) FR rates per 10-minute period in areas ipsilateral to seizure onset with atrophy and without atrophy were significantly higher that the FR rate in contralateral areas, none of which showed evidence of atrophy (*p=0.01, **p=0.02). b. Mean Ripple rates in relation to epileptogenic zone were not significantly different (from ref. 6 with permission).

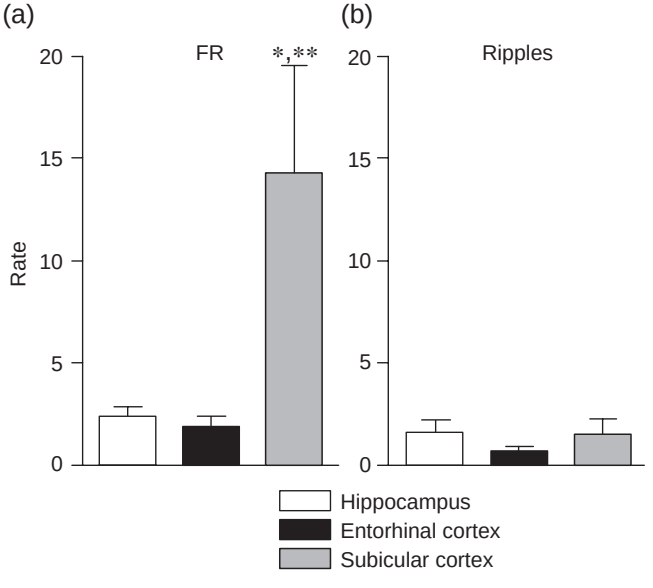

Figure 58.4 Rates of FR and ripples in relation to medial temporal location. c. Rate of FRs (per 10-minute period) in subicular cortex (n=4) was six times higher compared with rate of FR discharge in both hippocampus (n=27; *p=0.002) and entorhinal cortex (n=19; **p=0.001). d. Ripple rates were not significantly different between medial temporal structures. (from ref. 6 with permission).

Interestingly, subiculum has been implicated as a particularly epileptogenic region in patients with mesial temporal lobe epilepsy because of persistence of an immature excitatory response to the inhibitory neurotransmitter GABA.[18]

FR are associated with seizure generation

The intrahippocampal kainate rat model of mesial temporal lobe epilepsy displays both hypersynchronous and low-voltage fast ictal onsets, very similar to the types of ictal onsets seen in human mesial temporal lobe epilepsy.[19,20] The individual hypersynchronous EEG discharges that make up the hypersynchronous ictal events contain FR initially, and eventually are characterized by a complex consisting of FR followed by gamma frequency oscillations, referred to as an 'FR tail gamma complex'.[20] Interically, FR can be synchronized across distant structures, often beginning in dentate and rapidly occurring in entorhinal cortex, although they can begin in entorhinal cortex and rapidly appear in dentate[20] (Figure 58.5). The significance of the development of gamma oscillations at ictal onset is unclear, but these are believed to reflect inhibitory mechanisms[22,23] that may be a product of the so-called 'dentate gate',[24] which acts to prevent ictal discharges from propagating to the hippocampus proper and to structures outside the temporal lobe that are responsible for the manifestation of behavioral seizures. These hypersynchronous discharges in patients are either associated with auras, or no signs or symptoms.[19,25,26]

In the KA rat, hypersynchronous seizures occur preferentially during sleep and are unassociated with behavioral changes.[20] Hypersynchronous discharges, however, can rapidly evolve to low-voltage fast discharges which are then associated with contralateral propagation and complex partial seizures the human, and behavioral seizures similar to stage 5 amygdala-kindled seizures in the KA rat.[20] In the rat, low-voltage fast onset seizures also occur in the hippocampus during wakefulness, although they are much less frequent than the hypersynchronous ictal events. Occasionally, a single hypersynchronous discharge with FR precedes the low-voltage fast ictal discharge, but in most cases this is not observed.[2] Because these events in patients are usually regional, whereas hypersynchronous ictal onsets are much more focal, it is likely that the electrodes are not at the site of the seizure origin for low voltage fast onset, which is why the initial FR oscillation is not visible. These observations, however, strongly suggest that FR reflects the neuronal mechanisms responsible for seizure generation and are not merely a nonspecific effect of neuronal damage.

FR reflects mechanisms of epileptogenesis

In the KA rat, abnormal high frequency oscillations can be recorded in dentate gyrus days to weeks before spontaneous seizures appear.[27] Not all rats treated in this manner develop spontaneous seizures, and the appearance of FR predicts which rats will become epileptic (Figure 58.6). The earlier high-frequency oscillations are recorded, the earlier spontaneous seizures develop. FR also appear before mossy fiber sprouting can be detected, and there is no correlation between the location of FR-generating clusters and mossy fiber sprouting, suggesting that these two characteristic features of the epileptogenic hippocampus are unrelated.[20]

Fast ripples represent activity in small neuronal clusters

FR are not recorded homogeneously throughout epileptogenic structures, but are localized to small discrete areas approximately 1 mm^3 in volume (Figure 58.7).[10] The size and

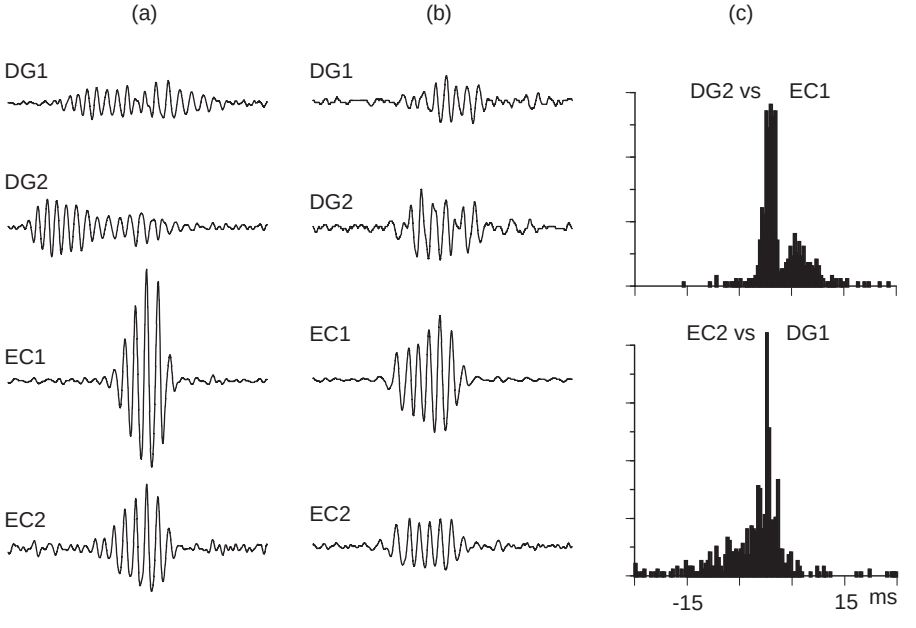

Figure 58.5 FR oscillations recorded in two areas of dentate gyrus (DG, DG2) and in two areas of entorhinal cortex (EC1, C2). a. Shows an example of FR oscillation occuring first in the recording site DG2 and than with different delay in other recording sites. b. Shows an example of FR oscillation occuring first in the entorhinal cortex. c. Crosscorellograms of FR occurrence between different recording sites. (from ref 22. with permission).

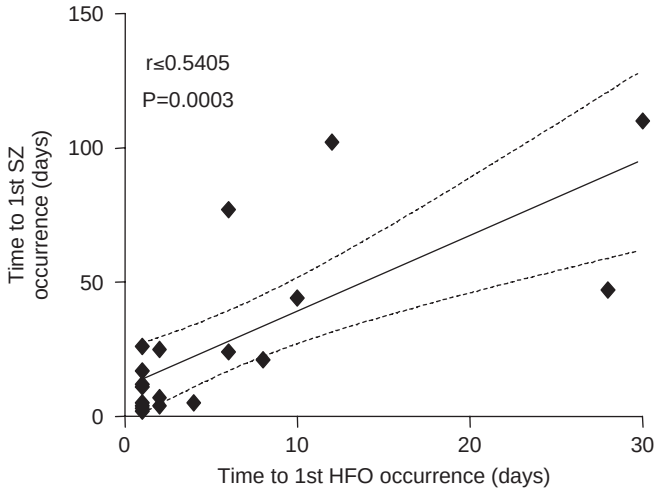

Figure 58.6 Correlation between first time of occurrence of high frequency oscillations (HFOs) and first day of seizure occurrence (from ref. 28 with permission).

location of these clusters remain stable over weeks to months (Figure 58.8), suggesting that they consist of tightly interconnected neurons that burst synchronously.[28] The volume of tissue capable of generating spontaneous or stimulation-induced FR can be increased, however, by application of small amounts of the GABA antagonist bicuculline.[28] This suggests a possible mechanism for seizure generation. Transient reductions in inhibition could cause these widely dispersed FR-generating neuronal clusters to increase in size, perhaps coalesce, and become synchronized until activity is sufficient to propagate and produce an ictal discharge.[29] This concept of ictal generation is supported by the observation that there is a positive correlation between the number of microelectrode contacts that record FR and seizure frequency (Figure 58.9), indicating that a greater density of FR-generating clusters makes it more likely that adjacent clusters will coalesce and synchronize so that the seizures might occur more frequently.

Conclusions

FR are abnormal high-frequency oscillations that appear to reflect fundamental neuronal disturbances responsible for epileptogenesis and epileptogenicity. FR can occur in conjunction with interictal EEG spikes, or can occur independently, but are strongly associated with brain tissue capable of generating spontaneous seizures. As such, FR are potential surrogate markers of epileptogenicity that could provide opportunities for directly identifying the location and extent of the epileptogenic zone. At present, however, there are two important issues that need to be resolved. First, FR have only been characterized in epileptogenic hippocampus and parahippocampal structures in patients with mesial temporal lobe epilepsy, and animal models of this condition. More research is necessary to determine whether FR can also provide similar opportunities to identify neocortical epileptogenic zones. Second, FR can only be recorded from microelectrodes within epileptogenic brain tissue using a

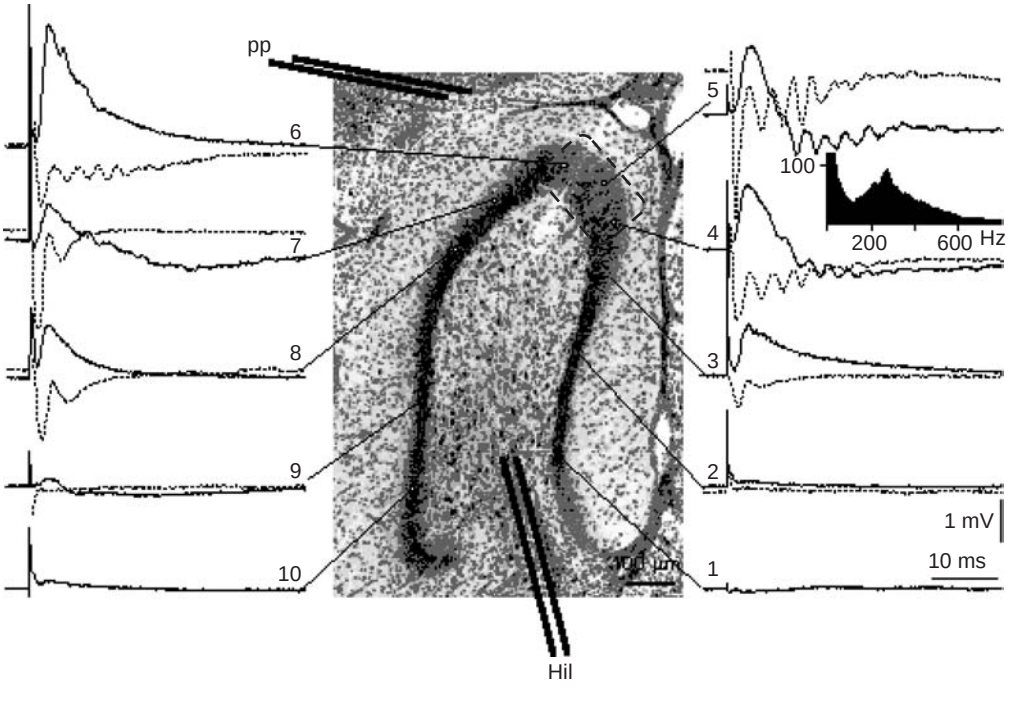

Figure 58.7 Map of evoked field potentials in the dentate gyrus slices obtained from an epileptic rat in response to perforant path (solid lines) and hilus (dashed lines) stimulation. Each recording is the average of five responses. Notice that FR-like responses are recorded at points 4, 5, and 6 in response to both perforant path and hilar stimulation outlined by dashed box. The inset is the power spectra of the evoked responses to hilus stimulation (from ref. 10 with permission).

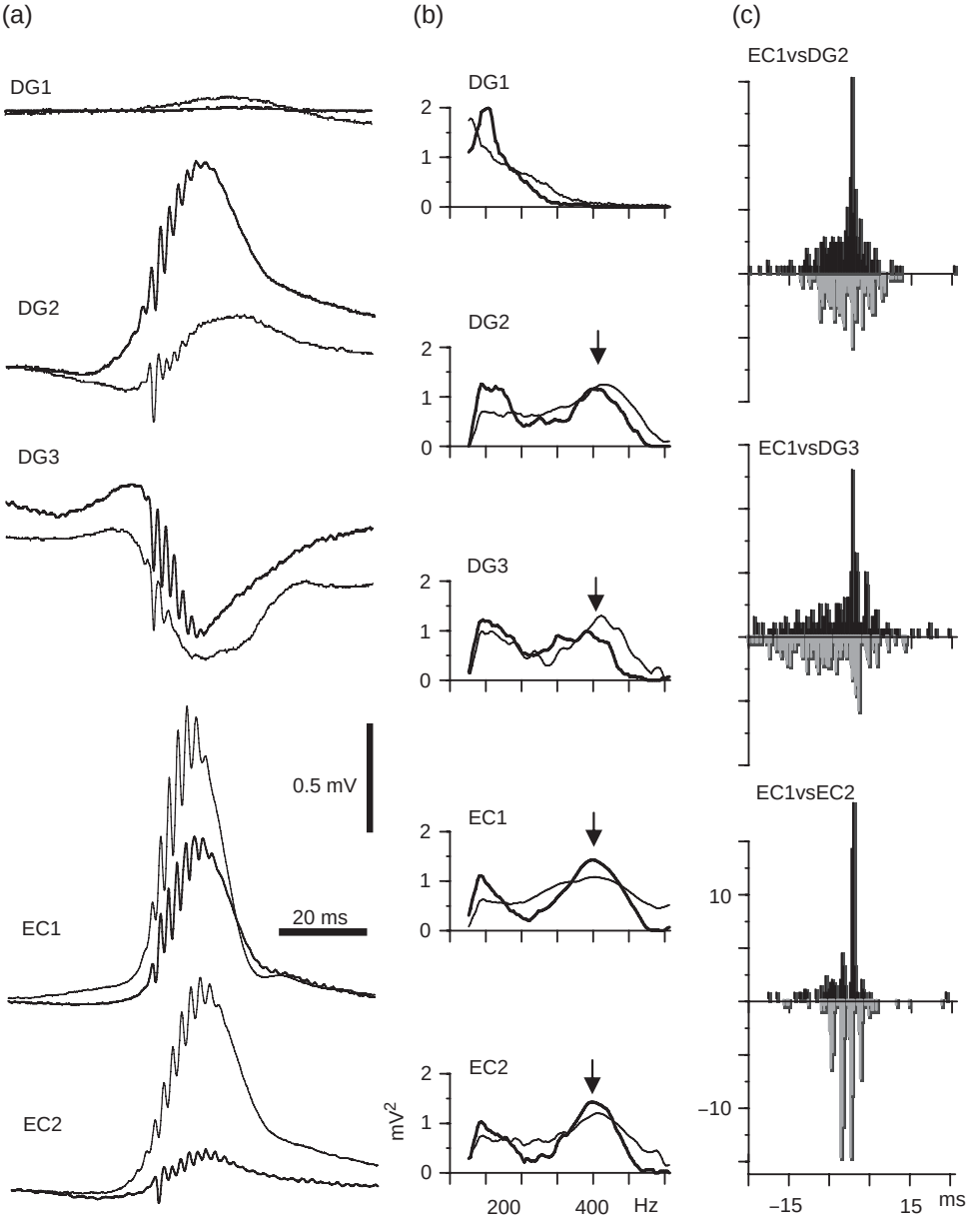

Figure 58.8 Characteristics of fast ripples recorded with five fixed microelectrodes within three different brain areas of the hippocampal-entorhinal circuitry ipsilateral to the kainic acid lesion in a single rat. DG1–anterior dentate gyrus; DG2–posterior dentate gyrus (3.5 mm from DG1); DG3–posterior dentate gyrus 1.5 mm away from DG2; EC1 and EC2–entorhinal cortex with 1.5 mm separation between the recording sites. 1.A. and 1.B., show FR recorded 47 days (heavy lines) and FR recorded 61 days (light lines) after kainic acid injection. A–averages of FR (second peak–see text) (n=300) in each recording site; B–power spectral analysis of averaged FR (n=300); C–crosscorrelograms between FR recorded at the EC1 site and FR recorded at EC2, DG2 and DG3. The upward black crosscorrelograms represent FR recorded at 47 days, and the downward, gray crosscorrelograms represent FR recorded at 61 days (from ref. 29 with permission).

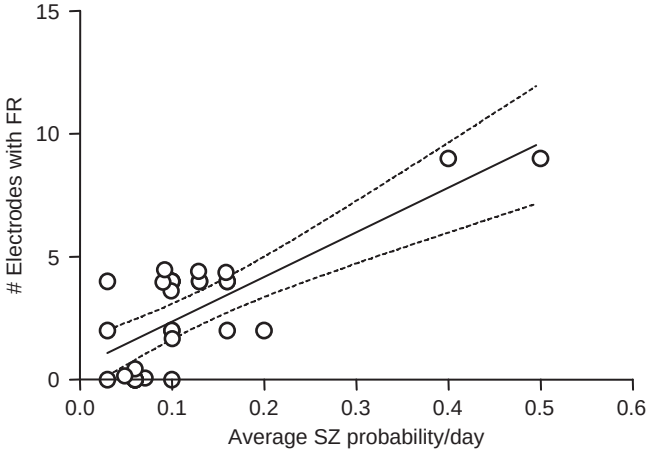

Figure 58.9 Correlation between the number of microelectrodes recording fast ripples and the average probability of seizure occurrence per day. Each circle represents one of the 22 epileptic rats. The number of electrodes implanted was always six pairs per animal. The coefficient of correlation (r) was 0.64, with P value < 0.0001. (from ref. 29 with permission).

combination of wide bandwidth and high sampling frequency. Techniques for recording FR with routine grid or depth electrodes would permit their use for directly determining the extent of the epileptogenic zone intraoperatively, or during chronic invasive monitoring. Noninvasive approaches to identifying the volume of tissue generating FR, in three dimensions of a whole brain, might ultimately be possible using MEG-MRI fusion, or EEG-fMRI averaging.

Acknowledgment

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59 Magnetoencephalography in the evaluation of the irritative zone

M Iwasaki and RC Burgess

Summary

This chapter reviews the use of magnetoencephalography (MEG) for detection and localization of epileptic spikes. Qualitatively, MEG records the same activity as the scalp EEG does, namely 'brain waves'. In spite of its high cost and limited availability, MEG has an advantages in source localization, because the magnetic field is not distorted by inhomogeneous tissue conductivity, thereby improving the accuracy of the computerized source modeling technique. Clinical usefulness of MEG has been shown in selected cases of intractable focal epilepsy undergoing surgical treatment. The MEG-defined irritative zone usually provides good agreement with that defined by invasive EEG. One recent study has shown that, in a subset of patients, MEG can provide critical information which supplements the standard evaluation for surgical decision making.

Introduction

Ever since magnetoencephalography (MEG) in humans became available, there has been a major interest in employing MEG for detection and localization of epileptiform activity.[1] Recently, whole-head MEG systems have increasingly appeared in clinical settings. However, many clinicians are still not familiar with this diagnostic method.[2] In this chapter, we first introduce the basic principles and issues related to the analysis and interpretation of MEG data; secondly compare MEG with scalp EEG, the counterpart technique most often used in defining the irritative zone; and lastly review the previous literature to discuss the advantageous use of MEG in presurgical evaluation of epilepsy. Although MEG is also used for preoperative functional brain mapping, we focus only on measurement and localization of interictal spikes by means of MEG. Several good review articles in this area are also available for further reference.[3–7]

Technical background

Instrumentation

MEG recording of weak magnetic fields generated by the brain, became practically available after the invention of the SQUID (superconducting quantum interference device) technique.[8] Since the SQUID operates at a very low temperature, the MEG system requires a bath (dewer) of liquid helium to cool the sensors. Today, multi-channel whole-head MEG systems are commercially available and have become the standard clinical systems. Typically, the system has 100 to 300 SQUID magnetic sensors arrayed on the inner surface of the dewer. The dewer has a head-shaped concavity to accommodate the subject's head in order to scan the entire circumference of the head (Figure 59.1). The MEG system is placed in a magnetically shielded room, because magnetic noise from the external environment, such as a ticking watch and cars moving outside the building, crucially interfere with the measurement of weak brain magnetic fields.[9,10] Ferromagnetic materials attached to the subject's body, such as a watch, buckle, medically implanted devices, or metallic contaminants from a previous craniotomy, should be removed before the measurement, if possible, or they may significantly reduce the quality of recording.

Genesis of the MEG signal

The neurophysiologic process that generates the MEG signal is exactly the same as that which produces the EEG.[11,12] Because of the structural polarity of pyramidal neurons, the fluctuation of the dendritic membrane potential is observed as a current dipole perpendicular to the cortical surface.[13] These tiny dipoles generated by many pyramidal neurons summate within a certain volume of cortex that is more or less synchronously activating, to generate a 'brain waves' seen by MEG and EEG. This summated activity may also be represented by a dipole or sheets of dipoles along the cortex.

A current dipole produces a magnetic field oriented clockwise to the orientation of the current ('right-hand rule', Figure 59.2).[14,15] MEG measures magnetic fields coming out of or going into the surface of the head sphere. Such measurable MEG activities are typically generated by tangentially-oriented dipoles. The strength of the magnetic field decreases in proportion to the square of the distance, according to Bio-Savart's law[9]. The skull and other extracerebral tissues are practically transparent to the magnetic fields. Therefore, the field patterns outside the head are distorted hardly at all by the inhomogeneous tissue conductivity of the cranium.

Acquisition and analysis of MEG

Magnetic fields picked up by the sensor coil are enhanced by the SQUID and sampled at several hundreds to thousands

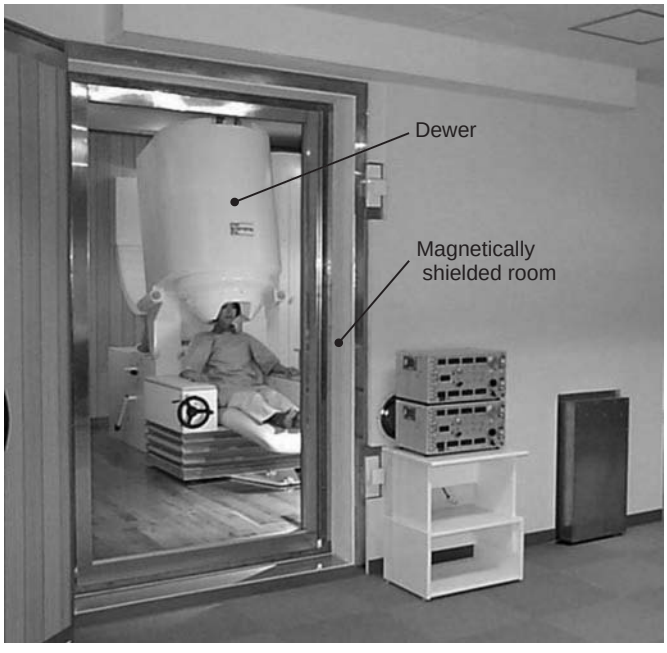

Figure 59.1 Typical arrangement for MEG measurement. The MEG system is placed in a magnetically shielded room. Instrumentation for conducting evoked potential or cognitive tests is outside the room and presents the stimuli through specialized feed-throughs. The dewer has a helmet-shaped concavity, into which the patient's head is placed. SQUID magnetic sensors are arrayed over the inner surface of the concavity (not visible), immersed in liquid helium. Recording may be performed in either a supine or sitting position.

Hz as discrete time signals. The resulting signals make up multiple traces of 'brain waves' measured at the sensor locations, in a fashion similar to EEG.[16]

For the first step of the analysis of MEG signals from epilepsy patients, they must be 'read' in order to find 'epileptic spikes'. This step is usually done manually by human interpreters scanning MEG brain waves, sometimes with help of the information from simultaneously-recorded EEG.

The generator of the chosen spike is then estimated by using computer-assisted source analysis software. Source analysis software analyzes actual observation in order to infer what the most likely phenomenon occurring in the head was; this inference from observations remote from the source is called the 'inverse problem' (Figure 59.3). The inverse problem in MEG in defining the location, distribution and amplitude of epileptic spikes is severely 'ill-posed', i.e., only a few parameters are available while there are numerous possibilities for the solution. Thus, to obtain a single 'presumed' answer, we always need to introduce artificial constraints or assumptions into the problem. The most popular assumption is an equivalent current dipole (ECD) model.[10,7] This model assumes that epileptic spikes emanate from a single (or multiple) dipole located at a certain point in the brain (i.e., a point source). An exhaustive, trial-and-error 'fitting' procedure seeks the location, orientation, and amplitude of the dipole that best explains the actual observation of magnetic fields. Because the model is too simple to entirely explain the natural phenomenon, the answer usually accompanied by another parameter quantifying the amount of the residual that the model does not explain (e.g., 'goodness-of-fit value').[18] It is experientially known that the ECD model provides a good approximation for localizing epileptic spikes in many cases.[11,19] The ECD model can be erroneous when the sources are distributed, however, and any epileptic spike may be more or less distributed.[20,21] Besides the simplicity of the model, the ECD approach is modified or biased by the analyzer's guess about the number and location of initial dipoles selected to start the search algorithm. There are several methods other than the ECD model that have been developed in an attempt to better approximate distributed sources or to eliminate the interpreter's biases.[22–24] None of the methods are perfect, and a completely reliable, automated, and objective method is still awaited.

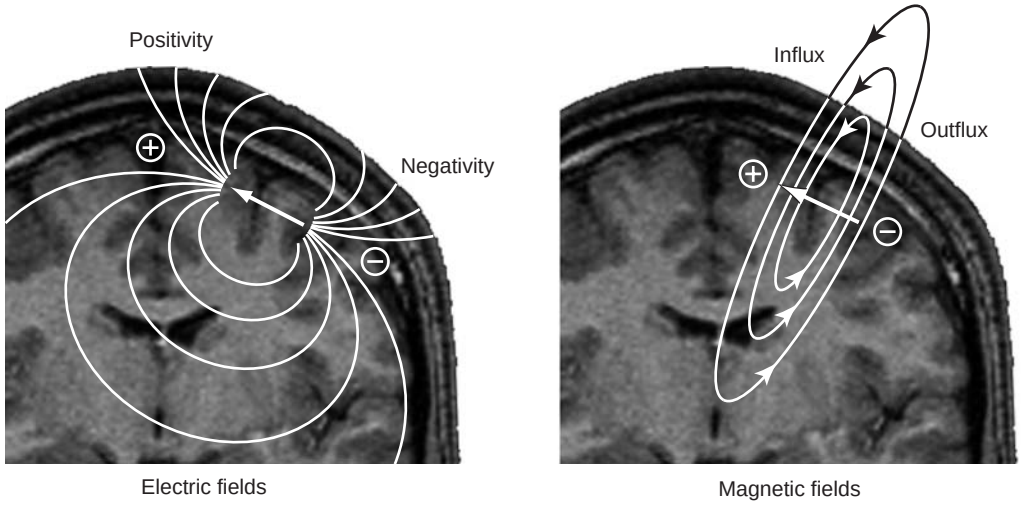

Figure 59.2 Electric fields and magnetic fields generated by a current dipole. A current dipole produces magnetic flux oriented clockwise to the current orientation. Dipoles tangential to the brain convexity are typically seen on the scalp surface as a pair of prominent field maxima representing the ingoing and outgoing magnetic flux. In contrast, dipoles perpendicular to the scalp contribute minimally to the surface field distribution. Electric fields are observed as a result of volume conduction of the electric charges from the positive and negative poles of the current dipole. (From Burgess RC, Iwasaki M, Nair D. Localization and field determination in electroencephalography and magnetoencephalography. In: Wyllie E, ed. The Treatment of Epilepsy,: Principles and Practice 4th edn. Philadelphia; Lippincott Williams and Wilkins: 2006:141–67 with permission).

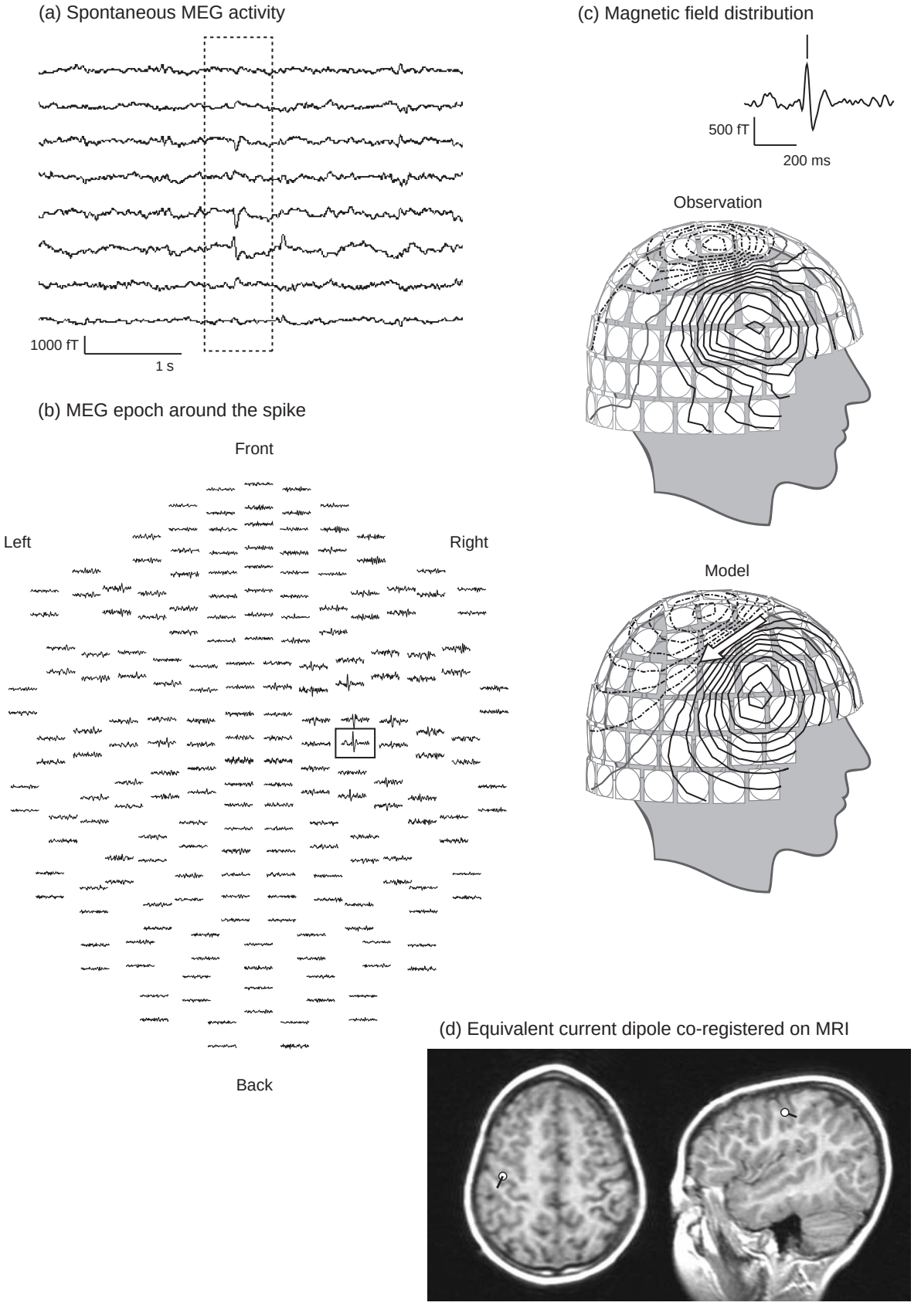

Figure 59.3 Inverse problem and spike source estimation by ECD model. Results of MEG evaluation and source localization are often shown co-registered with anatomic images. a. Typical MEG waveforms from sensors overlying the right central region; an epileptiform spike is outlined. b. MEG waveforms over the entire head during the bracketed epoch. c. The isocountours of the observed magnetic field distribution at the peak of the spike are shown along with the distribution generated by the computerized single equivalent current dipole model fit to the observed field. d. The location and orientation of the putative dipole source is shown on the MRI slices.

The result of source estimation is usually co-registered on the patient's brain MRI. When the ECD model is used, the image is typically shown as scattered dots and arrows representing the location and orientation of the dipoles for every spike analyzed (Figure 59.4). This picture is often referred to as 'magnetic source imaging (MSI)'. Actually 'imaging' is a misnomer, as this display is qualitatively quite different from the pixel- or voxel-based 'images' such as magnetic resonance imaging. The latter images utilize a large number of actually recorded data points, i.e., scanned pixels or voxels, to reconstruct a brain image. In contrast, the MSI utilizes only a limited number of parameters, i.e., MEG signals captured by a relatively small number of sensors, to 'estimate' the phenomenon occurring inside the head. The 'spatial resolution' of MEG is therefore lower than typical pixel- or voxel-based imaging modalities on a theoretical basis. However, in proper clinical use, the selection of appropriate models and assumptions does increase the reliability and spatial resolution of the estimation provided by MEG source localization software. Unfortunately, those factors are not generally accessible in MSI and are unknown to users. Clinicians who use MSI images must recognize that these operator dependent and manufacturer-specific factors play important roles and use caution.

Comparison with scalp EEG: similarities and differences

Since EEG and MEG are both measurements of the same underlying brain activity, MEG should be carefully compared with scalp-EEG to define its clinical role and establish its advantage.

MEG recording systems, together with a magnetically shielded room, dedicated computers, and running costs (e.g., liquid helium refills and annual maintenance contract) are highly expensive compared with conventional EEG systems. The machine is not portable, recording must be carried out within the shielded room, and recording duration is relatively short (10 minutes to a few hours). During the measurement, the patient must remain immobile.

For detection of underlying abnormalities, i.e. epileptic spikes, the MEG has power which is comparable to the scalp EEG.[26,27] The smallest activity detectable by the modality is determined by calculating the size of the brain volume that a sensor scans. The distribution and size of such 'sensitive volume' is very similar between MEG and scalp EEG, although the EEG can flexibly change the size by modifying the inter-electrode distance[28]. Simultaneous recordings of electrocorticography and MEG have shown that a considerable area of

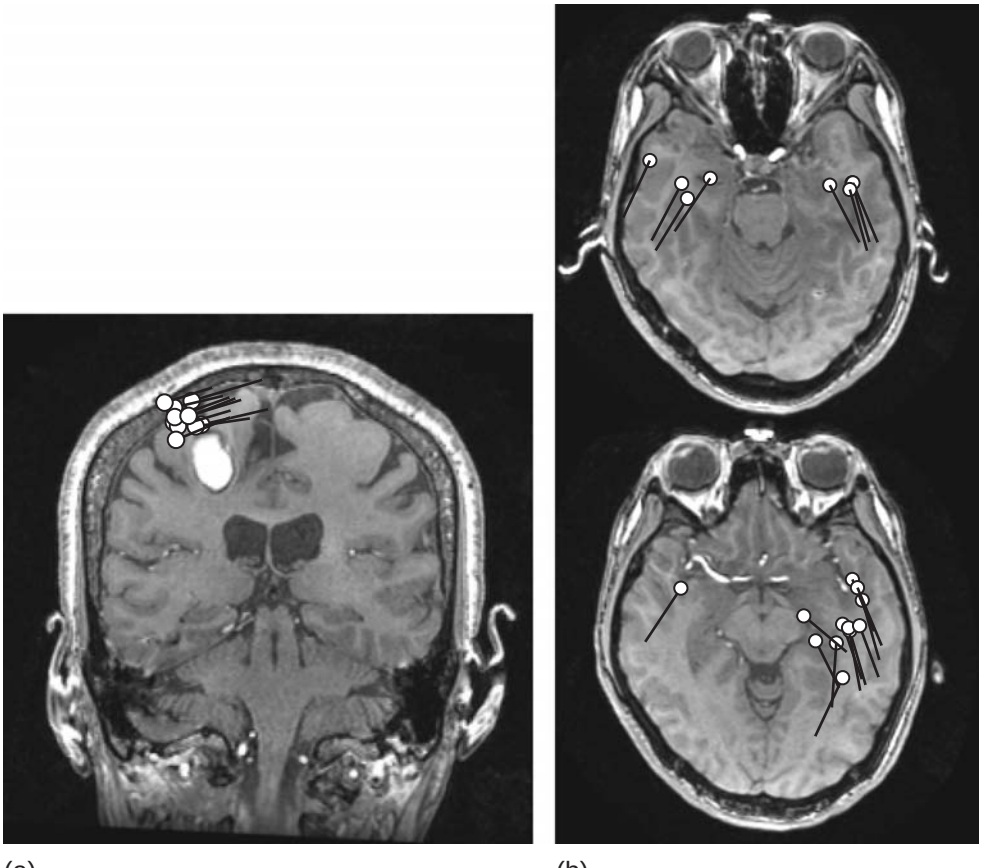

Figure 59.4 Typical examples of 'magnetic source imaging (MSI)', co-registration of equivalent current dipoles with anatomic images. White dots and black arrows indicate location and orientation of dipoles, respectively. a. A case with focal motor seizures caused by hemorrhagic cavernous angioma located in the right motor and premotor cortices. Dipoles are tightly clustered in the epileptogenic zone nearby the lesion. b. A case with nonlesional bilateral temporal lobe epilepsy. Dipoles are distributed in a relatively large area of bilateral temporal lobe. (Courtesy of Dr. Nobukazu Nakasato, Kohnan Hospital, Sendai, Japan).

the cortex must be activated in order for epileptic spikes to be captured by MEG.[29–31]

The detection ability of MEG and EEG is quite different in terms of the orientation of the current dipole.[32] MEG preferentially records tangential sources while EEG is better at recording perpendicular ones. However, since completely tangential or perpendicular sources are rare, the cortical area that MEG is sensitive to largely overlaps that of EEG.[33] Therefore, epileptic spikes are captured by both MEG and EEG in most cases, but the detectability (the number or signal-to-noise ratio of spikes) may differ significantly.[26,27] MEG and EEG are equally limited in their sensitivity to deep activity.

The greatest advantage of MEG derives from the feasibility of computerized source estimation techniques. Although the same computerized localization techniques are available for EEG, accuracy and reliability are higher for MEG. These models work much better in MEG, because magnetic fields are not distorted by the inhomogeneous tissue conductivity, and the volume conduction effect is often negligible.[10,34,35] The magnetic field distribution outside the head directly reflects the primary current of the source, making source modeling and calculation easier for MEG than for EEG.

Use of MEG to define the irritative zone

Temporal lobe epilepsy

Several MEG studies have focused on temporal lobe epilepsy (TLE), the most common form of intractable focal epilepsy.[36–40] It is known that MEG spike localization does not pinpoint the epileptogenic zone or seizure onset zone in mesial TLE. MEG detects interictal spikes generated in, or propagated to, the temporal neocortex.[41,42] Such irritative zone is occasionally separate from the mesial temporal region. Several recognizable patterns of MEG spike localization and orientation exist in TLE.[37,38]

The spikes localized in the anterior temporal neocortex, including those in the temporal tip with an orientation horizontal to the temporal lobe axis in a sagittal plane, and those in the superior or basal anterior temporal cortex with a vertical orientation, are relatively specific to mesial TLE. The other pattern is spikes localized vertically in the posterior temporal region, a pattern seen relatively frequently in patients with seizures originating from the lateral temporal lobe. However, this dipole pattern can also be seen in patients with mesial TLE.[39]

Studies of nonlesional TLE, in spite of limited number of case series available, have shown good correlation of MEG spike patterns and the seizure onset zone. Knowlton documented that three cases of nonlesional TLE, including two with mesial temporal onset and one with neocortical temporal onset, showed good agreement between MEG spike localization and the seizure onset zone, as confirmed by invasive EEG recording.[43] Baumgartner reported 11 cases of nonlesional TLE, including five with anterior temporal MEG spikes and six with posterior lateral MEG spikes. Invasive EEG recording was performed in three of those. In one, anterior spikes were associated with mesial temporal seizure onset; and in the other two with posterior spikes, seizure onset was more diffuse, including both mesial and lateral temporal lobes.[37]

Extratemporal lobe epilepsy

Most previous reports on the use of MEG in extratemporal cases document good agreement between MEG and invasive EEG for spike localization.[43–50] Some authors believe that MEG spike detection and the accuracy are better in extratemporal region than in the temporal regions – even superior to the scalp EEG.[51–53] Resection of the irritative zone as defined by MEG is correlated with better postoperative seizure outcome.[44,54] In selected patients with normal MRIs, MEG helps map the irritative zone, guide the correct placement of invasive electrodes for better surgical planning, or even obviate the need for invasive recording.[55,56] The distribution of MEG spikes has been employed to provide a hint about the extent of the epileptogenic zone, confirmed by invasive EEG: Spikes tightly-clustered in a small area suggest the seizure onset zone nearby. Loosely-distributed spikes tend to be associated with nonlocalizable seizure onset, suggesting a diffuse epileptogenic zone.[44]

Indications for MEG in presurgical evaluation of epilepsy

Although a good number of articles have been published on the use of MEG during the preoperative assessment of epilepsy surgery candidates, it is still not clear which subpopulation of patients can gain maximum benefit from MEG in terms of surgical decision making.

Stefan *et al.* conducted a retrospective review of the presurgical evaluations of 104 epilepsy patients in order to score the contribution of MEG relative to the other modalities.[57] The MEG findings were just 'confirmatory' in about a half of the cases (54%), 'additional' in 24%, 'additional information affecting the decision making in surgical strategy' in 10%, no contribution (no spikes detected) in 10%, and rarely 'contradictory' (2%). Although the study design is retrospective and the different nuances between 'additional' and 'additional in surgical decision making' were not clearly defined, this study implies that MEG can play a crucial role in estimating the epileptogenic zone and in surgical decision-making 'upon' the information collected from the other modalities such as MRI, video-EEG monitoring, and PET. On the other hand, this study shows that in more than half of patients who are undergoing presurgical evaluation, MEG does not add anything.[58]

Other studies have also attempted to relate the relative contribution of MEG, but unfortunately, no prospective study has yet been performed to address whether the addition of MEG to the standard evaluations improves the patient's outcome.[52,58] Although the selection criteria are as yet unknown, it is likely that patients should be carefully selected for MEG study, weighting its potential advantage against its high cost and limited availability.

The benefit of MEG recording is probably small in mesial TLE syndrome with hippocampal sclerosis, because clinical and imaging characteristics, along with the surgical strategy and outcome, are relatively well established. Therefore, the addition of MEG will most likely have marginal influence on the patient's outcome. The benefit of MEG is probably larger in neocortical epilepsy, especially in those with equivocal findings on MRI, EEG and other evaluations.[58,59] The addition of MEG may promote or discourage surgical treatment of those

patients with greater confidence than when evaluated without MEG, by supporting other evidence or by revealing new findings. The possibility that MEG can mislead exists, and clinicians must be careful not to overly depend on positive indications for surgical treatment from MEG.

MEG may have special advantages in patients with failed epilepsy surgery or previous craniotomy, since magnetic fields are not distorted by skull defects and other conductivity inhomogeneities.[60]

The key advantage of MEG over scalp-EEG is its improved accuracy in spike source localization. Co-registration of spike dipoles to the patient's MRI provides potentially rich information in estimating the epileptogenic zone. One can superimpose the result on other functional images,[61] and even bring it to the operating room as a part of the neuro-navigational system.[62,63] However, it is important that clinicians interpret the images carefully, because a) the MEG-defined irritative zone may not be identical to the epileptogenic zone or seizure onset zone, and b) the images include an unknown degree of error which is inherent to the source modeling technique.

Conclusions

It is likely that there is a subset of patients in whom MEG can be of significant benefit, either to help persuade for or against surgery, or to better help guide the boundaries of the surgical resection. Unfortunately, which subset this is, and how best to conduct the evaluation in these patients, is unknown at this time. A prospective evaluation of the clinical usefulness of MEG is still lacking. Such a study must be designed to determine whether the addition of MEG to the standard evaluations indeed leads to a better surgical outcome.[64]

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60 Magnetic resonance imaging in the evaluation of the irritative zone

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Introduction

Like physiological brain activity (and epileptic seizures), interictal epileptiform discharges (IED) and epileptic seizures are associated with alterations of cerebral blood flow and deoxyhemoglobin concentrations in the venous bed. BOLD-fMRI therefore should be capable of identifying the sources of IED in the same way that it can identify sources of functional activation from movement or cognitive processing. As BOLD-fMRI relies on contrasts between different defined stages and IED are usually subclinical phenomena, a second modality is necessary to identify these events. Hence, fMRI of the irritative zone was only made possible by recording EEG inside the MR scanner (EEG-correlated fMRI). The development of an EEG recording technique during fMRI acquisition has provided the opportunity to study directly hemodynamic surrogates of epileptiform activity and potentially combines both the millisecond time resolution of EEG with the millimetre spatial resolution of fMRI. In principle, it might be possible to evaluate the irritative zone also by other MR-techniques correlated to concurrent EEG-recordings, e.g., EEG-correlated perfusion measurements or MR spectroscopy, but there are currently no conclusive data available.

Whilst the 'ictal onset zone' is generally regarded as the best surrogate for the epileptogenic zone, ictal fMRI will remain restricted to exceptional cases for several practical reasons. Epileptic seizures usually occur unpredictably and are often associated with clinical symptoms that prevent acquisition of good quality fMRI data. Compared with ictal fMRI, mapping of interictal activity has several practical und conceptual advantages: (1) IED are a common phenomenon in many patients with epilepsy; (2) IED are usually not associated with stimulus-correlated motion and significant alterations of consciousness; and (3) taking into account the time resolution of fMRI, BOLD signal changes associated with single IED are less likely to be confounded with propagation effects than are those occurring with ictal activity.

Methodological aspects of EEG-correlated fMRI

The MRI scanner is a hostile environment for EEG-recordings. MR-compatible EEG recording equipment must ensure patient safety, sufficient quality of the EEG signals, and avoid compromising MR image quality. Since the first report on human EEG recording during MR imaging more than 10 years ago by Ives *et al.*,[1] these issues have been addressed by several studies and technical solutions have been proposed.[2–5] Several commercial systems for intra-MR EEG recordings are now available. The main specific features implemented in these systems are a battery-powered nonmagnetic amplifier with a fiberoptic link, a high dynamic range of the amplifier and careful choice of materials for the electrode assembly.

The most crucial practical difficulty that must be overcome before useful functional data can be acquired is EEG quality. The two most relevant artefacts obscuring the EEG recorded inside the MR scanner are (1) pulse artefact (or cardioballistogram) and (2) image-acquisition artefact.[6,7]

Cardioballistic and other movement-related artefacts are caused by movements of the body and EEG leads relative to the magnetic field of the MR scanner. This can be reduced by minimizing the area of the EEG wire loops, lead fixation and bipolar montage of the EEG with small inter-electrode distances. Remaining pulse artefact can be removed by averaging and subtraction of the artifacts synchronized to the ECG.[2,8,9] These methods provide a degree of EEG quality sufficient for the accurate identification not only of IED (2003),[10] but also sleep stages,[11] physiological EEG rhythms,[12] and evoked potentials [13] in the intervals between image acquisition.

During MR image acquisition, the EEG is obscured completely by large artefacts mainly due to induced voltages in the EEG leads subjected to the rapidly changing gradient fields. Two solutions to the problem of EEG-imaging artefact removal have been proposed.[3,9] Both rely on amplification with sufficient dynamic range to avoid saturation of the EEG amplifier due to the artefact. The method developed by Allen and co-workers uses a scanner generated slice-timing pulse. For each channel, online subtraction of a running time-averaged waveform is performed, followed by adaptive noise cancellation to reduce any residual artefact. Hoffmann *et al.* proposed a postprocessing filtering method based on the fast Fourier transform (FFT): segments of EEG without MR activity are compared with the FFT of the EEG recorded during imaging. Frequencies with amplitudes over a threshold determined based on the FFT of the normal EEG are then discarded. The inverted FFT gives the corrected EEG.

The ability to remove image artefacts determines the data acquisition of EEG-correlated fMRI experiments. Without image artefact removal, the EEG is obscured during imaging and interleaved data acquisition has to be applied. In epilepsy studies, this approach was introduced as spike-triggered fMRI. This method takes advantage of the delayed BOLD response

after a neuronal event. This makes is possible to observe the EEG recording online (which requires the presence of an experienced electroencephalographer during data acquisition) and start image acquisitions manually at a fixed interval after the event of interest (usually 3 seconds, as the BOLD response peaks at 2–7 seconds after an event) or during control periods. However, spike-triggered fMRI suffers from two main limitations, both linked to the obliteration of the EEG during the image acquisition. First, there are constraints on the scanning rate and the duration of each scan. The minimum time gap between successive image acquisitions must be of the order of 15 seconds to avoid signal variations due to the T1 signal decay, and the maximum duration of each image acquisition must be less than the expected duration of the BOLD response in order to ensure proper separation of the responses from events which may occur during image acquisition, and therefore remain undetected. Second, as mentioned above, the spike-triggered approach relies on assumptions about the BOLD response peak time and duration. However, spike-triggered fMRI is not able to reveal the hemodynamic response function due to a delayed image acquisition and the lack of preactivity baseline images.

With the possibility of image artefact subtraction, these limitations can be overcome by continuous and simultaneous EEG-correlated fMRI. In contrast to spike-triggered fMRI, continuous EEG/fMRI recording allows for full exploration of the temporal dynamics of activation in addition to spatial localization. For each voxel, an entire time series is available for interrogation in contrast to the limited number of time points available for comparison in spike-triggered fMRI. Another advantage is that continuous EEG/fMRI allows for post hoc analysis of the EEG-events of interest. Regarding image analysis, in spike-triggered fMRI there are no requirements to model the hemodynamic response. Scans can be simply grouped into spike and rest categories and a *t*-test can be performed to judge significance. In continuous EEG/fMRI, the IED are treated as events of interest in an event-related analysis of the fMRI data. This involves creating a model timecourse for the IED and convolving this function with an appropriate hemodynamic response function (HRF). This basis function is included in the analysis, and variance correlated to this model is compared to residual variance. Voxels are considered to be activated during IED when the modeled variance is significant compared to residual variance. As summarized by,[14] EEG/fMRI studies in epilepsy vary considerably in their analytical approach, including acquisition method, HRF model, as well as the statistical threshold reported as significant.

In general, the continuous EEG/fMRI technique is thought to lead to a greater sensitivity to identify BOLD signal changes associated with IED compared to the spike-triggered approach.[15] Continuous EEG/fMRI has largely replaced EEG-triggered fMRI not only in the field of epilepsy, but also in EEG/fMRI studies of sleep,[16] physiological EEG rhythms,[17] and evoked potentials.[18]

EEG-correlated fMRI in the evaluation of the irritative zone

So far, about 30 studies applying EEG-correlated fMRI to patients with epilepsy have been published. The first study using EEG-correlated fMRI in patients with epilepsy was reported by Warach *et al.* in1996.[19] In two patients with epilepsy, IED were associated with fMRI activations. In the following years several studies followed using spike-triggered fMRI.[20–25] Since 2001 an increasing number of studies using continuous EEG/fMRI were reported.[26–31] Most of the studies were performed in patients with focal epilepsy, often medically refractory epilepsy (Figure 60.1). A few studies concentrated on defined idiopathic epilepsy syndromes, like benign epilepsy with controtemporal spikes (BECTS, rolandic epilepsy) in children,[32,33] reading epilepsy[32] and idiopathic generalized epilepsy.[14,32,34–36]

In summary, the studies showed that EEG-correlated fMRI is a practicable method to be applied to patients with epilepsy showing frequent IED on scalp EEG. The EEG quality was sufficient to detect spontaneous IED off- or online. Discomfort or injuries of the patients due to the EEG-recording were not reported and the MR image quality was not significantly compromised by the EEG recording. In the patients with focal epilepsy, the activations were in general anatomically related to the proposed irritative zone, or other cortical zones anatomically related to the epileptic focus (as defined by interictal EEG, EEG source analysis, structural MRI, ictal video-EEG, or, in less than ten patients, intracranial EEG). In one of the largest studies, Krakow *et al.*[22] reported 24 patients investigated with EEG-triggered fMRI. Between 12 and 50 IED were captured per session. Twelve of the 24 patients showed reproducible focal activation, which occurred in close spatial relationship to the maximum of the IED on scalp-EEG. The range of pathologies included encephalitis, cortical dysgenesis, hippocampal sclerosis, low-grade astrocytoma, and dysembryoplastic neuroepithelial tumors (DNET). Nine patients had no detectable structural abnormality. Of the six patients with cortical dysgenesis, four showed activation in all cases located within the cortical malformation. In a patient with DNET, BOLD activation was shown adjacent to the lesion.[21] In accordance to more recent studies using continuous EEG/FMRI,[30,37] these results support the concept of varying relationships between the epileptogenic lesion and the irritative zone. Gray matter within cortical dysgenesis may have intrinsic epileptogenic properties, whilst other lesions, for example tumors, may generate IED in the vicinity.

Comparison of EEG/fMRI results with intracranial EEG and EEG source modeling

In some patients with refractory focal epilepsy, EEG/FMRI results could be compared with results of the presurgical evaluation and in a few patients surgery was carried out after the EEG/fMRI experiment. The first report correlating invasive recordings and pathological data with an EEG/fMRI activation was a single case study published in 1998.[20] The largest of the studies correlating invasive EEG recordings with EEG/fMRI activations was reported by Lazeyras *et al.*[24] A total of 11 patients were investigated with EEG-triggered fMRI, who also underwent presurgical evaluation for their epilepsy with video-EEG, PET, and SPECT studies. In eight of 11 patients, intracranial recordings were carried out, and in five of them, the irritative zone as determined by fMRI was

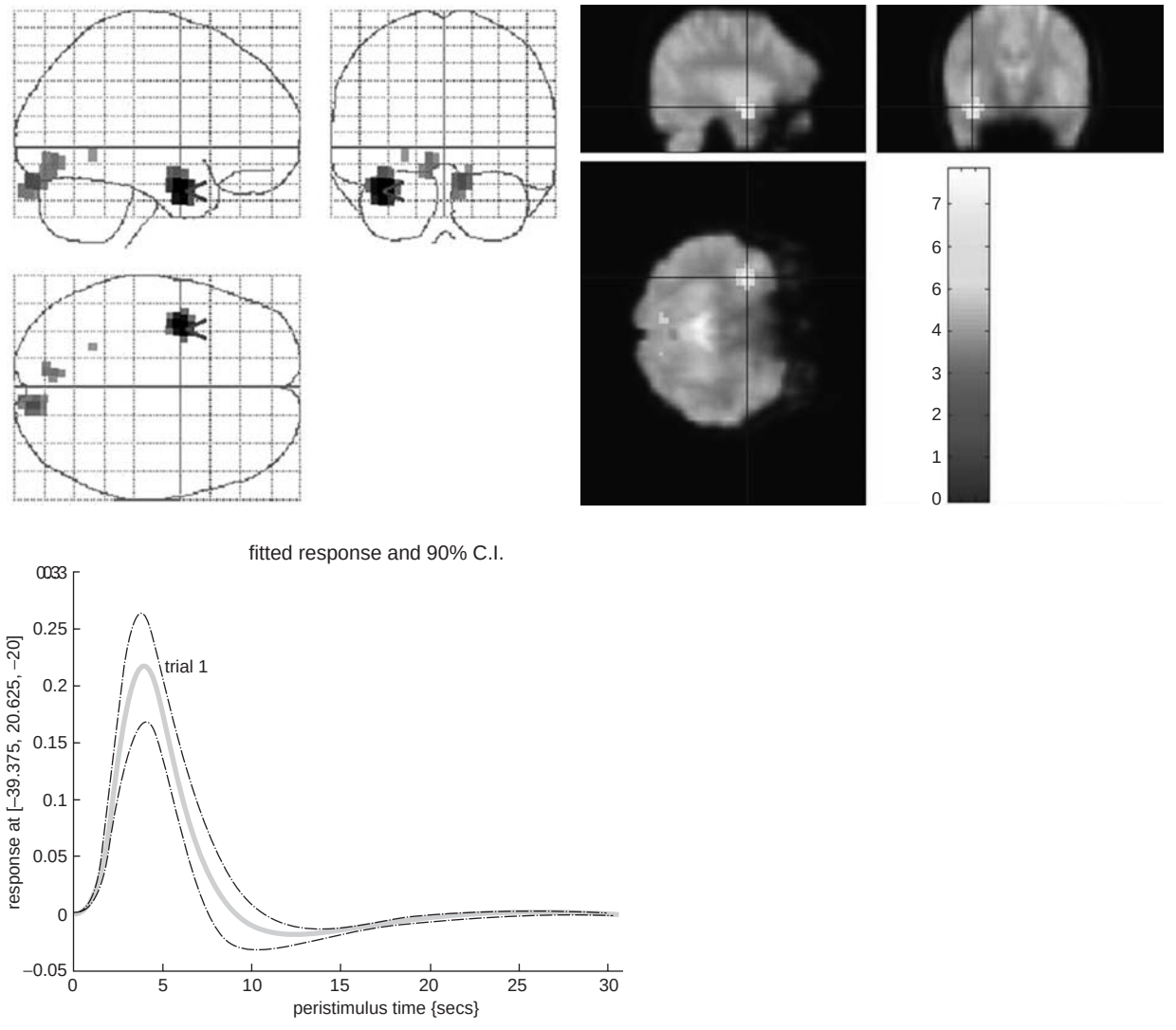

Figure 60.1 Result of a continuous IED-correlated fMRI study in a patient with complex focal seizures, a left hippocampal sclerosis and frequent left temporal IED. fMRI revealed a left temporal activation associated with IED (maximum indicated by arrow head in the glass brain and cross hair in the EPI overlay), which is concordant with the presumed irritative zone. There were significant negative BOLD signal changes associated with IED in retrosplenial areas (not displayed). The hemodynamic response is displayed below. (Courtesy of Afraim Salek-Haddadi, Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, United Kingdom.)

affirmed, but activation was not always anatomically restricted. In a recent large series[15] either spike-triggered or continuous EEG/fMRI was obtained and interpretable in 31 patients. Four patients underwent invasive recordings. Two patients had interictal activity in both temporo-occipital regions, one in the left medial frontal region, and one patient multifocal in the left frontal lobe. EEG/fMRI provided concordant information. However, it appears problematic to draw any conclusion from such small numbers, particularly as no data on the surgical procedures or outcome were provided. It therefore remains unclear whether EEG-correlated fMRI has the potential to replace invasive techniques to identify the irritative zone in a larger scale or, at least, provide additional information to guide the placement of invasive intracranial electrodes where necessary.

Comparison of EEG/fMRI results with EEG source localization was performed in few studies. In six patients with focal epilepsy,[38] spike-triggered EEG/fMRI responses were compared with EEG dipole source analysis from a separate session using 64 EEG channels. Over the six patients, mean distances between dipoles and the center of the nearest fMRI response of 4.2 cm (spatiotemporal approach), 3.5 cm (moving dipole fitted to the first negative peak of the spike), and 2.3 cm (moving dipole fitted to the positive peak of the spike). In a recent study,[39] 33 patients with intractable focal epilepsy arising from various brain regions were examined using EEG-correlated fMRI and EEG source analysis, the latter based on a full set of electrodes according to the 10/10 system. The mean distance between the dipole location and the voxel of maximum positive change was 58.5 mm, and 60.8 mm from the voxel with the largest negative value. The distance between the dipole location and the closest voxel with a significant positive activation was 32.5 mm, and with the closest negative voxel 34 mm. The authors felt that reasons for poor concordance could be the relative complexity and widespread distribution of the field associated with epileptic activity.

Benar *et al.*[40] quantified the concordance between EEG/fMRI results, stereotaxic EEG (SEEG) recordings and surface EEG in

five patients with focal epilepsy. It was concluded that SEEG largely validated the results of EEG/fMRI. When there was an intracranial electrode (intracerebral or epidural) in the vincinity of a fMRI activation peak, (in the range 20–40 mm), then it usually included one active contact. This was the case for both fMRI signal increases and decreases. The concordance between surface EEG and fMRI was not as good as the concordance between either of these noninvasive techniques and SEEG. The authors concluded that both techniques are complementary for the localization of the areas involved in the generation of IED. Within a distance of 20 mm, the average percentages of matches between fMRI peaks (positive or negative) and intracranial EEG were better than those between EEG source localization and SEEG.

Limitations of the interpretation of EEG-correlated fMRI

The clinical implementation of EEG-correlated fMRI and the interpretation of the fMRI activation maps is difficult for various reasons:

1. The limitations of surface EEG affect the clinical application of EEG-correlated fMRI. It is well known by electroencephalographers that the majority of EEG recordings from patients with epilepsy are entirely normal or show only nonspecific slowing. Invasive recordings from the cortex or deep structures such as the hippocampus however may show frequent spiking, not evident on surface EEG. Therefore, EEG-correlated fMRI of IED remains limited to the minority of patients with frequent IED on surface EEG. In order to overcome the limitations of surface EEG, methods have been suggested to detect IED-related BOLD signal changes without concurrent EEG recording. An example of such an exploratory, data-driven technique is temporal clustering analysis (TCA). It is based on the premise that activation would cause the number of voxels reaching their individual maximum values at any given point, to rise beyond a certain threshold. It makes no assumptions with regards to the proximity of the voxels that constitute the clusters and is limited in that each voxel will reach its maximum only once in the time series. Using this approach, Morgan *et al.*[41] analyzed fMRI data in nine patients with focal epilepsy acquired during rest in an attempt to localize brain activation associated with IED. By looking for a particular subset of variance, specifically changes of between 2 and 10% from the resting BOLD intensity level, focal fMRI activations with a high degree of concordance to electro-clinical data could be identified in six patients. It was proposed that resting fMRI with temporal clustering analyses without EEG could contribute to localize the irritative zone. However, these findings could not be reproduced so far by other groups, and theoretical and methodological problems of this approach were asserted, e.g., the association of the fMRI activations with head movement.[42]
2. The size of the fMRI activation cluster is greatly variable between studies and also between subjects in individual studies. Some patients have a widespread, multifocal activation, others show a circumscribed activation. The extent of the activation is critically dependent on the applied statistical threshold, which partly explains differences between studies. EEG-correlated fMRI may contribute to localize the source of IED, but currently it cannot provide information about its extent. The reason for the variability between patients who were studied with identical methodology and thresholds remains unclear. No significant correlations between clinical characteristics (e.g., epilepsy syndrome, spike amplitude) and the size of the fMRI activation were found. The same applies for the number of IED which have been analysed: In some patients even individual IED are associated with large activations [43] in other patients as many as 50 IED are not associated with significant activations.[22] In patients with widespread fMRI activation, another problem is to distinguish the primary sources from activation, which may represent areas of propagation. In such cases with equivocal information on localization, a combination of fMRI data with EEG source analysis may provide complementary information.[20,38]
3. Until now, the results of EEG-correlated fMRI have not been systematically validated with a gold standard, which are intracranial recordings and outcome after epilepsy surgery. Before EEG-triggered fMRI can be used as a decisive method to identify the irritative zone (and therewith provide information for localization of the epileptogenic zone), the relation between fMRI results, invasive EEG recordings and surgical outcome in relation to resection of the activated area has to be established. Furthermore, in all EEG/fMRI studies mentioned above, less than 300 patients were reported in total. Patients for EEG/FMRI experiments were in general highly selected, particularly with regard to the frequency of their IED. It is questionable if EEG/fMRI has the potential to be applied to relevant numbers of patients in a clinical setting.
4. The high percentage of negative results even in the highly selected patients (up to 50% in the larger studies using spike-triggered fMRI[22–25] currently hinders the wider clinical application of EEG-correlated fMRI. The physiological explanation of a negative fMRI result is most likely that there is a nonsignificant difference in the blood oxygenation between activation and control states. This might be due to there being only a modest cerebral hyperperfusion following an IED, or due to an absence of a true control state, e.g., such as ongoing epileptic activity not detected on scalp EEG. In both cases the relative signal change within the spike generator may not achieve significance. It has been reported that possibly certain characteristics of IED may lead to greater likelihood of fMRI signal changes, such as prolonged bursts of IED, higher amplitudes and larger fields of IED,[39,44] but the results have remained contradictory. As mentioned above, it is conceivable that continuous and simultaneous EEG/fMRI will increase the sensitivity of the method. Further, the use of higher strength magnets will increase the signal to noise ratio and hence fMRI sensitivity. Multichannel EEG has already been recorded in a 4 Tesla MR scanner on humans and in a 7 Tesla MR scanner in animals.[47] An improved signal to noise ratio may not only increase the proportion of fMRI-positive experiments, but may also reduce the number of analysed IED necessary for a significant fMRI activation, thus rendering this method applicable to patients with less frequent IED.

5. The significance of BOLD signal changes associated with IED is currently not well understood. In focal epilepsy, positive BOLD signal changes typically localize the generators of IED, i.e., the irritative zone. However, some patients show widespread or multifocal activations not related to the irritative zone. In addition, many patients show solely or additional negative BOLD signal changes in association with IED, especially associated with polyspike and spike- and slow-wave discharges of longer duration (bursts).[45] These 'deactivations' were observed in most EEG/fMRI studies, but yet not systematically investigated. As IED are a marker of the neural hyperexcitability underlying epilepsy, the observation of fMRI 'deactivation' is intriguing. In some patients, negative BOLD signal changes are in good spatial agreement with the presumed irritative zone and may represent processes of focal inhibition.[45] More frequently, the negative BOLD signal changes occur widespread and bilaterally. In patients with idiopathic epilepsy, generalized spike and wave discharges (GSWD) were associated with negative BOLD signal changes in bilateral frontal, parietal cortices and retrosplenial areas (precuneus, posterior cingulum).[14,17,35] Together with bilateral frontal and temporo-parietal areas, restrosplenial areas constitute a functional network that may be active in a default mode of brain function during rest.[46] This activation pattern may indicate an aberrant suspension of this network's functionality due to the generalized IED. However, similar deactivation pattern occur also with focal IED, indicating the BOLD signal changes associated with epileptiform activity do not only localize generators of IED within irritative zone, but indicate also complex changes of functional connectivity.

Conclusion

EEG-correlated fMRI has proved useful to provide insights into the generation of IED in patients with focal epilepsy. In selected patients with frequent IED, EEG-correlated fMRI has the potential to reproducibly identify cortical areas involved in generating IED, i.e. the irritative zone. So far, the sensitivity of the method is in the range of 50%. To determine the specificity of the method, further studies are necessary to compare the EEG/fMRI results with the diagnostic gold standards, which are intracranial EEG recordings and postoperative outcome after epilepsy surgery. Until these results are available, the utility of EEG-correlated fMRI in clinical epileptology cannot be definitely determined.

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61 Digital tools for reviewing the electroencephalogram: montage reformatting and filtering

TD Lagerlund

Introduction

Electroencephalographers often encounter records in which a transient phenomenon, such as an epileptic interictal or ictal discharge, is displayed such that its localization or interpretation is in doubt because the electroencephalogram (EEG) was recorded using a nonoptimal montage. Electroencephalographers recognize that there are particular advantages and disadvantages of any montage, including referential, longitudinal bipolar, and transverse bipolar montages. The most useful type of montage and the choice of reference depend on the type of EEG phenomenon being viewed.

Certain montages may make particular kinds of EEG phenomena more evident. For example, for examining a generalized spike-and-wave pattern that is predominantly parasagittal, an ear or mastoid reference (unilateral or averaged) may be appropriate. However, a focal temporal abnormality may cancel out and not show up well with use of an ipsilateral ear or mastoid reference. If a reference electrode is contaminated by the activity of interest, out-of-phase waveforms can appear in electrodes at a distance from the reference electrode, and only low-amplitude activity may be seen in electrodes near the reference electrode due to partial cancellation of activity in the 'contaminated' or active reference.[1] Bipolar montages have the advantage of avoiding contamination by an 'active' reference, but to properly localize the generators of various EEG waveforms by visual inspection of a bipolar montage requires the recognition of phase reversals in adjacent channels that share a common electrode. Phase reversals are much easier to recognize in transient waveforms and much more difficult to recognize in rhythmic activity or discharges. On a bipolar montage, looking for the channel that has the maximum amplitude can be misleading or falsely localizing.

Similarly, at times during EEG interpretation a transient phenomenon may be recorded while the EEG filter settings are inappropriate. This may occur, for example, if a seizure discharge is contaminated by muscle artifact, which could have been reduced or eliminated by use of a high-frequency filter. As another example, a transient slow wave may be attenuated by a low-frequency filter, but would have been more prominent if a less restrictive low-frequency filter setting was used.

A computer-based (digital) EEG system can eliminate these problems by allowing the montage and filter settings to be determined at the time the EEG is reviewed rather than at the time it is recorded. The EEG is recorded with minimally restrictive analog filter settings and with potentials at all electrodes measured with respect to a single common reference. A computer can then process the data as they are displayed on a screen or printer, reformatting the original referential montage to any desired referential or bipolar montage and digitally filtering the data as needed. If necessary, the same segment of EEG can be displayed repeatedly, using different montages and filters.

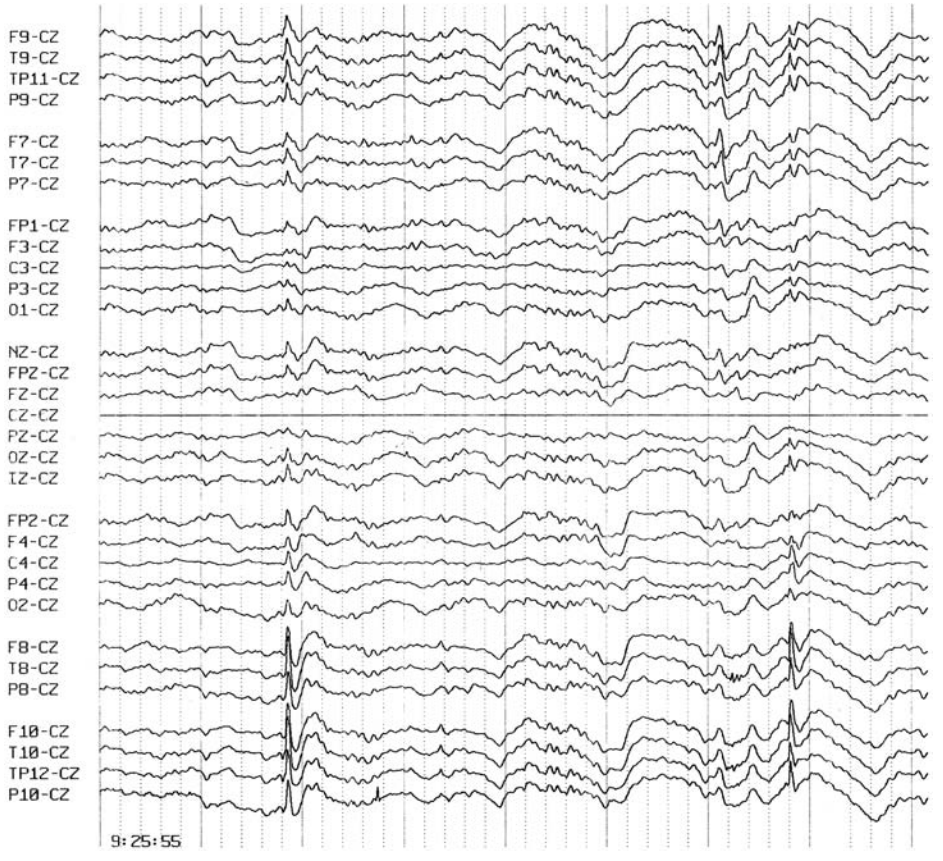
Reformatting to referential or bipolar montages

To generate a derivation such as $X_1–X_2$, which does not exist in the EEG as recorded, the computer looks for two existing channels, one of which records X_1 against a reference electrode and the other records X_2 against the same reference, and then subtracts the two. That is, $X_1–X_2 = (X_1–R) – (X_2–R)$, where R is the reference. This allows new referential and bipolar montages to be formed. For example, suppose that recorded EEG data include the following channels:

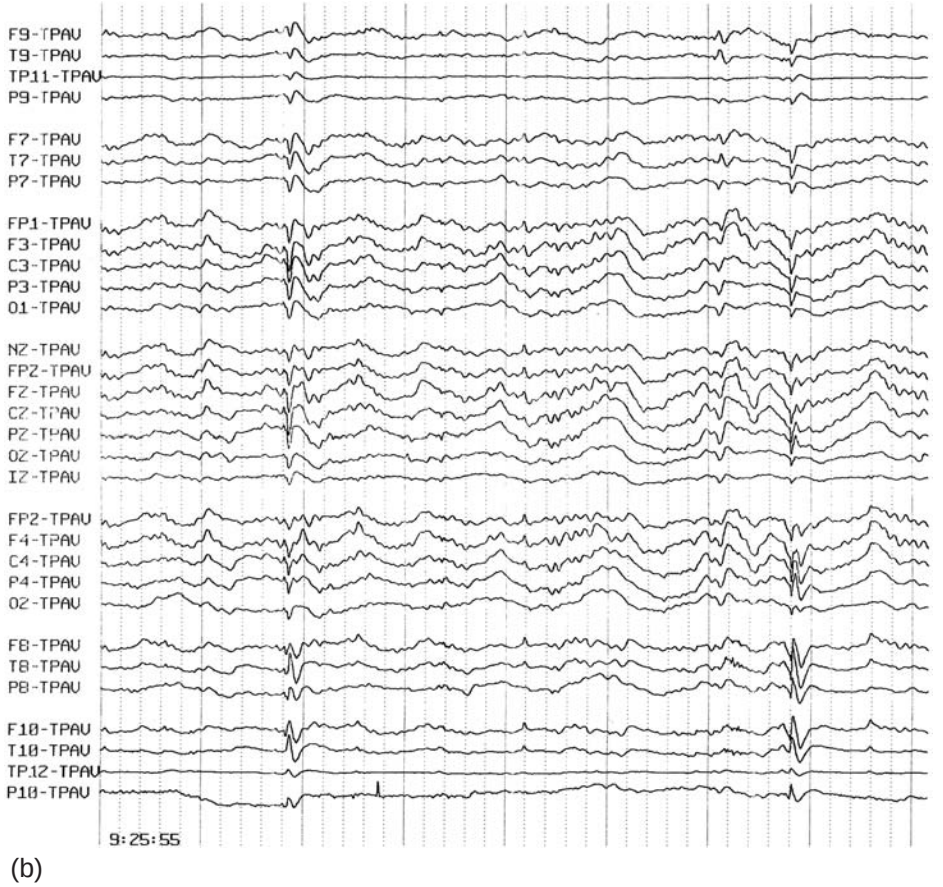
Channel	*Derivation*
1	$F_{p1}–C_z$
2	$F_{p2}–C_z$
3	$F_3–C_z$
4	$F_4–C_z$
5	$C_3–C_z$
6	$C_4–C_z$
7	$P_3–C_z$
8	$P_4–C_z$
9	$O_1–C_z$
10	$O_2–C_z$
11	$A_1–C_z$
12	$A_2–C_z$

A new referential montage with ipsilateral ear reference can then be created by subtracting pairs of channels as follows:

Channels	*Derivation*
ch1–ch11	$F_{p1}–A_1$
ch2–ch12	$F_{p2}–A_2$
ch3–ch11	$F_3–A_1$
ch4–ch12	$F_4–A_2$

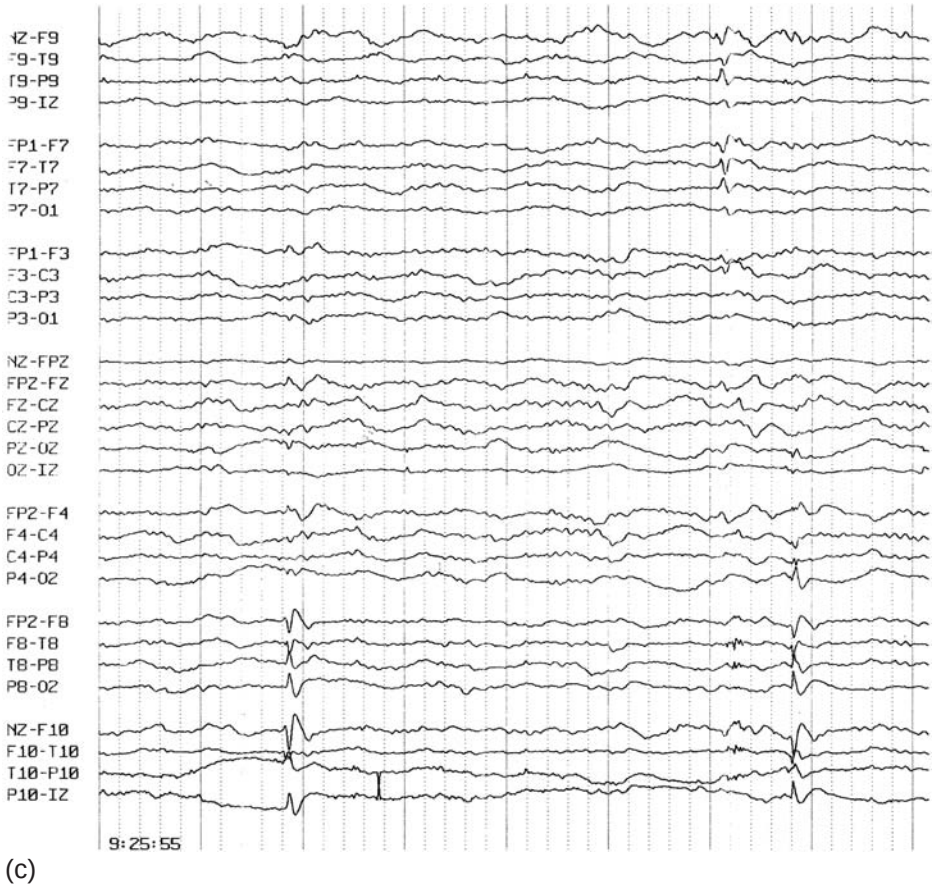


(a)



(b)

Figure 61.1 An electroencephalographic (EEG) recording showing interictal epileptiform discharges. a. EEG as recorded from a C_z reference. TP_{11} and TP_{12} are left and right mastoid electrodes. b. EEG reformatted to average mastoid (TPAV) reference.



(c)

Figure 61.1c cont'd, c. EEG reformatted to longitudinal bipolar montage. (From Lagerlund TD. Digital tools for reviewing the electroencephalogram: montage reformatting, filtering, and principal component analysis. In: Lüders HO, Comair YG, eds. Epilepsy Surgery 2nd edn. Philadelphia: Lippincott Williams & Wilkins; 2001: 367–77. Used with permission.)

Channels	*Derivation*
ch5–ch11	C_3–A_1
ch6–ch12	C_4–A_2
ch7–ch11	P_3–A_1
ch8–ch12	P_4–A_2
ch9–ch11	O_1–A_1
ch10–ch12	O_2–A_2

New reference electrodes can also be created by averaging data from two or more existing electrodes. For example, suppose an EEG is recorded with a C_z reference. A new derivation such as O_1–$A_{1/2}$ (where $A_{1/2}$ represents the average of the ear electrodes) can be calculated as O_1–$A_{1/2}$ = (O_1–C_z) – 0.5(A_1–C_z) – 0.5(A_2–C_z). Figure 61.1 shows the same interictal discharges viewed with various montages (one as recorded, two after reformatting).

Digital filtering of EEG

A digital filter is a computer program or algorithm that can remove unwanted frequency components from a signal. Just as for analog filters, they can be classified as low pass, high pass, band pass, or notch filters. Digital filters have several advantages over analog filters. First, they can be constructed and modified easily because they are software programs rather than hardware devices. Second, they can easily be made to have a relatively sharp frequency cut-off if desired (e.g., much sharper than the typical 6-db per octave roll-off of an analog filter). Third, if properly designed they need not introduce any time delay (phase shift) in the signal, as invariably happens with ordinary analog filters, and thus time relationships between different channels can be preserved even if different filters are used for each.

Most digital filters function by forming a linear combination (weighted average) of signal amplitudes at the current time and various past times.[2] The two types of commonly used digital filters are the finite impulse response (FIR) filter and the infinite impulse response (IIR) filter. The FIR filter output is a linear combination only of the input signal at the current time and past times. With this type of filter, the output necessarily becomes zero within a finite amount of time after the input signal goes to zero. The IIR filter output is a linear combination of both the input signal at the current time and past times ('feed-forward' data flow) and the output signal at past times ('feed-back' data flow). The output of the IIR filter may persist indefinitely in the absence of any further input because the output signal itself is fed back into the filter. IIR filters can be unstable and also have the undesirable property of noise buildup, since noise terms created by arithmetic round-off errors are fed back into the filter and amplified. For these reasons, FIR filters are easier to design. However, IIR filters may involve much fewer calculations and be considerably faster in operation than FIR filters having equivalent characteristics.

Figure 61.2a shows an example of an EEG segment contaminated by muscle artifact. In Figure 61.2b, filtering has

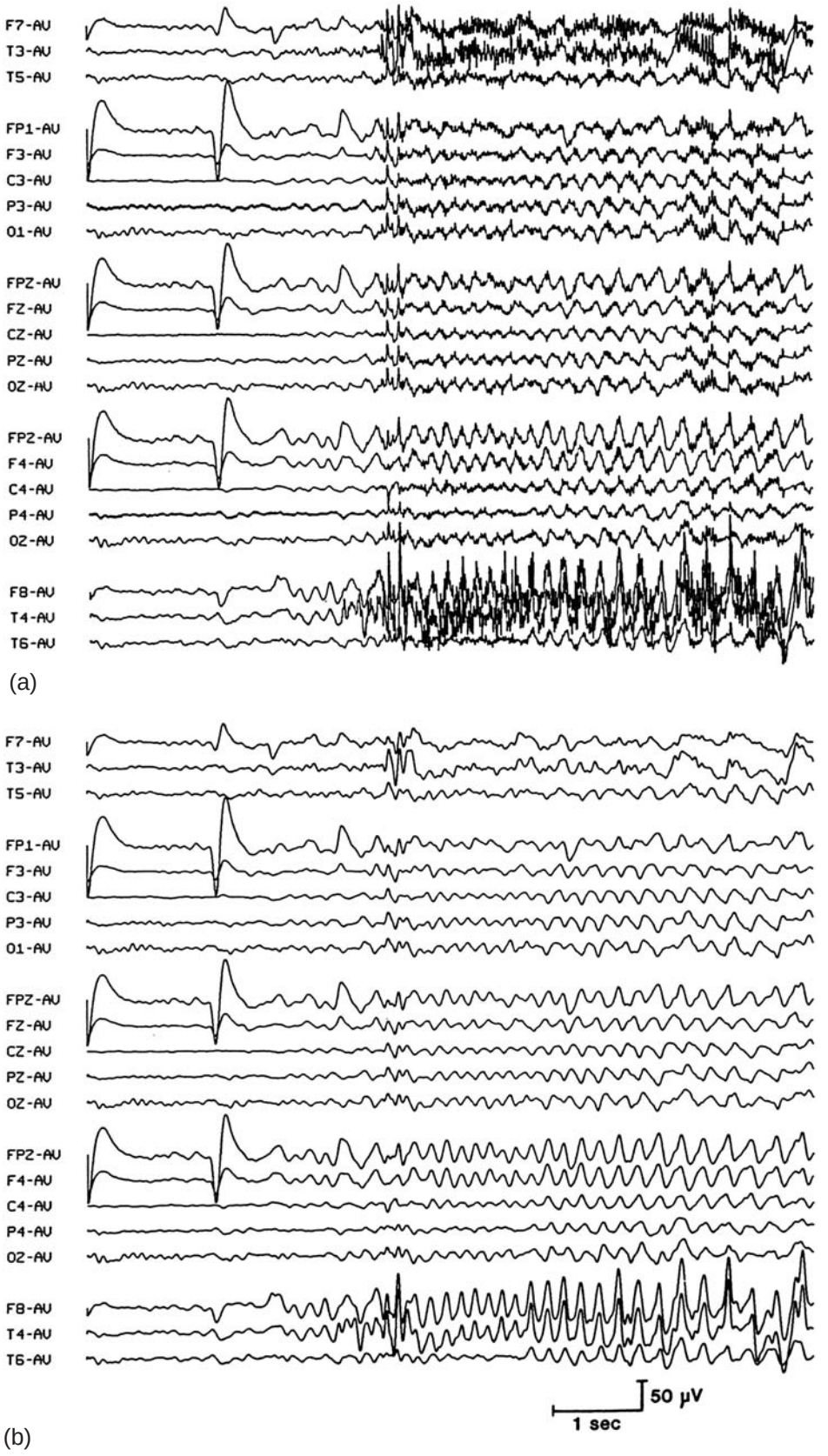


Figure 61.2 An ictal electroencephalographic (EEG) recording. a. EEG shown without filtering. b. EEG after use of a low-pass filter to remove unwanted muscle artifact. AV, average reference. (From Lagerlund TD. Digital tools for reviewing the electroencephalogram: montage reformatting, filtering, and principal component analysis. In: Lüders HO, Comair YG, eds. Epilepsy Surgery 2nd edn. Philadelphia: Lippincott Williams Wilkins; 2001: 367–77. Used with permission.)

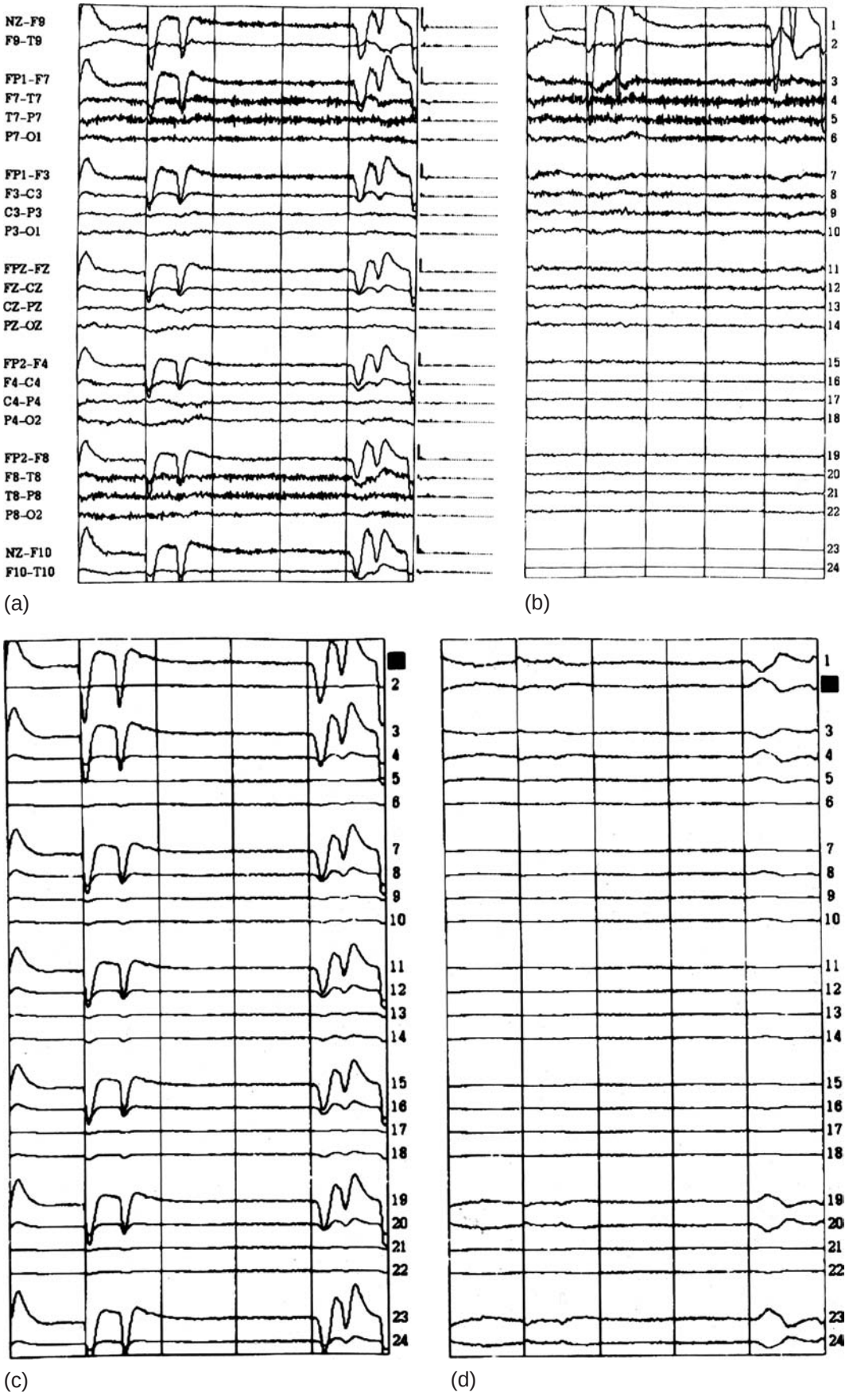
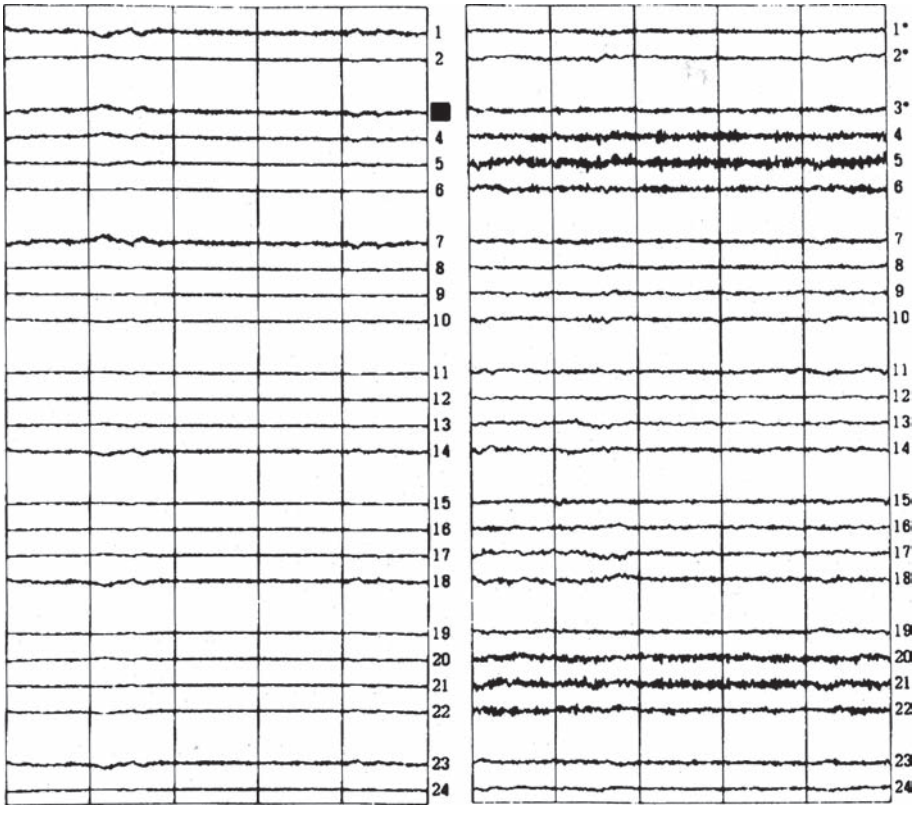


Figure 61.3 Principal component analysis (PCA) applied to an electroencephalogram (EEG) containing ocular movement artifacts. a. A 5-second epoch of EEG with a 24-channel bipolar montage. On the right is the mapping matrix resulting from PCA as a histogram for each channel. b. The 24 principal components resulting from PCA. c–e. The EEG reconstructed in turn from each of components 1–3. f. The EEG reconstructed from summing components 4–24, omitting components 1–3. (From Lagerlund *et al*.[8] Used with permission.)



(e) (f)

Figure 61.3e-f cont'd

eliminated most of the artifact, revealing the underlying seizure discharge.

Spatial filtering using principal component analysis

Principal component analysis (PCA) by singular value decomposition (SVD) may be used to analyze an epoch of multichannel EEG into multiple linearly independent components, or features; the original epoch of EEG may be reconstructed as a linear combination of the components.[3–5] The result of SVD includes the components, expressible as time-series waveforms, and the factors that determine how much each component contributes to each EEG channel. By omitting some components from the linear combination, a new EEG can be reconstructed which differs from the original in useful ways. For example, artifacts may be removed or features such as alpha may be enhanced by suppressing the remainder of the EEG.

The SVD algorithm[6,7] can express any $m \times n$ matrix **E** as a product of 3 matrices: $\mathbf{E} = \mathbf{PAM}^T$, where **P** is an $m \times n$ matrix such that $\mathbf{P}^T\mathbf{P} = 1$; **A** is an $n \times n$ diagonal matrix; and **M** is an $n \times n$ matrix such that $\mathbf{M}^T\mathbf{M} = \mathbf{MM}^T = 1$. SVD is a method for PCA. If **E** is an epoch of EEG (n channels, m time points), **P** contains n normalized principal components of the EEG (linearly independent components or features that can be combined to give the original EEG). **A** contains n amplitudes that apply to the n principal components. Defining $\mathbf{W} = \mathbf{PA}$ (unnormalized principal components, displayed as multichannel waveforms), $\mathbf{E} = \mathbf{WM}^T$. **M** is the mapping (set of weighting factors) used to combine the n components, which may be displayed as a topographic map or a histogram; M_{ij} is the contribution of the jth component to the ith channel.

By zeroing selected columns of **M** to give a new matrix **M′**, a new EEG epoch ($\mathbf{E}' = \mathbf{WM}'^T$) can be found containing some but not all principal components. For example, if component 2 contains only eye movement artifact and component 4 only electrocardiographic artifact, a new EEG without either artifact is formed by zeroing columns 2 and 4 of **M**. In a variation of this technique, the factors that reconstruct the modified EEG from the original epoch are stored as a matrix **S**.[8] Since $\mathbf{E} = \mathbf{WM}^T$, $\mathbf{EM} = \mathbf{WM}^T\mathbf{M} = \mathbf{W}$, then $\mathbf{E}' = \mathbf{WM}'^T = \mathbf{EMM}'^T = \mathbf{ES}^T$ where $\mathbf{S} = \mathbf{M}'\mathbf{M}^T$. This matrix **S** is applied to multichannel EEG at successive times to create a new EEG continuously in real time. Specifically, matrix **S** is applied to successive column vectors $\mathbf{e}(t)$ of EEG values at time t to give $\mathbf{e}'(t) = \mathbf{Se}(t)$. This matrix acts as a spatial filter with useful properties. Note that **S** is calculated from one selected EEG epoch; the SVD need not be repeated, saving computation time.

Figure 61.3a shows a 5-second epoch of EEG using a 24-channel bipolar montage, along with the mapping matrix from PCA as a histogram for each channel. Figure 61.3b shows the 24 principal components resulting from PCA. Figures 61.3c through E show the EEG reconstructed in turn from each of components 1 through 3. Component 1 contains vertical eye movement artifacts and component 2 contains horizontal eye movement artifacts; component 3 contains another ocular movement-related waveform; other components not shown contain other parts of the EEG.

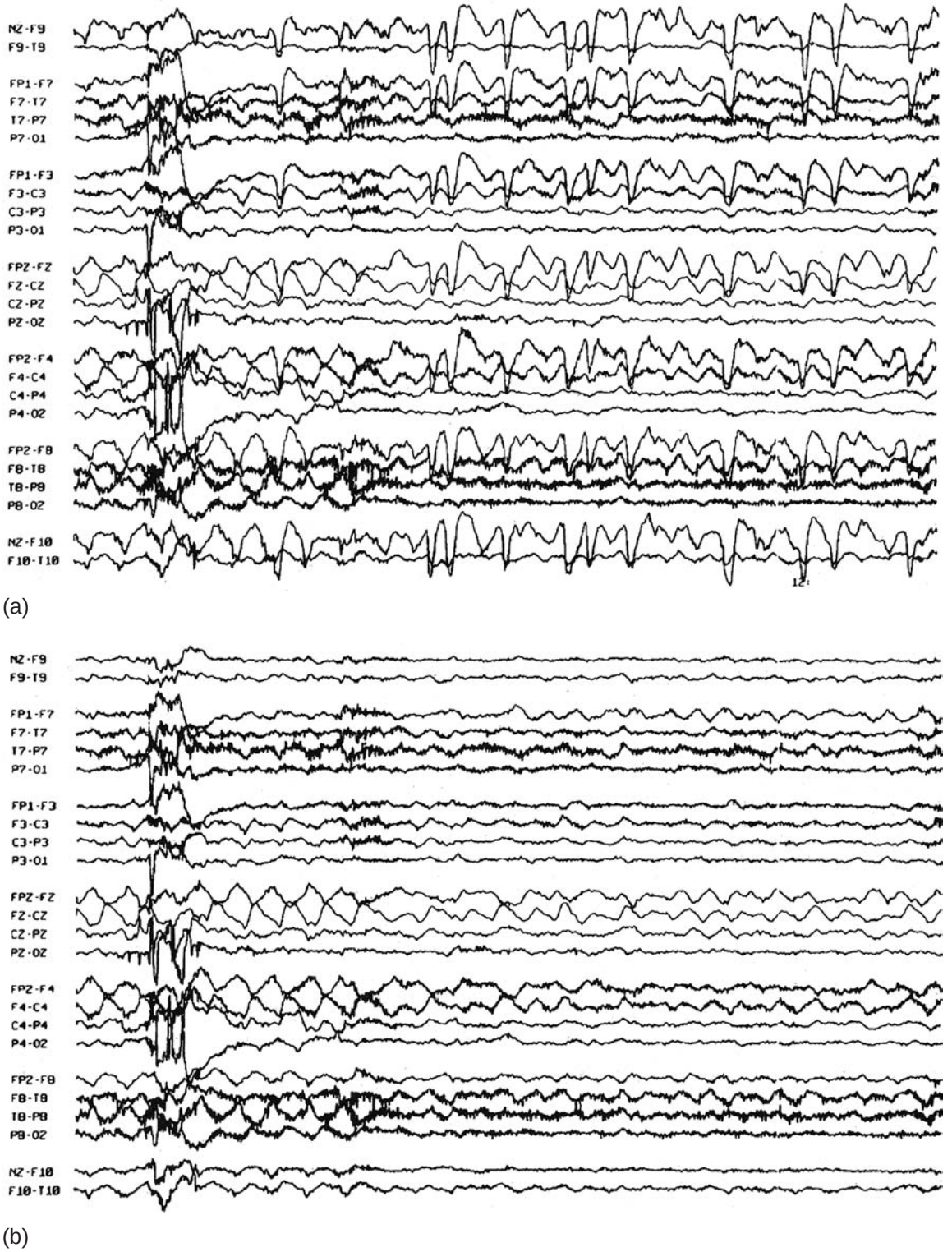


Figure 61.4 Spatial filtering of ocular movement artifacts with use of the principal component analysis results in Figure 61.3. a. A 12-second epoch of the electroencephalogram (EEG) on the same patient as in Figure 61.3. b. The same EEG after applying the spatial filter. (From Lagerlund *et al*.[8] Used with permission.)

Figure 61.3F shows the EEG reconstructed from components 4 through 24; ocular movement artifacts are almost completely removed. Figure 61.4A shows a 12-second epoch of EEG of the same patient as in Figure 61.3 at the end of a partial seizure, with rhythmic and polymorphic delta activity obscured by ocular movement artifacts. Figure 61.4B shows the same EEG after applying the spatial filter; ocular movement artifacts were largely removed, allowing the underlying slow waves to be seen. Some slow components in the frontal channels are attenuated but not removed; they are probably not ocular movement artifacts.

PCA is a useful method of removing artifacts or other unwanted features of an EEG while preserving or effectively enhancing other features. In effect, the method uses the spatial distribution across channels of artifacts or other waveforms as a 'signature' of the feature to be eliminated. All waveforms having the same spatial distribution are canceled out, whereas waveforms distributed differently are preserved. Thus, the matrix acts as a 'spatial filter', analogous in some respects to a digital 'temporal filter' designed to remove some frequencies from the EEG while preserving others.

The method works well for eliminating artifacts or activity with relatively high amplitudes and with a spatial distribution that remains constant throughout the EEG. Ocular movement and electrocardiographic artifact often have these characteristics. The method works less well for artifacts of relatively low amplitude and changing spatial characteristics, such as electromyographic artifact and some electrode artifacts; although elimination of these may not be achieved, a substantial reduction may still be attained.[8]

Acknowledgment

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62 Average reference and Laplacian montages

TD Lagerlund

The average reference montage

Electroencephalographers have long recognized the value of a truly inactive reference electrode. Although it is not possible to find a 'distant' (and thus truly inactive) reference for scalp electroencephalographic (EEG) recordings,[1] a possible compromise is the average reference. This reference is calculated as the mean, or average, of the potentials at all (or nearly all) available scalp electrodes. By using an average of all electrodes, potentials that deviate from the average but affect only one or two electrodes are averaged out. This concept works well unless a very high potential is recorded in one or two electrodes, such as with high-amplitude interictal spikes (Figure 62.1 a and b), or unless a moderate potential is recorded in a great many electrodes, such as with eye blink artifacts that often produce a high-amplitude deflection in several electrodes at once (Figure 62.2a and b). In these situations, the potential will appear with reverse polarity but attenuated amplitude in all channels of the average reference montage, such that the potential may be difficult to recognize.

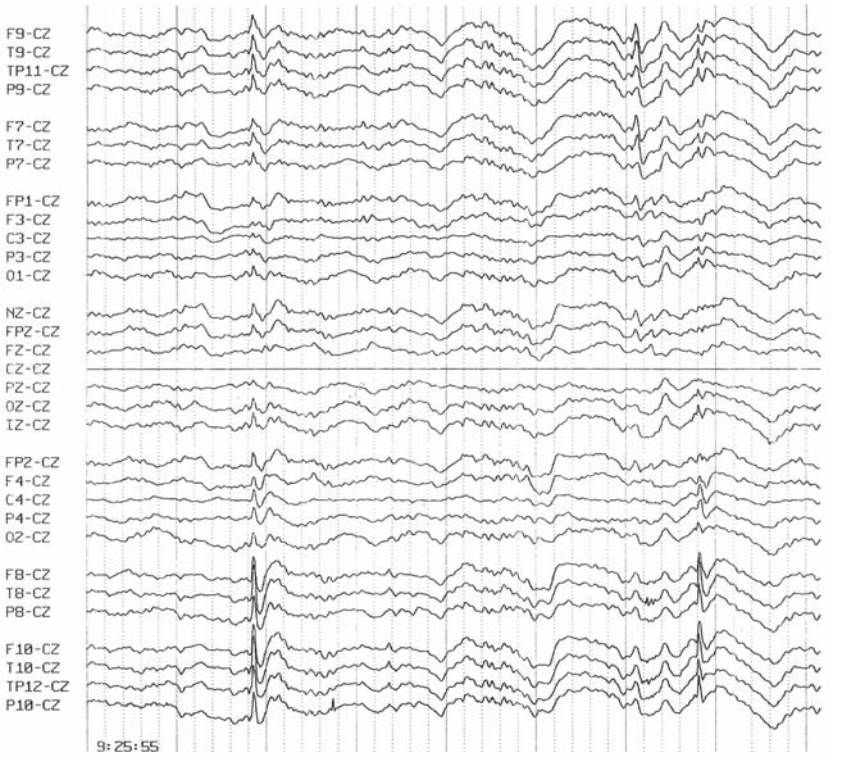
Considerable caution must be used in the interpretation of the average reference montage. Because the reference is the average of all electrodes, the potential at any given scalp electrode location depends on the location of all the other electrodes. Furthermore, when comparing any two channels, the relative phase and amplitude also depend on what all the other electrodes record. In Figure 62.3 Fourier analysis of a 2-second epoch of EEG containing alpha activity at 10.5 Hz was used to construct phase-magnitude plots for two different reference electrodes. Solid-line plots correspond to the left ear reference (A_1), and broken-line plots correspond to the same epoch but reformatted using an average reference. One apparent difference is that the F_{p2} electrode shows very low amplitude at 10.5 Hz in the left ear reference recording but large amplitude in the average reference recording. It may also be noted that the two labeled electrodes, F_z and C_z, are roughly in phase in the left ear reference recording (indicated by arrows pointing to the right) but out of phase (indicated by arrows pointing in opposite directions) in the average reference recording.[1] Of course, other choices of reference electrode would produce still other relative amplitudes and phases.

The Laplacian (source current density) montage

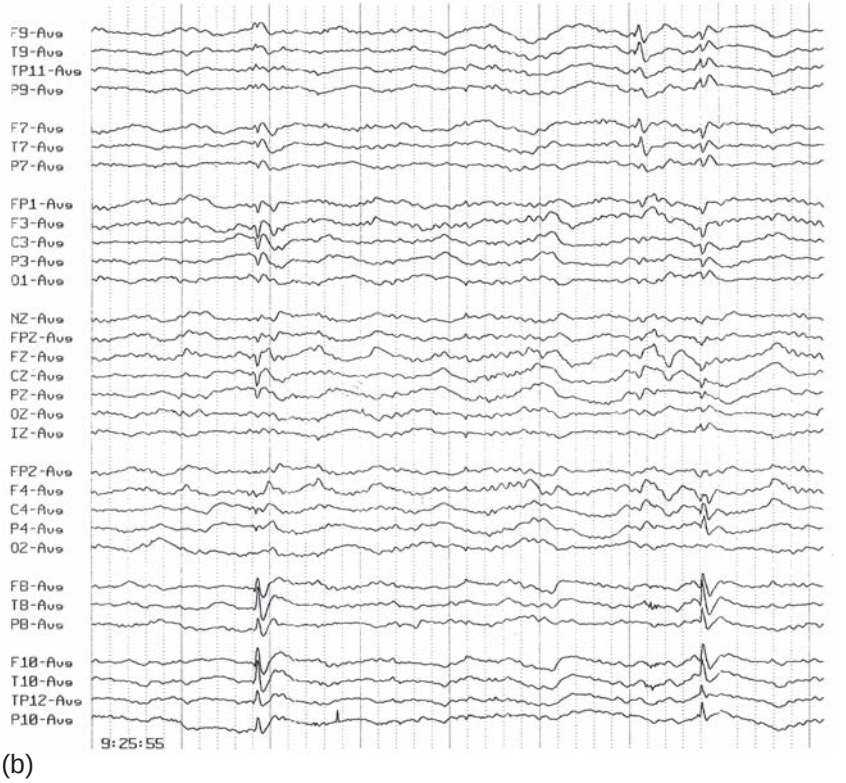
Electroencephalographers have used referential and bipolar montages commonly for many years, but the Laplacian, or source current density, montage[2–4] has not been widely used, primarily because few commercially available EEG machines implement it. However, it is relatively easy to implement a Laplacian montage in a digital EEG system, and it has several properties that make it a useful addition to the set of conventional referential or bipolar montages.

The name of this montage is derived from the mathematical concept of the Laplacian of a function of two variables, $f(x, y)$, defined as the curvature (second derivative) of the function f in the x direction plus the curvature of f in the y direction. The potential (voltage) on the surface of the head is a function of the two variables, x and y, representing coordinates on the head (for example, x could be distance in centimeters to the left or right of the origin, C_z, and y could be distance in centimeters anterior or posterior to C_z). The Laplacian of the potential is proportional to the radial current density (the current per unit volume flowing radially into a region of scalp from sources underneath). At a location with no underlying current sources, the Laplacian would be zero, whereas it would be maximal directly over a source (Figure 62.4). Thus, the Laplacian of the potential may be used to localize the underlying generators of the EEG. For this reason, a Laplacian montage is also called a source current density montage. As defined above, the Laplacian at a surface-positive potential peak is negative (corresponding to convex curvature of the potential peak; Figure 62.4). Thus, the Laplacian at a surface-negative potential peak is positive (corresponding to concave curvature of the potential peak). Thus, in practice a 'Laplacian' or source montage is often displayed as the negative of the Laplacian.

Although the potential at all locations on the head is not known, making an exact calculation of the Laplacian impossible, the nearest-neighbor method[3,4] is an easy method to approximate the Laplacian at positions corresponding to the location of the electrodes and is the one generally used to derive the Laplacian montage. The Laplacian at an electrode X

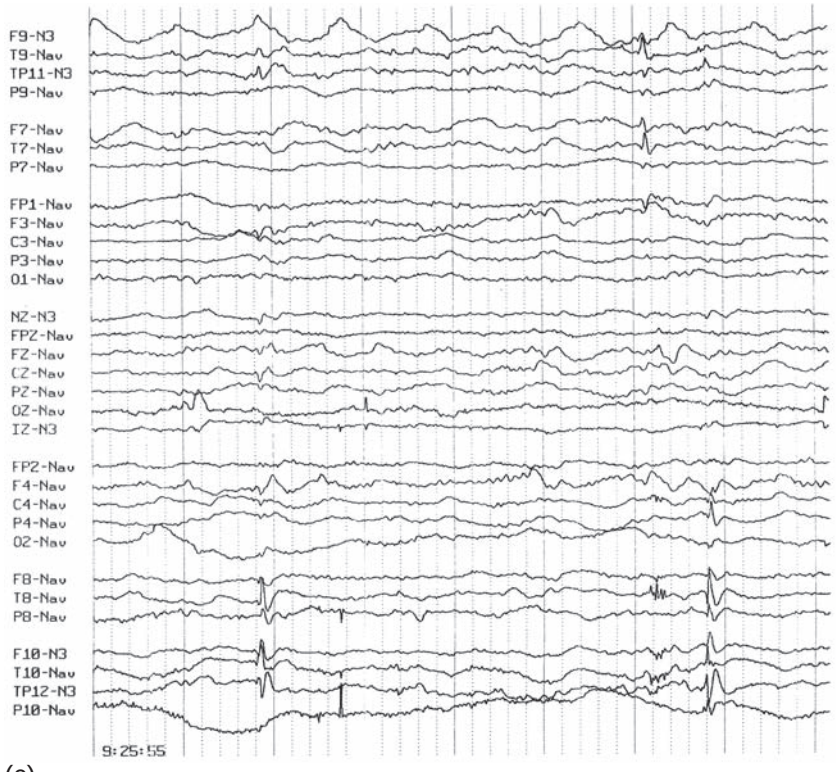


(a)



(b)

Figure 62.1 An electroencephalographic (EEG) recording showing interictal epileptiform discharges. a, As recorded from a C_z reference. TP_{11} and TP_{12} are left and right mastoid electrodes. b, Reformatted to average reference. c, Reformatted to longitudinal Laplacian montage. (a and c from Lagerlund TD. Digital tools for reviewing the electroencephalogram: montage reformatting, filtering, and principal component analysis. In: Lüders HO, Comair YG, eds. Epilepsy Surgery 2nd edn. Philadelphia: Lippincott Williams & Wilkins; 2001: 367–77. Used with permission.)



(c)

Figure 62.1 cont'd

can be approximated as the sum of the potentials at the four nearest neighbors to X minus 4 times the potential at X. To produce a derivation that has comparable amplitude and polarity to that of the original referentially recorded EEG, negative one-fourth of the Laplacian is usually calculated, which is the potential at X minus the average of the potentials at the four nearest neighbors to X. For example, at C_z the appropriate formula would be as follows:

C_z–Nav = (C_z–R)–0.25[(C_3–R)+(C_4–R)+(F_z–R)+(P_z–R)].

Here, R is the reference with respect to the measured potentials at C_z, C_3, C_4, F_z, and P_z. The notation 'Nav,' which stands for 'neighborhood average', indicates a fictitious reference electrode that is the average of the four neighboring electrodes.

In a Laplacian montage, as in a referential montage, the generator of a particular EEG waveform is generally located by the channel in which the amplitude of that waveform is maximal, rather than by a phase reversal as in a bipolar montage. However, a Laplacian montage is reference independent, like a bipolar montage. The most useful characteristic of a Laplacian montage is its ability to localize focal EEG features or waveforms more sharply than either referential or bipolar montages by removing unwanted contamination from signals originating at distant locations which are transmitted by volume conduction (the 'far-field' potential). Conversely, a Laplacian montage is a poor choice for examining generalized discharges. Figure 62.1 shows how the maximum of an interictal discharge can be most easily localized by using a Laplacian montage. The same discharge is shown as recorded from a C_z reference montage (Figure 62.1a), from an average reference montage (Figure 62.1b), and in a Laplacian montage (Figure 62.1c).

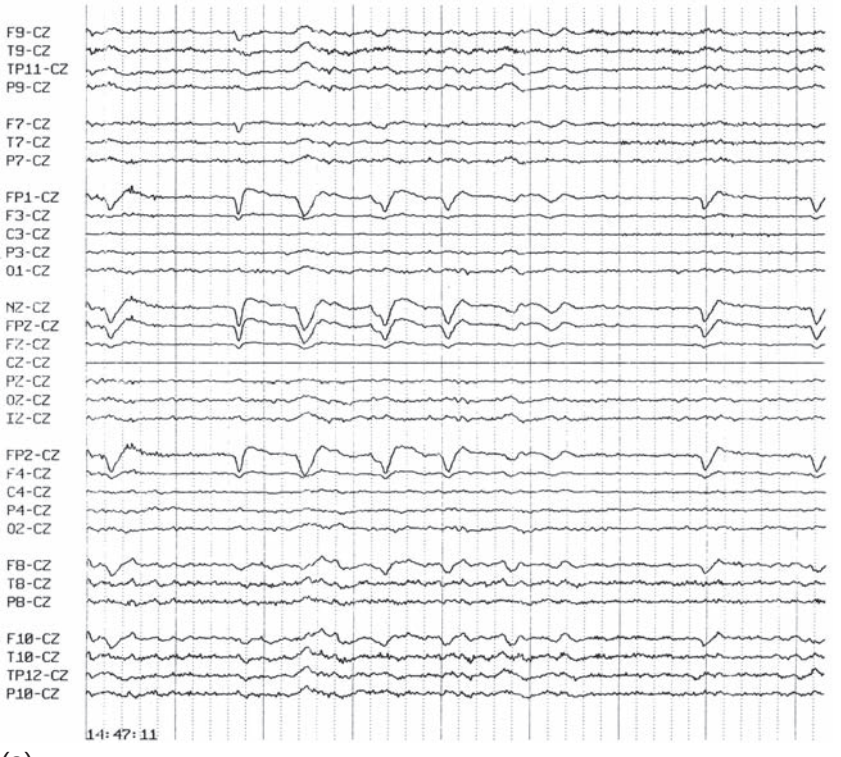
The neighborhood average approximation to the Laplacian is difficult to calculate at positions on the outskirts of the electrode array, where all four neighbors are not available. If three neighbors are available, an average of these (which may be denoted as 'N3' instead of 'Nav') may be used. Alternatively, additional electrodes[5] may be placed on the head in a circle passing through the nasion (N_z), inion (I_z), and the points just anterior to the tragus of the ears (T_9 and T_{10}) (Figure 62.5). These electrodes may be used in the calculation of the Laplacian at the frontopolar, lateral frontal, temporal, and occipital electrode positions and are also useful in their own right for recording ictal and interictal discharges originating in mesial and inferior temporal lobe structures (Figure 62.1c).

When the distances from an electrode to all of its neighbors are not equal, the neighborhood average must be modified by multiplying each potential in the average by the reciprocal of the distance. That is, each neighboring electrode potential is divided by the distance between that electrode and the center electrode; the results are summed, and from this sum the potential at the center electrode multiplied by the sum of the reciprocal distances is subtracted.[6,7] As noted earlier, negative one-fourth of the Laplacian is typically calculated, rather than the Laplacian itself. For example, if the F_{pz} and N_z electrodes are located at the positions shown in Figure 62.5, the appropriate formula would be as follows:

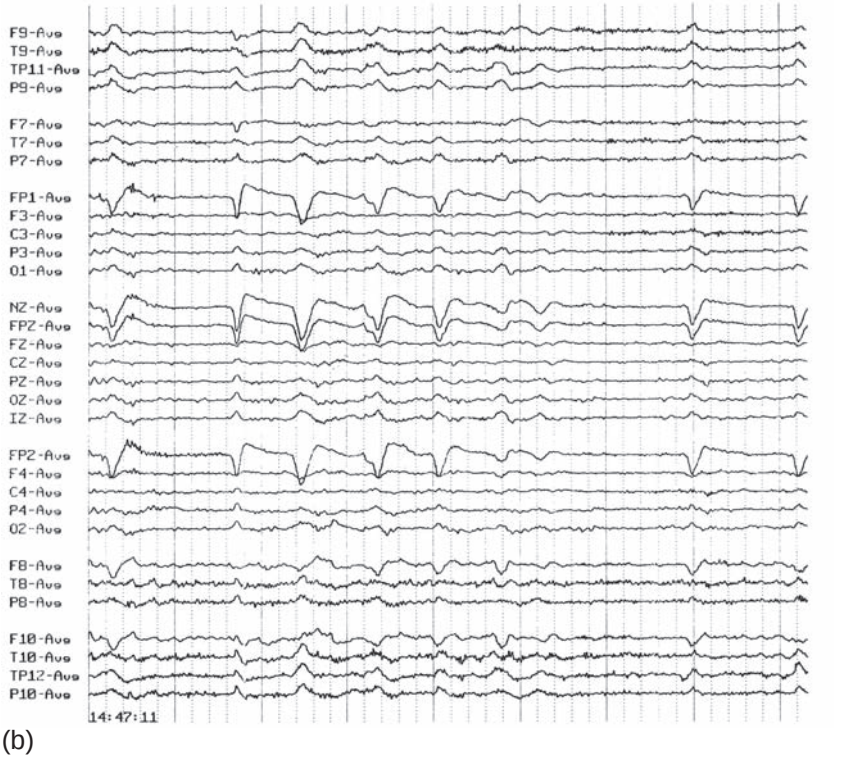
F_{pz}–Nav=0.875(F_{pz}–R)–0.25[(F_{p1}–R)+(F_{p2}–R)+(N_z–R)]–0.125(F_z–R)

because the distances from F_{pz} to F_{p1}, F_{p2}, or N_z are half the distance from F_{pz} to F_z in the 10–20 system.

The nearest-neighbor average approximation to the Laplacian is more accurate (closer to the true Laplacian, or



(a)



(b)

Figure 62.2 An electroencephalographic (EEG) recording showing eye blink artifacts. a, As recorded from a C_z reference. TP_{11} and TP_{12} are left and right mastoid electrodes. b, Reformatted to average reference.

radial current density) when the distance to the neighboring electrodes is small, but considerable error may be introduced with larger interelectrode spacing. The usual 6- to 7-cm interelectrode distances in the 10–20 system provide reasonable accuracy for most EEG potential distributions, but EEG features with complicated or rapidly varying spatial characteristics (such as relatively superficial tangentially oriented dipoles) can be misrepresented by an array of electrodes with standard (20%) spacing. This misrepresentation is an example of spatial aliasing, analogous to the aliasing in the time domain which occurs when a signal is sampled at too slow a rate to adequately represent its higher-frequency components. With spatial aliasing, the Laplacian montage calculated using the neighborhood average approximation may show artifactual phase reversals.

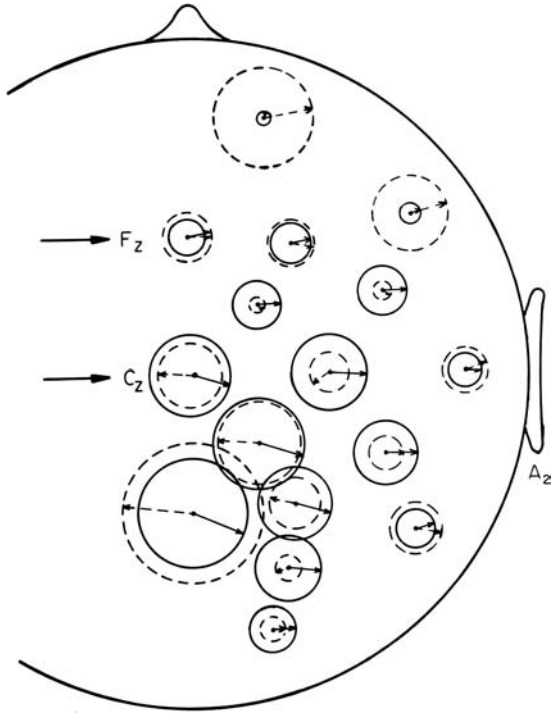


Figure 62.3 Electroencephalographic (EEG) phase-magnitude plots derived from a power spectral (Fourier) analysis of a normal waking EEG at 10.5 Hz (the spectral peak of the alpha rhythm). The radius of each circle is proportional to the amplitude at that location, and the angle of the arrow indicates phase. Solid and broken line plots correspond to an A_1 reference and average reference, respectively. (From Katznelson.[1] Used with permission.)

This occurs because the neighborhood average (which is contaminated by more distant, independent features rather than reflecting only the immediate surrounding potential), when subtracted from the central electrode potential to give the Laplacian, introduces the more distant activity reversed in phase. This problem may be seen in Laplacian derivations calculated with a 4-electrode average surround but occurs more frequently when only three electrodes are available for the surround (as for electrodes F_{p1}, F_{p2}, O_1, O_2, F_{pz}, and O_z when additional nasion and inion electrodes are not available).

More accurate approaches to calculating the Laplacian have been devised, but these involve more computation. One method is to calculate a neighborhood average for each electrode by using all of the available electrodes rather than just the four nearest neighbors, multiplying the potential at each electrode in the average by the inverse (or the square or cube) of the distance between that electrode and the central electrode.[8] This distance-weighted approach to the Laplacian is empirical but does sometimes eliminate or minimize the effects of spatial aliasing.

Other methods use an interpolation technique based on an analytic expression for the potential over the entire head surface that is fitted to the recorded potentials at each electrode position. The 'true' Laplacian can then be calculated from the analytic formula by differentiation. This type of approach not only allows a more accurate Laplacian to be calculated at the electrode locations, but also provides a means for generating interpolated data for drawing spatial maps of the potential or the Laplacian. Some of the interpolation techniques that can be used include two-dimensional rectangular surface splines,[9,10] three-dimensional rectangular splines projected onto a spherical surface[11,12] or ellipsoidal surface,[11] realistic scalp surface two-dimensional thin-plate splines,[13] spherical surface splines,[6,9,14] the spherical harmonic expansion,[7,15,16] or a single- or multidipole source model.[17]

Using matrices in reformatting montages

The mathematical concept of a matrix is a rectangular array of numbers (elements of the matrix) arranged in rows and columns. A matrix with only one column (or one row) is sometimes called a vector. Matrices with the same number of rows and columns can be added and subtracted by adding or subtracting corresponding elements, and a matrix can be multiplied by an ordinary number by multiplying each element by that number. Two matrices of appropriate dimensions can also be multiplied. Multiplication of a matrix **A** by **B** to give **C** involves multiplying successive elements in the *i*th row of **A** by corresponding elements in the *j*th column of **B** and summing the products to give the element in the *i*th row and the *j*th column of **C**. This definition of matrix multiplication turns out to be the most useful one, because each element of the product matrix is a linear combination of various elements of the original matrices.

If the set of measured potentials at each electrode position on the head at any instant of time t is represented as a 1-column matrix (a vector) called $\mathbf{e}(t)$, then the potentials in a reformatted montage at the same instant of time can be represented as another vector called $\mathbf{e}'(t)$. Then, it is possible to construct a montage-transformation matrix **S** such that $\mathbf{e}'(t) = \mathbf{S}\mathbf{e}(t)$; that is, the EEG data vector is reformatted to a new montage by multiplying it by the matrix **S**. Appropriate choices of the **S** matrix can be devised to reformat referential to referential, referential to bipolar, or referential to Laplacian montages, as well as to generate new channels by averaging subsets of electrodes or interpolating linearly to points between existing electrodes. Even the distance-weighted Laplacian calculation and many of the interpolation techniques used to calculate Laplacians can be expressed as a matrix multiplication. Many other types of computer processing of EEG data can be expressed in this manner as well, provided that the transformation performed on the EEG data is linear. For example, the spatial deconvolution technique[18] uses an approximate model of the volume-conductive properties of brain, skull, and scalp to estimate cortical surface potentials from recorded scalp surface potentials. Another example is the spatial filter described in Chapter 64.

The use of matrices for montage reformatting and related processing in computer-based EEG displays has several advantages. First, it provides a uniform framework by which the electroencephalographer may specify a type of reformatting or processing to be done. Each channel in the EEG display is calculated as a linear combination, with appropriate weighting coefficients (some of which may be zero), of all the recorded channels. For example, to calculate a bipolar derivation X_1–X_2, appropriate weights would be +1 for the X_1–R input channel, −1 for the X_2–R input channel, and 0 for the rest of the inputs. To calculate a nearest-neighbor approximation to a Laplacian of C_z, the required weights would be +1 for the C_z–R channel, −0.25 for the C_3–R, C_4–R, F_z–R, and P_z–R channels, and 0 for the rest.

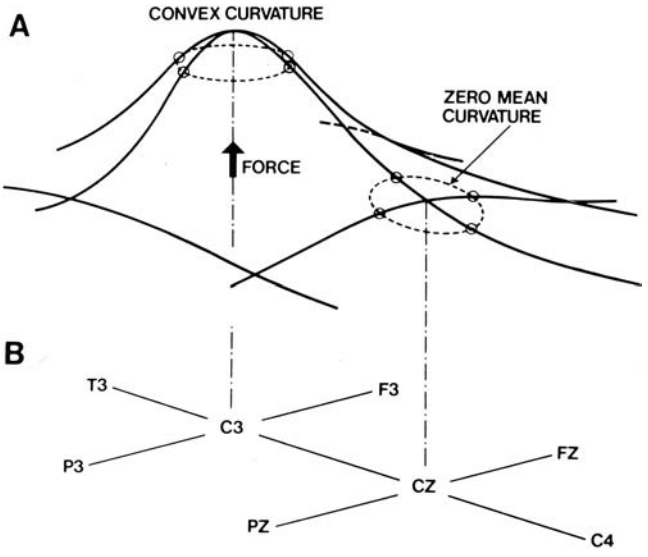


Figure 62.4 A plot of scalp potential $V(x, y)$ as a function of scalp position (x, y) resembles the profile of an elastic membrane displaced by a localized force. a, An upward force produces a bulge in an elastic membrane which extends over some distance. The mean curvature of the membrane in the x and y directions (Laplacian) is negative where the force acts but is zero at other locations because of cancellation between the positive (concave) curvature in the x direction and the negative (convex) curvature in the y direction (Laplace's theorem). Similarly, a cortical current source produces a peak in the scalp potential which spreads widely in all directions, but the Laplacian of the potential is nonzero only in the immediate vicinity of the source. b, The Laplacian at C_3 and C_z may be approximated from the potentials measured at an array of neighboring electrodes. (From Wallin and Stålberg.[4] Used with permission.)

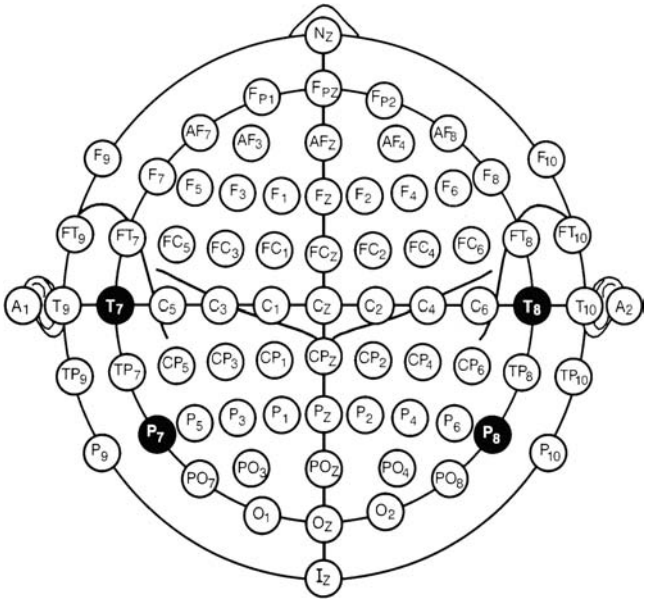


Figure 62.5 An extension of the 10–20 system of electroencephalographic electrode nomenclature. New electrodes with 10% spacing, including on the inferior circle passing through nasion and inion, are defined. (From Electrode Position Nomenclature Committee.[5] Used with permission.)

Second, use of matrices allows multiple successive transformations of the EEG to be performed in a single step, saving computer time by precalculating a single matrix that represents the combined transformations as a product of the matrices representing each successive transformation step. For example, if the matrix **B** transforms from a referential to a longitudinal bipolar montage and the matrix **A** transforms from a C_z reference to an average ear ($A_{1/2}$) reference montage, then the product matrix **BA** will first transform from a C_z to an $A_{1/2}$ reference and then from this to a bipolar montage. Of note, it can be shown by doing the multiplication that **BA** is equal to **B**, since it does not matter which referential montage one starts with when calculating a bipolar derivation; a bipolar montage is reference independent. As another example, suppose that matrix **B** transforms from a referential to a bipolar montage and matrix **S** performs spatial filtering of EEG recorded in that bipolar montage. Then, the matrix **A**=**SB** will, in one step, transform the referentially recorded EEG to a spatially filtered bipolar EEG.

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63 Automatic detection of epileptic spikes

P LeVan and J Gotman

Introduction

In addition to the paroxysmal bursts of electrical rhythmic activity that characterize seizures, the electroencephalogram (EEG) of epileptic patients commonly features abnormal interictal activity, mostly in the form of sharp transient spikes. An appropriate investigation of these interictal discharges is often critical for the diagnosis and evaluation of epileptic patients, providing valuable complementary localization information for candidates for epilepsy surgery. Quantification of the timing and amplitude of the spikes can be an important indicator of the brain area where the seizures originate.[1] The documentation of ictal and interictal activity is generally accomplished with long-term monitoring sessions that can last several days. This is necessary because the EEG of epileptic patients may potentially display several types of spikes or seizures originating from various locations. The occurrence of some of these spike or seizure types may be quite sporadic, thus requiring a lengthy monitoring session to record all the events of interest. Moreover, various analysis methods may necessitate the recording of a large number of spikes from the same type; for example, many source localization methods rely on the averaging of several spikes to obtain more accurate results.

While seizures are frequently accompanied by clinical manifestations, spikes are purely electrographic events that can only be identified by a careful review of the EEG recording. However, the review of a continuous recording lasting several days can be a tedious and expensive task. Despite the possibility of using computers to digitally display the EEG on screen at an accelerated speed, the examination of a 24-hour recording may still take a few hours. In the last several years, the development of automatic spike detection methods has greatly facilitated this process. This chapter will introduce some of these methods and evaluations of their performance. Difficulties and limitations associated with automatic spike detection will also be presented.

Recording interictal activity

The interictal activity specific to epilepsy consists of spikes, sharp waves, and bursts of spike-and-wave. Patients with epilepsy also have abnormalities of background, which can be analyzed by computer methods. Paroxysmal interictal activity occurs unpredictably and sometimes infrequently. To obtain a full documentation of the different types of abnormalities, the traditional short recording may not be sufficient. Long-term monitoring may be required, including periods of the different stages of sleep, which most often activates and modifies interictal patterns.[2] The reduction of antiepileptic drug (AED) doses, often done during long-term monitoring to precipitate seizures, also results indirectly in increased spiking; it has been shown that spikes are more frequent after seizures.[3–5] It is clear that complete review of recordings lasting days and nights is an awkward method to document interictal activity: automatic detection methods can be very helpful.

Past methods

The usual approach in early systems for automatic spike detection consisted of (a) selecting EEG sections lasting 1 or 2 minutes, free of artifacts and including a sufficient number of spikes; (b) devising a method for their detection; and (c) comparing results of automatic detection to what qualified electroencephalographers considered 'true' spikes. Details of the various detection methods have been reviewed extensively.[6] In general terms, these methods relied on one of two approaches: In the first, the EEG is broken down into elementary waves, and the method then attempts to identify waves having morphologic characteristics normally associated with spikes (amplitude, duration, sharpness). In the second, the EEG is analyzed to find statistically improbable events of short duration. With most methods, very acceptable performance was obtained, usually with 80–90% of 'true' spikes detected and a low rate of false-positive detection. Many publications ended with statements such as, 'As computers become more powerful and less expensive, practical implementation of this method will be simple.' Computers did in fact become more powerful and less expensive faster than anybody had expected, but most methods did not reach practical implementation. One major reason is that the detection problem became much more complex when longer sections were analyzed; artifacts and normal transients had to be included, and they caused numerous false detections. In addition, some methods were not readily adaptable to online analysis and were therefore of limited practical utility. For short recordings, human inspection generally performs sufficiently well, so that there is little use for spike detection in these cases. Automatic methods would thus be most useful for prolonged recordings. It should be noted, however, that perfect performance is unlikely to ever be obtained by automatic systems. After all, EEG experts also show a less than perfect sensitivity; there is some inherent

variability associated with the subjective interpretation of EEG records.[7] Ambiguous EEG transients may or may not be marked as spikes by different reviewers.

It should also be noted that many clinical applications do not require the identification of all the spikes present in a given recording. A representative sample of all types of spikes occurring in a patient's EEG is generally sufficient for diagnosis and evaluation purposes. Automatic spike detection methods can thus be most useful in the role of identifying all potentially interesting events in the EEG, so that a human reviewer can then select the most relevant ones.

Difficulties of the problem

The major difficulty of spike recognition methods is their reliance on a very incomplete definition of a spike. The definition quoted by many publications is 'a sharp transient, easily distinguishable from the background, having a duration of less than 70 ms for a spike and 70 to 200 ms for a sharp wave' (adapted from Chatrian *et al.*)[8] This definition is extremely incomplete, because it lacks features for differentiating transients with the same local morphology that are not spikes, such as eye blinks, vertex sharp waves, isolated alpha or spindle waves, electrode artifacts, and movement artifacts. Such transients are common during prolonged EEG recordings, when automatic spike detection is useful. Figure 63.1 shows a typical example of results from standard spike detection methods; genuine spikes are mixed with false detections caused by nonepileptiform transients.

Which characteristics allow a human interpreter to separate an epileptiform sharp wave from an eye blink, even though the waves themselves may have the same morphology and emerge from a similar background? These characteristics most likely relate to the context in which the waves appear; this context likely encompasses a much wider space and time than the background activity surrounding the spike. When interpreting a wave having the morphology of a spike, the human observer takes into account events in other channels (spatial context) and in earlier and later parts of the recording (temporal context), and even non-EEG information, such as the age or clinical state of the subject. Optimism about early detection methods was based on a failure to appreciate how much spike identification relies on context.

It must be noted that the problems discussed above do not affect the ability to detect most epileptiform spikes, but they result in a large number of false-positive detections. For this reason, it is possible to make practical use of an automatic spike detection method, as long as it is conceived as a method to detect a high proportion of the spikes along with a possibly large number of nonepileptiform transients, rather than as a method to detect only spikes. Such a practical implementation was made with the spike detection algorithms developed at the Montreal Neurological Institute.[9,10] Pietila *et al.*[11] presented a system including automatic segmentation of the EEG followed by feature extraction. Compared with Gotman's system, this system showed a higher sensitivity but a lower specificity.

Newer approaches

Artificial neural networks (ANNs) have become a popular method for pattern recognition, including spike detection. By being presented with a sufficiently large number of training examples comprising spike and nonspike data, the ANN can learn to recognize spikes from background EEG. A representative set of features characterizing the EEG needs to be specified in advance (e.g., amplitude, sharpness, etc.), but it is not necessary to explicitly describe the morphology of a spike. The ANN automatically determines which combinations of features are characteristic of spikes by adapting its output to reflect the training data. The performance of ANN methods depends on the selection of an appropriate set of features and on the use of a sufficiently large training set containing a wide variety of spike patterns. It is also necessary to specify a priori the structure of the ANN; large networks can handle complex classification tasks, but may risk overfitting the training data and thus be unable to generalize to other types of spikes. It is also very difficult to investigate the operation of a large ANN; the network essentially acts as a black box that outputs classification values depending on the features it receives as inputs. One of the earliest use of ANNs for spike recognition was reported by Gabor and Seyal,[12] who obtained a good performance but evaluated their method on a very small sample.

When designing a neural network method, it is crucial to select an appropriate set of features to use as inputs to the ANN. The relatively short duration of spikes offers the opportunity to use the raw EEG data points as network inputs, thus foregoing the extraction of features. Webber *et al.*[13] using a relatively small data set for evaluation, compared the use of the raw EEG to that of preprocessed variables (including width, sharpness, slope, and amplitude) in the ANN and concluded that a better performance was obtained by using the preprocessed parameters. Ozdamar and Kalayci[14] obtained good performance with an ANN trained on raw EEG, but Ko and Chung[15] revisited the data and suggested that the results were erroneous due to inappropriate data preparation.

When using raw EEG instead of preprocessed parameters, the ANN needs to recognize all combinations of the data that can be relevant for the classification task. A very complex ANN will thus be required to obtain a satisfactory performance. It is possible to simplify the problem by using only a small amount of raw EEG as input, as was done by Kurth *et al.*[16] who used a data window of only 100 ms. However, the use of such a short window prevents their method from taking into account characteristics such as the slow wave that often follows interictal spikes. The lack of temporal context makes it difficult to prevent false detections caused by transients whose morphologies are locally similar to spikes. Their results are difficult to compare with other methods because they only used a limited dataset for validation, and they had separate ANNs trained and tested individually on the same patients. To reduce the complexity of spike detectors using raw EEG as inputs, Acir and Guzelis[17] proposed a multistage approach where the data is first reduced by identifying nonstationary transients using an autoregressive linear predictor. Only the identified transients are then further examined, by using the raw signal in a support vector machine for classification as spike or nonspike. A sensitivity of 90.3% with 9.5% of false detections was reported after validation with 4.2 h of EEG from seven patients.

The use of extracted features instead of raw data can result in simpler classifiers for spike detection. Wilson *et al.*[18] designed several simple rules for spike detection, and then

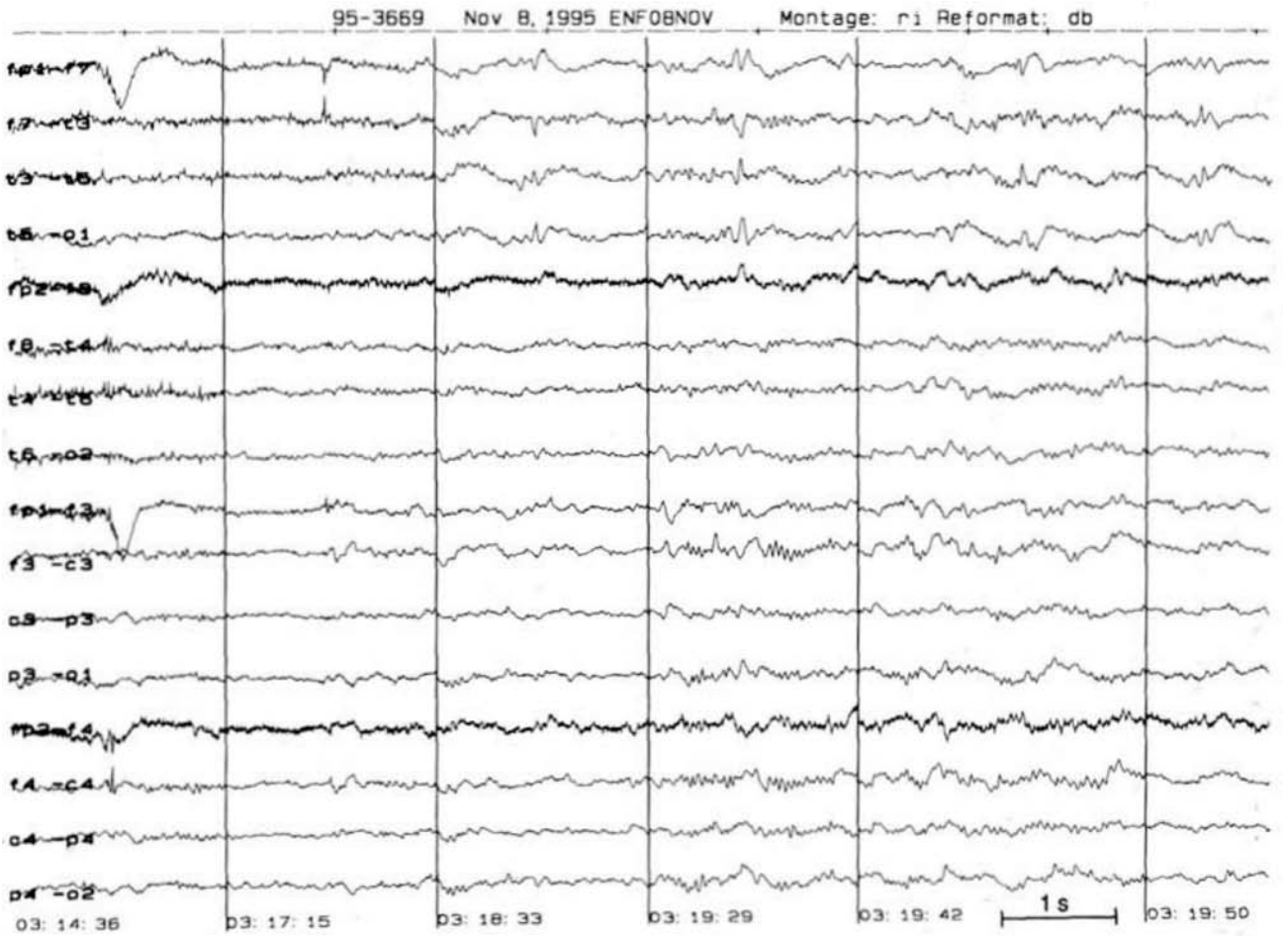

Figure 63.1 EEG sections recorded through automatic spike detection (method of Gotman.[10]) Vertical lines represent discontinuities in the recording; sections shown here represent automatically detected events during a 5-minute period (see time at the beginning of each section, at bottom of figure). The intervening EEG is not shown. The method enables detection of genuine spikes and sharp waves that are not very prominent (four rightmost sections). They are mixed with nonepileptiform transients (two leftmost sections). Even with false detections, the method provides valuable data reduction.

used multiple small ANNs to learn each rule. These rules included, for example, whether the spike was followed by a slow wave, or whether the spike stood out from local rhythmic activity. It was then easier to interpret how each small ANN implemented the individual rules. Wilson *et al.* also used a training set where EEG data epochs were marked with a probability value rather than a dichotomous classification as a spike or nonspike. This allowed the system to process ambiguous spikes without having to decide on a definitive classification. Hellmann[19] used cross-correlation to identify candidate spikes that resembled a given template, followed by classification using an ANN with various features, such as amplitude, slope, and timing information. The use of a template results in a system that is patient-specific and can only identify one type of spike at a time. Nevertheless, this method could be useful if the time of occurrence of known spike morphologies is desired, such as in functional imaging applications. In addition to ANNs, other data mining models can also be used to automatically generate classifiers for spike detection. Valenti *et al.*[20] implemented C4.5 decision trees and naïve Bayesian classifiers with good results, but EEGs from only three patients were used for training and validation.

There has been some interest recently in using wavelet analysis to identify interictal spikes in EEG records.[21–24] Wavelet features can be useful to describe the time and frequency relationships that exist between the spike and the following slow wave. These methods are well suited to the characterization of transient signals such as spikes.

Use of a broad context for spike detection

Another approach to improving detection performance is to make automatic methods operate more like humans, that is, to allow them to use information from a wide context. This is a simple concept but difficult to implement, because the context encompasses a very large amount of information and it must be decided which part of that information is relevant low spike detection. It is this selection process that humans do so well. Glover *et al.*[25] described a context-based system aimed largely at reducing false spike detections by making use of a wide spatial context; information from all EEG channels, as well as from electromyographic, electro-oculographic, and electrocardiographic channels is used to assess whether a transient in a particular channel is likely to be epileptiform.

An approach has been proposed by Gotman and Wang[26,27] in which a wide temporal and spatial context is used to decide on the nature of a sharp event. The method is termed state-dependent spike detection because criteria for spike detection are rendered dependent on the state of the EEG. Five states were defined in which spike detection should be performed

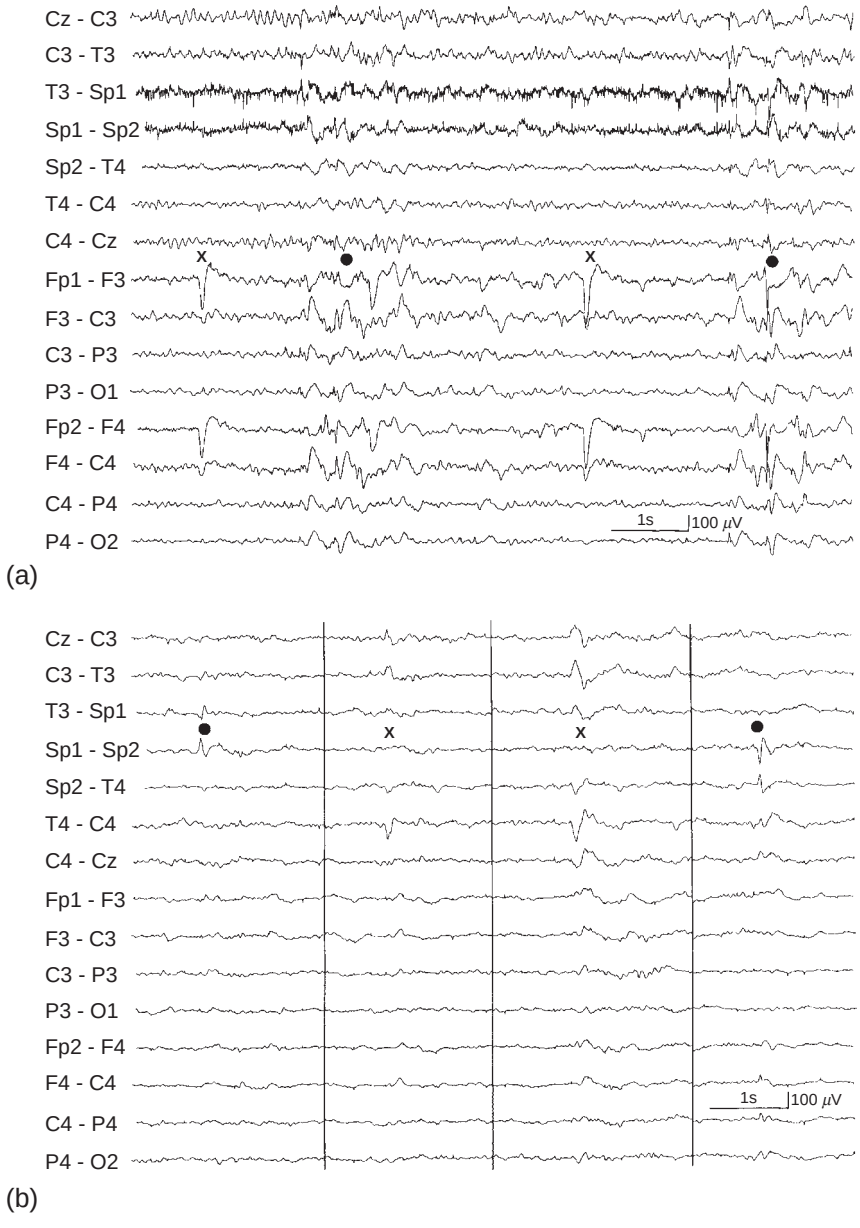

Figure 63.2 Use of spatial and temporal context in spike detection. Nonepileptiform transients are selectively rejected (rejected events marked with *x*). a: During active wakefulness, as determined by automatic state classification, waves having the morphology and distribution of eye blinks are eliminated. b: During phasic sleep, sharp waves having a maximum at the vertex are eliminated. Reproduced from Gotman and Wang.[27]

differently; active wakefulness, quiet wakefulness, desynchronized EEG, phasic EEG, and slow-wave EEG. In fact, in these different states it is not so much that spike detection has to be done differently, but rather that false detections have to be handled by different means. In active wakefulness, for instance, one must be particularly aware of symmetric frontal sharp waves that may be caused by eye blinks, whereas there is no such concern in the phasic EEG state; in that state, sharp waves maximal at the vertex are a problem (Figure. 63.2). The method was evaluated in 20 patients, each having close to 2 hours of EEG covering all states; it showed a reduction in false detection of 65% and an increased sensitivity of 35%, compared with the original method. Flanagan *et al.*[28] suggested an improvement to this method by using an equivalent current dipole to model each detection. The goodness of fit and the position of the dipole were then used as features to reject nonspike artifactual transients. It was not necessary to obtain an accurate localization of the spike generator; a simple dipole model provided sufficient information to reject many false detections. Using an independent data set of 20 patients to validate the method, Flanagan *et al.* reported a 53% decrease in false detections, while only removing 4.3% of true spike detections, compared to the original method of Gotman and Wang.[26,27]

Whether neural networks or more traditional methods are used, it is unlikely that local wave morphology is sufficient to differentiate epileptiform transients from other transients. Some form of context sensitivity appears necessary.

Conclusion

Automatic spike detection is a more difficult task than researchers in this area originally thought. An expert

electroencephalographer normally uses information from a wide spatial and temporal context to identify spikes during the visual review of an EEG recording. However, most computer methods are based on the analysis of a short window of EEG at a time. While powerful pattern recognition algorithms such as artificial neural network classifiers can achieve a very high sensitivity for spike detection, these methods also identify nonepileptiform transients whose morphologies are similar to spikes. Nevertheless, considerable data reduction can be achieved by automatic spike detection methods. False detections, if they are not too numerous, can be quickly removed during a manual review of the detected events. This procedure results in a significant economy of time, since the EEG record no longer needs to be reviewed in its entirety.

Recently, improvements in the performance of spike detection methods have been achieved by incorporating knowledge of a wider context, such as the state-dependent spike detection method mentioned above. This approach greatly reduced the amount of false detections by automatically rejecting artifacts or other nonspike transients that are known to occur during various clinical states. Further developments in this area will probably result in much better performance approaching that of humans. However, given that even human experts display some variability when marking spikes in EEG records, it is unlikely that perfect performance can be achieved by automatic systems. Nevertheless, these systems can still be extremely helpful when combined with a subsequent human validation of the detection results.

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64 Source localization of electroencephalography spikes

TN Townsend and JS Ebersole

Introduction

For generations electroencephalographers have used visual inspection of scalp-EEG traces in various montage combinations in order to localize the source of epileptogenic spike and seizure potentials. Most of these schemes were an attempt to identify the negative voltage field maximum. The assumption implicit in these efforts was that the cerebral source underlay the electrode(s) recording this field maximum. As we will discuss below, this assumption is only correct in limited circumstances. Now that EEG recording and display are done digitally, there are far easier and more accurate ways to determine location (size, shape, and temporal stability) of voltage field maxima. Analysis of this voltage topography over the entire head is the basis of all EEG source localization methods. We will review several of these methods and demonstrate how they can be used clinically to localize epileptogenic foci non-invasively.

Attributes of cerebral spike sources and effect of source attributes on resultant spike fields

There are several physical and functional attributes of cerebral sources that influence how an epileptic spike will appear when recorded by scalp EEG. If there is a consistent relationship between scalp-EEG spikes and their cerebral sources, we can use EEG analysis to localize the origin of this epileptic activity reliably. In this section we will describe, and explain the basis for, some of these relationships.

When synaptic excitation and/or inhibition occur in the brain, there is electrical current flow into and out of neurons. This leads to the generation of an electrical potential gradient in the extracellular space of the cortex. If a sufficient number of geometrically aligned neurons (such as pyramidal cells) are simultaneously active, their potentials can summate to create a field that is detectable by the EEG. The orientation of this extracellular voltage field is the same as the net orientation of the pyramidal cells and orthogonal to the surface of the cerebral cortex generating it (see Figure 64.1). Epileptic transients are usually negative when recorded from electrodes on and directly above the cortical surface. However, electrodes which are on the opposite side of the active cortex record a positive potential. Thus electrodes recording the positive potential can be located anatomically in the underlying white matter or even on the scalp on the opposite side of the head. This leads us to a key concept; scalp-EEG voltage fields have a dipolar configuration, i.e., two maxima, one negative and one positive.[1] Sometimes the second maximum is not recorded because it is located on the 'southern hemisphere' of the head where commonly few electrodes are located.

Physical factors of cerebral sources that influence the scalp EEG voltage field are location, orientation and surface area. The *location* of the generator will clearly influence the position of the scalp EEG voltage field, however cerebral *surface area* involved also plays an important role. If the surface area of the generator is too small, no scalp EEG field will be generated. A longstanding maxim is that at least 6 cm^2 of gyral cortex must be similarly active to produce a spontaneous scalp EEG field.[2,3] In a recent study a comparison was made between the surface areas of intracranial-EEG sources that had scalp-EEG spike correlates and those that did not. The investigators demonstrated that typically at least 10 cm^2 of active cerebral cortex was necessary to generate a scalp spike.[4] They also showed that the origin of prominent scalp EEG spikes is considerably larger, namely 20–30 cm^2.

Source orientation is another important factor influencing scalp-EEG voltage fields. It is the orientation of the cerebral source that determines the location of the voltage field maxima on the scalp. For example, a cerebral source that is oriented tangentially to the scalp will produce no potential directly above it. Instead, there will be two maxima located on either side of the source (see Figure 64.1). A radially oriented cerebral source, on the other hand, produces a scalp field maximum directly above it. Accordingly, sources located in midline interhemispheric and basal cortical regions produce tangential fields while lateral convexity sources yield radial fields.[1,3] It frequently occurs that opposite banks of a sulcus as well as gyral crowns are active simultaneously. The activity on opposing sulcal banks cancels each other, leaving only the radial field of gyri to be appreciated on the scalp-EEG.

Functional factors related to cerebral sources that influence scalp EEG voltage fields are amplitude, synchrony and propagation. The relative amplitude of a negative versus positive field maximum determines the cerebral source location. If one draws a 3D line connecting the negative and positive scalp field maxima, the source is located along this line (Figure 64.2). The relative amplitude of the negative to positive maxima determines the source's location along the line. For example, if the negative maximum is of relatively higher amplitude, the cerebral source is located closer to it. In addition, sources that are deep in the brain tend to produce larger fields with lower potential amplitudes and more shallow gradients. To the contrary,

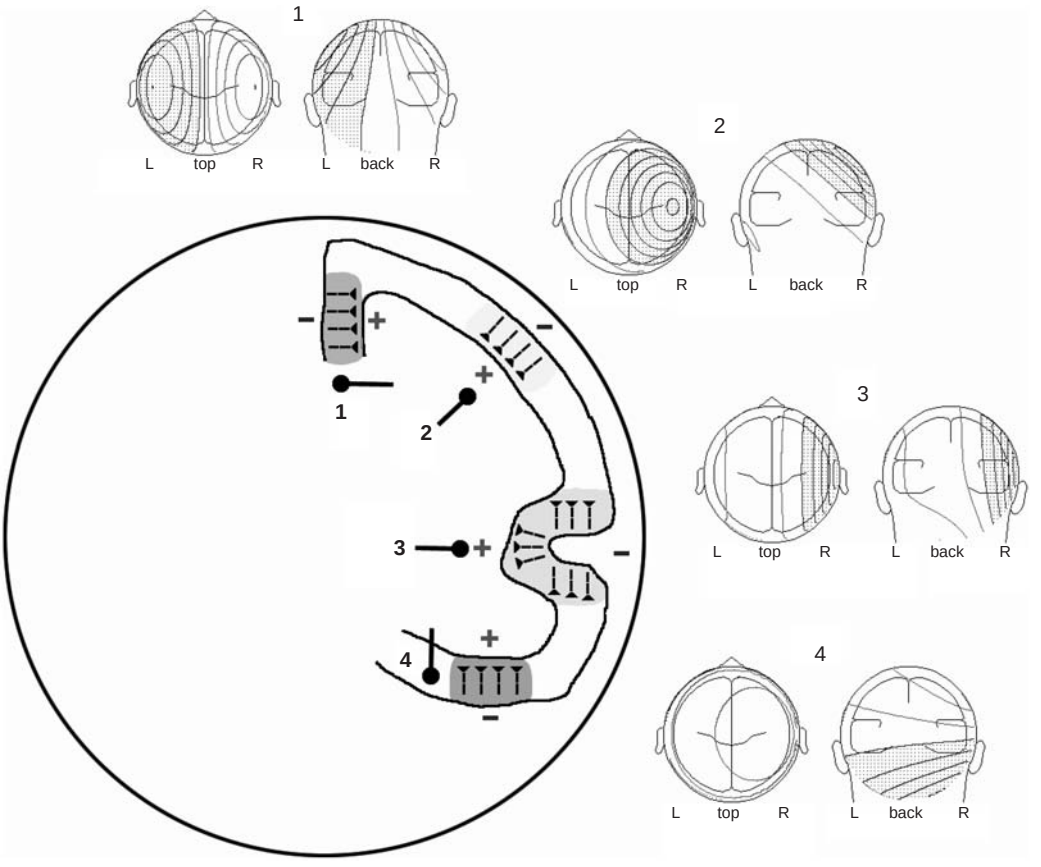

Figure 64.1 Example cortical sources 1–4 depicted in a schematic head/brain in coronal cross-section. Typical pyramidal cell orientations are shown for each source. Resultant scalp voltage field topography for superficial laminar depolarization is displayed above each source as isopotential lines of field strength (speckled=–negative, clear=positive). Typical dipoles modeling these sources are depicted beneath each source. Note that simple and more complex cortical convexity sources (1 and 2, respectively) produce radial fields with negative maxima directly above them and positive maxima contralaterally. Radial dipoles deep to the cortex model these sources. Interhemispheric source 3 and temporal base source 4 produce tangential fields with negative and positive maxima displaced on either side of the source and essentially no potential directly above them. Tangential dipoles deep to the cortex model these sources.

superficial sources yield small field of high amplitude and steep voltage gradients. Synchrony and propagation of cerebral sources also influence the scalp voltage field. Scalp spike EEG voltage fields that change in magnitude over time, but not in shape and orientation, are generated form discrete sources. A spike voltage field that changes in shape and location over time suggests a changing geometry in the cerebral source, which is most likely related to propagation.[3]

Spike voltage topography

Spike voltage topography has been used for 20 years as a method of analyzing EEG. The rationale for this, as discussed in the previous section, is that the *shape* of the voltage field, in addition to the location of the maxima and minima, provide valuable information for localizing its cerebral source. This information cannot be gleaned easily by mere visual inspection of the EEG. Most investigations in this field have focused on the analysis of temporal lobe epileptiform activity, in particular on the question of distinguishing spikes of basomesial versus lateral temporal origin by means of voltage topography. This can be difficult or impossible to do with visual inspection of the EEG.

The Cleveland Clinic Epilepsy group has used one form of spike voltage topography to analyze interictal activity in patients with fronto-temporal spikes. The location of the negative field where the spike voltage is at least 80% of the maximum amplitude recorded value is where importance is placed. If this maximum is situated over a unilateral fronto-temporal region and if there is a convergence of other data pointing to the same site, then surgery can be performed without invasive recording.[5,6]

Others have argued that this amplitude criterion is not likely to distinguish spikes from the baso-mesial versus lateral temporal regions because the negative maximum of both these groups of spikes is located in the same 'fronto-temporal region'.[7] Rather the voltage topography over the entire head is used to make this distinction. In one study,[7] 24 patients with fronto-temporal EEG spikes recorded during 2–7 days of continuous VEEG. Data were recorded to a common reference electrode on the mastoid located contralateral to the spike focus. Additional subtemporal electrodes were used ipsilateral to the focus. Eight of the patients underwent simultaneous scalp and subdural/strip/depth EEG recordings and scalp spikes from those recordings were also analyzed topographically. These results were compared with the location of the cerebral source as determined by invasive electrode recording. The investigators found that fronto-temporal spike voltage fields were much easier to assess using topographic maps than visual inspection of EEG traces. Furthermore, the topographic maps allowed investigators to distinguish two types of temporal spike voltage fields

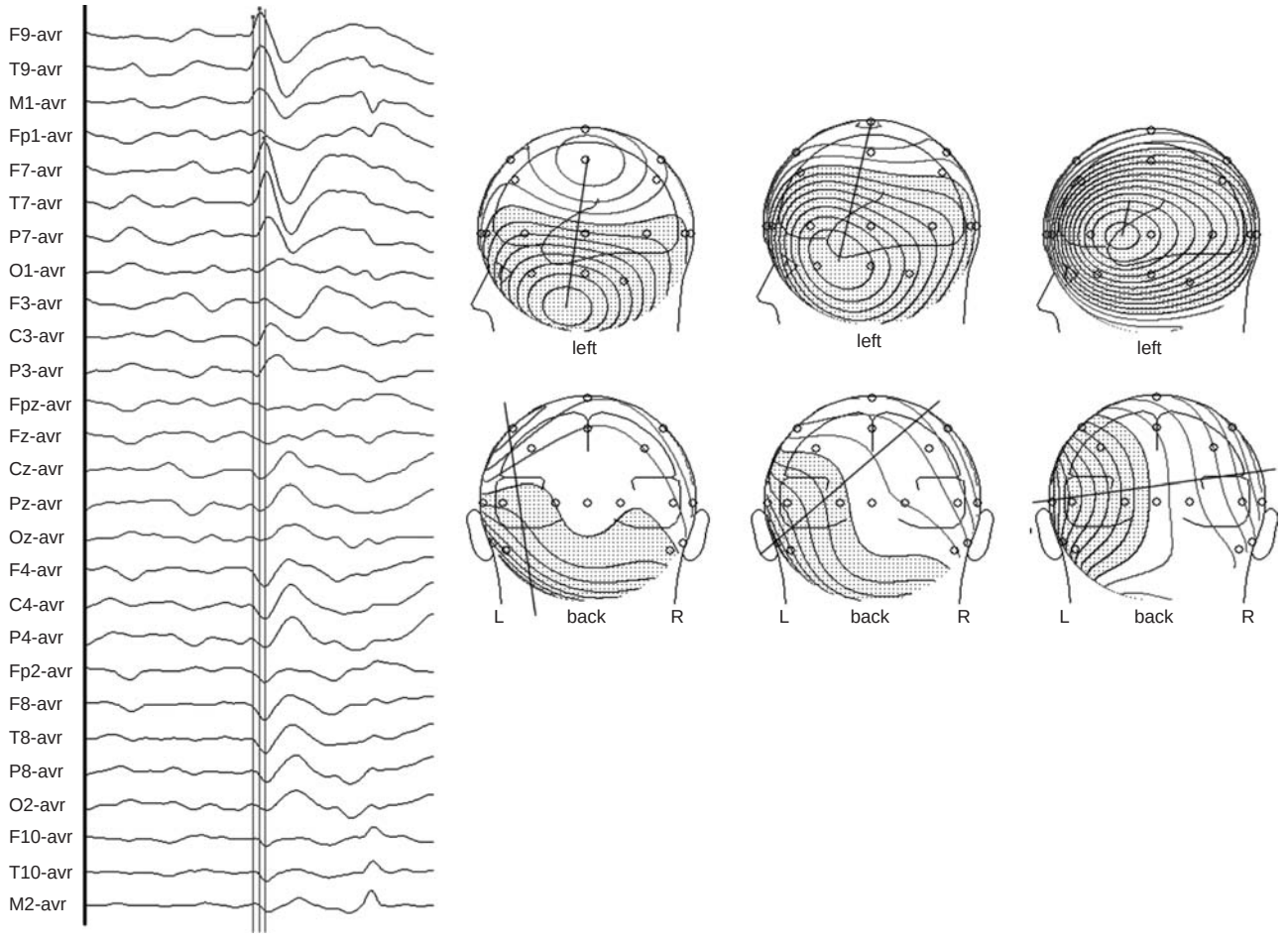

Figure 64.2 Scalp-EEG of a left temporal spike is shown at left. In this and subsequent figures scalp-EEG is illustrated in common average reference. Cursors mark three time points on the rising phase of this spike. Topographic maps depict the scalp voltage fields at these three points in isopotential lines. In this and subsequent figures voltage field negativity is shown as a speckled region and positivity as a clear region. A three-dimensional line defining field orientation connects the two maxima. Note that early in the spike the field is vertical and tangential. Later it is oblique, and at the spike peak the field is horizontal and radial. Such change in the location of voltage field maxima and field orientation are the result of spike propagation across basal and into lateral temporal cortex.

(Figure 64.3). Both had voltage fields with a maximum negativity around F8–T4. One spike group (Type 1) had a negative field that was relatively confined to the infero-lateral temporal region and had a steep voltage gradient. A distinct associated positive field was located in the contralateral vertex region. The second group of spikes (Type 2) had a negative field that was more diffuse and had more shallow voltage gradients. The associated positive field was of low voltage and located in the opposite temporal area. 13 patients (54%) had Type 1 spikes and nine patients (38%) had Type 2 spikes. Most of the patients had more than 80% of their spikes being of one type, although there were two patients (8%) with an equal number of Type 1 and 2 spikes. Out of the eight patients who underwent intracranial electrode monitoring, four had Type 1 and four had Type 2 spikes. Three of the four patients with Type 1 spikes had seizures arising from the medial temporal structures and one had frequent spiking from the prehippocampus and hippocampus. Of the patients with Type 2 spikes, intracranially recorded seizures were localized to nonmedial temporal or extratemporal regions. MRI studies of the patients with Type I spikes showed that nine out of 11 had hippocampal atrophy ipsilateral to the spikes. Eight of nine patients with Type 2 spikes had MRIs: one showed hippocampal atrophy but four had lesions in the nonmedial temporal lobe regions. The two patients who had equal numbers of Type 1 and 2 spikes had hippocampal atrophy. Investigators concluded that spike voltage topography can enhance the electroencephalographer's ability to understand the spatial characteristics of interictal spikes which are not readily appreciated using the usual bipolar EEG montages. It was noted by the investigators that although common average references can be used to enhance visual inspection of EEG spikes, topographic voltage display makes these features even more apparent.

Further studies have since demonstrated that the distinction between Type 1 versus Type 2 temporal lobe spikes is more complex. Voltage fields can evolve over time from Type 1 to 2 or vice versa. The location of the field maximum may also shift without a change in spike type. Accordingly, a thorough analysis requires the review of voltage field evolution, using a series of topographic maps, starting from the initial spike deflection to its peak. The earliest voltage fields are those most likely related to the cerebral source, rather than to propagated activity.[1]

Source modeling fundamentals

Three-dimensional EEG source localization is a logical extension of voltage topography. This form of EEG analysis could

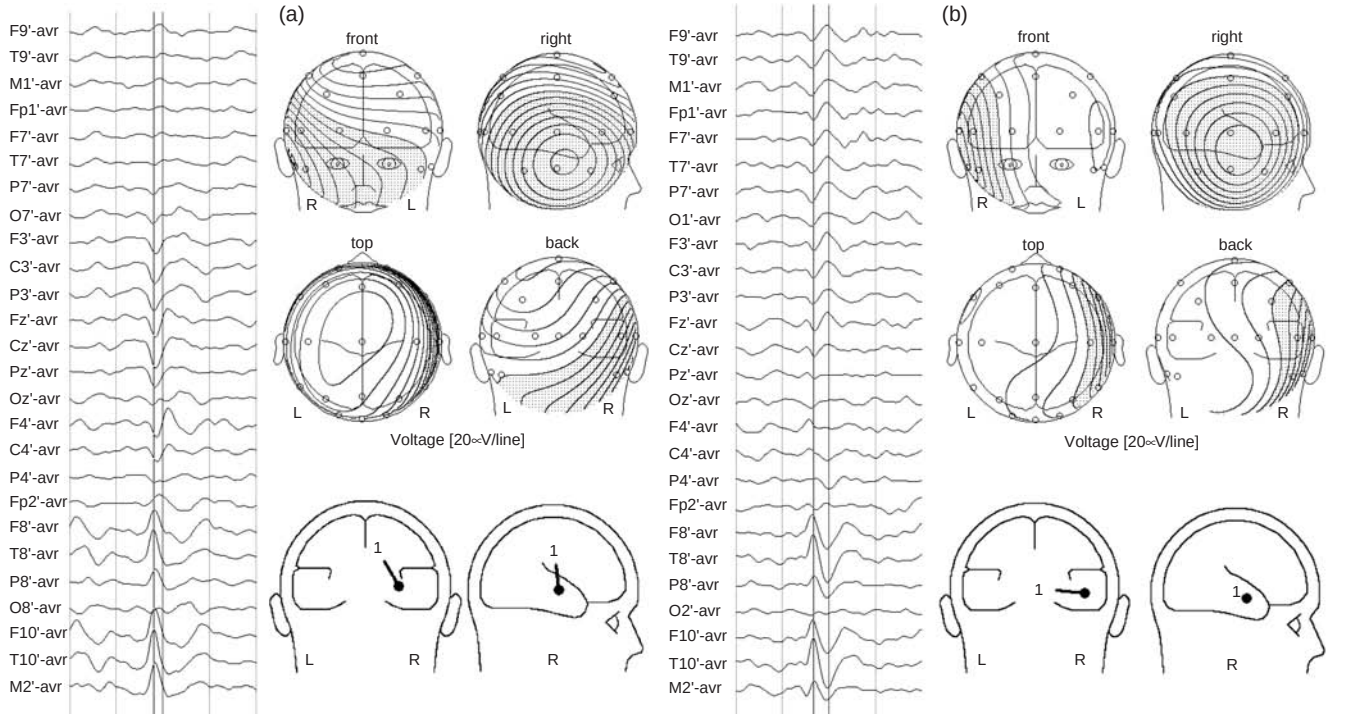

Figure 64.3 Scalp EEG, voltage fields, and single dipole models of (a) Type 1 and (b) Type 2 temporal lobe spikes.

help clinicians determine the location of foci for surgical resection and/or placement of invasive electrodes. Dipole modeling is one of the most well studied techniques for doing this type of 3D analysis of epileptiform EEG potentials.

Because scalp electrodes are relatively distant from the cortical neurons that generate the EEG, their cellular currents can be approximated as a dipole.[1] Dipole localization is based on the physical principles of volume conductor theory.[8–10] This states that for every dipolar source within a volume conductor, there can be only one resultant potential field distribution on the surface of the conductor. This is called the *forward solution*. The usual problem for the electroencephalographer is the opposite, namely determining the dipolar source given a measured EEG field. This is known as the *inverse solution*. Unlike the forward solution, there is no unique solution to the inverse problem because sources within a volume conductor can sum linearly to produce the resultant scalp field. As a result, many different source configurations can generate the same potential distribution across the scalp.[11]

In order to constrain the possible solutions to the inverse problem, certain a priori assumptions are usually made. These assumptions about the electromagnetic and geometric properties of the volume conductor are usually contained in the head models that are used in the inverse calculations and are expressed within what is called the *lead field matrix*.[11] To solve the inverse problem this lead field matrix is multiplied by an estimated dipolar source to produce a scalp potential distribution (i.e., the forward solution for that set of dipoles). This result is then compared with the actual scalp EEG topography. This is iteratively done with multiple possible dipole locations until the best match with the least unexplained variance is found (Figure 64.4).

An accurate head model is, therefore, essential for performing accurate dipole analysis. Several types exist, with the major distinction being between *spherical* and *realistic* head models. Spherical models, wherein the head is modeled as multiple concentric spheres, are the simplest. Accordingly, calculations solving the inverse problem are less complex and considerably faster. However, the head is not a sphere with uniform conductivity, so the accuracy of these models is questionable when precise localization of epileptic foci is the goal. An alternative is the *spherical head model with anatomic constraints* (SMAC). This method warps a given patient's 3D brain-MRI to a best fitting sphere. This allows for the simpler calculations of a spherical model, but provides more accurate results because one can exclude unlikely solutions (white matter etc.) from the possible solution space.[11,12]

However, it is now widely accepted that a *realistic* head model offers the most accurate dipole solutions for cerebral sources. The most popular of these is the BEM (boundary element method) (Figure 64.5). BEM models take into account the nonspherical shape of the head, particularly at the tissue boundaries between brain, skull and scalp.[13–16] The method achieves this by modeling these interfaces as triangular elements that form a mesh. The conductivity heterogeneities are then modeled by 'secondary dipoles' which are placed in the center and perpendicular to each surface element. The strength of the secondary dipoles is ultimately calculated in proportion to the conductivity difference and the electrical potentials, which are assumed to be constant over a particular surface element. Another realistic head model called the FEM (finite element method) tessellates the whole volume of head and allows investigators to consider individual anisotropic conductivities. For example, in contrast to the BEM, the FEM method can take skull defects into account instead of treating the skull as if it has uniform conductivity throughout its extent. However, full benefit the FEM head model has not been acheived because detailed information on tissue conductivities are not yet available.[11,15]

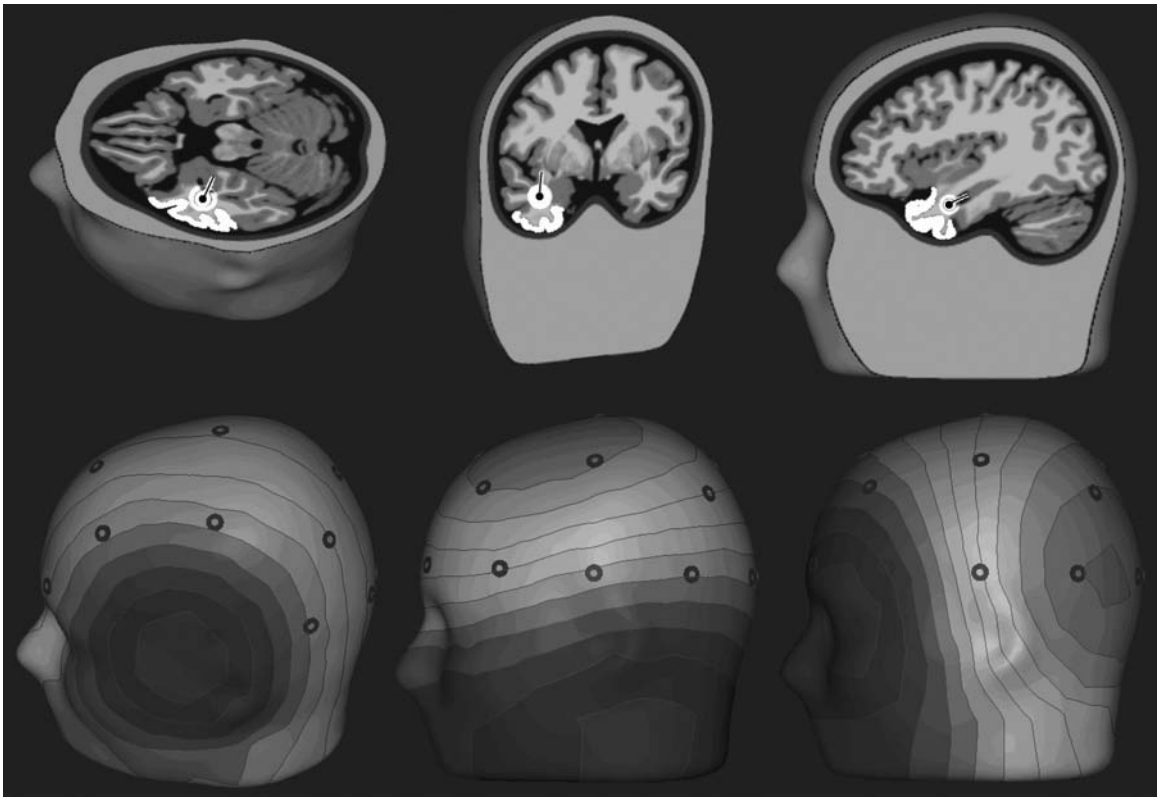

Figure 64.4 Illustrated as whitened cortex are the three most common types of temporal lobe spike sources, their resultant scalp voltage fields, and equivalent dipole models. Left to right: lateral temporal cortex, temporal base cortex, temporal tip cortex. Note that all the dipole models are located in temporal lobe white matter, but the dipole orientations differentiate the sources. Horizontal radial=lateral cortex source, vertical tangential=basal cortex source, horizontal AP tangential=tip cortex source. Note also that dipole orientation is orthogonal to the net orientation of the source cortex.

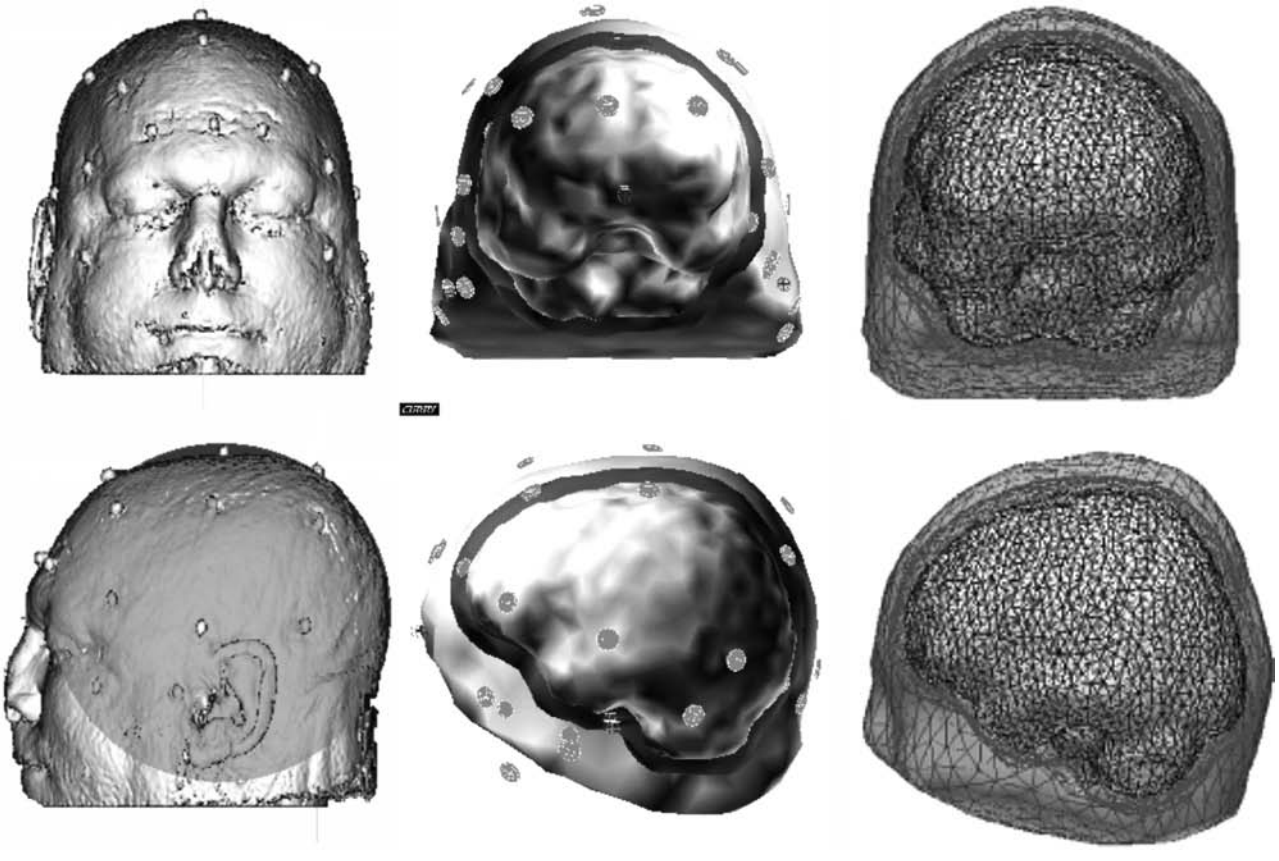

Figure 64.5 Middle: Realistic boundary element method (BEM) head model illustrating inner and outer surfaces of skull and scalp derived from 3D MRI reconstructions. Right: tessellation of these surfaces into a triangular mesh. Left: Shaded circle on patient's head depicts the typical shape of a spherical head model. Note the divergence of the brain and skull base from this spherical shape.

EEG recording and preprocessing for spike localization

In addition to the selection of a head model, there are several aspects of EEG recording and preprocessing that can improve the quality of the data for dipole modeling of spikes. A frequent question involves how many electrodes are necessary for accurate EEG dipole analysis? In the literature numbers from 21 to 123 can be found. However, if this technique is to achieve practical clinical application in the epilepsy monitoring unit, a balance needs to be struck between optimal high density sampling and the practicality of such electrode applications in a clinical setting.

Accurate source localization does require recording as much of the scalp voltage field as possible in a uniform fashion. Non-uniform sampling can distort results.[11] In the standard International 10–20 electrode distribution, the temporal electrode chain passes across the superior aspect of the temporal lobe. In order to sample the potential field from the basal frontal, temporal and occipital regions of the scalp, electrodes that lie inferior to this chain need to be used (Figure 64.6). Sphenoidal and/or 'anterior temporal' electrodes may be useful in this regard. However, for dipole modeling purposes, an entire chain of supplementary inferior temporal electrodes provides a better assessment of the voltage fields.[11,15] Recent investigations have demonstrated that not much is gained when using more than 40–64 electrodes when modeling spike or seizure potentials. This is because epileptic sources are spatially large (as compared to sensory evoked potentials, for example) and thus produce voltage fields of low spatial frequency.[15]

One can also co-register scalp EEG fields and dipole models to the patient's 3D MRI by digitizing the scalp electrodes and certain head landmark fiducials (such as nasion, preauricular points) (Figure 64.7).[15] Although standardized electrode co-ordinates can be used for screening purposes, the use of digitized, true 3D electrode locations will produce a more accurate dipole or other source model that is necessary when using the source analysis in a presurgical evaluation.

Because spikes commonly propagate into adjacent cortex, the voltage fields measured at progressively later latencies are less likely to reflect the initial source. For this reason the rising phase of the initial spike potential is considered the best time range for identifying the spike origin.[17] Unfortunately the signal-to-noise ratio is lower here than at the spike peak. Accordingly any source model is less accurate at this time. This limitation can be overcome by averaging multiple spike potentials.[18] This will reduce the background EEG noise and enhance the early spike signal in much the same way that sensory evoked potentials are made more evident. Unfortunately spikes cannot be triggered at will, nor are they necessarily all similar, as in the case of evoked potentials. Rather than simply rely on morphological similarity, it is best to review the voltage topography of each spike and average only those that have the same field shapes and temporal evolution.

Source models for spike localization

The most simple source localization model is the *single equivalent dipole*. This technique takes into account the entire EEG voltage field at a given time-point and then, using an iterative minimization technique, searches for a single dipole located in the head that best accounts for the given voltage field. This method is most appropriate for single and discrete sources that produce stable voltage fields showing little change shape or position over time (Figure 64.8).[15] If the source is more

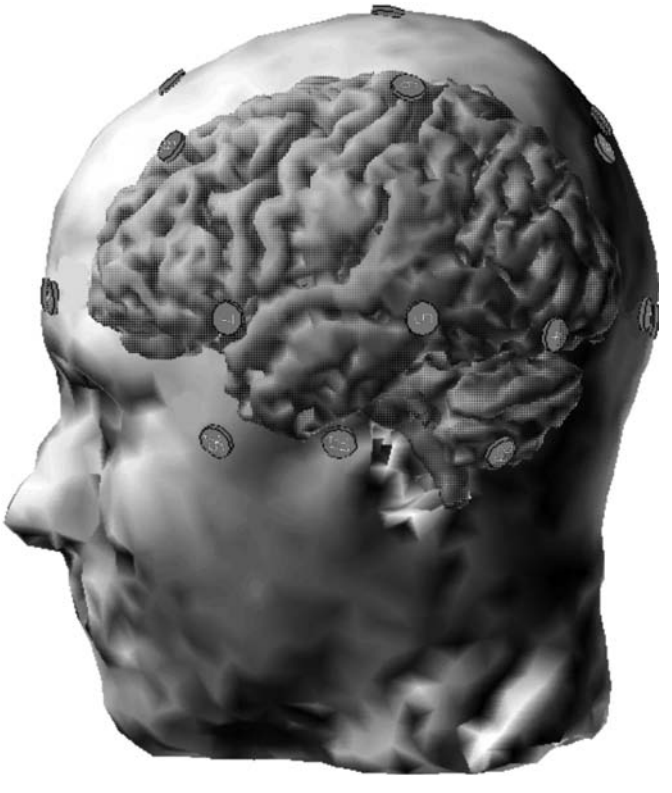

Figure 64.6 Standard International 10–20 scalp electrodes plus supplementary inferior temporal electrodes are displayed on a three dimensional MRI reconstruction of a brain and head. Note that the standard temporal chain of electrodes passes across the upper portion of the temporal lobe, while the supplementary inferior temporal chain of electrodes are in a better position to record from the base of the temporal lobe.

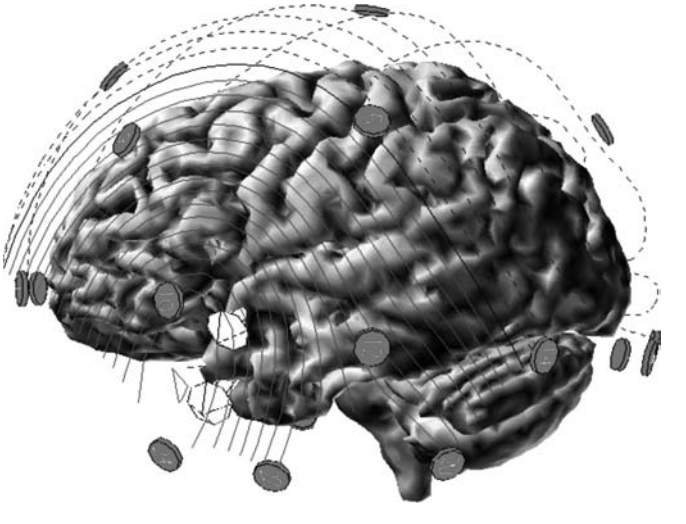

Figure 64.7 Three-dimensional co-registation of a patient's brain, scalp electrode positions, voltage field of a left temporal spike, and dipole models of that spike. Inverse solutions were obtained using a spherical head model (upper dipole) and a BEM realistic head model (lower dipole).

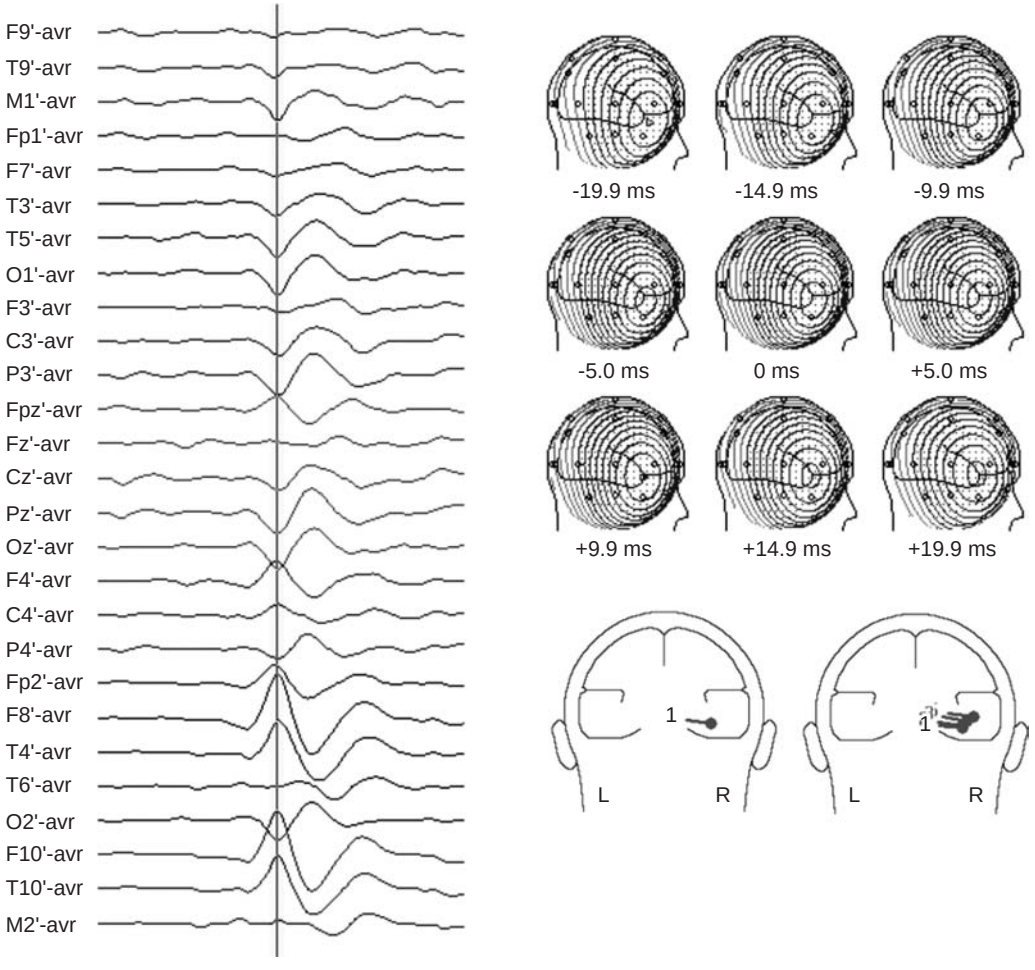

Figure 64.8 Scalp EEG of a right, Type 2 temporal spike. Cursor denotes 0 msec latency. Middle: sequential voltage topography of the spike. Note stable shape of the fields over 70 msec. Right: single and moving dipole models of the spike. Note that voltage field stability and tight cluster of the moving dipole model suggest a simple source for which a single dipole model is appropriate.

complex, this method will oversimplify what may be several spike sources into one single source, and no consideration will be given to possible spike propagation.[3]

It is possible to analyze more complex spikes and their propagation patterns using other methods, however. These models should be applied to spikes where voltage field topography reveals changing location and shape of maxima over time.[15] In the *single moving dipole model*, a separate dipole is calculated for each time point of interest during the spike. The dipole will change slightly in location and/or orientation with each alteration of the voltage field. Thus it will appear to 'move' (Figure 64.9).[3] This is reliable means of modeling propagation over time if it is unidirectional and if the propagation terminates before the original source repolarizes. Moving dipole models that spiral or make sudden changes in direction may be the result of multiple sources that are overlapping in time and space. In these cases, single dipole models are misleading and should not be used.[15]

Another method that takes into account overlapping activity from several cortical generators is the *spatiotemporal dipole model*.[3,19,20] In this method, dipoles are fixed in location and orientation but are permitted to vary in strength and polarity over time. Several dipoles may be active for each time point that is analyzed, but the goal is to obtaining the fewest number of fixed dipoles that can account for the voltage field both spatially and temporally.[3] These data allow the investigator to determine the best location for the spike source at a particular moment in time, as well as the relative strengths of contributing sources over the time period in question.

There is no single unique solution when solving for more than one dipole. In order to come up with the most realistic solution, one must use a priori knowledge about the most likely location of cerebral sources for a given EEG voltage field. For example, the early rising phase of an EEG spike and its corresponding voltage topography is most likely associated with a single cerebral source as opposed to later spike components when propagation could have occurred. Therefore, it is best to model early spike evolution with a single dipole first and then use additional dipoles for any unexplained residual fields. If a spike propagates, several dipoles may be necessary to account for the evolving voltage field produced by the contributions of multiple sources.[15]

The equivalent dipole is a useful model for the sources of EEG spikes, but it is not a very realistic one given that scalp-EEG spikes are produced by large areas of cortex being activated synchronously (6–10 cm^2). There is, however, a growing body of research concerning *extended* or *distributed source models*. These models are based on the reconstruction of brain electrical activity in a 3D grid or 2D surface of solution points. The number of possible source points is significantly greater than the number measurement points of the scalp, therefore the solution is highly underdetermined.

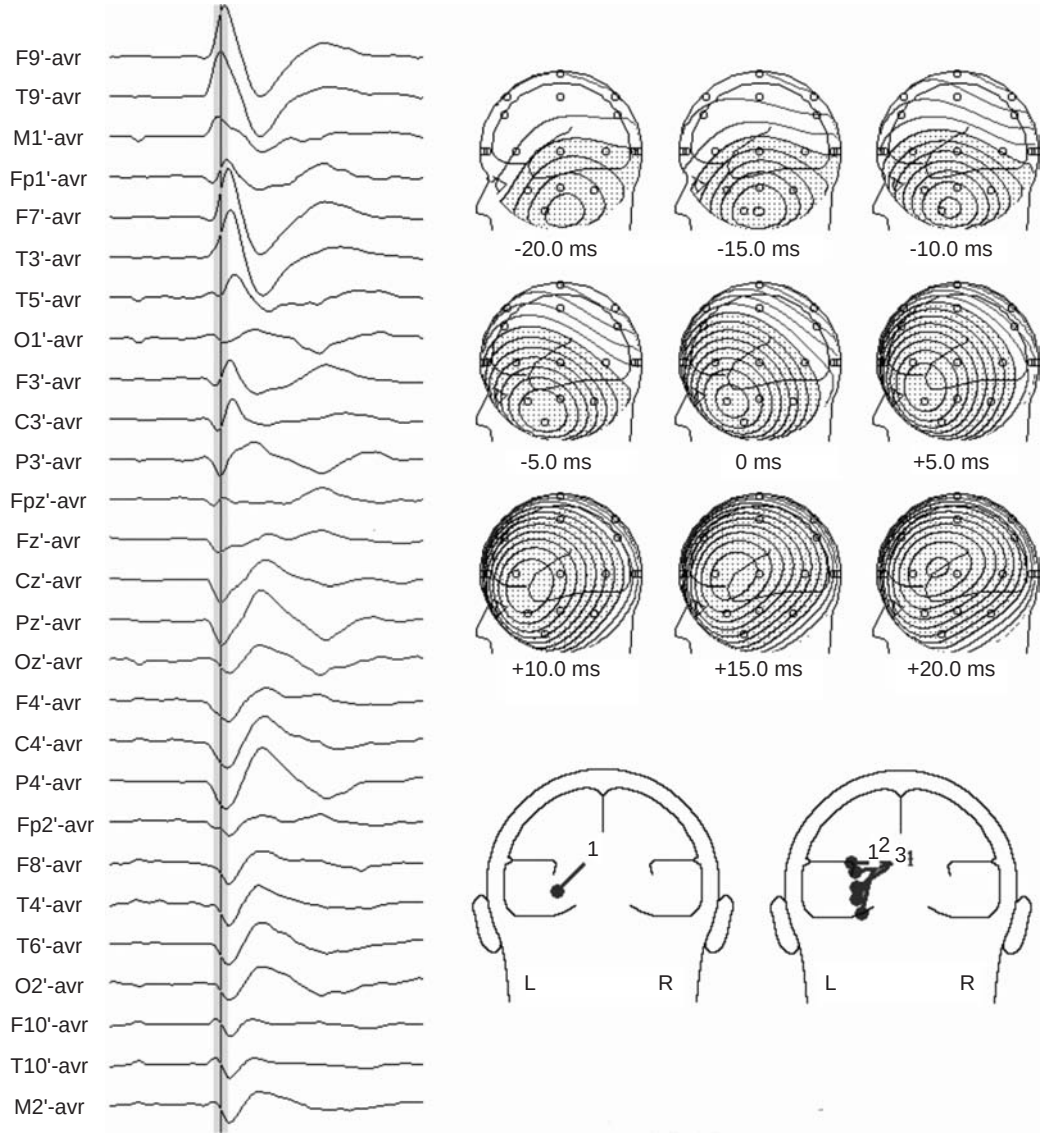

Figure 64.9 Scalp EEG of a left, Type 1 temporal spike. Cursor denotes 0 msec latency. Middle: progressive change in the sequential voltage topopraphy of the spike is evident. Right: single, moving dipole models of the spike. Single dipole at spike peak is oblique in orientation, while moving dipole model shows a progression in dipoles from vertical tangential to horizontal radial that suggests spike propagation.

However, in these exended models there are typically no assumptions about the numbers of possible points involved in the solution. The location of each potential solution point is fixed but their orientation and strengths can vary. The aim is to find a unique configuration of solution points that closely explains the surface EEG voltage field.[11] Certain assumptions are necessary in this type of analysis in order to restrict the number of possible solutions. These may involve pure mathematical constraints, while others take biophysical information into account. Ultimately the success of these models depends on how well the assumptions mirror reality.

Clinical application of source models

Most clinical investigations involving source localization of EEG spikes have studied temporal lobe epilepsy using dipole models. Recall that spike voltage topography in this patient population distinguished two types of spikes: *Type 1* generated by the medial/basal temporal lobe cortex and *Type 2* generated by lateral temporal lobe neocortex.[7] When modeled in 24 patients these two spike types differed significantly only in terms of dipole orientation.[7] The Type 1 spikes have a voltage field topography with basal temporal negativity and vertex positivity. Dipole models of these spikes had a mean dipole elevation of 42 degrees (SD5.0) from the horizontal. Type 2 spikes have voltage field topography showing negativity on the ipsilateral lateral temporal region and positivity on the opposite lateral temporal region. The mean dipole elevation was only 2 degrees (SD 10.0) for these spikes. Thus Type 1 spike dipoles are more vertical in orientation with both a tangential and radial component, whereas Type 2 spike dipoles are predominantly radial and horizontal.

When spike patterns were analyzed using methods that use multiple dipoles to model the spike activity, different patterns were observed between Type 1 and Type 2 spikes again. Type 1 spikes usually were best modeled by two dipoles, one vertical and tangential to lateral convexity and the other

horizontal and radial. Simultaneous intracranial recordings have subsequently validated the assumption that the vertical tangential dipole represents activity form the basal temporal region (not amygdala or hippocampus alone) while the horizontal radial dipole originates from the lateral temporal region.[21] Some spikes originating from basal temporal region had a propagation pattern to the temporal tip cortex. This activity is modeled best with dipoles that are horizontal in the antero-posterior direction, often in combination with another dipole of a different orientation. Finally, Type 2 spikes usually require only one horizontal radial dipole to model the activity even over time.[22]

Source localization has also been performed on extratemporal spikes. In particular, centro-temporal spikes in children with Benign Rolandic Epilepsy of Childhood (BREC) has been well studied. Initially spike voltage topography identified two spike categories: those with the typical horizontal dipole with a centro-temporal negative maximum and frontal positivity, and those spikes with atypical nondipolar complex voltage fields.[23] This study of 400 patients found that the atypical spikes were more likely to be found in BREC patients with other neurological abnormalities. Various subsequent studies using dipole analysis of rolandic spikes have had mixed results regarding confirmation of the existence of these two categories of spikes, and whether spike category correlates with different clinical phenotypes.[24–26] van der Meij, W. 2001.

There has also been some investigation of spikes in patients with focal cortical dysplasia.[18] In the this study nine patients (age 3.5–15.9 years) were studied who had focal epilepsy, an MRI suspicious for focal cortical dysplasia, and simultaneous MEG and EEG showing more than five EEG spikes. Single dipole analysis, as well as multiple dipole analysis of averaged spikes, were performed. A four-shell spherical head-model was used.

Ninty-three percent of the source models of the averaged and single EEG spikes localized to the MRI lesions. This source localization was validated by intracranial recordings in three of five of patients who underwent resective surgery. All had excellent outcomes. Two patients whose spike sources were localized outside the resected area had poor surgical outcomes.

Source model validation

Attempts have been made to test the reliability of dipole models of both interictal EEG spikes and of ictal EEG patterns. In two studies by Merlet and Gotman[27,28] spikes and seizures from previously recorded scalp-EEG data were compared to combined scalp and intracranial EEG data recorded at a later date. They confirmed that spikes recorded only from the hippocampus and/or amygdala on intracranial EEG were not recordable on scalp EEG. Larger areas of cortex must be involved in order to generate scalp spikes (estimate of around 6–8 cm^2). They also concluded that simple spikes were more reliably modeled by dipoles (error of about 1–2 cm) than complex propagating spikes or ictal patterns. The main limitation of these studies was that the dipole analysis was performed on spikes and seizures recorded in a prior EEG session with a 28-channel scalp data, whereas only 4–8 scalp electrodes were used during the intracranial EEG to attempt to identify the same spike populations as recorded earlier.

Lanz *et al.* have also published a study series using simultaneous scalp and intracranial EEG to confirm that dipole modeling can reliably distinguish spikes originating from the medial/basal temporal region versus the lateral temporal region.[29,30] As previously reported by Ebersole, orientation of the dipole was the major feature distinguishing the two groups of spikes in these studies as well.

In a recent study of 44 patients with partial epilepsy using 123 channels of EEG, Michel *et al.*[3] demonstrated that an extended source model (Epifocus) was capable of correct lobar localization in 90 % of patients and correct sublobar localization in 79%, when compared to the eventual surgical resection site that eliminated the patient's seizures. However optimal validation of dipole or other forms of source analysis as a reliable technique for localizing spike and seizure sources will require a prospective clinical trial using simultaneous scalp and intracranial EEG. The scalp data must be recorded with a sufficient number of electrodes to perform accurate dipole modeling, and the location of the intracranial electrodes must be co-registered with the patient's 3D MRI in order to localize the actual sources anatomically. This type of study has yet to be completed.

Conclusions

Dipole and other forms of source modeling provide a modern means for estimating the location and character of the cerebral source of epileptogenic spike and seizure potentials. These techniques are based on sound physiological and physical principles. They represent a more advanced and quantitative method of epileptogenic focus localization than that of simple visual inspection of EEG traces. However, it must be understood by those who use these techniques that the solutions are 'models' of the true sources. As such they must be interpreted with knowledge of the limitations of each technique. EEG source modeling is a worthy addition to, not a replacement for, other diagnostic procedures in the evaluation of epilepsy.

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65 Antiepileptic drug withdrawal in presurgical evaluation: advantages, disadvantages, and guidelines

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Introduction

For adequate presurgical evaluation, activation of the interictal epileptiform activity and access to ictal EEG and the clinical semiology of the patient's habitual seizures is still considered indispensable for an adequate lateralization and localization of the epileptogenic zone. The clinical aim and main advantage of antiepileptic drug (AED) withdrawal is to activate the interictal activity and to realize an increase of the natural frequency of the patient's seizures in order to reduce the duration of invasive or noninvasive long term EEG and video monitoring (LTM) for presurgical evaluation. Even for typical cases of mesial temporal lobe epilepsy (MTLE), most centers require at least three to five successfully recorded seizures. Less familiar forms of epilepsy, notably extratemporal seizure disorders, may require considerably more seizures for a reliable localization of the of the ictal onset zone and an estimate of the associated epileptogenic zone.[1–3] Long term EEG/CCTV procedures have implicit constraints on mobility and privacy which constitute a major burden for the patients. Moreover, LTM procedure is relatively labor intensive and expensive. Reducing LTM-time thus seems warranted and partial or total AED withdrawal is a generally accepted and widely applied method for this purpose.

However, the procedure is also associated with a potentially high number of disadvantages that may constitute health risks to the patient. Due to a lack of systematic data and a benefit-to-risk ratio analysis it is not clear if the advantages justify exposing the patient to the disadvantages. Although it is recommended that safety protocols should be used when withdrawing AEDs,[4–6] the available published[6] and anecdotal data suggests a lack of common practice, even within individual centers. This is not surprising, given the great heterogeneity in clinical material (type of epilepsy, lesions, etiologies, drug regimens) and local facilities.

In this chapter, the available literature will be summarized and analyzed. This will be complemented with the outcome of a survey concerning practice and experience with AED withdrawal for presurgical monitoring carried out in 37 European, NorthAmerican and Australian epilepsy centers (see acknowledgements). Some guidelines will be formulated which may further help to develop more generally applicable protocols for AED withdrawal procedures for presurgical monitoring.

Advantages: increased seizure frequency and reduction of monitoring time

AED withdrawal increases seizure frequency during AED tapering or while being effectively free of medication (AED serum level confirmed)[7–14] and generally shortens the total LTM recording time. This effect may vary between individual AEDs. The shortest reported average time for successful LTM in a group of patients with MTLE was 4.8 days.[15] Other studies reported average LTM periods ranging from 5.5–7.6 days.[16–19] All these studies are characterized by heterogeneity in patient population, etiology and method of AED withdrawal. No valid comparison is possible to identify any association between the method of AED withdrawal and the reported variations of LTM time and this is also corroborated by the outcome of our survey.

In general, AED withdrawal seems to be effective for seizure activation regardless of type of epilepsy, notably shortening the 'time to first seizure'.[6,7,12,15,17,20] Although extratemporal epilepsies show a stronger tendency to early seizures,[17,21,22] the total time needed to accomplish a successful recording did not differ significantly between the temporal and extratemporal groups, with exception of one study of 36 patients which suggested a slightly longer than necessary LTM time in temporal lobe epilepsy (TLE) patients.[17] Moreover, the reported frequency of the different seizure syndromes and types at home does not appear to predict the length of stay in the Epilepsy Monitoring Unit (EMU).[20] Obviously this situation will be different in childhood epilepsy syndromes with typically multiple seizures per day.

Other methods of activation do not appear to have the same rate of success. Neither sleep deprivation nor photic stimulation were effective in eliciting seizures during LTM.[4,23] Hyperventilation (HV) during LTM remains a matter of debate. Anecdotal evidence suggests its efficacy, and numerous centers, including our own, regularly apply HV during presurgical monitoring; published data however are equivocal. One study reports seizures elicited by HV when applied three times a day, for 5 minutes for multiple days in about 25% of patients, especially those with TLE.[(24)] Another found no effect of a single episode of HV for 5 minutes only.[25]

Medication withdrawal may enhance interictal abnormalities. Withdrawal of CBZ, VPA and PHT is associated with increased bursts of interictal epileptiform activity and slowing

in patients that also show an increased frequency of seizures. This advantage might be of limited value, because it is absent in patients that do not react to AED withdrawal with an increased frequency of seizures. Also, increased interictal spiking is reported to be widespread and not necessarily most prominent at the seizure focus. Promising effects are found with spectral analysis of the EEG: a greater absolute delta activity ipsilateral to the seizure focus less than 20 hours after a typical seizure may have lateralizing/localizing value.[26]

One minor advantage could be a positive effect of withdrawal on performance in neuropsychological tests. In a small group of patients with TLE, the lateralizing results of selective memory tests proved to be most reliable when testing was performed during the withdrawal period.[27] Language testing in patients with a probable left-sided TLE, however, should probably not be performed during AED withdrawal since in the same study these patients' test results deteriorated significantly.

Another minor advantage is the unexpected awareness of chronic unnoticed drug toxicity, because subtle symptoms disappear following AED withdrawal during LTM. This may lead to adaptation of the drug regimen by the treating physician.

Disadvantages: withdrawal symptoms, clustering of seizures, status epilepticus and associated morbidity

Possible disadvantages of AED withdrawal during LTM are medical complications directly or indirectly associated with pharmacokinetic changes or the occurrence of 'unwanted seizures or seizure events' certainly if resulting in prolonged LTM or time in hospital. 'Unwanted' seizures are generalized tonic-clonic seizures (GTCS), seizure clusters, and status epilepticus (SE), all of which are associated with complications such as trauma, systemic complications secondary to seizures (respiratory, cardiac or metabolic), psychiatric side effects (anxiety, mood disorders, insomnia, and psychosis), and possibly mortality.[4,5] Moreover, when measures have to be taken to intervene on these seizures; this prolongs, rather than shortens the duration of stay.[15] Seizures can also be considered 'unwanted' if they compromise the process of lateralizing and localizing in a technical sense.[14,18,28]

The AED withdrawal associated incidence of GTCS – single events or clusters – varies between 36 and 69%. These can be seizures that have been absent for years.[8,10,15] The rate of occurrence for clusters of CPS and/or secondary GTCS (sGTCS), sometimes called flurries of seizures or serial seizures), is also considerable and seems to increase in association with withdrawal. Reported incidence varied between 48 and 62%[8,11,15,29]compared to an incidence of seizure clustering in the home situation of only 30%.[20,30] For SE most reported incidence rates vary between 0 and 3%.[6,15,31] One remarkable study reports a rate of up to 50% of convulsive SE (convulsive activity for more than 30 minutes) in their patients.[28] This frequency appears extremely high, compared to other studies and our own and anecdotal experience; unfortunately, no specifics are provided concerning the method of AED withdrawal or the number of patients involved.

Unfortunately, the definitions for these types of seizures vary which makes it very difficult to determine specific complication rates. The current definitions for 'cluster' all include at least three seizures in a time span of 24 h, because seizures that occur within 8 h of a prior seizure are more likely to arise from a concordant focus than seizures more widely separated in time; this implies dependence and not randomness.[30] Some studies use even more strict definitions. One study made a distinction between GTCS only (three or more) and CPS only (five or more).[8,11,12] Another study made a distinction for a cluster of three or more seizures in 24 h versus a time span of 4 h.[6,13–15,28] Also for status epilepticus (SE) the definitions vary. Most studies that systematically looked at the relation between potential risk factors and SE used the old definition of clinically or electrographically ongoing signs or symptoms of ictal activity for 30 minutes or more. One study suggested that a definition of SE should also depend on seizure type and relate to abnormal duration of a seizure compared to the average duration of that type of seizure (e.g., CPS lasting 5 minutes or more).[6] This would be in accordance with more recent proposals for a new classification of SE[32] which, if applied in the LTM patients, probably would lead to higher reported incidence rates of SE, but not necessarily to higher rates of secondary morbidity.

The occurrence of 'unwanted seizures or seizure events' such as clustering or SE might be related to an increase of cortical excitability, as documented during the phase of CBZ or LTG withdrawal in healthy volunteers.[33] The observation of increased interdependence of seizures occurring less than 8 h separated from each other seems to indicate increased hyper excitability in certain focal areas.[30] Occurrence of seizure clustering at home is seen more often in patients with extratemporal epilepsy and possibly it is associated with a history of head trauma. Other risk factors are longer duration of the epilepsy and intractability.[13,30] Less conspicuous factors such as MTS on MRI, and possibly more than one seizure focus may also be associated with seizure clustering during LTM.[28] In their turn, seizure clustering both at home and during LTM constitutes a risk factor for SE.[13,14,28] It is claimed that the occurrence of clusters is predictable. With the use of the Poisson process it seems possible to make a calculation of the expected frequency which could be compared to the real seizure frequency at any time. Other approaches are also used. However, these methods depend very much on reliability of the patient reports/diaries. Also they become less accurate if the patient has a very high frequency of seizures, since the random fluctuations could be falsely identified as a cluster.[30]

Trauma, specified as fractures, joint dislocations, and external or internal soft-tissue injuries may result from seizures. Notably elderly patients appear prone to compression fractures of the vertebrae.[4] Trauma is not only associated with sGTCS, but also with partial seizures with violent automatisms such as particular forms of frontal seizures or due to accidents during seizures with impaired consciousness. Precise information on incidence rates is not available but the incidence appears very low. One report describes an unusual cluster of a humeral fracture in three patients within one year (3% of the annual recordings). All three had been treated with AEDs for many years; possibly this resulted in bone mineral loss which could explain the unusual incidence rate.[34]

In most EMUs specific care is taken to create a safe environment and to prevent the patient from becoming injured during a seizure. Alternatively, patients are kept in bed for most of the time and are always escorted by an experienced

paramedic when they have to move around the ward. Part of creating a safe environment involves the exclusive employment of experienced staff, i.e., nurses and technicians who are able to anticipate the occurrence of 'unwanted seizures' and take adequate action. More consistent use of a guideline or protocol might further reduce the risk of occurrence of these 'unwanted events'.[6]

Other possible complications are respiratory problems and renal insufficiency. The former predominantly appear to be associated with sGTCS in the elderly.[4] Moreover, they constitute the most serious possible complication of SE. Especially a long tonic phase in sGTCS and a protracted course of SE will cause hypoxia and respiratory acidosis. Renal insufficiency results from prolonged episodes of convulsive SE associated with excessive nephrotoxic release of myoglobine resulting from muscular damage.

Cardiac problems pose a potential problem that is associated with seizures and not with AED withdrawal per se. Risk groups are the elderly[4] and patients with known cardiac rhythmical problems, but one prospective study[35] reports it as a potentially more general problem. The authors detected postictal depression of the S-T segment in the ECG in 40% of 23 patients who exhibited an increased heart rate during the seizures. These changes indicate preischemic conditions in patients with epilepsy who were otherwise healthy. A possible relation with sudden unexplained death in epilepsy (SUDEP) was hypothesized. In this study the medication had been withdrawn from all patients, but there is no further discussion of the possible effects of medication withdrawal on heart function. The study does imply, however, that an increased seizure frequency carries an increased risk of cardiac complications in a potentially large group of patients.

Psychiatric and cognitive problems may present as a direct effect of medication withdrawal, independent of seizures or subsequent to seizures. Postictal psychosis (PIP) constitutes for about 25% of all cases of psychoses of epilepsy (POE). Although these are not necessarily directly drug related, they are seizure related and can occur with or be aggravated by clusters of seizures.[36] AED withdrawal for presurgical evaluation thus may provoke PIP. The incidence, following acute AED withdrawal, was reported to be up to 6.4%.[37] Commonly, ictus and PIP are separated by a lucid interval of 12 to 72 hours (mean 70 hours). Extratemporal foci are present in 30% of the affected patients (mainly frontal cortex or the cingulate gyrus).[36, 37] PIP has also been correlated with the presence of bilateral ictal and interictale foci in the limbic temporal region, hyperactivity in the bilateral frontal and temporal hyperactivity, as measured with HMPAO-SPECT,[38] with possible ictal activity in the left amygdala in one patient.[39] Other risk factors are lower verbal IQ, absence of febrile convulsions and absence of temporal mesial sclerosis. The most commonly reported psychiatric disturbances associated with AED withdrawal were depression and anxiety and then psychosis (PIP). A history of psychiatric problems is a risk factor for worsening of PIP and other postictal psychiatric complaints.[37, 40]

Interictal psychosis which represents approximately 9% of all cases of POE[36] is a persistent state not associated with ictal events; de novo transient interictal psychosis, provoked by AED withdrawal (VGB) has been described.[41] In the rare case that AED withdrawal and LTM would be performed in patients with active psychosis medication, specific complications can arise when they are treated with antipsychotic drugs (AP), such as clozapine, resperidone, olanzapine, chlorpromazine, thioridazine and also haloperidol, and when carbamazepine (CBZ) is reinstituted. CBZ can reduce serum levels of APs by as much as 60%.[36]

Mortality during LTM for presurgical evaluation has not been officially reported, not even in studies that specifically deal with mortality incidence in epilepsy surgery populations.[42–44] Incidence of mortality in patients who are evaluated and operated is 2.4/1000 person-years which is less than half the incidence of SUDEP in patients who, following evaluation, are rejected for surgery (6.3/1000 person-years).[44]

Nevertheless, one has to acknowledge that the LTM setting with AED withdrawal produces a situation in which reported risk factors pertaining to SUDEP may be introduced or provoked. High seizure frequency, polytherapy with AEDs, and (frequent) changes of AED doses have all been shown to increase the risk of SUDEP.[45] As mentioned earlier, seizures that are accompanied by an increased heart rate may also be followed by early signs of cardiac ischemia.[35] CBZ withdrawal has been associated with abnormal shift of the sympothovagal balance toward sympathetic activation during sleep; this could be a predisposing factor to SUDEP in the presence of seizure induced hypoxia.[46]

Although SE in general is associated with a high rate of mortality, this holds true predominantly for patients with acute encephalopathy. Patients, selected for presurgical evaluation do not usually have severe underlying encephalopathy, with the exception of children with catastrophical epilepsy (but in this group AED withdrawal usually is not indicated). Moreover, LTM provides conditions that allow early detection of SE which is why treatment is usually started in an early phase with a high rate of success. These two factors minimize the risk of mortality due to SE; given the overall low incidence of reported SE during LTM with AED withdrawal, the risk of death, due to SE during LTM appears negligible.

Aside from these physical risks, one has to consider the risk of attempted suicide. Suicide risk in the general epilepsy population is five- to ninefold higher than in the general population.[40] After withdrawal of medication, patients may show symptoms usually associated with increased suicidal risk (suicidal ideation, self-deprecation, hopelessness, and guilt). There are no reports of actual attempted suicides. However, should these symptoms be not acted upon, they could present a risk, especially in patients with psychiatric symptoms that are aggravated by a high frequency of seizures.[40]

Withdrawal of medication can result in the 'drug holiday' phenomenon.[47] Also in the clinical setting, of this type of recording this could be mistaken for an improvement of seizure frequency. In a prospective study, medication was withdrawn from 82% of 60 patients of whom 92% had partial epilepsy. Especially in the patients that used CBZ or PHT before and after recording, the lag time between discharge following LTM and the first extramural seizure was increased compared to the normal inter seizure intervals. Moreover, the time to first seizure increased with longer LTM 'off medication time'. Although hospitalization in itself is known to change seizure frequency independent of changes in AEDs, the drug-specific changes (CBZ and PHT compared to other AEDs that were withdrawn without effect), still indicate an effect of withdrawal.[47,48]

Drug specific advantages and disadvantages as reported in literature and the survey

Acute drug withdrawal within the setting of LTM is different than the more gradual drug withdrawal in general practice. This part of the review is also based on a very specific literature search for complications that arose from AED withdrawal in the setting of presurgical evaluation and thus is far from comprehensive regarding all possible drug withdrawal effects. The phase of withdrawal is usually defined as the first four or five half-life times of the drug that is withdrawn. Most authors who report on drug characteristics during acute AED withdrawal included a baseline phase (before withdrawal), a withdrawal phase, and the phase where serum levels of the drug are 'subtherapeutical' or undetectable. The term 'withdrawal symptoms' commonly does not refer to seizures, but more to other negative physical or mental effects.

Carbamazepine withdrawal increases the frequency of CPS both in the withdrawal phase and thereafter. In the withdrawal phase it is associated with clustering of CPS, sGTCS and isolated sGTCS; the occurrence of sGTCS in this phase was associated with 'fast withdrawal'. After this phase sGTCS were reported, but not clusters.[7,11,12,15,17,19,49–51] A shift towards sympathetic activation of the cardiac sympathovagal balance during sleep has been reported.[46] Withdrawal symptoms would be expected to be similar to those of tricyclic antidepressants, because of the similar chemical structure, but in one study where CBZ was withdrawn slowly (fastest rate 200 mg/2 days) these symptoms did not occur.[49] Fast withdrawal of CBZ did result in mood changes, notably anxiety.[52]

Clonazepam withdrawal has been associated with *de novo* interictal psychosis, interpreted as a withdrawal syndrome.[39,53] In both studies the drug had been acutely withdrawn. The symptoms were dysphoria, irritability, aggressiveness, anxiety, and hallucinations. Another withdrawal effect that has been described is delirium with catatonic features. This was associated not only with Clonazepam, but also with Clorazepate dipotassium.[54]

Lamotrigine (LTE) withdrawal increases the frequency, duration and severity of CPS during the withdrawal phase, according to one study with quick withdrawal (in 3 days to zero). For sGTCS there was a change in successive phases with aggravation and marked prolongation of the clonic phase rather than the tonic phase during withdrawal and of the tonic phase during the drug free period. The frequency of sGTCS increased only in patients who used CBZ in addition to LTG.[51]

Phenobarbital, when withdrawn quickly, increases the frequency of CPS both during the withdrawal phase and in the drug-free period. The critical serum level was reported to be 20–15 mg/l. The drug reportedly also caused first ever clusters of CPS or sGTCS.[3,7,15,55] Moreover, barbiturate withdrawal may result in nonconvulsive status epilepticus (NCSE).[56] If the drug is withdrawn slowly then withdrawal seizures probably do not occur.[7] Phenobarbital withdrawal has been associated with unexpected CPS that seemed to originate from outside the expected target area. Possibly these secondary localizations represent latent onset zones in patients with multifocal localization-related epilepsy. In one case surgery with resection of the target area yielded poor results, despite the unexpected CPS.[7]

Primidone is associated with an increased frequency of CPS in both the withdrawal phase and the drug-free phase. In the withdrawal phase it may provoke sGTCS.[7,8]

Phenytoin was associated with an increase in CPS and sGTCS during withdrawal and the drug-free phase. However, one study mentioned that this increase occurred only after 10 days counting from the moment where the serum levels were measured to be undetectable.[7–9]

Sodium valproic acid has an anticonvulsant effect that outlasts its measurable presence in the serum. In the drug-free phase it can cause an increased duration of CPS and also an increased frequency of hypermotor seizure symptoms.[19]

One respondent to our survey reported psychosis following withdrawal of Vigabatrine (VGB), a drug otherwise associated with psychosis notably following starting, not withdrawal.[41]

Results of the survey

We distributed a survey among colleague epilepsy centers while in the process of improving our own safety protocols, inquiring into their AED withdrawal procedures for presurgical monitoring, use of protocols, results and possible unwarranted experiences. The questions were simple and not formulated in the context of a scientific project. The answers obtained from 37 of 110 centers that were addressed, however, add to the limited published data and thus are included in this overview.

The more general data that pertain to the strategy of withdrawal are listed in Table 65.1 Most centers do withdraw medication in most patients. Usually there is no AED-withdrawal-specific medical emergency or calamity protocol. AED withdrawal is usually begun at, or right after, start of the recording procedure, less frequently between admission and beginning of the recording, and hardly ever in an outpatient setting. AEDs are usually withdrawn one at a time and at a gradual rate, usually to half or one-quarter of the daily dose. Most responders indicate that withdrawal rates are drug dependent and the following factors could change standard strategies: reported seizure frequency, seizure type, and history of SE. History of PIP, physical/neurological status, age, and invasive recording were deemed less important factors. A large number of centers (50%) agreed that BDZs and barbiturates are drugs that should not be tapered. A few centers, however, recommended slow tapering or preclinical tapering and some of them even listed these drugs as eligible for a full stop.

We specifically inquired about the occurrence of complications: SE, PIP, mortality, and 'other'. From the data we received, it was usually possible to approximate incidence rates. The incidence rate for SE ranged from 0–2% in 31 (out of 37) centers who responded to this item (0% for nine centers (29%), 2% for three centers (10%), and ranging around the mode of 1% for the others). A higher incidence rate is found in some centers that record invasively with subdural grids: in one center four out of 24 grid-patients needed intervention for 'probable SE' (17%). The rates for CSE (convulsive SE) only are lower. Only some centers responded with total rates for all types of SE; on follow-up inquiry usually their cases were evenly distributed between NCSE and CSE. We did not inquire about the exact definitions used to establish a case of SE.

Table 65.1 General preferences in methods of withdrawal in 37 centers worldwide

Do you withdraw	Always; mostly; occasionally; never	3%; 62%; 35%; 0%
Protocol present	Yes; no	19%; 81%
Preclinically/outpatient	Always; mostly; occasionally; never	0%; 11%; 38%; 51%
Clinically before recording	Always; mostly; occasionally; never	6%; 29%; 43%; 23%
Clinically during recording	Always; mostly; occasionally; never	19%; 56%; 25%; 0%
If polytherapy; how	One AED; more AEDs; all; varies	54%; 27%; 5%; 14%
Rate of withdrawal	Gradually; direct to full stop; varies	82%; 12%; 6%
Max dose reduction	¼; ½; ¾; full/varies	6%; 42%; 31%; 22%
Depending on AED	Yes; no	84%; 16%
Which of these are important for withdrawal strategy	Reported seizure frequency	95%
	Seizure type	84%
	History of SE	95%
	History of PIP	35%
	Physical/neurological status	27%
	Age	24%
	Invasive study	43%
Are blood levels monitored	Before; during; after; after AED introduction	43%; 35%; 22%; 57%
IV line present noninvasive	Always; mostly; occasionally; never	50%; 11%; 11%; 28%
IV line present invasive	Always; mostly; occasionally; never	76%; 3%; 5%; 11%*

*10% of the centres did not perform invasive recording.

In the case of PIP, 61% of the responding centers reported an incidence rate of 0%, and the remaining centers a range 0–5%, (mode 1%). The withdrawal related mortality rate was 0% for all centers. 'Other complications' resulted in varying individual feedback of the responders. Of the 36 centers that replied, 80% reported a 0% incidence rate; for the remaining 0–0.4%, with one exception of a center which mentioned 2% miscellaneous complications.

The following complications were specifically reported: a broken vertebra, fracture of the shoulder/spine, mild head trauma, and renal failure after SE. Due to large variability in AED withdrawal methods and the limited set up of the survey it was not possible to analyze the relation between the occurrence of these complications and specific withdrawal regimens.

Some drug-specific complications were reported as individual feedback by the responding centers. Bromide withdrawal was followed by an increased frequency of sGTCS in a patient with an SCV1A-mutation. BDZ and/or barbiturates were associated with atypical or provoked seizures. Acute BDZ withdrawal has been associated with a myoclonic status in two patients. Clonazepam withdrawal has been associated with exacerbation of seizures. LEV was reported to produce severe seizures in some patients, when tapered. Need for caution was reported with the use of LTG in combination with VPA. Probably this refers to the rapid reintroduction of the two drugs in combination which was associated with liver failure in the discussion of at least one report.[57] Also in this context the risk for Stevens-Johnson syndrome was mentioned. PHT withdrawal once provoked a cluster of GTCS in a child that subsequently developed ventricular fibrillation. VGB was mentioned as a relatively high risk for psychosis, associated with tapering of the drug. Patient compliancy with AED therapy can be reduced after withdrawal and reinstitution of therapy. The drug-free episode can be experienced as a relief from troubling side effects. This has been noted in multiple patients in multiple centers.

Overall, the varying and drug-specific practices among centers reflected consensus concerning the basic general rule for tapering of AEDs, specifically stated by numerous respondents: withdrawal of medication is first and foremost patient specific.

Recommendations

The recommendations that now follow are based on the literature review and the survey.

1. A single binding protocol is not practical, yet all presurgical monitoring procedures should be performed in a well-structured and standardized way, guided by and recorded in a standard document which should conform to published or local guidelines.
2. This document must be created, brought up-to-date and be available before planning and scheduling the monitoring procedure. During monitoring it must be available at the patient's bedside and annotated at least three times/24 hour. It may be created separately from the patient's standard clinical file. This file, however, should also be present during monitoring. Following conclusion of monitoring the monitoring file should be incorporated in the master file.
3. The document should record all relevant patient specific information, with the following items included: seizure history, general medical history, seizure semiology, aura, frequency, duration, tendency to clustering, history of SE or seizure-related accidents, associated cardiac or respiratory signs or symptoms, full medication history, history of changes in aura or seizure pattern, side effects or untoward events related to changes in AED, other medication, hypersensitivities, disturbances of haemostasis, psychiatric problems (spontaneous or associated with seizures). This information must be available before scheduling of monitoring.

4. Patients, family and/or carers have the best knowledge concerning seizure characteristics and should be consulted during the preparation of the document. Specific inquiries should be made concerning other diseases and medications, risk factors for clustering, SE, SUDEP, injury or psychiatric problems. Relying on previous correspondence or written data in the patient file exclusively should be discouraged.
5. In order to improve comprehensiveness the document should generally have a checklist format rather than open items. All items should be checked (skipping items should not occur; describe as 'not known' or 'not relevant', if applicable). However, space should be reserved for notes/descriptions where relevant, e.g., in case of semiology description, or for jargon used by the family or patient to describe their seizure symptoms.
6. A summary of specific risk factors involved in the procedure of AED withdrawal should be provided at the end of this part of the document. This should include possible drug interactions (AED to AED or AED to other drugs) in the course of withdrawal or during reinstitution.
7. A day-to-day AED withdrawal schedule should be made before start of monitoring, including specific pharmaceutical or procedural interventions in case of unwanted events. Patient-specific conditions that should lead to adaptations of the schedule or interventions should be predefined. Adaptation of the original schedule is possible but must be motivated in writing.
8. AED withdrawal should be individualized and determined first by patient-specific parameters and experience, second by pharmacokinetics and only lastly by presumed mechanism of action of individual AEDs.[5]
9. In patients with (multiple) daily seizures (often children or patients with frequent extratemporal lobe nocturnal seizures) AED withdrawal is usually not indicated.[4]
10. AED withdrawal for presurgical monitoring should be exclusively performed in a clinical setting.
11. If possible, monitoring should be performed in the presence of a family member or carer who can recognize changes in a patient's behavior or seizure pattern earlier than paramedical personnel. For children this presence is mandatory.
12. The monitoring environment must be designed to optimize patient safety and minimize risk of secondary trauma. Beds should be supplied with safety pillows. Emergency equipment must be available, including means for respiratory support and resuscitation. At least one qualified staff member, experienced with seizures and medical emergencies, should be physically present at all times.[4,5]
13. Independent of the obligatory recording of all changes in medication, time and dose of all drug administrations, occurrence and description of reported or observed seizures, peri-ictal and postictal phenomena and other clinical events and the usual associated observation and test results, a general assessment of the patient's physical and psychological condition should be noted at least 3 times/24 hours. Changes should be emphasized. For patients undergoing intracranial monitoring, additional surgically-determined parameters may have to be monitored.
14. In the absence of patient specific contraindications, AEDs can be withdrawn at a rate of 33–50% of the prescribed daily dose per day. In the case of polytherapy, withdrawal of one drug is preferred. AEDs that offer maximum protection against sGTCS to be withdrawn last.
15. Preferable drugs for first withdrawal are CBZ (or OCB) and VPA. VPA might be withdrawn at full stop, possibly unless combined with LTG. PHT withdrawal should be considered of limited value for limited periods of monitoring but, if relevant, should be performed at full stop in a clinical setting. Benzodiazepines and barbiturates should be withdrawn as last resort only or not at all. For most of the new generation AEDs there is a lack of experience and caution is advisable.
16. Alternative provocation methods can be combined with AED withdrawal. HV appears to be the most effective, notably in patients with TLE. Sleep deprivation probably is effective only in patients who report it as a provocative factor and should be applied with caution in patients with increased risk of unwanted events.
17. Following reported or observed seizures, patient should be assessed for neurological, neuropsychological or psychiatrical sequellae and should be monitored for possible ongoing EEG or ECG abnormalities. Notably following GTCI and when in bed, the patient should not be allowed to lie in full supine or full abdominal position and the unobstructed airway-passage should be secured.
18. Predefined conditions that warrant immediate interventions should include GTCI continuing for more than 2–3 minutes or seizure clusters exceeding the patient specific pattern either in number, time interval, or seizure characteristics. Seizure clusters should be defined depending on seizure type: 2 GTCI within 12 hours: intervention; within 24 hours, no acute intervention. 3 CPS within 4–6 hours: intervention; within 24 hours: no intervention. Series of tonic-myoclonic seizures habitual for the patient: no intervention; if unusual or de novo for this patient: intervention.
19. For a first GTCI lasting for more than 2–3 minutes or a first atypical seizure cluster, intervention may be limited to acute and short acting drugs such as benzodiazepines, in order not to interfere with the continuation of the monitoring. If severe or atypical seizures persist at unusual short intervals, regular medication should be reinstituted in part or completely, possibly with temporary, additional drugs (benzodiazepines, phosphenytoin). Deterioration of background EEG (a possible predictor of SE) or cardio-respiratory changes during or after seizures may be considered arguments for earlier reinstitution of regular AEDs and the same applies for elderly patients with a long history of seizures and AED use following atypical GTCI. Drug interventions, additional to reinstitution of regular AEDs, should be guided by locally accepted protocols for treatment of acute seizure disorder or SE.
20. Postmonitoring reintroduction of regular AEDs should be fast. For CBZ, PHT, LTG, VPA and LEV, when prescribed as monotherapy, reintroduction within 24 hours is possible, accepting some risk for minor and transient intoxication signs, notably for CBZ and PHT. In cases of polytherapy reintroduction should be individualized

(e.g., in the case of LTG combined with VPA). Depending on the clinical situation, additional BDZs may be prescribed for a few days to minimize the risk of additional seizures, clusters or SE during the postmonitoring period.

21. All AEDs should be reintroduced to the premonitoring dosages, unless specific arrangements have been made with the responsible treating physician. Patients who experience positive effects of monitoring associated drug withdrawal should consult the responsible physician for possible adaptation of treatment.

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66 Effects of sleep and sleep deprivation on seizures and the electroencephalography in epilepsy

N Foldvary-Schaefer

Introduction

Interactions between sleep and epilepsy have been recognized since antiquity. However, prior to the last few decades, knowledge in this area was based solely on clinical observations. More recently, the use of video-EEG and polysomnography has significantly extended early observations. This chapter addresses the effects sleep and sleep deprivation on seizures and the EEG in epilepsy.

Effects of sleep on epilepsy

In 1947, Gibbs and Gibbs were the first to perform a systematic study of the diagnostic yield and localizing value of recording sleep during the EEG.[1] Among 500 patients with epilepsy, they observed interictal epileptiform discharges (IEDs) in 36% of waking EEGs, increasing to 82% with sleep. Sleep activated independent epileptic foci in some patients who had only one focus awake. The likelihood of detecting IEDs by recording sleep was greatest for patients with psychomotor seizures and least for those with petit mal. Patients with psychomotor seizures often had normal EEGs awake, but 95% had IEDs during sleep. Interest in this area spanning decades has produced countless publications on the effects of sleep on the EEG in epilepsy.

Effects of sleep on interictal discharges in focal epilepsy

Many investigators have observed the activation of IEDs by non-rapid eye movement (NREM) sleep in focal epilepsy.[2–12] In 1958, Gloor and colleagues found that 90% of over 300 patients with TLE had IEDs awake but the frequency was greater during sleep in 57%.[13] In another series, roughly 30% of patients with medically refractory TLE had IEDs only during sleep.[11]

Most report that spike rate increases at sleep onset, gradually peaks in SWS and then falls in REM sleep to levels lower than seen in wakefulness.[6,9,10,12,14,15] The field of an interictal discharge often expands during NREM sleep (ipsilaterally and even contralaterally), occasionally accompanied by the appearance of new foci. The field tends to become more diffuse in SWS compared to light NREM sleep and is often most constricted during REM sleep.[2,4,10,12,15]

Sammaritano *et al.* prospectively studied IED variability in sleep and wakefulness in 40 patients with medically refractory TLE undergoing presurgical evaluation.[12] The accuracy of IED localization was confirmed by surgery (in 32), electrocorticography and scalp ictal recordings. Spike rate was greater in sleep than awake in 39 of the 40 cases, and maximal in SWS in 78%, REM sleep in 13%, and light NREM sleep in 7% of cases. New independent foci appeared in NREM sleep in 53% but during REM sleep in only four patients. The extent of the epileptic field, analyzed for 15 unilateral foci that showed spiking in all three states, demonstrated the field to be more extensive in NREM sleep compared to wake in ten, unchanged in four, and more restricted in one case. Comparing REM sleep with NREM sleep, the field was more restricted in 12 and unchanged in three cases. Epileptic foci were identical during wakefulness and REM sleep in 19 and disappeared during REM sleep in 17 who had spikes during wakefulness. The localization of primary epileptogenic area was more reliable in REM sleep than wakefulness and in wakefulness than SWS. Spiking was concordant with the epileptogenic temporal lobe in REM sleep in 51% of cases and was never discordant (in the remainder, no spiking was observed in REM). Similar findings have been reported in depth electrode evaluations in TLE patients.[10,14,15] Recently, Adachi *et al.* found that the sleep EEG was more accurate that the awake EEG in predicting the epileptogenic temporal lobe in 83 patients seizure-free following temporal lobe resection.[16] Unilateral IEDs during NREM sleep were correctly lateralized in every case.

The effect of sleep on IEDs in patients with extratemporal lobe epilepsy (XTLE) has been less extensively studied. Epileptiform discharges were most frequent during SWS in three patients with extratemporal foci.[17] Localization during REM sleep best predicted the epileptogenic focus.

Several researchers have studied how sleep influences spike rate in children with benign childhood epilepsy with central-midtemporal spikes. In one series of 11 patients, rolandic spikes occurred most often during SWS, especially during the first cycle of NREM sleep.[18] Spike densities were greater on the ascending slope of a sleep cycle (deepening NREM sleep) and less on the descending slope (lightening SWS to stage 2 to stage 1 en route to REM sleep). Rolandic spikes appear to be related to spindle synchronization and therefore maximal during stage 2 sleep.[6,19] These studies suggest that sleep differentially affects the expression of IEDs in epilepsies arising from different regions.

Effect of sleep on interictal discharges in generalized epilepsy

Patients with generalized epilepsy also show variation in the occurrence of IEDs with sleep and wakeulness. Gibbs and Gibbs found sleep was less important as an activator of sleep in most cases of IGE because these patients usually have IEDs in their routine wake EEGs.[1] Still, IEDs in idiopathic generalized epilepsy (IGE) are usually further activated during sleep.[20–27] Interictal discharges usually increase in NREM sleep gradually from sleep onset to the appearance of SWS, diminish sharply in REM sleep, and increase sharply in the morning after awakening.[20,28] The morphology of generalized IEDs is also affect by the sleep/wake cycle. During NREM sleep, generalized spike-wave discharges often become more disorganized, increase in amplitude and slow in frequency, sometimes with the addition of polyspikes, whereas the morphology in REM sleep is similar to wakefulness.[25,26]

Physiological basis for NREM sleep activation of interictal discharges

The neuronal networks that generate wakefulness, NREM, and REM sleep give rise to different physiological characteristics influencing the likelihood that a seizure will occur. The two most salient state-specific components that determine seizure propagation are the degree of synchronization of cellular discharges and the presence or absence of antigravity muscle tone.[29,30] NREM sleep represents a state of EEG synchronization and relative preservation of antigravity muscle tone. Synchronous oscillations of cortical neurons that generate sleep spindles, K complexes, and tonic background slow waves promote seizure propagation during NREM sleep. REM sleep is characterized by desynchronization of the EEG and loss of skeletal muscle tone. Desynchronization of the EEG impedes seizure propagation during REM sleep and wakefulness. Preservation of antigravity muscle tone during NREM sleep permits expression of seizure-related movements; its absence during REM sleep blocks the clinical expression of seizures.

Effects of sleep on seizures

Before the development of EEG, research on sleep and epilepsy in the late 19th and early 20th century focused on the relation of seizures to clock time and sleep. In 1880, Féré graphed seizure occurrence over a three-month period in hospitalized patients on his service for the mentally ill.[31] He found nearly two-thirds of seizures occurred between 8 p.m. and 8 a.m. and that insufficient sleep seemed to activate seizures. Gowers noted that 21% of 850 institutionalized patients had seizures exclusively at night (nocturnal epilepsies), 42% only during the day (diurnal epilepsies), and the remaining 37% either night or day.[32] He further observed that: (1) sleep onset and awakening were periods of particular vulnerability for nocturnal seizures; (2) nocturnal seizures most often occurred near the end of the sleep period (around 5 a.m. to 6 a.m.) and less often 1–2 hours after sleep onset; (3) diurnal seizures clustered in the early morning and late afternoon. Some years later, similar observations were made in a study analyzing the timing of 2524 convulsions in institutionalized patients leading to the conclusion that seizure peaks occur in response to falling asleep and waking up.[33]

Three decades later, Dieter Janz described 'awaking epilepsy' as an epileptic syndrome characteristic of idiopathic epilepsy with generalized tonic-clonic seizures (GTCs).[34] Subsequent work emphasized how preferential timing of GTCs in relation to the sleep/wake cycle had diagnostic and prognostic significance. Among 2825 patients, GTCs occurred in sleep in 44%, at awakening in 33%, and randomly in 23% of cases.[35] Janz felt that this type of classification had etiological significance, as awakening epilepsies were unlikely to have a known organic cause (10%), whereas sleep and random epilepsies more often did (23%, 54%, respectively). Juvenile myoclonic epilepsy became the prototypical awakening epilepsy, commonly precipitated by a lack of sleep. It is now recognized that several epilepsy syndromes are characterized by seizures occurring predominately or exclusively from sleep or upon awakening (Table 66.1).

More recently, video-EEG monitoring techniques and successful surgical resection have been studied to further detail the relation of different focal epilepsies to the sleep/wake cycle. Sleep appears to activate frontal seizures more often than temporal seizures.[36–38] Secondary generalization of partial seizures tends to occur more often during sleep (28%) compared to wakefulness (18%), and frontal lobe seizures tend not to secondarily generalize during sleep.[36–40] Herman *et al.* found that 57% of frontal lobe seizures arose from sleep compared to only 44% of neocortical temporal, 40% of mesial temporal, and 13% of parieto-occipital lobe seizures.[38]

Few studies have examined circadian rhythmicity of seizures in humans. Quigg *et al.* compared clock times of seizures in patients with mesial TLE (MTLE), XTLE, and lesional TLE and in a rat model similar to MTLE in which rats

Table 66.1 Sleep and wake epilepsies

- **Sleep epilepsies**
  - Benign focal epilepsy of childhood with centro-temporal spikes
  - Frontal lobe epilepsy
    - Supplementary sensorimotor area
    - Autosomal dominant nocturnal FLE
  - Lennox-Gastaut syndrome
  - Epilepsy with continuous spike wave in sleep (CSWS)
- **Awakening epilepsies**
  - Juvenile myoclonic epilepsy
  - Absence epilepsy
  - Epilepsy with grand mal seizures on awakening

become epileptic after electrically induced limbic status epilepticus.[41] Subjects with MTLE had twice as many seizures during light hours (7 a.m. to 7 p.m.) than dark hours, with a peak incidence of 3 p.m. Seizure distribution in rats maintained in a 12-hr light-dark cycle with lights on at 7 a.m. and those kept in constant darkness was similar to the pattern observed in humans with MTLE. The authors argued that the fact that rats and humans with MTLE behaved similarly despite marked differences in the sleep/wake cycle between species (180° out of phase) suggests that factors other than the sleep/wake cycle regulate seizure occurrence. In contrast, seizures from patients with XTLE and lesional temporal foci occurred randomly with a peak incidence of extratemporal seizures in the morning, usually associated with awakening, suggesting the absence of a circadian influence.

Pavolva *et al.* more recently confirmed the day/night differences in patients with TLE and XTLE epilepsies.[40] Forty-one percent of the XTLE seizures began during sleep versus 19% of seizures in patients with TLE. Forty-six percent of TLE seizures occurred between 3 p.m. and 7 p.m.; had they been truly random, only 17% of seizures would have occurred during this period of time. Forty-seven percent of XTLE seizures occurred between 7 p.m. and 11 p.m. These studies illustrate how circadian influences might affect seizure timing, varying by the type and location of the generator. Mesial temporal seizures may be particularly vulnerable to circadian effects.

Effects of sleep deprivation on epilepsy

The effect of sleep deprivation on epilepsy has been the subject of much investigation and extensive reviews.[42–44] In the following discussion, total sleep deprivation (TSD) is defined as 24 hours or more of sleep loss; shorter periods of sleep loss are considered partial sleep deprivation (PSD).

Effects of total sleep deprivation on interictal discharges

Early case series reported convulsions in normal subjects following profound sleep loss.[44,46] While some of these individuals were also subjected to other stressors, sleep deprivation was the only factor common to all.[45] Subsequent larger studies in sleep-deprived military personnel found a significantly higher incidence of seizures than previously reported in similar, nonsleep-deprived populations.[47,48] However, the applicability of these findings to the epilepsy population was unclear. In the largest of these population-based studies, subjects with epilepsy and other medical disorders were excluded.[48] Concurrent EEG studies of normal subjects[47,49] and subjects referred for diagnostic evaluation[47,41] demonstrated a clear increase in IEDs following TSD.

These early reports stimulated the investigation of sleep deprivation as an activation technique in epilepsy. In the first systematic study, sleep-deprived EEGs (SDEEG) were performed after 26–28 hours of wakefulness in subjects with at least one seizure and a normal routine EEG, patients with convulsive epilepsy and IEDs on routine EEG, and subjects with neurologic disorders other than seizures.[51] Epileptiform abnormalities were recorded in 34, 56 and 0% of cases, respectively. No difference was observed between patients with generalized motor or psychomotor seizures.

In a series of studies in the 1980s, Degen and colleagues compared the effects of TSD on EEGs of subjects with different seizure types and epilepsy syndromes.[52–54] For most seizure types, they found that spontaneous sleep and sleep-deprived recordings produced similar activation rates (awakening grand mal 77% vs. 71%; atypical absence 78% vs. 72%; absence epilepsy 69% vs. 71%; complex partial seizures 49% vs. 51%). They also noted that seizures were more likely to be activated by sleep or sleep deprivation in patients with IGE than focal epilepsy.

One long-debated controversy is whether the IED activation produced by TSD is due to sleep itself (greater amounts of sleep recorded, sampling effects) or due to an independent activating effect. Some have argued that TSD does not offer greater activation than sleep alone[54,55] while others believe TSD does activate IED independent of sleep induction.[51, 57–63] Only a few have designed studies to answer this question.

Rowan *et al.* found a significantly greater IED yield following TSD compared to routine wake and drug-induced sleep EEGs; IEDs were recorded in 28% of their subjects only following TSD and TSD activated a new epileptic focus in 7% of cases.[63] As the yield of recording IEDs due to repeated recordings was estimated to be in the range of 14% to 19%, the authors claimed their findings were unlikely to be due to sampling effects. Declerck studied the timing of IEDs following TSD in 588 patients with epilepsy.[64] IEDs appeared in the first 30 minutes in 46%, after 1 hour in 57%, after the second hour in 69%, after the third hour in 73%, and after the fourth hour in 75% of cases. He argued that the greater yield of recording IEDs over time was produced largely by the presence of sleep alone (sampling effect). A recent prospective study of 721 subjects who had a second EEG (routine, drug-induced sleep, or TSD) after an inconclusive initial EEG found a significantly greater percentage containing IEDs after TSD as compared to a second routine record (22.6% vs. 9.5%).[65] In another study, recording sleep during a routine EEG provided additional information that led to a more accurate diagnosis in 20% of cases, but sleep was only critical for the diagnosis in 2%.[66]

When comparing sleep and TSD, only a few studies have attempted to control for duration of the recording.[56,57,63] Veldhuizen *et al.* found the spike rate was highest following TSD and lowest in routine wake EEGs when routine, drug-induced sleep, and TSD recordings of similar duration were performed in random order in 70 subjects with epilepsy.[56] They attributed this finding to a greater proportion of recording time spent in sleep in the TSD EEGs. Activation rates were greater after TSD (93%) compared with drug-induced sleep (86%) and wake (65%). However when analyzed during the wake period only, activation rates were comparable (24, 28, and 35%, respectively).

Several studies have suggested TSD can be useful in activating IEDs in wakefulness, especially in patients with IGE.[52–54,56,58,61,62,65,67–71] Fountain *et al.* found 7% of subjects had IEDs during wakefulness only after TSD.[57] However, another study quantified spike rates by state before and after TSD and found lower rates of spiking in wakefulness after TSD.[55]

TSD enhances responses to hyperventilation and intermittent photic stimulation[51,71,72] and provokes photoparoxysmal responses that remit with treatment in sleep-deprived patients.[73] Aguglia *et al.* found activation was greater following

TSD during a sleep EEG in untreated patients with epilepsy, whereas treated patients had comparable activation rates following each procedure.[74] Several studies have shown that TSD is equally, if not more effective in children with epilepsy.[62,67,69,71,75]

Table 66.2 summarizes findings of comparative studies demonstrating activation of IEDs by TSD in 23–93% of patients with definite or suspected seizures.[44,54,56–59,62,65,68,70,71,74,76–79]

Effects of partial sleep deprivation on interictal discharges

Partial sleep deprivation in epilepsy has been much less extensively studied. Limited work suggests that partial sleep loss may be an effective activation method,[80–85] however no studies compare the effects of PSD and TSD. Most studies utilizing PSD protocols examine pediatric subjects. In a prospective study of over 200 children with newly diagnosed epilepsy and normal routine EEGs, a repeat recording after PSD (sleep limited to 7 hours in children 3–10 years of age and 5 hours in adolescents) produced IEDs in 35% of cases.[81] Epileptiform abnormalities were present in wakefulness only in 15% and one subject experienced a generalized motor seizure. Kubicki *et al.* reported activation rates of 54% when restricting older children to 5 hours and younger children to 8 hours of sleep.[83] Peraita-Adrados *et al.* reported activation rates of 36% when they asked adults to sleep 3 hours less than usual, adolescents 2 hours, and children 1 hour in a retrospective study of 686 patients with at least one seizure and a normal routine EEG.[85] A second SDEEG, in 40 subjects in whom the first sleep-deprived recording was normal, detected IEDs in 39% of cases. In a study of 396 patients under 17 years of age, sleep was achieved after PSD in 77% of cases in contrast to 44% of subjects not sleep-deprived, supporting the feasibility of the technique in younger patients.[86]

Gilbert *et al.* compared the activating effects of routine and sleep-deprived EEGs (>11 years: awake after midnight; 3–11 years; awake after 2 am; <3 years: awake after 4 a.m.) versus PSD (awake 2 hours past usual bedtime in children ≥2 years and no napping in children < 2) in 820 patients.[87] They found sleep occurred in 22% of routine, 44% of PSD, and 57% of sleep-deprived EEGs. No procedure was superior in terms of the yield of recording IEDs.

Recommendations for the use of sleep deprivation in clinical practice

Based on the available evidence, SDEEG has proven effective in increasing the yield of EEG when initial recordings are inconclusive. Adults undergoing SDEEG should remain awake for 24 hours prior to the study and recordings should begin early in the morning with a period of wakefulness, recording at least one complete sleep cycle. As the yield appears to increase progressively with time, longer recordings are encouraged.[64] The study should end with a period of wakefulness during which hyperventilation and photic stimulation are performed. Sleep should be restricted as much as possible in children and adolescents unable to comply with TSD. The risk of seizures is low (1.2–5.8%).[67,71,72,76] Whether lesser amounts of sleep restriction are as effective is unknown.

Does sleep deprivation activate seizures?

Patrick and Gilbert in 1896 were the first in modern times to report the ill effects of sleep deprivation in humans.[88] While studying the effects of psychotropics in the late 1950s, Rodin became the first to describe the effects of sleep deprivation on seizures and the EEG.[44] Subsequent reports described GTCs in military personnel following prolonged sleep deprivation, estiimating the risk of a sleep-deprived seizure to be 1/10 000

Table 66.2 Activation of interictal discharges by sleep and total sleep deprivation

		% Activation		
	N	REEG	SEEG	SDEEG
Mattson, 1965	123	28	–	40
Pratt, 1968	114	0	–	41
Donzal, 1969	52	19	–	42
Geller. 1969	25	–	–	32
Bechinger, 1973	485	5.8	–	26.4
Bechinger, 1976	175	–	–	73
Tartura, 1980	322	14/51[1]	–	54/31[1]
Arne-Bes, 1982	135	13	–	53
Rowan, 1982	41	20	35	58
Veldhuizen, 1983	72	65	86	93
Logothetis, 1986	86	0	–	38
Roth, 1986	434	10	–	42
Degen, 1987	190	0	53	53
Aguglia, 1994	41	0/0[2]	60/57[2]	95/62[2]
Fountain, 1998	29	0	–	52
Ropakiotis, 2000	195	0	28 [3]	23

REEG = routine EEG; SEEG = sleep EEG; SDEEG = 24-hr sleep-deprived EEG.
[1]Pediatric/adult
[2]Untreated/treated
[3]*N* = 40

after 24 to 36 hours of TSD and 1/2500 after two or more days without sleep.[47,48] However, the applicability of these findings to patients with epilepsy was unclear as this study and others excluded subjects with epilepsy and other medical disorders.

Sleep deprivation has long been recognized as a seizure precipitant, reported by 25% of epileptic patients, more often in those with awakening epilepsy.[46,61,89,97] Most of these observations are based on patient self-reports. In one series, 37% of patients reported that two or more hours of sleep loss contributed to or activated seizures.[61] Based on a review of seizure and sleep diaries, Neugebauer *et al.* found that seizures were more likely to occur following nights of short or interrupted sleep in 38% of cases.[95] Two larger questionnaire-based studies of adults with epilepsy found that 18–24% of adults reported sleep deprivation as a seizure trigger.[91,97]

Due to the pressures of modern society, people with epilepsy are vulnerable to the effects of chronic PSD. Its effects on seizures have only been addressed in one study in which night sleep duration was correlated with seizure frequency in 14 patients with TLE.[96] Subjects maintained sleep and seizure diaries for 2 years, logging 682 seizures. They considered a particular night as PSD when the patient slept 1.5 hours less than usual, and oversleep (OS) when they slept at least 1.5 hours longer than their mean sleep duration. They studied whether seizures occurred more or less often within 48 hours of sleep-deprivation or oversleep. Of 4995 recorded nights, 91% were characterized as normal sleep nights, yet only 58% of seizures followed normal sleep, while 34% followed PSD and 8% followed OS. The probability of occurrence of a seizure was significantly higher after PSD (0.58) than normal sleep (0.09) and OS (0.28). In eight subjects, PSD was felt to play a decisive role, while three subjects demonstrated a marked sensitivity to the OS condition. These findings suggest that modest amounts of sleep loss can precipitate seizures.

Clinical neurophysiologists often subject patients to PSD during long-term video-EEG monitoring to activate seizures. However, in a study of 84 patients with medically refractory epilepsy, the number of seizures per day was not significantly greater in sleep-deprived subjects versus controls.[98] Further studies are needed to better understand the impact of PSD on seizure threshold and identify the most vulnerable populations.

Conclusions

Over many years, researchers have compiled a large body of evidence confirming interrelationships between sleep and epilepsy. Synchronized NREM sleep facilitates and desynchronized REM sleep discourages seizure occurrence. Sleep deprivation provokes seizures and interictal discharges in some patients with epilepsy. The effects of sleep on IEDs can have important implications in epilepsy surgery candidates because new independent epileptic foci may appear in sleep and REM sleep may demonstrate the narrowest localization of the primary epileptic focus.

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SECTION 7

The ictal onset zone

67 The ictal onset zone: general principles, pitfalls and caveats

A Arzimanoglou and P Kahane

Introduction

The 'ictal (or seizure) onset zone' is defined as the 'area of cortex that initiates clinical seizures'.[1] Although this definition is apparently simple and clear it generates a number of questions. At least five are of crucial importance:

1. Is it possible to define the 'ictal onset zone' without having recorded a seizure?
2. What is the meaning of the term 'clinical seizure'
3. What do we understand when talking about 'initiation' of a seizure?
4. Do we dispose of specific markers that can precisely define this region?
5. Is the identification of the ictal onset zone operant when it comes to surgery?

Is it possible to define the 'ictal onset zone' without having recorded a seizure?

It seems rather obvious that the proof of a seizure being generated within a given cortical region of variable extent cannot be provided without the recording of the seizure. If the opposite was feasible it would mean that using other investigational means (interictal EEG, bipolar modeling, structural or functional neuroimaging, etc.) it would be possible to constantly obtain a reproducible information, superimposed to what is obtained from seizure recordings. Abundant current literature indicates that such an option is an exception rather than the rule. For example, the relationship between regions that generate spikes and those that generate a seizure are far from being constant. This brings us back to the old debate on 'green versus red spikes',[2] debate still open despite abundant data now available from IRMf-EEG studies or from the use of source localization techniques. Even in the case of lesional epilepsies, for example in the presence of a dysplastic cortical lesion in which interictal spikes (or at least some of them) could be considered a reliable marker of the extension of the lesion 3–5, invasive recordings often demonstrate that the topographic relationship between the spikes and the onset of seizures may vary (Figure 67.1).

What is the meaning of the term 'clinical seizure'

By definition 'the ictal onset zone' refers to that region of the cortex at the origin of *clinically* detectable seizures. Such a definition indirectly leads to the question of how we define 'subclinical seizures'. Are these 'discharges' considered as seizures or not? Such discharges, very similar in terms of morphology to what can be observed at the onset of a clinical seizure, are often observed without any clinical accompaniment. The occurrence of accompanying symptoms may vary according to the localization of the discharge and to its electrographic pattern. This is notably true in temporal lobe epilepsy, in which an ictal discharge can remain confined to the amygdala[6] or to the hippocampus[7], the most often without any associated signs. It has been shown that subclinical seizures may have a high localizing significance,[8] even if the recordings of such 'subclinical' discharges do not exempt one from recording the fully developed electro-clinical seizures. In which case, the discharge at seizure onset may additionally involve other cortical structures, or cortical structures which are different from the area exhibiting 'subclinical' paroxysms (Figure 67.2).

This ambiguity on 'clinical' *versus* 'subclinical' seizures is reflected in the definition of the ictal onset zone when it is stated that the seizure onset zone includes the portion of the irritative zone that generates repetitive spikes 'that have enough strength to produce clinical ictal symptoms when invading eloquent cortex'.[1] In other words, what value should be attributed to 'spikes' in general, and particularly to those spikes occurring in the (supposed) noneloquent cortex? Are these 'symptomatic spikes' morphologically similar to those which, though located at the same place, do not give rise to any symptoms? And if recognizable, what is their significance with respect to the ictal onset zone?

Lack of an answer to the question of 'subclinical' *versus* 'clinical' seizures, and the introduction of the concept of 'symptomatic spikes' in the definition of the seizure onset zone may maintain the confusion between the concepts of seizure onset zone, irritative zone, and symptomatogenic zone. Defined as such the 'ictal onset zone' should theoretically be delineated on the basis of the very first clinical symptoms produced by 'hyperactive cortical neurons' that generate interictal spikes capable of producing, under certain circumstances, afterdischarges.

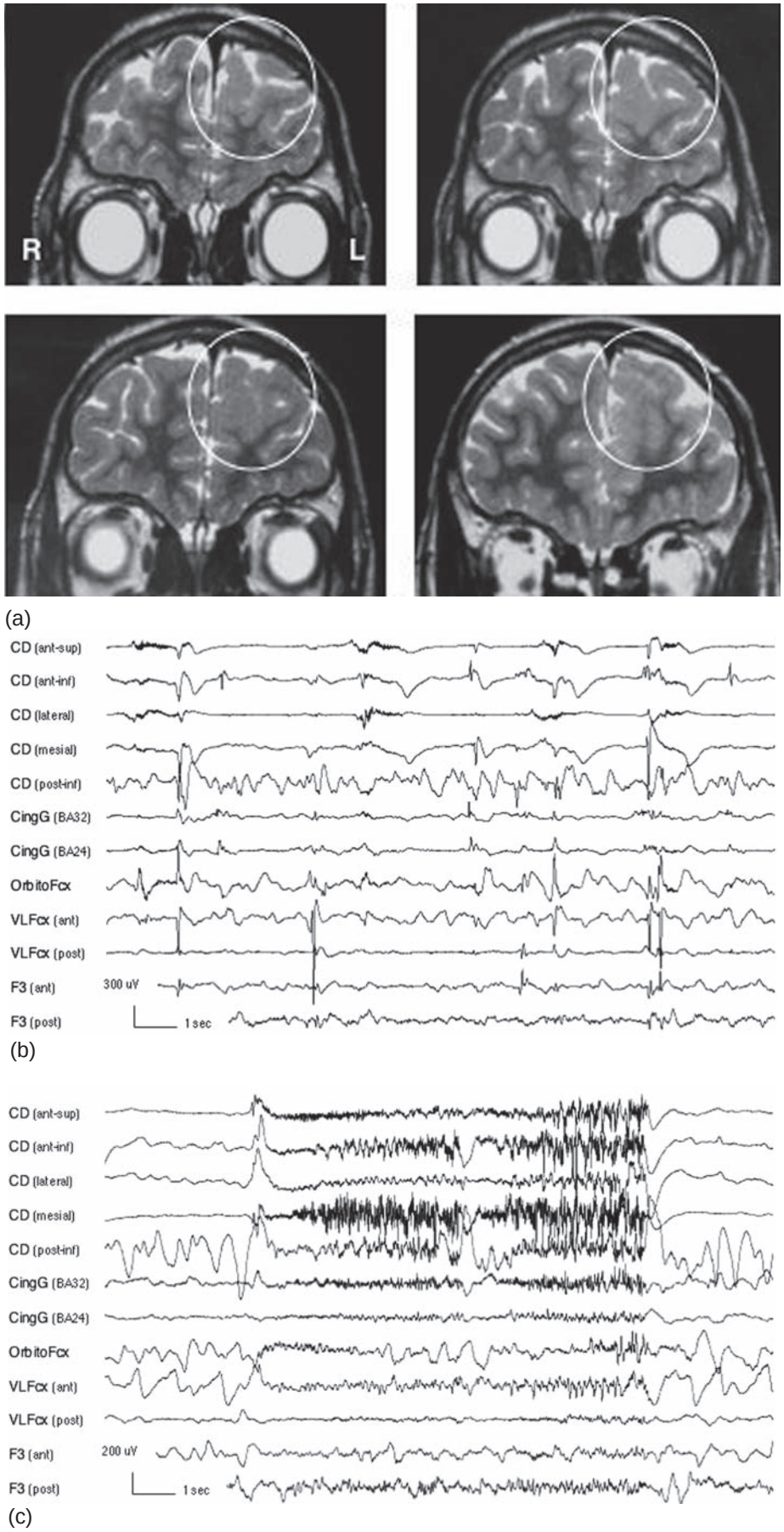

Figure 67.1 Nine-year-old boy suffering from drug-resistant hypermotor seizures. a. MRI: Left frontal cortical dysplasia (Type 2b on pathological examination) limited to the polar part of the 1st frontal gyrus. b. SEEG investigation, interictal activity. The main findings consist in the occurrence of bursts of low amplitude fast rhythms within the lesion, the distribution of which predominated over the antero-superior and lateral part of the dysplastic lesion. Interictal spikes were also recorded within the lesion, as well as over mesial and lateral frontal lobe structures distant from the lesional process.c. SEEG investigation, electro-clinical seizure. The seizure begins not only in the cortical dysplasia (at recording sites that were not strictly the same as those that exhibited fast rhythms interictally), but also within the cingulate cortex (BA 32).

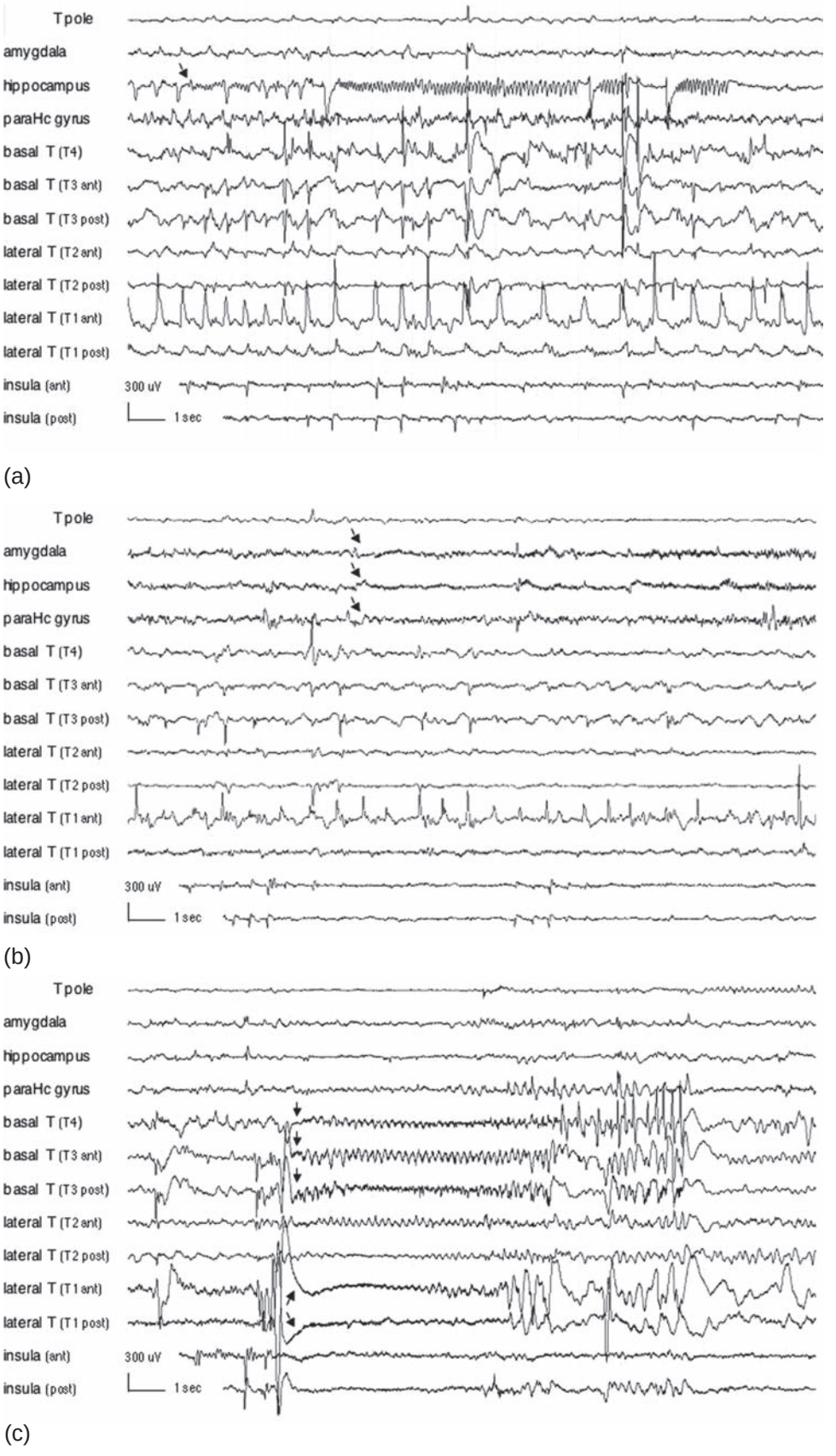

Figure 67.2 SEEG study in a 41 years old left-handed woman with right hippocampal sclerosis (right hemispheric dominance for language). a. Subclinical discharge well located within the hippocampus (arrow). b. Electroclinical seizure characterized by a feeling of distress over the head, pallor, arrest of activity, gestural and oroalimentary automatisms and dystonic posturing of the left arm. The ictal onset (low voltage fast activity) involved not only the hippocampus but also the amygdala and at a lesser degree the parahippocampal gyrus (arrows). c. Other electroclinical seizures were recorded, clinically characterized by auditory symptoms with word finding difficulties. The ictal onset involved in such cases the basal and lateral temporal cortex (mainly the first temporal gyrus), sparing mesio-temporal lobe structures (and notably the hippocampus).

The theoretical concept of ictal onset zone would be of great practical value if:

1. the 'ictal onset zone' was always localized in a sufficiently eloquent cortex to always manifest the very first clinical symptoms, ideally always detectable (in that case the ictal onset zone would be the cornerstone of the 'symptomatogenic zone', and theoretically it could in some cases fully overlap with it);
2. the interictal spikes of the 'ictal onset zone' were always of sufficient 'strength' to give rise to clinical symptoms (and in that case the ictal onset zone could overlap with the 'irritative zone').

In summary, it remains to be agreed if we will consider as ictal onset zone *the area in which arises the fast synchronizing discharge, prior or concomitant to the clinical onset of the seizure, or if we have to include the 'minimal' adjacent cortical area necessary to generate the first clinical symptoms.* In the first case the definition is an *electrophysiological* definition, which somewhere raises once again the issue of the significance of subclinical seizures. In the latter case the definition is an electro-clinical one which overlaps with the definition of the 'symptomatogenic zone'.

What do we understand with 'initiation' of a seizure?

If we accept the principle that the definition of the 'ictal onset zone' can only be based on seizure recordings, how do we integrate the notion of 'seizure initiation'? How do we define the region of 'seizure initiation'?

It certainly cannot be the cortical region that when removed (or disconnected) allows seizure freedom, since in that case it would correspond–by definition–to the epileptogenic zone.

To illustrate and discuss this ambiguity we will use the example of a lesion (cortical dysplasia or DNET) that has been removed rendering the patient seizurefree. According to the current definition this can be considered as the proof that the 'epileptogenic zone' has been removed (or that it was included in the cortical tissue removed). It also signifies that the seizure onset zone was part of the resected cortical tissue. Adversely, this cannot be interpreted as a proof that the seizures implicated, at onset and simultaneously, the totality of the removed cortex. In other words, even within one lesion, the zone that 'initiates' a seizure can be smaller than the epileptogenic lesion (Figure 67.3), and we can even have a number of seizure onset zones within the same epileptogenic lesion.

Consequently, we prefer *a pragmatic and electrophysiological* definition of the ictal onset zone, as the cortical area(s) from where the first clear ictal electrical change is recorded, using intracranial electrodes. To be retained, such a change must occur just prior to the clinical onset of the seizure (defined as the time of the first visible change in the patient's behavior, or when the patient indicates he is experiencing an aura). It would manifest as a fast synchronizing discharge (low-voltage fast activity of various frequency or recruiting fast discharge of spikes), the pattern and frequency of which may vary according to the cortical structures from where it arises.[9–11]

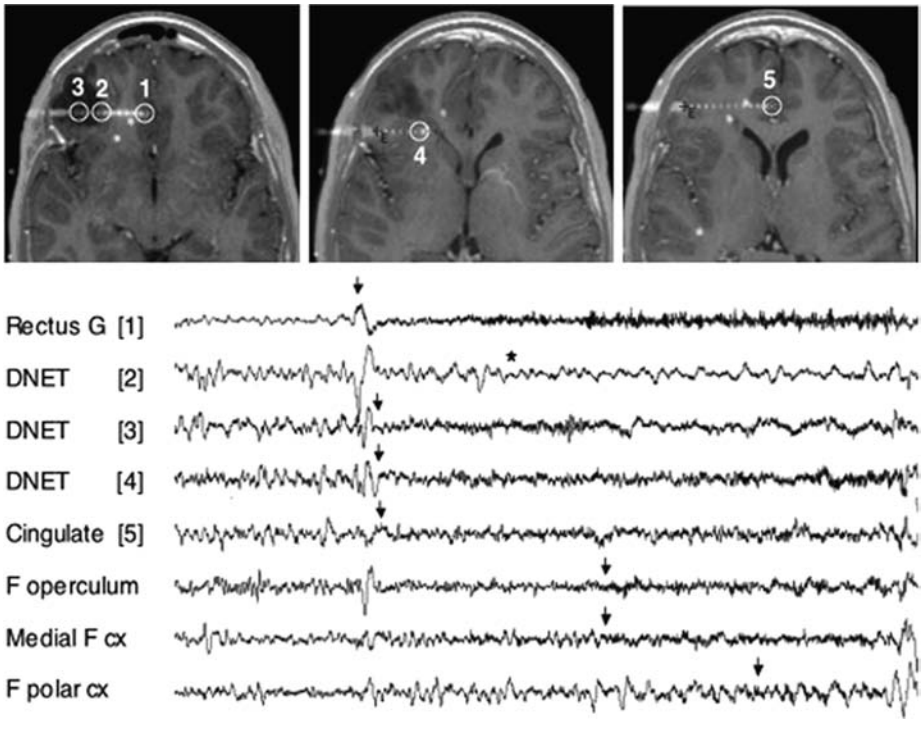

Figure 67.3 SEEG investigation in a 22-year-old woman with a right frontal basolateral dysembryoplastic neuroepithelial tumor. The seizure is initiated in the (nonlesional) rectus gyrus where it appears prominent, involving also the lesion and, at a lesser degree, the (nonlesional cingulate cortex). The fast activity then spreads over the frontal operculum, the mesial frontal cortex and, later, over the frontal pole (see arrows). Note that part of the DNET is not involved at seizure initiation but only a few seconds later (black star).

It is understood that in this context recognition of the seizure onset zone depends upon:

1. the spatial sampling of the electrodes;
2. the way 'a clear electrical change' is defined, knowing that its pattern may vary depending on the structures implicated;
3. our capacity to identify eventual triggering events of a seizure (in which case we also need to decide, for example when dealing with a reflex seizure, if we will consider as initiation zone the region that includes the triggering stimulus or only the region that generates the clinical seizure). Finally, we need to decide if the concept of 'seizure initiation' will include or exclude concepts introduced by the mathematical analysis of EEG signals, showing that some modifications can be detected much earlier than the appearance of the first clearly identifiable EEG changes.[12]

Do we dispose of specific markers that can precisely define this region?

From our point of view, for both clinical and neurophysiological reasons, current available investigation tools do not allow an exact measurement and precise delineation of the ictal onset zone.

From a 'clinical expression' point of view (if we accept the definition that a 'seizure' implies the presence of clinical symptoms) we can identify with today's available means only what the patient reports or what our audio-video tools, coupled to clinical examination during a seizure, can identify. Experience has shown that even in cases where the ictal onset zone is suspected to be in a very eloquent cortical area, the clinical symptoms obtained are in almost all cases the result of a 'very early' spread of the ictal discharge. It is highly probable that a limited number of 'hyperactive cortical neurons' have the capacity to act as a trigger (and in that sense these neurons represent the ictal onset zone) but they are unable to translate this hyperactivity to clinical symptoms. To do so they need to activate a neuronal circuit, capable of translating this activation to concrete symptoms. For example, even when dealing with a very well described primary somatosensory aura, it is highly improbable that Brodmann areas 1, 2, and 3 represent, as a whole, the 'ictal onset zone'. Consequently, even in cases where the ictal onset zone is localized in eloquent cortical areas, we can expect an accurate localization only by scalp or invasive EEG techniques and, eventually, ictal single photon emission computed tomography (SPECT). Whether these tools, however, are really able to reliably and consistently delineate the ictal onset zone remains a highly debatable issue.

Scalp electrodes offer a broad coverage of brain activity. Analysis of interictal and/or ictal EEG can in most of the cases provide strong clues suggesting the side and the approximate location of the seizure onset zone. However, as discussed in Chapter[71] Foldvary-Schaefer chapter in this book scalp EEG has relatively low sensitivity for the detection of the seizure onset zone because of the distance between the electrodes and the suspected triggering cortical region. Small discharges at the 'level' of the seizure onset zone are not detected or are already modified by the propagation to neighboring areas. The presence of a localized flattening, or even better of a fast localized activity, provides some clues for the identification of the cortical areas implicated at onset[13] but by no means can be considered as pointing to the cerebral structures that really generated the seizure.

Ictal SPECT provides only an indirect view of what is going on during a seizure. The simple fact that the tracer injection takes place only after the onset of the clinical seizure (that by definition follows the electrical onset) renders impossible the localization of the zone of seizure initiation. The tracer is captured after 15 seconds following IV administration and consequently it reflects both the regions of seizure onset and seizure propagation. Even within the artificial setting in which the tracer is injected before seizure onset (for example, seizures induced by electrical stimulation), the variations of cerebral blood flow observed are not systematically correlated to the topography of the underlying discharge, as this was demonstrated by ictal H20-PET,[14] and by ictal SPECT.[15]

Invasive cortical surface electrodes see Chapter[73] by xx in this book offer the advantage of eliminating some of the scalp EEG inconveniences (shorter distance, absence of scalp, bone and dura mater barriers). However, they can only cover the cortical surface and therefore do not provide access to deep seated cortical areas and sulci. Consequently they are often not in direct contact with the suspected ictal onset zone and can only better capture discharges that are part of the early propagation process. The quality of spatial sampling of intracerebral electrodes, when compared with subdural grids or strips which cover a larger cortical surface, can appear inferior since recordings are taken from a series of paired leads which only explore a very restricted part of the cortex see Chapter[74] by Kahane and Francione in this book). However, this depends obviously on the spatial sampling of the Stereotactic intracerebral EEG (SEEG) investigation,[16] so that caution is required to ascertain that the fast discharge which is supposed to mark the ictal onset is really localized at the place where it has been recorded (i.e., a volume of brain tissue approximating a cubic centimeter).

Is the identification of the ictal onset zone operant when it comes to surgery?

One of the major difficulties to which we are confronted in epilepsy surgery derives from the fact that the electrophysiological criteria used intracranially, for defining the most epileptogenic region, are not clearly determined. Neuronal mechanisms associated with the emergence of epileptic seizures, indeed, are still largely unknown, though several indices suggested that the transition from the interictal to the ictal state is not sudden. Recent studies conducted in epileptic patients by means of intracranial macroelectrodes have shown that epileptic seizures can begin with low amplitude fast activities in the gamma frequencies range,[17–20] and that in the period between seizures, there are brief bursts of high frequency oscillations (60–100 Hz) which seem to have the same spectral characteristics as the seizure onset activities.[21] These 'interictal' fast oscillations (are they truly 'interictal'?) seem to be recorded only in the seizure onset zone, supporting the idea that they are pathological oscillations. Whether they have rela-

tionships with fast ripples (high frequency oscillations up to 500 Hz) recorded in humans when using microelectrodes[22] is a very important issue, since these latter could be the signature of the cortical regions capable of generating spontaneous seizures. If this is to be confirmed in the near future, the capability to identify such rapid oscillations by noninvasive techniques (for example MEG-EEG) would be a major challenge.

Furthermore, we are living in an era where further developments in the understanding of the mechanisms underlying seizure generation (i.e., the result of what an ictal onset zone is supposed to produce) are constantly becoming available. Such developments will soon provide us, among others, with more precise data on the distribution of neurotransmitters and receptors involved in the pathogenesis of the epilepsies. It is to be expected that the important advances that recently became possible by the development of neuroimaging and numeric video-EEG techniques will continue to evolve, coupled to advances in genetics and in pharmacogenomics. The consequences of such an approach are evident, particularly if we integrate the fact that a number of epilepsies are not potential surgery candidates and that 'the ictal onset zone' concept should also be applicable to nonsurgical epilepsies. Being able to identify the ictal onset zone even in nonsurgical cases is not just a theoretical issue. Because if we were able to define the ictal onset zone in all epilepsies, we could then go a step further and define the eventual pharmacological reactivity of a given region. Factors influencing the 'road to a seizure' could then be better identified and controlled, which would also lead to a better approach, and eventually control, of the cognitive consequences frequently encountered.

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68 Noninvasive electroencephalography in the evaluation of the ictal onset zone

N Foldvary-Schaefer

Introduction

The seizure onset zone is the area of cortex from which clinical seizures are generated and is closely related to the epileptogenic zone, the area of cortex capable of producing seizures, the complete removal of which is necessary to produce a seizure-free state.[1] Noninvasive EEG is routinely used to localize seizures 1-1, however, due to a variety of factors, precise delineation of the seizure onset zone is not possible.

General concepts of noninvasive EEG

Epileptiform activity does not necessarily originate from cortical tissue directly beneath or even in the vicinity of the recording surface electrode(s). Seizures originating in functionally silent cortex produce symptoms only when the ictal discharge spreads to symptomatic areas that may be at some distance from the generator. Therefore, the distribution of epileptic discharges on noninvasive EEG depends upon a variety of factors, including the spatial characteristics of the generator and the conductive properties of the surrounding tissue. The yield of noninvasive EEG varies with the depth, size and orientation of the generator and the duration and synchronization of an epileptic discharge.[2] Electrical activity of the brain is attenuated by the impedance characteristics of the intervening tissue, cerebrospinal fluid, meninges, skull and scalp. Higher frequencies, which are commonly observed during the evolution of ictal patterns, are attenuated more than lower frequencies. There is no consistent or direct relationship between the amplitude of epileptic discharges recorded simultaneously from intracranial and surface electrodes. Spikes recorded from subdural or depth electrodes are frequently not seen on noninvasive EEG.[3] As a result, epileptic activity is apt to escape detection or produce widespread discharges of limited localizing value, particularly when arising from deep or midline areas.

The location of the generator, seizure type, state of the patient, recording technique and seizure frequency may also affect the expression of epileptiform activity on noninvasive EEG. Nonrapid eye movement sleep (NREM) and sleep deprivation are potent activators of interictal discharges and seizures.[4,5] Prolonged sleep deprivation activates interictal discharges in approximately 40% of epileptic subjects with normal wake EEGs.[6] As compared to wakefulness, spike rate is increased during NREM sleep and reduced during rapid eye movement (REM) sleep.[7,8] The extent of the field is typically more restricted in REM sleep as compared to wakefulness, while extension of the field and new spike foci are observed in slow wave sleep (stages 3 and 4 NREM). Therefore, the localization and distribution of epileptic activity in REM sleep may be a better indicator of the seizure onset zone than NREM sleep or wakefulness. Spike rate increases markedly during the first 24 to 48 hours after a clinical seizure.[9,10] Changes in antiepileptic drug concentrations do not appear to expression of interictal discharges.[10,13]

Special recording techniques are particularly helpful in the localization of focal epilepsies arising from deep or midline regions and when the seizure onset zone is confined to a small area of cortex. Closely spaced scalp and semi-invasive electrodes improve the yield of spike detection over the standard 10–20 system.[14] Epileptic activity is more commonly observed in patients with temporal lobe epilepsy (TLE) as compared to epilepsies arising from deep or midline regions. This is particularly true when sphenoidal or additional scalp electrodes are employed.

Anterior temporal epileptic activity is best defined noninvasively using additionally placed electrodes recording from the basal or mesial temporal regions. Surface electrodes placed 1 cm above a point one-third the distance between the external auditory meatus and the external canthus (T_1, T_2), FT_9, and FT_{10} electrode placements of the 10–10 system and sphenoidal electrodes increase the yield of recording interictal discharges in patients with TLE.[15,16] Several investigators have found sphenoidal electrodes superior to scalp electrodes alone in detecting temporal lobe seizures.[17–19] However, this was not confirmed by two recent studies investigating the utility of sphenoidal electrodes in TLE.[20,21]

Despite the above limitations, the distribution of epileptic activity on noninvasive EEG provides a reasonable estimate of the seizure onset zone in many cases. While, the extent of interictal discharges tends to be larger than the area of cortex from which a seizure originates, it is generally believed that the interictal EEG provides more reliable localizing information than ictal recordings. This is because a seizure has usually spread outside the seizure onset zone by the time an ictal pattern is detected by surface electrodes. In a series of patients with TLE, the presence of a single interictal spike focus in the anteromesial temporal region accurately predicted temporal lobe onset whether the surface ictal EEG was focal, regional or

lateralized.[22] In cases with multiple temporal foci or mid to posterior temporal epileptiform activity, the interictal focus was less accurate in predicting the seizure onset zone.

Overview of noninvasive ictal EEG

Ictal recordings have long been considered a critical component of the pre-surgical evaluation. However, with the exception of TLE, the localizing value of ictal EEG not been extensively studied. Most studies include patients with focal epilepsy in whom precise location and extent of the epileptogenic zone is unknown, presumed or not reported. Variations in EEG interpretation largely preclude comparison across studies.

The transition from the interictal to the ictal state is variable and may be difficult to identify, particularly when seizures are brief or occur during state changes.[23] An abrupt cessation of interictal spiking immediately before ictal onset has been described.[24] Focal seizures are typically characterized by rhythmic sinusoidal activity in the beta, alpha or theta range or repetitive discharges that evolve in frequency, field or amplitude.[23–27] Variations in seizure evolution consisting of increasing or decreasing amplitude and/or frequency have been described.[24,28] Isomorphic patterns, such as the repetitive interictal discharges that characterize seizures in some of the idiopathic generalized epilepsies, are typically not observed in focal epilepsy.[23] Ictal discharges limited to one or two electrodes are relatively uncommon in noninvasive recordings. A sudden generalized or lateralized suppression or attenuation of amplitude has been reported in seizures arising from the orbitofrontal, mesial frontal and temporal regions.[27,29,30] With few exceptions, there is no clear correlation between the specific pattern and frequency of ictal onset activity and the location of the seizure onset zone.[24,31] Clinical manifestations frequently precede EEG onset. Approximately 10% of complex partial seizures are not accompanied by EEG change.[24,32]

It is generally accepted that the early appearance of paroxysmal fast activity during focal seizures reflects proximity of the ictal onset zone to the recording electrode. However, this concept was not confirmed by a study comparing seizures from patients with lateral versus mesial epileptogenic lesions.[31] Paroxysmal fast activity was observed in seizures arising from the inferior aspect of the supplementary sensorimotor area (SSMA) and cingulate gyrus, where the distance between surface electrodes and the generator is considerable. This pattern was virtually never observed at the onset or during the course of seizures in patients with hippocampal sclerosis (HS), suggesting that its presence may require extensive neocortical activation or vary with the pathologic substrate.

The localizing value of noninvasive ictal EEG is largely dependent upon the location of the epileptogenic zone. Using lateralized rhythmic theta and alpha activity, postictal slowing and activity at seizure onset as criteria for localization, only 47–65% of extratemporal seizures were correctly lateralized as compared to 76–83% of temporal lobe seizures.[33] Another study combining temporal and extratemporal cases localized by depth electrode recordings found only 21–38% of seizures to be correctly localized and less than one-half correctly lateralized.[34] In a series of predominately temporal lobe seizures, the ictal EEG correctly localized 40% and lateralized 9% of seizures, while the remainder was nonlateralized or uninterpretable.[35] Methodological differences likely contribute to these findings.

The postictal EEG can be extremely valuable in localizing seizures. Postictal regional or lateralized delta activity and attenuation are reliable predictors of seizure origin.[33,36,37] In one study, lateralized delta during the postictal state predicted the side of seizure origin in 96% of TLE cases.[38]

Few have studied the reproducibility and reliability of ictal patterns in focal epilepsy. In 68% of patients with TLE, the first recorded seizure was representative of subsequent seizures and was concordant with the final localization of the epilepsy in 91% of cases.[39,40] When the initial seizure was nonlocalized, particularly if it occurred in sleep, subsequent seizures were likely to remain nonlocalized.[40] Patients with unilateral interictal discharges are more likely to have consistent ictal patterns than those with bitemporal independent spike foci.[39] A minimum of four seizures was required to identify 100% of 18 patients with ictal patterns arising from both temporal regions independently.[39] However, in a recent series of 32 children with presumed focal epilepsy, the ictal onset was similarly localized in all recorded seizures in only ten cases.[41] Seizure outcome after anterior temporal lobectomy (ATL) was comparable whether or not video-EEG monitoring was performed in patients with unilateral temporal interictal discharges concordant with neuroimaging and functional studies, emphasizing the importance of the interictal EEG.[42,43] In extratemporal epilepsy, the first recorded seizure was correctly localized in 61% of patients.[44] Correct localization of the first recorded seizure occurred most often in dorsolateral frontal lobe epilepsy compared to seizures arising from other locations.

We previously compared the distribution and morphology of ictal patterns in nearly 500 focal seizures of 72 patients arising from different regions.[31] Localization of the epileptogenic zone was confirmed by the presence of a seizure-free 1-1 state following surgical resection. Noninvasive ictal EEG was more likely to be correctly localized in TLE than extratemporal epilepsy. Localized ictal onsets were seen in 57% of seizures and were most common in mesial temporal lobe epilepsy (MTLE), dorsolateral FLE and parietal lobe epilepsy (PLE), while lateralized onsets predominated in neocortical TLE, and generalized onsets in mesial FLE and occipital lobe epilepsy (OLE). The time to appearance of the most localized/lateralized pattern occurred at the EEG onset in 79% and within 10 seconds of onset in 91% of seizures. Approximately two-thirds of seizures were ultimately classified as localized, 22% generalized, 4% lateralized, and 6% mislocalized. False localization or lateralization occurred almost exclusively in parietal and occipital lobe seizures. Overall, noninvasive ictal EEG adequately localized 72% and correctly lateralized an additional 7% of cases. Ictal EEGs were entirely mislocalized in only two patients and were localized to more than one region in four cases. Arguably, these cases were chosen for surgery because components of the pre-surgical evaluation (ictal EEG included) demonstrated localizing features. Therefore, the localizing value of ictal EEG may be slightly overstated and not necessarily representative of video EEG monitoring results from refractory epilepsy patients overall.

In contrast to the Cleveland Clinic findings, Lee and colleagues found only 42% of nearly 300 neocortical seizures

to be localized.[45] Localized EEGs were more common in lateral TLE (52%) and OLE (70%) than FLE (23%) and PLE (10%). False localization was observed in a minority of EEGs in all groups (4.5–9.9%). Theta rhythms were most common in neocortical TLE while beta activity predominated in seizures arising from the occipital lobe. In a recent study by the same investigators, ictal EEG correctly localized the resected lobe in 63 of 89 patients (71%) with nonlesional neocortical epilepsy who underwent invasive evaluations.[46]

Noninvasive ictal recordings of simple partial seizures (SPS) are significantly less likely to yield useful information compared to partial seizures with overt manifestations. Electrographic changes were detected in only 21% of SPS in one series, more often in those with motor (33%) than nonmotor (15%) manifestations.[47] Proximity of the recording electrode to the motor cortex is one proposed explanation for this finding. The use of additional closely spaced scalp electrodes increases the yield of noninvasive EEG during SPS.[48] Another series found the ictal EEG to be localized in only six of 41 SPS, the majority showing no discernable EEG change.[45] These findings illustrate the limitations of noninvasive EEG during seizures with relatively limited clinical manifestations.

Temporal lobe epilepsy

Mesial temporal lobe epilepsy

Noninvasive ictal EEG manifestations of seizures arising from the temporal lobe have been well described. Rhythmic 5- to 9-Hz activity, localized to the temporal region, appearing at onset or within the first 30 seconds of the electrographic or clinical seizure onset is observed in 80 to 90% of patients with MTLE (Figure 68.1).[27,49–53] Lateralized or nonnlateralized ictal patterns are seen in less than 10% of seizures of mesial temporal origin. We recently identified this pattern in 90% of seizures and 91% of patients with unilateral HS and found that the ictal EEG was localized to the temporal lobe from the onset in 76% of cases.[31] Of 261 extratemporal seizures, none began with rhythmic temporal theta activity, and only 5% had this pattern at some time during the evolution. In pediatric series of MTLE due to HS; 20 (71%) of 28 cases and 21 (60%) of 35 cases, respectively had ictal patterns localized to the temporal region.[54,55] False lateralization has been observed in 0–18% of patients with presumed TLE, however, the higher percentage was reported in patients studied prior to the advent of high-resolution MRI.[27,31,49,50,53] In another series, ictal EEGs were consistently nonlateralized in only 4% of patients with HS or other temporal lobe lesions.[56] Rhythmic theta at ictal onset was significantly more common in patients with moderate to marked hippocampal atrophy (79%) than those with mild or no hippocampal atrophy (19%) and a positive correlation between the median frequency of the initial ictal discharge and the severity of HS has been reported.[52] A seizure-free outcome after temporal lobe resection is significantly more likely in patients with ictal recordings localized to the lesioned temporal lobe (83%), as compared to those with nonlateralized seizures (63%) or seizures that propagate contralaterally (46%).[57] However, rarely the ictal onset is mislateralized to the contralateral temporal lobe in MTLE due to a severely sclerotic hippocampus (the burned-out hippocampus). This was observed in five of 109 cases with suspected TLE who underwent depth electrode evaluation at two large epilepsy centers.[58] Bilateral independent seizure onsets, asynchrony of ictal activity over the two temporal lobes and switch of ictal activity from one hemisphere to the other are predictive of bitemporal epileptogenicity.[59] Lateralized postictal slowing or background attenuation correctly predicts the side of seizure origin in 96–100% of cases.[33,49]

The results of several studies suggest that the yield of additional information with noninvasive ictal recordings is limited when the MRI and interictal EEG are concordant in cases of suspected TLE (i.e., HS with anterior temporal discharges). In the largest series, ictal and interictal EEG lateralization was concordant in 92% of 170 cases; all patients with unilateral hippocampal atrophy had concordant EEG findings.[60] Ictal and interictal EEG was discordant in only 2.9% of patients, all of whom had bilateral interictal discharges. In 84 patients with unilateral hippocampal atrophy and concordant interictal EEG, 76% of ictal tracings were concordant with the presumed side of seizure origin, whereas, 4% were discordant and 20% were indeterminate.[61] Over 90% of patients had an excellent post-operative outcome regardless of the degree to which the ictal EEG agreed with other findings. In another series of 24 patients with unilateral hippocampal atrophy and concordant interictal EEG, ictal recordings were correctly localized in over 80% and lateralized in approximately 90% of seizures.[51] The majority of seizures were localized or lateralized to the side of the imaging lesion and interictal focus in 95% of cases. Concordance of MRI and interictal EEG was most closely associated with surgical outcome after temporal lobe resection; 77–80% of patients were seizure free regardless of the ictal EEG.[62] However, the mere presence of a lesion does not assure causality, as rarely the MRI can be misleading in localizing the seizure onset zone.[63] Video-EEG monitoring provides the opportunity to analyze clinical semiology, rule out nonepilepticss seizures and identify extratemporal abnormalities that may suggest the presence of dual pathology.

Neocortical temporal lobe epilepsy

While, neocortical and mesial temporal seizures may be indistinguishable by noninvasive ictal EEG, some features have been shown to be useful in differentiating the two.[64,65] An initial, regular 5- to 9-Hz inferotemporal rhythm was found to be more specific for hippocampal onset seizures.[64] However, the presence of this pattern requires the synchronous recruitment of adjacent inferolateral temporal neocortex. In fact, seizures confined to the hippocampus produce little or no change on noninvasive recordings.[66] Neocortical seizures are more often associated with irregular, polymorphic 2- to 5-Hz lateralized (less commonly, regionalized) patterns or nonlateralized arrhythmic activity (Figure 68.2).[64,65,67] Patients with seizures with a regular 5- to 9-Hz rhythm at the onset having a temporal or subtemporal distribution were significantly more likely to be seizure free after ATL than those with irregular, slow rhythms (<5 Hz) having a widespread lateral temporal distribution.[68] Bilateral ictal patterns, particularly when appearing early in the evolution of

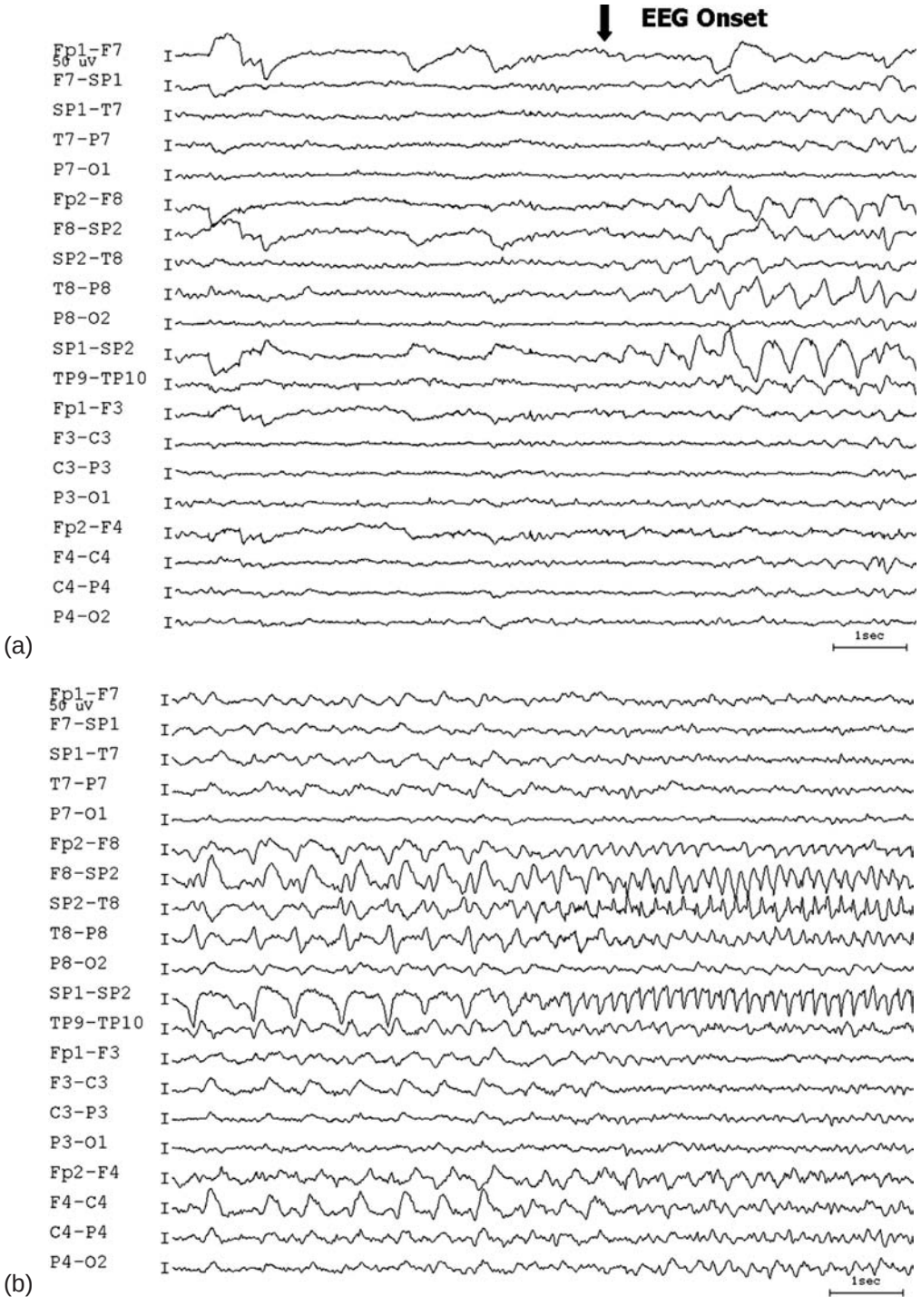

Figure 68.1 Consecutive 10-second epochs of a seizure arising from the right mesial temporal region in a woman with refractory TLE and right HS. The arrow depicts seizure onset from REM sleep (a) with repetitive spiking that evolves to rhythmic theta phase-reversing at SP2 within 10 seconds of EEG onset (b). The clinical onset occurred 30 seconds later.

a seizure[67] and hemispheric rhythmic activity[65] are additional features suggesting neocortical temporal origin. Delta frequency ictal onsets were significantly more common in patients with mild or no hippocampal atrophy (63%) than those with moderate to marked atrophy (13%), further supporting the notion that seizures arising predominately from mesial structures attain greater frequencies than those originating in temporal neocortex.[52] Although lateralized ictal patterns are significantly more common in neocortical TLE than MTLE, nearly three-quarters of neocortical seizures are still localized.[31]

The ictal EEG in frontal lobe epilepsy

Several factors contribute to the reduced yield of noninvasive EEG in FLE. These include the inaccessibility of much of the frontal lobes to surface electrodes, the rapid spread of seizures

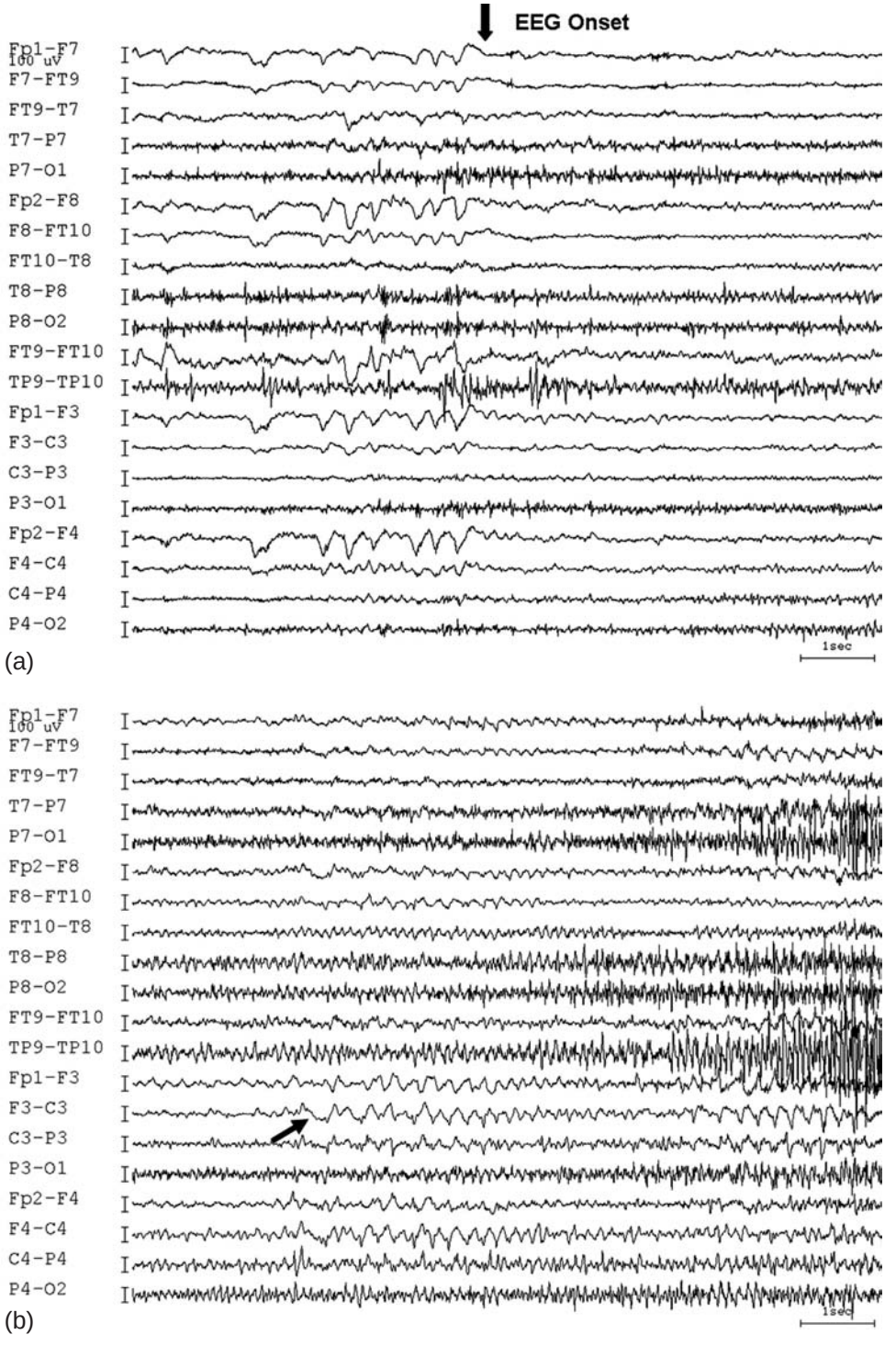

Figure 68.2 Two consecutive 10-second epochs of a seizure in a young woman with a right temporal pole malformation of cortical development and normal mesial temporal structures. EEG onset is characterized by diffuse suppression (a) evolving within seconds to a hemispheric alpha rhythm followed by contralateral rhythmic slowing (b, arrow). Habitual seizures were characterized by a behavioral arrest with oral and manual automatisms evolving rapidly (within 10 to 15 seconds) to a generalized motor seizure beginning several seconds prior to the EEG onset. These findings are characteristic of neocortical TLE.

within and outside the frontal lobe, secondary bilateral synchrony and bilateral epileptogenesis due to bifrontal injury, and variability in size of the seizure onset zone.[69]

Frontal lobe partial seizures are typically brief, beginning and ending abruptly, and are frequently characterized by excessive movement or tonic posturing resulting in obscuration of the EEG.[69–71] In our series of nearly 500 focal seizures, virtually all seizures that were entirely obscured or had no EEG change were of frontal lobe origin.[31] Ictal recordings were either obscured by muscle or failed to identify changes in 44% of 100 subjects with nocturnal FLE.[71] Similar findings are observed in children in whom the ictal EEG commonly shows bifrontal, bilateral independent, multifocal patterns or no identifiable change.[72] Approximately one-third of frontal lobe seizures are not accompanied by discernable rhythms[70,73,74] and another one-third are characterized by nonlateralized

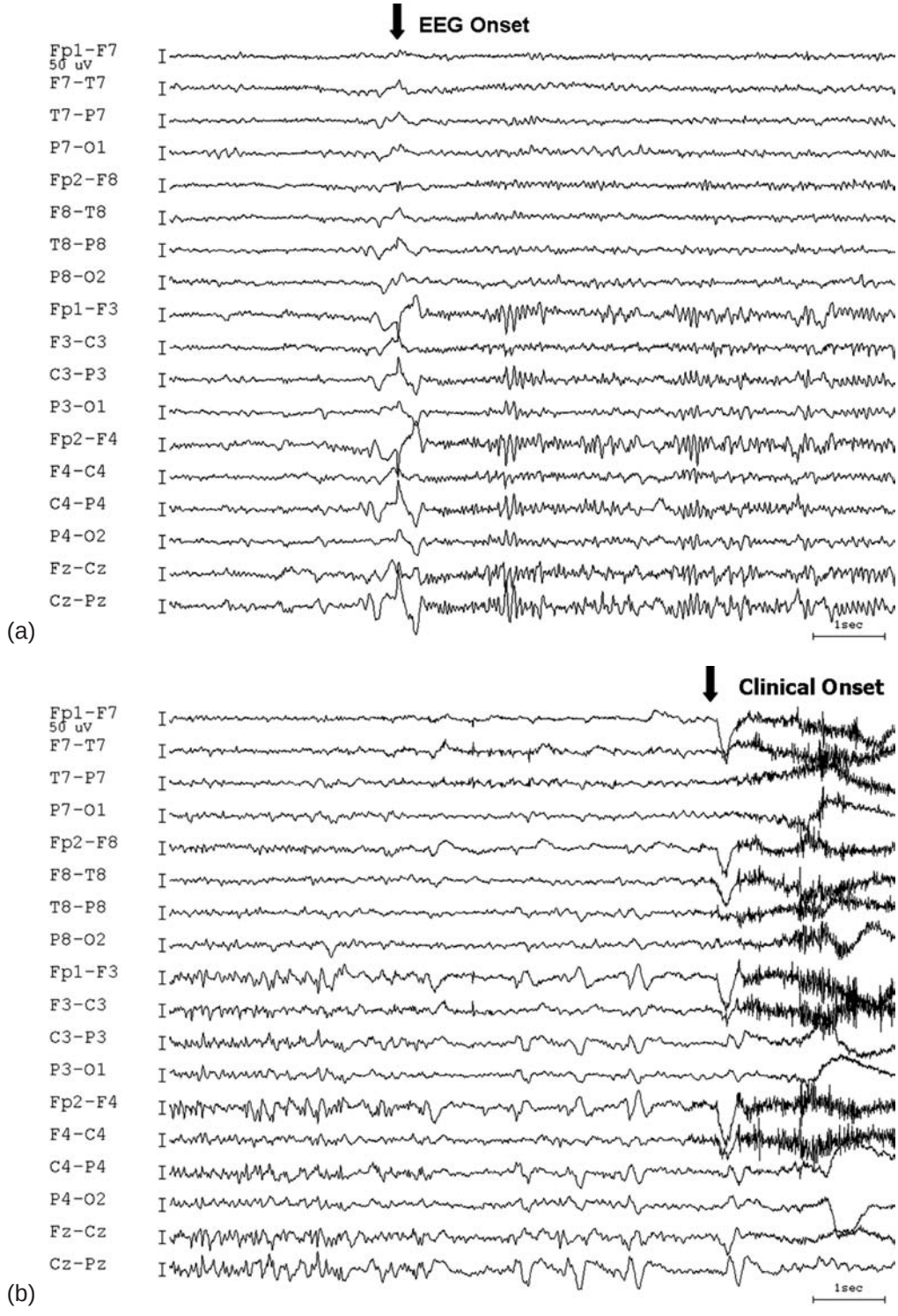

Figure 68.3 Left mesial frontal (SSMA) seizure characterized by brief axial tonic posturing with preserved awareness. The ictal EEG demonstrates a vertex spike (a, arrow) followed by bilateral frontocentral paroxysmal fast activity arising from sleep. Seizures occurred multiple times per night. The clinical onset (b, arrow) occurred 16 seconds later.

slowing, rhythmic activity or repetitive spiking.[69] Lateralized or localized patterns are seen in 33–50% of cases.[69–71,74–76] Mislocalization to the contralateral frontal or temporal region has been described.[70] In contrast to temporal seizures, frontal seizures are less likely to demonstrate focal patterns.[76]

Mesial frontal epilepsy and cingulate gyrus

Seizures arising from the mesial frontal lobe are particularly challenging to localize noninvasively. Supplementary sensorimotor area seizures are typically obscured by artifact of have no definite ictal pattern.[31,73,77] In fact, the clinical and electrographic manifestations are shorter than in seizures arising from virtually any other area.[31] Rhythmic alpha, beta, or theta at or adjacent to the midline was observed in 45% of cases in one small series.[73] In another series, the ictal onset most commonly consisted of generalized suppression or paroxysmal fast activity (Figure 68.3).[31] Rarely, the ictal pattern may be maximal over the contralateral hemisphere. Known as paradoxical lateralization, this phenomenon is observed when a generator is

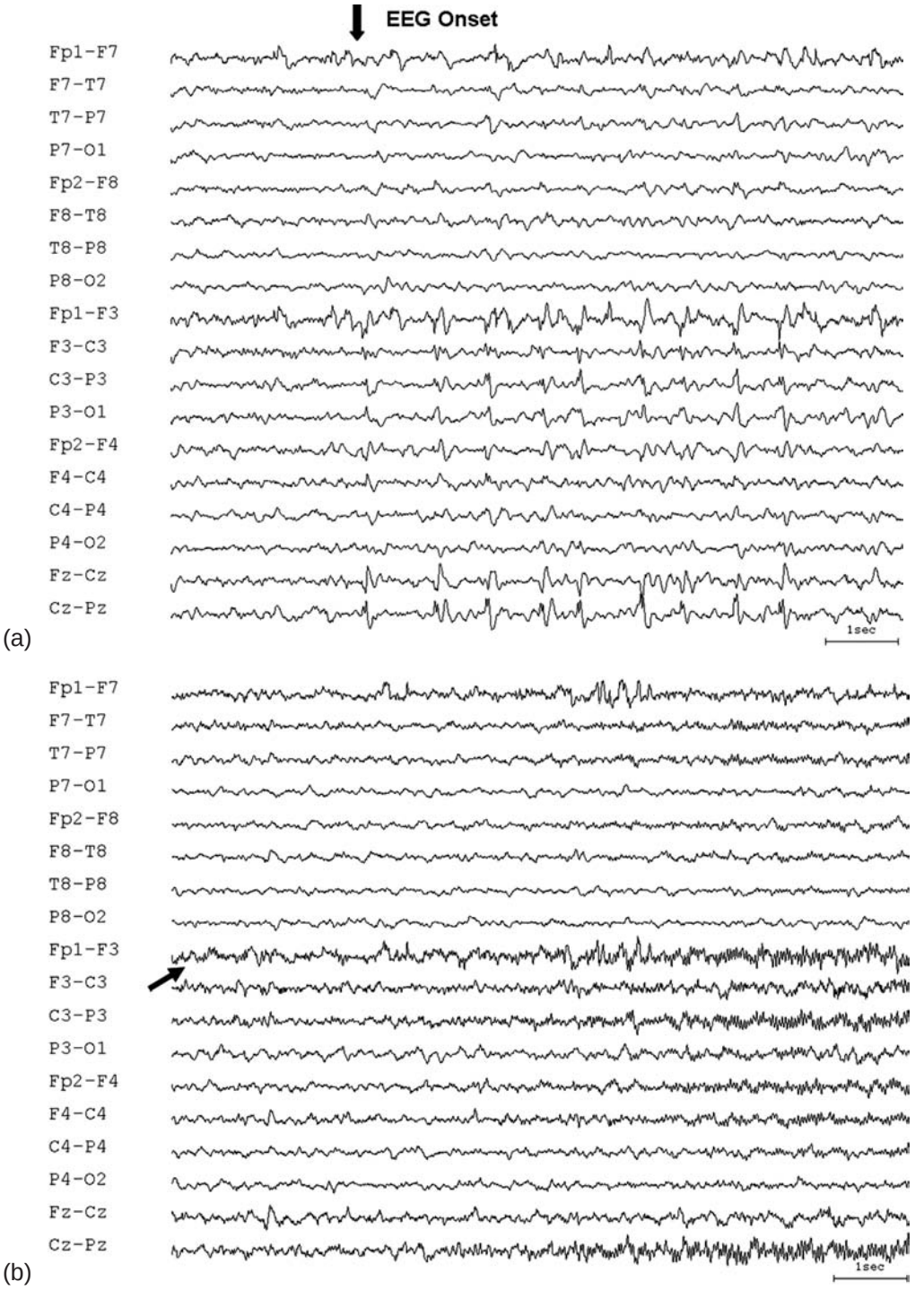

Figure 68.4 Repetitive spiking (a) evolving within 10 seconds to paroxysmal fast activity (b) in a seizure arising from the left dorsolateral frontal region due to a malformation of cortical development.

located within the interhemispheric fissure and produces an obliquely oriented dipole that projects to the opposite hemisphere.

Ictal EEG correlates of seizures arising from the cingulate gyrus have not been adequately detailed. In the only systematic study (see Chapter 44), ictal patterns obtained from seven patients with cingulate lesions on MRI were determined to be regional vertex in four cases; the remainder were nonlocalizable (two) or lateralized (one) to the lesioned hemisphere (personal communication, Eliana Garzon). In only three cases (43%), did the ictal EEG correctly predict the side of the lesion.

Basal frontal epilepsy

The noninvasive EEG is equally challenging in orbitofrontal epilepsy. Among four such cases seizure free following resective surgery in the literature, none had localized ictal recordings.[78–80]

Lateral convexity frontal epilepsy

Seizures arising from the lateral convexity are commonly localized (68% in one series) and typically consist of rhythmic alpha, beta or repetitive spiking (Figure 68.4).[31,77] Focal beta activity at the ictal onset was present in 26% of 54 patients with intractable lateral frontal seizures. Unlike lateralized ictal onsets,

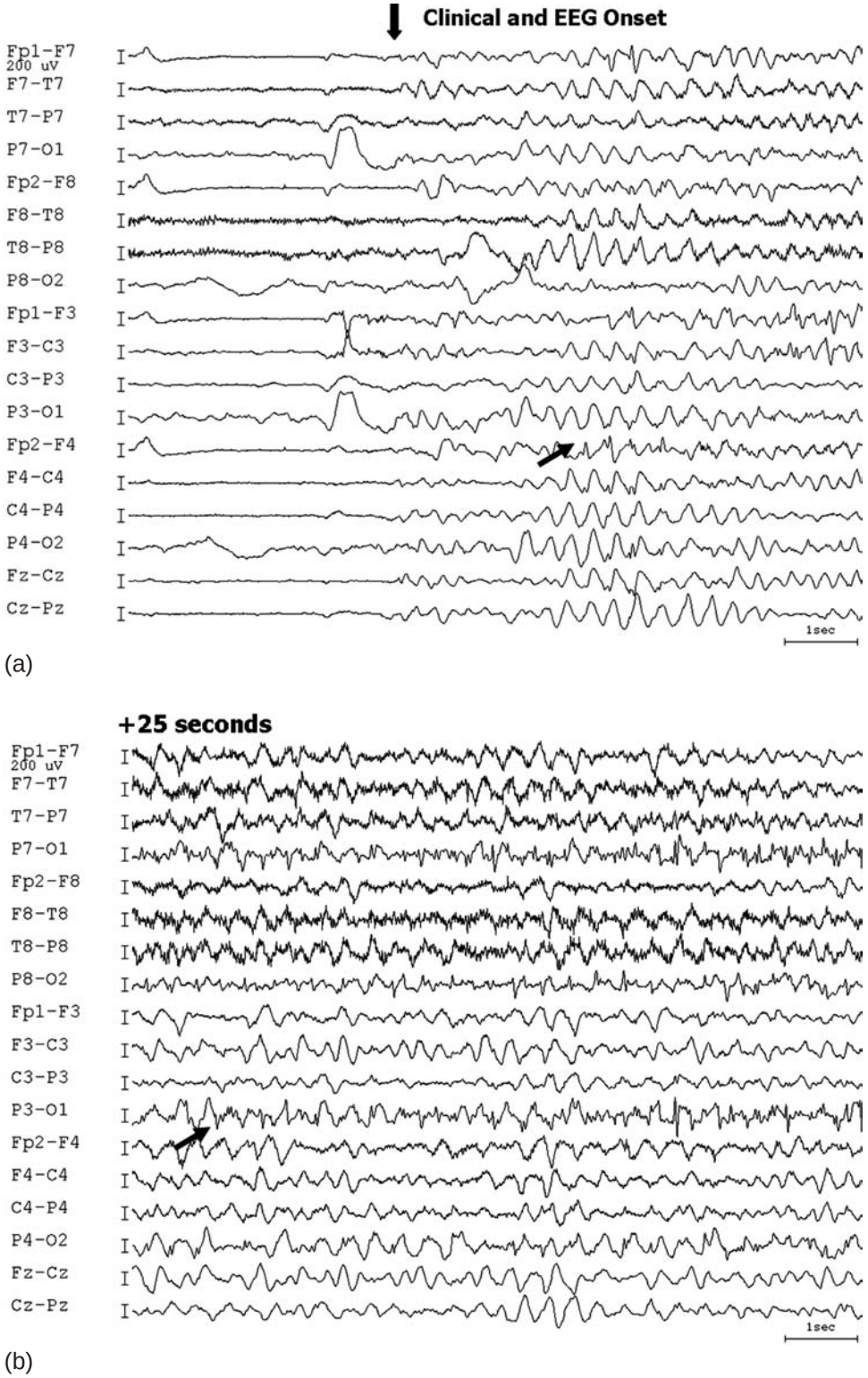

Figure 68.5 Two nonconsecutive epochs of a seizure arising from the left parieto-occipital region. The ictal onset (a) is characterized by rhythmic delta, initially maximal in the left hemisphere that becomes generalized within 2 seconds and evolves to spiking in the contralateral frontal region (arrow). The ictal recording otherwise remains nonlateralized until repetitive spiking (arrow) emerges from the area of the epileptogenic lesion 25 seconds after EEG onset (b).

focal beta at the onset was associated with an excellent surgical outcome independent of MRI findings and the location of the epileptogenic zone.[81]

The ictal EEG in parietal lobe epilepsy

Seizures arising from the parietal lobe usually present with lateralized somatosensory auras or nonspecific sensations evolving to asymmetrical tonic posturing, unilateral clonic activity or contralateral version when the ictal discharge propagates to the frontal region.[82] Temporal lobe activation produces alteration of awareness and automatisms.[82,83] Consequently, the ictal EEG varies with the pathway of propagation and may erroneously suggest temporal or frontal lobe origin. Simple partial seizures of parietal lobe origin frequently produce no discernable EEG change.[47,84] Other

seizure types are more commonly associated with diffuse suppression, nonlateralized rhythmic activity or lateralized changes.[82–84] In a series of 11 patients with lesional PLE, nonlateralized patterns were observed in eight patients; the EEG was localized in only one case.[82] Localized ictal onsets were recorded in 4 of 36 patients with nontumoral PLE, the majority of the others having lateralized patterns.[83] In another early series, lateralized patterns were observed in five of six patients.[85] These initial reports do not detail the location or extent of the epileptogenic zone. In a recent series of 14 seizure-free patients with lateral PLE based on MRI and/or invasive ictal recordings, the noninvasive ictal EEG localized the epileptogenic lobe in only five cases and was lateralized in one, nonlateralized in one, and falsely lateralized to frontal, temporal or occipital regions in seven cases.[86] The Cleveland Clinic series findings were more favorable, as 55% of seizures from seven patients with lateral parietal lesions seizure free following lesionectomy had localized ictal onsets and 62% of recordings were deemed localized.[31] However, mislocalization to the frontal or temporal region was observed in 16% of seizures, and 54% of seizures had independent, bilateral rhythms, highlighting the limitations of noninvasive recordings in PLE (Figure 68.5).

The ictal EEG in occipital lobe epilepsy

As in the case with PLE, the clinical and ictal electrographic manifestations of occipital lobe seizures reflect different patterns of propagation.[87,88] Invasive recordings demon-strate propagation from the occipital region to the mesial temporal structures, the supplementary motor area or dorsolateral frontal convexity before generalization.[88] Infrasylvian spread to the temporal lobe produces alteration of awareness and automatisms. Suprasylvian spread to the mesial frontal lobe produces asymmetric tonic posturing, while propagation laterally results in focal motor or sensory seizures.

Ictal recordings show diffuse suppression or rhythmic activity that is usually generalized but may be lateralized or maximal over the temporo-occipital region.[87,88] Seizures localized to the occipito-temporal region were observed in approximately 50% of cases, however, localization was restricted to the occipital region in less than 20% of case.[87,89] Among six patients seizure free after resective surgery in the Cleveland Clinic series, nearly 70% of seizures had localizing features.[31] However the ictal onset was typically generalized; only 21% of seizures were localized to the occipital region at the onset. The time from EEG onset to appearance of a localized rhythm was longer than seizures arising from any other area. Mislocalization was observed in 28% of seizures; in most cases, occipital seizures were mislateralized to the contralateral occipital lobe, although ipsilateral fronto-temporal ictal patterns were also observed. Even more favorable EEG characteristics were observed in another series of 16 patients with occipital epilepsy seizure free following resective surgery.[90] The ictal EEG was localized in 13 (81%) of 16 cases, and lateralized, nonlateralized and mislateralized in one case each, although the location of lesions within the occipital lobe was not provided.

A recent study was the first to compare the clinical and electrographic manifestations of seizures arising from the lateral and mesial occipital surfaces.[91] Among 41 cases, seizures were correctly lateralized in 20 (49%) and mislateralized in one (2%). The majority of the first five recorded seizures were correctly localized in four (36%) out of 11 patients with laterally originating occipital seizures versus none of 20 patients with mesial occipital seizures. These findings support the widespread and variable propagation of occipital lobe seizures and highlight the limitations of ictal EEG, particularly in epilepsies arising from deep or interhemispheric structures.

Conclusion

Noninvasive EEG remains extremely useful in the localization of focal seizures. However ictal recordings cannot precisely delineate the seizure onset zone. Very little is known about the yield of noninvasive ictal recordings in epilepsies arising from areas such as the orbitofrontal cortex, cingulate gyrus and mesial occipital region. However, anecdotally, it would seem that the value of ictal recordings is limited in these cases. As neuroimaging continues to improve and the need for cost containment increases, the role of noninvasive ictal recordings may need to be redefined.

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69 Indications for invasive electroencephalography evaluations

SR Sinha, NE Crone, and RP Lesser

Introduction

At the dawn of the modern era of epilepsy surgery in the early and middle portions of the 20th century, acute invasive intracranial recordings were commonly used to determine the extent of resection of epileptogenic tissue.[1–3] These recordings typically provided information about interictal epileptiform discharges and only rarely about ictal activity. Thus, they were, and are, helpful in defining the 'irritative zone', the region of cortex that generates interictal epileptiform discharges[4]; however, they usually cannot define the 'epileptogenic zone', the region of cortex that can generate epileptic seizures. With modern advances in imaging techniques (especially MRI scanning) and the use of scalp video-EEG to record actual ictal EEG data, acute invasive intracranial recordings have become a much less important part of the evaluation of patients for epilepsy surgery. However, there are many situations in which chronic invasive intracranial recordings using subdural or depth electrodes are essential for the optimal management of a patient.[5,6] This chapter will discuss the indications for invasive EEG evaluations in the modern era, and will focus on the use of subdural electrodes. Details of the specific techniques are covered in other chapters of this book. Some illustrative examples are given at the end of this chapter.

Selection of patients for invasive EEG recording

A substantial fraction of patients with epilepsy are intractable to treatment with antiepileptic drugs, either due to lack of efficacy or intolerable side effects. For patients with partial-onset seizures who continue to have seizures in spite of adequate trials of two or more appropriate antiepileptic medications, trials of additional medications, even in combination, offer little chance of obtaining seizure freedom.[7] In contrast, for appropriate patients with partial-onset seizures, surgical resection of the seizure focus can offer significant improvement in their seizure control. Beyond basic evaluations such as anatomical (MRI) and functional imaging studies (i.e., PET scans or MR spectroscopy) and interictal EEG recording, presurgical evaluation generally requires ictal video-EEG recording. In situations where the localization of the seizure focus by ictal scalp-EEG and ictal clinical semiology are consistent with a known lesion on imaging studies, surgical resection can sometimes be performed without additional testing (Table 69.1, Figure 69.1a). An additional requirement is that the lesion be far removed from eloquent cortical areas (such as motor cortex or language areas). A common example is unilateral mesial temporal sclerosis on MRI with clinical and EEG findings consistent with a focus in that temporal lobe.[8] Another example is a patient with a known tumor in the region of ictal-EEG onset. Such patients can often proceed to surgical resection without invasive EEG monitoring[9]. In fact these cases are often the ones in which surgery is most successful in controlling seizures.

However, there are many situations in which noninvasive testing is inadequate for proceeding to surgical resection. Jayakar proposed that relative indications for invasive EEG recording include normal imaging, extratemporal location, discordant noninvasive data, proximity to eloquent cortex, tuberous sclerosis, and cortical dysplasia.[10] In broader terms, any situation where the criteria in Table 69.1 are not met should be considered for possible invasive EEG monitoring. These include situations where the ictal scalp-EEG is nonlateralizing (see Case 1) or lateralizing but nonlocalizing (see Case 2). Walczak *et al.* found that scalp-EEG lateralized the epileptogenic region to one side in 47–65% of extratemporal cases and 76–83% of temporal lobe cases.[11] Other authors have reported that scalp EEG was localizing in as few as 42% of cases with a neocortical onset and may falsely localize the site of onset in 4.5–9.9% of cases.[12] The use of additional scalp electrodes beyond the standard international 10–20 system, may improve localization.[13] Even with a localizing scalp-EEG, invasive recording is often necessary in cases where there is no corresponding lesion on imaging to guide the resection (Figure 69.1b). Invasive recording is essential in situations where noninvasive tests are discordant. One example of this situation would be when the ictal EEG pattern does not co-localize with an obvious imaging abnormality (see Case 5).

Lastly, invasive recording can be useful in situations where the ictal pattern or lesion is close to eloquent cortex, e.g., motor cortex or language areas (see Cases 3 and 4). Once the site of seizure onset has been determined, using either invasive or noninvasive means, one must consider the functional consequences of resecting the presumed epileptogenic tissue. This is based on several pieces of information, including normal functional neuroanatomy. In addition tests such as the intracarotid sodium amobarbital (Wada) test are useful

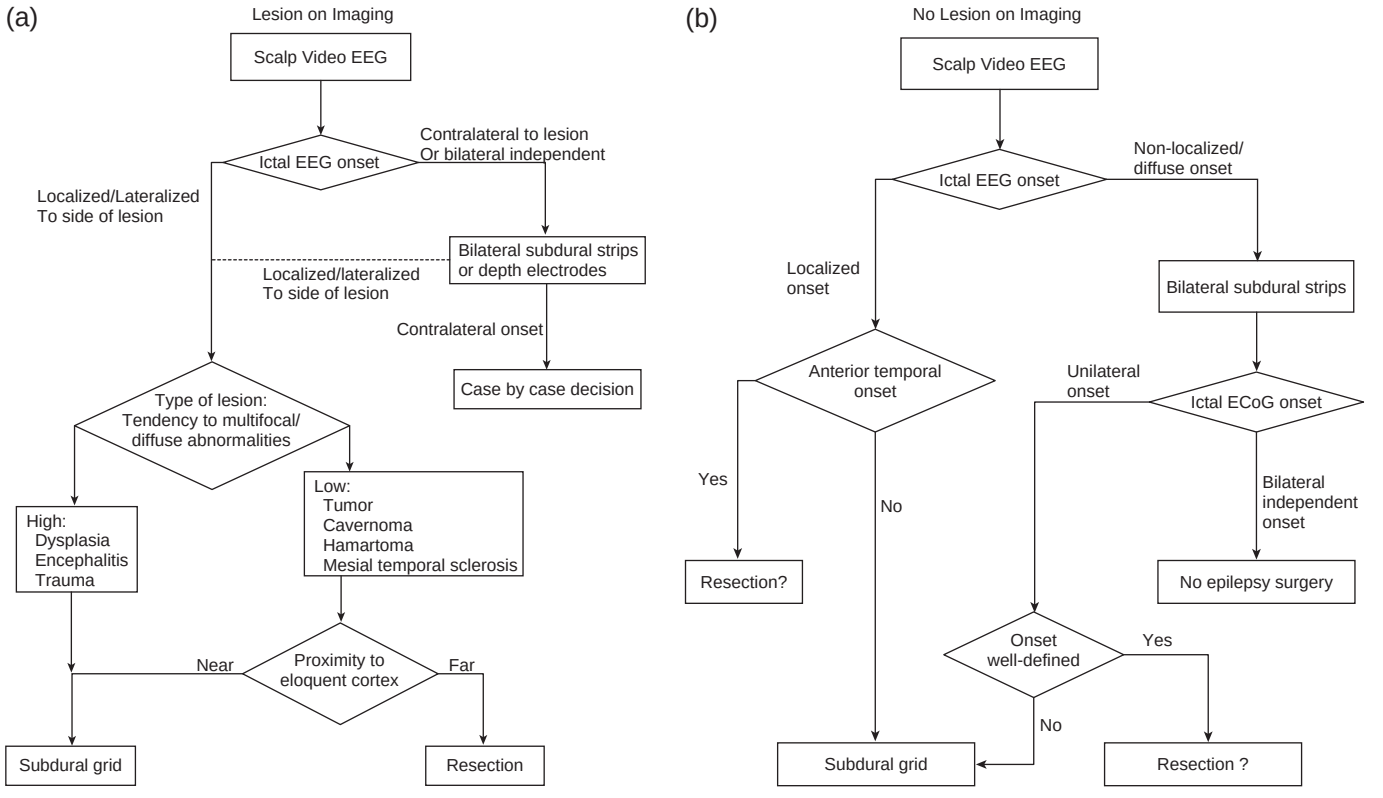

Figure 69.1 Flowcharts demonstrating the decision-making process involved in determining if a particular patient needs invasive EEG monitoring. a. Suspected epileptogenic lesion on imaging studies. b. No epileptogenic lesion on imaging studies. See text for more details.

for lateralization of language[14] and memory.[15] Functional MRI and magnetoencephalography are also being increasingly used for localization of language, sensation, movement, and memory. However, at present cortical mapping using implanted subdural electrodes provides a unique opportunity to precisely map the relationship between the epileptogenic zone and functional areas.[16,17] Furthermore, because the same electrodes are used for both cortical mapping and mapping the epileptogenic zone, the precise relationship between eloquent cortex and the epileptogenic zone can be determined. Resection can be planned using the subdural electrodes as landmarks (see Case 3). Also, unlike mapping with acute invasive electrodes during surgery, this type of mapping allows sufficient time for confirming results and mapping large areas, including those outside the immediate exposure of the craniotomy. One of the major disadvantages of stimulation is the possibility of provoking epileptiform discharges that can confound the results of testing and even provoke clinical seizures[18]; for example, see Case 4.

In some situations in which the scalp-EEG adequately identifies a seizure focus that has a corresponding lesion on imaging studies invasive monitoring might still be appropriate. The most common examples are situations in which the seizures are associated with multifocal damage to the brain or in which the epileptogenic zone is larger than the abnormality apparent on imaging studies. These situations include meningoencephalitis, tuberous sclerosis, head trauma, cortical malformations. For example, with malformations of cortical development or focal cortical dysplasias, the epileptogenic area is often larger than the lesion visualized on imaging studies and possibly extends well beyond the histological lesion.[19–21] In such cases, mapping of the 'epileptogenic zone' using invasive EEG might be important for successful surgery even when scalp EEG, clinical semiology and imaging are in rough agreement.

Some have proposed the use of direct stimulation of intracranial electrodes to localize seizure foci. Some studies have suggested that the threshold for provoking clinical seizures and/or afterdischarges is lower near the seizure focus. However, many factors beyond the intrinsic excitability of a piece of tissue determine its response to electrical stimulation. This includes the quality of contact between the electrode and the cortex (e.g., intervening cerebrospinal fluid, hematoma, or meninges), the orientation of the cortex in relationship to the electrode(s), and the background state of the brain at the time of stimulation (e.g., awake vs. asleep, attentive vs. inattentive). In addition, there is significant variability in thresholds at

Table 69.1 Requirements for proceeding to surgery without invasive recording

1. Well-localized ictal-EEG.
2. Semiology consistent with presumed seizure focus.
3. Known lesion by imaging studies at site of seizure focus.
4. Absence of other candidate intracranial lesions.
5. Seizure focus remote from known eloquent cortex.
6. Presumed etiology of epilepsy does not predispose to diffuse or multiple foci.

different points within a small area and at the same point during different trials.[18] Some have suggested that electrical stimulation could be used to provoke afterdischarges/seizures to confirm the location of the seizure focus after it has been mapped by other means[22]; however, we have not found this to be reliable.

Advantages of invasive EEG recordings

Invasive recordings offer many advantages compared to scalp-EEG. These include improved spatial resolution, sensitivity and frequency range, and decreased noise from the environment and from the patient (e.g., EKG and muscle artifact). It has been estimated that an interictal spike needs to activate >6 cm^2 of contiguous cortex to be detected by a scalp electrode.[23] Thus, many epileptiform discharges that are apparent on intracranial recordings are missed on scalp EEG.[24,25] The same epileptiform discharge recorded with subdural electrodes will be approximately an order of magnitude larger in amplitude compared to scalp-EEG.[26] In addition to increased sensitivity, intracranial EEG also broadens the frequency range that can be recorded. The improved frequency range is especially important for neocortical seizure foci, where the ictal pattern often consists of beta and gamma, or higher, frequencies. Higher frequencies are preferentially attenuated by the skull and scalp and are additionally obscured by muscle artifact. Ultrahigh frequencies, which may prove to be useful for seizure localization,[27] can also be recorded with invasive techniques but not with scalp-EEG. Another advantage of invasive recordings is the ability to access structures that are not well evaluated with scalp EEG. These include cortical areas such as the orbitofrontal portion of the frontal lobe, basal portions of the temporal and occipital lobe and interhemispheric portions of the frontal, parietal or occipital lobes (see Case 4). They also include deep structures such as the mesial temporal lobe, periventricular nodular heterotopia,[28] and other deep lesions.

Disadvantages of invasive EEG recording

Beyond the basic risks related to undergoing anesthesia for a surgical procedure, invasive recordings also pose a risk of hemorrhage, infection and cerebral edema. Complication rates are highly variable and depend on many factors including the expertise/experience of the surgeon,[29] the type of procedure, the number of electrodes being used, and the length of implantation. For example, in one series, complications were significantly more likely in cases with >60 electrodes, >10 days of implantation, older age of patient, and left-sided procedures.[30] Complication rates also appear to be declining with time, likely as a result of changes in electrode design, better aseptic techniques, and decreased implantation times.[31] These factors help explain the broad range of complication rates in the published literature. For subdural grid electrodes, infection rates range between 4–14% and bleeding rates are between 3–8%.[30,32,33] Infarction and significant cerebral edema are much rarer. For subdural strip electrodes placed through burr holes, complication rates are generally much lower, 1–4%,[33–35] and primarily involve infection and hematoma. Cerebral edema is rarer, but more likely when large numbers and/or bilateral strips are used. With depth electrodes, the main complication is hemorrhage, with rates in the 1–4% range.[36]

Another important disadvantage of invasive recordings is their limited coverage. Unlike scalp recordings, which typically provide a sampling of all accessible cortical regions, invasive recordings only cover specific areas.[37] Thus, if the actual seizure focus is covered by an electrode, than it will be correctly identified; however, if it is not, then the apparent seizure focus will appear to be the first location that is covered by an electrode. However, this could be a site of seizure spread, not seizure onset. An extreme example would be a situation where the seizure focus is actually in the right hemisphere but subdural electrodes are placed only over the left hemisphere (based on falsely lateralizing imaging and/or scalp EEG recordings). In one series of patients, poor sampling of the epileptogenic zone was felt to be responsible for a failure to localize the seizure focus in 13 out of 110 cases.[38] Thus, great care needs to be taken in evaluating all the noninvasive data to plan placement of the invasive electrodes. Sometimes, this concern also forces the use of larger numbers of invasive electrodes than would be necessary otherwise, i.e. if the noninvasive data are unclear or discordant, more electrodes may be necessary to cover the possible areas of seizure onset.

Another disadvantage of invasive electrodes is the additional cost incurred, which includes the surgical procedures, the electrodes themselves, and a longer hospital stay, typically about 7–10 days and including 5–7 days of video EEG monitoring.

Case examples

Case 1: Scalp EEG is nonlateralizing

This patient was a 33-year-old right-handed man with diabetes mellitus type I and hypothyroidism and seizures since age 29. Seizures began with a feeling of *déjà vu*, and tingling in the arms, and typically progressed to staring, confusion and oral automatisms. Seizures had responded only partially to trials of several medications. Physical exam was significant for some deficits in short-term memory but was otherwise nonfocal. MRI of the brain and PET scan were normal. Previous EEGs had shown some spikes and focal slowing in the left temporal regions. Video-EEG monitoring with scalp-EEG recorded eight typical seizures; two had their onset in left temporal-frontal head regions; the others were nonlocalizing. In the absence of any abnormality on imaging studies, it was felt that the scalp-EEG data was not sufficient to lateralize the patient's seizure focus. Therefore, bilateral subdural strips were placed through burr holes over the frontal and temporal lobes (Figure 69.2a). On this admission, all clinical seizures showed a left temporal-frontal onset (a more precise localization was not possible with the limited sampling provided by strips). In addition, four electrographic seizures, without obvious clinical accompaniment, were also recorded; three

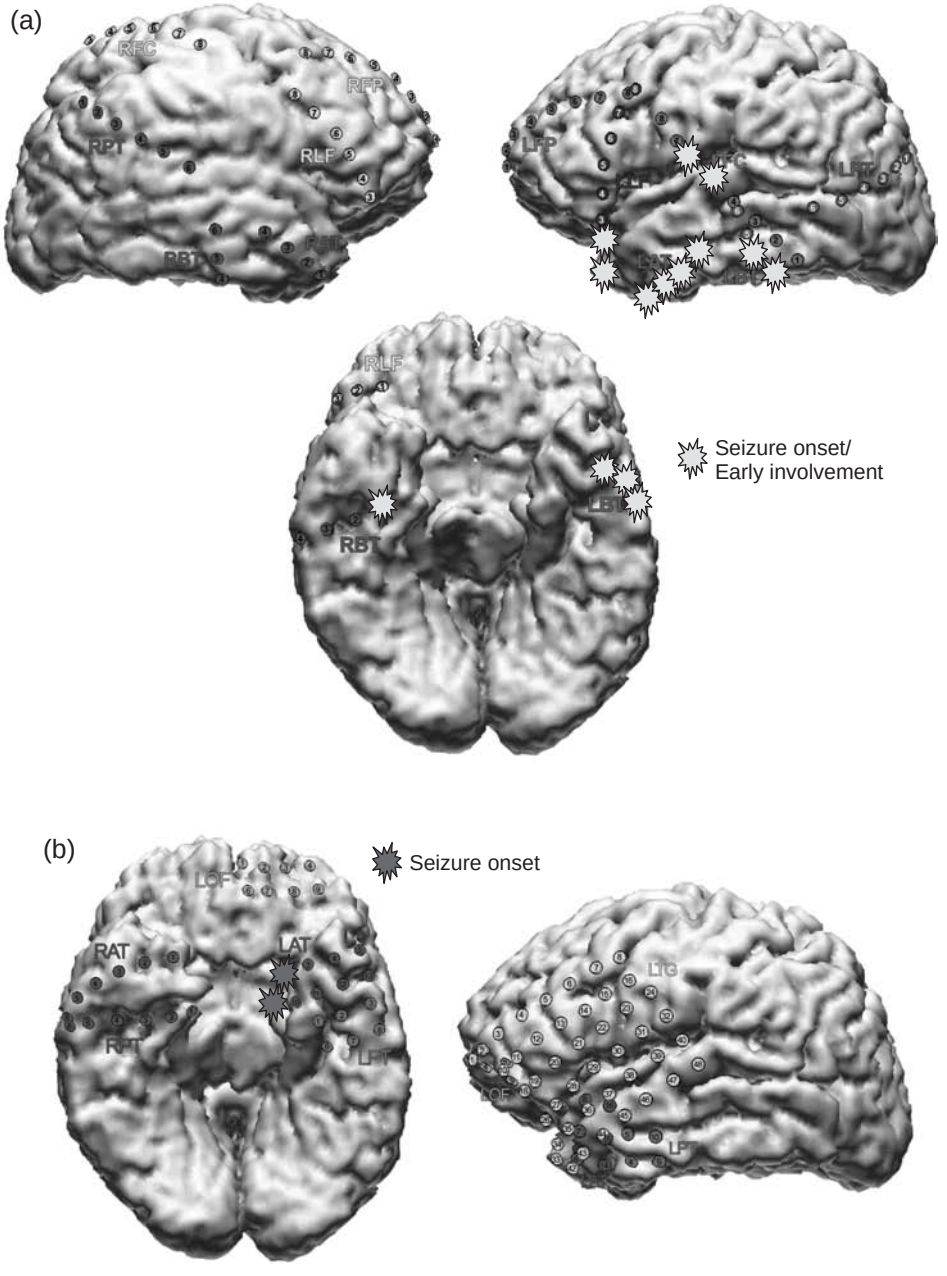

Figure 69.2 See case 1 for details. a. Reconstructed images based on preoperative MRI of the brain and postoperative 3D head CT showing the locations of subdural strips used to lateralize the patient's seizures. The electrodes where seizures appeared to start are indicated. Note: due to the limited coverage obtained with subdural strip electrodes, it is usually not possible to distinguish between the true seizure onset and areas which may only be involved early in the seizure. b. Reconstructed images showing the grids and subdural strips used to localize the patient's seizures. The electrodes where the seizures started are indicated.

originated from the left temporal-frontal region; however, the fourth suggested a possible right-sided focus. Of note, the subdural strips covering the right temporal lobe were not symmetric with those on the left in the anteromesial portion of the temporal lobe (Figure 69.2a, inferior view). Thus, while the majority of the evidence suggested a left temporal-frontal seizure focus, a right temporal focus with rapid spread to the left might have been missed.

In the next step, the patient had extensive subdural grids placed over the left temporal and frontal lobes, including the orbito-frontal surface and the mesial and basal portion of the temporal lobes (Figure 69.2b). Two subdural strips were placed over the mesial/basal portion of the right temporal lobe through a burr hole. On this admission, all seizures originated from the most mesial and anterior contacts over the left temporal lobe. At the completion of this recording, the patient underwent a standard left temporal lobectomy, including the amygdala and hippocampus. As a result, the patient had marked improvement in his seizures.

This case provides a good example of the utility and limitations of invasive EEG recording. Without intracranial electrodes, it would not have been possible to localize the patient's seizure focus and provide the opportunity for surgical resection. However, this case also points out the limited coverage provided by intracranial electrodes. A larger number of electrodes could have been placed during the first

surgical procedure, but at greater risk to the patient. Often, subdural strips, as in the first procedure, are adequate to localize the seizure focus. However, this case also illustrates the difficulties in accurate placement of subdural strips through burr holes.

Case 2: Scalp EEG is lateralizing but nonlocalizing

The patient was a 29-year-old right-handed man with a history of meningoencephalitis at age 6 and seizures since age 9. His seizures consisted of loss of awareness, oral automatisms and drooling. His seizures occurred approximately once a month, in spite of trials of multiple medications. Physical examination was significant for loss of vision in the left eye only. MRI of the brain was normal. A PET scan showed subtle left temporal hypometabolism. Video-EEG with scalp electrodes showed diffuse semirhythmical slowing in the left fronto-temporal region followed by build-up of rhythmic activity in the temporal-frontal head regions, maximum in the temporal regions. Thus, scalp-EEG was lateralizing but not localizing. Therefore, the patient underwent placement of extensive subdural grid electrodes covering the left temporal and frontal lobes, including the orbitofrontal region and the mesial and basal aspects of the temporal lobe (Figure 69.3a). With these electrodes, the seizures appeared to originate from the most medial and anterior contacts on the temporal lobe (Figure 69.3b). The patient underwent a standard left anterior temporal lobectomy and showed marked improvement in the control of his seizures. This case illustrates the situation of a nonlesional patient in whom the scalp EEG was lateralizing but not localizing and intracranial electrodes were necessary for precise localization.

Case 3: Scalp EEG localizes the epileptogenic region to be near eloquent cortex

The patient was a 34-year-old right-handed woman with a history of intractable complex-partial seizures (staring and decreased responsiveness) that remitted for several years after resection of a left posterior temporal dysembryoplastic neuroepithelial tumor. However, her seizures subsequently returned including some secondarily generalized tonic-clonic

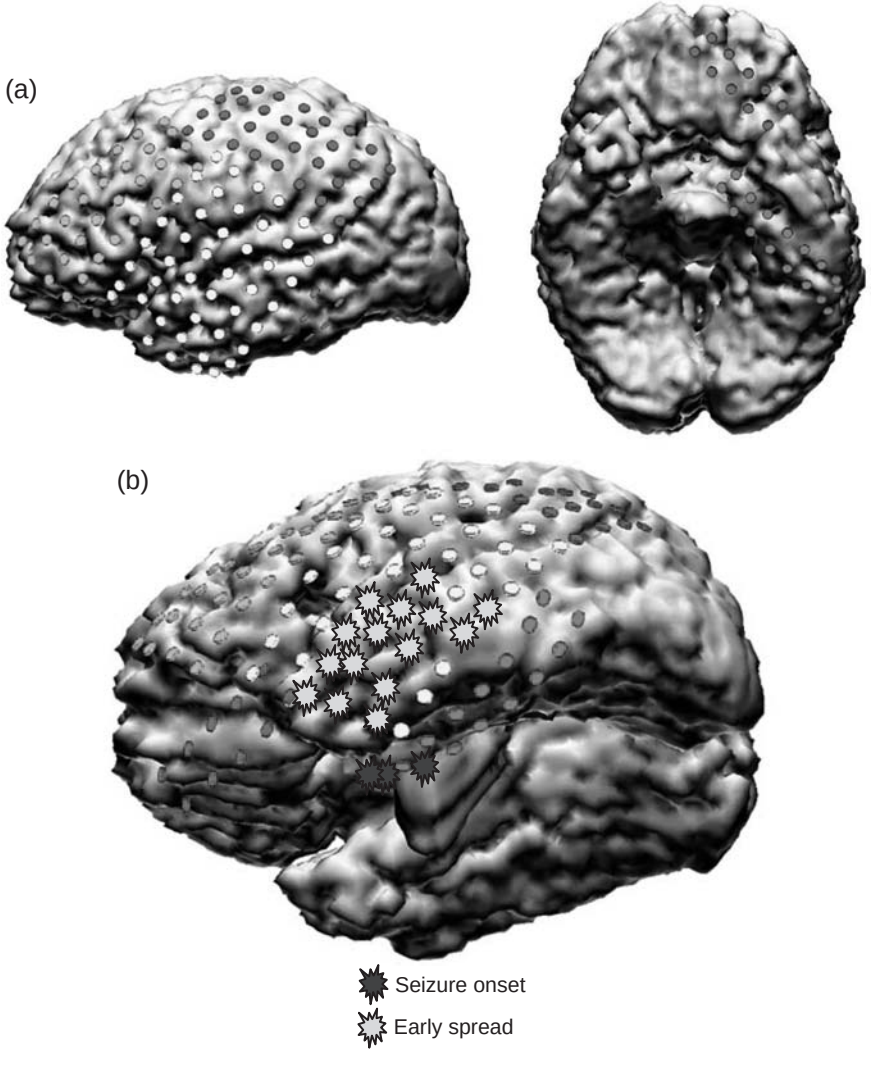

Figure 69.3 See Case 2 for details. a. Reconstructed images showing location of subdural grids (lateral and inferior view). b. Reconstructed image (inferior oblique view) showing the sites where the patient's seizures started and those involved very early in the seizure.

seizures and episodes of complex-partial status epilepticus, in spite of continued use of multiple antiepileptic medications. Video-EEG monitoring with scalp electrodes confirmed that the seizures still originated from the left temporal region. MRI of the brain showed no evidence of residual or recurrent tumor. Intracarotid sodium amobarbital test (Wada test) had previously shown that the patient's left hemisphere was dominant for language. Due to the proximity of eloquent cortical areas to the presumed area of seizure focus, a large subdural electrode array was placed over the posterior portion of the left temporal lobe (extending up to the frontal and parietal lobes as well) with some additional strips wrapping around the inferior aspect of the temporal lobe (Figure 69.4a). Several clinical seizures were recorded and appeared to originate from the lateral contacts on the left temporal lobe. In addition, there were electrographic seizures arising from contacts on the lateral aspect of the basal temporal-occipital cortex. When language function was mapped using electrical stimulation of these same electrodes (Figure 69.4b), some language areas were found to overlap with contacts involved in the electrographic seizures. Thus, the resection margins (Figure 69.4a, dashed lines) were selected to preserve all areas with significant language function, even though this left some presumably epileptogenic areas intact. After this resection, the patient had some limited improvement in her seizures; her language function was entirely preserved. This case illustrates the situation in which both scalp EEG and a known lesion localize the epileptogenic region near eloquent cortical areas and intracranial electrodes are used both for precise seizure localization and for functional mapping. It also illustrates the importance of removing the entire 'epileptogenic zone' for seizure control.

Case 4: Lesion is in a location not well-surveyed by scalp EEG and near eloquent cortex

The patient was a 19-year-old right-handed woman with seizures since age 14. Seizures consisted of flashing lights in the left inferior quadrant of the visual field followed by pounding headaches. These occurred 4–5 times per week in spite of trials of multiple antiepileptic agents. MRI of the brain revealed a calcified lesion in the right occipital region; cerebral angiography was unremarkable (Figure 69.5a). Scalp EEG revealed seizures originating in the right occipital region, near electrode O2. Because of the deep midline location of the lesion and the proximity to primary visual cortex, it was felt that scalp-EEG was not sufficient to precisely delineate the epileptogenic zone, and differentiate it from eloquent cortex. Thus, the patient underwent invasive EEG monitoring. A large grid was placed over the right occipital region and a smaller grid was placed in the interhemispheric fissure between the two occipital lobes (Figure 69.5b). Both interictal and ictal recordings showed that the seizure focus was limited to the superior contacts of the interhemispheric grid (Figure 69.5c). This was superior

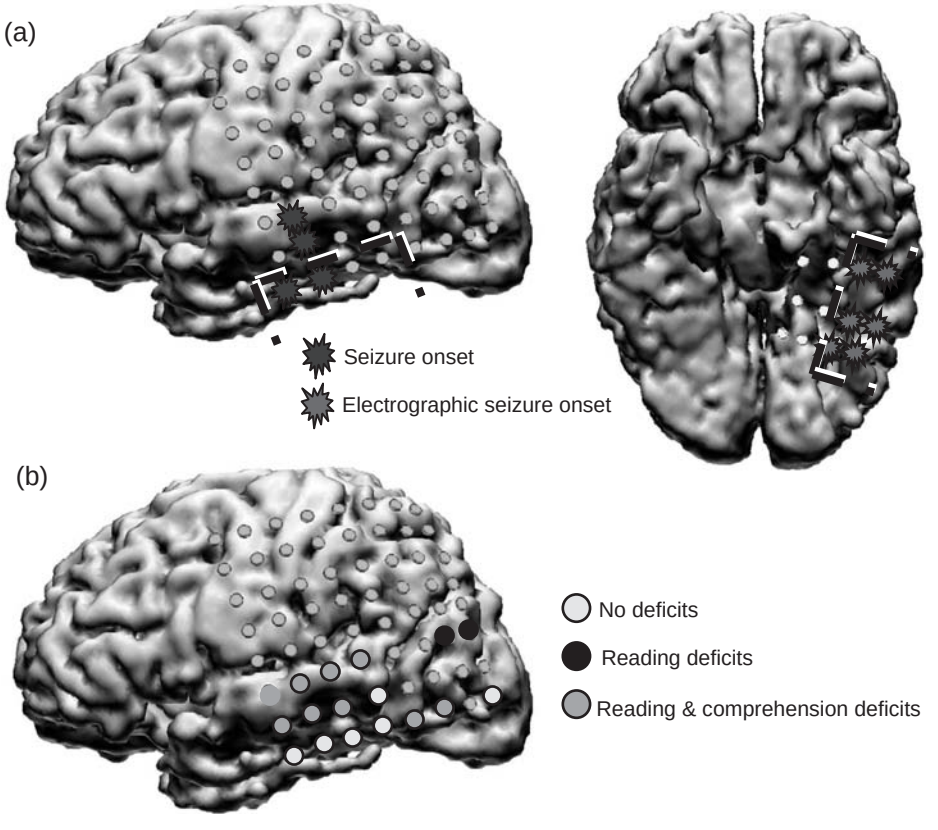

Figure 69.4 See Case 3 for details. a. Reconstructed images showing location of grids along with the site of seizure onset (both clinical seizures, blue, and electrographic seizures without associated clinical activity, red). The dashed lines represent the margins of the planned resection. This based on consideration of the site of seizure onset and the results of cortical mapping shown in b. b. Results of cortical mapping of language function.

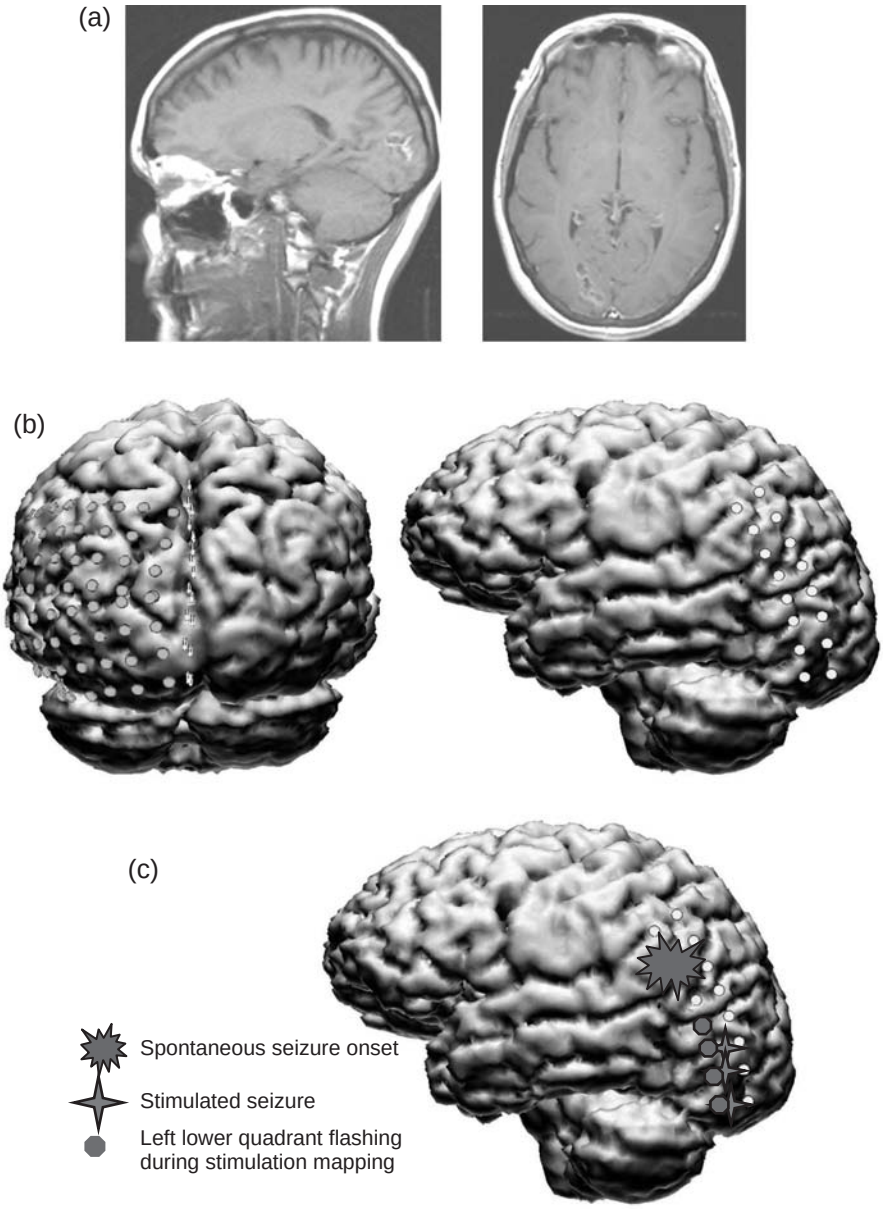

Figure 69.5 See Case 4 for details. a. Sagittal and axial T1-weighted MRI showing location of calcified lesion in the midline of the right occipital lobe. b. Reconstructed images showing the grids placed in the interhemispheric fissure between the occipital lobes and on the lateral aspect of the occipital and parietal lobes. c. Reconstructed image showing site of seizure onset along with results of cortical mapping and sites where stimulation provoked seizures.

to the presumed primary visual cortex based on MRI and cortical stimulation mapping. Thus the resection was tailored to remove the known lesion and the region covered by these contacts, with the goal of sparing vision. Note the occurrence of electrical stimulus evoked seizures from regions that were not the focus for the spontaneous seizures. After surgery, the patient continued to have occasional simple partial seizures consisting of flashing lights and headaches. She also had an irregular inferior quadrant visual defect in the left hemifield, but most of her vision on that side was preserved. In this case, although the scalp-EEG suggested a seizure focus near a known imaging abnormality, invasive EEG was necessary for two reasons. First, the abnormality was deep to the surface of the brain in an area not easily assessed by scalp-EEG. Second, the abnormality was near eloquent cortex.

Case 5: Scalp-EEG and imaging are discordant

The patient was a 22-year-old right-handed man with seizures since age 21. Seizures consisted of staring, inappropriate answers to questions, automatisms, and excessive drooling with no recollection of the event. Seizures continued every 1–2 months in spite of multiple medications. MRI of the brain showed a 1 cm lesion in the posterior portion of the cingulate gyrus on the right (Figure 69.6a), which had not changed for over 6 months. By MRI plus magnetic resonance spectroscopy, the lesion appeared to be a low-grade tumor. Routine EEGs were normal. With video/EEG with scalp electrodes, interictal spike- and slow-wave complexes were seen over the anterior to middle portion of the right temporal lobe. With his typical seizures, right temporal activity was noted at onset. Even though scalp-ictal and interictal-EEG and clinical semiology suggested seizure

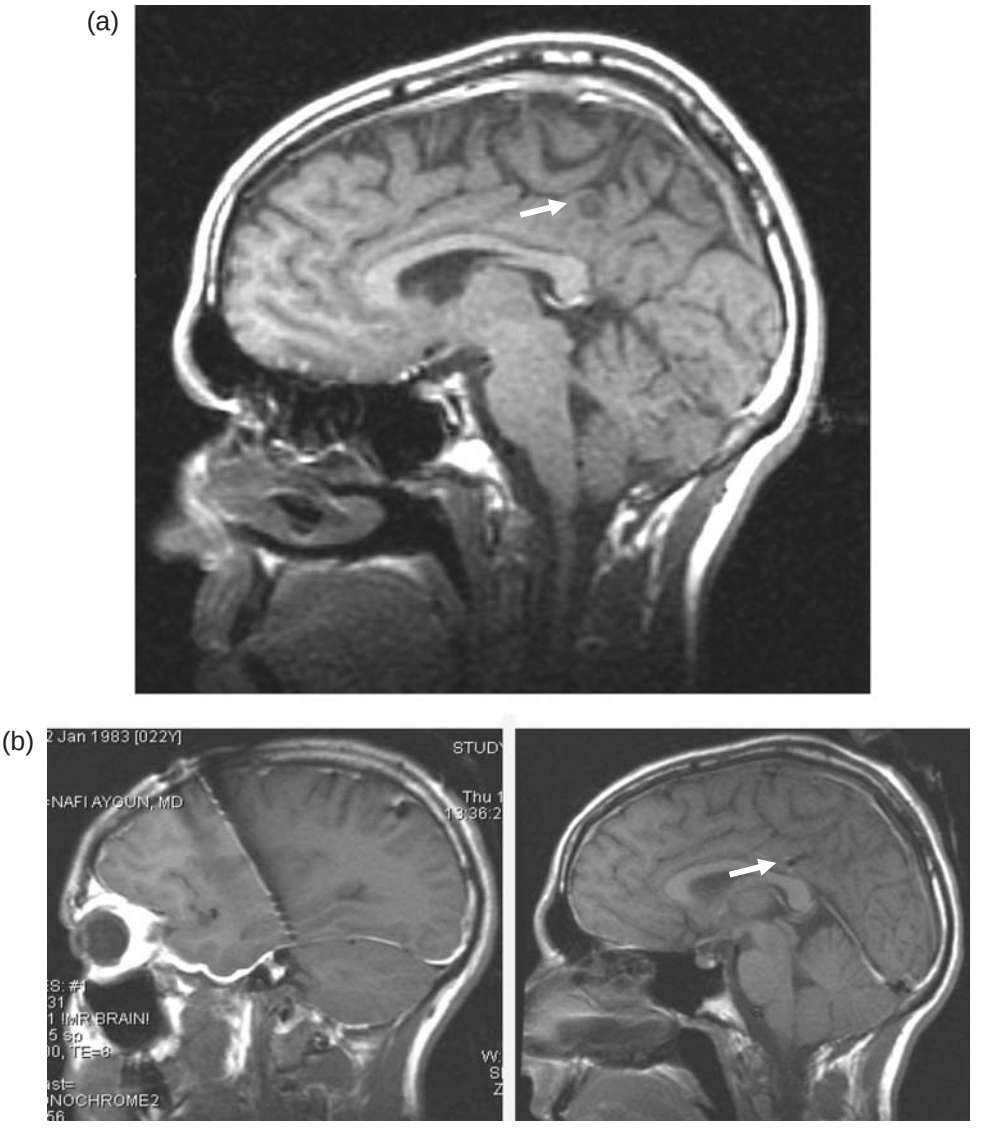

Figure 69.6 See Case 5 for details. a. Sagittal T1-weighted MRI showing location of lesion near right cingulated gyrus (arrow). The remaining of the MRI was normal. b. Sagittal T1-weighted MRI showing track of depth electrodes placed in the right hippocampus (left), and cingulate gyrus (right, arrow).

onset in a surgically favorable site, the anterior right temporal lobe, the presence of a lesion near the right cingulate gyrus raised concerns that scalp-EEG might have mislocalized the site of seizure onset. For this reason, depth electrodes were placed in the right amygdala, right hippocampus and through the right cingulate lesion (Figure 69.6b). Depth electrode recordings revealed that the earliest ictal discharges were in the right cingulate lesion, preceding discharges in the right hippocampus by 6–9 seconds. Thus, the right temporal lobe was a site of seizure spread and may have produced much of the clinical symptomatology (the 'ictal symptomatogenic zone'[4]) but was not part of the 'epileptogenic zone.' The patient underwent resection of the right cingulate lesion. After surgery, the patient no longer had seizures and had no deficits. In this case, invasive electrodes were essential in resolving differences between scalp-EEG, which localized the seizure focus to the right temporal region, and a known lesion at a site not easily assessed by scalp EEG.

Summary

As the above examples illustrate, there are many unique situations that can arise in the course of evaluating a patient for epilepsy surgery. Studies and procedures must be tailored to each individual situation; however, there are basic principles that can be applied as shown in Figure 69.1 and Table 69.1. Invasive EEG recording is neither something to be avoided nor something to use indiscriminately. In situations where there is uncertainty about the location of the seizure focus or about the safety of resecting the seizure focus, i.e., due its to proximity to eloquent cortex, invasive EEG can be invaluable. However, it is also important to acknowledge the risks and limitations of invasive EEG evaluations. First, the question(s) to be addressed by the invasive EEG recordings should be formulated; only then can a surgical plan be made that is likely to be implemented with an acceptable level of risk compared to the likely benefit. If appropriate questions and plans cannot be formulated, invasive recordings may not be needed.

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70 Invasive electrodes in long-term monitoring

GH Klem and S Nehamkin

The ability to provide long-term monitoring implies that there are adequately trained technologists, skilled in the use of a variety of monitoring equipment. This equipment includes EEG instrumentation, video recording devices, and electrical stimulation equipment to map functional cortex with either direct cortical stimulation of invasive electrodes or evoked potentials from the scalp or invasive electrodes. The variety of electrodes, both scalp and invasive, extracranial as in eye and EKG electrodes, and other devices including pulseoximetry to monitor for oxygen desaturation during events are also routinely used in the long-term monitoring setting. Particular training in the recognition and management of seizures and medical emergencies must be emphasized. Incorporation of these diverse techniques routinely used in both adult and pediatric long-term monitoring units often make the technologist's role significantly more demanding than in the routine EEG laboratory.

In April 1939, Penfield performed trephination over both temporal regions and placed electrodes on the dura, intending to lateralize seizure origin in a patient with bitemporal epilepsy. The patient underwent serial EEGs with this technique. Since this time in medical history it has been shown that localization of epileptic foci and areas of elequent cortical funcation with appropriately placed epidural, subdural, and depth electrodes has helped to make epilepsy surgery a safe and efficacious option for the successful treatment of epilepsy that is refractory to medication. Invasive electrodes can be used both for monitoring and stimulation of the underlying tissue to identify functional cortex.

Epidural pegs

Epidural electrodes were first used by Hans Berger.[1] Berger's epidural electrode consisted of a needle inserted epidurally in the area of a skull defect. Many other epidural electrode types have been developed since, including a wire balled fused at the end of the wire as described by Jasper, or an array of multiple contacts imbedded in flexible Silastic stips.

There are cases where the usual EEG scalp recordings, even when combined with the use of sphenoid electrodes, do not provide clear evidence of the onset of a focal seizure. When this occurs, it may be difficult to use electrical activity in planning for a more invasive surgical approach in localizing the seizure foci. Epidural electrodes or epidural peg electrodes placed over a variety of locations covering the scalp may be employed.

The epidural peg electrode consists of a 3/16 inch stainless steel disk embedded in a mushroom-shaped body of Silastic. A multistranded stainless steel wire is soldered to the disk and exits through the cap of the electrode. The length of wire exiting the peg is approximately 20–25 cm in length and terminates with a standard electrode jack. These electrodes are placed in the operating room with the patient under general anesthesia. The surgeon places the electrode under the skin, opening the cranium with a twist drill allowing the electrode direct contact with the dura. Localization for the sites is determined through previous recording sessions and special anatomical considerations derived from imaging studies.

Technical recording considerations when using epidural pegs include adjustment of the sensitivity setting on the EEG recording equipment to the range of 20–30 microvolts per millimeter (μV/MM), as compared to the usual range for scalp recordings.

Sphenoid electrodes

The routine use of sphenoid electrodes for all patients with a history of complex partial seizures aids in the localization of epileptiform discharges. These electrodes in combination with standard scalp electrodes may help in defining whether the foci is in the lateral or mesial structures of the temporal lobe. Although it is generally agreed that the sphenoid electrodes record primarily from the temporal lobe, there is no real evidence that they do not pick up activity from the orbital frontal cortex.

The sphenoid electrode consists of a multistranded stainless steel or platinum wire that is insulated except at the tip. Inserted transcutaneously through the mandibular notch the electrode wire that is placed ranges from 50–75 mm and is inserted with a 20 or 22 gauge needle that is removed leaving the electrode wire in place. Sphenoid electrode packages are gas sterilized. These electrodes are inserted using aseptic technique at the patient's bedside. Topical anesthetics, or in some cases a light sedative, are used prior to electrode placement.

Foramen ovale electrodes

Foramen ovale electrodes have been used to record from mesial temporal structures and are less invasive than depth electrodes.[2] The electrode consists of platinum pellets embedded

on thin wire in a Teflon tube. The contacts are usually 1–1.5 cm apart and the wires run through the tube exiting at a connector. The electrodes are inserted percutaneously in the operating room through a small incision in the cheek. Passed through a 20 gauge needle, entering Meckel's cave cistern, the electrode is then advanced so that the most proximal contact rests at the level of the foramen ovale. These electrodes, like sphenoid electrodes, are placed bilaterally. Flouroscopy is used in the operating room to verify placement location. Foramen ovale electrodes are well tolerated by most patients, including adolescents.

Subdural arrays

The subdural array is a 'grid' or 'strip' of electrodes placed directly on the cortex or dura under general anesthesia in an operating room.[3–6] Subdural strip electrodes, generally consisting of four to ten contacts spaced at 0.5–1 cm intervals in a single row Figure 70.4. Subdural stips may be placed through a burr hole. Subdural grids are often designed anywhere from two to ten rows in length and four to eight rows in width, with a variety of intraelectrode spacing options, shaped as square, rectangle, or with a curved edge, and are placed through a craniotomy Figures 70.5 and 70.6. The location and size of the subdural array is determined by the results of previous recordings, localization of an intracranial lesion or AVM, vasculature, and scar tissue. Adequate coverage for the most accurate localization must include any lesion or structural abnormality and the surrounding cortex.[7–14] The epileptic onset zone may not be located within the borders of the identified structural abnormality, therefore the surrounding tissues must be thoroughly investigated by appropriate coverage with invasive electrodes Figure 70.8.

Subdural electrodes consist of stainless steel or platinum disks embedded in a flexible sheet of medical grade silicone. The electrode is soldered to a stainless steel multistranded wire. The wire is insulated with a Teflon coating. Wires are arranged on the array in an order that allows the surgeon to cut out one or more of the electrode disks in order to adapt the array to the surgical site without compromising the integrity of the electrode. The wires are then gathered into a flexible Silastic tube that terminates into a microminiature connector. The use of this small connector allows the surgeon to tunnel the cable away from the site of the burr hole or craniotomy and exit the scalp through a stab wound. The microminiature connector is then attached to the input cable that will plug into the EEG amplifiers.

When a large number of electrodes are required, i.e., an 8 × 8 subdural grid of 64 electrodes, the wires that are connected to the disks are brought through the Silastic tubes terminating in two or four microminiature connectors and number or color coded as 1 through 16, 17 through 32 and so on, corresponding to the pin positions of the amplifier. The total combined number of electrodes, scalp, sphenoidal, subdural, depth, and noncephalic, is limited by the number of amplifier inputs. Our institution, University Hospitals Case Medical Center, utilizes Nihon Khoden equipment which presently allows for 192 electrodes.[15–22]

Depth electrodes

Depth electrodes have been used to record from a variety of locations, primarily from the mesial structures of the temporal frontal, and occipital lobes. The most common use of depth electrodes is for localization of the seizure focus within the temporal lobes, especially when lateralization is difficult (Figures 70.1 and 70.2).

These electrodes consist of multiple stainless steel or platinum contacts approximately 2–5 mm wide usually spaced at 2–5 mm intervals encirciling a closed plastic, 0.8 mm tube. The number of contacts is typically between six and twelve. Three dimensional reproductions of the brain recreated with MRI and/or CT imaging allows for minimally invasive implantion of these electrodes through burr holes in a surgical setting. Depth electrodes are often used along with other invasive electrodes to maximize coverage.

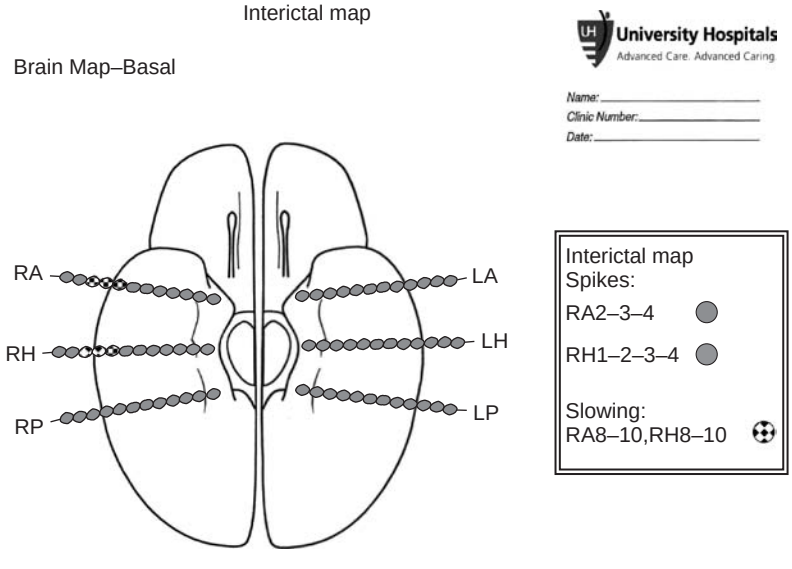

Figure 70.1 Interictal map.

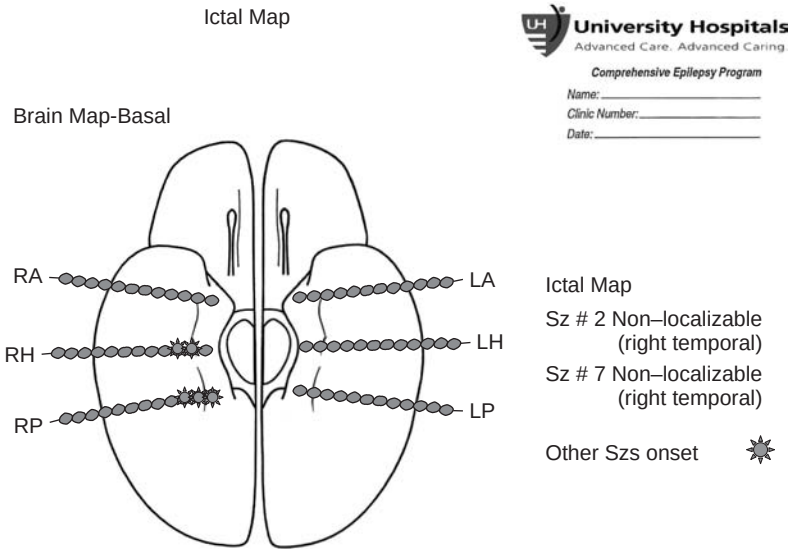

Figure 70.2 Ictal map.

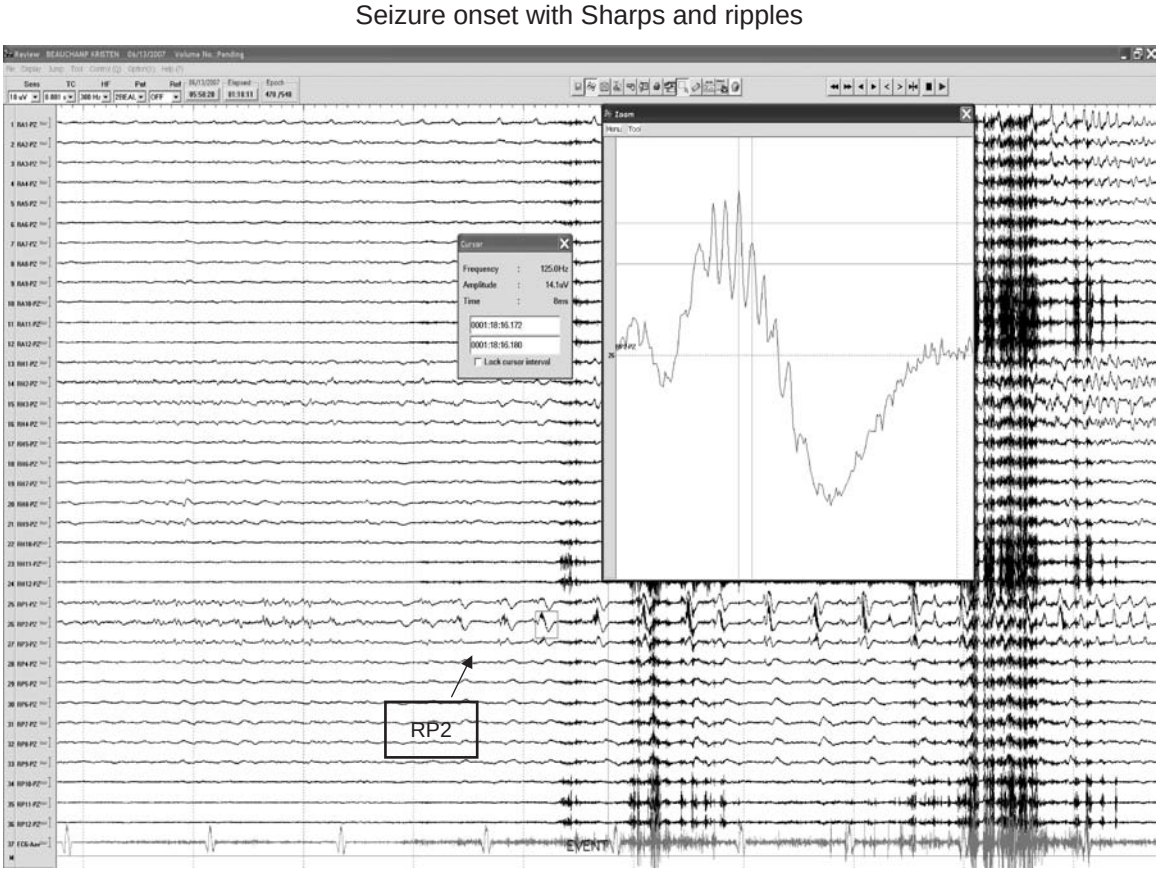

Figure 70.3 Seizure onset with Sharps and ripples.

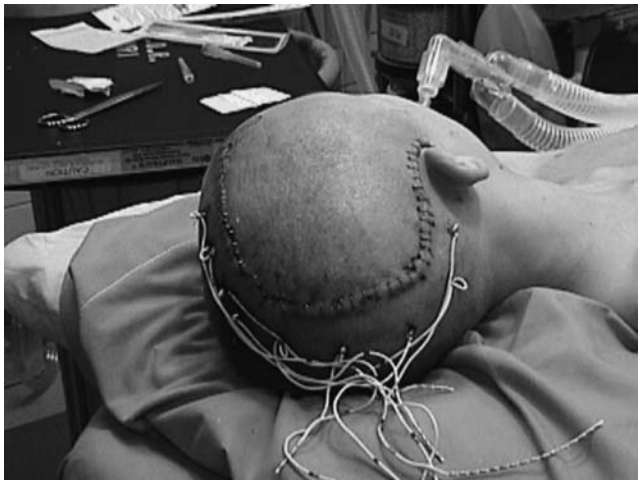

Figure 70.4 Subdural strip electrodes.

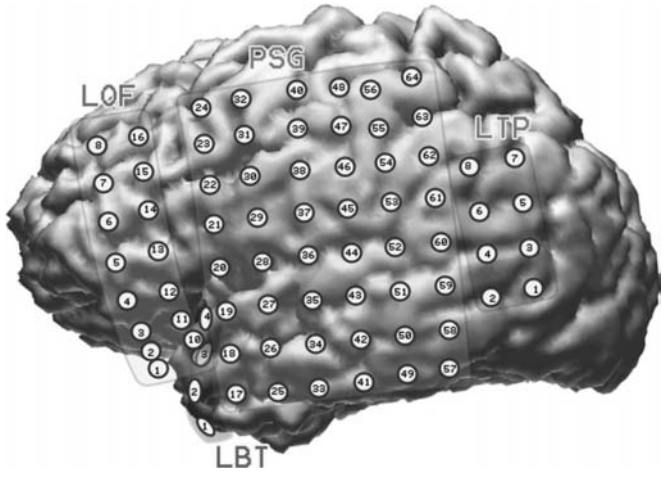

Figure 70.6 Subdural grids designed from two to ten rows in length and four to eight rows in width, with a variety of intraelectrode spacing options, shaped as square, rectangle, or with a curved edge, are placed through a craniotomy.

Electrical stimulation

Electrical stimulation of the subdural stip and grid electrodes and depth electrodes in the long-term epilepsy monitoring unit and the operating room provides detailed information for localizing cortical function relative to the seizure onset zone which is the ultimate surgical target. The patient can be tested at the bedside without the need for any type of local or generalized anesthesia. The rate of testing can be slow allowing time for the patient to rest during relatively long testing periods and in the event of a clinical seizure, either spontaneous or activated by the stimulation.[23–28]

Electrical stimulation of invasive electrodes may be done with a variety of devices. The free-standing battery-powered Integra Ojeman stimulator, or stimulation delivered through the EEG recording equipment like the Nihon Khoden equipment used at University Hospitals Case Medical Center Epilepsy Monitoring Unit are both reliable options. Electrical stimulation parameters for invasive electrodes consist of 50 Hz, 0.2–0.5 msec alternating polarity square wave pulses of varying duration, usually 5 seconds in length. The surrounding EEG activity is watched for afterdischarges. An after discharge is defined for our purposes as a retetitive sharpwave clearly distinguished from the ongoing interictal activity, which occurs immediately following the electrical stimulation and involves one or more electrodes, including always the electrode stimulated Figure 70.7. The duration must exceed 1 second following cessation of the stimulus.

Stimulation begins at 0.5–1 mA and increases in increments of 0.5–1 mA until an after discharge occurs, functional alterations occur, or until an intensity of 15 mA is reached. Functional alterations are defined as the occurance of motor contractions, sensory phenomena in the resting patient, or impairment of activity if stimulation occurs during the performance of a task.

It is possible that electrical stimulation will not provide the information desired due to the position of the subdural or depth electrodes. In these cases additional electrical stimulation may be carried out in the operating room. Stimulation may be carried out under light sedation with the patient awake, speaking and following commands, or with the patient under

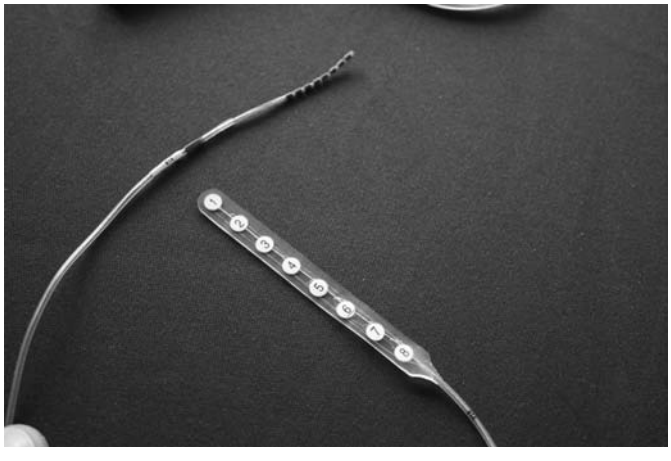

Figure 70.5 Subdural grids.

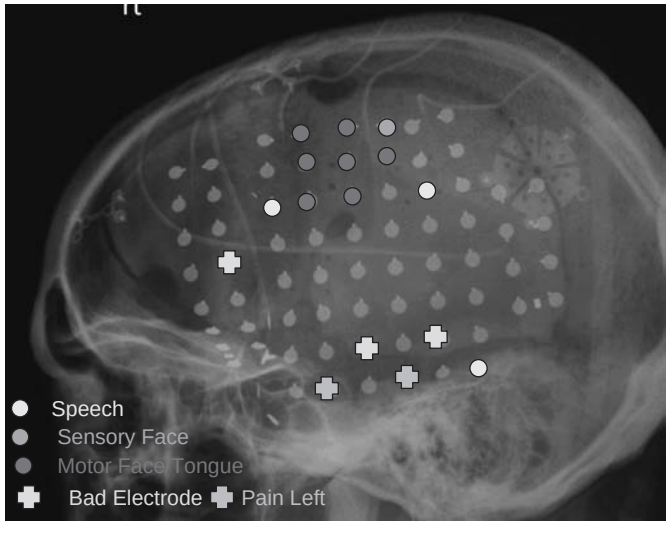

Figure 70.7 Electrical stimulation of invasive electrodes.

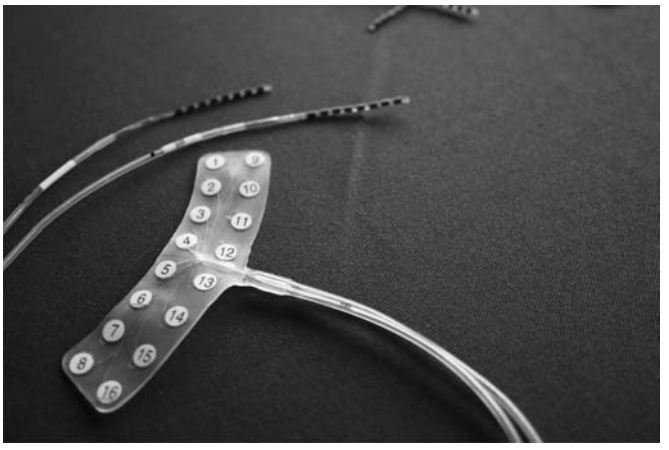

Figure 70.8 Subdural invasive electrodes.

general anesthesia with no muscle relaxant on board to watch motor movements. EEG activity is closely monitored to determine if afterdischarges or seizure activity occurs.

Evoked potentials

Somatosensory evoked potentials elicited by stimulation of either the median nerve or posterior tibial nerve may be recorded from the invasive electrodes to identify afferent areas. Visual-evoked potentials are routinely recorded from electrodes placed on the occipitals lobes. These techniques combined with direct cortical stimulation assist in identifying cortical function that may not be found in the predicted region of the brain based on normal anatomy.[29–33]

Evoked potentials may be performed either at the patient's bedside or in the operating room. Mapping for central sulcus, especially in a patient that may not be able to cooperate during other cortical mapping procedures is a reliable technique for localization.

Conclusion

The ability of current EEG recording equipment to allow sampling rates as fast as 5000 Hz coupled with the quality of invasive electrodes has created major advances in the field of epilepsy. Recording and identifying high frequency oscillations, called ripples, of 200 Hz and greater, prior to seizure onset may soon be shown to offer more precise localization of epileptic foci Figure 70.3. The priority for all medical professionals should always be maintaining or creating the best quality of life possible for each patient. Advances in computer technology relative to EEG recording equipment, functional mapping techniques, imaging devices, image guided surgical techniques, and invasive electrode options have come together to help insure safe and successful outcomes for epilepsy surgery patients.

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71 Foramen ovale and epidural electrodes in the definition of the seizure onset zone*

HG Wieser and K Schindler

Introduction

The objective of presurgical evaluation of patients with focal drug-resistant epilepsy is to delineate the primary epileptogenic zone. The epileptogenic zone is defined as the brain tissue that has to be surgically removed to render the patient seizure free.[1] However, the epileptogenic zone is a theoretical concept, a way to think about the structure of the epileptic brain. Therefore it is not surprising that no single diagnostic method is able to detect the epileptogenic zone alone. Instead, a series of methods such as detailed analysis of seizure semiology, noninvasively and invasively recorded ictal and interictal EEG, MRI, PET, neuropsychological assessments and in some patients ictal SPECT and MR-spectroscopy, are clinically applied. The epileptogenic zone is then approximated by the brain region that is shown to be pathologically altered by these different methods. In this process the results of the diverse methods used are differently weighted. One of the most important pieces of information is where the seizures start, i.e., where the seizure onset zone is localized. Actually, other definitions of the epileptogenic zone or epileptogenic focus contain the seizure onset zone as an integral part.[2] The initial ictal activity of cortical neuronal networks is typically characterized by fast oscillations, i.e. oscillations in the frequency range of 20 –100 Hz or even higher.[3,4] Specifically important in regard to presurgical evaluation is that localized high-frequency activity has been found to be associated with good surgical outcome.[5] In addition, recent findings indicate that high frequency epileptiform oscillations do not only spatially delimit the seizure onset zone, but also may occur more often before seizures and therefore be helpful to detect a preseizure time period,[6] which is a precondition for developing an EEG based seizure prediction method.[7] In vivo and in vitro animal experiments and computer simulations even imply that fast cortical oscillations may have a causal effect in seizure initiation and may be physiologically sustained by interneuronal gap junctions or by synchronizing effects of the electric field.[8,9] An important practical problem in presurgical evaluation is that these high frequency cortical oscillations – so important in localizing the seizure onset zone – can not be reliably recorded by scalp electrodes. This is on one hand because of the frequency dependence of transmission from cortex to scalp with a strong attenuation of higher frequency activity due to mutual cancellation by spatial summation.[10] On the other hand, electrical activity from contracting scalp muscles – often occurring at seizure onset – obscures activity of cortical origin most strongly in the frequency range above 20 Hz.[11] A way to work around these technical and biological limitations is to use intracranial electrodes, which are mostly unaffected by electromyogenic artefacts and monitor high frequency activity much better. Intracranial electrodes comprise different categories. In this chapter we mainly focus on foramen ovale (FO) electrodes, but also give a brief description of epidural peg electrodes. The latter have been used much less during recent years, mainly due to the very good risk/benefit ratio of other methods such as FO electrodes. A representative case report illustrates how certain limitations of FO electrodes may be compensated for by additional subdural strip electrodes.

Development history of FO and peg electrodes

The FO electrode recording technique was developed in Zürich in 1983/4[12] in order to simplify the neurophysiological investigation of the presurgical evaluation protocol for candidates for selective amygdalohippocampectomy (AHE). Prior to 1983, stereoelectro-encephalography (SEEG) had been used in Zürich in the majority of patients being evaluated for epilepsy surgery.[13–15] Accumulated SEEG experience revealed that the mesial temporal lobe structures, and in particular the hippocampus, the parahippocampal gyrus and the amygdala, play the crucial role as seizure generating structures in most patients with temporal lobe epilepsy (TLE). Based on these findings, in 1975 the so-called trans-sylvian amygdalohippocampectomy (AHE)[16] was developed and has in the following become the surgical approach of *first choice* for surgical treatment of mesial TLE (MTLE) in Zürich, but also in many other centers. Data obtained from Engel's survey carried out prior to the 1992 Palm Desert Conference showed that already then 15 centers (15%) had been using FO electrodes. FO electrodes had been used only in 5% of all

*A similar chapter has been published in Engel J Jr and Pedley TA (eds) Epilepsy: A comprehensive Textbook (Lippincott-Raven Publishers, Philadelphia, 1997) 1707–17 and is going to be published in the second edition of this book (Chapter 171; in preparation)

reported patients operated on 1986–1990 (*n*=7664), but in 21% of 662 reported AHE patients.[17]

Peg electrodes were developed at the Cleveland Clinic in 1988.[18,19] They are usually used as sentinel electrodes in combination with other invasive techniques for obtaining epidural ictal recordings.

Indications

FO and peg electrode recording techniques have been referred to as *intermediately invasive* or *semi-invasive* approaches.

Peg electrodes allow artifact free recording of the electrocorticogram in relatively small but widely separated regions of the cortical convexity to determine surgical suitability in patients in whom the clinical, electrographic and neuroimaging information did not well localize the seizure onset zone. They were also designed to be used when exact placement of a subdural grid array was uncertain from the clinical, neuroimaging and scalp EEG data. Therefore, peg electrodes may serve as sentinel electrodes contralateral to subdural grid placement in order to confirm that ictal discharges are not starting contralaterally. Depending on the particular clinical circumstances, peg electrodes may be used with other electrodes including foramen ovale electrodes, depth electrodes, and subdural strip and grid arrays.

FO electrodes record from the mesial aspects of the temporal lobe. Compared to intracerebral depth-, subdural grid-, and most probably also to subdural strip electrodes they are 'less invasive', but nevertheless the possibility of complications is inherent to the FO electrode technique, too. Therefore its use should be restricted to presurgical evaluation of possible candidates for epilepsy surgery. Due to their monitoring restricted to the electrical activity of mesial temporal lobes their main indication is for patients with TLE and in particular for patients suffering from the syndrome of MTLE.[20]

Whereas in Zürich during the period 1970–1983 a total of 94 patients underwent SEEG exploration and this resulted in a total of 69 operations (73%), from 1984 until today FO electrodes have been used in a total of 263 patients resulting in a total of 235 operations (83%). In 18% FO electrodes were combined with other invasive recording techniques. Table 71.1 lists details in this respect.

It is interesting to have a look at the Zürich AHE series, which started in 1975. In this context, it is important to remember that since 1978 there was CT, since 1985 MRI, since 1987 SPECT, since 1988 PET, and since 1987 31P-, and since 1993 proton magnetic resonance spectroscopy (1H-MRS) at the Zürich center.

This Zürich AHE series now contains a total of 512 AHE patients. 275 (53.7%) had intracranial EEG monitoring, 32 (6.2%) had SEEG only, 198 (38.7%) had FO electrodes only, 45 (8.8%) had combined intracranial electrodes (SEEG and FO, FO and strips/grids). The remaining 237 (46.3%) had AHE without intracranial recordings (Table 71.2). Table 71.2 shows the obvious trend for less invasive presurgical evaluation in candidates for AHE: In the last years the percentage of AHE without intracranial presurgical evaluation amounted to 69.2%.

Despite the overall less invasive presurgical evaluation, the seizure outcome at 1 year after AHE improved steadily over time. In the 1975–1992 period Engel Classes I–IV were 69, 9, 13, 9, and 9% (*n*=254); in the period 1993–1999 the respective numbers are 75, 10, 13, and 2% (*n*=115); in the period 2000–2001 the outcome assessment for 50 AHE patients revealed 89, 11, 0, and 0%.[21]

Table 71.3 lists the types of operations in the most recent consecutive 100 patients with FO electrodes. In these 100 patients who had FO-electrodes alone (*n*=67) or in combination with other intracranial electrodes (*n*=33), 87 patients had resective surgery, mainly AHE (*n*=72). In 13 patients the results of the presurgical evaluation did not indicate ablative surgery. The relatively high number of patients with FO in combination with other intracranial electrodes (33%) reflects two trends. First, MTLE patients with clear-cut concordant findings undergo AHE without intracranial recordings, and secondly, our center is increasingly confronted with more difficult cases in whom more elaborated intracranial seizure monitoring is necessary.

Technical aspects: electrode design, insertion and removal, and recording from the FO electrodes

In recent years several types of FO electrodes have become commercially available. However, the original FO electrodes

Table 71.1

		Bilateral	Unilateral		no of Electrode Contacts				
	Total	R+L	R	L	1	3	4	8	10*
Patients	**263**	252	6	5	34†	1	138	7	83
FO with thermoel.**	14	6	5	3					
		FO combined with additional intracranial electrodes							
		+SEEG	+Strip	+Strip +Grid	+ Grid				
Patients	**48**	14	31	2	1				
%	18	5	12	0.8	0.4				

R = right hand side
L = left hand side
†first FO EEG was recorded from a patient with trigeminal neuralgia
*43 DIXI Electrodes (DIXI microtechniques, France), the remaining were designed in our own laboratory
** thermoelement for research purpose (Landolt *et al.*,1995 (23))

Table 71.2 Number of selective amygdalohippocampectomies total and break-down into four time spans and type of presurgical evaluation (invasive, semi-invasive, non-invasive). 1975-1985, pre-MRI era; 1986-1992, intermediate era; 1993-1999 and 2000-Sept 2005, ECoG era. with modern techniques. The latter is divided according to earlier outcome studies (Wieser *et al*., 2003 (21)). Prof. G.Yasargil was succeeded by Prof. Y.Yonekawa at the beginning of 1993

	1975-1985		1986-1992		1993-1999		2000-Sept 2005		Total	
	n	%	n	%	n	%	n	%	n	%
Number of AHE	103		151		115		143		512	
AHE with SEEG alone	31	30.1	1	0.6	0		0		32	6.2
AHE with combined intracranial electrodes (SEEG+FO; FO+strips/grids)	7	6.8	3	2	32	27.8	3	2.1	45	8.8
AHE with FO alone	3	2.9	84	55.6	70	60.9	41	28.7	198	38.7
AHE with non-invasive EEG	62	60.2	63	41.7	13	11.3	99	69.2	237	46.3

used in Zürich were home made.[22] In brief, these electrodes consist of ten Teflon-insulated, helically wound silver wires (diameter 0.1143 mm=0.0045 inches) ending in ten poles. They are mounted on a 'surgical', i.e., highly corrosion-resistant stainless steel wire 0.1 mm in diameter. This carrier, isolated with a special varnish, has adequate mechanical properties. It is flexible enough and has a special end to avoid penetration of the arachnoidal-pial layer. Each pole consists of 90 parallel windings and is 2 mm long. The distance between two contacts is 2 mm. The external diameter of the FO electrode in use is such that it passes through a special splittable 18-gauge cannula (produced and marketed by Medialimed SA, 1604 Puidoux, Switzerland). This splittable cannula (Figure 71.1B) has an external diameter of 1.23 mm and an internal diameter of 0.93 mm and permits the 4-pin connector to be mounted, soldered, and the stabilizing insulator poured in well before implantation. The electrode impedance ranges from less than 200 ohms to a maximum tolerated 700 ohms, respectively, whereas the DC offset potential is less than 2 mV. Electrodes can be armed with other specific recording devices. Temperature-sensitive devices, have been used in 14 patients,[23] and special ictal and interictal DC recording with monopolar FO electrodes were carried out in five patients.[24]

Insertion of the FO electrode can be done under local anesthesia. Currently, however, the procedure is done under general anesthesia in Zürich.

With the stylet inside the special cannula, the FO electrode is inserted 3 cm lateral to the oral commissure and directed along the intersection of two orthogonal planes: (*a*) the plane defined by the insertion point, a point on the lower eyelid corresponding to the medial border of the pupil, and the tip of the electrode directed towards the foramen ovale, and (*b*) a plane defined by the insertion point, a point 5 cm anterior to the external meatus acusticus, and the tip of the electrode directed towards the foramen ovale (Figure 71.1A).

To avoid asystoly (atrioventricular block has been reported) we administer atropin before insertion. The patient usually responds to the passage of the needle through the foramen ovale with a wince and a brief contraction of the masseter muscle. After withdrawal of the stylet, cerebrospinal fluid usually drops and the electrode can then be carefully positioned under radioscopic control. In most instances, the tip of the electrode slips without any resistance into the caudal end of the ambient cistern. As can be seen from Figure 71.2F–H, modern 3D image reconstruction and

Table 71.3 Therapeutic actions after presurgical evaluation in the last consecutive 100 patients with FO electrodes

Therapeutic actions after presurgical evaluation with FO electrodes alone (n 67) or in combination with other intracranial electrodes (n 33)[a]	N pts (May 1995–June 2005)
AHE	72
Resection in TL or adjacent areas, other than AHE	8
Re-operation in TL	2
Operation outside Zurich in TL	5
VNS	2
No surgery	11

[a] FO *and* strip (n 28); FO *and* grid (n 2); FO *and* grid *and* strips (n 2); FO *and* SEEG (n 1)

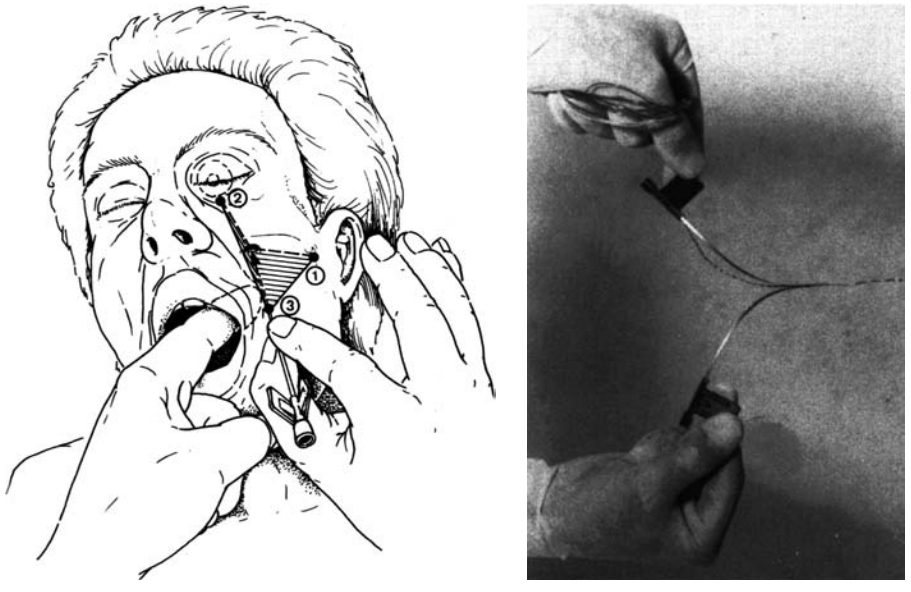

Figure 71.1 a. Insertion technique of FO electrodes according to the technique of Kirschner[30] using the landmarks of Härtel.[31] 1 = point 5 cm anterior to external auditory meatus. 2 = medial pupillary point. 3 = electrode entry side 3 cm lateral to oral commissure. The index finger is in the pterygoid fossa. The needle is inserted as described in the text, then the special splittable cannula is withdrawn and broken as displayed in b. (Modified from Wieser and Morris, 1997).[33]

superposition techniques of CT and MRI allow for more precise studies of the anatomical details in relation to the FO electrodes.[25]

The splittable cannula is then withdrawn and broken (Figure 71.1B) and the freed electrode is fixed by the use of a special clamp to the skin. Gauze and adhesive tape cover the electrode where it penetrates the skin. Oral antibiotic protection is given throughout the recording period and is continued for 3 days after removing the electrode.

For the removal of the FO electrode, anesthesia is not necessary. During the withdrawal of the electrode a short-lasting painful sensation in the ipsilateral teeth is relatively common and the patients should be carefully informed about this possibility before the explantation.

Montage, recording and analysis

Whereas more sophisticated DC recording was done hard wired with 32 channels in the laboratory (Figure 71.3), long-term digital video-EEG monitoring in AC mode is now possible with up to 128 channels with the patient on the ward.

For routine monitoring an uninterrupted bipolar montage connecting the ten contacts of both FO electrodes is recommended, as shown in Figure 71.4. The other channels are used for simultaneous scalp EEG and polygraphy, if indicated. Figures 71.4 and 71.5 give examples of ictal EEG recordings obtained with this system.

In Figure 71.6 the case of a 19-year-old patient is illustrated. He suffered from pharmaco-resistant epilepsy. At the beginning of his habitual seizures he would briefly scream and cross his arms. The latter was a 'semi-automatic' sign he had learned to use over the years to indicate the beginning seizure to his parents. After becoming confused he would then normally try to get up and walk away (Figure 71.6A–F). MR imaging revealed atrophy and signal hyperintensity of the mesial temporal lobe structures on the left (Figure 71.6G). In addition, slight atrophy of the lateral left temporal lobe was detected. Because of the pronounced ictal motor signs frontal seizure onset or rapid seizure spread to the frontal lobes were considered. Therefore bilateral FO and additional strip electrode recordings (Figure 71.6H) were used to localize the seizure onset zone. Seizures were demonstrated to always begin in the left mesio-temporal region (Figure 71.6I). However there was intensive interictal epileptiform activity in the left latero-temporal region. Because of the latter finding and the slight atrophy of the left mesial and lateral temporal lobe a resection of the anterior two thirds of the left temporal lobe was performed. Histological examination revealed hippocampal gliosis and loss of neurons and a slightly abnormal focal layering of the neocortex. The patient has been free of seizures and of auras (ILAE outcome 1a) since surgery.

Epidural peg electrodes design

Epidural peg electrodes (Figure 71.7) are mushroom shaped composites of silastic plastic with a 'cap' diameter of 12.7 mm, a slightly tapered stalk and the tip is a 4.5 mm disc electrode made of either platinum or stainless steel. The electrodes are made with different stalk lengths to adapt to different thicknesses of the skull. A1–1.5 cm scalp incision is made to expose the skull at the predetermined electrode positions. A twist drill with a 'stop' is used to create a 4.5 mm burr hole; the electrodes are then inserted by hand into the hole. The 38-gauge Teflon-coated steel wire from the electrode is threaded through a surgical needle and exits the scalp approximately 2 cm distant to the electrode itself. The scalp over the electrode is then sutured. The Bethel Epilepsy Center reported on a slightly smaller version of the original epidural peg electrode.[26]

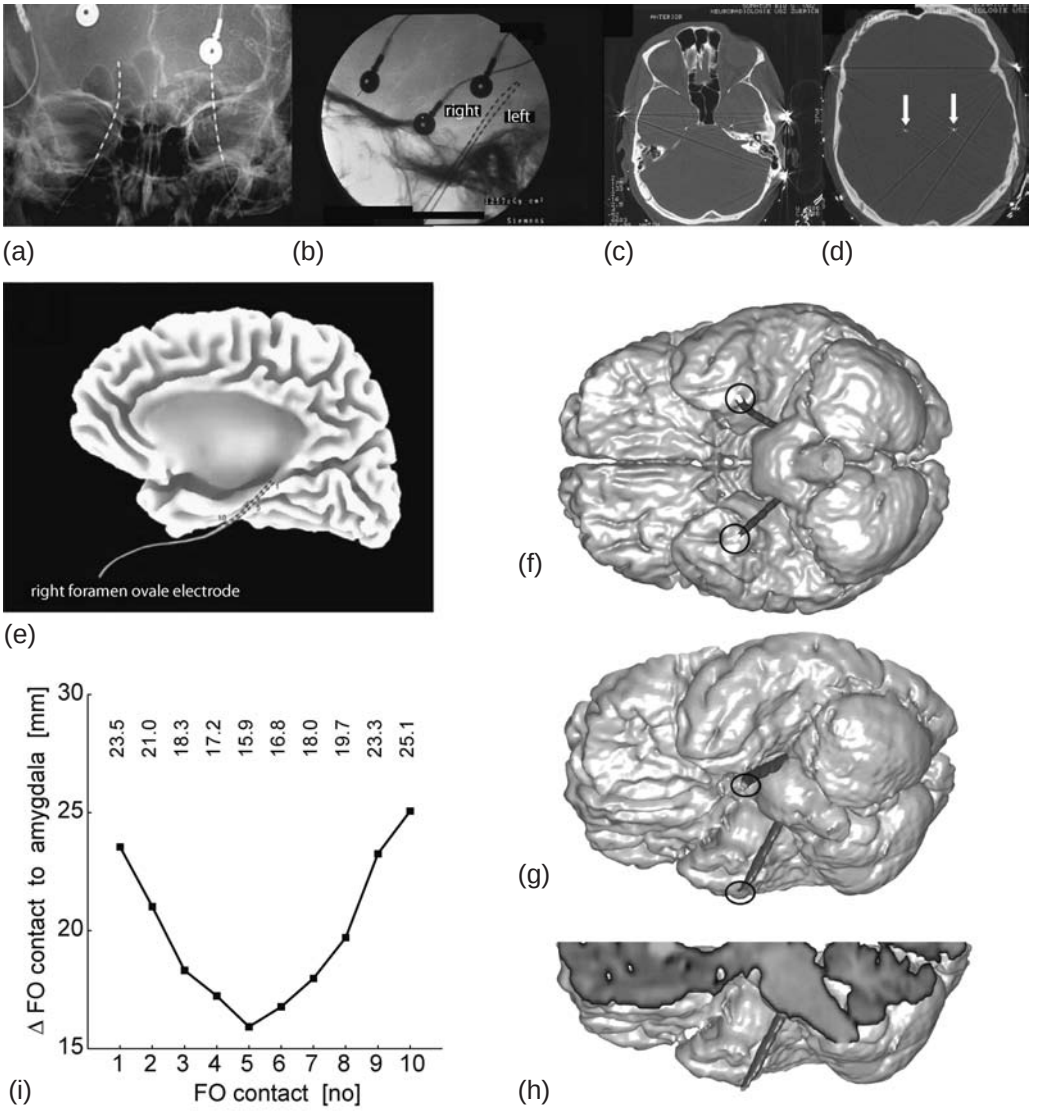

Figure 71.2 Position of implanted 10-contact FO electrodes as illustrated by ap (a), lateral (b) X-ray and CT imaging (c,d), as well as schematic drawing (e) and three-dimensional anatomical location (f–h) of FO electrodes. In f–h the intracranial course of both FO electrodes is shown in red. The positions of the foramina ovale are marked by the open circles. i. Mean distance of each FO contact to the center of the amygdala. f–i With kind permission of PD Dr.Urs Schwarz; e with kind permission of Dr. Dominik Zumsteg. (See Color plates.)

Patients data of the Zürich FO electrodes series

With two exceptions (the first FO electrode patient had no epileptic seizures, but trigeminal neuralgia, and one patient had aggressive outbursts thought to reflect limbic seizures), all patients who underwent FO electrode implantation in Zürich had medically refractory complex partial seizures with or without secondary generalization. In most of the patients, prior to FO electrode implantation, there was rather strong suspicion of mesiobasal limbic seizure foci, as evidenced from the seizure symptomatology, interictal and ictal scalp-EEG, neuropsychological examinations, structural (CT, MRI) and functional (SPECT and PET) imaging. These patients were evaluated with the aim of demonstrating a unilateral mesiobasal limbic seizure focus with the degree of confidence necessary for surgical intervention. Thirty patients had less clear evidence for mesiobasal TL seizure onset with some contradictory findings pointing to lateral TL or extra-TL seizure onset. These patients were evaluated simultaneously with FO and stereotactic depth electrodes. In 18 patients mesiobasal limbic seizure onset was rather unlikely. These patients underwent long-term monitoring with FO electrodes in order to definitively rule out mesiobasal limbic seizure onset (in which case they would have been no longer candidates for surgical treatment) or to prove a possible secondary pacemaker role of one mesiobasal TL (in which case a so-called 'palliative' AHE would be considered as a treatment option).

Seventeen percent of this series were considered inoperable and 80% underwent surgery, mostly selective AHE. In the last 10 years 87% of patients with FO electrodes underwent resective surgery (see Table 71.3). Patients evaluated by FO electrodes prior to AHE did not differ significantly in their postoperative seizure outcome when compared to the overall AHE series evaluated mainly by SEEG.[27, 28]

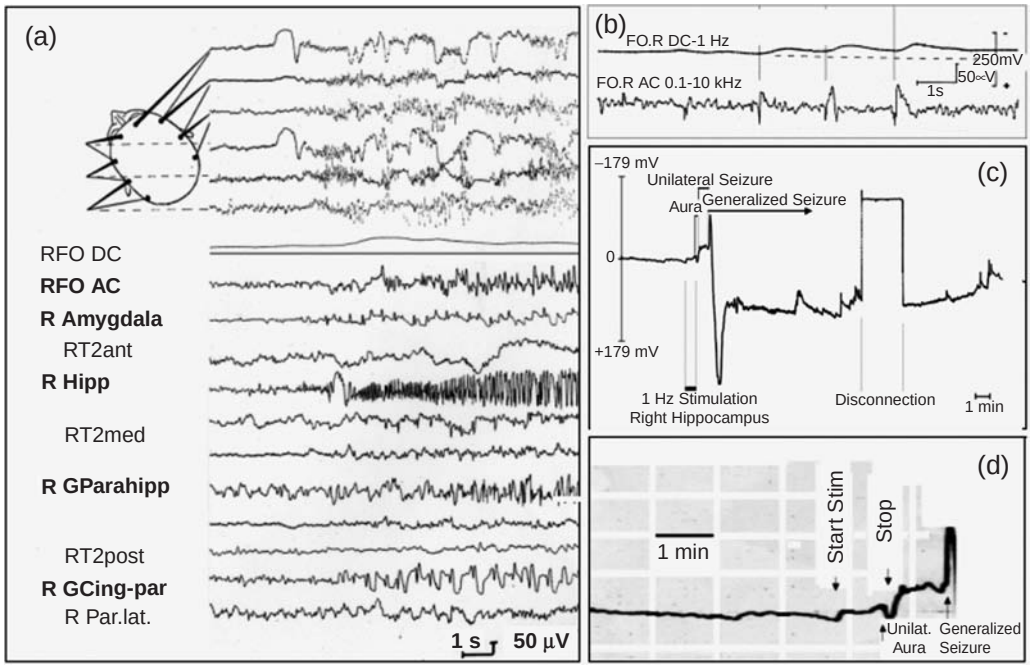

Figure 71.3 DC-recordings with self-made special FO electrodes. a. Section of combined scalp- FO-electrode- and depth-electrode-EEG recordings with a right hippocampal (R Hipp) seizure discharge with modest spread to the right amygdala, the right parahippocampal gyrus (R GParahipp) and to the ipsilateral parietal cingulate gyrus (R GCing-par) which is reliably depicted by the ipsilateral FO electrode (RFO AC) and accompanied by a negative DC shift (RFO DC). b. Repetitive spikes in the FO electrode recorded in AC mode are accompanied by stepwise negative DC-shifts. c and d (D, detail of C): DC shifts recorded by FO electrode with DC amplifier during an electrically induced partial seizure with an aura and secondary generalisation. During the electrical train stimulation of the hippocampus (Start Stim, Stop) a slight negative shift is seen, which increases during the induced seizure discharge in the hippocampus. With onset of the secondary generalized seizure a further marked DC negativity can be observed, which then inverts to DC positivity. This DC positivity is most probably due to the reference electrode used. The reference electrode for DC recording was a disk-shaped sintered Ag-AgCl electrode 12.5 mm diameter (In Vivo Metric Systems, Healdsburg, CA) subgallealy implanted over the vertex at Cz. The FO electrode used for DC recording consisted of a cylindrical Ag-AgCl pellet (0.4 mm diameter and 4 mm length; for further details see Wieser *et al.*, 1985).[12]

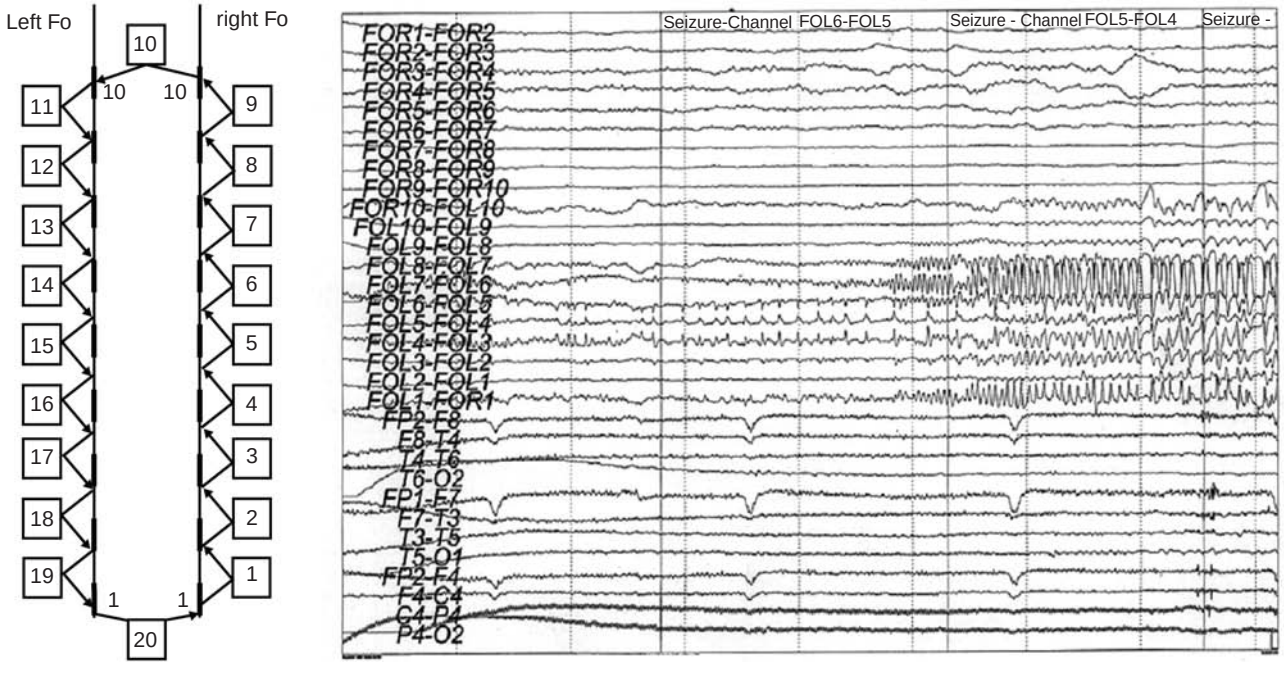

Figure 71.4 On the left the montage for recording from 10-contact FO electrodes is displayed. For routine long-term seizure monitoring we prefer the depicted closed chain with 20 channels (number in boxes). An example of a FO-electrode-recorded seizure onset at contact 5 of the left FO electrode (FOL5) with repetitive 6–7/s sharp waves and evolving rhythmic more wide-spread spike discharges of 19/s. Note that the scalp-EEG channels do not show the seizure onset.

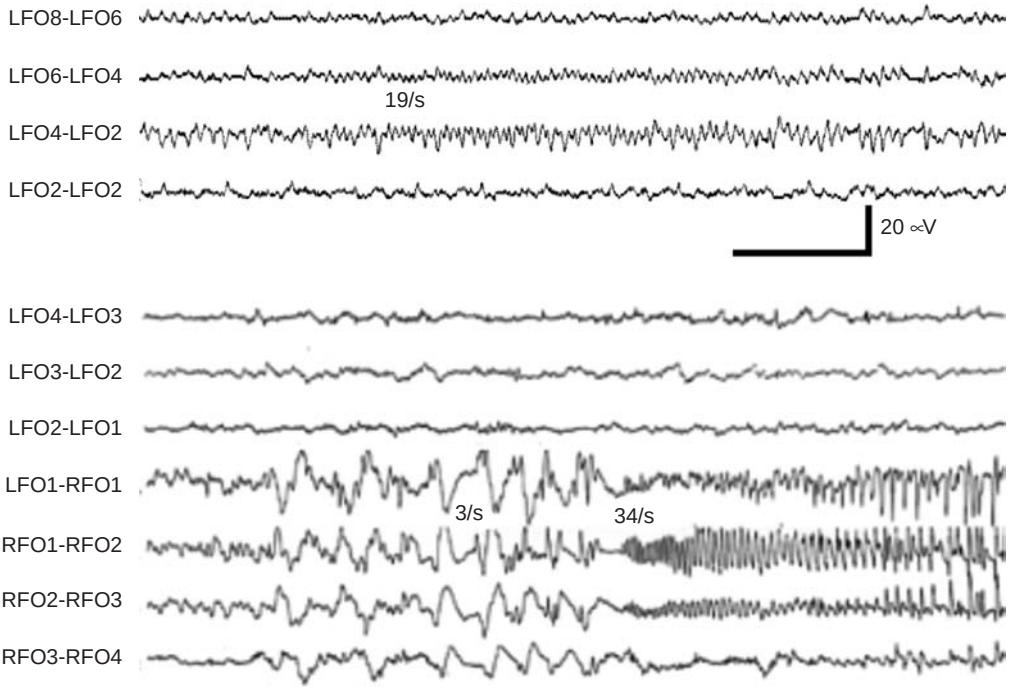

Figure 71.5 Two examples of FO electrode recorded seizure onset patterns in two patients. A. High-frequency low-amplitude spike trains recorded with 10-contact FO electrodes. B. 'Hypersynchronous onset pattern' recorded with 4-contact FO electrodes.

Comparison of FO and peg electrodes with other recording techniques

Advantages

FO electrodes provide a definite advantage over scalp EEG and over sphenoidal electrodes. In a recent study it was for example shown that intracranially recorded epileptiform discharges may often only be detected by scalp electrodes after averaging (Figure 71.8).

In several instances, where the Zürich group has used sphenoidal and FO electrodes simultaneously, it was clearly shown that FO electrodes are superior in detecting epileptiform activity from the mesial region of the temporal lobes.[27] This is particularly true for epileptiform discharges originating in the posterior hippocampal formation. In comparison with depth electrodes the FO electrodes reliably pick up epileptiform activity generated or involving the hippocampal formation. Pure amygdalar discharges may, however, escape detection in the FO electrodes. A further advantage of FO electrodes is that they offer an excellent possibility to monitor mesial TL EEG changes in selective TL amobarbital tests.

As has been shown, appropriate intracranial EEG recorded from depth electrodes or FO electrodes in combination with scalp EEG is indispensable for a reliable interpretation of the amobarbital effects of the selective tests. FO electrodes proved to be very useful, to monitor electrophysiologically the topo-selective effects of amobarbital in the so-called selective temporal lobe amobarbital tests.[29]

The increase of delta activity is considered to be the most typical amobarbital-induced EEG effect. Other amobarbital-induced EEG patterns are isoelectric lines, the burst suppression pattern, and high and low voltage beta-activity. In the Zürich selective temporal lobe amobarbital series the delta-increase, the 'activation-phenomenon' and the spike-reduction were observed both with scalp- and with intracranial electrodes, but the activation-phenomenon and the spike-reduction were only detected with intracranial-EEG recording techniques. As expected, delta increase at the site of amobarbital action was the most commonly observed EEG pattern and was present in 75%. Interestingly a somewhat unexpected delta-increase was also observed contralateral to the side of injection in 36% of the tests. As a rule contralateral delta-increase was, however, markedly less pronounced and shorter in duration.

In a comprehensive study,[29] in which the amobarbital-induced memory performance was correlated with the amobarbital-induced EEG changes, a significant correlation between the dosage and the duration of the EEG changes ($p < 0.05$), was found, but there was no significant correlation between the dosage and the EEG pattern. Moreover, the appearance of an 'activation phenomenon', i.e., the evocation or increase of spikes (or other epileptiform graphoelements) predisposed to a marked decrease of the memory performance not only for material specific for the side of injection, but also for material specific for the contralateral, noninjected hemisphere. Combined FO electrode- and scalp-EEG monitoring during selective TL amobarbital tests is therefore superior in several aspects to functional imaging of the injected area. This is because appropriate EEG monitoring is able to detect the amobarbital induced dysfunction better in time and gives additional information on provoked epileptic phenomena.

In summary, the Zürich experience indicates that the FO electrode has substantially facilitated the presurgical evaluation of the majority of candidates for temporal lobe surgery by decreasing the risks of more invasive neurophysiological evaluation without significant loss of information.

The main advantages of peg electrodes are that they can be used as sentinel electrodes with better, i.e., muscle artifact-free recordings, of cortical activity. The risks and costs of insertion

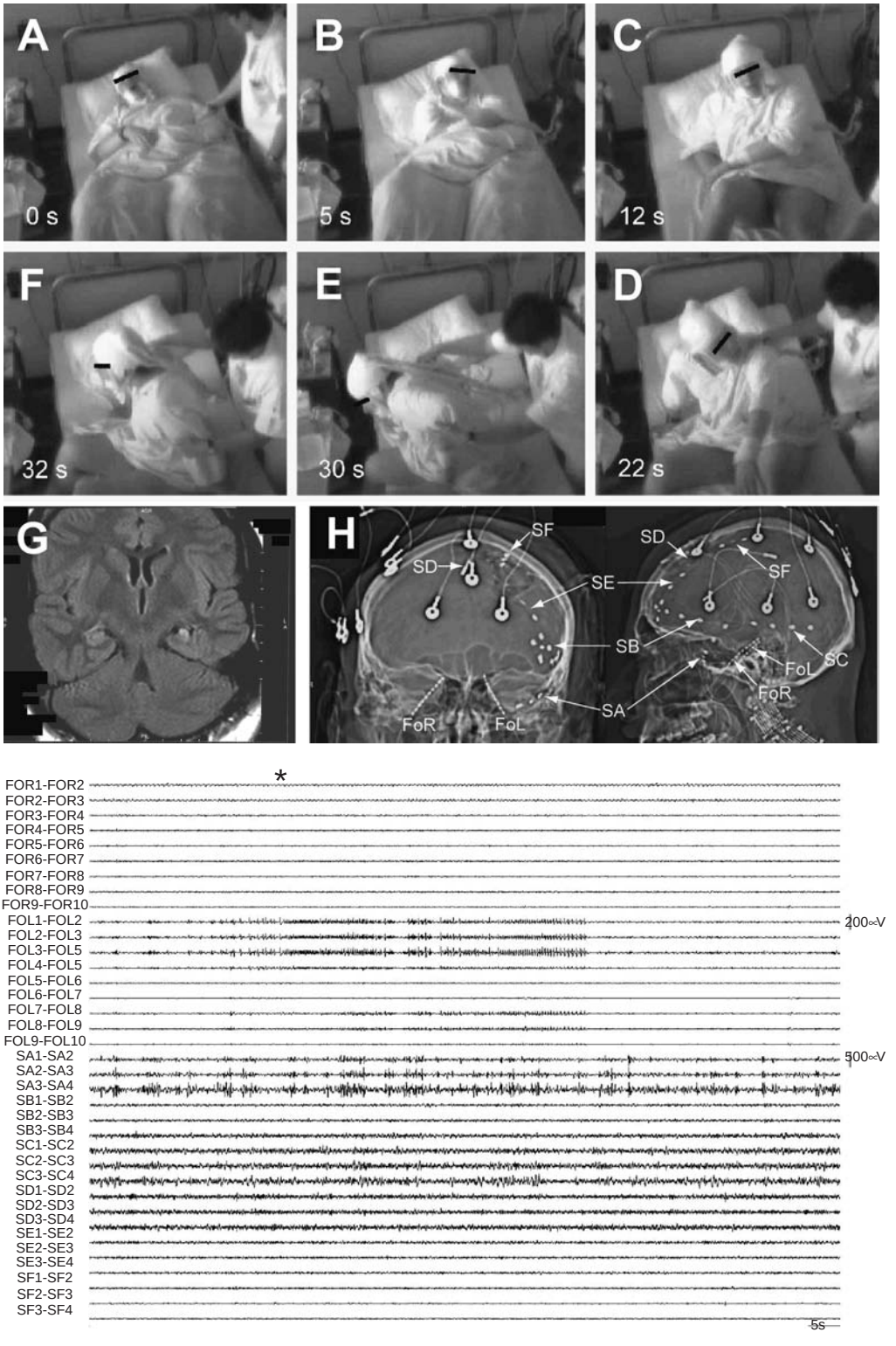

Figure 71.6 'Tailored' presurgical evaluation with FO and additional strip electrodes. A–F. Seizure semiology consists of an initial scream, then crossing of the arms, confusion and deambulation. G. MR imaging (FLAIR sequence) indicates signal hyperintensity and atrophy of the left hippocampus. In addition slight atrophy of the left lateral temporal lobe structure is visible. H. Localisation of electrodes. FOR and FOL are 10-contact FO electrodes. SA-SF denote additional 4-contact strip electrodes. I. EEG during the seizure is displayed in A–F. Seizure onset is first recorded with FOL. There is intense interictal epileptiform activity recorded by SA. * = clinical seizure onset (initial scream).

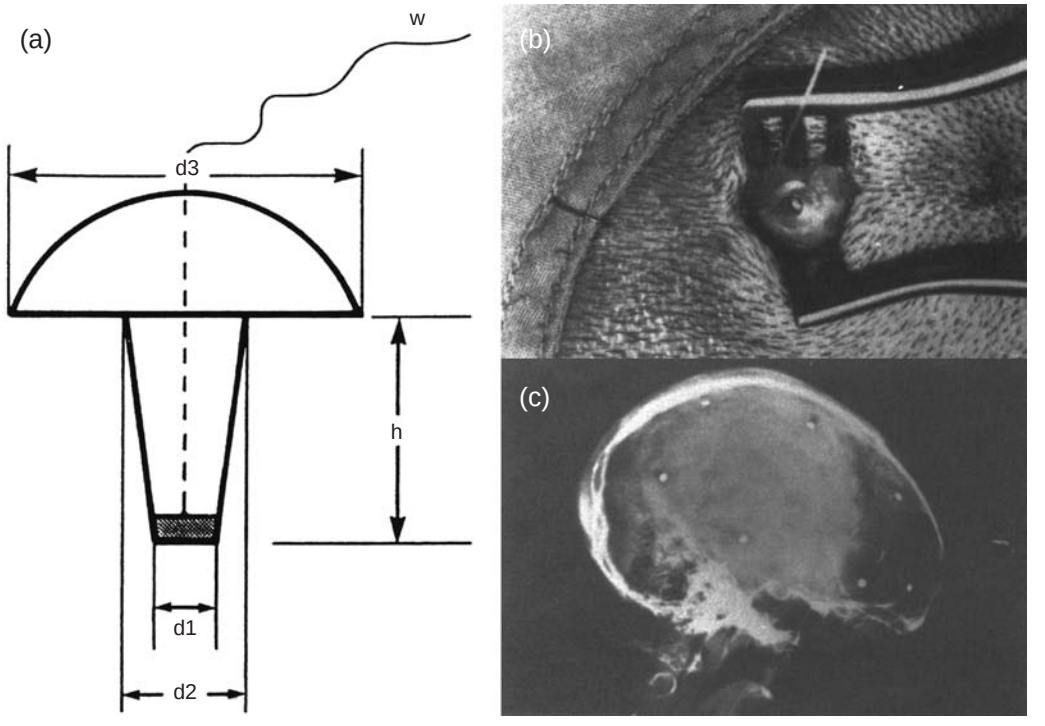

Figure 71.7 Epidural peg electrodes. a: The electrode consists of a stainless steel or platinum disc embedded into a mushroom-shaped silastic housing. The stalk has a gradual taper from a maximum diameter (d2) of 4.7 mm to a tip diameter (d1) of 4.5 mm. Stalk heights (h) range from 3–19 mm in 2-mm increments to match skull thickness. The cap has a diameter of 12.7 mm (d3) and a height of 2.5 mm (MDX4-4210, Dow Corning Corp., Midland, MI). The peg is implanted via 1.5-cm scalp incision and burr-holes (b). c: lateral skull X-ray with epidural peg electrodes (Modified from Wieser and Morris, 1997[33]; original sources see Barnett *et al*. 1990[18] and Awad *et al*. 1991.[19]

are considerably less than that for grid electrodes, but peg electrodes may not obviate invasive intracranial evaluations.

Limitations

FO electrodes have definite limitations: The nature of the FO electrode recording technique implies that only restricted questions can be answered, namely: (a) do the seizures originate at the mesiobasal temporal lobe structures? If yes, (b) are they constantly lateralized? In addition, (c) information is obtained as to whether the seizure origin is more anterior or posterior. However, if the seizures do not originate at one mesiobasal temporal lobe, the patient is by definition no longer a suitable candidate for 'curative' selective AHE, and it must then be decided whether further evaluation is indicated with a view toward more extensive temporal lobe or even extratemporal surgery.

There is evidently a risk of falsely localizing an apparent seizure origin in the mesiobasal TL and missing the true origin outside these structures when the FO electrode technique is used. The best way to minimize this risk is to carefully study the clinical features accompanying the seizures by recording the occurrence of the subjective auras and/or the objective signal symptoms and to correlate these with the simultaneously recorded EEG. In addition, as already mentioned, FO electrodes can be combined with other recording techniques, such as subdural strips as illustrated by the case described above (Figure 71.6).

The most reliable seizure onset patterns recorded with the FO electrodes are the high-frequency low-amplitude discharge pattern and the so-called 'hypersynchronous' seizure onset pattern (Figure 71.5)[28]. In the absence of these patterns, the localization of the seizure onset zone should be questioned. A very local decrement at the FO electrodes is the most frequently observed initial seizure pattern in the Zürich FO electrode series. If it was followed within 3–5 seconds by a high-frequency discharge at the same localization, it is also a reliable pattern for seizure onset localisation. From analysis of simultaneous recordings from depth electrodes inserted directly into limbic structures, such as the amygdala, anterior and posterior hippocampus, and parahippocampal as well as fronto-orbital and cingulate gyrus, and from FOelectrodes, it became evident that a very local initial flattening of the EEG record from the FO electrode was nearly always associated with a high-frequency low-amplitude discharge observed in the stereotactic depth recordings from the hippocampal formation and/or amygdala. Usually the FO electrodes pick up mesial temporal lobe epileptogenic activity very reliably.

Only in the very rare cases of prolonged discharges totally confined to the amygdala and not affecting the hippocampal formation, the FO electrode may miss these amygdala discharges (Figure 71.9). This is because the amygdala behaves like a closed electrical field. In our SEEG series, however, these amygdalar seizures account for only about 3% of all psychomotor seizures.

The limited placement of peg electrodes represents their main limitation. The usage of the epidural peg electrodes at the Cleveland Clinic has declined significantly over the past years. In part these changes reflect surgical preferences but to a large extent they are due to improvements in non invasive evaluations including (1) high-resolution MRI scans, (2) volumetric analysis of the hippocampus and (3) digital EEG allowing reformatting and filtering of data. It has also become apparent that

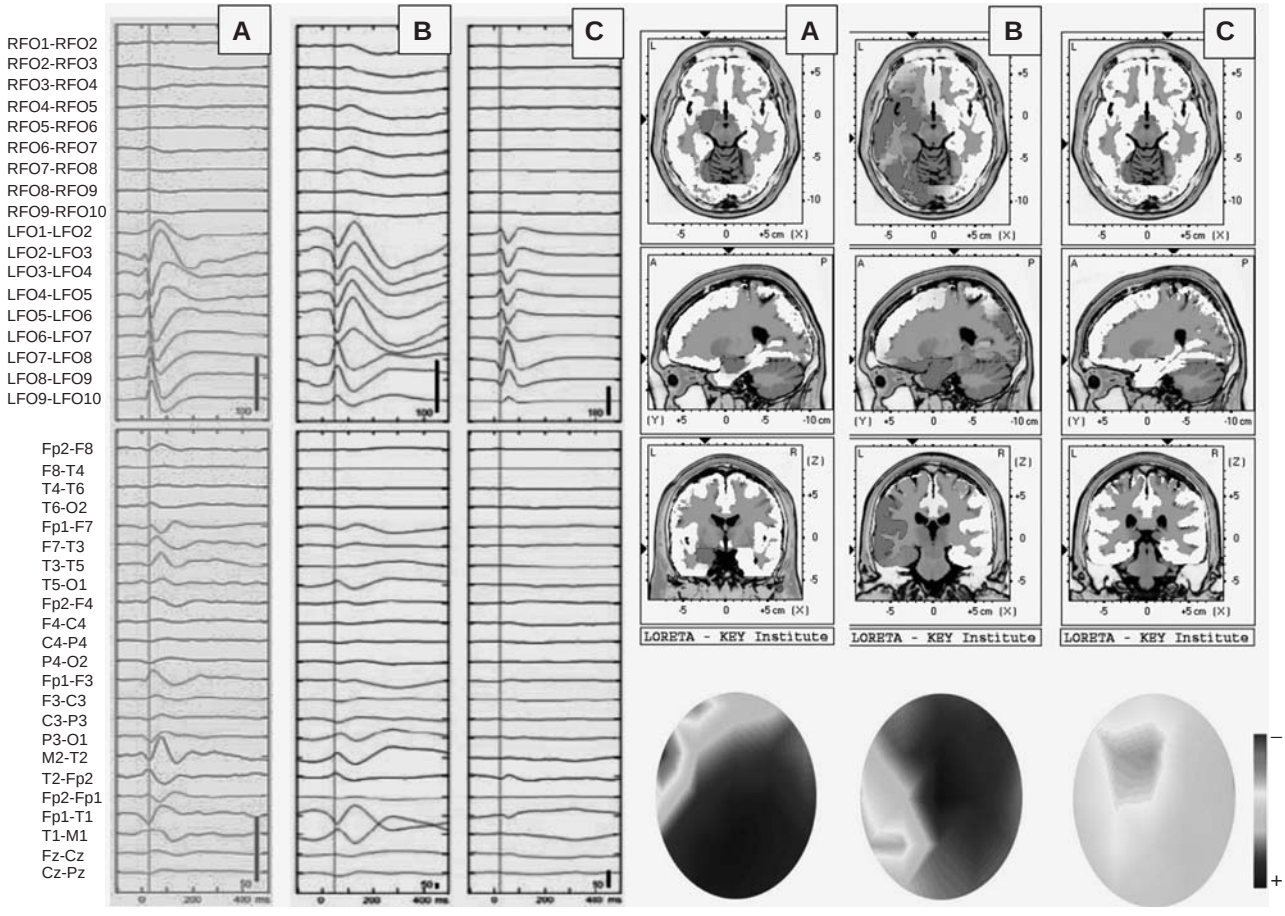

Figure 71.8 Averaged FO electrode and scalp EEG spikes for three representative interictal epileptiform discharges (A,B,C) and statistical LORETA (low-resolution electromagnetic tomography) solutions shown as two-dimensional orthogonal brain slices (right upper part) representing significant cortical activation during the ascending phase of the intracranial spike and topographic voltage maps (right bottom). For A 199, for B 90, and for C 180 events have been used for averaging and statistical nonparametric testing of each spike. Constellation A, i.e., a very restricted activation of ipsilateral mesial temporal lobe, was seen in 11/15 studied patients and represents 19/30 IED patterns (63.3%). The averaged intracranial spike could be reliably detected in the scalp-EEG after averaging. Constellation B, i.e., a widespread neocortical activation involving frontal and temporo-posterior structures, occurred in 5/15 patients and represents 6/30 IED patterns (20.0%). The spikes could be reliably detected in the scalp-EEG without averaging! Constellation C, i.e., a very restricted mesial temporal spike, occurred in 4/15 patient and represents 5/30 IED patterns (16.7%). The spikes could not be detected in the scalp-EEG, despite averaging. Courtesy of Dr.Dominik Zumsteg; see also Zumsteg *et al.*, in press).[32]

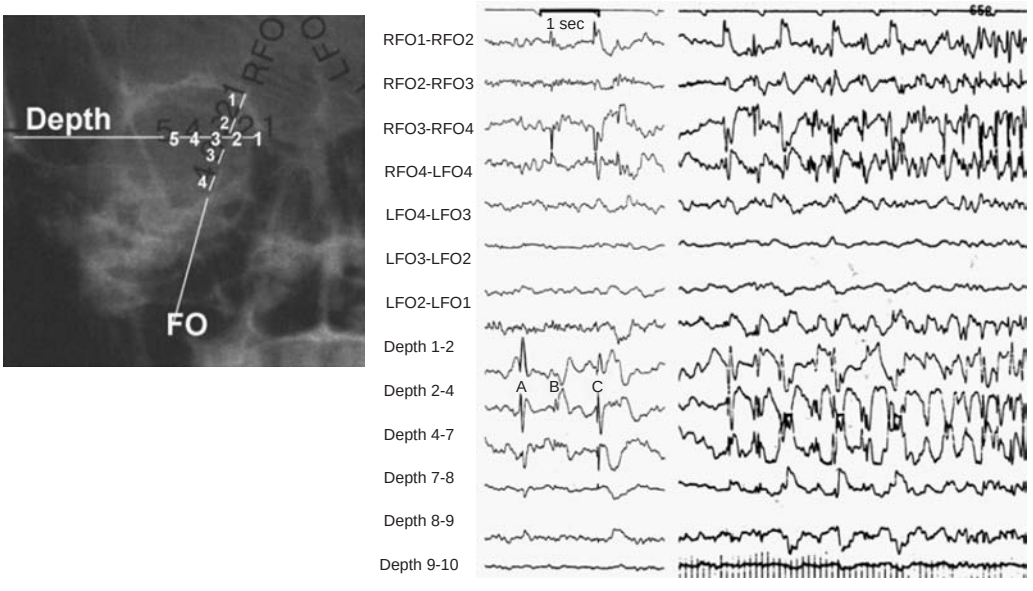

Figure 71.9 Combined depth- and FO electrode recording with interictal spikes A,B,C (left) and ictal discharge (right). Note the discrepancies between spikes recorded in depth and FO electrodes. Spike A, obviously generated in the right amygdala, is not reliably reflected in the FO electrode contacts, whereas spikes B and C and the discharge at the right are visible in both electrode types, although with obvious form differences. (Modified from Wieser and Morris,1997).[33]

in evaluation of a patient with a focal epilepsy but whose studies include no focal MRI abnormalities and no localizing EEG abnormalities epidural peg electrodes are unlikely to demonstrate a clear epileptogenic focus. In other words they are not very helpful in this kind of 'fishing expedition'.

Complications

In 1987 we had one serious complication in the Zürich FO series consisting of a subarachnoid hemorrhage, which led to a transient upper pontine syndrome. MRI-documented subarachnoid hemorrhages without any neurological deficits occurred in two other patients. Meningitis occurred in two patients and was treated by innaveneas antibiotics without sequels. Placement of FO electrodes may be associated with transient morbidity, especially facial pain. Temporary facial pain has occurred in 19% of our patients. Two patients reported mild transient temporo-mandibular joint dysfunction. Recurrence of labial herpes was seen in 5%. A transient hypo- or dysesthesia, localized in one corner of the mouth, was reported in 9% of the cases. There were no other side effects or complications, and, in particular, no persisting trigeminal impairments.

One patient pulled out one FO electrode in a postictal confusional state, one patient damaged one electrode during shaving. Since the information was not sufficient both had to be reimplanted.

Complications of epidural peg electrodes

By the end of 1993, approximately 77 patients had over 500 epidural peg electrode insertions and studies at the Cleveland Clinic; at the Bethel Epilepsy Center 36 patients underwent evaluation using approximately 420 epidural peg electrodes. In these patients no major complications were seen. In one Cleveland patient a single cortical contusion was discovered on CT scan.

Culturing the peg electrodes at time of removal yielded a bacterial colonization rate of approximately 22% in the Cleveland Clinic Series; no patient had a clinical infection due to these electrodes. The lack of clinical infection was in part due to prompt treatment with appropriate antibiotics if the electrode cultures proved positive.

Costs

The costs of FO and peg electrodes are considerably less compared to other invasive techniques. Insertion of FO electrodes can be done in local anaesthesia and does not require a sophisticated neurosurgical procedure or a neuroradiological examination under stereotactic conditions. Usually no intensive care is necessary and patients with FO electrodes alone can be evaluated outside highly specialized units. However, the major expenses derive from the long-term monitoring and they are similar whether the electrodes used are semi-invasive or invasive.[17]

Future directions

Whereas FO electrodes may be viewed as a major step in making presurgical evaluation less invasive, the usefulness of peg electrodes remains limited.

It is our guess that FO electrodes will continue to be increasingly used in nonlesional TLE patients being candidates for AHE, whereas the use of peg electrodes obviously declines. Arguments for this prediction are that in TLE very effective standardized surgical procedures are offered and the main goal of the preoperative evaluation is to answer the question whether or not a patient is a suitable candidat for one of these surgical procedures. In nonlesional extratemporal epilepsies, however, exact localisation of the epileptogenic area remains still a very demanding and difficult task asking for usually – at least additionally – invasive intracranial recording techniques.

Conclusions

From the Zürich experience based upon strict indications the semi-invasive technique of FO electrode recording is suitable for the evaluation of potential candidates of AHE. Since AHE has virtually abolished larger TL resections in Zürich a considerable proportion of patients considered for surgical treatment of TLE are candidates for bilateral FO electrode evaluation. The aim of the FO electrode implantation is to record and study the patient's spontaneously occurring habitual seizures.

Epidural peg electrodes are a useful and safe addition to the surgical epileptologist's toolbox. However, they should be seen as being complimentary to other invasive electrodes and not as a replacement.

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72 Subdural electrodes

MZ Koubeissi

Introduction

Success of resective surgery for intractable epilepsy is dependent on accurate localization of the epileptogenic focus. Whereas all areas of interictal epileptiform discharges need not be resected in order to achieve seizure control,[1] the most reliable criterion for localizing epileptic foci for subsequent surgery is identification of the area of onset of spontaneous seizures.[2,3]

Localizing epileptogenic focus can be achieved with higher accuracy by recording intracranial ictal discharges, than by other localizing abnormalities, such as imaging, neuropsychological testing, extracranial EEG recordings, and seizure semiology.[4-6] The majority of the cases monitored with intracranial electrodes will have successful localization of the epileptogenic region leading to resection.[7] Henry *et al.* found that the ictal onset zones in 47 of 50 patients, who had had inconclusive extracranial ictal EEG, were successfully localized with intracranial recordings, leading to efficacious resections in 38 patients, regardless of the neuroimaging findings.[5] Even in situations when there is evidence of more than one epileptogenic focus, monitoring with intracranial electrodes may help identify the focus most responsible for the patient's stereotypical seizures, the resection of which promises to at least lessen the burden of epilepsy.[4]

The indications for monitoring with subdural electrodes and the implantation procedures are discussed elsewhere in this book, but will be briefly reviewed here.

Indications

Selected patients can undergo resective epilepsy surgery without the need for intracranial monitoring. This commonly occurs when noninvasive presurgical results, including electrophysiologic and neuroimaging data, are concordant.[8] However, there are situations when extraoperative monitoring with subdural electrodes is needed to allow identification of the area of ictal onset and its relation to brain regions that need to be preserved by epilepsy surgery. This permits maximal resection of epileptogenic cortex with minimal functional deficits.

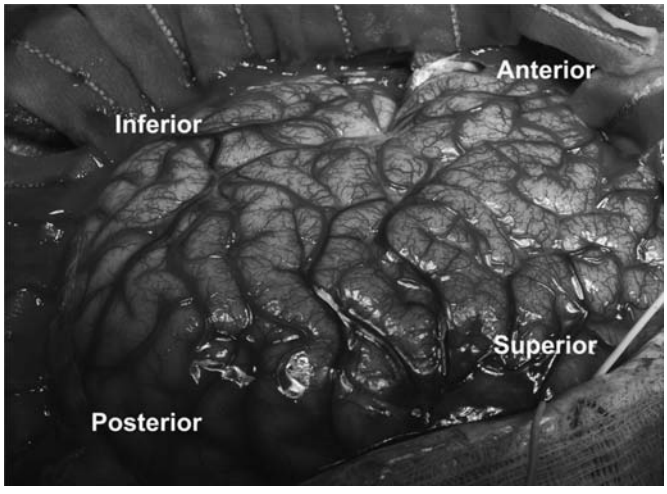
The following scenarios are examples of situations where subdural electrode implantation is needed. Subdural electrodes are used for localization of ictal onset in patients with medically intractable epilepsy, who have no medical or psychiatric contraindications for invasive monitoring, when:

(1) less invasive studies fail to lateralize or localize the epileptogenic focus, e.g., seizure semiology strongly suggests the area of origin, but extracranial EEG fails to lateralize the ictal discharge,
(2) neuroimaging is normal despite clinical evidence of localization-related epilepsy,
(3) localization of ictal onset by extracranial EEG is discordant with the results of neuroimaging, raising the question of dual pathology,
(4) extracranial EEG and MRI data are concordant, but are discordant with seizure semiology, location of interictal epileptiform discharges, or results of neuropsychological evaluation, and
(5) mapping of cortical function is needed, as in patients who appear to have epileptic foci close to, or overlapping with, their eloquent cortex.

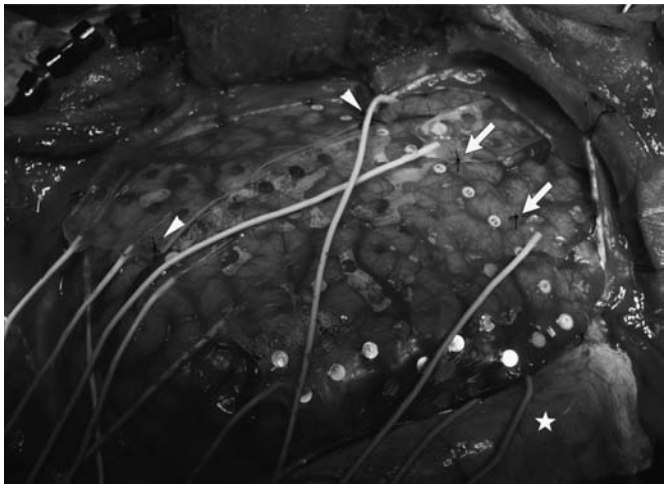
Procedure

Subdural grid electrodes are implanted under general or local anesthesia. Commonly used electrodes consist of platinum-iridium[9] or stainless steel discs[10,11] with exposed surfaces of 2.3 mm diameter. They are embedded in a transparent soft silastic sheet, and are evenly spaced with an interelectrode distance of 1 cm. Depending on the indication, they can be placed over the cortical convexity, within the interhemispheric fissure, and over the basal surface of the brain. For example, in patients with dominant temporal lobe epilepsy (TLE), a 6×8 or an 8×8 grid is usually implanted over the perisylvian cortex, and a combination of strips, or a smaller grid, is implanted over the basal temporal cortex. Usually, half of the perisylvian grid is above the sylvian fissure and half is below it. The grid allows electrocortical stimulation mapping of language, as well as the inferior sensorimotor strip that includes the tongue and the inferior portion of the hand areas. In patients with seizure foci in other regions, implantation of subdural electrodes is tailored to maximize the chances of covering the epileptogenic region; they can be implanted over the visual, sensorimotor, or supplementary motor cortices.[12] Subdural electrodes are anchored in place by suturing the silastic sheet to the overlying dura mater (Figure 72.1).

Subdural strips consist of 4–8 disk electrodes, with an interelectrode distance of 1 cm. They are placed along with grid electrodes through a craniotomy, or through burr holes on either side to help lateralize seizure focus. A common procedure is to implant three to four strips through a frontal burr hole, and three to four through a temporal burr hole on each side. Such an implantation is needed for lateralization of the seizure focus.



(a)



(b)

Figure 72.1 Intraoperative photographs help determine the location of most subdural electrodes with respect to cortical anatomy. a. Left craniotomy in a patient who had been monitored by scalp electrodes with poor localization of seizure onset in the left hemisphere. b. Extensive subdural electrode implantation aims at maximizing the chances of identifying the area of ictal onset as well as mapping eloquent cortical areas. The dura mater has been retracted (white star). The subdural electrodes are embedded in a transparent silastic sheet that allows visualization of the underlying gyral anatomy, and is carefully fitted over the cortical surface and sutured to the overlying dura mater. Note that the 8×8 suprasylvian grid is sutured to two 2×5 frontal grids (arrows) and to a 4×8 infrasylvian grid (arrowheads), and that each cable connects two rows of electrodes to the EEG amplifier.

Intraoperative photographs are important for determining the location of some electrodes with respect to gyral anatomy (Figure 72.1). Some electrodes, however, cannot be directly visualized intraoperatively, as they do not lie within the margins of the craniotomy. The position of such electrodes, and that of strip electrodes implanted through burr holes, are verified by postoperative X-rays, and by superimposition of postoperative volumetric CT scan (with 1.0 mm axial slices to reconstruct the patient's skull and locations of subdural electrodes) on a cortical surface rendering of a preoperative volumetric magnetic resonance image (MRI) (Figure 72.2). Once implanted, the patient undergoes continuous video/EEG monitoring for 1–2 weeks for accurate localization of the seizure focus and mapping of eloquent cortical function.[13,14]

Seizure patterns

Interpreting ictal patterns recorded by subdural electrodes requires awareness of not only pathologic patterns, but also physiologic and artefactual phenomena. Familiarity with such patterns is needed for identification of the epileptogenic zone, defined as the zone whose resection or complete disconnection is necessary and sufficient to eradicate seizures.[15] The ictal onset zone, where the first electrical changes are detected, *regardless of their morphology*, prior to the clinical manifestations of the seizure (Figure 72.3), is presumably included within the epileptogenic zone.[16]

Early ictal patterns recorded by subdural electrodes may take one of various morphologies, including rhythmic sinusoidal waves, irregular spike discharge, spike and wave activity, and low voltage fast activity.[16] These patterns are not different from those described in extracranial recordings. Blume *et al.*, studied the ictal pattern of partial seizures recorded by scalp EEG in 66 patients,[17] and reported electrodecremental pattern in 11% of the seizures recorded, sinusoidal waves in 47%, and repetitive epileptiform discharges (most commonly spikes and sharp waves) in 39%. Originally, guidelines for interpreting intracranial ictal tracings were anecdotal, but the criteria for identifying ictal patterns recorded by subdural electrodes have been evolving. High frequency oscillations, for example, are now recognized as an electrographic ictal signature.[18] This has become possible, in part, because digital EEG, unlike analog EEG, is not dependent on the response rate of the pen, and can have sampling frequencies of up to 10 kHz, allowing recognition of faster frequencies. Numerous studies over the past three decades assessed the morphological patterns of ictal EEG, and correlated them with brain region, pathology, and surgical outcome.[7,16,18–20]

In the context of describing an analog-digital circuit that detects electrographic seizures, Babb *et al.* defined seizures as high-frequency, high-voltage spikes lasting 5 seconds.[2] They argued that, while physiologic brain activity tends to show an inverse relation between voltage and frequency, ictal discharges can have a high frequency (up to 30 Hz), but will still maintain a high amplitude. The same objective of automatic recognition of seizures lead Gotman *et al.* to define ictal discharges as activity that is paroxysmal, rhythmic, and sustained.[21] Other authors defined ictal discharges recorded from intracranial electrodes as significant and specific deviation of EEG patterns from the baseline that consists of electrodecremental patterns or rhythmic activity *with or without apiculate waveforms.*[22]

Spencer *et al.* defined intracranially recorded seizure onset as sustained and rhythmic EEG patterns, with frequencies higher than 2 Hz, that are state-independent and different from the background.[7] Such a definition of early ictal patterns precluded assessment of low-voltage fast rhythms in their series, although the authors acknowledged that low-voltage fast activity is a recognized ictal pattern and resection of tissue where such pattern is localized, is associated with a good seizure control prognosis.[23]

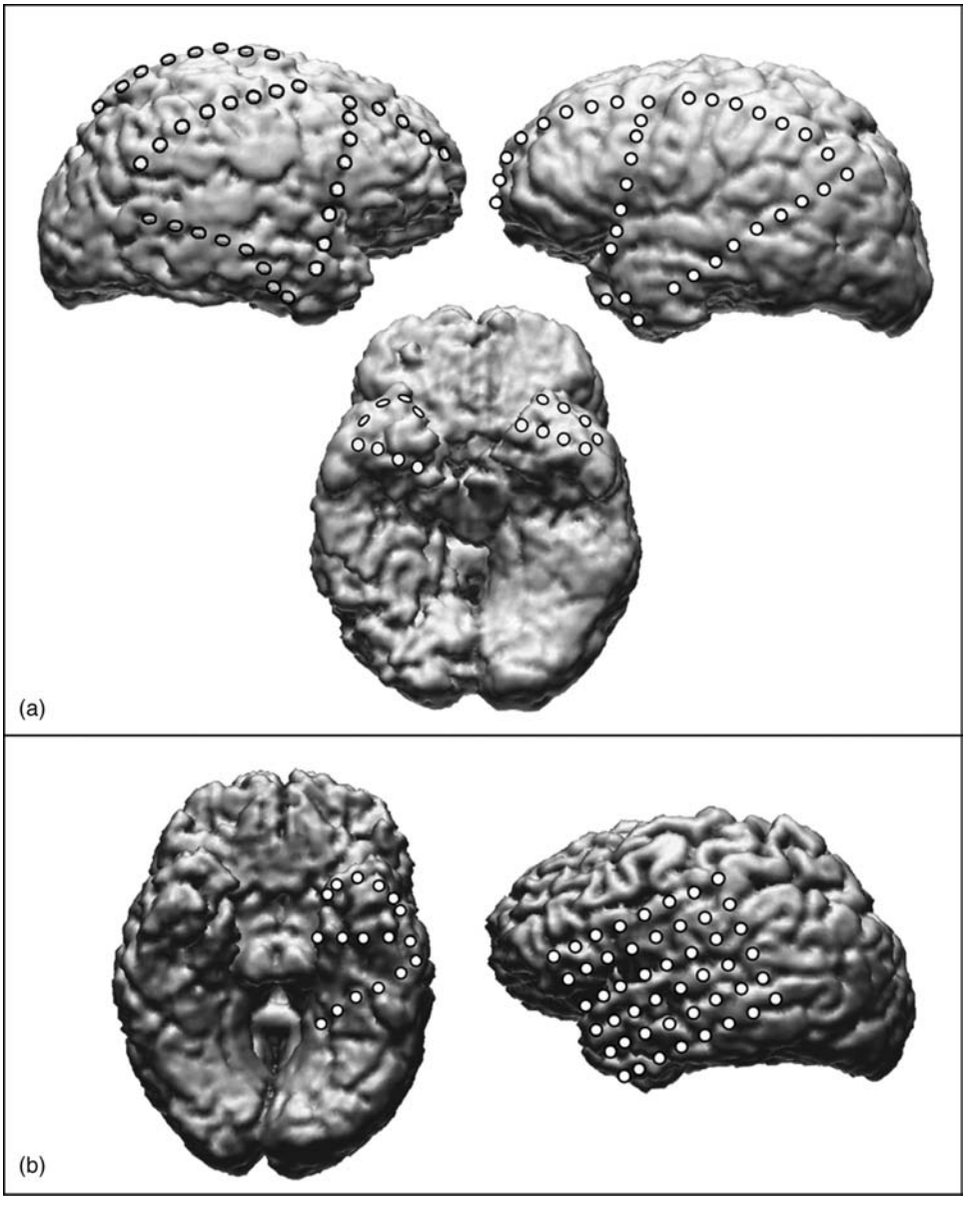


Figure 72.2 Cortical surface rendering of a presurgical volumetric magnetic resonance image (MRI), with the location of subdural electrodes from a postoperative volumetric head computed tomography (CT) scan superimposed. The coregistration (done with Curry software, Compumedics Neuroscan, El Paso, TX) allows three-dimensional visualization of the implanted electrodes in relation to gyral anatomy. a. Bilateral strip electrodes are placed through burr holes in order to help lateralize the seizure focus. Three (left) and four (right) strips are placed through frontal burr holes, and three through temporal burr holes on each side. b. This is a patient whose extracranial EEG showed an ictal discharge in the left frontotemporal regions several seconds after the clinical seizure onset (see also Figure 72.3). Grid electrodes were implanted over the left frontal and temporal lobes with an 8 × 8 grid covering the perisylvian cortex, and three 1 × 6 strips sampling the basal temporal cortex.

Low voltage fast activity

The pioneers of EEG included a gamma band to represent activities higher than 35 Hz, but this band was of very limited clinical use as the analog EEG machines were limited by the response time of the stylus, in addition to using a 'standard' low pass filter of 70 Hz.[9] The first reports of intracranial recordings that associated high frequency activity with ictal electrodecremental pattern on scalp EEG date back to 1950, when Mazars and collaborators performed corticographic recordings of epileptogenic foci before they attempted surgical resection.[24,25] A decade later, Bickford and Klass reported that 19 of 350 seizures started with generalized electrodecrement.[26] This pattern was later associated with tonic seizures, infantile spasms and Lennox-Gastaut syndrome, but some authorities later argued that most partial seizures are initially associated with a low-voltage fast pattern if electrodes are close enough to the seizure focus.[9,27] Morris *et al.* described regional electrodecrement in association with complex partial seizures of temporal lobe origin.[11] The invention of digital EEG, and extraoperative monitoring of patients with implanted subdural electrodes, led to further characterization of high frequency activity as an ictal pattern.[9,18,19,27]

With higher digital sampling frequency and low pass filter, even higher frequency oscillations may be detected that will aid is identifying epileptogenic cortex (see Figure 72.5). Fisher *et al.* recorded seizures with subdural electrodes sampling the EEG at 2000 points per second, and using a 300-Hz low-pass filter.[9] They found that the EEG signal included within the

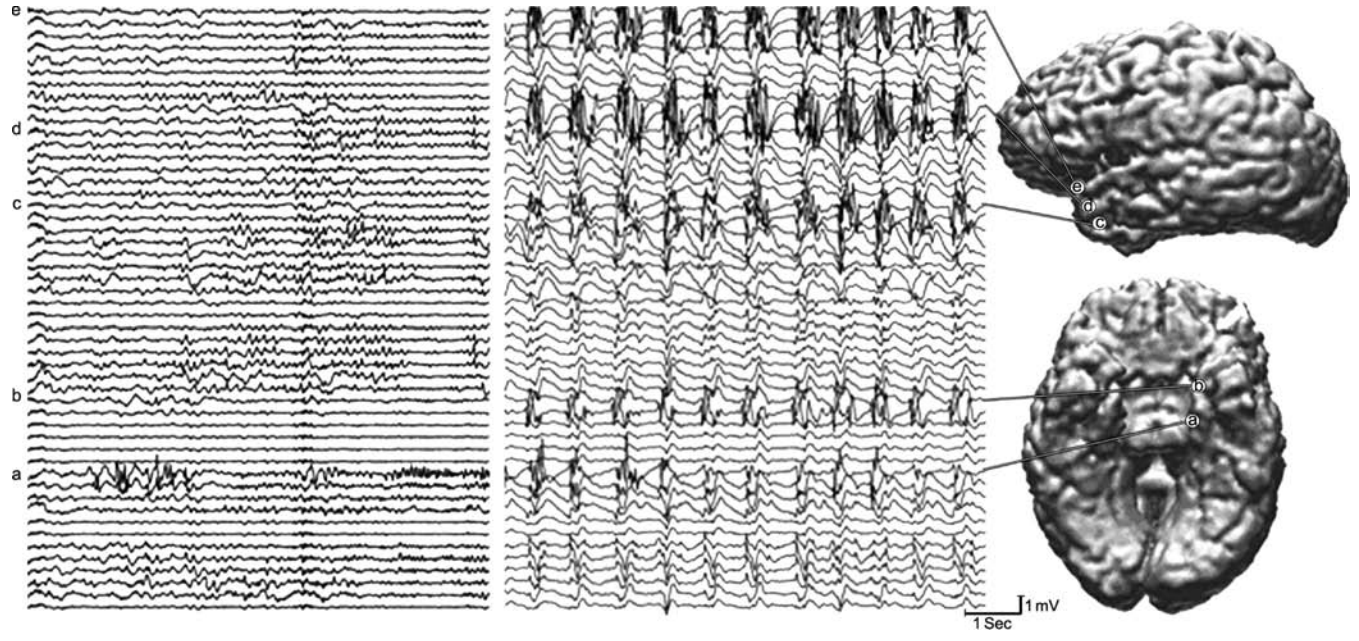


Figure 72.3 Ictal EEG recorded intracranially in the patient whose subdural electrodes are shown in Figure 72.2b. Clinical seizure onset, semiologically identical to what has occurred without discernible scalp EEG changes during prior extracranial monitoring, is now seen in association with an electrographic ictal discharge localized to the left mesial temporal region (first page, electrode a). The second page, approximately 1 minute later, shows a fully evolved ictal discharge, which would have become evident by scalp electrodes at that stage. The locations of the most active electrodes are shown on the brain surface.

ictal electrodecremental pattern consisted of a 'conventionally invisible' high-frequency band, illustrating the importance of high-frequency recordings in localizing seizure foci. At the start of seizures, the 40–50 Hz portion of the frequency spectrum was doubled and the 80–120 Hz portion increased five times in the region of epileptic focus, but not in remote areas. The same authors reported evidence of high-frequency activity originating in one frontal lobe by subdural electrodes when scalp-EEG recording revealed diffuse electrodecrement as an ictal pattern.[27] Semiologically, seizures associated with this pattern were dialeptic, dystonic, tonic, atonic, or a combination of more than one type. Worrell *et al.* found that 62% of neocortical seizures recorded by subdural electrodes were preceded by an increase in high-frequency activity in the 20 min prior to the clinical onset of the seizure.[18]

Alarcon *et al.* used subdural, as well as intracerebral electrodes, to record 78 complex partial seizures.[16] They studied five seizure patterns: electrodecremental events, low-voltage fast, short bursts of irregular sharp waves intermixed with slow activity, regular epileptiform discharges, and rhythmic ictal transformation. In 12 out of 15 patients, electrodecremental events constituted the early ictal pattern. The authors also reported that interictal spectral EEG power was generally below 12 Hz,[16] but ictal changes appeared more complex and not always localized to one area.

A 2006 study concluded that high frequency oscillations occur in epileptogenic areas, both mesial temporal and neocortical, but rarely in areas of seizure propagation.[19] The presence of high-frequency oscillations at seizure onset is considered a measure of proximity of the recording electrodes to the epileptogenic focus, whereas absence of such activity indicates poor localization (see Figure 72.4).

Ictal patterns and specific pathology

Since extraoperative monitoring with subdural electrodes became common use, several studies attempted to correlate locations of the seizure onset zone and ictal patterns, with their pathologic substrates. However, it is unclear whether specific ictal patterns are strictly related to certain tissue pathology, and it appears that the morphology of the ictal discharge is, at least in part, determined by an interaction between the anatomic location and tissue pathology.[28]

Correlation between electrocorticographic data and pathology has been studied most in TLE. A study that used lateral and basal temporal subdural electrodes in patients with intractable TLE demonstrated that epileptogenic lesions were likely located in the immediate vicinity of structural lesions.[11] The authors also found that macroscopic lesions (i.e., ones that could be seen by head CT scan or by the naked eye intraoperatively) were more likely to be lateral temporal, whereas microscopic lesions were basal or mesial. An earlier study in patients with TLE concluded that ictal and interictal EEG recordings yielded different conclusions about the presence and nature of pathology.[29] Other studies related spike-wave discharge or repetitive spikes with cortical dysgenesis,[30] periodic spikes preceding seizure onset with reduced cell count in the CA1 region of the hippocampus, and the latency of the ictal discharge propagating to the contralateral hippocampus with reduced cell count in the CA4 region.[31]

Spencer *et al.* studied the ictal pattern of 166 seizures in 26 patients recorded intracranially with a combination of depth and subdural electrodes, and correlated the morphological manifestations of the ictal pattern with the pathology of the resected tissue.[7] They found that 58% of temporal lobe

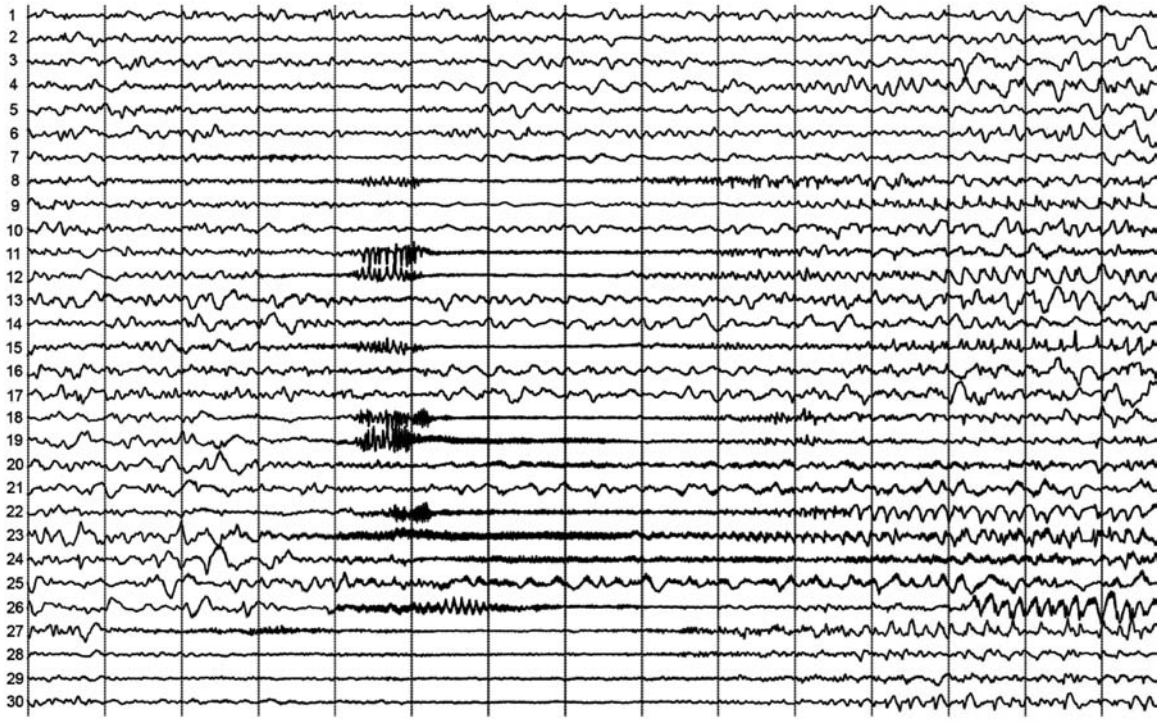


Figure 72.4 Ictal tracing from right occipital lobe subdural grids in a 20-year-old patient with intractable seizures manifesting as elemental visual phenomena in the left hemifield, followed by alteration of awareness, and occasional secondary generalization. This is a bipolar montage with channels 1 through 17 covering the lateral parieto-occipital convexity, and channels 18 through 30 covering basal and medial occipital regions. The digital sampling frequency is 1000 Hz. Notice the regional low voltage, high frequency (approximately 200 Hz) ictal discharge.

seizures with initial ictal discharge frequencies of <13 Hz were associated with positive pathology (including mesial temporal sclerosis), compared with 96% of those with initial frequencies of >13 Hz ($p < 0.00001$). On the other hand, extratemporal seizures with an initial ictal discharge frequency of <13 Hz were significantly associated with abnormal pathology, and those with a frequency of >13 Hz with normal tissue. However, all seizure patterns and frequencies were seen in both mesial temporal and extratemporal seizures, and separate seizures were recorded with discharge frequencies of either greater or less than 13 Hz in half of their patients. Conversely, in patients with extratemporal seizures, abnormal pathological findings were not associated with variability of seizure onset frequency. Temporal lobe seizures are more likely than extratemporal seizures to exhibit variable frequency of the initial ictal discharge in the same patient.

A study in patients with neocortical epilepsy showed that ictal patterns consisting of gamma range activity were likely to be seen in extratemporal locations and tended to be of regional onset.[28] However, beta frequency activity was seen more commonly in temporal lobe seizures and those with more focal onset. Different pathologic substrates were not associated with differences in onset frequency. Of note, seizure freedom was not related to onset frequency or distribution. Another study found no relation between spatial distribution of ictal onset and pathology,[32] but at least two studies[29,33] associated focal onset with reduced hippocampal cell density.

Localizing value of ictal patterns

Localization of the epileptogenic zone can be approximated by the onset of an electrographic seizure, provided it occurs prior to, or at least concomitantly with, the clinical onset. The localizing value of the ictal pattern can be assessed by the surgical outcome, as seizure freedom after epilepsy surgery indicates that the epileptogenic region was included in the resection.

Faster frequencies at the onset of the ictal discharge probably signify that the recording electrodes are closer to the ictal onset zone than those with slower onsets.[28] Slower onset frequencies may represent propagated activity,[34] and regional onset may indicate volume diffusion or spread from a distant generator.[35] This view is corroborated by the good outcomes after epilepsy surgery being associated with low-voltage fast activity at seizure onset,[36] and with focal onset seizures.[29] Some authors, however, found no relation between surgical outcome and the spatial extent of the seizure onset.[28]

Alarcon *et al.* used a combination of depth and subdural electrodes to correlate electrographic patterns with surgical outcome in patients with complex partial seizures.[16] They reported early electrodecremental patterns with frequencies below 40 Hz in the majority of their patients. Whereas localized high-frequency patterns correlated with favorable outcome after epilepsy surgery, diffuse electrodecremental patterns were not associated with poor outcome. The authors argued that diffuse electrodecremental patterns may not be part of the ictal process itself.

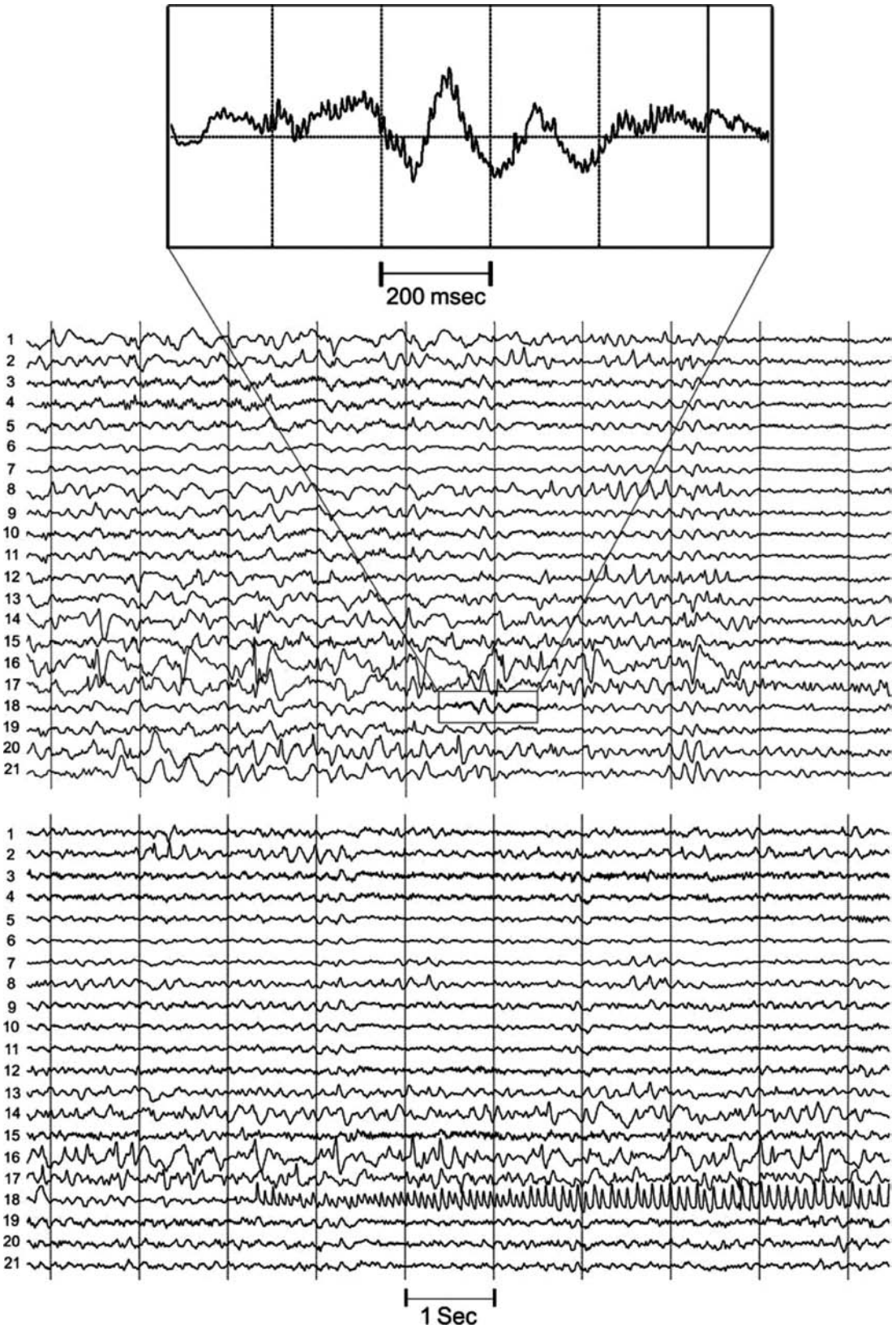


Figure 72.5 Ictal tracing from a right perirolandic subdural grid in a 33-year-old patient with intractable daily seizures manifesting as left hand sensory symptoms, which then involve more proximal arm regions and face. At times, this is followed by motor symptoms and occasional secondary generalization. Extracranially recorded EEG has shown no ictal discharge is association with seizures manifesting as mere left hand sensations without further progression. With subdural electrodes, however, there is one-to-one correspondence between the onset of her sensory seizures and bursts of fast (85–90 Hz) activity (upper page and insert). Channel 18, where the fast activity is seen, corresponds to a contact over the hand area of the primary somatosensory cortex (confirmed by electrical stimulation mapping). Note that the fast activity is followed 2–3 seconds later by regional electrodecrement (last 2 seconds of the upper page), and, several seconds later, by a higher voltage rhythmic spike discharge. Digital sampling frequency is 1000 Hz, and the low-pass cut-off frequency is 300 Hz. Decreasing the frequency of the low-pass filter increases the likelihood of missing the initial high-frequency activity which is most localizing to the seizure onset zone. Of note, resecting the cortical tissue corresponding to the initial burst of high-frequency oscillation (electrode 18) resulted in total cessation of seizures.

Limitations

The major limitation of recording with subdural electrodes is that they sample only a limited area of the cortex, which increases the likelihood of missing the epileptogenic region. To maximize the chances of covering the area of ictal onset, epileptologists generally plan the implantation after extensive preoperative testing. Nevertheless, in some patients it may be difficult to determine whether the ictal discharge recorded by a certain subset of subdural electrodes is originating from that area or propagating to it. The initial patterns of local onset and propagating electrographic seizures may be identical, although one study found that rhythmic theta-delta activity may be unique to propagating seizures.[34] In addition, the spatial extent of the ictal onset zone may be difficult to determine if the initial ictal discharge is detected by electrodes at the border of a grid.

Another limitation of recording with subdural electrodes is in patients with deep seizure foci. Although depth electrodes only parsimoniously sample the cortex and cannot be used for mapping of cortical function, they are superior for recording from the mesial temporal structures[37] and from some patients with neuronal migration disorders.[38] Even when subdural electrodes cover the hemispheric convexity, they record activity from only a limited area of the neocortex, and may miss electrical activity in the banks of fissures or sulci. Lüders *et al.* argued that the inability of subdural electrodes to record from cortical infoldings may explain the difficulty of detecting auditory evoked potentials with perisylvian plates,[12] as the auditory cortex is likely probably located deep in the supratemporal plane.[39]

In TLE, subdural electrodes led inadequate or even false localization of ictal onset in two studies using simultaneous subdural with depth electrodes.[40,41] Another study found that lateralization of the seizure onset zone, when detected by subdural electrodes, was always concordant with depth electrode recordings, but subdural electrodes were less sensitive in detecting hippocampal seizures.[37] Other authors showed that concordant lateralization by depth and subdural strip electrodes was seen in the majority of recorded seizures in patients with TLE, although some seizures were falsely localized by subdural electrodes.[42] The authors concluded that accurate localization is achieved by basal temporal subdural electrodes when the parahippocampal region is covered.

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73 Stereoelectroencephalography

P Kahane and S Francione

Introduction

In the presurgical evaluation work-up of patients suffering from drug-resistant partial seizures, intracranial EEG has been in use for more than 50 years. This practice not only generated considerable historical and practical information, but also continues to hold an important role in the precise definition of the epileptogenic zone in a consistent percentage of patients. Invasive EEG, indeed, is still performed on 25–50% of patients at most epilepsy surgery centers, depending on the referral population. Among the broad group of invasive procedures, and more especially in the field of 'depth recordings', some conceptual and technical aspects make the stereoelectroencephalography (SEEG) very particular since, from the begining, it has been conceived by Talairach and Bancaud as a comprehensive methodology and not only as a diagnostic tool.

Theoretical basis

Historical background

The basic principle of Bancaud and Talairach approach was to study the seizures themselves, through what they named the 'anatomo-electro-clinical correlations'.[1–3] Under this term, they regarded the chronological occurrence of ictal clinical signs as crucial, reflecting the spatio-temporal organization of the epileptic discharge within the brain. Their clinical analysis of ictal events, beyond a simple description, consisted, on one hand of interpreting the symptoms according to documented cortical topology, and on the other hand of analyzing them chronologically to imagine a logical spatial evolution of the intracerebral discharge. Understanding this temporal dynamic of ictal symptoms with respect to brain anatomy implied that 'ictal electroencephalographic changes must be recorded at the very point where they occur (anatomo-electrical relationships) and that their initial or secondary reverberations on the clinical picture (electro-clinical relationships) must be evaluated as the discharge spread'.[2] Such an approach was rendered technically feasible thanks to the advent of atlases providing the spatial coordinates of most telencephalic structures, as well as the development of neurosurgical techniques that allowed to target and reach such coordinates[4,5] (see Chapter 104). The selection of the structures to be explored was based on a very careful analysis of all the data – notably clinical – collected during the noninvasive presurgical investigations in order to formulate one or several hypothesis concerning the site(s) of seizure onset, and the pathways of preferential ictal spread.[1–3,6–8] The implantation strategy was then 'custom-tailored', and electrodes were placed according to the prior hypotheses, in a way that enabled to interpolate intracerebral EEG activity within the interelectrode space. The underlying concept was therefore very different from other intra-cerebral EEG procedures referred to as 'depth recordings'[9–11] the aim of which was primarily to ensure the side of seizure onset in temporal lobe epilepsies, or to differentiate frontal lobe seizures from temporal lobe seizures. Intracerebral targets were in such cases relatively standardized in order 'to avoid biasing the exploration strategy in favor of one's preferred localizing hypothesis'.[12]

It was clear, when considering the SEEG method, that if the pre-SEEG hypotheses were wrong, the placement of intracerebral electrodes would be inadequate, the interpretation of SEEG findings was likely to be erroneous, and surgical results would be probably poor.[13] Conversely, if the pre-SEEG hypotheses were correct, the resulting implantation strategy would allow to help to identify the amount of brain tissue that must be ideally resected, and to reliably anticipate the patient's postoperative outcome according to the surgical possibilities and limits.

SEEG today

Technically speaking, the SEEG method has evolved with time: 'acute' recordings has became 'chronic', electrodes have been reduced in size, electro-clinical correlations have been improved thanks to the advent of audio-video-EEG monitoring system, and intracerebral targets are currently assessed using MRI. Conceptually, 'the song remains the same', and a SEEG study cannot be performed without having previously hypothesized what the preferential origin and spread of the seizures could be.[13–16]

As for many epilepsy surgery centers, the overall proportion of our patients evaluated by invasive recordings has decreased over the last decade. However, the subset of patients who can benefit from the use of SEEG remains significant and, in our centers, approximately 40% of resective surgical procedures are performed so far after SEEG recordings.[14] Schematically, such recordings are needed when noninvasively obtained data remain insufficiently concordant, when they are discordant or inconclusive, and when they suggest an early involvement of highly eloquent areas, providing that the questions derived from the noninvasive protocol are clear, and that the patient is likely to benefit from surgery.

Implantation strategy

Since there are no standard targets for electrode implantation, the selection of the structures to be explored must be determined individually, mainly on the basis of both clinical and scalp-EEG seizure pattern(s).[1–3,6–8,13–15] This assumption is even true in lesional epilepsies where a SEEG study may remain indicated. In such cases, the presence of a lesion will influence the implantation strategy, as far as the relationships between the lesion itself and the region of seizure generation must be clarified. Nonetheless, the leading principle is still to investigate all the cortical areas, the ictal involvement of which is suspected on the *main* basis of ictal electro-clinical information.

Yields of electro-clinical findings

Today, evidence has accumulated on the diagnostic value of seizure symptoms, and many studies have been – and continue to be – conducted in this way. Most tend to attribute to isolated signs, as well as to clusters or evolution of a few signs, a lateralizing or localizing significance.[17] This kind of clinical analysis, although helpful, remains very different from the working method that Talairach and Bancaud emphasized: in their mind, indeed, ictal clinical symptomatology must be viewed as a whole (this led to the notion of *seizure pattern*). Particularly, it was clear for them that seizure symptoms (and more particularly the 'signal-symptom'), when taken individually, could lead to erroneous interpretation.[1] The emergence of an identical clinical sign may result, indeed, from the ictal disorganization of cortex regions which, even if different, may have common subcortical projections. For instance, an ascending epigastric sensation, 'typically' of (mesio-)temporal lobe origin,[18] may as well translate an ictal involvement of the insular cortex[19] as that of the mesial prefrontal cortex,[20] or be the first manifestation of a discharge circumscribed within a hypothalamic hamartoma.[21] Additionally, symptoms of highly localizing value are rare and, even in such ideal condition, the localizing sign must be integrated chronologically to make an extrapolation of the anatomical origin of the seizure. Focal clonic jerks, for instance, which are the expression of the ictal involvement of motor cortex, will not have the same value at the beginning of an ictal episode initiated by paresthesia in the same body segment (strong probability that the perirolandic region was initially affected), than after the occurrence of auditory hallucinations (propagation of a posterior perisyslvian discharge to the motor strip), or than at the end of a fit beginning with a rising epigastric feeling followed by oroalimentary and gestural automatisms (no localizing value). Finally, the emergence of some signs of relatively poor localizing significance (e.g., gestural automatisms), especially in a late phase of the seizure, may only reflect the simultaneous or sequential dysfunction of several cortical areas – thus probably of several efferent systems – without giving any indication, per se, on seizure origin. A good example is given by the supposedly highly localising significance of 'frontal' hypermotor behavior, which have been recently described during seizures of temporal[22] or insular origin.[23]

Nowadays, ictal clinical patterns are assessed at best by video-EEG monitoring, but careful attention must also be paid to the historical evolution of symptomatology. This latter may have evolved with time, so that auras or focal signs of high localizing significance may have disappeared during the course of the disease, or still exist only in a few occasions but have not been documented during long-term video-EEG monitoring. The cortical areas to which these clinical manifestations refer will have to be taken into account for the adjustment of electrodes positioning.

Although crucial, the localization hypothesis suggested by ictal clinical picture should be confirmed and completed by careful analysis of the concurrent ictal scalp-EEG discharge. This remains essential to confirm the clinical hypothesis when this latter is clear, but above all to improve it when ictal symptoms are ambiguous and fail to indicate a clear-cut localization or lateralization. In that respect, emphasis is put on the identification of the first ictal EEG change that occurs prior to the first clinical symptom, and more specifically on the identification of a well-localized low-voltage fast activity which is likely to reflect an underlying fast-synchronizing intracerebral EEG discharge. As a matter of fact, such a scalp EEG pattern has been recently found to be predictive of a good surgical outcome in frontal lobe epilepsy.[24] However, a low-voltage discharge may not appear on the scalp recording, especially if it is well-limited and located deep in the cortex. In such a case, particular attention must be paid to a well-localized flattening of the EEG trace, or to the disappearance of well-localized interictal EEG abnormalities, which are both good indicators of the region of seizure origin. Altogether, these scalp-EEG patterns of seizure onset are particularly helpful for identifying the core region of the future implantation, but they cannot account for the whole brain area which is involved by the discharge. It is thus of particular importance to also evaluate the cortico-cortical propagation of the discharge, which is at best assessed by a careful analysis of the spatial evolution of the scalp-EEG discharge from the onset of the seizure to its end. Unfortunately, scalp-EEG discharges may quickly be widespread or bilateral, or multiregional, so that the preferential spread pattern may be particularly difficult to define.

The recording of the patients seizures, although crucial, does not exempt one from analyzing interictal EEG abnormalities which may influence in part the final placement of the electrodes, particularly when their distribution does not match with the territories that are suspected to be involved by the seizures, or when ictal recordings are fairly informative due to movement artifacts, as during hypermotor seizures.

Essential rules for electrodes implantation

Although all the SEEG studies are designed, a priori, on the basis of patient's individual characteristics, the analysis, a posteriori, of all our investigations shows that they can be schematically grouped in several implantation patterns, according to the main cortical regions that were targeted[25] (see Chapter 104). However, the exact drawing of electrodes placement is never identical for one patient to another one, and it closely depends on all the noninvasive features previously collected (see below the illustrative case). As a rule, the position and number of intracerebral electrodes (Figure 73.2a) must be designed to address the following issues:

1. Demonstrating that brain regions suspected to be involved in seizure onset and early propagation (the 'epileptogenic zone') show the expected ictal pattern. This requires the suspected brain regions to be implanted (Figure 73.2b).

2. Considering the possibility that this pattern might in fact reflect the propagation of an ictal discharge generated elsewhere. This requires a comprehensive review of such alternative hypothesis, and the intracerebral evaluation of part or all of the corresponding brain structures (depending on the number and the likelihood of these hypotheses) (Figure 73.2c).
3. Delineating the border of the 'epileptogenic zone' as precisely as possible, in order to perform the minimum cortical resection. This requires the placement of intracerebral electrodes in brain structures located outside the theoretical limits of the suspected 'epileptogenic zone' (Figure 73.2d).
4. Assessing whether the removal of the cortical areas involved in seizure generation will be possible or not. This requires the investigation of the eloquent areas that are of interest, relatively to the hypothetical 'epileptogenic zone', and with respect to the possible boundaries of the planned resection (Figure 73.2d).
5. Evaluating the precise relationships between an anatomical lesion (when present) and the 'epileptogenic zone'. This requires to investigate, whenever possible, the epileptogenicity of the lesion itself and in any cases of the surrounding cortex, the number of the 'lesional' electrodes to use depending on the morphology, extent and anatomical location of the lesional process (Figure 73.2b).

Illustrative case

This 32-year-old right-handed patient, without any familial nor personal antecedent of epilepsy, started having seizures at the age of 8 years. During childhood, the fits were initiated by auditory illusions associated with blurred vision, which were followed by a loss of contact and left oculo-cephalic deviation, possible fall, and rare secondary tonic-clonic generalisation. The episodes persisted until the age of 12 years when clobazam was associated to carbamazepine and phenobarbital. Around the age of 17, seizures recurred, beginning with a sensation of nausea in the stomach during which the patient was able to speak, followed by a loss of contact with gestural and verbal automatisms. Since then and despite numerous medications, seizures persisted with a mean seizure frequency of six to nine episodes per month, without any prolonged seizure-free intervals. Ictal symptomatology changed at the age of 21: seizures started with a sensation of pleasure ('a spiritual pleasure'), rarely associated with an epigastric feeling or with a *déjà-vécu* impression. These auras could remain isolated without language disturbances, or could be followed by a global sensation of 'switching off' (lowering of the sounds and visual blurring) as the prelude to the loss of contact, the features of which were not well described.

At the age of 30, the patient came at the C. Munari Epilepsy Surgery Centre for presurgical evaluation. Neurological examination was normal and neuropsychological evaluation demonstrated a deficit in both verbal and visuo-spatial memory functions. The only persisting aura consisted in an inconstant and brief feeling of pleasure, which might precede the loss of contact with staring and a few gestural, verbal and oro-alimentary automatisms; the postical phase was characterized by deambulatory behaviors and complex verbal automatisms. Seizures could also occur in clusters of brief and pauci-symptomatic fits, during which the patient experienced a sort of ecstatic state with a clear spatio-temporal disorientation; he was still able to speak and had an almost correct working and social behaviour.

MRI (Figure 73.1) showed in the right temporo-occipital junction a slightly expansive lesion involving the cortex of the collateral sulcus and the surroundings fusiform and lingual gyri. These gyri appeared thickened with a discrete hyposignal in inversion-recovery sequences and a clear and more widespread hypersignal in FLAIR images. The superior part of the lesion presented with a cystic component of less than 1cm in diameter. The diagnosis of tumor, possibly a dysembryoplastic neuroepithelial tumor, was suggested. No other MRI abnormalities were found, especially concerning the right hippocampus and the temporopolar region.

Video-EEG monitoring showed, interictally, a clear asymmetry of background activity (8–9 Hz, mid amplitude) which appeared more regular and better represented over the left posterior regions. Slow waves and rare spikes were recorded over the right fronto-temporal region. Spikes frequency was increased during sleep, with a phase reversal over F8, but also T4 and T6. Occasionally, left temporal asynchronous spikes were also recorded. Five electro-clinical seizures were recorded during wakefulness. In all, the patient was able to warn and

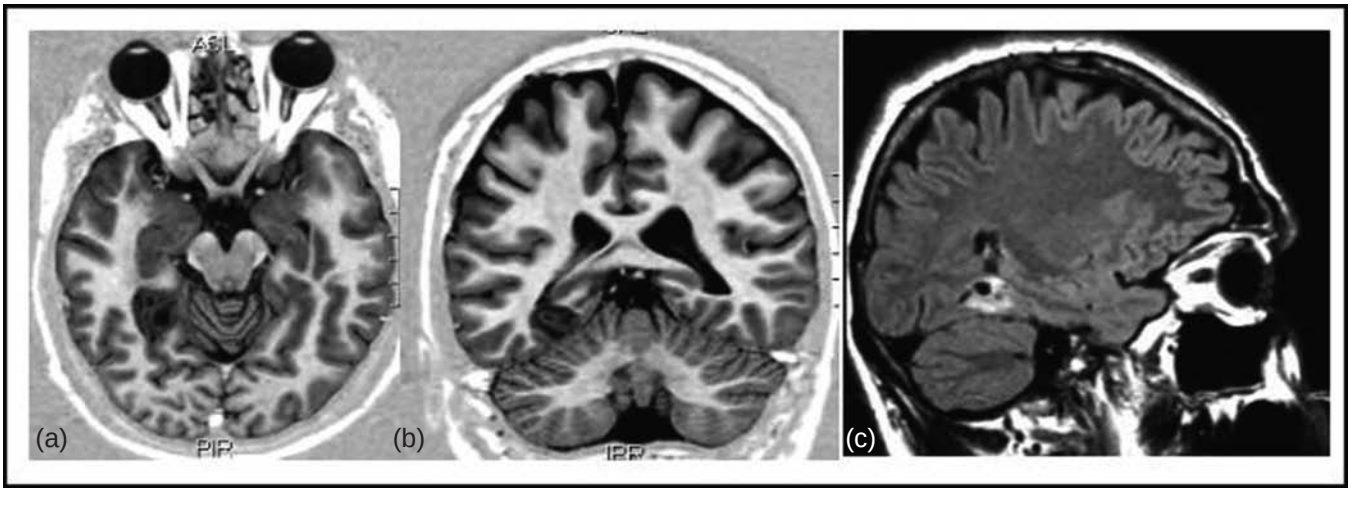

Figure 73.1 Pre-operative MRI (patient of the illustrative case). a: axial view, inversion-recovery sequences; b: coronal view, inversion-recovery sequences; c: sagital view, FLAIR sequences.

dialogue with the observer for the first 10 seconds. Then, the contact was impaired with staring, verbalization of a few stereotyped words, occurrence of a few activities of swallowing and discrete chewing. The episodes lasted less than 1 minute, at the end of which recovery of language function was total within a few seconds. EEG correlate was poor at the initial phase of the fit, but a clear rhythmic theta activity occurred while the patient became unresponsive: this activity mainly involved the right anterior temporal region, with a latter spread over the right parieto-central and left temporal regions.

These anatomo-electro-clinical features led us to propose to the patient a SEEG investigation (Figure 73.2a), the main aims of which were to define the relationships between the lesion with its different components (Figure 73.2b), mesiotemporal lobe structures (Figure 73.2b), and the visual and auditory cortices (Figure 73.2c). The SEEG study aimed also at evaluating how the different parts of the temporal neocortex and the adjacent temporo-parietal and temporo-occipital regions could participate in seizure early spread.

Recording and stimulation procedures

Thanks to many technical progresses such as the advent of long-term audio-video-EEG monitoring systems, most – if not all – SEEG studies are nowadays conducted extraoperatively in chronic conditions. Altough the monitoring systems utilized vary from one center to another, two main technical features are required to provide reliable information: the system must be able to sample the signal at a high frequency rate (at least 256 Hz, but recent work in patterns of seizure onset suggests potential benefit of using at least 512 Hz and even more), and to acquire the signal from at least 64 channels (but it is clear that this is a strict minimum, and twice, or even more, that number is optimal, and currently used). In our centers, we choose one of the contact sites in the white matter as reference and depth EEG activity is displayed using bipolar recordings between contiguous contacts. SEEG activity is

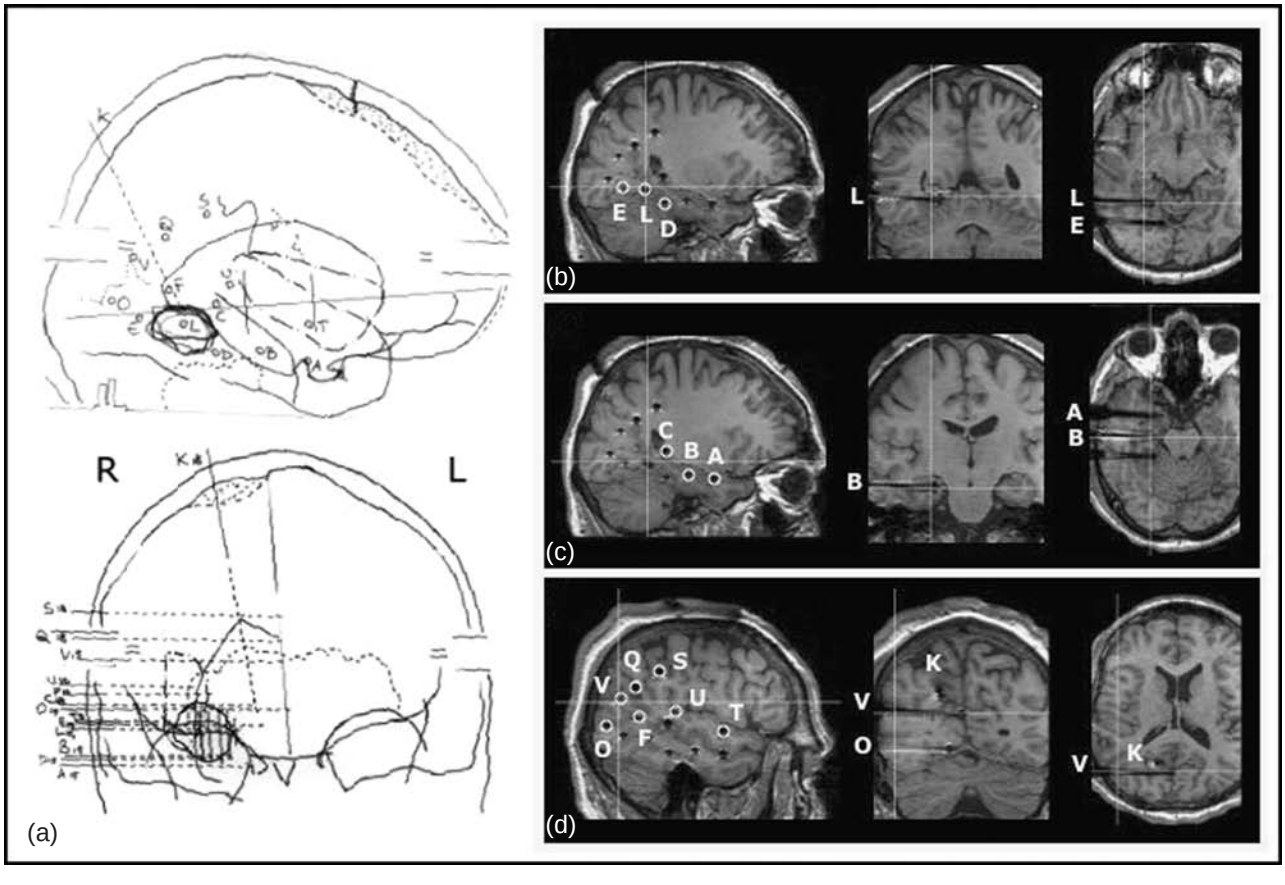

Figure 73.2 Implantation of intracerebral electrodes (same patient as in Fig.1). a: SEEG scheme, lateral and frontal view of the skull; b, c, d: multiplanar reconstructions (sagittal, coronal and axial views) of the MRI performed with the implanted intra-cerebral electrodes. b: position of the electrodes exploring the suspected ictal onset zone, including the lesion (L) and the peri-lesional cortex located anteriorly (D) and posteriorly (E); c: position of the electrodes recording mesial temporal lobe structures (A: amygdala, B: anterior hippocampus, C: posterior hippocampus), the role of which in early propagation (or even onset) of the seizures had to be clarified; d: localisation of the other intra-cerebral electrodes utilised in this case for a complete definition of the cerebral structures involved in the primary and secondary organisation of ictal discharges: i) superior temporal gyrus (electrodes T and U) due to auditory illusions described in the patient's history; ii) visual cortex (internal leads of electrodes F, O, V, K) both for clinical (blurred vision) and functional reasons; iii) lateral cortex of the temporo-occipital and temporo-parietal junctions since in our experience, such 'pauci-symptomatic' fits may result from an the ictal involvement of this extended neocortical region.

often recorded along with a limited number of EEG needle electrodes, the electrocardiogram is systematically monitored, and other parameters such as the electromyogram or the oculogram may at times be assessed.

Recordings are performed under different conditions (waking, after sleep deprivation, or during night sleep when necessary), over a period of 1 to 3 weeks, with a gradual reduction of patient medication when necessary. Patients are continuously observed by a member of the epilepsy team in order to obtain a precise description of subjective patient experience at seizure onset, as well as to test awareness, language, muscle tone and sensory-motor functions. Particularly, attention is focused on the signs and symptoms which cannot be assessed by reviewing retrospectively the videotapes, and more especially on the initial subjective symptoms which may be forgotten at the end of the seizure. In our experience, it is not necessary to capture systematically a predefined number of ictal episodes, but it is mandatory that the fits recorded are similar to the patient habitual seizures, and well documented. Recording of several seizures, however, is usually necessary, particularly in those of patients in whom ictal symptomatology is fairly stereotyped. The aim is to be able to analyze the main elements of the clinical symptomatology before one can establish electro-clinical correlations.

Electrical stimulations are performed for several days under continuous video-EEG control. The goals are the reproduction of the aura, the induction of an electroclinical seizure, and/or the localization of an eloquent cortical area that has to be spared during surgery. Following our standard clinical practice,[26] stimulations are performed at 1 Hz and 50 Hz (depending on the level of excitability and on the type of clinical signs that one expects to elicit by stimulating a given structure) and applied between contiguous contacts at various levels of the electrode axis. Advantages and limits of the stimulation during SEEG procedure is the object of Chapter 71.

Interpretation of SEEG findings

It is not possible to systematize, in this chapter, all the findings provided by a SEEG study, since each investigation is designed for a specific problem, and the number and type of structures evaluated vary according to the problem under investigation. Schematically, the interpretation of a SEEG study aims first at constructing a preoperative composite 'drawing' of the brain area to be removed (what we could call the 'what-to-remove area'), which could be easily followed in the operatory theatre. The determination of this area depends above all on the study of the anatomo-electro-clinical correlations evidenced during the seizures themselves, also taking into account the features of subclinical discharges and of interictal abnormalities, as well as the effects of electrical stimulation.

Seizure analysis

Seizure analysis represents the principal guide of the whole SEEG approach, as it allows to define what the mentors of Sainte-Anne School named the 'epileptogenic zone', i.e., the 'site of the beginning and of the primary organization of the epileptic seizures'.[8] However, what was clear in Bancaud and Talairach's minds from their earliest clinical experiences was that the topographic determination of the epileptogenic zone could not be based only on electrophysiological criteria: it depended on the study of electro-clinical correlations, this term underlining the importance to assess not only the precise anatomical location of the site of origin and early spread of the ictal discharges, but also how these SEEG changes gave rise to the clinical symptoms.

Ictal onset

In SEEG terminology, the ictal onset zone ('site of the beginning ...,) can be defined as the cortical area(s) where the first clear ictal electrical change is recorded. The SEEG assessment of this area, however, depends on the spatial sampling of the SEEG investigation, so that caution is required to ascertain that the site of seizure origin has been unequivocally identified. Nevertheless, it is reasonable to attribute to the first clear ictal electrical change a reliable localizing significance, providing: **(1)** that this change occurs prior to the clinical onset of the seizure, and **(2)** that it manifests by a fast synchronizing discharge (low-voltage fast activity or recruiting fast discharge of spikes), the pattern and frequency of which may differ from one region to another one.[27–29] The lack of one of these two criteria implies an incorrect SEEG investigation, so that the ictal onset zone, as well as the epileptogenic zone (which by definition should include the ictal onset zone), cannot be defined. In such condition, success or failure of surgery, if eventually performed, will not provide any valuable information. Conversely, the coincidence of clinical and relevant ictal electrical findings, and a fortiori the appearance of clinical onset after such ictal SEEG changes, both tend to indicate that the positioning of at least some electrodes is correct (Figure 73.3).

Primary organization of the discharge

The definition of the ictal onset zone, however, only helps in defining part of the epileptogenic zone, the main difficulty being then to evaluate 'how much of the cortex contiguous to the site of origin is recruited into action to produce a clinical seizure'.[30] Bancaud and Talairach assumed that this issue could be answered, at least in part, by considering also the cortical areas participating in early seizure spread ('... the primary organization of the epileptic seizures'). Under this term, particular attention deserves the spatial extent of seizure discharges at the moment where the first clinical sign(s) occurs, as well as the coherence between the localization of the discharge and the (expected?) type of the concomitant symptom(s) (Figure 73.3). Also, attention must be paid on the types of SEEG changes that occur during seizure evolution: once again, emphasis is put on cortex areas that are able to generate fast synchronizing discharge, including not only those recruited successively from the ictal onset, but also those exhibiting such a fast activity *de novo* during the course of the initial discharge (Figure 73.3). In any cases, what must be considered as an 'early' or a 'late' SEEG change cannot be assessed in terms of seconds, or tens of seconds, so the repertoire of ictal patterns are rich and the propagation times variable. This probably explains why Talairach and Bancaud used preferentially the term of 'primary organization of the epileptic seizure' than the term of 'early seizure spread'.

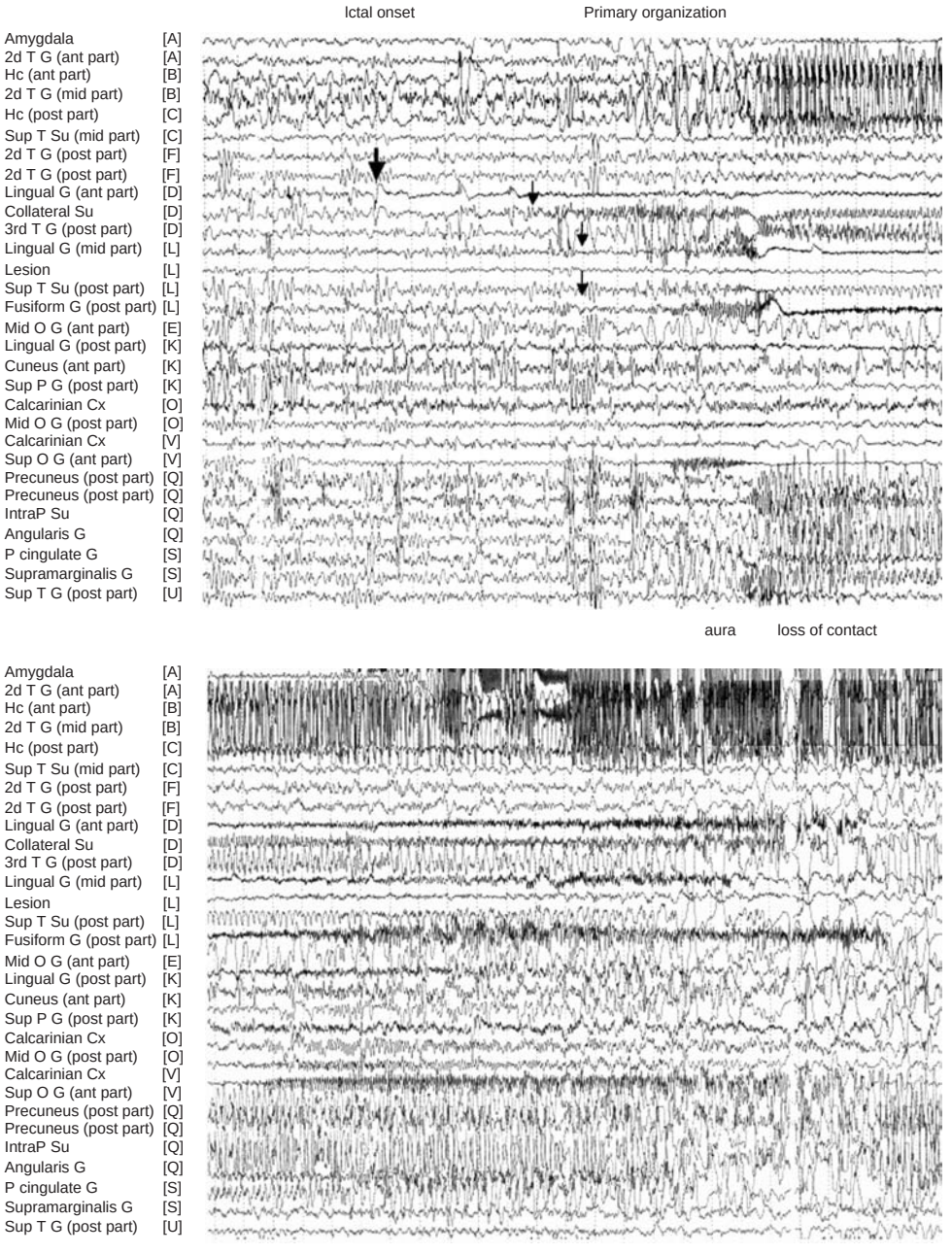

Figure 73.3 SEEG recording of an electro-clinical seizure (same patient as in Fig.1,2).G: gyrus; Su: sulcus; T: temporal; Hc: hippocampus; P: parietal; O: occipital; 1st/2d/3rd: first/second/third; ant/post: anterior/posterior; sup: superior. Letters in brackets refers to the recording electrodes (see Fig.2). a: The seizure starts in the anterior part of the lingual lobule, an immediately peri-lesional structure, with a low voltage fast discharge (first arrow); 4 seconds later, this activity involves, in a slower way, the collateral sulcus, the mid part of the lingual lobule and the posterior part of the fusiform gyrus (small arrows); two seconds after, the fast discharge spread out of the borders of the peri-lesional area, involving the third temporal gyrus as well as the superior and mid occipital gyri. At that time, the hippocampal formation begins to exhibit a spiking activity. During all this period, the patient, who was talking with one of the observers, does not report any symptom but looks like watching around with an interrogative expression. Ten seconds after the ictal onset, he stares for a while before saying: 'I guess I'm having an aura'. Immediately after he stops answering and obeying to the observer, even if he can continue looking at her. The electrical correlate of this sudden clinical modification is easily identified and consists, on one hand, in the abrupt acceleration of the low voltage fast discharge, especially over the lingual and fusiform gyri, and on the other hand in the sudden occurrence of a high amplitude spike-and-wave discharge within the hippocampus which seems to evolve independently. b: During the second part of the fit, the discharge is widely extended, involving almost all the explored structures.

Postictal findings

Early postictal findings, although not clearly specified in Talairach and Bancaud's work, are part of the analysis of any seizures recorded during SEEG investigation. Particular attention has been paid to those cortex areas exhibiting, at seizure termination, major attenuation and/or suppression of their background activity. Insofar, Toussaint *et al.*[31] have recently reported that postictal SEEG suppression accurately localized the seizure onset zone in a majority of frontal lobe cases, while it appeared more widespread in temporal lobe patients, involving both areas of ictal onset and seizure propagation. Postictal spikes were, in this study, of relatively poor localizing significance, in accordance with other works.[32] Certainly, postictal patterns have been neglected in the literature and further work is needed to set their actual role in the surgical decision.

Subclinical discharges

In any cortical location, a rhythmic activity or a fast activity mimicking an ictal discharge may develop focally without any accompanying symptoms. It is reasonable to attribute to such 'subclinical seizure activities' a high localizing significance, in as much as they have been correlated with an excellent outcome after surgery.[33,34] However, even when this kind of paroxysmal activity is present on the traces, the recording of the fully developed electro-clinical seizures remains mandatory. Subclinical discharges, in fact, may differ in terms of morphology and/or location from the clinical ictal discharge, or may appear identical to the early part of a clinical seizure which later involves other cortical structures.[35]

Interictal abnormalities

Lesional area

In SEEG terminology, the *lesional zone* refers to the brain area which is revealed by an abnormal slow-wave activity or, in some cases, by a major alteration of background activity or by an electrical silence.[6,7,13,36] These features, especially when caricatural, presume an underlying macroscopic alteration of the neural tissue, making common the anatomical overlapping of the electrically defined *lesional* zone with the 'epileptogenic lesion' (currently the most often revealed on MRI). Due to this good correlation, when slow-waves are present in the 'negative MRI area', neuroimaging evaluation should be improved in that specific region. However, the topographic distribution of the slow-waves does not always match with a lesion as assessed on pathological specimens. Thus, although the significance of such nonparoxysmals events remains unclear, it seems legitimate to carefully consider the area which exhibit continuous delta wave activity for the final surgical decision, even in the absence of a corresponding MRI anatomical lesion.

Irritative area

One of the cortical zones identified at the end of a SEEG study is the *irritative zone*, which includes the structures mainly involved by spike activity. Due to the abundance of these paroxysms and to their great variability in firing pattern and location, the definition of the irritative zone often represents a difficult diagnostic problem. In particular, the topographic relationships with the 'epileptogenic zone' must always be carefully evaluated since, in many occasions, the two zones can strongly differ in localization or show only a partial overlapping.[13] In a surgical perspective, however, it would be a mistake to ignore the extent of interictal spikes, whether they are focal or not. Indeed, they can provide additional confirmation of localization, but also may even prove of more important localizing value than seizure recording. This is typically the case of Taylor's focal cortical dysplasia (type II), whose peculiar interictal pattern could be considered as a good marker of the extent of the dysplastic cortex that needs removal to abolish the seizures.[37–39] Particular attention has to be paid, moreover, to those spikes that do not disappear at seizure onset; this persistence, indeed, might suggest that they do not depend on a pathophysiological process common to the underlying area(s) of seizure onset, and therefore that they might be part of what Lüders and colleagues named the 'potential seizure onset zone'.[40]

Intracerebral electrical stimulation

Intracerebral electrical stimulations represent a mandatory part of a SEEG study, not only for localizing eloquent cortical areas, but also (and often mainly) for eliciting seizures.[26,41,42] This latter application may prove very helpful in many controversial circumstances: (1) when spontaneous ictal discharges are widely extended from the onset of the seizure; (2) when they apparently arise 'independently' from different brain structures; (3) when regions initially silent at seizure onset seem to activate abruptly during the ictal discharge, showing in the further phases an asynchronous electrical build up that is different in terms of frequency and morphology from the primary seizure discharge. In these cases, induction of a complete and habitual seizure sequence by electrical stimulation militates for the inclusion of the stimulated structure in the surgical plan. Elicitation of auras may also help by identifying relay and subrelay areas that are essential for the final construction of ictal clinical picture, especially when those symptoms have disappeared in the course of the disease, or still exist occasionally and were not documented spontaneously. Even in this figure, however, the correct interpretation of elicited auras has to take into account, according to Talairach and Bancaud, the possibility of the activation of regions (cortical and subcortical) remoted from the stimulation site. Therefore, and mainly when a local ictal discharge has not been concomitantly elicited, caution is required when establishing a causal relation between a stimulated structure and the occurrence of a given symptom.[3] The role of electrical stimulation for defining the ictal onset zone is detailed in Chapter 71.

Surgical implications

Schematically, the 'what-to-remove area', wherever its location may be, can be defined either as focal, regional (lobar), multilobar, or multifocal. Surgery, in any cases, is designed according to the results of SEEG findings so that tailored resections are the rule rather than the exeption (see Chapter 104) (Figure 73.4).

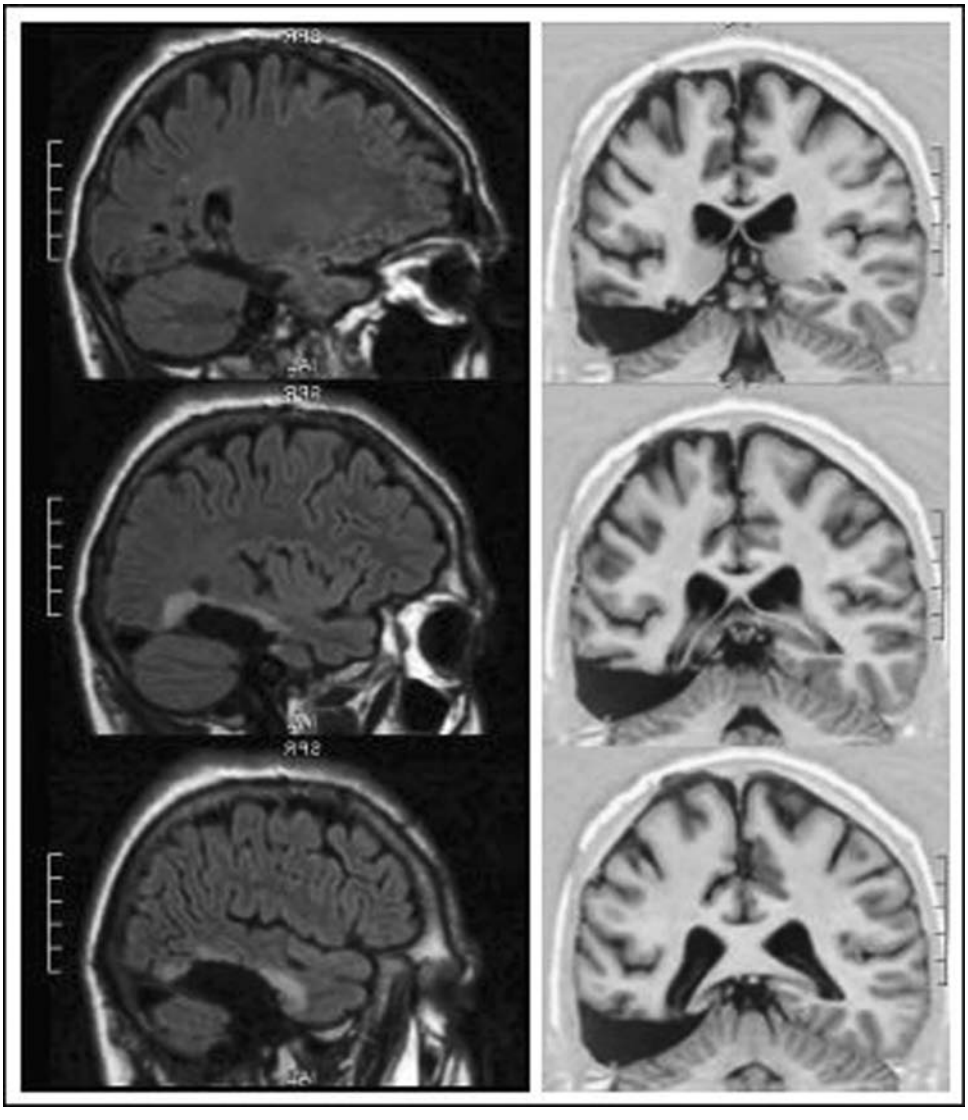

Figure 73.4 Tailored cortical resection (same patient as in Figures 70.1–70.3). Coronal Inversion Recovery (up) and sagittal FLAIR slices from the post-operatory (6 months) MRI study.

Focal discharges

Discharges affecting only a well localized area do exist, showing as many clinical correlates as the combination of topographic and electrical features that one discharge may produce. This is true in temporal lobe epilepsy, where an ictal discharge can remain confined into the amygdala[43] or the hippocampus,[44] the most often without clinical accompaniment; but it is also a common finding in most cortical locations. In fact, one must be sure of the accuracy of the 3D spatial sampling of the SEEG investigation before defining as *focal* such an ictal discharge. As a consequence, very limited cortical resections are uncommonly performed on the basis of SEEG findings. It remains a peculiar finding, which is mainly seen in cases of *focal* epileptogenic lesions. However, small 'epileptogenic zones' may exist even in cryptogenic cases, as recently shown by the therapeutic effect of stereotactic radiofrequency lesion of a very restricted frontomesial epileptogenic 'focus' generating dyskinetic behavior and laughter.[45]

Lobar discharges

In most patients, the area that has to be removed is localized inside the borders of a single lobe, even if ictal discharges may affect initially different structures of the lobe. Therefore, relatively standardized cortical resections can be performed without taking into account some of the subtle variabilities that can be observed in electrophysiological terms and sequential involvement of different structures. This is even true in temporal lobe epilepsy where increasing evidences suggest that the classical subdivision between mesio-temporal and neocortical discharges is an oversimplification.[29,46,47] In extratemporal epilepsies, similar considerations can be done but, due to the more limited experience in this field, the difficulty in the identification of clear cut and reproducible anatomo-clinical patterns is probably greater than in temporal lobe epilepsy.[48–51]

Multilobar discharges

A few years ago, Claudio Munari and colleagues[52] emphasized that in about 20% of patients studied by SEEG, the 'epileptogenic zone' included distinct (but interconnected) regions of different lobes of one hemisphere, and consequently should be defined as 'multilobar'. This condition, though uncommon, has been reported in other studies,[50,51,53–56] and does not represent a purely theoretical discussion: as demonstrated by Munari *et al.*,[52] more than 80% of patients were cured when

the epileptogenic zone was completely (or almost completely) removed, while when the removal was clearly incomplete, the percentage of seizure-free patients dropped to 10%. Thus, the possibility that an epileptogenic zone may extend outside the boundaries of one lobe must be taken into account. For instance, when looking at surgical failures in temporal lobe epilepsy, a consistent percentage of patients are likely to suffer from 'temporal plus' epilepsy (Ryvlin and Kahane),[57] so that identifying this 'multilobarity' might enable to tailor a more extensive corticectomy with a probably better surgical outcome.

Multifocal discharges

In our experience, the indication of depth recordings to understand whether the 'epileptogenic zone' is unifocal or multifocal is rare. In general, patients with electro-clinical evidence of different seizure types are excluded from surgery after the non-invasive phase of the evaluation. However, in a restricted and well-selected number of cases, especially when a lesion is present, the realization of a SEEG may help in establishing whether the different seizure types have a link in between. The results of the SEEG study performed in these conditions may allow to demonstrate that the different seizure types, although multifocal, are in fact part of a widely extended area which can be safely removed.[58] Another striking example of this possibility is represented by patients in whom an hypothalamic hamartoma is associated with multiple seizure types, and in whom SEEG recordings demonstrated that laughing (or crying) attacks, the hallmark feature of the syndrome, were linked to ictal discharges confined to the hamartoma.[21] Such examples are rare enough to be mentioned, so that caution is required whenever different kind of seizures have been clearly documented during scalp-EEG monitoring, and recognized by the patient and/or his family as the habitual seizures. Thus, in our experience, most of the true multifocal epilepsies defined during SEEG procedure are not expected from the non invasive protocol and, as a consequence, the idea of surgery is often abandoned, or eventually dictated by the possible efficacy of surgery on the predominant or more disabling seizure type.

Conclusions

The SEEG is not a presurgical evaluation tool, but a complete methodology which emphasizes the importance to study the spatio-temporal dynamics of seizure discharges (the 'epileptogenic zone'), and not only their starting point (the 'ictal onset zone'). Obviously, it cannot be considered as *the* ideal method for defining the cortical areas that have to be removed to cure the patients. However it has survived the huge development of modern neuroimaging and other noninvasive localizing techniques, and has greatly helped our understanding of ictal clinical symptomatology of partial epileptic seizures. For these reasons, it remains a reliable way to assess the origin and extent of an epileptic discharge within the cortex, even in the absence of any neuroimaging abnormality.

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74 DC recordings to localize the ictal onset zone

A Ikeda

Introduction

Interictal epileptic neuronal discharges were expressed as PDS (paroxysmal depolarization shift) and its pathophysiology has been revealed by abnomal channel activity of the cell membrane labeled as channelopathy, or by excitatory amino acid receptor abnormality, and so on. Furthermore, it is also pointed out that the glia performs important roles in buffering functions that help to maintain the uptake of potassium and glutamate, and other aspects of the extracellular circumstances of neurons.[1,2] A change in the microenvironment of the neuron by glial dysfunction could be another important aspect of epileptogenesis.

Since it is most likely that focal cortical epileptogenicity is almost always accompanied by gliosis, i.e., abnormally accumulated normal and abnormal glial cells, except for the functionally determined focal epilepsy such as benign rolandic epilepsy, dysfuction of the glia in epileptic focus could be one of the biggest modulating factors. Ictal direct current (DC) shifts reflect not only epileptic neuronal discharges but also passively depolarized glial activity following depolarization of the epileptic neurons, or the glia plays as an amplifier of the ictal DC shifts, as described below, and thus ictal DC recording could provide very important information about core epileptogenicity in patients with intractable partial epilepsy as surgical candidates.

In this chapter, clinical application of ictal DC recording is described mainly by means of invasive recording techniques, and its usefulness for surgical candidates with intractable partial epilepsy is discussed.

Ictal DC shifts

Generator mechanism and experimental epilepsy

When EEG is recorded with an infinite time constant, slow potentials can be recorded as the DC shifts, which are believed to reflect (1) directly the physiological as well as (2) pathological activity of the central neurons and glia.[3] DC shifts during generalized seizures induced by various drugs in experimental animals were studied by Goldring *et al.*[4] in the 1950s, and clear negative shifts were associated with initial EEG changes consisting of paroxysmal fast activity.

Field potentials recorded during interictal, epileptic activity are transient changes in neuronal membrane potential called PDS occurring in individual neurons.[5,6] As the interictal activity, it starts with steep depolarization which, having exceeded the membrane threshold, triggers a series of action potentials, followed by a plateau for 80 to 100 msec. It is then followed by steep repolarization and further hyperpolarization (Figure 74.1).[7,8]

As the ictal activity, simultaneous recording of intracellular and extracellular (field) potentials in experimental animals revealed that an intense depolarization of neuronal elements in the epileptic focus is associated with the intense DC negative shifts (Figure 74.2)[9], and initially with high frequency discharges. In the 1940s, the experimental model of epilepsy was well developed also by topical application of penicillin, and the observation of slow ictal DC shifts was done by using the DC amplifier in 1965.[10,11] In penicillin-induced seizures, DC negative shifts were associated with tonic seizure showing low-voltage multiphasic pattern. The center of the focus had the surface negative shifts of the highest voltage, and the voltage became gradually smaller with increasing distance from the center. The shifts were positive in the area much further distant from the center.[11] Epicortically recorded negative shifts had no reversal of the polarity beneath the center of focus by microelectrode analysis of the field. Maximum negativity was observed at a depth of 1–1.5 mm corresponding to layer V.[12] Those findings suggest that the intense negative shifts at the center of the penicillin epileptic focus are related to intense depolarization of pyramidal neurons, i.e., PDS, in that area, and that nearly the entire length of the neurons is depolarized with the source of current flow lying in the axons and dendrites. On the other hand, DC shifts in seizures induced by strychnine had a reverse sign of polarity at 400 micron in depth from the surface, suggesting the different epileptogenicity of the pyramidal neurons from those of penicillin focus.[13] The similar DC shifts were also observed in seizures at the hippocampus evoked by electric stimulation.[14]

Role of glia in ictal DC shifts

In addition to intense depolarization of the epileptic neurons, it is also important that glial cell plays a significant role in generating slow cortical shifts.[7] Glial cells are intermingled with neuronal structures, and the glial fibers are electrically coupled by low-resistance electrical junctions to build up an extended functional network as a 'syncytium'.[15] Glial cells do not generate action potentials or postsynaptic potentials. However, glial membrane potentials are not constant, and since action potentials of neurons are associated with the

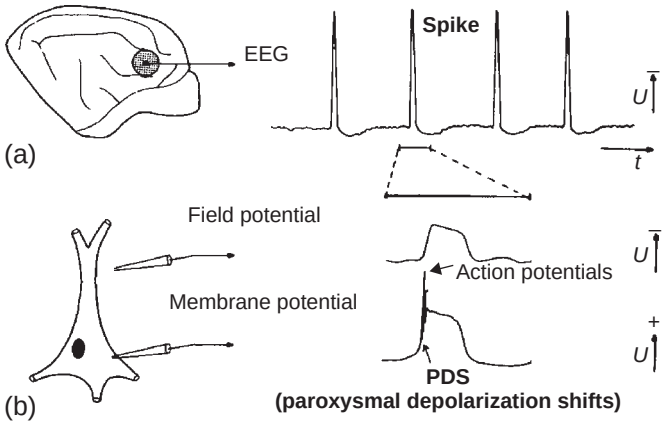

Figure 74.1 EEG (a), and extracellular field potential and membrane potential changes (b) of pyramidal neurons during interictal activity elicited by topical application of penicillin to the cortical surface. The sweep speed in b is five times that in a. (Modified from ref. 7 with permission.)

extracellular potassium concentration increase, it causes depolarization of glial cells (Figure 74.3). If the potassium concentration does not affect the entire glial cell membrane and remains increased only locally, the potential gradients build up along the glial cells, giving rise to intra- and extracellular current flows similar to the ones described in reference to neuronal synaptic transmission. It is also shown that glial, as compared with neuronal, membrane potentials are more sensitive to changes in extracellular potassium concentration in the physiological ranges. Therefore, it is most likely that extracellular field potentials including DC shifts are amplified significantly by glial cells.[16]

Recently, furthermore, in experimentally produced cortical dysplasia (reactive gliosis), astrocytes surrounding the lesion showed a significant reduction in K_{IR} (the activity of inwardly rectifying K^+ channels) and compromised potassium buffering capacity for accumulated extracelluar potassium.[2] It thus may suggest (1) the augmentation of the ictal DC shifts by the abnormal glial function, and (2) possible role of the glia in modulating epileptic activity in the seizure focus.

Recording technique

Clinically, equipments including amplifier and computer hard wares have been currently advanced, and the recent development of epilepsy surgery provided us with the opportunity to investigate ictal DC shifts in human epilepsy.

Practically, the DC amplifier is not necessarily essential for recording slow shifts, but an AC amplifier with long time constant could be allowed to record slow shifts as long as the following three conditions are carefully considered from the methodological point of view: 1) the kind of metals used for the electrode, (2) the size of recording surface, and (3) input impedance of the amplifier.

With regard to the property of the metal of which electrode is made, a nonpolarized or reversible electrode is essential to minimize electrode potentials which could distort slow potential signals. Currently available nonpolarized electrodes are made of Ag/AgCl. However, nonpolarized metals including Ag/AgCl are toxic to the brain tissue. Therefore, when used as intracranial electrodes, the only metals available are polarized or nonreversible ones, such as stainless steel, platinum, and gold. Each metal has its own electrode capacity as demonstrated by Cooper. (Figure 74.4)[17] Among the nonreversible electrodes, platinum is better than either gold or stainless steel to slow potentials.

Since the recording electrode could be represented by a series of resistance and capacitance (R-C circuit), it has the property of a low-frequency filter. Capacitance of electrodes, also combined together with the input impedance of the amplifier, acts as a low-frequency filter (LFF). Since the capacitance is proportional to the recording surface of the electrode, the large electrode surface such as subdural contacts minimally attenuates slow potentials; namely, LFF becomes open. On the contrary, depth electrodes which have a small contact surface may hardly record slow potentials.

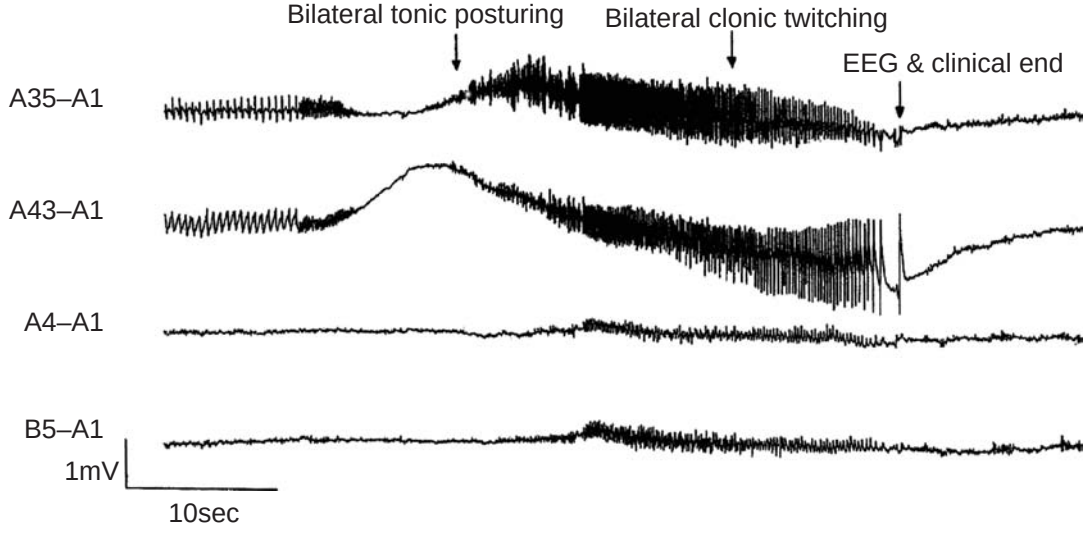

Figure 74.2 Subdurally recorded ictal DC shifts with the setting of time constant of 10 sec in a 48-year-old patient (right parietal lobe epilepsy). 2–3 Hz rhythmic activity at the A42 and 43 are suddenly replaced by high-frequency, low-amplitude activity and 4 sec later by electrodecremental pattern. A slow negative shift is selectively observed at A43 at that time, and then spread to A35 and B5. (Modified from ref. 18 with permission.)

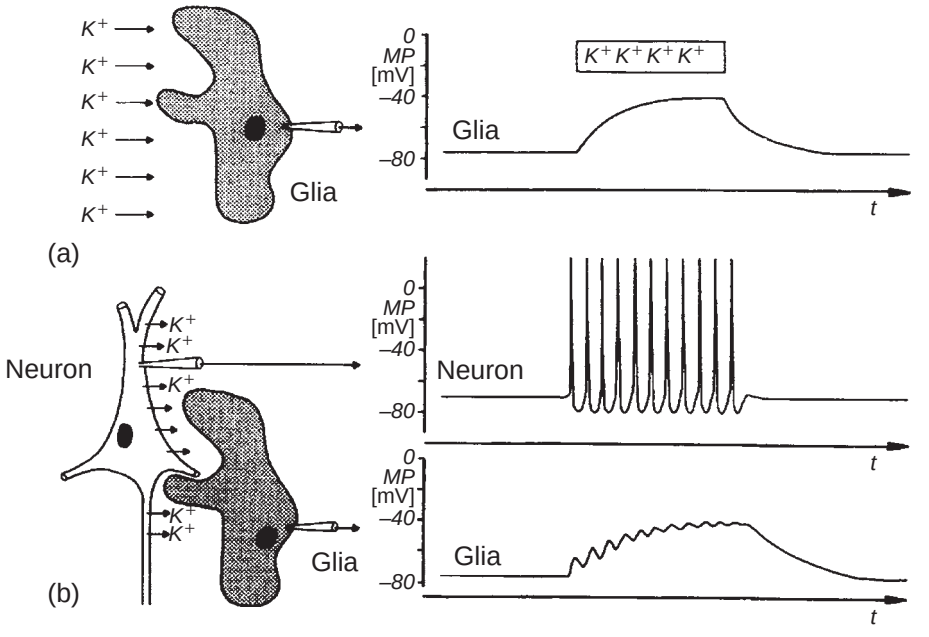

Figure 74.3 Functional linkage between neuronal and glial activities. Increased potassium concentration in the extracellular space close to the glial cell passively depolarizes glial membrane potentials (a). The similar situation in (a) for glial cells is produced by repetitive firing of neurons, and it leads to a sustained depolarization of the neighboring glial cell (b). (Cited from ref. 7 with permission.)

Previously, amplifiers used to have relatively small input impedance less than 1 Mohm, as in Cooper's experiment in 1963 in Figure 74.4. Huge input impedance of more than 50 Mohm is currently available, which minimizes the effects of electrode potentials. Therefore, under the current recording conditions using an AC amplifier, platinum electrodes can record slow cortical potentials provided that widely-opened LFF, with huge input impedance of more than 50 Mohm, and large electrode contact surface are used. Since stainless steel electrodes recorded slow potentials as well as platinum electrodes in our previous study,[18] the difference electrode capacitance of metals can be overcome by the other factors described here. Therefore, Figure 74.5 represents the property of the metals under the recording condition adopted at that time, i.e., small input impedance (750 kohm) of the amplifier and wire electrodes with a small recording surface.

Nevertheless, especially when attempts are made to record with scalp electrodes, the artifact contamination-like movements and galvanic skin responses are still always carefully taken into account, as mentioned later.[19–22]

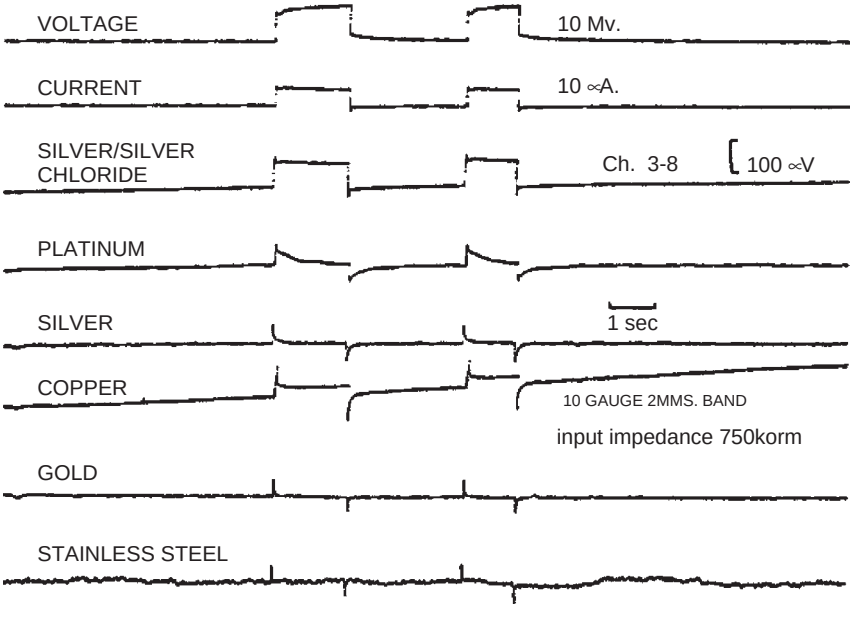

Figure 74.4 Characteristics of various metallic electrodes to reproduce a 10 mV, 10 microA square wave input. It was recorded by using a DC amplifier with an input impedance of 750 kohm and electrodes of wire type. (Cited from ref. 17 with permission.)

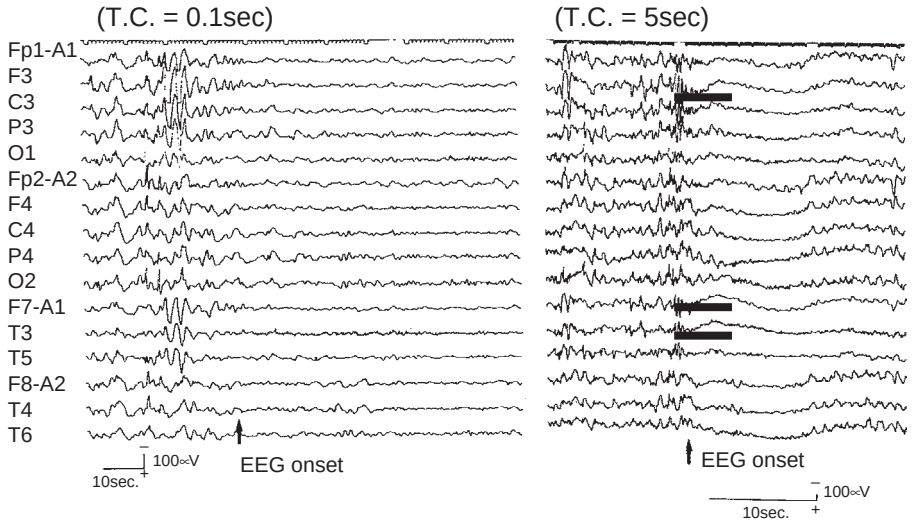

Figure 74.5 Left: Ictal EEG pattern displayed with the conventional LFF setting of 1.0 Hz (time constant of 0.1 sec) recorded by scalp electrodes in a 9-year-old patient with intractable temporal lobe epilepsy. Background activity is first suppressed and a diffuse electrodecremental pattern occurs (as shown by an arrow labeled as EEG onset). Right: Ictal EEG pattern of the seizure shown on the left is displayed with the LFF setting of 0.03 Hz (time constant of 5 sec). A clear negative shift (shown by thick, short bars) started occurring exclusively at F7, F3 and T3, exactly at the time when the diffuse electrodecremental pattern appeared (as shown by an arrow labeled as EEG onset). The peak amplitude of the negative shifts is −300 μV. (LFF = low frequency filter.) (Cited from ref. 19 with permission.)

Scalp-recorded DC shifts in human focal epilepsy

Usually scalp-recorded ictal DC shifts are not successfully recorded, because movements during clinical seizures could cause significant artifacts mainly due to the fluctuation of electrode potentials. Recent trials of scalp recording of ictal DC shifts in patients with focal epilepsy suggest its usefulness, although the degree of sensitivity varied between the studies.[19–21] We recorded slow ictal negative shifts in four patients (three with neocortial epilepsy and one with temporal lobe epilepsy) who had more than ten seizures per day and thus, the incidence rate of ictal DC shifts were calculated. Scalp-recorded ictal DC shifts were observed in 14–40% of all the recorded seizures and were restricted to 1–2 electrodes, very closely related to the onset of high frequency, low-voltage ictal activity (electrodecremental pattern) (Figure 74.5). Those seemed to be absent when the seizures were less intense among many recorded seizures.[19,20] It was thus suggested that scalp-recorded ictal DC shifts were highly specific, but the low sensitivity was to be taken into account in clinical applications. Another group also demonstrated that scalp-recorded ictal slow DC shifts were always recorded in 35 recorded seizures from five patients with intractable mesial temporal lobe epilepsy (MTLE), using Ag/AgCl electrodes employing a DC amplifier,[21] although their group pointed out the significant effects of non-neuronal generators for scalp-recorded slow shifts at the same time.[22]

For generalized epilepsy, slow shifts associated with spike and wave complexes were previously observed,[23–25] mainly in patients with petit mal. Chatrian *et al.*[26] carefully investigated slow negative shifts and concluded that these shifts occurred during the spike and wave complex paroxysms, and that they were generally unrelated to galvanic skin responses and were not generated by potential changes due to eye movements. The slow negative shifts never preceded the appearance of spike and wave activity in the EEG, but occasionally would outlast the paroxysm for a brief time.

Ictal DC shifts with invasive electrodes in human partial epilepsy

Subdural electrodes

Currently invasive recording with subdural grid electrodes is widely used in epilepsy surgery in order to delineate an epileptogenic zone by analysis of ictal and interictal activity, and to map the eloquent zone by electric stimulation or various, sensory evoked potentials.

When recording ictal activity in patients with extratemporal lobe epilepsy, intracranial ictal recordings often reveal diffuse or ill-defined ictal patterns, which make localization of the ictal onset zone difficult.[27]We have investigated ictal DC shifts accompanying clinical seizures from subdural electrodes chronically implanted in patients with intractable partial seizures mainly from the neocortical area. We concluded that, in addition to a careful interpretation of the conventional ictal EEG recording, an analysis of the ictal DC shift could be useful to better localize the ictal onset zone. In our laboratory, ictal DC shifts were investigated from more than 30 patients (mainly neocortical epilepsy and MTLE) with chronically implanted subdural grid electrodes in our laboratory (Figures 74.2, 74.6–74.9).[18, 20, 28–31]

Commercially available subdural grid electrodes of 3 mm in diameter and 1 cm center-to-center interelectrode distance were used. Electrodes made of platinum were used in all of the patients except for one (Patient 1 in Ikeda *et al.*, 1996)[18] in whom ones made of stainless steel were employed. For recording slow EEG shift, instead of DC amplifiers, AC amplifiers having an input impedance of 200 or 80 Mohm were used with a long time constant of 10 sec and high frequency filter

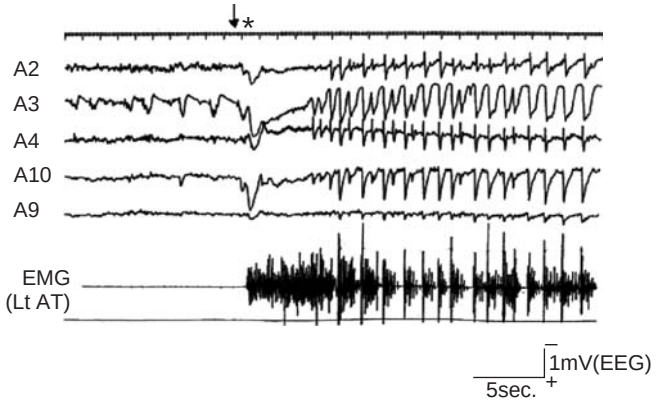

Figure 74.6 Subdurally recorded ictal DC shifts associated with a simple partial seizure (supplementary motor seizure clinically) in a patient with intractable right frontal lobe epilepsy. Just after a large transient positive activity at the time of clinical seizure onset, as demonstrated by tonic EMG discharges from the tibialis anterior muscle (Lt. AT), negative shifts are localized exclusively at A3 and A10. These two electrodes belonged to the ictal onset zone defined by the conventional ictal EEG changes (high amplitude spiking in the later part of ictal period). An arrow indicates the ictal EEG onset, and an asterisk indicates the clinical onset in this figure and also in Figures 74.7–9. EEG is displayed with LFF setting of 0.016 Hz, also in this figure and Figures 74.7–9. (Cited from ref. 20 with permission.)

(HFF) of 100 Hz, and all signals were digitized and stored at a sampling rate of 200 Hz per channel. All subdural electrodes were referenced to one subdural electrode placed over the lateral convexity which, on stimulation, did not elicit any symptoms or show any ictal or interictal epileptiform discharges.

As the results, with long-term follow-up of surgical outcome after surgery in our patient group, we analyzed ictal DC shifts in 24 patients with intractable partial epilepsy (19 of them with more than 1 year of follow-up period, mean of 3.9 ± 2.1 years) (16 with neocortical epilepsy and eight with MTLE). The DC shifts were recorded in 23 out of 24 patients (96%) and were observed in 87% of recorded seizures on the average in each patient. The DC shifts predominantly occurred associated with electrodecremental pattern (11 patients: 48%) and with 10–15 Hz rhythmic fast activity (10 patients: 44%). Simple partial seizures associated with 2–4 Hz spike discharges were not associated with slow shifts except for one patient. The slow shifts were mainly negative in polarity. They occurred at or before the clinical onset in 16 patients (70%), and followed in seven patients (30%), most patients of the latter group had the diagnosis of MTLE. It was invariably located in a more restricted area as compared with the epileptogenic zone defined by conventional EEG finding. As seizure control among the 19 patients with more than 1 year of follow-up, 11 patients (58%) were for Class I (Class Ia: 7, Class Ib: 4), 6 (32%) for Class II, and 2 (11%) for Class III. Out of two patients in Class III, one (FLE) with four years of follow-up, belonged to Class I in the first 2 years, and another (PLE) with 3 years of follow-up, belonged to Class Ib in the first year. It was concluded that 1) subdurally recorded ictal DC shifts in humans were almost invariably recorded regardless of underlying etiology or epilepsy type, and that 2) the more restricted localization can aid in delineating ictal onset zone before surgery. Most of them had a good seizure control without surgical deficits probably because of resection of core epileptogenic zone by means of DC shifts, but some of them had a good seizure control only during initial 1 to 2 years. It may imply that 1) real, core epileptogenic zone was not detected in spite of DC recording, or that 2) those patients newly developed epileptogenicity after surgery.[30]

Another institute also provided the similar conclusion based on the suddurally recorded ictal DC shifts from the parahippocampal gyrus in five patients with MTLE.[32]

Judging from the basic experiments as described above, the ictal DC shifts seem to have a close relationship with the electrodecremental pattern seen in conventional EEG recording. These periods are frequently associated with paroxysmal

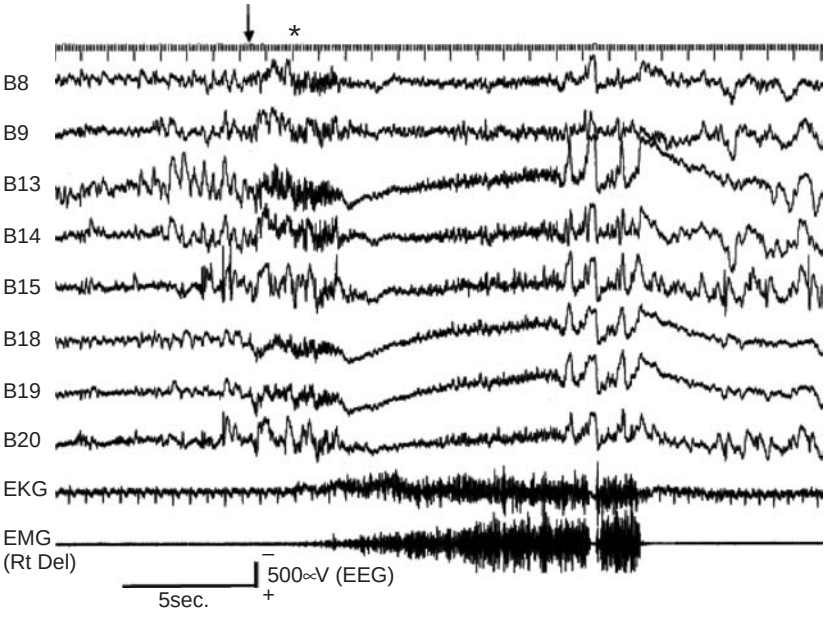

Figure 74.7 Ictal DC shifts were observed at B13,18 and 19 where conventional low amplitude fast activity occurred just 1–2 sec before the onset of DC shifts. It was recorded from a patient with left frontal lobe epilepsy. (Cited from reference 29 with permission.)

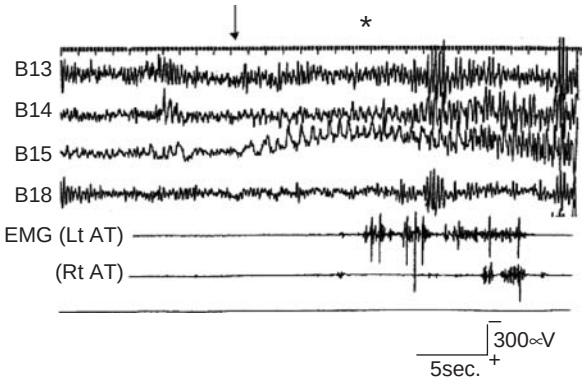

Figure 74.8 Ictal DC shifts were observed associated with about 1 Hz rhythmic activity in the conventional ictal pattern, but this occasion was less popular. It was recorded from a patient with right frontal lobe epilepsy. (Cited from ref. 19 with permission.)

low-amplitude, fast activity and usually they are also related with a very fast spreading of the ictal activity. Therefore, it is most likely that DC shifts seen with subdural electrodes in human epilepsy is an expression of highly synchronized PDSs of the pyramidal cells which occur in association with maximal intensity and rapid spreading of the ictal activity, leading to rapid involvement of extensive cortical areas. This highly synchronized PDSs of the pyramidal cells may occur relatively early during the ictus but may also occur later. DC shifts occur in close temporal relationship with this sudden seizure spread that could also be associated with a diffuse electrodecremental pattern. The fact that the DC shift is apparently more localized than the electrodecremental pattern and that these electrodecremental patterns in the conventional subdural EEG recording not infrequently occur just at the beginning of the seizures, especially in neocortical epilepsy, and also at least in the middle course of the ictal period at the parahippocampal gurus of MTLE, suggest that the DC shifts could greatly assist us in localizing the epileptogenic zone in human epilepsy.[28]

Other invasive electrodes

Wieser *et al.*[33] successfully recorded the ictal slow negative shifts from foramen ovale electrodes in patients with MTLE. (The size of input impedance of the amplifier was not described.) In their results, DC records with foramen ovale electrodes were satisfactory during the initial ictal period if the beginning of the clinical seizure was not accompanied by gross movements of head or trunk, and a slow shift was observed even in cases in which spiking was restricted to a small volume of mesio-basal limbic structures and therefore not clearly visible in the simultaneous AC mode record (Figure 74.10).[34] Therefore, they concluded that negative epicortical DC shifts recorded by the foramen ovale electrode are a sensitive indicator of epileptic activity within the underlying deeper structures, and that it is clinically useful at least to decide the side of ictal onset.

Depth and epidural electrodes failed to record slow ictal DC shits in four patients with the LFF setting of 0.01 Hz on an AC amplifier with an input impedance of 20 Mohm, when they employed stainless steel electrodes with a small recording contact.[35] However, recently, ictal slow shifts were investigated (LFF of 0.1 Hz) by means of depth electrodes placed in the hippocampus in 32 seizures of five patients with MTLE, and 84% of the seizures were associated with localized positive slow shifts at ictal onset, ranging from 1.5–11.5 sec. They concluded that ictal slow shifts at the onset of depth-recorded seizures is an excellent visual aid for localizing the epileptogenic focus.[36]

Clinical significance

Ictal DC shifts represent sustained PDSs occurring in epileptic neurons, and thus reflect the nature of the neurons and adjacent glial cells in the epileptogenic area. When recorded in human epilepsy, especially, for presurgical evaluation by means of subdural grid electrodes, negative shifts were observed by currently available equipment: platinum electrodes using an AC amplifier with a very high input impedance (>50 Mohm) and opened LFF (< 0.016 Hz). The recorded slow cortical potentials can aid to delineate an epileptogenic area with high sensitivity and specificity, and thus provide additional information to the conventional ictal EEG findings. However, invasive recording with either depth or epidural electrodes may not record reliable slow shifts probably because recording conditions for DC shifts are not fulfilled technically.

In patients with intractable partial epilepsy, especially of neocortical origin, cortical malformation including cortical

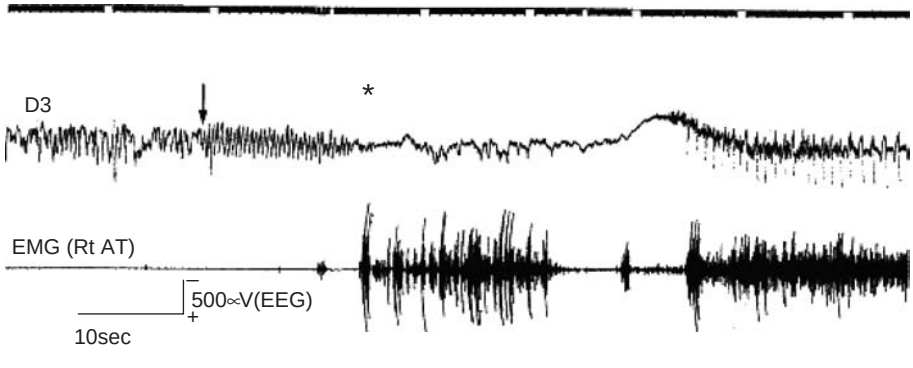

Figure 74.9 On rare occasion, ictal DC shifts were observed much after the onset of clinical and conventional ictal EEG pattern. It simply reflects that ictal DC shifts occur once a large population of neurons simultaneously discharge, and if it occurs later after the clinical onset, the onset of ictal DC shifts are then observed much after the clinical onset as shown in this figure. It was recorded from a patient with right parietal lobe epilepsy. (Cited from ref. 19 with permission.)

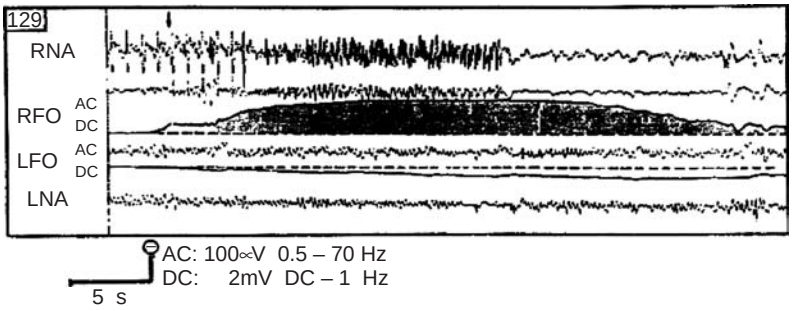

Figure 74.10 AC and DC recordings with right- and left foramen ovale electrode (RFO, LFO) together with stereo-EEG from the right and left amygdalar nucleus (RNA, LNA) during a seizure induced by repetitive, single-pulse electrical stimulation of the right hippocampus in a patient with mesiobasal temporal lobe epilepsy. The arrow indicates the onset of seizure characterized by an olfactory aura. (Cited from ref. 34 with permission.)

dysplasia is one of the most prevalent and disabling causes. Cortical dysplasia or cortical malformation has been relatively well delineated by MRI FLAIR image recently, but frequently it is not visible even by the most powerful machine. It was recommended that the whole area of cortical dysplasia as revealed by MRI should be resected to obtain the best seizure control. Recently, it was shown that resection guided by MRI does not always stop seizures in these patients. Namely, the MRI negative area is also a very important zone for seizure generation in patients with focal cortical dysplasia.[37,38] Usually, cortical dysplasia can generate very frequent interictal spikes that mimic ictal discharges because of its long-lasting repetitive discharges.[39] In addition, some areas of cortical dysplasia generated scanty spikes or just irregular slow activity.[40,41] Since epileptic spikes can reflect the dipoles generated in the cortical layers, cortical dysplasia would not always generate convenional spikes or dipoles, but only ill-defined ones, presumably depending on the degree of distortion of the cortical layers. Ictal DC shifts would be well defined even in cortical dysplasia where cortical layers were distorted, as long as epileptic firing neuronal pools and surrounding gliosis are preserved. In our patient series with subdural electrodes, only one patient so far who showed no ictal DC shifts had cortical dysplasia located within the white matter but not on the cortical surface at all.

Ictal DC shifts usually provide information of epileptogenicity which is equally as useful as conventional ictal EEG changes, being thus regarded as redundant information in surgical candidates with very clear seizure focus. However, ictal DC shifts could provide very important information to delineate core epileptogenicity, especially in patients having cortical dysplasia invisible to MRI.

In scalp recording in human focal epilepsy, little clinical application has been done so far. From the viewpoint of clinical practice, with currently available equipment as mentioned above, scalp-recorded ictal DC shifts were not sensitively recorded, but once recorded, high specificity may aid in localizing the epileptogenic zone even in scalp-recorded data for presurgical assessment.

High frequency ictal/interictal activity

Since highly synchronized PDSs of the pyramidal cells occur at the beginning of seizures or relatively early during the ictus, DC shifts occur associated with an electrodecremental pattern, i.e., low-amplitude very fast ictal activity. High-frequency repetitive discharges of more than 100 Hz can also delineate the ictal onset zone in patients with neocortical epilepsy by means of invasive recording.[42] Furthermore, discrete burst oscillation between 100 and 500 Hz (such as ripple for 100–200 Hz, and fast ripple for 250–500 Hz) was identified as interictal activity in the epileptogenic area mostly in animal experiments.[43] Recently, in patients with both MTLE and neocortical epilepsy, this high frequency activity (100–200 Hz) was well defined in the primary seizure focus or very discrete focus, near the time of seizure onset, and thus it would delineate core epileptogenicity and common property of epileptogenicity regardless of etiology.[44] Opening of an analysis window to both extremely slow and fast activity would be very important to add clinically useful information in invasive presurgical recording.

Summary and prospects

Ictal DC shifts have been observed in the animal epilepsy experiments, and whose physiological significance was well suggested previously. However, clinical applications or studies in human focal epilepsy was infrequently done until recently, mainly because of the limitation of equipment, including amplifier and computer hardware, especially digital EEG systems.

As suggested by animal experiments, at the beginning of seizures, ictal DC shifts most likely occur together as an expression of highly synchronized PDSs of the pyramidal cells which occur in association with maximal intensity and rapid spreading of ictal activity.[5,6,10] It also strongly reflects glial function and dysfunction, i.e., passive depolarization as the result of massive depolarization of the epileptic neurons with accumulated extracellular potassium, and its impaired buffering function, respectively. Currently recording techniques have been advanced, and the recent development of epilepsy surgery provides us with the opportunity to investigate. On the other hand, new ictal EEG analysis techniques are required because conventional ictal EEG findings at times fail to localize an epiletogenic zone as seen in cortical dysplasia. Careful analysis of ictal DC shifts will lead us to valuable information with regard to epileptogenicity in human focal epilepsy.

Although great technical advances enable us to record and analyze ictal DC shifts in patients having intractable

partial epilepsy, the condition is not optimal for possible artifacts and unstable electrode potentials even in invasive recording situations, and much more in scalp recording. More suitable recording electrodes and relevant amplifier circuits for DC shifts would enhance clinical usefulness in the near future.

Acknowledgments

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75 fMRI in the evaluation of the ictal onset zone

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Introduction

Functional MRI (fMRI) encompasses the study of neural activity by measurement of alterations in the MRI signal caused by neuronally driven changes in blood oxygenation levels. Magnetic resonance spectroscopy (MRS) whilst also providing information on neuronal function is reviewed elsewhere (Chapter 88).

fMRI has a number of advantages over other functional imaging techniques. (1) it is noninvasive, allowing repeated studies in the same patients, (2) the temporal resolution is such that a response to brief neural events can be captured, and (3) spatial resolution is of the order of a few millimetres. This allows the mapping of neural correlates of interictal discharges seen on surface EEG, i.e., the irritative zone during simultaneously acquired EEG and functional MRI (see Chapter 60). Imaging the ictal onset zone however may provide added insights into seizure generation and propagation.

Major practical limitations exist. For robust analysis a seizure needs to be captured in its entirety during a scan session and subject motion is a serious confound in fMRI analysis.[1,2] Nevertheless, a number of studies have been carried out in individual patients with frequent partial seizures.

Methodological considerations

The increases in regional cerebral blood flow in response to neural activity, that forms the basis of many current functional imaging techniques, were recognized over a century ago.[3] The extensive blood-flow increase during epileptic seizures was first described after direct visualization of macroscopic changes peroperatively.[4,5] This can be captured with SPECT,[6] PET,[7] and gadolinium-enhanced MRI.[8]

The rate and spatial extent of the neuronally-driven blood flow increase greatly exceeds that of local oxygen consumption, resulting in a regional decrease in venous deoxyhaemoglobin levels. Oxy- and deoxyhaemoglobin have different magnetic properties.[9] A time series of whole-brain images that are sensitive to changes in deoxyhemoglobin levels can be acquired using a fast image acquisition sequence–echo planar imaging (EPI).[10] Each brain image or volume is typically acquired in approximately 3 sec. The haemodynamic response reaches a peak at around 5 sec from the onset of neural activity and returns to baseline over 20–30 sec and can be captured in its entirety with fMRI; thus providing an endogenous contrast agent, termed the Blood Oxygen Level Dependent (BOLD) response.[11] The terms 'activation' and 'deactivation' are operationally defined as increases or decreases in BOLD response, directly linked to neural activity.

The signal-to-noise ratio in fMRI is low, a few percent at 1.5 Tesla. BOLD fMRI cannot be used to detect low-frequency state-related changes because of large intersessional variability and scanner noise characteristics. Together with a slow hemodynamic response function (HRF) relative to neural activity, the detection power of fMRI is limited to the narrow frequency band within which most conventional fMRI paradigms operate, i.e., active and rest states alternating, or events occurring, every 20–30 sec. Most commonly fMRI is used to map neural responses to a particular experimental task or stimulus. This is presented either as brief events or blocks, repeated over the course of an fMRI session (typically of 10- to 20-minute duration) to improve signal to noise. Advances in statistical analysis packages and computer processing power allow complex regression analyses to look for areas of significant correlation between the task or stimulus and the fMRI signal time course. A thresholded statistical map (the statistical parametric map or SPM) is used to show the spatial distribution of significantly correlated voxels. Clearly the experimental paradigms used in conventional fMRI studies are not possible in the study of ictal events with fMRI.

Early reports of ictal fMRI used a number of exploratory analysis methods. These include visual inspection of image time series, cross-correlation analyses and variance maps; however these lack the robustness of a formal statistical framework. More sophisticated exploratory techniques are being developed, that do not rely on the statistical correlation of an experimental paradigm. These have not yet been applied to imaging seizures. They include principle component analysis (PCA) and independent component analysis (ICA) of fMRI data.[12,13]

Sources of noise in fMRI include subject motion, respiratory and cardiac effects, scanner noise (low-frequency drifts) and neuro-physiological confounds from changes in the subject's resting state. Of these, subject motion will cause the greatest change in MRI signal. The type and timing of the motion with respect to the event of interest can have a greater effect than the actual extent of motion. Sudden motion, i.e., jerks, even on the submillimeter scale is sufficient to contaminate data and lead to false-positive activations if it is correlated with the event of interest.[2] Similarly changes in heart rate or respiration that can accompany seizures can also affect MRI

signal and confound data.[14] Examination of voxel time series for temporal maxima, known as temporal clustering analysis, has been proposed as a means of identifying fMRI changes to interictal activity.[15] However a close temporal relationship between subject motion as measured by realignment parameters (the six linear transformations used to realign successive scans to the same space) and the time points of voxels reaching their maximum temporal clusters has been shown.[16]

The spatial extent of fMRI activations is influenced by the voxel size, and spatial smoothing used during preprocessing to maximize signal to noise ratios. Typical voxel sizes are of the order of 3–5 mm, with smoothing of 6–10 mm. BOLD fMRI measures changes on the venous side of the circulation, such that large draining veins can result in false activations at a distance from the true neuronal activity.[17,18] In the surgical setting errors in co-registration between functional and structural images can occur, in part due to the different distortions inherent in EPI and T1-weighted volumetric acquisitions.[19] Where statistical analyses are used, the extent of an 'activation' is also influenced by the threshold at which the image is viewed. Finally the spatial extent of the decrease in deoxyhaemoglobin greatly exceeds that of the neural activity driving the haemodynamic changes, 'watering the garden for the sake of one thirsty flower'.[20]

Comparison with PET, SPECT, and SEEG

Notwithstanding the limitations outlined above, fMRI has a relatively high spatial resolution, of the order of several millimeter's resolution, and a temporal resolution of several seconds. The correlates of brief neurological events can be captured in a way that is not possible with other neuroimaging techniques.

Measuring changes in glucose metabolism or cerebral blood flow with PET has little to offer in directly imaging the ictal onset for the following reasons. For blood flow PET, the radioisotope $H_2{}^{15}O$ has a very short half-life, of around 2 min, such that only seizures occurring by chance at the time of prearranged scans could be captured. Glucose metabolism is measured with[18] flouro-deoxy-glucose (^{18}FDG). Although the half-life of the isotope[18] FDG is around 2 hours, the brain uptake of tracer can take 30 to 45 minutes such that acquired images after injection made at seizure onset will be made up of an amalgam of ictal and postical activity, which compromises localizing value.[7]

SPECT (Chapter 79), despite its lower spatial resolution has significant advantages over both PET and fMRI in imaging seizures, and at the present time is the only potentially clinically applicable method of imaging seizure onset.[21] The most commonly used SPECT tracers, ^{99m}Tc-hexamethylproplenamine (^{99m}Tc-HMPOA) and ^{99m}Tc-ethyl cysteinate dimmer (^{99m}Tc-ECD) are stable for several hours. The patient is monitored on the telemetry unit with an intravenous cannula in place and arrangements for isotope injection at the onset of a seizure. The isotope forms a stable bond once it crosses the blood–brain barrier. Patients can then be scanned some hours after the seizure when it is medically safer, and they are better able to lie still in the scanner. Any delay to tracer injection, and the time taken for tracer binding results in activations in areas of seizure propagation rather than onset.[22,23] The relatively low temporal and spatial resolution of SPECT necessitate a careful interpretation of results, taking into account delay to tracer injection from seizure onset, seizure duration, underlying pathology that may affect perfusion, as well as processing strategies used in analysing the images. Subtraction of ictal from interictal scans and coregistration with MRI (Subtraction Ictal SPECT Coregistered with MRI (SISCOM)) improves accuracy.[21]

EEG remains the optimum modality in studying seizure onset and propagation. However the distance of surface electrodes from the site of seizure onset, the filtering effects of skull and scalp and the lack of a unique solution due to the inverse problem, and rapid propagation of discharges confound dipole source localization.[24] Intracranial recordings can overcome this,[25] however they are highly invasive compared to functional imaging or surface EEG, and coverage is limited to the immediate vicinity of the implanted electrodes such that clear hypotheses regarding the location of the ictal onset zone are needed before their use.[26] The search for a noninvasive imaging modalitiy that can identify the site of seizure onset for surgical resection, or better inform the placement of intracranial electrodes therefore continues.

Ictal fMRI studies

Focal epilepsies

A total of five case reports of fMRI of ictal activity in humans have been published (Table 75.1), in addition to a study using fMRI to image the preictal state. These are detailed below.

Jackson *et al.* [27] used single-slice fMRI to obtain BOLD sensitive images in a 4-year-old child with Rasmussen's encephalitis, and frequent motor seizures involving the right face. Images were obtained every 10 s from a single slice in blocks of 10 min. Images were analyzed by subtracting baseline images from those acquired during seizures. Analysis was by way of visual inspection. No motion correction or formal statistical analysis was applied. Signal increases were seen in left hemisphere gyri in five clinical seizures. A similar change was also seen during a period that was not associated with a clinical seizure, felt to be subclinical activity. Whilst this case showed the potential of fMRI to detect seizure activity, the contribution of motion effects, caused by the single slice moving in and out of the imaging plane leading to the detected signal changes, remain a possibility.

Detre *et al.*[28] described fMRI activation with suspected subclinical seizure activity. The patient had right focal motor seizures, affecting the face. There was no simultaneous EEG recording during fMRI and there was no clinical evidence of seizure activity. Scans were acquired every 4 sec for 11 min. After standard preprocessing with realignment and spatial smoothing, images were displayed as an animated cine loop and inspected visually. Focal signal-intensity changes were seen in the posterior left frontal lobe, which correlated in both duration and spatial localization with ictal activity on EEG. The patient went on to intracranial implantation and surgery. A 1 cm^2 area of cortex identified on corticography was resected; pathologic examination revealed chronic gliosis. The resected area, as seen on postoperative structural MRI, showed close spatial concordance with the area of fMRI

Table 75.1 Summary of case reports of ictal fMRI studies summarising patient details, data acquisition and analysis methods used and main findings

Reference	Clinical data	Seizure detection	Functional MRI	Analysis	Main ictal fMRI finding
Jackson *et al.*[27]	4 year old male: right sided partial motor seizures of body and face **Etiology** Rasmussen's encephalitis **MRI** L hemisphere thickened cortex with abnormal signal in grey matter **Routine EEG** Interictal: Widespread slow and occasional L parietal spikes. Ictal: Irregular slow waves over anterior frontotemporal regions preceded by twitching **Sedation** IV Diazepam	Facial movement	**Scanner** 1.5T Siemens SP4000 **Sequence** Multi shot FLASH (TE/TR 60/85ms, matrix 62×128. FOV 230mm, flip angle 40°	Visual inspection of subtraction images and time courses extracted from subsequently selected areas	L hemisphere cortical signal increase
Detre *et al.* [28,29]	25 yr old male: R focal motor seizures of face **Etiology** cryptogenic **MRI** widespread left hemisphere atrophy **Routine EEG** Interictal: Increased theta during wakefulness Ictal: No definite ictal findings	Clinical observation	**Scanner** 1.5T GE signa **Sequence** Single shot GE-EPI (TE/TR 50/4000 ms, 64×64 matrix, FOV 240mm, 16×5 mm slices no gap). **Coverage:** whole brain **Time resolution:** 4s	Visual inspection of thresholded percentage change images and time courses extracted from selected cluster. Concordant areas with 3-4% signal increases	Area focal signal increase concordant with subsequently identified region on corticography
Krings *et al.* [30]	62 yr old female, Jacksonian march L leg **Etiology** glioblastoma multiforme **MRI** R central space occupying lesion **Routine EEG** Ictal and interictal EEG normal	None	**Scanner** 1.5T Phillips Gyroscan **Sequence** Multishot GE-EPI (TE/TR 35/2200ms Voxel size 3×5×5mm flip angle 35°) **Coverage:** Whole brain **Time resolution:** 2.2s	Visual inspection of thresholded percentage change images and time courses from selected clusters	2 perilesional areas of signal increase and one of decrease, starting 60 seconds before the onset of the seizure
Salek-Haddadi *et al.* 2002[31]	47 year old male, left fronto-temporal electrographic seizure. **Etiology** cryptogenic **MRI** normal **Routine EEG** Interictal: Left fronto-temporal spikes	Concurrent EEG	**Scanner:** 1.5 GE signa **Sequence:** GE-EPI (TE/TR 40/3000 64×64 matrix, FOV 240, 21×5mm interleaved slices) **Coverage:** Whole brain **Time resolution:** 3 seconds	SPM99 according to the general linear model. Modeling of ictal event as boxcar with motion parameters as nuisance covariates	L fronto-temporal signal increase with subsequent prolonged undershoot before return to baseline
Morocz *et al.* 2003[33]	48 yr old female, music induced complex partial seizures **Etiology** cryptogenic **MRI** normal **Routine EEG** Interictal: normal Ictal: left temporal theta and high frequency	Self reporting by button press	**Scanner** 1.5T Philips Gyroscan **Sequence** Gradient echo PRESTO TE/TR 35/5000ms, 3.75×3.75mm, slice thickness 3.5mm flip angle 30°	SPM99, boxcar of inducing music versus non-seizure inducing music; and seizure sessions versus non-seizure sessions	L temporal signal increase during music induced seizures.

activation. Further cross-correlation analysis was used to examine time-dependent alterations in regional signal intensity that correlated with signal-intensity changes from this cortical seizure focus.[29] Signal changes in the left ventrolateral thalamus showed a high degree of temporal correlation with signal changes in the left frontal cortical seizure focus, suggesting functional connectivity between the thalamus and the cortical focus.

Krings *et al.*[30] reported on a patient with a right frontal glioma. She was experiencing up to five events an hour at the time of the study. A 33-sec Jacksonian march involving the left leg with 'calf shaking' was imaged with fMRI. One hundred and two scans were acquired with a temporal resolution of 2.2 sec per scan, i.e., around 3 min of scanning. An automated image realignment algorithm was used to minimize the effects of interimage motion-related artifacts. For each voxel, the percent change in T2* signal fluctuations was calculated for each time point, against a baseline (mean of MR signal of the first 20 images of a given voxel). These were color coded on a thermal scale, overlaid onto an anatomical image and visualized by scrolling through the functional images in an animated loop. Only voxels exhibiting percentage signal changes larger than 1.5% from baseline were visualized to minimize random MR signal noise.

Three perilesional areas with signal intensity changes related to seizure activity were seen with signal changes of between 2.2–3.5%. The temporal evolution of signal change in each of these regions differed, beginning at 60 seconds before (an increase of up to 2.2%), 30 sec before (a decrease of up to 3.5) and at the onset of the seizure (an increase of up to 3.1%). The last region was in the left foot area as determined by previous motor fMRI. It is not clear from the report whether changes of similar percentage changes were seen elsewhere in the brain at other times during scanning. A temporal resolution of 2.2 sec is too slow to allow imaging of the propagation of electrical activity. The authors conclude:

> the identification of cortical areas with different types of hemodynamic seizure-related changes may help in delineating seizure generators from areas with propagated activity, even if the propagation time is too fast to be detectable with fMRI.

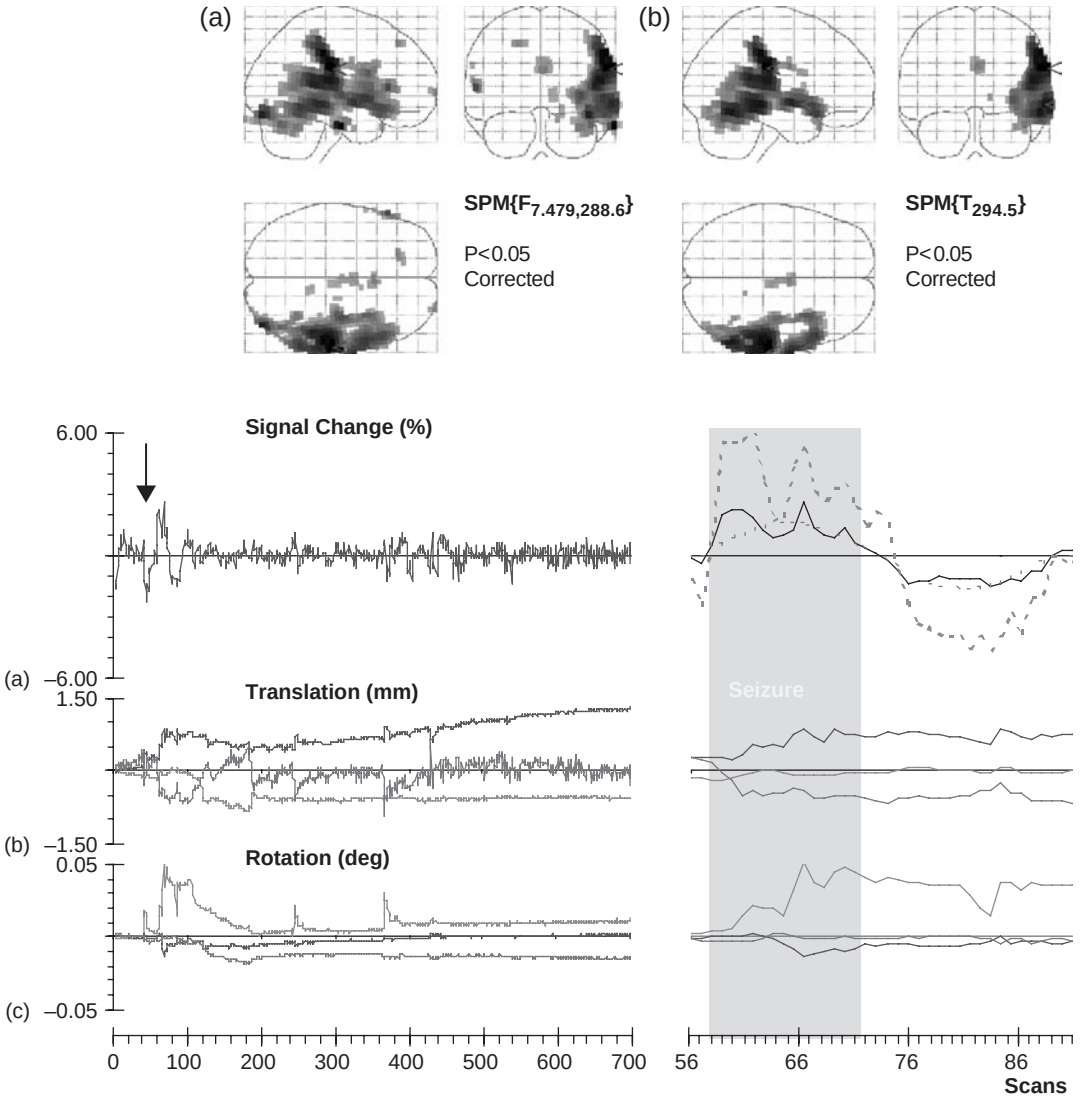
Salek-Haddadi reported a case of ictal fMRI based on an electrographic seizure recorded on simultaneous continuous EEG.[31] The simultaneous recording of EEG during fMRI being necessary to fully correlate ictal activity with fMRI measures. A 47-year-old man with frequent partial and secondarily generalized seizures was scanned with continuous EEG and fMRI (EEG-fMRI) for 35 min (700 scans), as part of a study of interictal epileptiform discharges. An electrographic seizure, with a focus at F7/T3 of approximately 40 sec occurred early into the study. Images were realigned to the same space and spatially smoothed. fMRI data was analyzed according to the general linear model, with the recorded seizure as an effect of interest and the realignment parameters as nuisance covariates. An extensive area of activation was seen extending posteroinferiorly from the left insular gray matter, through the temporal lobe insula, along the superior and middle temporal gyri to the left fusiform gyrus; anteriorly to the left inferior frontal gyrus; and superiorly up to the left inferior parietal lobule. A smaller cluster was also evident within the gray matter of the ipsilateral cingulate gyrus. The mean signal rise was 2.5% (maximum 5.5%) with a prolonged undershoot (Figures 75.1–3). The undershoot most likely represented more prolonged oxygen consumption, following the peak in blood flow response, than is seen in the normal physiological HRF. The authors stress the importance of a robust statistical framework for the analysis of ictal fMRI.

Reflex epilepsies

The reflex epilepsies[32] although rarely, if ever considered for resective epilepsy surgery provide unique opportunities to study the epileptogenic zone with fMRI, given that ictal events can be induced during fMRI scanning; once appropriate ethical considerations and consent have been addressed.

Morocz *et al.*[33] studied a 48-year-old woman with music induced complex partial seizures. Scanning took place in blocks with previously identified 'epileptogenic' music alternating with music that was known not to induce seizures. Statistical analysis revealed two patterns of BOLD signal change, one related to the actual triggering of music-induced seizures in the left anterior temporal lobe, the right gyrus rectus and ventral frontal lobes, and the other related to exposure to the specific epileptogenic music in the orbitofrontal lobes only. The authors speculate that emotional processing of music in the orbito-frontal areas may have initiated the seizure cascade.

Reading epilepsy is characterized by brief jaw jerks associated with EEG spikes when reading specific texts. Generalized seizures can follow if reading persists in the face of increasing jaw jerks. Archer *et al.*[34] studied two patients with spike triggered fMRI and reading epilepsy. Subjects read text back projected onto a screen during fMRI scanning. EEG was recorded continuously and scanning was triggered 2.5 sec after the occurrence of an EEG spike to acquire one brain volume. An identical 'rest' volume was acquired after a 20-sec period of no spikes. fMRI of a standard reading task was also acquired using a 30-sec block design of reading text versus fixating on a cross hair. Spike versus rest scans were compared by means of an unpaired t-test. Reading-related spike activity was seen bilaterally in the inferior precentral gyrus, central sulcus, basal ganglia, and globus pallidus. Signal change of 2.5% in cortex and 1% basal ganglia was seen in association with jaw jerks and spikes. Koepp and Salek-Haddadi (unpublished work) studied nine patients with reading epilepsy using an MR-compatible system for scalp-EEG, submental EMG, left-handed button press, and online audio recording to detect reading-induced orofacial myocloni (ORM). Language and motor (hand/mouth) mapping did not show any abnormalities, compared to normal subjects. One patient had abundant ORM in association with left-frontal spikes occurring on silent reading. In a further five patients, symptoms were only elicitable on reading aloud so events were selfindicated. Induced spikes or jaw jerks were associated with consistent activation patterns within left motor and premotor areas in five of these six patients, in Brodman area (BA) 47 in 2/6, in the striatum (4/6) and thalamus (2/6). Taken together these studies demonstrate the potential cortical and subcortical circuitry involved in reading induced seizures.[35]



Figures 75.1 and 75.2 fMRI signal change during electrographic seizure captured during EEG-fMRI recording session. Fig 75.1 a) SPM {F}: the SPM 'glass brain' display shows areas of significant correlation to the EEG recorded seizure, these results were obtained using a Fourier set of basis functions, spanning the seizure event, and (b) results obtained using a single sine wave regressor spanning the seizure. Realignment parameters were included as confounds. The statistical maximum is shown in red. Fig 75.2. (a) Regional time series. On the left, the first eigenvariate is shown as extracted from the principal cluster of the SPM {F} for the entire experiment. Seizure onset is indicated by the arrow. On the right and rescaled, the maximum signal change is also shown (green) along with the sine wave regressor (red). The seizure interval is shaded in grey. Percentage changes are with respect to the grand session mean. (b,c) Realignment parameters. The X, Y, and Z translations in units of millimeters are shown in red, green, and blue, respectively, and the corresponding rotations given underneath in degrees. (reproduced from Salek-Haddadi *et al*. 2002, with permission from the publisher). (See Color plates.)

The Preictal state

Mathematical analyses of EEG frequency components suggest the presence of a preictal state.[36] Federico *et al.*[37] studied the fMRI signal changes minutes prior to a seizure in three patients with frequent sleep onset seizures. Patients were sleep deprived for one night and scanned the following morning under close supervision, until a seizure occurred. There was no concurrent EEG monitoring. Images were analysed by comparing fMRI signal between two 1-minute blocks–at one minute before seizure onset compared with in one case, 3 and the other two, 5 min before the seizure. The full signal time course of regions of interest based on differences detected in this comparative analysis was examined. Two patients showed BOLD activations ipsilateral to the site of presumed seizure onset, whilst the other had contralateral changes. The significant fMRI signal changes were attributed to altered neuronaly driven hemodynamics in the preictal state; although without EEG it is possible that changes in sleep–wake cycle that preceded the seizures may have also been captured. Comparing similarly spaced 1-minute blocks at other points in the time series would have given some indication of the specificity of their findings, and other possible confounding effects in the data. The use of concurrent EEG, and possibly some form of independent motion detection would be advantageous in these studies.

Animal studies

Capturing seizures during the scan session, and lack of independent knowledge of the seizure focus limit the study of ictal activity with fMRI in humans. Animal models are commonly

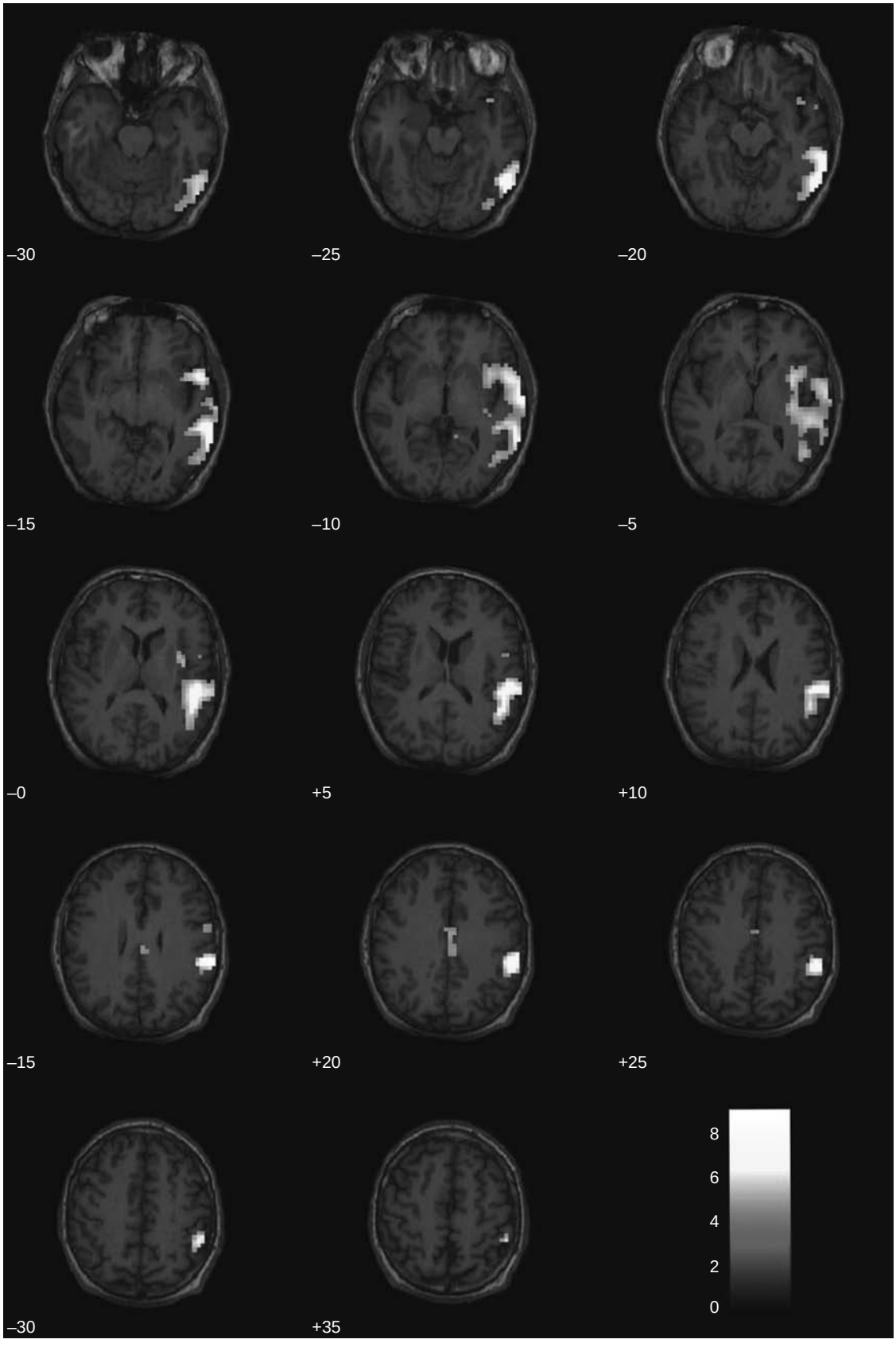


Figure 75.3 Anatomical overlay. The seizure related activation obtaining from Figure 75.2b is shown overlaid onto consecutive slices of a co-registered T1-weighted scan. (Reproduced from Salek-Haddadi *et al*. 2002, with permission from the publisher).

used in the development of antiepileptic drugs, neurophysiological and histochemical studies. Well established models include the penicillin and kindled seizure models, and genetic epilepsy models.

Opdam *et al.*[38] developed a sheep model of penicillin induced focal seizures specifically for the purpose of studying ictal activity measured with fMRI and simultaneous intracranial EEG. An intracranial EEG probe was placed on the cortical surface with a penicillin delivery port. EEG acquisition was interleaved with MRI scanning. Data was analysed by means of the variance of the time series of each voxel. These variance maps were overlaid onto the raw images for anatomical localisation. Areas of greatest variance, which included the injection site and the ipsilateral amygdala were considered to be part of a cortical–sub cortical circuit in seizure propagation. This study demonstrated a proof of principle, the main outcome being the development of a large animal model that could be studied with fMRI. Their observations of BOLD changes were preliminary. More sophisticated analysis, for instance modelling the EEG with fMRI according to the general linear model, would be more robust to signal to noise issues and may yield clearer spatio-temporal localizations.

Future applications and conclusions

fMRI of ictal activity has been limited to a few cases. A number of analytical techniques have been used. Many of these deviate from an accepted dogma in fMRI analysis of rigorous statistical correlations that include the whole time series from whole brain. Using fMRI to image the ictal onset zone is doubly confounded in that scanning needs to take place during a seizure and that motion correlated with the event of interest makes interpretation of fMRI data very difficult. Most paradigm-related fMRI studies set a threshold for subject motion above which data sets are discarded, something ictal fMRI studies cannot afford to do.

The spatiotemporal resolution of fMRI is much higher than the other imaging modalities of PET and SPECT. Nevertheless the BOLD response, peaking at 5 sec and spread over around 30 sec makes the study of seizure progression difficult, this is probably best summed up by Salek-Haddadi *et al.*:

> Sampling of an inherently noisy fMRI time series at low temporal resolution concealing a single relatively brief, undefined, and sluggish BOLD fluctuation would not permit inferences regarding the spatiotemporal cascade. Similarly the relative length of an HRF in relation to the ictus prohibits any meaningful subdivision of the epoch for modeling as other than a single event without prior knowledge of subtle interactions and nonlinearities for instance. Moreover, even were sequential activation to be evincible, any extrapolation of temporal relationships to the underlying neural activity would be hampered by interregional variability within the HRF'.

A more direct and quantitative measure of rCBF can be obtained using perfusion or arterial spin labeling (ASL) MRI. ASL-MRI uses magnetically-labeled in flowing arterial blood as an endogenous tracer for measuring CBF.[39] This is achieved by modifying the magnetization of arterial H-protons proximal to the tissue of interest. This elicits a local change in longitudinal magnetization of subsequently perfused tissue that is proportional to inflowing blood. Subtraction of sequentially acquired images, with, and without arterial spin-labeling (tag and control images) provides a measure of this inflowing blood. Like BOLD fMRI, this can detect evoked changes in blood flow correlated with neural activity of a task or stimulus.[40,41] An advantage of ASL over BOLD is that low-frequency state-related changes can be imaged, and between-session comparisons are valid.[40] Furthermore ASL-MRI images the arterial side of circulation and is therefore not confounded by false activations in draining veins. A submillimeter spatial resolution has been demonstrated with ASL-MRI.[42]

With current methods ictal fMRI is unlikely to be a useful tool in 'routine' presurgical work-up. Advances in scanner hardware with higher field strength will increase both temporal and spatial resolution. Algorithms for motion correction in frequency space prior to the reconstruction of raw images although not currently available for BOLD fMRI could greatly reduce the problems encountered with subject motion.[43] Appropriate MR physics and data analytical expertise is crucial.

Ultimately functional imaging is used to make inferences about brain function, rather than giving a direct measure of that function. In the context of epilepsy surgery ictal fMRI could allow inferences to be made about lateralization and localization of epileptogenic foci, and generate hypotheses for the placement if intracranial EEG electrodes. Functional imaging findings need to be considered with results of other investigations, and awareness of the methodological limitations of any technique fully appreciated, particularly if findings are used to plan surgical interventions.

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76 Ictal SPECT in the definition of the seizure onset zone

GD Cascino and D Lachhwani

Introduction

Partial or localization-related epilepsy is the most common seizure disorder in the patient being considered for surgical treatment.[1] The majority of patients with adult-onset recurrent seizures have partial epilepsy.[2–4] Individuals with partial epilepsy experience focal seizures that variably are associated with altered awareness, automatisms, localized or lateralized neurological deficits, or secondarily generalized tonic-clonic seizures.[3–4] Most patients present with more than one seizure-type. The presence of the neurological symptoms at seizure onset may be used to localize the epileptogenic zone, i.e., site of seizure onset and initial seizure propagation.[1,2] Approximately 30–40% of newly diagnosed patients with epilepsy will experience medically refractory seizures that are physically and socially disabling.[3–6] Most individuals with a pharmacosensitive partial seizure disorder respond to the first or second antiepileptic drug (AED) medication.[3–6] Less than 10% of patients who fail to respond to the initial AED therapy will be rendered seizurefree with subsequent pharmacotherapy.[3–6] Polypharmacy with the concomitant use of three or more AEDs has not been shown to increase the efficacy of therapy in patients with medically refractory seizures, but may significantly increase dose-related adverse effects.[4–6] A seizure disorder is often considered intractable when the neurological illness is medically, socially or physically disabling.[2–6] The combination of AED neurotoxicity and recurrent focal seizures may significantly alter the quality of life of the individual. The goals of treatment include rendering the individual seizurefree, avoiding additional morbidity, and allowing the patient to become a participating and productive member of society.[1,7–10]

Surgical treatment of epilepsy

Epilepsy surgery is an effective and safe therapy for selected patients with intractable localization-related epilepsy.[1,2,7–12] Surgically remediable epileptic syndromes have been identified that assist in the selection of operative treatments for intractable partial epilepsy.[10] These individuals usually experience a significant reduction in seizure tendency associated with an improvement in quality of life following a focal corticectomy.[2,7,8] Patients with medial temporal lobe epilepsy and partial seizures related to foreign-tissue lesional pathology may be highly favorable candidates for epilepsy surgery.[7,11–14] The superior efficacy of surgical treatment compared to AED medication in patients with temporal lobe epilepsy has been demonstrated.[8] The efficacy of anterior temporal lobectomy in patients with mesiobasal limbic seizures arising from the amygdalohippocampal complex has been confirmed.[7,8,12–14, 16–18] The majority of patients with medial temporal lobe epilepsy have pathological findings consistent with focal hippocampal neuronal loss and astrogliosis.[12–14,16–18] Patients with a lesional epileptic syndrome may have an underlying tumor, vascular anomaly or malformations of cortical development (MCD) as the etiology of a medically refractory partial seizure disorder.[10,11,14,15,18,19] The common tumoral surgical pathologies encountered in patients with lesional epilepsy include low-grade glial neoplasms, gangliogliomas, and dysembryoplastic neuroepithelial tumors.[7,14–18] The vascular anomalies include cavernous hemangiomas, and angiographically identified or occult arteriovenous malformations.[10] The MCD present in patients with a localization-related epilepsy include focal cortical dysplasia, polymicrogyria, hamartoma, and schizencephaly.[10,19] Other focal structural abnormalities, such as encephalomalacia related to prior trauma, hemorrhage or stroke, also may develop an intractable seizure disorder and be considered for surgical treatment.

Individuals with medial temporal lobe epilepsy and lesional epilepsy frequently have an abnormal structural magnetic resonance imaging (MRI) study that demonstrates with a high sensitivity and specificity the underlying epileptogenic pathology.[2,10,12,13,17–20] Patients with focal structural neuroimaging abnormalities may be classified as having *substrate-directed* partial epilepsy.[20] MRI has proved essential in the selection and evaluation of patients for surgical treatment of an intractable partial seizure disorder.[7,10,12,13,16–18] The MRI study is almost invariably abnormal in patients with primary brain neoplasms and vascular anomalies.[20] The sensitivity and specificity of the MRI is more variable in patients with microscopic MCD such as focal cortical dysplasia.[19] A comprehensive presurgical evaluation is conducted in patients with MRI-identified structural abnormalities, e.g., changes consistent with mesial temporal sclerosis or a foreign-tissue lesion (Tables 76.1 and 76.2). The EEG-identified ictal onset and initial seizure propagation, i.e., epileptogenic zone, in conjunction with other neurological studies is used to establish a relationship between the MRI findings and the underlying the epileptic brain tissue [12,13,15–18] (Tables 76.1 and 76.2). The demonstration of concordance between the pathological substrate and the ictal onset zone indicates a highly favorable

Table 76.1 Surgically remediable epileptic syndromes

Selected epileptic syndromes	MRI	SISCOM	Pathology
Substrate-directed			
Medial temporal lobe epilepsy	> 90%	–	MTS
Lesional epilepsy: tumor	100%	–	Ganglioglioma, glioma, DNET
Lesional epilepsy: vascular anomaly	100%	–	Cavernous hemangioma, AVM
Lesional epilepsy: malformation of cortical development	80–90%	–	FCD
Non substrate-directed			
Neocortical (extrahippocampal)	0%	75%	Gliosis, focal cell loss, none

MTS = mesial temporal sclerosis; DNET = dysembryoplastic neuroepithelial tumor; AVM = arteriovenous malformation; FCD = focal cortical dysplasia.
Adapted from Cascino GD. Advances in neuroimaging: surgical localization. Epilepsia 2001;42:3–12.

operative outcome in selected individuals.[2,7,11,13–16,18] The most common and effective operative strategy in patients with a substrate-directed partial epilepsy involves a focal cortical resection of the epileptogenic zone with excision of the surgical pathology.[10,11] The extent of lesional pathology extirpation is of significant prognostic importance in these individuals.[1,2,9] Postoperative MRI findings are important to assess the anatomical resection, and to evaluate the presence of residual or recurrent lesional pathology.

MRI Methodology

The MRI seizure protocol at the Mayo Clinic includes: (1) sagittal T1-weighted imaging with minimum echo time (TE) and 500 msec repetition time (TR) required for whole-head coverage with 5-mm thick contiguous sections; (2) whole-head coronal three-dimensional volumetric spoiled gradient-echo (SPGR) acquisition is performed with minimum full TE and TR, 192 views, one repetition, 1.5 mm section thickness with 124 partitions, 22 cm field of view, and 45°flip angle; and (3) coronal spin-echo (SE) imaging is performed with TE of 30 and 80 msec, TR greater than 2000 msec, 20 cm field of view, 4 mm section thickness and 2 mm intersection gap, and 192 views with one repetition.[12,13,18] An oblique-coronal fluid attenuated inversion recovery (FLAIR) sequence is also obtained.[13] The FLAIR sequence allows the pathological signal change to be differentiated from the physiological signal alteration related to cerebrospinal fluid.[13] An enhanced study will be performed if a space-occupying lesion is detected in the unenhanced study. Currently studies are performed on a 1.5 Tesla or 3 Tesla scanner.

Nonsubstrate-directed partial epilepsy

MRI studies that do not reveal a focal structural pathology that is the putative etiology of the medically refractory focal seizures are classified as nonsubstrate-directed partial epilepsy.[20] This would include individuals with a normal MRI study or the presence of nonspecific findings, e.g., diffuse atrophy and T2-weighted signal changes, that do not indicate the pathology underlying the epileptogenic zone. Patients with nonsubstrate-directed partial epilepsy have neocortical or amygdalohippocampal seizures.[18,20] The pathology in these patients at the time of epilepsy surgery includes gliosis, hippocampal cell loss, focal cortical dyspalsia or no histopathological alteration.[18,20] Approximately 50–60% of patients with a normal MRI study are seizurefree following an anterior temporal lobectomy.[18] Unfortunately, less than 50% of patients with nonsubstrate-directed epilepsy with neocortical and extratemporal seizures are rendered seizurefree following

Table 76.2 Presurgical evaluation

Performed Invariably	Performed variably	Performed selected centers
History and examination	Video-EEG (intracranial)	SISCOM
Routine EEG	Electrocorticography	MRS
MRI head	FDG-PET	PET receptor studies
Video-EEG (extracranial)	Interictal-ictal SPECT	Functional MRI
Neuropsychology	Sodium amobarbital study	MRI hippocampal volumetry

Performed invariably: almost always obtained prior to epilepsy surgery.
Performed variably: available at most epilepsy centers, used in selected candidates.
Performed selected centers: not widely available.
MRI: magnetic resonance imaging.
PET: positron emission tomography.
SPECT: single photon emission computed tomography.
SISCOM: subtraction ictal SPECT co-registered to MRI.
MRS: magnetic resonance spectroscopy.

surgical treatment.[12,15,18] An estimated 20–30% of these patients with frontal lobe epilepsy will enter a seizure remission following a focal cortical resection.[15,18] An important reason for the unfavorable operative outcome in patients with nonsubstrate-directed partial epilepsy is the inherent difficulty in localizing and even lateralizing the epileptogenic zone.[15,18] The potential limitations of interictal and ictal extracranial EEG monitoring in patients with partial seizures of extrahippocampal origin have been welldefined.[15,18] The anatomical region of seizure onset may represent a continuum in these patients that lends itself to an incomplete resection of the epileptogenic zone. Advances in imaging have assisted the evaluation and treatment of operative candidates with nonsubstrate-directed partial epilepsy.[21–26]

Single photon emission computed tomography

Single photon emission computed tomography (SPECT) is the preferred functional neuroimaging technique for peri-ictal imaging in patients with partial epilepsy being considered for surgical treatment.[21,25,29–39] Interictal SPECT studies involve cerebral blood-flow imaging using radiopharmaceuticals, principally either technetium-99m-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) or ^{99m}Tc-bicisate, that have a rapid first-pass brain extraction with maximum uptake being achieved within 30–60 sec of an intravenous injection.[21,29–31,36] These studies may produce a 'photograph' of the peri-ictal cerebral perfusion pattern that was present soon after the injection.[31] The SPECT images can be acquired up to 4 hours after the termination of the seizure so that the individual patient can recover from the ictus prior to being transported to nuclear medicine. SPECT studies have an important clinical application in the potential identification of the epileptogenic zone.[31]

Peri-ictal SPECT studies have been confirmed to be useful in patients with temporal lobe epilepsy to identify a region of focal hyperperfusion.[25] The rationale for interictal SPECT imaging at present is to serve as a reference for a baseline study for the interpretation of ictal SPECT images. The diagnostic yield of ictal SPECT has been established to be superior to interictal SPECT in patients being considered for surgical ablation procedures. The recent development of stabilized radiotracers that do not require mixing immediately before injection, such as ^{99m}Tc-bicisate, has made ictal SPECT more practical in patients with extratemporal seizures that often are not associated with an aura and may have a shorter seizure duration.[36]

Subtraction ictal spect co-registered to MRI (SISCOM)

The imaging paradigm using computer-aided subtraction ictal single photon emission tomography (SPECT) co-registered to MRI (SISCOM) has been used in patients with intractable partial epilepsy.[31–42] The protocol was introduced by O'Brien and colleagues at Mayo Clinic.[31,32] (Figures 76.1–3). SISCOM represents an innovation in neuroimaging that may be useful in the evaluation of patients with focal seizures being considered for surgical management. Other methodologies including ictal SPECT using statistical parametric mapping has also been shown to have a high diagnostic yield in localizing the site of seizure onset.[43] The localized blood flow alteration demonstrated using SISCOM may be intimately associated with the epileptogenic zone.[31] Subtracting normalized and co-registered ictal and interictal SPECT images, and then matching the resultant difference image to the high resolution MRI for anatomical correlation has been shown to be a reliable indicator of the localization of the epileptogenic zone in patients with localization-related epilepsy [32–35] (Figures 76.1–3). SISCOM in a series of 51 patients had a higher rate of localization (88.2 vs. 39.2%, $p < 0.0001$), better inter-observer agreement, and be a better predictor of surgical outcome than visual inspection of the interictal and ictal images.[31] The study demonstrated the inherent problems with visual interpretation of either peri-ictal or interictal SPECT studies alone.

The methodology used for SISCOM involves co-registering of the interictal to the ictal SPECT study by matching the surface points on the cerebral binary images of the two procedures[32,35,36] (Figure 76.1). The normalized interictal image is subtracted from the normalized ictal image to derive the difference (subtraction) in cerebral blood flow related to the partial seizure (Figure 76.1). Thresholding of the subtraction image to display only the pixels with intensities greater than two standard deviations above zero is performed. Finally, the images with intensities of more than two standard deviations are co-registered onto the structural MRI (Figures 76.1–3). Following implantation of subdural electrodes for chronic intracranial EEG monitoring the electrode positions can be segmented from a spiral CT scan and co-registered with the SISCOM image[33] (Figure 76.1). This allows the determination of the relationship between the localized peri-ictal blood flow alteration and the ictal onset zone.

The SISCOM region of blood flow alteration is a surrogate for the localization of the epileptogenic zone independent of the pathological finding.[38] The clinical parameters that are signficant in determining the diagnostic yield of SISCOM include the duration of the seizure and the length of time of the injection from ictal onset.[21,31] The seizure should be at least 5–10 sec in duration and the time from seizure onset should be less than 45 sec.[31] The SISCOM findings also correlate with the operative outcome. Patients with a SISCOM alteration concordant with the epileptogenic zone are most likely to experience a significant reducation in seizure tendency if the focal cortical resection includes the region of peri-ictal blood-flow change.[31,38] The disadvantages of a SISCOM study include the need for hospitalization and long-term EEG monitoring, the use of radioisotopes for two imaging procedures, and the required presence of habitual seizure activity. The indications for SISCOM in patients undergoing a presurgical evaluation include: nonsubstrate-directed partial epilepsy and conflicting findings in the noninvasive evaluation (Figures 76.2 and 3). SISCOM may be use to identify a 'target' for placement on intracranial EEG electrodes.[33] The presence of a SISCOM alteration may obviate the need for intracranial EEG recordings in selected patients. For example, patients with nonsubstrate-directed partial epilepsy of temporal lobe origin may not require chronic intracranial EEG monitoring if the extracranial ictal EEG pattern and peri-ictal SPECT studies are concordant. SISCOM also improves the diagnostic

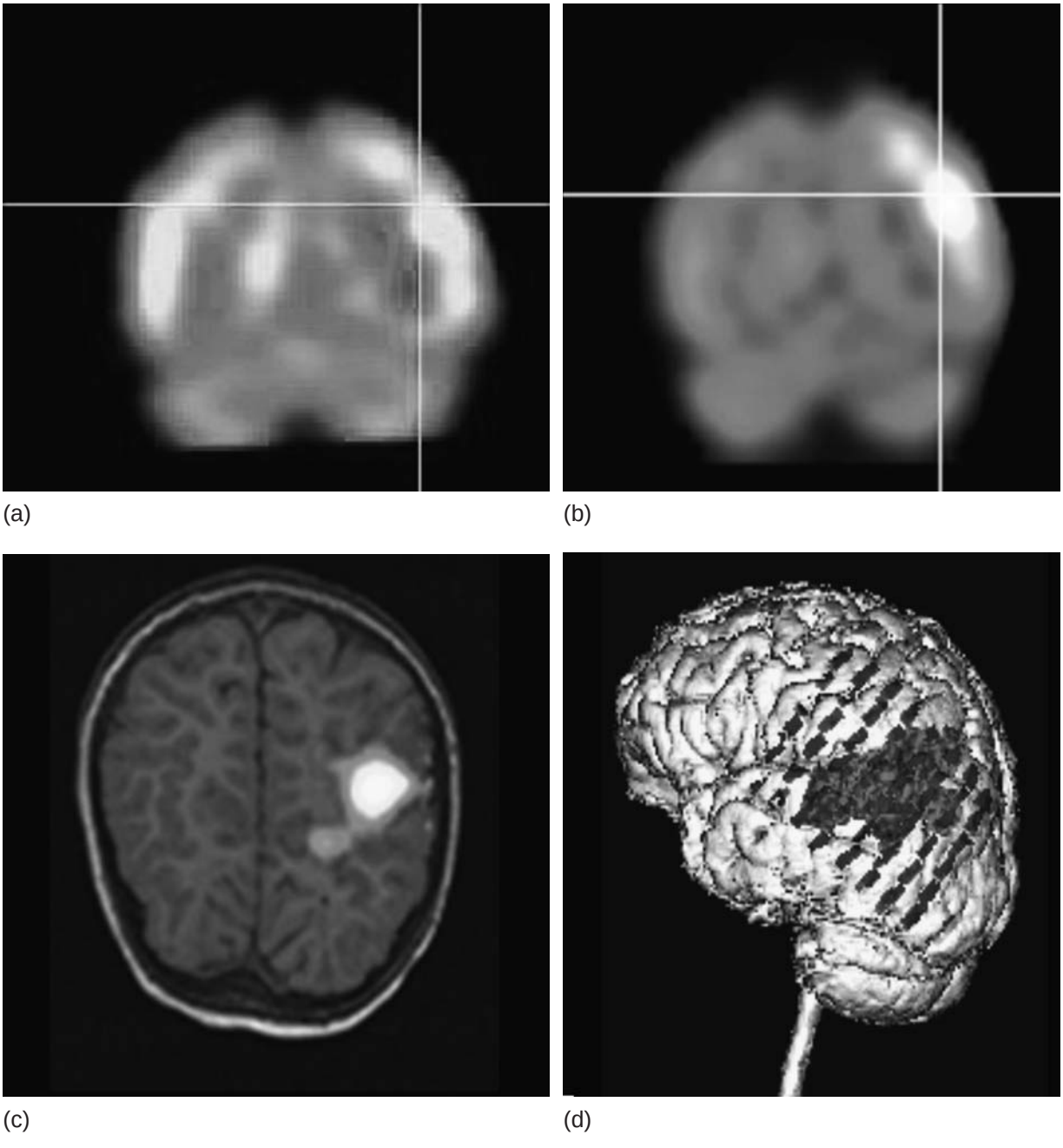

Figure 76.1 Subtracted peri-ictal SPECT co-registered to structural MRI (SISCOM) in a patients with intractable partial epilepsy and an ill-defined MRI abnormal in the left partietal lobe region. On visual inspection the interictal (a) in the oblique-coronal plane shows no obvious abnormality. The ictal (b) SPECT images suggest a left hemisphere region of ictal hyperperfusion. The subtracted study (c) reveals a localized abnormality. The SISCOM *focus* (d) is present in the left partietal lobe. The placement of a subdural grid was superimposed over the region of ictal hyperperfusion. Pathology demonstrated focal cortical dysplasia. (Note: The left side of the brain is on the right side of the figure.)

yield of postictal studies in patients with intractable partial epilepsy.[34]

The superiority of SISCOM in localizing the epileptogenic zone, particularly in extratemporal epilepsy, has been previously demonstrated.[38] The prognostic importance of the SISCOM *focus* in patients undergoing a focal cortical resection for partial epilepsy of extratemporal origin has been evaluated[38] (Figures 76.2 and 3). The operative outcome was assessed in 36 patients with extratemporal epilepsy who had a preoperative SISCOM study.[38] The presence of a localizing SISCOM alteration concordant with the epileptogenic zone was a favorable predictor of an excellent surgical outcome ($p < 0.05$).[38] Eleven of 19 patients (57.9%) with a concordant SISCOM *focus* and three of 17 patients (17.6%) with a nonlocalizing or discordant SISCOM, respectively, were rendered seizurefree or experienced only rare seizures. Approximately three-quarters of the patients with a localized SISCOM abnormality had a normal structural MRI. In addition, this study demonstrated that the extent of resection of the SISCOM *focus* was also of prognostic importance ($p < 0.05$).[38] Failure to resect the neocortical region intimately associated with the localized blood-flow change concordant with the ictal onset zone was a predictor of an unfavorable operative outcome.[38]

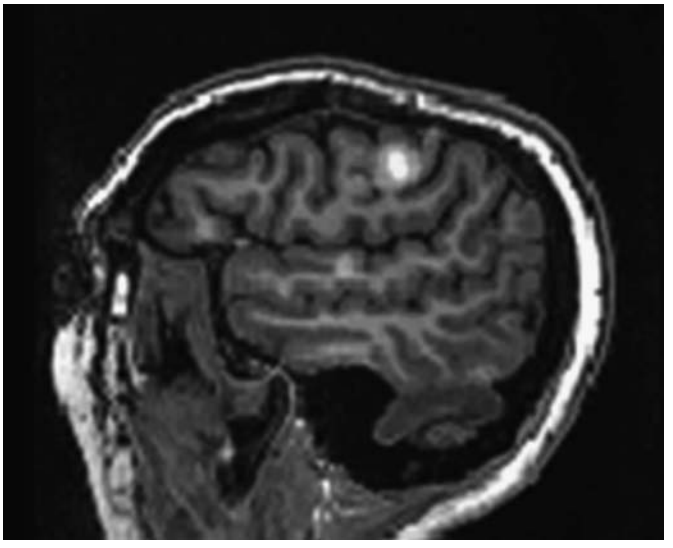

Figure 76.2 Subtracted peri-ictal SPECT co-registered to structural MRI (SISCOM) in the sagittal plane in a patient with right posterior mesial frontal lobe seizures. MRI study was normal. The surgical pathology revealed focal cortical dysplasia. (Note: The right side of the brain is on the left side of the figure.)

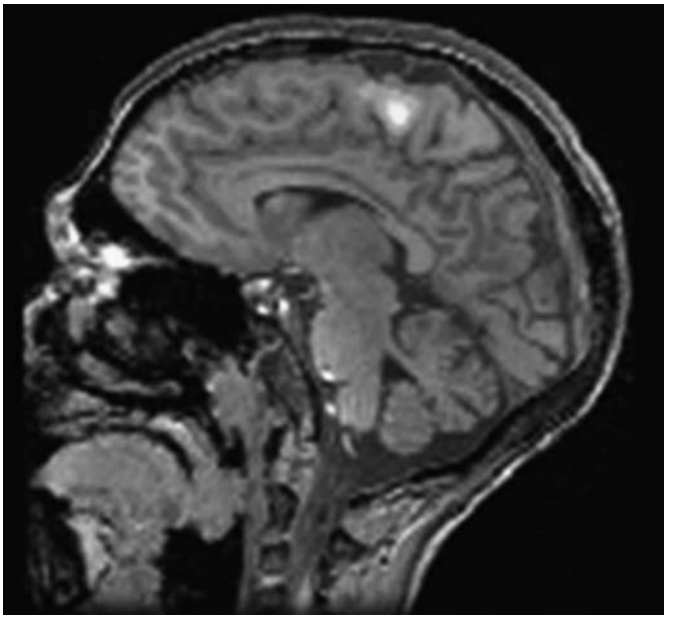

Figure 76.3 Subtracted peri-ictal SPECT co-registered to structural MRI (SISCOM) in the in a patient with a left frontal lobe seizures. MRI study was normal. The patient had focal motor seizures involving the right upper extremity. Pathology revealed only mild gliosis. (Note: The right side of the brain is on the left side of the figure.)

The diagnostic yield of SISCOM has also been examined in patients with focal cortical dysplasia.[41] As previously noted, these individuals may have unremarkable structural MRI studies and present with intractable partial epilepsy of neocortical origin. SISCOM images were localizing in 19 of 22 patients (86%); including eight of ten individuals with normal MRI studies.[41] SISCOM localization was concordant with MRI in 91%, scalp ictal EEG in 93%, and intracranial ictal EEG in 100%. The presence of a localizing SISCOM image also correlated with a lower postoperative seizure frequency score ($p < 0.05$).[41]

SISCOM has also been evaluated in the identification of the ictal onset zone in patients being considered for reoperation.[44] These individuals were 'surgical failures' and continued to experience an intractable seizure disorder. Fifty-eight patients were evaluated for reoperation.[44] The average age of the patients was 31 years (range, 2–56 years). The SISCOM study revealed a hyperperfusion localized alteration in 46 of 58 patients (79%). Thirty-three of 46 (72%) imaging abnormalities were adjacent to the previous surgical site, e.g., posterior to the margin of resection, and eight of 46 (17%) were remote but in the ipsilateral cerebral hemisphere. The hyperperfusion focus was in the contralateral hemisphere in the five of 46 patients (11%). The SISCOM study was indeterminate in 12 patients (21%). The site of the scalp-recorded ictal-EEG onset zone was concordant with the SISCOM focus in 32 of 46 patients (70%). The SISCOM finding was concordant with both the ictal-EEG pattern and MRI site of the previous resection in 28 of 46 patients (61%). The ictal-SPECT studies were correlated with the localization of the seizure onset zone in the 15 patients who underwent chronic intracranial EEG monitoring. The SISCOM abnormality correctly lateralized the site of seizure of seizure onset in 12 of 15 patients (80%).[44] The localized imaging alteration was concordant with the ictal onset zone in seven of 15 patients (47%). In five patients (33%) the SISCOM finding was ipsilateral, but remote, from the site of seizure onset. In three patients (20%) the SISCOM study was either indeterminate ($N = 2$) or revealed a localized abnormality contralateral to the epileptic brain tissue ($N = 1$). Twenty-six of the 31 patients (84%) were followed 6 months or longer after reoperation. The seizure outcome at 1 year or longer postoperatively could be determined in 24 of the 26 patients. Only one of the 26 patients (4%) had a MRI-identified pathological substrate prior to reoperation. Eleven of the 26 patients (42%) had a favorable operative outcome and five individuals (19%) were rendered seizurefree. The predictive value of SISCOM was assessed in 23 of the 26 patients with a localized hyperperfusion alteration who underwent reoperation. The SISCOM-identified abnormality was concordant with the epileptogenic zone in 20 of 23 patients (87%). The results of the ictal SPECT study in this group of patients, however, did not achieve statistical significance ($p = 0.23$). The effect of SISCOM findings on operative outcome was also not significant when patients with indeterminate findings were included with individuals with discordant findings ($p = 0.19$).[44]

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77 Automatic detection of epileptic seizures

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Overview and scope

Automatic seizure detection, the method of using computers to detect epileptic seizures based on recorded electrographic signals, has made significant advancements over the past three decades. While the field started with simple detection algorithms based on the shape of the electrographic waveform, it has matured to incorporate advanced signal processing methods and classification algorithms such as wavelet transforms and support vector machines. The motivations for seizure detection have evolved from off-line processing of electrographic data for further review by the clinician to completely implantable systems that provide electrical stimulation in response to detected seizure activity. In this chapter, we first discuss the motivations, algorithm design considerations, and limitations of automatic seizure detection. We then review different computational algorithms and address the advantages and disadvantages of the different approaches. Finally, we discuss the algorithms that are implemented in commercially available systems as well as the current state-of-the-art, automatic seizure detection in an implantable device.

Before proceeding, it is important to understand the differences between seizure detection, spike detection, and seizure prediction. The earliest computer algorithms for parsing electrographic data focused on the detection of specific electrographic features such as spikes and sharp waves.[1–4] Spike detection algorithms were developed to relieve the clinician from the tedious task of counting spikes, and also to provide a more consistent and automated evaluation of electrographic data. However spike detection algorithms are not effective in detecting all types of seizures because of the large variation in electrographic seizure patterns.[5] Therefore, seizure detection has developed into a separate class of electrographic analysis. Seizure detection is also distinguished from seizure prediction. Seizure prediction attempts to forecast probable seizures or determine the probability of a seizure well in advance of a seizure onset (by minutes or hours) based on electrographic of physiological changes. While seizure prediction may provide an early indication of a probable event, seizure prediction algorithms do not identify the actual onset or time of the seizure. Because the goals and motivations for spike detection and seizure prediction are not the same as for seizure detection, they are not discussed in this chapter. The reader is referred to Gotman *et al.*[6] and Brown *et al.*[7] for a review of various spike detection algorithms and to Litt and Echuaz[8] and Mormann *et al.*[9] for a review of seizure prediction algorithms.

Background

Motivation for seizure detection

The conventional clinical use of automated seizure detection algorithms is to identify abbreviated epochs of interest out of a typically large and unabridged electrographic dataset, for example, as acquired during long-term monitoring of an epileptic patient. When used to monitor on-line electroencephalographic (EEG) activity, the detection systems can be configured to trigger an auditory or visual signal to alert the attending clinician or caregiver of the event. When used off-line, detections can also be used as markers to identify epochs for further review, thus reducing the time and effort needed to review EEG records. While human visual analysis of the data is still considered the gold standard for identifying seizures, seizures can often be missed. Because of the often-limited human resources and the improvement of commercially available seizure detection algorithms, epilepsy monitoring units are relying more heavily on computer-aided systems for seizure detection.[5]

Early seizure detection algorithms were developed during an era of relatively limited computational power and primarily for off-line EEG analysis. Advancement in computer technologies over the past three decades has allowed for the development of more powerful seizure detection algorithms, real-time computation, and ambulatory detection systems. These developments have expanded the range of applications for seizure detection. Among these applications are ambulatory seizure warning systems designed to alert the patients to an imminent seizure,[10,11] and responsive therapy delivery systems that may provide electrical or pharmacological therapy in response to a detected event.[12–14] With the miniaturization of computer processors, a completely implantable device that performs seizure detection and delivers responsive electrical stimulation has been developed (NeuroPace, Inc., Mountain View, CA).*[15]

*The NeuroPace® RNS™ system is currently in clinical trials for the treatment of refractory epilepsy.

Seizure warning systems and responsive therapy applications are practicable in cases such as partial onset or focal seizures, where an electrographic onset may be observable seconds or minutes before the first clinical sign,[16,17] or before progression to a more serious complex partial seizure or generalized seizure. This early electrographic onset may provide a window where a warning can be delivered, or electrical, chemical, or other treatment applied in order to interrupt progression to a more generalized event. Such applications have been proposed by several authors,[10,12,13] but are not yet common due to the technological barriers involved.

Algorithm design considerations

In each of the seizure detection applications discussed above, there are a number of considerations that shape the detection algorithm. The sensitivity and specificity of an algorithm determine its performance in detecting seizures (correct positives), missing seizures (false negatives), and incorrectly detecting seizures (false positives). In the case of diagnostic seizure identification, a false positive may be more tolerable than a false negative. For example, a false positive may still provide valuable information for localizing the epileptogenic zone; moreover a neurologist can quickly discard false detections upon review.[18] On the other hand, a false negative may lead to a misinformed diagnosis. If the missed seizure is representative of a secondary event, an overly specific detection algorithm may result in a missed seizure type or epileptogenic zone.[19] Other applications, such as seizure counting or responsive therapy systems, may require that detection be set conservatively, so that seizures are counted, or therapy delivered, only when detection of the event is certain. Frequent false positives in a seizure warning system may render the system ineffective, as alarms will eventually be ignored.

Detection timing also plays a meaningful role in algorithm development. In the case of diagnostic seizure identification or seizure counting, detection at any time during the event may be adequate. However, early seizure detection is critical for seizure warning or responsive therapy systems. In these applications, detection at the earliest electrographic onset may be able to provide a warning or deliver therapy before the seizure becomes widespread or generalized, and potentially even before the patient becomes aware of the seizure.[20] Early detection can also be important for facilitating localization during ictal imaging procedures, such as single-photon emission computed tomography (SPECT), where the timing between the seizure onset and injection of a radiotracer at the start of the procedure is critical for identifying the true onset region; delayed injections may result in visualization of secondary foci or seizure spread.[10]

Another consideration for seizure detection algorithms is whether or not 'future' data may be used to further specify detection. In other words, detection algorithms may detect seizures based on either causal methods, which use past and present data, or acausal methods, which use past, present, and future data. Real-time systems that must respond as early as possible to a seizure onset usually operate on causal data only. Off-line seizure detection systems may employ more accurate acausal signal processing methods.[19] When acausal algorithms are used in on-line applications, they detect seizures with a time lag due to their reliance on future data. Diagnostic seizure identification and seizure counting are examples of applications that can benefit from the increased accuracy of acausal methods.[19] In comparison, seizure warning and responsive therapy systems must operate in real-time using causal methods because of their need for rapid response.

Most seizure detection algorithms allow user input to adjust detection performance. This may be either manual adjustment of sensitivity parameters, or more involved user-directed training of the algorithm.[10,20,21] For example, the clinician may need to annotate the first few seizures, select parameters specific to the patient's seizures (e.g., frequency range or type of electrographic onset), or provide feedback of false detections. The added input may greatly improve the accuracy, specificity, and possibly early detection of seizures, however, the increased time required to personalize the detection algorithm and the additional burden on the clinician may make these techniques practicable only in long-term applications, such as in implantable technology.

There are a number of other considerations that influence the development of seizure detection algorithms, such as whether the electrographic data are from intracranial or surface electrodes, the age of the patient (neonatal, pediatric, or adult), and the available computational resources (implantable device versus external device). All of these issues need to be addressed for each application of a seizure detection algorithm.

Limitations

A fundamental limitation to the accuracy of seizure detection systems is the quality of the electrographic data and the conditions under which they were acquired. Electrode location is a critical variable in seizure detection, since seizures may be missed if electrodes are not positioned appropriately. This may be particularly relevant in the case of focal seizures and/or under the conditions of scalp recording.[16,22] Temporal resolution is also an issue in seizure detection. Due to computational and data storage limitations, early electrographic data were sampled at 200 Hz or less. Moreover, data were often filtered to exclude frequencies above 40 Hz based on the understanding of epileptic discharges at the time.[18] Even now, high frequency sampling is not common, despite the recent literature and interest in high frequency oscillations involved in epileptogenic localization, and seizure generation and onset.[23–29] Scalp monitoring and intracranial recording may also be susceptible to artifacts. A patient's movement during a seizure can obscure the electrographic onset of the event. In the past, electrographic epochs affected by artifacts were often excluded. A number of groups are currently developing algorithms to continue to improve signal quality.[30,31]

Electrographic features of seizures

Clinical versus electrographic seizures

Before reviewing seizure detection algorithms, one must consider what an electrographic seizure is and how it relates to clinical or behavioral seizures. Gotman[5] dissociates these two terms, describing a 'behavioral' seizure as the behavioral manifestation of an epileptic seizure, and an 'electrographic' seizure as an abnormal paroxysmal EEG pattern. In most cases, the behavioral and electrographic events can be

observed concomitantly. However, a behavioral seizure can be observed in the absence of an electrographic correlate. If the seizure was a true epileptic event, it may be assumed that abnormal activity is present in the brain, but was not recorded due to the limitations in recording technology. Conversely, if an electrographic seizure is observed with no behavioral correlate, the seizure may be referred to as a 'pure electrographic seizure' or a 'subclinical' seizure. In many situations, detection of subclinical events is still meaningful for seizure localization[32–35] or for responsive therapy.[36,37] Moreover, the lack of overt behavioral manifestations does not preclude a clinical event; some clinical symptoms are negative, such as speech arrest, aphasia, amnesia, neglect, and motor arrest, and can only be observed under specific conditions.[33,38–40]

Ictal morphology

One of the most challenging aspects of automated or computer-aided seizure detection is that seizure morphology is so varied, from patient to patient, within a patient, and within a seizure. Electrographic onset patterns for partial epileptic seizures have been described as low-amplitude desynchronization, polyspike activity, low-voltage fast, rhythmic waves, rhythmic spike, spike-wave, or sharp-wave, and possibly even nondescript.[23,41–44] As seizures progress, the morphology can evolve into a different electrographic pattern.[41] The earliest computerized seizure detection algorithms focused on a single feature of the electrographic signal.[45–47] These algorithms were effective in identifying high-amplitude events such as those associated with generalized tonic-clonic seizures. However, because they were feature-specific, they often failed to detect seizures with different morphologies.

The spectral and electrographic appearance of ictal activity depends on whether the EEG was acquired on the scalp or intracranially. While scalp electrographic recordings are most common, intracranial ictal electrocorticography is thought to provide the most reliable information for localizing seizure foci.[48] Electrographic data acquired from intracranial electrodes may contain higher frequency information and different electrographic features as compared to scalp recordings.[42] For these reasons, algorithms have been developed specifically for seizure detection based on intracranial data.[11,12,48–50]

Neonatal seizure detection also forms a distinct class from adult seizure detection. Electrographic features during both the baseline and ictal periods differ between neonates and adults. Neonatal seizures are characterized by narrow band rhythmic discharges, repetitive spiking and very slow rhythmic discharges.[51] In fact, some features that are considered to be ictal in an adult may be normal in the infant, and vice versa.[52] Although this chapter focuses on adult seizure detection, a number of papers have been published that focus on neonatal seizure detection algorithms. The reader is referred to Faul *et al.*[53] for review.

Methods for automatic seizure detection

Trending-based seizure detection algorithms

Many successful seizure algorithms rely on comparing the features of the current period of time to earlier 'background' data in the same EEG record. These detection algorithms are referred to as 'trending' algorithms because the current epoch of interest is compared to a continually-updating background trend. Trending algorithms are sensitive to rapid or paroxysmal changes compared to the background activity, and typically require minimal user input or training since detections are based on historical electrographic data from the patient. Continuously updating the background trend allows for consistent detection around the clock, since the current epoch is always being compared to a relative baseline. For instance, during sleep, the background might be very different than during active wake, but paroxysmal events are detected in both states because these algorithms look for relative changes compared to a recent baseline. If a detector is used to mark events for future visual inspection, the timing of detection relative to the onset of the electrographic event is not critical. For this application, the delay from the electrographic onset to detection may be quite long (e.g., > 20 seconds),[20] and a relatively high false positive rate (e.g., 1/hour) is tolerable.[19,48]

The detection algorithm described by Gotman[18,19] was one of the first successful trending seizure detectors. It has been tested on both scalp and intracranial EEG recordings, and is now commercially available (see Stellate Section). Gotman noted that the majority of seizures contained paroxysmal, sustained rhythmic activity with a fundamental frequency between 3 and 29 Hz at some point during the event.[18] Thus, the detection algorithm focused on detecting paroxysmal rhythmic activity within those frequencies. First, the EEG signal is low-pass filtered and decomposed into half-waves (elemental segments that are representative of the amplitude and frequency of the signal). Aggregate measures of the half-waves within an epoch, such as the average amplitude, average duration, and coefficient of variation of the duration are extracted for each epoch. A detection occurs when the average half-wave amplitude in the current epoch is significantly greater than the background, and the coefficient of variation and average half-wave duration are within a specified range, indicative of rhythmic activity. The current epoch is defined by a short window (e.g., 2 seconds) and the background is defined by an extended window (e.g., 16 seconds, ending 12–20 seconds prior to the current epoch).

This algorithm was further extended in 1990 to include a second 'background' segment after the current epoch (e.g., 8 seconds).[19] The second background was included to reduce the number of false detections due to short events. Qu and Gotman (1993)[21] later extended the algorithm again by incorporating false seizure detections from earlier monitoring sessions of an individual patient to further reduce the false-positive rate during subsequent sessions of the same patient. However, the limitation of all of these detection algorithms is that seizures consisting of irregular EEG with mixed frequencies as well as low-voltage fast events that are not followed by high-amplitude rhythmic activity can be missed.

A similar trending seizure detection method was developed specifically for intracranial EEG recordings.[48] This algorithm was designed to detect both high-frequency and high-amplitude activity. The absolute magnitude of sample-to-sample differences is calculated, where a large magnitude is indicative of a steep slope or rapid change in the signal. Within each 5-second epoch, the number of large magnitude differences is counted. A seizure is detected when a segment has an increased count compared to the running average counts of

the background. The advantage of this system is that it detects high frequency activity very well. However, it may be insensitive to some low frequency events.

Another implementation using the trending approach was reported by Osorio *et al.*[12] This algorithm was developed specifically to detect seizures in real-time. In this algorithm, the signal is first filtered using a wavelet transform that is sensitive to power changes between 5 and 45 Hz. Then the signal is filtered using a non-linear median filter to rapidly detect changes while overlooking very brief signal changes. The final step compares the median power of the current epoch (2 seconds) to a background (30 minutes, smoothed with exponential forgetting). This algorithm results in earlier detection[54] and shorter detection latencies (3.6–5 seconds)[37] than the algorithms discussed above. It also includes several manually-adjustable parameters associated with frequency band, filter percentile, background length, and patient-specific optimization. However, atypical seizures will still go undetected, which is a problem for patients who do not have a stereotyped electrographic seizure onset. Also, seizures that contain frequencies outside of the frequency range specified can go undetected.[37]

Preclassification-based seizure detection algorithms

A second category of seizure detection algorithm leverages statistics derived from previously classified EEG to properly sort novel EEG into seizure and non-seizure categories. These prior data are used either to train a classification algorithm, such as an artificial neural network, or to provide a prior distribution for Bayesian methods. Preclassification-based algorithms differ from each other in two main facets: (1) the extracted EEG features used for detection and (2) the method used to classify the EEG.

Feature extraction

As with trending-based detection, the first step in a preclassification-based algorithm is to identify a feature or set of features upon which detection is determined. Relevant features can include statistics describing temporal features of the data, such as RMS amplitude,[55] or measures of the frequency content.[55–57] Three types of frequency analysis are commonly used in feature extraction: the Fourier transform, wavelet transform, and matching pursuit decomposition. Frequency analysis methods involve a tradeoff between time and frequency resolution. This tradeoff governs the method's robustness to transient noise, ability to represent rhythmic behavior, and to some extent detection response time. The Fourier transform and its derivatives (e.g., short-term Fourier transform and fast Fourier transform) have long been used to analyze EEG frequency content.[58] The Fourier methods are efficient and easy to implement. However, they are subject to broadband spectral interference in response to abrupt frequency changes because the time resolution is uniform across the frequency spectrum. This property negatively affects accurate characterization of EEG frequency in the presence of fast transients such as spiking.[58,59]

Wavelet-based frequency analysis provides excellent time resolution at higher frequencies and good frequency resolution at lower frequencies. Unlike Fourier analyses, where the signal is decomposed into sine and cosines, in wavelet analyses, segments of the signal are decomposed using a family of finite functions called 'wavelets'. In a family of 'wavelets', the primary waveform or 'mother' wavelet is scaled and shifted to form the 'daughter' wavelets, thus allowing for increased temporal resolution at higher frequencies. This property minimizes the broadband distortions due to brief spiking or sharp-wave transients seen in Fourier-based analyses. The discrete, wavelet transform is commonly used for EEG frequency analysis.[10,60,61] Khan and Gotman[62] compared a discrete wavelet-based trending detector to a prior Gotman trending detector, attaining equivalent sensitivity with an 86% decreased false-positive rate.

Finally, the matching pursuit algorithm, a similar non-linear signal decomposition method (further discussed in the Persyst Reveal Section), provides extensive flexibility in managing the time-frequency resolution trade-off, even within a single frequency band.[55] The matching pursuit algorithm is robust against sharp transients and shows good frequency resolution within seizure EEG.[55,57] Wilson *et al.*[55] use matching pursuit in their commercialized Reveal algorithm, reporting satisfactory improvements in both accuracy and false-positive rate as compared to their previous fast-Fourier transform (FFT)-based detector.[63]

Classification

The second step of preclassification-based seizure detection algorithms is to categorize novel EEG data based on the features of preclassified EEG. Three approaches are commonly used for classification: artificial neural networks (ANNs), support vector machines (SVMs), and Bayesian methods.

Artificial neural networks describe a class of methods where 'neural networks' are trained to categorize EEG epochs as either seizure or non-seizure based on a manually preclassified set of EEG examples. The training or learning phase is typically an iterative process that generates rules to minimize the cost function or error. After the initial training, new EEG data are classified based on the rules created during the initial learning phase. Thus, the examples used in the training set are critical to the success of an ANN approach.[64,65] In the Reveal algorithm, matching pursuit-based feature vectors are processed through both ANN-generated and hypothesis-driven rules. The algorithm achieved competitive sensitivity with exceptionally low false-positive rates.[55] ANNs have also been used heavily in other automated seizure detectors over the last decade.[63,65–68]

Support vector machines use preclassified data to calculate a border that maximally separates the boundary cases of non-seizure EEG and seizure EEG. Novel data are then classified by where they fall relative to the defined border. In a patient-specific study, Shoeb *et al.*[10] combined this classification method with a wavelet-based analysis to achieve competitive true-detection rates for novel EEG data with a relatively low false-detection rate. The group noted their SVM classifiers' robustness to class-imbalanced training data, a property highly applicable to seizure detection due to the usual scarcity of seizure EEG relative to non-seizure EEG. Other theoretical advantages of the method include robustness to over-fitting, a guarantee of global optimization, and relatively low increase in model complexity with increasingly large feature vectors.

The Bayesian method of seizure detection described by Saab and Gotman (2005)[11] classifies novel EEG epochs by calculating the likelihood of the epoch being seizure data given prior probabilities from preclassified EEG data. This calculation assumes

that the features in the data are independent, characterized by Gaussian distribution, and differentiable by class (e.g., have different mean and/or variance in seizure versus non-seizure EEG). When a novel EEG epoch is introduced, the formulation uses Bayes' theorem to calculate the probability that an epoch belongs to the seizure class. If a measure based on that probability crosses an arbitrary threshold, it is classified as a seizure. This method also provides controls for balancing detector sensitivity against false-detection tolerance. The group observed sufficiently improved sensitivity to a previous method,[19] and sufficiently fast execution time to merit further exploration of the classification method in real-time seizure detectors.

Advantages and disadvantages

Preclassification-based seizure detection algorithms offer certain advantages relative to trending-based algorithms. When employing the right technologies in a patient-specific context, excellent detector performance can be achieved at a low false-positive rate.[10,55] Moreover, establishing these classification-based algorithms may require less manual manipulation of parameters than some trending-based detectors (e.g., half-wave), as rule and threshold development can occur mostly in the machine-based classifier.

This family of methods also has disadvantages relative to trending algorithms. Shoeb *et al.*[10] found that their preclassification-based detector performed poorly when used in a general clinical setting due to dissimilarity between training examples and new patient EEG data. Although this could also occur with most trending-based detection algorithms, the latter can be corrected by quickly altering trending parameters and thresholds whereas preclassification-based detectors may require training on possibly hours of data for each new patient, depending on their seizure rate. One group controlled for this effect by exclusively extracting normalized EEG features.[11] Another disadvantage of these methods is that they can only detect those seizure types that have been previously observed and hand-classified in a training set, requiring additional training in the case of a patient's newly observed seizure type.

State-based algorithms

A third category of seizure detection algorithms identifies a seizure state, irrespective of the recent background activity or previously categorized seizures. These algorithms are not dependent on the relative changes in the signal; rather they measure the absolute state of the current epoch and compare that state to a non-seizure state, which is either defined previously or acquired from the data. State-based detection algorithms operate by identifying the one feature or set of features (often non-linear) of the electrographic activity that is most representative of the seizure state. Several such features have been identified in the literature, including total energy, power, or variance,[49,69] Lyapunov exponents,[70] Kolmogorov entropy,[71] and minimum description length.[72] With this class of detection algorithms, detection may often occur seconds to minutes before the electrographic onset (as identified by the epileptologist). Therefore the distinction between seizure detection and seizure prediction becomes less clear, and these techniques are sometimes referred to as methods for 'early' seizure detection, seizure anticipation, or preseizure state detection.[73]

The earlier methods to detect a change in state were based on the power or variance of the signal, either within a specific frequency band or across all frequencies. This method of detection is simple and requires minimum computational power. Detection occurs when power within a frequency band is above a threshold.[69,74] In some cases changes in the accumulated energy occurred as early as 50 minutes before the electrographic onset.[74]

More elaborate state-based methods make use of non-linear dynamics for seizure detection.[70,75,76] These techniques focus on the change in the predictability or chaos of the neural system prior to or during the seizure. Iasemidis *et al.*[70] proposed the use of the short-term Lyapunov exponent, a measure of the short-term predictability in a non-linear dynamic system. They found that during a seizure, the maximum short-term Lyapunov exponent is reduced, indicating decreased chaos and increased predictability of the system. The Kolmogorov entropy, another measure of the complexity of a dynamic system, describes the level of uncertainty about the future state of the system. As with the Lyapunov exponent, the Kolmogorov entropy has been shown to decrease prior to a seizure with detection of a trend as early as 40 minutes before the electrographic onset.[71] Minimum description length is yet another way to define the complexity of the signal by estimating the minimum number of bits needed to describe the data.[72] This method has been proposed for neonatal seizure detection, where seizures are typically very rhythmic, and therefore defined by a low minimum description length. Other similar measures such as correlation dimension[73] and multidimensional probability evolution[77] have also been proposed.

For all of these non-linear dynamic methods, the main drawback is that they often require a large amount of stationary data to estimate parameters, and the computational complexity may be difficult to implement in real-time, particularly for ambulatory or implantable applications.

Clinical implementations

Commercial seizure detection algorithms

There are two major commercially available seizure detection systems; they are provided by Stellate Systems, Inc. (Montreal, Quebec, Canada), and Persyst Development Corporation (Prescott, Arizona). Stellate offers five different specialized seizure detectors: (1) a seizure onset detector, (2) a seizure pattern detector, (3) Icta-S for scalp EEG, (4) Icta-D for intracranial recordings, and (5) a newborn seizure detector. In addition to these stand-alone seizure detectors, several companies have incorporated Stellate algorithms into their EEG monitoring systems. Persyst offers their Reveal seizure detection algorithm. These commercially available algorithms employ a combination of the techniques and methods discussed above. All of these seizure detection algorithms can be run either on-line or off-line.

Stellate

The detection algorithms that are available in the Stellate package are summarized here; they are described in detail in several prior publications.[11,18,19,51,78]

The Stellate seizure and onset pattern detector algorithm evaluates each EEG channel individually by comparing a brief (2 seconds) epoch sliding window with a background sliding window (15–16 seconds). The epoch and background windows are separated by a gap (12–20 seconds).[19] The EEG signal is decomposed into half-waves and subsequent analysis is based on these half-waves. The seizure detector is triggered when several conditions are met:

1. The epoch amplitude must exceed the background amplitude by a specified value.
2. A candidate detection must occur in the same or the following epoch on a specified number of channels.
3. The frequency of the candidate seizure must exceed a specified value.
4. The coefficient of variation within the epoch, which is inversely correlated with rhythmicity, must be below a specified value.

The Icta-S algorithm is optimized for scalp EEG recordings. This algorithm is based on Bayes' formula and uses features and probabilities developed from a training data set to probabilistically determine whether a seizure has occurred. Epochs of 2 seconds are compared with a 30-second baseline period, separated by 1 minute.[11] Epochs with a high seizure probability affect the seizure probability of the following two epochs. As with the seizure and onset pattern detectors, amplitude, frequency, and coefficient of variation are used to identify candidate seizure epochs.

The Icta-D algorithm is optimized for intracranial recordings, which contain more variability in patterns, amplitudes and frequencies. It differs from the Icta-S algorithm in that epochs of 4 seconds are compared with 2-minute baseline periods.[78] Also, it was trained on intracranial data instead of scalp EEG.

The neonatal seizure detector combines three detection algorithms: (1) detection of rhythmic discharges, (2) detection of multiple spikes, and (3) detection of slow rhythmic discharges. A spectral analysis method is used to detect rhythmic discharges of 0.5–10 Hz using overlapping 10-second epochs compared to 20 seconds of background, separated by a 60-second gap. Multiple spikes are identified within high-pass filtered, 10-second epochs. Only spikes above a specified threshold are counted and the number of spikes within a 10-second epoch must exceed a minimum value. Slow rhythmic discharges less than 0.5 Hz are detected using low-pass filtered EEG data and the same half-wave and trending-based analysis method as described in Gotman (1990),[19] using overlapping 10-second epochs compared to a 20-second background, separated by a 60-second gap.[51]

Persyst Reveal

The Persyst Reveal algorithm is described in detail by Wilson *et al.* (2004)[55] and summarized here. In this algorithm, EEG data are filtered and downsampled to 32 Hz, restricting the maximum frequency analyzed to 16 Hz. Each channel of the data is segmented into 2-second epochs with a 1-second overlap. A matching pursuit decomposition is applied resulting in a set of Gabor 'atoms', describing the time-frequency evolution of each 2-second epoch; only the first two atoms are selected for the analysis. Epochs are also described by total RMS amplitude, maximum amplitude excursion, and summed duration of amplifier saturation. Epochs containing excessive artifact, based on amplifier saturation and maximum amplitude excursion, are rejected. Several hand-coded and data-trained neural net functions are used to identify rhythmicity and seizure events based on features of the atoms and epochs. Additionally, a clustering function is applied to a moving 60-second window to group consecutive epochs based on similarity into background, seizure and offset sections. These functions are described below.

1. A hand-coded function computes a 'rhythmicity' value for each atom that is maximized when the atom half-wave-amplitude, atom-half-wave-slope, atom-half-wave-count, and atom-duration are maximized.
2. A neural net function computes a 'distinguished-from-window' value that indicates how well an atom is distinguished from the window based on atom-amplitude, atom-duration, and atom-frequency.
3. A hand-coded function computes a 'seizure-score' for the epoch that is maximized when the previously computed rhythmicity and distinguished-from-window values are maximized.
4. A neural net function calculates a 'seizure-candidate' value based on seizure frequency and the seizure score.
5. A neural net function calculates a 'seizure-is-perceived' value based on the candidate seizure duration, the seizure-candidate value, and the absence of exceptionally high maximum amplitudes, indicative of artifacts.
6. A neural net function calculates a 'composite-seizure-is-perceived' value based on the first- and third-best channels seizure-is-perceived values, as well as the amplitude and frequency differences between successive epochs.

NeuroPace® RNS™ system

The NeuroPace RNS System is an implantable system capable of performing real-time seizure detection and responsive electrical stimulation (Figure 77.1, Figure 77.2). At this time, the system is being evaluated in clinical trials to assess the safety and efficacy of responsive neurostimulation for the treatment of medically intractable partial-onset epilepsy. The implantable components of the system include (1) a neurostimulator, which senses and stores electrographic activity, performs detection, and delivers electrical stimulation; and (2) chronically implanted depth and strip leads, which are used to sense and provide stimulation. The external components include (1) a Programmer, used to program detection and stimulation settings and retrieve stored information (e.g. electrographic activity) from the neurostimulator; and (2) a wand, which allows wireless communication between the neurostimulator and the Programmer. A patient data transmitter is also provided, to allow uploading and monitoring of device data between clinic visits. These data are uploaded via the Internet to a central patient data management system, and may be reviewed by physicians.

Detection algorithm

The detection algorithms implemented in the RNS Neurostimulator are designed to be computationally efficient and highly optimized in order to perform real-time seizure detection within the constraints of currently available

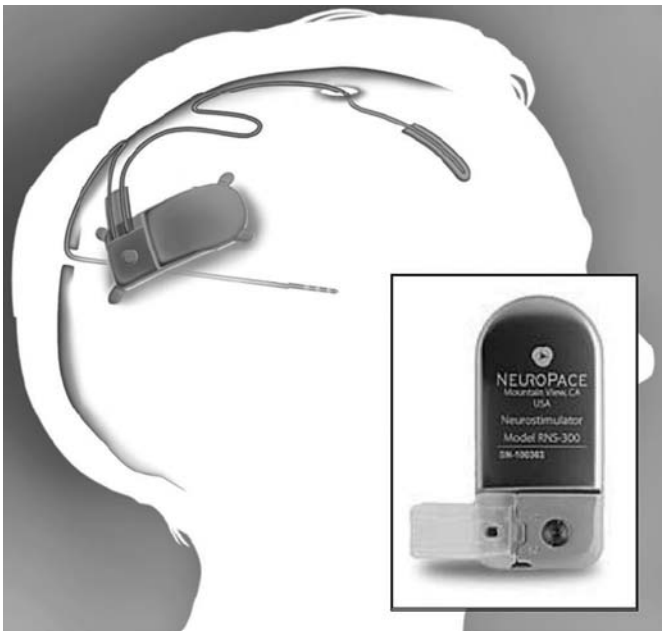

Figure 77.1 Schematic illustration of the implanted RNS Neurostimulator, depth lead and cortical strip lead. The RNS Neurostimulator (inset) is designed to match typical skull thickness and curvature, and is intended for implant in a ferrule, or socket, placed in a craniectomy. Up to two leads may be used with the system; each may be a depth lead or cortical (subdural) strip lead, and each has four electrode contacts, which are used for sensing and providing stimulation. In order to provide early seizure detection and delivery of focal electrical stimulation, leads are positioned using standard neurosurgical techniques as close as possible to the seizure focus or foci.

implantable technology, such as limited power and processing capabilities. Three fundamental detection algorithms (or tools) are provided, which are based on the half-wave, line length, and area features extracted from the EEG. The detection tools are highly configurable and can be adjusted by the physician to optimize the sensitivity and specificity trade-off for each individual patient. The tools can also be combined to yield even more specific detection.

The half-wave algorithm used in the RNS System is similar to that of Gotman (1982),[18] and is used to detect spikes and rhythmic activity occurring in specific frequency ranges. The neurostimulator segments the EEG at local minima and maxima (excluding deviations smaller than a programmed threshold), resulting in half-waves the amplitude and duration of which are representative of the amplitude and frequency components of the EEG. Half-waves that exceed a physician-programmed amplitude and duration are counted; the number of these half-waves occurring within a given window length must exceed a certain threshold for detection to occur.

The line length algorithm, described by Esteller *et al.* (2001),[79] is similar to fractal-dimension measures and is used to identify changes in both amplitude and frequency. The line length is defined as the average of absolute sample-to-sample differences within a window. A short-term sliding window average is compared to a long-term sliding window average. The short-term window and long-term window durations can be configured to optimize detection of specific features. A detection occurs when the short-term measurement exceeds an absolute or relative threshold (Figure 77.3). A negative threshold can also be used to detect decreases in line length, which may represent a period of electrodecrement or decreased frequency.

The area feature,[80] is similar to an energy or power measurement[81] and is used to identify changes in overall signal energy without regard for frequency. Area is defined as the average absolute area-under-the-curve within a window. As with line length, a short-term window average is compared to a long-term background window average, and detection occurs when positive or negative threshold is exceeded (Figure 77.3).

The output of the half-wave, line length and area tools from the same or different EEG channels may be combined to identify specific electrographic events. In addition, the output of a tool may be assigned a persistence duration to facilitate detection of events in sequence. For instance, a seizure onset consisting of a series of spike-wave events followed by elevated gamma might be identified by a half-wave spike detector, given several seconds of persistence and a line-length detector sensitive to the increase in frequency.

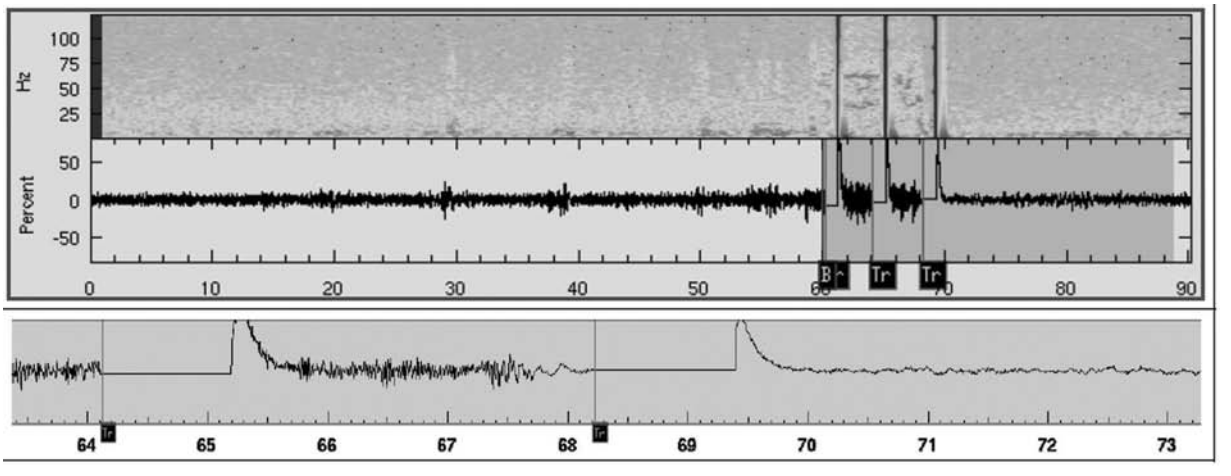

Figure 77.2 Example of a possible seizure termination by responsive stimulation. The upper panel shows the FFT spectrogram and time series for a single cortical EEG channel. The lower panel shows a close-up of the time series around the time of termination. In the time series plots, detection is indicated by the vertical blue line and the 'B' label, and responsive stimulation is indicated by the vertical red lines and the 'Tr' labels (the first is partly obscured by the 'B' label). (See Color plates.)

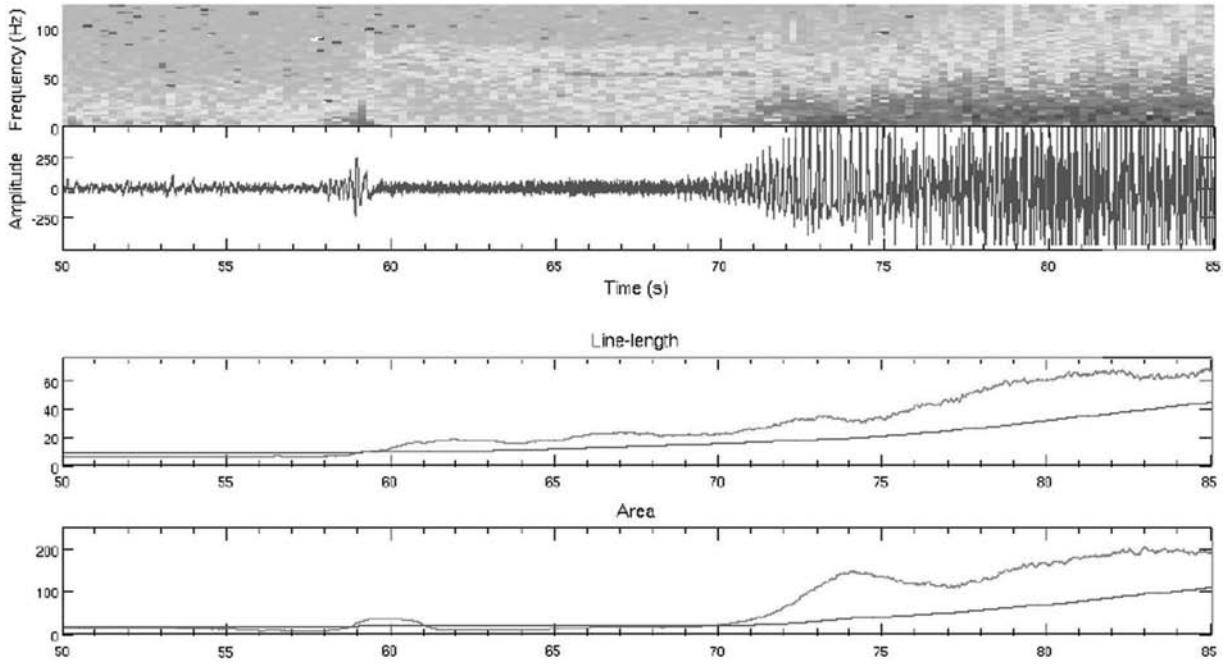

Figure 77.3 Demonstration of the line-length and area algorithms. The upper panel shows the FFT spectrogram and time series of a single cortical EEG channel at a seizure onset. The middle panel displays the data represented by the short-term (red) and long-term (blue) line length features. In this example, the short-term window is 2 seconds and the long-term window is 30 seconds. Detection occurs when the short-term trend exceeds the long-term trend (e.g., at ~59 seconds). The bottom panel displays the detection using the area algorithm. As with the line-length algorithm, detection occurs at ~59 seconds and redetection occurs at 70 seconds. Note that the line-length detection is sensitive to both changes in frequency and amplitude, whereas the area detection is sensitive to amplitude. (See Color plates.)

Advantages

Implantable systems have the unique advantage of operating on a chronic, continuous and relatively artifact-free stream of electrographic data from an ambulatory subject. This information is valuable to both the clinician and researcher, and has been used to study such topics as circadian variation in the intracranial EEG.[82] These data can be further used to optimize seizure detection for a given patient, or to control responsive stimulation delivered by the implantable device. In addition, bipolar signals recorded and analyzed by an entirely-implanted device are particularly resistant to external noise.

Limitations of implantable technology

These advantages do not come without limitations; at present implantable seizure detection is technologically constrained in comparison with methods proposed for off-line or non-implantable applications. This is due to many factors, including limited power, computational restrictions, and limitations in electrode placement. An implantable device must either be rechargeable or possess a battery life on the order of years. In either case, the power available to perform seizure detection is strictly limited. This manifests as a limit on clock speed for the implantable microcontroller. Whereas current desktop computers may perform more than 10^9 operations per second, an implantable device may be constrained to fewer than 10^6 operations per second. Detection tools are constrained to those that may be reasonably implemented in low-power digital hardware. This may require discrete approximations to complex methods, such as line length for fractal dimension. Moreover, the complexity of a device increases drastically as more channels are added. While in-hospital epilepsy monitoring may use grids of 64 or more contacts, implantable devices are currently limited to far fewer contacts and channels. This means that localization must be determined with some accuracy before use of an implantable device.

It is expected that these boundaries will expand greatly as technology advances; however, implantable applications of seizure detection will always be constrained by the resources available in a small, chronically implanted device.

Conclusions

Automated seizure detection is a rich problem area for signal analysis. A range of algorithms have been developed for this purpose. Each of the approaches has its own strengths and weaknesses, owing to the complexities of seizure waveforms, tradeoffs between sensitivity and specificity, tradeoffs between accuracy and latency, and platform constraints. In this chapter, we have reviewed a number of computational algorithms for seizure detection. While the field has grown in leaps and bounds over the past three decades, there is still no single solution to the complex problem of automated seizure detection, and there may never be. As the field continues to develop along with the acceleration of computer technology, we expect advancement in the area 'state-based' or early seizure detection algorithms as well as significant progress in ambulatory and/or implantable detection systems. These developments will be invaluable to the understanding and treatment of epilepsy.

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78 'Preictal' predictors of epileptic seizures

F Mormann, K Lehnertz, and CE Elger

Outline of the chapter

Our understanding of the mechanisms that lead to the occurrence of epileptic seizures is rather incomplete. If it were possible to identify preictal precursors from the EEG of epilepsy patients, therapeutic possibilities could improve dramatically. First attempts to predict the occurrence of seizures from EEG time series were started in the 1970s. Studies on seizure prediction have since then advanced from preliminary descriptions of preictal phenomena and proof of principle studies via controlled studies to studies on continuous multi-day recordings. Following the mostly promising early reports, the recent years have witnessed a debate over the reproducibility of results and suitability of approaches. The current literature is inconclusive as to whether seizures are predictable by prospective algorithms. Prospective out-of-sample studies including a statistical validation are missing. Nevertheless, there are indications of a superior performance for approaches characterizing interactions between different brain regions by means of quantifying relations between signals from different recording sites. Prediction algorithms must be proven to perform better than a random predictor before prospective clinical trials involving seizure intervention techniques in patients can be justified.

In this chapter we will critically review the literature from the emerging field of seizure prediction and discuss the problems and pitfalls associated with the design and evaluation of seizure prediction algorithms.

Introduction

To epilepsy patients for whom complete seizure control can not be achieved, e.g., by medical or surgical treatment, it is the sudden, unforeseen way in which seizures strike 'like a bolt from the blue' that represents one of the most disabling aspects of the disease. Apart from the risk of serious injury, there is often a severe feeling of helplessness that has a strong impact on the everyday life of a patient. It is obvious that a method capable of predicting the occurrence of seizures could significantly improve the therapeutic possibilities[1] and thereby the quality of life for epilepsy patients.

A question of particular interest is whether apart from clinical prodromi, which are found only in some patients,[2,3] characteristic features can be extracted from the continuous EEG that are predictive of an impending seizure. If it were possible to reliably predict seizure occurrence from the EEG of epilepsy patients, therapeutic concepts could move from preventive strategies (e.g., long-term medication with AEDs) towards an on-demand therapy, e.g., by excretion of fast-acting anticonvulsant substances or by electrical or other stimulation in an attempt to reset brain dynamics to a state that will no longer develop into a seizure.

In principle there are two different scenarios of how a seizure could evolve: It could either be caused by a sudden and abrupt transition in which case it would not be preceded by detectable dynamical changes in the EEG. Such a scenario would be conceivable for the initiation of seizures in primary generalized epilepsy. Alternatively, this transition could be a gradual change (or a cascade of changes) in dynamics which could in theory be detected. This type of transition could be more likely in focal epilepsies.[4]

Several seizure-facilitating factors are known. In the context of his 'reservoir theory', Lennox[5] has defined seizure facilitation as the input of sensory, metabolic, emotional, or other yet unknown factors that '… fill up some reservoir until it overflows', which in turn results in a seizure. Among others, state of consciousness, sleep deprivation, stress, disturbances of electrolytes and acid-base balance, sensory stimulation and exposure to drugs are factors known to facilitate seizures.[6] Apart from the rare exception of sensory-evoked or reflex epilepsies, however, these factors are rather unspecific and highly variable since they depend on individual habits, susceptibility, and daily routine. Clinicians who care for patients with epilepsy have long known that individual patients can identify periods when seizures are more likely to occur, though they can rarely specify an exact time when seizures will happen. Reported prodromal symptoms include mood changes, irritability, sleep problems, nausea, and headache.

There are also physiological studies in small numbers of patients, usually collected serendipitously before seizures, that support the existence of a preictal period. Weinand and co-workers[7] detected a significant increase in blood flow in the epileptic temporal lobe starting 10 min before seizure onset that spread to both temporal lobes 2 min before seizure onset. Similarly, Baumgartner and colleagues[8] demonstrated increased blood flow in the epileptic temporal lobe in two patients, 11 and 12 minutes respectively, before seizure onset. Using near-infrared spectroscopy in three patients, Adelson and co-workers[9] reported an increase in cerebral oxygen availability that began more than 13.5 h, and was identified as early

as 1.5 h, before documented seizure onset. Preictal changes in other variables, such as R-R interval on the ECG[10–12] may also have predictive value, perhaps as epiphenomena related to seizure precursors, in some types of epilepsy. More recently, functional magnetic resonance imaging has demonstrated changes in perfusion prior to seizure onset.[13]

Knowledge about basic mechanisms leading to seizures has mainly been derived from animal experiments. Although there is a considerable bulk of literature on the topic, the underlying electrophysiological and neurobiochemical mechanisms are not yet fully explored. Moreover, it remains to be investigated to which degree findings from animal experiments can be transferred to human epilepsies. During recent years, a variety of potential ictogenic (seizure generating) mechanisms have been identified in experimental models of focal epilepsy, including alterations in synaptic and cellular plasticity and changes in the extracellular milieu. It is still a matter of debate, however, whether these mechanisms can be regarded as specifically ictogenic, apart from their critical role in normal brain function. On the level of neuronal networks, focal seizures are assumed to be initiated by abnormally discharging neurons (so-called bursters;[14–18] see Yaari and Beck[19] for an overview) that recruit and entrain neighboring neurons into a critical mass. This build-up might be mediated by an increasing synchronization of neuronal activity that is accompanied by a loss of inhibition, or by processes that facilitate seizures by lowering the threshold for excitation or synchronization. In this context, the term 'critical mass' might be misleading in the sense that it implies an increasing number of neurons that are entrained into an abnormal firing pattern. This mass phenomenon would be easily accessible to conventional EEG analysis which, to date, has failed to detect it. Rather, the seizure initiating process might better be visualized as a process in which an increasing number of critical interactions between neurons in a focal region and connected units in an abnormal functional network unfold over time.

Based on these concepts, a number of studies have aimed at characterizing this collective neuronal behavior from the gross EEG in order to allow definition of a transitional preictal phase. In this chapter we will give an overview of the literature on this topic and the current state of this rather young research field and critically discuss some of the methodological problems and pitfalls involved in the design and testing of seizure prediction algorithms.

The history of seizure prediction

For a better understanding of the practical problems in this field, in this section we categorize the literature on seizure prediction according to methodological standards. A chronological overview is given in Table 78.1.

Early approaches

After some early work on the predictability of seizures dating back to the 1970s,[65] attempts to extract seizure precursors from the EEG were carried out by different groups using mostly linear approaches such as spectral analysis[66–68] or pattern detection by analyzing spike occurrence rates.[69–73]

Preictal phenomena

Following the advent of the theory of nonlinear systems in the 1980s, time series analysts became aware of seizure prediction as a potential field of application. In the early 1990s, Iasemidis and co-workers[74] calculated the so-called largest Lyapunov exponent from the intracranial EEG of epilepsy patients by means of a moving window analysis and reported a decrease of this measure minutes before an epileptic seizure. Some years later, a French group of researchers reported a preictal decrease of a measure termed correlation density prior to seizures in a large group of patients.[22] The same group developed another measure named dynamical similarity index, which quantified changes in dynamics relative to a constant reference window at the beginning of a preictal recording. They found changes in dynamics prior to seizures in both intracranial[23,24] and scalp EEG recordings.[28]

Common to all these studies is that their focus of interest was entirely limited to the preictal period and that they did not include evaluation of interictal control recordings (i.e., periods from the seizure-free interval other than the presumed preictal period). By thus neglecting the issue of specificity, these studies rendered an incomplete evaluation of the investigated measures' suitability for seizure prediction.

Proof-of-principle studies

Another group of studies tackled the issue of specificity by comparing preictal changes in dynamics to interictal control recordings, although the findings reported in these studies remained on an exemplary level. Navarro *et al.*[36] used selected examples of five of their patients to show that drops in their similarity measure occurred more frequently before seizures than during the interictal EEG. In 2000, Mormann *et al.*[25] reported changes in synchronization between different brain areas before seizures that were not found in exemplary seizure-free recordings. In two reviews of their own work, Le Van Quyen and co-workers[31,32] referred to a submitted study including eight patients with neocortical epilepsy that seemed to confirm these findings. In 2003, Chávez *et al.*[42] published exemplary results using phase synchronization analysis after band-pass filtering of the EEG and reported preictal changes in synchronization to occur predominantly in the beta band.

Controlled studies on predictability

In the first *controlled studies* comprising defined groups of patients with preictal *and* interictal control recordings, measures like the correlation dimension,[20,21] dynamical entrainment[29] (defined by the authors as the convergence of largest Lyapunov exponents in certain selected channels), accumulated signal energy,[30,52] simulated neuronal cell models,[37] or phase synchronization[38,39] were shown to be suitable to distinguish interictal from preictal data. These studies were followed by a number of studies (mostly carried out on more extensive data bases) that found a substantially poorer predictive performance than presumable from earlier reports for the correlation dimension,[47] the similarity index,[46] and accumulated energy.[51] Whether these measures performed at all better than random could not be answered by these studies since the statistical validation scheme applied did not include corrections for testing of multiple channels and seizures

Table 78.1 Studies on seizure prediction and their relevant characteristics (see text). Adapted from Mormann *et al.* Curr Opin Neurol 2006 (in press)

Authors	Year	Type of EEG	Characterizing measure	Patients	Seizures	Total EEG (h)	Interictal controls (h)	Type of analysis	In-sample parameter optimization	Retrospective best channel selection	Prospective	Assumed preictal period (min)	Sensitivity (%)	False-positive Rate (FP/h)	Mean prediction Time (min)	Statistical validation of performance
Lehnertz & Elger[20,21]	1998	iEEG	Correlation dimension	16	16	21	16.9	statistical	yes	yes	no	30	94	0	12	no
Martinerie *et al.*[22]	1998	iEEG	Correlation density	11	19	13	0	algorithmic	no	yes	no	20	89	n.a.	3	no
Le Van Quyen *et al.*[23]	1999	iEEG	Similarity index	13	23	15	0	algorithmic	no	yes	no	20	83	n.a.	6	no
Le Van Quyen *et al.*[24]	2000	iEEG	Similarity index	9	17	11	0	algorithmic proof of principle	no	yes	no	20	94	n.a.	4	no
Mormann *et al.*[25]	2000	iEEG	Phase synchronization	2	3	4	1.8		no	yes	no	n.s.	100	0	n.s.	no
Cerf *et al.*[26]	2000	iEEG	Correlation integral	7	9	n.s.	1.8	statistical	yes	yes	no	60	100	0	n.s.	no
Hively *et al.*[27]	2000	sEEG	Dissimilarity measures	n.s.	20	40	0	algorithmic	yes	no	no	262.5	100	n.a.	52	no
Le Van Quyen *et al.*[28]	2001	sEEG	Similarity index	23	26	26–35	0	algorithmic	no	yes	no	60	96	n.a.	7	no
Iasemidis *et al.*[29]	2001	iEEG	Dynamical entrainment	5	58	266	53.9	statistical	yes	yes	no	variable	91	n.s.	49	no
Litt *et al.*[30]	2001	iEEG	Accumulated energy	5	30	>312	50	statistical	yes	no	no	180	90	0.12	19	no
Le Van Quyen *et al.*[31,32]	2001	iEEG	Phase synchronization	8	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	no	n.s.	77	n.s.	several min	no
Lehnertz *et al.*[33]	2001	iEEG	Correlation dimension	59	95	>145	>115	algorithmic	yes	yes	no	n.s.	47	0	19	no
Protopopescu *et al.*[34]	2001	sEEG	Dissimilarity measure	41	46	261	73.9	algorithmic	yes	yes	no	60	95	0	n.s.	no
Jerger *et al.*[35]	2001	iEEG	7 different measures	4	12	1	0	algorithmic	yes	yes	no	3	100	n.a.	2	no
Navarro *et al.*[36]	2002	s+iEEG	Similarity index	11	41	53–142	12–60[c]	algorithmic	no	yes	no	90	83	0.31[c]	8	no
Schindler *et al.*[37]	2002	sEEG+FO	Simulated neuronal cells	7	15	144	n.s.	algorithmic	yes	no	no	variable	100	n.s.	83	no
Mormann *et al.*[38]	2003	iEEG	Synchronization/ Correlation	10	14	31	15	algorithmic	yes	no	no	240	86	0	86 / 102[h]	yes

Continued

Table 78.1 cont'd

Authors	Year	Type of EEG	Characterizing measure	Patients	Seizures	Total EEG (h)	Interictal controls (h)	Type of Analysis	In-sample parameter optimization	Retrospective best channel selection	Prospective	Assumed preictal period (min)	Sensitivity (%)	False-positive rate (FP/h)	Mean prediction time (min)	Statistical validation of performance
Mormann *et al.*[39]	2003	iEEG	Phase synchronization	18	32	117	49	algorithmic	yes	no	no	240	81	0	4–221	no
De Clercq *et al.*[40]	2003	sEEG	Similarity index	12	n.s.	n.s.	0	algorithmic	no	yes	no	60	0	n.a.	–	no
Niederhauser *et al.*[41]	2003	iEEG	Sign periodogram transf.	5[a]	31	336	335	algorithmic proof of principle	yes	yes	no	2	94	0.08[f]	5–80 sec	no
Chàvez *et al.*[42]	2003	iEEG	Phase synchronization	2	6	22	9		yes	yes	no	90	n.s.	n.s.	>>30	no
Hively & Protopopescu[43]	2003	sEEG	Dissimilarity measure	41	46	261	73.9	algorithmic	yes	no	no	60	88	0.02	35	no
D'Alessandro *et al.*[44]	2003	iEEG	Feature selection	4	46	n.s.	160	algorithmic	yes	yes	no[d]	10	63	0.28	3	no
Iasemidis *et al.*[45]	2003	iEEG	Dynamical entrainment	5	28[b]	214	n.s.	algorithmic	no	no	yes	180	83	0.17[f]	100	no
Winterhalder *et al.*[46]	2003	iEEG	Similarity index	21	88	588	509	algorithmic	yes	yes	no	30[e]	42	0.15	n.s.	no
Aschenbrenner *et al.*[47]	2003	iEEG	Correlation dimension	21	88	588	509	algorithmic	yes	yes	no	50[e]	34	0.10	n.s.	no
Van Drongelen *et al.*[48]	2003	s+iEEG	Kolmogorov entropy	5	5	5	0	algorithmic	yes	no	no	60	60	n.a.	21	no
Li *et al.*[49]	2003	sEEG	Marginal predictability	8	24	37	13.3	statistical	no	no	no	60	n.s.	n.s.	n.s.	no
Drury *et al.*[50]	2003	sEEG	Marginal predictability	14	44	59	14.7	statistical	no	no	no	60	n.s.	n.s.	30	no
Maiwald *et al.*[51]	2004	iEEG	Accumulated energy	21	88	588	509	algorithmic	yes	yes	no	32[e]	30	0.15	n.s.	no
Gigola *et al.*[52]	2004	iEEG	Accumulated energy	4	13	26	10.5	statistical	yes	n.s.	no	70	92	0	n.s.	no
D'Alessandro *et al.*[53]	2005	iEEG	Feature selection	2	19[b]	177	140	algorithmic	no	no	yes	10	100/13[g]	1.10/0.71[g]	2/n.s.[g]	no
Esteller *et al.*[54]	2005	iEEG	Accumulated energy	4	42	294	>168	algorithmic	yes	yes	no[d]	180[e]	71	0.11[f]	85	no
Harrison *et al.*[55]	2005	iEEG	Accumulated energy	5	51	311	<92	statistical	no	no	no	60	0	–	–	no

Iasemidis *et al.*[56]	2005	iEEG	Dynamical entrainment	2	11[b]	41	>8	algorithmic	no	no	yes	120	82	0.15[f]	78	no
Jerger *et al.*[57]	2005	iEEG	Synchronization/ correlation	1	9	18	9	statistical	no	no	no	60	22	–	–	yes
Jouny *et al.*[58]	2005	iEEG	Complexity/ synchrony	2	25	177	n.s.	statistical	no	no	no	60	0	–	–	no
Le Van Quyen *et al.*[59]	2005	iEEG	Phase synchro-nization	5	52	305	25–120	algorithmic	yes	no	no[d]	variable	69	n.s	187	no
Mormann *et al.*[60]	2005	iEEG	30 different measures	5	51	311	>107	statistical	yes	yes	no	5–240[e]	n.s.	n.s.	–	yes
Kalitzin *et al.*[61]	2005	iEEG	Phase clustering	3	20	>75	n.s.	statistical	yes	yes	no	–	n.s.	n.s.	–	no
Navarro *et al.*[62]	2005	iEEG	Similarity index	13	129	227	0	algorithmic	no	yes	no	120	64	n.a.	>13	no
Chaovalitwongse *et al.*[63]	2005	iEEG	Dynamical entrainment	10	64[b]	597	>404	algorithmic	no	no	yes	180	69	0.15[f]	72	yes[i]
Harrison *et al.*[64]	2005	iEEG	Correlation dimension	20	960	2347	n.s.	statistical	yes	no	no	90 / 15[e]	0	–	–	no

n.s.: not specified; n.a.: not analyzed; iEEG: intracranial EEG; sEEG: surface EEG; FO: foramen ovale electrodes.
[a] Selected out of a group of 10 patients.
[b] Results listed are those obtained for out-of-sample testing data after in-sample optimization on training data.
[c] Only from five selected patients.
[d] Algorithm designed to run prospectively, but results are reported for training and testing data together.
[e] Various predefined prediction horizons were analyzed.
[f] Uncorrected false-positive rate including preictal periods.
[g] Separate results reported for two different patients.
[h] Separate results reported for two different measures.
[i] Inconclusive validation: surrogate seizure times are not treated in the same way as original seizure times.

(cf. Schelter *et al.*).[75] Around this time a controversy evolved regarding both the reproducibility of earlier studies[40] and the problems and pitfalls associated with nonlinear measures used to characterize EEG time series.[76–78]

Continuous multiday recordings

Around the turn of the millennium when mass storage capacity became more widely available, epilepsy centers were able to store the complete data acquired during presurgical monitoring without the necessity to select sample recordings. In 2005 a series of studies from different groups was published that were carried out on a set of five continuous multiday recordings provided by different epilepsy centers for the First International Collaborative Workshop on Seizure Prediction[79] held in Bonn in April 2002. The aim of this workshop was to have different groups test and compare their methods on a joint data set. Results from the different groups for the most part showed a poor performance of univariate measures.[53–55,58,60] A better performance was reported for bivariate measures.[56,59,60] One of these studies found a discriminative power for interictal and preictal amplitude distributions for certain measures of synchronization that was shown to be significant using a rigorous statistical validation, while many univariate measures, including the correlation dimension, the Lyapunov exponent, and the signal energy, were not able to discriminate the preictal from the interictal period above chance level.[60]

Prospective studies

The first attempts to test seizure prediction algorithms in a prospective manner were carried out by Iasemidis *et al.*[45] and D'Alessandro *et al.*[53] The sensivity and specificity rates obtained were unacceptable for clinical implementation. Whether the performance of the algorithms was at all better than random was not investigated. A recent study by Chaovalitwongse *et al.*[63] attempted such a validation based on a method proposed 2 years earlier,[80] but the authors did not apply the exact same analysis procedure to the seizure times surrogates as to the original onset times so the results must be regarded as inconclusive.

Summary

During the 1990s, a number of studies raised a high optimism about seizure prediction becoming feasible for clinical application in the near future. The focus of these studies, however, was limited to analyzing short and selected data segments, and numerous methodological caveats were disregarded. In the past 5 years many studies were published that questioned both the validity and reliability of these findings by showing that earlier optimistic results could not be reproduced.

For the field of seizure prediction to advance towards clinical applications, it is inevitable that future studies on seizure prediction place a strong emphasis on sound methodology and include a rigorous statistical validation. In the next two sections of this chapter we will therefore address some of the methodological issues and caveats involved in the designing and testing of seizure prediction algorithms before pointing at possible future developments.

Conceptual issues

This section addresses issues that need to be resolved prior to designing a study on seizure prediction.

Prediction, forecasting, or anticipation?

In the strict sense of the words, prediction or forecasting of an event means the ability to determine in advance the time of its occurrence with a certain precision. The term anticipation on the other hand implies an uncertainty as to when exactly an event will occur. This latter concept better fits the design of seizure prediction algorithms which usually assume a seizure to occur within a certain time period after an alarm is issued without knowing its exact onset time. Throughout the literature, however, the three different terms are for the most part used interchangeably.

The type of EEG: intracranial or surface recordings?

While the majority of seizure prediction studies to date have been carried out on intracranial recordings, some studies have also used surface recordings (cf. Table 78.1). Intracranial recordings bear the advantage of a higher signal-to-noise ratio and a better spatial resolution, and the data can be considered mostly artifact free. They also bear the potential advantage of allowing to record directly from the seizure-generating region. Surface recordings on the other hand are less invasive and could in principle be used in an ambulatory setting to monitor a patient's seizure situation in his/her usual environment. This would, however, require a high compliance on part of a patient due to the impairment of constantly wearing an EEG cap.

Furthermore, if seizure anticipation algorithms proved to be successful, they would most likely be implemented in an implantable, closed-loop warning or intervention system. The feasibility of such systems has already been proven by intracranial brain stimulation devices that are currently being tested in clinical trials for their ability to reduce seizure frequency. The usefulness of scalp EEG recordings for studies on seizure anticipation can therefore be regarded as rather limited compared to intracranial recordings.

The events to be predicted: clinical or electrographical seizures?

Another important issue is the selection of the ictal events that should be predicted by an algorithm.[79] While the benchmark for clinical application would clearly be the forecasting of clinical seizure events, subclinical seizures today are mostly regarded not as a different entity, but as a milder variant of the same dynamical event that constitutes a clinical seizure. It is therefore arguable whether it is reasonable to exclude subclinical ictal events in a prediction algorithm. Nevertheless, most studies so far have restricted themselves to the analysis of clinical seizures.

Similarly, the onset time of a seizure can be determined either from the first clinical signs or from the first visible EEG changes. Since there is often some uncertainty in the assessment of clinical symptoms, particularly in complex partial and absence seizures, it is reasonable to determine the seizure

onset electrographically, especially if intracranial recordings from the seizure onset zone are available.

Algorithms that aim at an early detection of the electrographical seizure onset, which may occur several seconds before the first clinical symptoms should not be regarded as seizure prediction algorithms, but rather as early seizure detection algorithms (e.g., Osorio *et al.*).[81]

Data requirements and data completeness

While it is on the one hand desirable to use data sets for analysis that contain a large number of seizures, it is also desirable to have a sufficient time interval between consecutive seizures, so they can be regarded as independent events. If seizures are too closely spaced (clustered seizures) it becomes difficult to separate the postictal period from a presumed preictal state (cf. Jouny *et al.*)[58] as the exact duration of either of the two is unknown.

Note in this context that the average seizure frequency in a monitoring unit of up to three events per day[82] is about 30 times higher than a typical seizure frequency of three per month under normal circumstances.[83] If a false prediction rate obtained in the epilepsy monitoring unit corresponded to a situation where every other alarm is a false alarm (positive predictive value of 50%), then the same false prediction rate under normal circumstances would result in only one out of 60 alarms being a correct warning (positive predictive value of 1.7%) (cf. Winterhalder *et al.*).[46]

EEG recordings used for studies on seizure prediction should ideally comprise EEG data recorded continuously over several days. Recording gaps due to diagnostic procedures during the presurgical work-up (e.g., structural MRI to verify electrode placement) are usually unavoidable and are not considered a major drawback. Since during the presurgical monitoring, patients are constantly undergoing changes that could have a confounding influence on characterizing measures of the EEG (e.g., tapering of medication), it is advisable to use all interictal control data available since a restriction to, e.g., the first 24 h of EEG could introduce a confounding bias.

Assessing the performance of a prediction algorithm

In this section we will discuss some of the problems and pitfalls involved in the evaluation of an algorithm for seizure prediction.

Moving window analysis

In order to judge the relative merit of the different studies on seizure prediction published to date, it is necessary to realize how the performance of a seizure prediction technique is assessed. Most of the prediction techniques published up to now have certain common features: They use a moving window analysis in which some (linear or nonlinear) characterizing measure is calculated from a window of EEG data with a predefined length, then the subsequent window of EEG is analyzed, etc. The duration of these analysis windows usually ranges between 10 and 40 sec. Depending on whether the employed measure is used to characterize a single EEG channel or relations between two or more channels, it is referred to as a univariate, bivariate or multivariate measure, respectively. The moving window analysis thus renders *time profiles* of a characterizing measure for different channels or channel combinations.

Statistical vs. algorithmic approaches

The study design used to evaluate these time profiles in a next step can be either statistical or algorithmic (cf. Table 78.1). A *statistical* design is retrospective by nature and usually compares the amplitude distributions of the characterizing measures from the interictal with those from the *assumed preictal period* in one way or another. The temporal structure of the time profiles is usually not preserved in this type of analysis. Such a design can be useful to investigate and compare the potential predictive performance of different characterizing measures under different conditions.

An *algorithmic* analysis on the other hand uses a design that produces a time-resolved output, i.e., an output for every point of a time profile. With respect to practical application, the algorithm should ideally be prospective, i.e., its output at a given time should be a function of the information available at this time. Prediction algorithms usually employ certain thresholds. If the time profile of a characterizing measure crosses the threshold, the algorithm produces an alarm. This alarm can be either true or false, depending on whether it is actually followed by a seizure or not. For this distinction, it is necessary to define a *prediction horizon*, i.e., the period after an alarm within which a seizure is expected. If an alarm is followed by a seizure within the prediction horizon, it is classified as a true alarm (true positive), otherwise it is regarded as a false alarm (false positive). In addition, it may be useful to require a minimum time interval between an alarm and a seizure occurrence in order to count this alarm as a successful prediction if the algorithm is to be used for seizure prevention. This *minimum intervention time* can be introduced as an additional constraint. (Note that in the literature, sometimes different definitions are used for these quantities, e.g., one group has used the term 'seizure occurrence period' instead of prediction horizon and 'seizure prediction horizon' instead of minimum intervention time.)[46,47,51] In studies that employ a statistical instead of an algorithmic design, the prediction horizon corresponds to the assumed preictal period.

Sensitivity and specificity

If a seizure is not preceded by an alarm within the prediction horizon, this will be counted as a false negative. A less trivial question is how to quantify true negatives. In principle, every single window of the moving window analysis that is outside the duration of the assumed preictal period (i.e., one prediction horizon prior to a seizure) and does not produce an alarm could be counted as a true negative. However, since *sensitivity* is usually quantified as the number of seizures with at least one alarm within the preceding prediction horizon divided by the total number of seizures, it is reasonable to define *specificity* based on the prediction horizon, too. If, for instance, the prediction horizon is 3 h, the sensitivity quantifies the fraction of correctly classified preictal 3-h segments, while the

specificity measures the fraction of correctly classified (consecutive) interictal 3-h segments.

In order to avoid any ambiguity in statistically quantifying the specificity of a prediction algorithm, most studies have instead reported specificity rates measured as false predictions per hour. Unfortunately, also for false prediction rates, different definitions are found in the literature. Several groups have determined false prediction rates by counting all false positives and dividing this number by the total duration of the analyzed recording.[41,45,54,56,63] This definition ignores that for each seizure contained in the recording, there is a preictal period (i.e., the prediction horizon) during which every alarm is counted as a true prediction, and false predictions cannot occur by definition. Other groups have therefore used corrected false prediction rates that were calculated only for the interictal period.[38,39,46,47,51]

In this context it is important to realize that a reported false prediction rate cannot be judged independent from the prediction horizon since in a prospective prediction algorithm a false alarm will leave the patient mistakably awaiting a seizure for the duration of the prediction horizon. It is only after this duration that the patient will know if the alarm was a false warning or not.

Consider as an example[56] an algorithm with a 2-h prediction horizon that yields a sensitivity of 9/11 = 82% of predicted seizures and an uncorrected false prediction rate of 6/41h = 0.15/h. If we take into account that the uncorrected false prediction rate includes the preictal periods during which no false prediction can occur by definition, the corrected false prediction rate (assuming the preictal periods are nonoverlapping) is 6/19h = 0.32/h, thus more than twice as high. If we consider furthermore that after each false prediction, the patient needs to wait for 2 h before knowing if it was indeed a false prediction, the performance of our example (assuming that false predictions are not spaced closer than the prediction horizon) may leave a patient $6 \times 2/19 = 63\%$ of the interictal period waiting for a seizure that will not occur while still failing to anticipate every fifth seizure. An algorithm yielding the same results for a prediction horizon of 10 min would instead leave the patient in futile expectation of a seizure only in 3% of his/her seizure-free time. This example shows that a prediction rate should be judged in view of the prediction horizon used by the algorithm and that it is the product of these two quantities that should be compared across studies.

A better way to assess the specificity of a prediction algorithm would be to report the portion of time from the interictal period (i.e., the interseizure-interval without the preictal period) during which a patient is not in a state of falsely awaiting a seizure.

In general any algorithm can be tuned (e.g. by varying the alarm threshold) to yield a higher sensitivity at the cost of a lower specificity and vice versa. For a closed-loop intervention system, the desired relation between these two quantities will depend on the invasiveness of the intervention technique under consideration. If the intervention does not impair the patient, a higher false prediction rate will be tolerated up to the point where a constant intervention (such as a duty-cycle stimulation from implantable deep brain stimulation devices, cf. Vonck *et al.*)[84] is possible that could be performed without a prediction algorithm.

The problem of in-sample optimization

Another important issue in the evaluation of a prediction algorithm is the use of *a posteriori* information. For a prospective prediction algorithm, this type of information is not available. Two typical cases of using *a posteriori* information are found in the literature: (1) in-sample optimization of parameters of the algorithm and (2) *a posteriori* selection of one or more channels with optimum performance.

In-sample optimization or training of parameters is present whenever parameters used for the calculation of the characterizing measure of the EEG or of the prediction algorithm itself are adjusted to produce optimal performance of the algorithm for a given set of data. Such an optimization is likely to result in an overestimated performance that will not be reproducible when applying the algorithm to other, out-of-sample testing data that was not used in the optimization process. In order to assess the true performance of a prediction algorithm, it is therefore inevitable to test it on out-of-sample data.

Another way of using *a posteriori* information relates to the selection of channels that are able to discriminate an interictal from a preictal state. The great majority of studies have shown that out of the available number of recording channels, only a limited number carry information that can actually be used for the detection of a preseizure state, while the remaining channels are likely to increase the number of false detections without contributing to the detection sensitivity of an algorithm. The task at hand is to decide in advance which channels are best suited for the purpose. While many early studies reported preictal changes in channels within or close to the seizure onset zone,[20–24] more recent ones found channels in more remote, in some cases even contralateral, areas to carry the relevant information.[44,63,64,59,60]

Several studies have attempted to tackle this problem by using the first few seizures to select the appropriate channels and/or parameters for the algorithm before trying to detect precursors of the seizures that follow.[44,53,54,59] Such a procedure implies that the spatio-temporal dynamics preceding a seizure do not change from seizure to seizure. Iasemidis *et al.*[45,56] designed an algorithm using a selection of channels that is readjusted after every seizure such that it would have been optimal for the seizure that has just occurred. Such a procedure is based on the implicit assumption that preictal dynamics change to a certain degree from seizure to seizure, but that the preictal dynamics of a seizure still depend on the dynamics of the previous one. If these algorithms reliably proved to be better than a random prediction, they could, in addition to being beneficial for patients, provide valuable clues for new theories on the mechanisms involved in ictogenesis.

The need for statistical validation

If an algorithm is designed to run prospectively, its quasi-prospective out-of-sample performance can be tested retrospectively on continuous long-term recordings that were not previously used for parameter optimization or channel selection. Once this quasi-prospective performance (in terms of correct alarms and false alarms with respect to the given prediction horizon) has been assessed, it remains to be tested whether it is indeed superior to that of an algorithm working with random prediction. For this aim, Winterhalder and

collegues have designed a framework to assess the performance of such a random predictor.[46,75]

In retrospective statistical studies on predictability, however, it may be desirable to investigate and compare the potential predictive performance of different characterizing measures for various thresholds and parameters. In this case the use of a random predictor for statistical validation would require Bonferroni corrections for multiple testing that can be difficult to perform. Here the concept of seizure time surrogates as introduced by Andrzejak *et al.*[80] can provide a means for statistical validation. In this process, artificial seizure onset times are generated by randomly shuffling the original inter seizure-intervals. Using these surrogate seizure onset times instead of the original onset times, the EEG data is then subjected to the same algorithm or prediction statistics that was used for the original onset times. Only if the performance of the algorithm for the original seizure times is better than the performance for a number of independent realizations of the surrogate seizure times, can the null hypothesis, namely, that a given algorithm cannot detect a preseizure state with a performance above chance level, be rejected. The advantage of this type of statistical validation is that it can be applied to any type of analysis, algorithmic or statistical. A modification of this surrogate test has recently been proposed based on a constrained randomization of the time profile of the characterizing measure.[85]

Future perspectives

Prospective out-of-sample algorithms with statistical validation

The next problem that needs to be tackled by seizure anticipation algorithms is to design algorithms to run (quasi-) prospectively on unknown, out-of-sample data. If the algorithms require a training phase in which some seizures are used to adjust patient-individual parameters and perform a feature or channel selection, the requirements on the individual data sets increase since a larger number of seizures per individual data set will be needed. Performance results should be reported only for the testing data.

Before addressing the question whether an obtained performance might be sufficient for clinical application, it needs to be tested whether a performance is at all better than chance. To this aim, methods for statistical validation are inevitable. These methods can be based either on bootstrapping techniques[38,57,60,80,85] or on the performance of a random prediction process[46,75] derived analytically.

Mechanisms of ictogenesis

While many studies on seizure prediction placed their emphasis on algorithmic prediction, their primary focus of interest was not directed towards the underlying mechanisms of seizure generation. A number of recent studies have attempted to increase our understanding of the dynamics of ictogenesis. Both in temporal lobe and neocortical epilepsies, high frequency oscillations were found to play a role in the initiation of epileptiform potentials and seizures.[86–88] In another recent study on patients with temporal lobe epilepsy, the so-called phase demodulation of intracranial EEG recorded interictally during intermittent electrical stimulation was found to yield important clues for possible dynamical scenarios that lead to seizure onsets.[61] Schiff and coworkers[89] successfully used canonical discrimination analysis to search for dynamically distinct stages of epileptic seizures in humans. A further promising approach is to model EEG signals to gain a better understanding of the mechanisms of ictogenesis.[90,91] For an excellent and detailed review on recent findings in quantitative EEG analysis, refer to Stam.[92]

Given the rather poor performance of the seizure prediction algorithms designed to date, it is likely that a better understanding of the mechanisms involved in seizure generation may stimulate the design of improved methods and algorithms.

Confounding variables

Another key to the improvement of algorithms could be a better understanding of the interictal period and all of its confounding variables that may influence the characterizing measures used in the algorithms and may thereby decrease the algorithm's sensitivity or specificity. Studies on continuous multiday recordings have identified distinct circadian fluctuations of synchronization measures.[85] Particularly different vigilance state, e.g., slow-wave sleep, seem to have a substantial influence on these measures. A further confounding influence on characterizing measures has been described for the blood levels of carbamazepine.[93] Little is known to date about the influence of different cognitive or emotional states.[94] Once the influence of these confounding variables is better understood, it can be taken into account by an algorithm to increase its predictive performance.

Conclusions

The more rigorous methodological design in many recent seizure prediction studies has shown that many of the measures previously considered suitable for prediction perform no better than a random guess.[55,60] On the other hand, evidence has accumulated that certain measures, particularly measures quantifying relations between recording sites as a correlate of interaction between different brain regions, yield a promising performance[56,59,60] that ranges above chance level, as evidenced by rigorous statistical validation.[60]

The few studies that have used prediction algorithms in a quasi-prospective manner (i.e., without the use of *a posteriori* information) either did not include a statistical validation[45,53,56] or did not apply it correctly.[63]

The design and evaluation of prospective seizure prediction algorithms involves numerous caveats that need to be regarded. The current literature allows no definite conclusion as to whether seizures are predictable by prospective algorithms. To answer this question, future studies need to rely on sound and strict methodology and include a rigorous statistical validation.

The next necessary step in the field of seizure prediction will be to test on long-term recordings whether the prediction algorithms devised to date are able to perform better than a random predictor in a quasi-prospective setting on out-of-sample data. This step is an indispensable prerequisite to justify prospective clinical trials involving invasive seizure intervention techniques based on prediction algorithms such as electrical brain stimulation in patients.

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79 Effect of anticonvulsant withdrawal on seizure semiology and ictal electroencephalography

CT Skidmore and MR Sperling

Introduction

Prior to performing epilepsy surgery, an intensive evaluation process is conducted to define the boundaries of the epileptogenic region. Characterizing seizure semiology and the EEG pattern of habitual seizures is a key component of this process. This is typically accomplished through monitoring in a video-EEG unit. It is important to ensure that all relevant seizure types are captured to ensure an accurate diagnosis. Moreover, it is important to make certain that the observed seizures have been accurately assessed, and that the observed EEG and behavioral characteristics are reliable. While the optimal number of seizures that should be recorded is uncertain, many strive to capture at least three typical seizures during hospital admission. This figure, however, depends upon the quality of the EEG recordings, results of other diagnostic testing, number of clinical seizure types, and other factors. While video-EEG monitoring can be accomplished during a brief hospital stay in many patients, those who have less frequent seizures (less then weekly) would require prolonged hospital stays. Since prolonged hospitalization can be emotionally taxing and injurious to patient finances, it is desirable to attempt to minimize hospital length of stay. In addition, there are external pressures from insurance companies for efficient monitoring stays, and the number of available video-EEG monitoring beds is limited. Therefore, any method that can shorten the length of stay can benefit patients, reduce the cost of presurgical investigations, and improve health care access.

For these reasons, various techniques have been utilized in an attempt to temporarily increase seizure frequency, thereby shortening the hospital stay. The most common provocation maneuver is antiepileptic drug (AED) withdrawal. This is generally a safe and effective means for provoking seizures. This chapter will review the data regarding its effect on seizure semiology and ictal EEG.

Effect of AED withdrawal on seizure frequency

Before assessing the effect of AED withdrawal on seizure semiology and ictal EEG, one must determine whether withdrawal truly provokes seizures. Marks *et al.*[1] found a significant increase in seizure frequency when AED levels were subtherapeutic or absent in a study of 35 patients. Marciani *et al.*[2] reported the effects of AED withdrawal on seizure frequency in patients who were monitored on and off AEDs. In 12 of 17 patients who had no seizures on AED therapy, seizures were provoked by AED withdrawal, and in 16 of 23 patients who had baseline seizures there was a clear increase in seizure frequency. So and Gotman[3] reported the seizure rate in three controls and in eight patients whose AEDs were withdrawn. They found a clear increase in seizure frequency during AED withdrawal in comparison with controls, whose seizures occurred less frequently. Several studies demonstrate that carbamazepine (CBZ) withdrawal increases both seizure frequency and the rate of occurrence of secondarily generalized seizures.[4–9] Bromfield *et al.*[10] demonstrated an increase in seizure frequency during phenytoin (PHT) withdrawal, Zhou *et al.*[7] noted no change in seizure frequency during valproate (VPA) withdrawal, and Wang-Tilz *et al.*[11] found an increased seizure frequency during lamotrigine (LTG) withdrawal. Based on these studies and many other reports in the literature, it seems apparent that AED withdrawal increases seizure frequency.

Effect of AED withdrawal on seizure semiology and ictal EEG

Spencer *et al.*[12] reported results in 25 patients who had intracranial EEG monitoring. They compared seizure semiology and ictal EEG before and after the withdrawal of AEDs. They identified four patients who had atypical semiology or ictal EEG onsets during the withdrawal phase; however these patients were already determined to have multifocal or bilateral epileptogenic zones during the baseline phase. One patient had atypical semiology and multifocal onsets, which was different from the baseline phase, however this patient failed surgery after excision of the region from which typical seizures emanated. He was found later to have seizures emanating from the contralateral hemisphere. They concluded that AED withdrawal successfully provoked typical seizures in the majority of patients, and that atypical seizures may suggest a latent multifocal predisposition that may not be surgically remediable. However, after this report Engel and Crandall[13] reported a single patient who had an intracranial bitemporal

implant for seizure localization who had typical seizures emanating from the right temporal lobe and atypical seizures arising from the left temporal lobe. Based on the scalp evaluation and intracranial data he underwent a right temporal lobectomy and was seizure free for 4 years at the time of the report. They cautioned that atypical seizure semiology and ictal EEG data may be secondary to distant hyperirritability secondary to the primary epileptogenic focus or possible direct irritation from the implantation of the depth electrode. In addition to this patient they also commented on four additional patients who had atypical ictal EEG who 'benefited from surgery' and while atypical data is a poor prognostic sign, it should not be an absolute contraindication. Marciani and Gotman[14] reported data from 14 patients who had typical seizures recorded with intracranial EEG while taking stable doses of medication and during drug AED withdrawal. Only one patient had a clinical seizure with altered semiology and ictal EEG onset compared to their baseline seizures. However, this seizure occurred after an insignificant change in a single AED dose and the patient then had several typical seizures during aggressive drug withdrawal. In the remaining patients, seizure semiology and ictal onset in the EEG were not affected by AED withdrawal, even during seizure clusters and secondary generalization. Marks *et al.*[1] reported that five out of 35 patients had atypical clinical seizures during drug withdrawal. Two of these patients were thought to have multifocal disease, and the other 3 had atypical seizures both during the baseline and withdrawal phase, so AED withdrawal was probably not responsible for changes in ictal EEG findings. Seventeen of their patients had intracranial ictal data recorded while taking AEDs and during AED withdrawal. One patient who had a right temporal lesion had a diffuse ictal onset with the first seizure during drug withdrawal, but four other seizures recorded after this had focal onset. One patient missed several doses of clonazepam, apparently by mistake, which resulted in simultaneous neocortical and hippocampal onset. However, once the clonazepam was restarted all the remaining seizures had focal onset in the hippocampus. Bardy[15] reported no change in seizure semiology in 11 patients undergoing AED withdrawal for video-EEG monitoring, and So and Gotman[3] reported that while eight patients with intracranial EEG had more frequent and severe seizures during AED withdrawal, a variety of measures including latency of interhemispheric spread, seizure duration for a given seizure type (i.e., complex partial seizure), and localization were not affected.

Based on these studies, it appears that the overwhelming majority of seizures occurring during AED withdrawal display typical semiology and ictal EEG. However, as noted by Engel and Crandall,[13] the existence of atypical seizures should not necessarily prevent surgery from being carried out. Atypical seizures may signal the presence of a latent epileptogenic focus, but they may either be dependent upon the primary focus or be amenable to AED therapy should it persist after surgery.

Effect of specific AEDs on seizure semiology and the ictal EEG

Most published data address the effect of withdrawal of older AEDs on seizure semiology and the ictal EEG. They do not address how withdrawal of most newer AEDs influence these features. With these constraints in mind, we will attempt to review the information available for each individual AED.

Carbamazepine

Duncan *et al.*[9] and DeToledo *et al.*[6] reported no new seizure types provoked by withdrawal of CBZ. These studies were limited though since they were based on clinical follow-up and not video-EEG monitoring. Zhou *et al.*[7] studied 20 patients taking CBZ and undergoing video-EEG monitoring. They analyzed the presence of hypermotor features, oroalimentary automatisms, hand automatisms, ictal speech, and secondary generalized tonic and/or clonic signs before and after the withdrawal of CBZ, and noted an increased frequency, duration, and intensity of most ictal signs with CBZ withdrawal. However, the scalp ictal onset and initial seizure semiology was not altered by CBZ withdrawal. Spencer *et al.*[12] evaluated eight patients with intracranial EEG before and after the withdrawal of CBZ. Three of these patients were determined to have multifocal or bilateral EEG onset in the baseline and CBZ withdrawal phases. None of the patients with unilateral focal onset had atypical clinical semiology or EEG onset. However two of the patients with multifocal disease had atypical EEG onset captured during drug withdrawal.

Valproate

Duncan *et al.*[9] reported no new seizure types in 25 patients undergoing VPA withdrawal. However, this was an outpatient study without video-EEG correlation. Zhou *et al.*[7] evaluated 13 patients taking VPA with video-EEG monitoring. They found no effect on seizure frequency or seizure intensity, but seizure duration was increased. They did report that the amounts of hypermotor components of the seizures were increased, but initial ictal signs and EEG onset were unchanged.

Phenytoin

Duncan *et al.*[9] reported no new seizure types in 22 patients withdrawn from phenytoin (PHT) as outpatients. Spencer *et al.*[12] reported two patients who were studied with intracranial EEG before and after PHT withdrawal. One patient had multifocal EEG onset and the other had bilateral EEG onset during baseline and withdrawal phases. Although new seizure types were not captured during the withdrawal phase, the patients did not have unilateral focal disease, and it is difficult to assess the effect of PHT withdrawal on ictal EEG and semiology.

Phenobarbital/primidone

Spencer *et al.*[12] evaluated four patients on phenobarbital (PB) and one patient on primidone (PMD) with intracranial EEG before and after AED withdrawal. One patient on PB had focal ictal EEG onset and clinically typical seizures before and after withdrawal of PB. A second patient had a typical clinical seizure with EEG onset in the right temporal lobe in the baseline phase, but had atypical clinical and electrographic

seizures during PB withdrawal. This patient was later found to have seizures emanating from the left hemisphere, as described previously. The other two patients had multifocal or bilateral disease and both had atypical seizures on EEG compared to the baseline phase. One of the patients also had atypical clinical seizures during drug withdrawal. Only one patient had seizures during the baseline and withdrawal phases on PMD, and this patient did not have any atypical seizures or ictal EEG onsets.

Lamotrigine

Wang-Tilz *et al.*[11] noted an increased seizure severity and duration with LTG withdrawal, but no definite increased frequency of secondary generalized seizures. The ictal EEG onset and initial seizure semiology was not altered by LTG withdrawal.

Risks associated with AED withdrawal

The concern about quality and character of seizures observed during drug withdrawal is more than matched by a concern about safety. If drug taper provokes more frequent and severe seizures, it may be associated with an increased risk of complication. Several possibilities exist, including secondary generalized tonic-clonic seizures, status epilepticus, neuronal injury, cognitive impairment, and bodily injury.

Status epilepticus perhaps raises the most concern, but its incidence during controlled AED withdrawal in a hospital setting is apparently quite low. In several studies of patients monitored with video-EEG before and after AED withdrawal, there were no reported cases of status epilepticus.[2,7,11,16,17] This could be due to the existence of protocols to treat seizure clusters and prolonged generalized tonic-clonic seizures early in their course, or due to under-reporting of status epilepticus. There are numerous reports of an increased incidence of seizure clusters during AED withdrawal, and some of these might fulfill criteria for status epilepticus. The incidence of clusters varies from study to study as do the definitions of a seizure cluster. Marks *et al.*[1] defined seizure clusters as >3 seizures within a 48-hour period. They reported seizures clusters in four patients on stable AED therapy and in 18 patients during AED withdrawal of 35 patients. Yen *et al.*[16] defined seizure clusters as >3 per 24-hour period, and reported that approximately 50% of their patients (n=102) experienced at least one seizure cluster during video-EEG monitoring with aggressive AED withdrawal. In our experience, status epilepticus can occur during drug taper, and the incidence ranges between half and one percent. We have observed tonic-clonic, tonic, complex partial, and absence status during drug withdrawal. In part, distinguishing between a seizure cluster and status epilepticus can be difficult, but when a series of seizures occur without full return of neurological function between the seizures,[18] it is reasonable to diagnose status epilepticus. Hence, it is our belief that some patients who have been reported as having had seizure clusters probably had brief bouts of status epilepticus.

Secondarily generalized seizures may either occur de novo or increase in frequency during drug withdrawal. These have the potential of causing morbidity such as lacerations and other trauma, bone fractures, aspiration, and cognitive impairment. It is particularly concerning when patients with no prior history of secondarily generalized seizures or who have only rare secondarily generalized seizures have them during the evaluation. Most studies report an increase in the frequency of secondary generalized seizures during AED withdrawal.[2,7,11,16] This appears to be especially true for CBZ withdrawal,[2,4,7,8,11] but is also reported for phenytoin.[2,4,10] The occurrence of new secondarily generalized seizures or the re-emergence of secondary generalized seizures in patients who had them rarely occurred in 9% of patients studied by Yen *et al.*[16] and in 3/20 patients studies by Wang-Tilz *et al.*[11] There is no data documenting that lamotrigine, valproate, or primidone withdrawal increase the frequency of secondarily generalized seizures,[2,7,11] but it seems intuitive that it must happen at times; indeed, we have occasionally seen this phenomenon with these drugs at our institution. In contrast, Swick *et al.*[17] found no correlation between AED withdrawal and the occurrence of secondary generalized seizures, and found that the only predictor of their occurrence was a prior history of secondary generalized seizures. However, this does not comport with the rest of the literature, nor our experience.

Other complications are infrequent, but have occurred on occasion. We have observed a brachial plexus injury with persistent limb paresis after a de novo secondarily generalized seizure in one patient, several bone fractures, a few shoulder dislocations, bruising, and many severe tongue and cheek bites. In addition, after secondarily generalized seizures or clusters of complex partial seizures, many patients have reported memory defects that have lasted for up to several weeks. On the other hand, patients occasionally experience injury as a consequence of seizures when AED doses have not been altered. Therefore, how much drug taper increases risk cannot be known without a randomized study, which has never been performed and likely never will be done.

Conclusion

AED withdrawal is an effective means of temporarily increasing seizure frequency in epilepsy monitoring units to ensure that an adequate number of seizures are recorded for diagnostic purposes. Drug withdrawal generally seems to lead to seizures that can be confidently analyzed as part of the presurgical evaluation process. Concerns that drug taper may provoke atypical seizures appear largely unjustified, and most data suggest that this phenomenon, if it occurs, is rare. Data regarding the effects of drug withdrawal is needed for many AEDs that came into use in the 1990s and afterward, but our clinical experience suggest that there is probably no difference compared with older drugs. The major disadvantage appears to be the provocation of seizure clusters and secondarily generalized seizures, which pose risk to the patient. Risk can be averted or reduced when epilepsy monitoring units employ clinical protocols for aggressive medical treatment when an unusual number of seizures or unusually severe seizure occurs. This may prevent the development of status epilepticus or injury. We advise that treatment be implemented automatically. Physicians should place orders in the hospital chart to initiate therapy once a certain predetermined seizure threshold is

reached in advance of problems developing, so that effective treatment is not delayed. Depending upon the type of seizure and how frequently seizures occur, one of several options can be used. Either one can prescribe a large dose of the oral agent that was being tapered, give an oral dose of a benzodiazepine, or administer an intravenous dose of a benzodiazepine.

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80 Zone of electrical stimulation induced seizures in subdural electrodes

R Schulz

Definition of zone of electrical stimulation induced seizures

Electrical stimulation of the cortex can elicit afterdischarges (ADs), subclinical EEG seizure patterns, auras (SIA), and clinical seizures (SIS). Auras and clinical seizures can occur with nonhabitual or habitual symptomatology. Electrical stimulation takes place extraoperatively with implanted electrodes (subdural grid electrodes or depth electrodes), or intraoperatively by the neurosurgeon using stimulation electrodes. The area of responses can be defined as the zone of electrical stimulation induced seizures (ZESIS). The actual ictal onset zone as defined by spontaneous seizures is not always congruent with ZESIS so that ZESIS also includes cortex which is potentially epileptogenic, e.g., after the surgical removal of the actual seizure onset zone or pacemaker zone.

From a historical perspective, SIA and SIS have been important in cortical localization since Fritsch and Hitzig discovered the irritability of the cortex using electrical stimulation in animals.[1] Seizures were induced by electrical stimulation, by mechanical palpation of the brain during surgery, by local or systematic application of drugs, and by peripheral stimulation (e.g., photic stimulation). During the first decades stimulation concentrated on the motor cortex. Cortex outside the central region was mostly disregarded. Fritsch and Hitzig stimulated the motor cortex and elicited epileptic seizures with increased stimulation intensity. They strongly influenced Jackson who focused his studies on the semiology of unilateral motor seizures. Jackson argued that local symptoms like cloni of an arm imply a local lesion of the brain. Jackson also coined the term 'variety of epilepsy' for seizures characterized by 'dreamy states'.[2] Krause used the term 'petit mal' for seizures lasting only a few seconds regardless of the semiology, including auras, tonic seizures, and absences.[3] Cushing assumed that the epileptogenic zone could be identified through auras elicited by electrical stimulation of the cortex when he wrote that in the future it would be possible 'to pick out with an electrode areas of the brain from which the sensory aura of a focal convulsion has originated' and speculated that this methodology would eventually lead toward 'operative localization of subcortical irritative lesions of the immediate postcentral field.' When mentioning subcortical lesions he was referring to lesions which cannot be detected by intraoperative inspection.[4]

Foerster was the first to use extensive stimulation outside the central cortex and reported on somatosensory, auditory, olfactory, gustatory, visual SIA, and prefrontal SIS.[5] Foerster and Penfield reported the provocation of habitual seizures and auras by mechanical irritation and by stimulation with faradic current in a summery of 12 cases.[6] In their stimulation studies, they carefully documented responses from the primary sensory and motor area and the occurrence of SIA and SIS. Furthermore, they outlined the visible epileptogenic lesion and the borders of the resections. In six of 12 cases (50%) the patient's habitual seizure or aura was elicited by electrical stimulation. In two patients the cortical area with SIA or SIS was located within the epileptogenic lesion, in four patients the cortical area with SIA or SIS lay close to the epileptogenic lesion (1 cm or less). In all six patients the cortical area from which a habitual aura or seizure was elicited was resected together with complete removal of the epileptogenic lesion. Apparently Foerster assumed that the area with SIA was part of the epileptogenic zone which had to be resected to achieve seizure freedom.

The initiative to develop epilepsy surgery further was taken by Penfield after the foundation of the Montreal Neurological Institute in 1934. In a study relating the Montreal experience, intraoperative stimulation reproduced habitual auras in 44 out of 80 patients (55%) with nontumoral parietal lobe epilepsy, in ten out of 25 patients (40%) with tumoral parietal lobe epilepsy[7], and in 37% of 29 patients with occipital lobe epilepsy.[8] Some of the patients with SIA are illustrated in detail in Penfield and Jasper's compendium 'Epilepsy and the functional anatomy of the human brain'.[9]

Penfield and Jasper[9] considered SIA to be an important criterion for delineating the limits of resection: 'Electrical stimulation is the original method of initiating focal cortical epileptic discharge, and is still one of the best.' They carefully adjusted the stimulus intensity to initiate local discharges in a very restricted area of cortex: 'Areas most susceptible to afterdischarges, especially if associated with the aura or onset of the patient's seizure, indicate a hyperirritable cortex which may be the focus of spontaneous epileptic seizures.' Penfield and Jasper also commented on SIA/SIS after spread from a distant source, suggesting that the SIA/SIS zone rarely leads to false assumptions about an epileptogenic region in silent cortex: 'Volleys of nerve impulses arriving in a hyperirritable area of the cortex from different distant sources may serve to initiate epileptiform discharge in a manner similar to the direct stimulation of a hyperirritable cortex.' In one of their

documented cases, they commented that 'distant stimulation had its effect by means of neuronal conduction along connecting pathways.' But they mostly found a convergence of irritative and SIA/ SIS zone: 'In the majority of cases, however, there is a close correlation between a spike focus and the area of susceptibility to prolonged afterdischarges. … There is also fairly good correspondence between the area of prolonged afterdischarges and the site from which the aura or onset of the attack was reproduced by electrical stimulation.' In most cases the SIA zone was resected.

In summary, Penfield and Jasper already discussed the present opinion of hyperirritable cortex – as documented by SIA/ SIS, afterdischarges, and interictal spikes – which in a minority of cases can also be triggered over a distance via connecting pathways of propagation.

In 1954 Foerster, Penfield, and Jasper had used and had further developed the diagnostic means of the EEG in epilepsy surgery. Since that time brain imaging has considerably changed the diagnosis of the epileptogenic lesion so that preoperative, noninvasive detection is now possible in most cases in contrast to the previous reliance on EEG and, during surgery, inspection, electrocorticography, and assessment of SIA/ SIS.[10,11] On the other hand, depth electrodes and subdural grid electrodes were essential in further contributing to the evolution of EEG and they now permit prolonged extraoperative evaluations with assessment of interictal and ictal EEG, mapping of functional cortex, and systematic registration of SIA, ADs, and SIS.

Defining ZESIS with subdural grid electrodes

The technology and evaluation with subdural grid electrodes (SDE) in general have been outlined in Section 7 of this book. SIA and SIS occur as a by-product of electrical cortical stimulation for functional mapping. The stimulation current is increased in steps of 0.5–2 mA up to the maximum intensity of 15 mA or to the occurrence of functional responses, SIA or SIS. To discern accidental auras or seizures we usually only include SIA/SIS which occur more than once. To avoid eliciting a seizure after the first SIA at a given electrode we usually reduce the following stimulation current by 1 mA and stop the stimulation at this electrode after occurrence of the second SIA. SIA/SIS should occur without afterdischarges to exclude the triggering of remote cortical regions and make localization as precise as possible. On the other hand, the facilitation of pathways to a more distant pacemaker zone for auras and seizures indicates the irritability or epileptogenicity of all neurons involved.

The threshold of afterdischarges (ADs) is low, especially in the primary motor and primary sensory areas (M1, S1),[12] with easy triggering of a nonhabitual seizure semiology.[13] The delineation of ADs and subclinical EEG seizure patterns is often not possible. Indeed, the EEG glossary of the International Federation of Clinical Neurophysiology defines ADs as EEG seizure patterns induced by electrical stimulation.[14] Inoue and co-workers presented the EEG example of right temporal repetitive ADs with decreasing frequency, of 70 s duration, accompanied 30 s later by a contralateral, left temporal EEG seizure pattern and a habitual clinical seizure in a patient with left mesial temporal lobe sclerosis.[15] In this case, the morphology of the EEG pattern with large-amplitude, low-frequency epileptiform discharges (similar to PLEDS), immediately after stimulation suggests ADs; the evolution of the frequency, however, suggests an EEG seizure pattern. The left temporal EEG seizure pattern was identical to the EEG pattern in spontaneous habitual seizures, clearly different to ADs. Obviously, there are gradual shifts in the epileptogenicity from ADs to clear-cut EEG seizure patterns. The threshold of ADs varies from day to day and even from stimulation to stimulation.[16] To minimize ADs, antiepileptic medication is kept at a high level and often benzodiazepines are used.

Afterdischarges, subclinical EEG seizure patterns, SIA, and SIS contribute to ZESIS. To our knowledge, systematic studies about the diagnostic value of ADs and stimulation-induced subclinical EEG seizure patterns in defining the epileptogenic zone do not exist.

In a retrospective and prospective study of 31 patients, we evaluated the value of SIA in defining the extent of the epileptogenic zone.[17] Sixteen of 31 patients (52%) had SIA. The epilepsy syndromes were classified as follows: frontal lobe epilepsy eight, parieto-occipital lobe epilepsy three, temporal-lobe epilepsy three, perirolandic epilepsy one, and nonlocalizable focal epilepsy one. In three patients the habitual first subjective sign of the seizure was not an aura in the strict sense of the term but a sensation of movement of an eye, a sensation of clonic jerks on one side of the mouth, or the inability to speak (aphasic seizure). SIA were elicited at one to 20 electrodes per patient (mean 4.8). SIA occurred on stimulation above the epileptogenic lesion in 75% of the patients (12 out of 16), in three patients 1 cm from the lesion, in one patient 2 cm from the lesion. The zone of SIA overlapped with the EEG seizure onset zone in 75% of the patients (12 out of 16); in three patients the EEG seizure onset zone was 1 cm away, and in the other patient SIA were located on the convexity of the cortex whereas the EEG seizure onset was on the mesial plate adjacent to the opposite limits of the lesion. Overlap of the SIA zone with the irritative zone of interictal spikes was observed in only 50% of the patients (eight out of 16).

Relating surgical outcome to complete or incomplete resection of the epileptogenic lesion, the EEG seizure onset zone, the SIA zone, and the irritative zone of interictal spikes we found a significant correlation of surgical outcome only with the total removal of the epileptogenic lesion. Complete or incomplete resection of the EEG seizure onset zone, the SIA zone or the irritative zone did not permit prediction of the surgical outcome. However, the value of resecting the other zones in addition to the lesion could not be established because the number of patients was too small for statistical analysis with stepwise logistic regression.

De Salles and co-workers reported a small series of 12 patients with invasive diagnosis using subdural strip electrodes. In eight patients cortical stimulation was performed.[18] The authors argued that

> confirmation that with intracranial recordings was important for the final decision of resection, especially for the patient who experienced speech arrest, usual seizures and aura during cortical stimulation. …

Cortical stimulation confirmed the seizure focus by inducing the usual seizures or aura in 75% of the patients undergoing electrical stimulation.

Surgical results were not mentioned in this study.

Defining ZESIS intrasurgically

Although extensive intrasurgical stimulation of the cortex for cortical mapping of eloquent areas was standard procedure in earlier days of epilepsy surgery, it is the exception nowadays and mostly confines itself to a definition of the language areas (Broca, Wernicke) or the primary motor cortex. The registration of SIA requires stimulation while the patient is awake. Anesthesia is demanding for both the patient and physician under these circumstances and as a consequence is applied only when the insertion of subdural grid electrodes is not possible and when functional mapping of language is necessary.

The stimulation parameters are largely identical to extraoperative stimulation. We usually start at a current intensity of about 7 mA and increase in steps of 1–2 mA up to 15 mA. Instead of stimulation tweezers we use subdural strips so that the registration of ADs is also possible. After the occurrence of ADs stimulation is stopped to avoid the risk of SIS of the wakeful patient during surgery. The stimulation protocol has to take place within 1 hour or less, resulting in considerable time pressure so that SIA only rarely occur.

Conclusions

The definition of ZESIS in SDE is usually a by-product of cortical mapping for language areas. The mapping of somatosensory and motor cortex is mostly done by SSEP and MEP during surgery and under considerable time pressure so that SIA/SIS rarely occur. Consequently only small evidence exists about the relative value of ZESIS versus other zones (e.g., lesion zone, irritative zone of interictal spikes or ictal EEG onset zone) with regard to postoperative seizure prognosis. Electrical stimulation is not undertaken merely for the definition of ZESIS because of possible complications of the implantation of SDE. On the other hand, neurologists and neurosurgeons will take the knowledge gained about a ZESIS together with other relevant information into consideration to delineate the borders of resection. A ZESIS in close vicinity to an epileptogenic lesion, with good convergence of the irritative and ictal onset zone, will be resected in most cases. A ZESIS with some distance to the epileptogenic lesion raises the doubt of propagation within a hyperconnective epileptogenic network and will often not be resected.

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SECTION 8

The epileptic lesion

81 The epileptogenic lesion: general principles

HM Hamer and S Knake

Concept of the epileptogenic lesion

The most common cause of focal epilepsies is a morphological brain abnormality, the epileptogenic lesion. The concept of the epileptogenic lesion, however, is not without difficulties. Any alteration of the brain that can be identified by the pathologist could be considered an epileptogenic lesion but for the purposes of clinical practice, an epileptogenic lesion usually refers to a cerebral abnormality detected by invivo neuroimaging or by the surgeon. This concept was established with the introduction of CT scans but the development of magnetic resonance imaging (MRI) had the greatest impact on neuroimaging in epilepsy. The most frequent pathologies identified in partial epilepsy are hippocampal sclerosis (HS), vascular malformations, tumors, and malformations of cortical development (MCD). MCD constitute a large group of cortical malformations with distinct histopathological abnormalities revealing variable degrees of epileptogenicity.

Establishing the etiology early in the course of epilepsies helps defining the prognosis and has the advantage to determine the possibility or even necessity of surgical treatment in the future. A potentially epileptogenic lesion detected by neuroimaging is predictive of good surgical outcome in frontal as well as in temporal lobe epilepsies.[1–3] However, imaging of epilepsy patients can be challenging, since epileptogenic lesions frequently are small and difficult to detect. Moreover, their extent may be underestimated by MRI studies which is especially true in patients with MCD.[2,4]

Relationship between epileptogenic lesion and epileptogenic zone

The presence of a structural lesion on imaging of epileptic patients usually implies that the epileptogenic zone comprises the lesion or lies in its immediate vicinity. However, the relationship between a lesion seen on imaging studies and the epileptogenic zone may be complex. Cortex extending far beyond the epileptogenic lesions seen on MRI studies, such as MCD or post-traumatic gliotic lesions, may appear normal on imaging but abnormal at a microscopic level and may be part of the epileptogenic zone. In noninfiltrating lesions, such as vascular malformations, the epileptogenic zone includes frequently the adjacent cortex. In cavernous hemangiomas, the main underlying mechanism for seizure generation is most probably pathologic changes in the surrounding tissue due to hemosiderin deposits. On the other hand, postencephalitic lesions demonstrated by MRI were often widespread and even discordant to the seizure onset zone.[5,6] This supports the observation that even incomplete removal of an assumingly epileptogenic lesion rendered a minority of patients seizure free.[7]

Not every lesion detected on structural imaging necessarily represents the epileptogenic lesion (Figure 81.1) and there is no definite way to predict by structural imaging to which extent the lesion identified on MRI overlaps with the epileptogenic cortex. Therefore, detailed video-EEG monitoring is required to establish the relationship between the structural lesion seen on imaging studies and the irritative and seizure onset zone. In selected cases, invasive recordings are necessary to achieve this goal. As a rule, the lesion can be considered epileptogenic, when irritative and seizure onset zone are overlapping with the lesion or are in the immediate neighborhood.

If cortical areas which harbour the seizure onset zone but extend beyond the lesion are included in the resection, a better postoperative outcome was found as compared to simple lesionectomy.[8] This confirms studies which showed that pure lesionectomy is associated with poorer outcome than 'epilepsy surgery' in a variety of etiologies.[9] However, there are no convincing data to assume that the pathophysiology of epilepsy is the same for all different epileptogenic lesions nor is there reason to expect the postoperative prognosis to be the same.

Magnetic resonance imaging (MRI)

MRI is clearly the most important imaging modality to detect structural cerebral abnormalities. Imaging strategy, quality and image interpretation have a major impact on the likelihood of detecting a lesion. Prior clinical and test information can assist in defining the possible location of the epileptogenic zone and should guide the MRI examination. Patients in whom a focal neocortical epilepsy is suspected should be imaged with a protocol that includes whole head thin-sectioned high-resolution 3D T1-weighted and T2-weighted images and should also comprise a gradient echo T2 sequence. If mesial temporal epilepsy is suspected, the protocol should include high-resolution images scanned perpendicularly to the axis of the hippocampus to detect primary and secondary signs of hippocampal sclerosis. T1-weighted, T2-weighted and FLAIR sequences are usually employed.

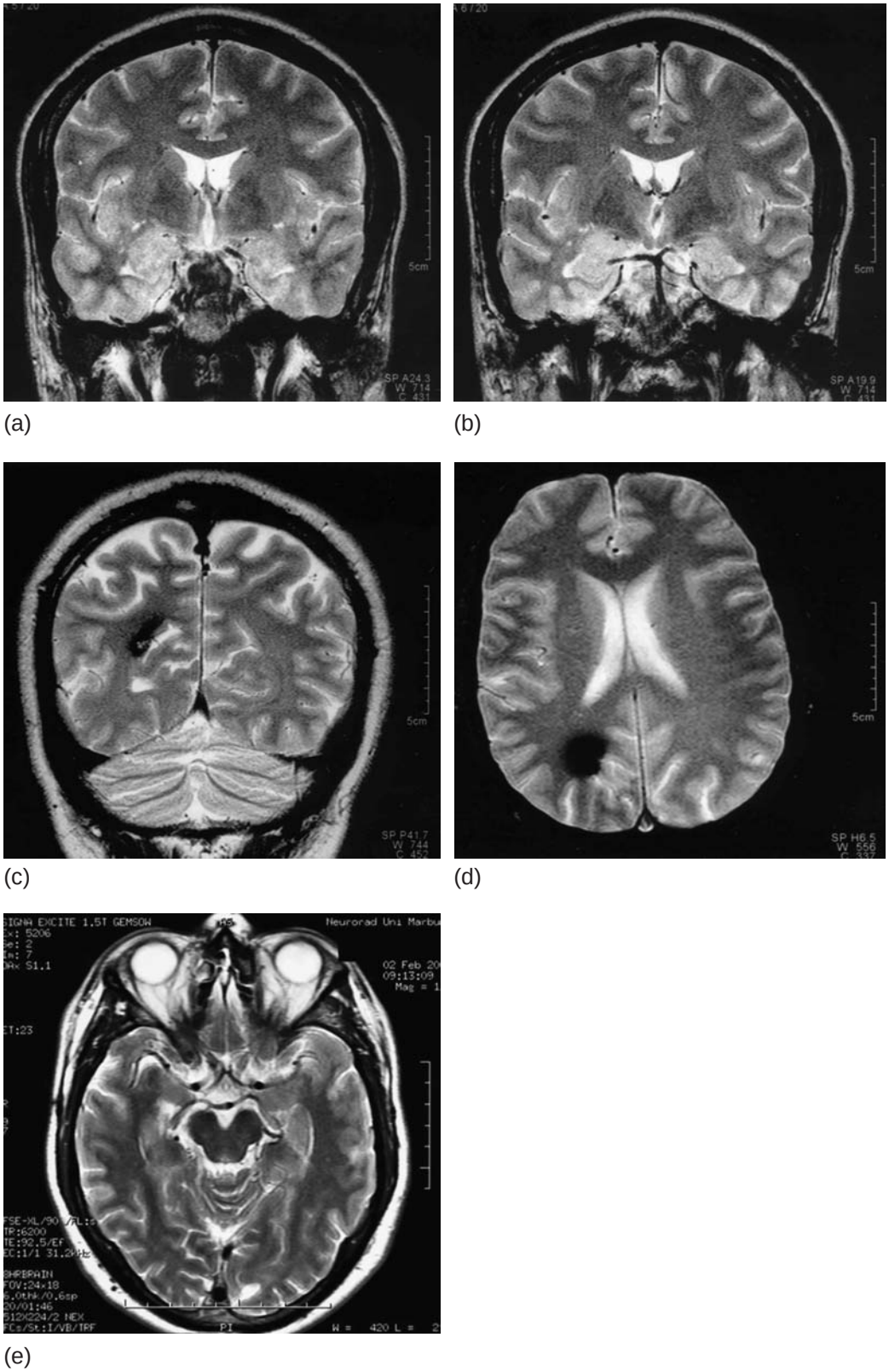

Figure 81.1 35-year-old patient with medically refractory right hemispheric epilepsy leading to automotor seizures. Dual pathology was seen on MRI (hamartoma in the right amygdala (a, b), which was not detected on the first routine MRI and right parietal cavernous hemangioma (c, d). Video-EEG monitoring revealed right anterior temporal seizure patterns and interictal sharp waves exclusively recorded maximal in the right sphenoidal electrode which localized the seizure onset and irritative zone to the hamartoma. The patient remained seizure free after selective removal of the hamartoma (e).

Scans through the rest of the brain should be analysed carefully to rule out dual pathology.

Recent improvements in MRI have greatly increased the preoperative ability to identify epileptogenic lesions and to define their extent and nature. Image quality is generally enhanced by increasing the signal to noise ratio (SNR) available in a given scan time. The SNR can be improved in MRI by replacing the standard quadrature head coil by phased array (PA) surface coils and by going to field strengths higher than 1.5 T (Figure 81.2).[10] These improvements increased lesion detection in patients with focal epilepsy.[11] Phased array studies should particularly be considered in patients with focal epilepsies and medically refractory seizures.

Additional developments in MRI techniques and image sequences, such as magnetisation transfer imaging,[12] or double inversion recovery,[13] have enabled further identification of abnormalities in patients in whom conventional MRI did not isolate a cause for focal seizures.[14] Presurgical detection of brain lesions permit estimation of the spatial relationship of epileptogenic cortex to eloquent cortex and, if necessary, allow a more targeted placement of intracranial electrodes.[11] Besides, the use of modern MRI in conjunction with stereotactic neurosurgery provides the opportunity to correlate the operating field with rendered views of the images acquired preoperatively and, thus, helps to tailor the resective procedure.

However, there is still a subset of patients whose focal lesions will not be detected even by best quality neuroimaging and an experienced reader. Imaging research is directed to such patients. Advanced techniques in postacquisition processing analysis such as diffusion tensor imaging,[15,16] cortical thickness analysis,[17] automated subcortical volumetry, cortical parcellation or statistic parametric mapping[18–20] are innovative techniques whose potential to better define areas of structural brain abnormalities especially in so far 'nonlesional' patients is currently explored.

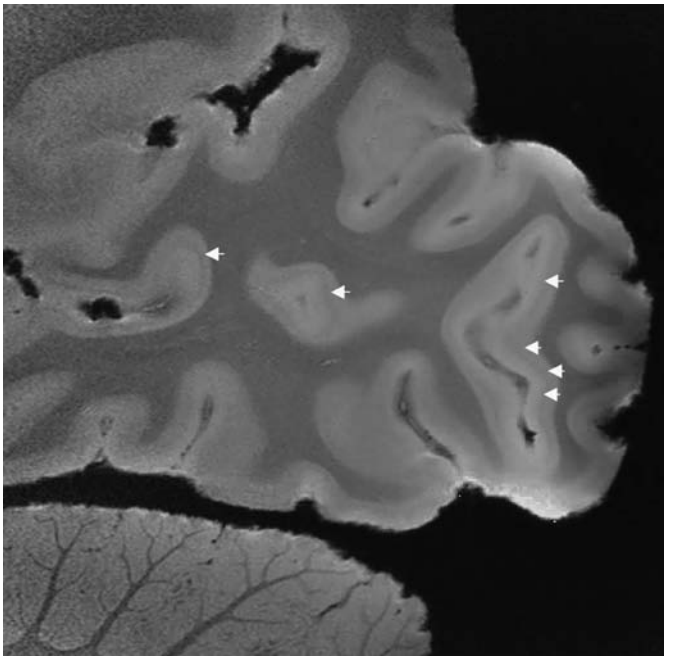

Figure 81.2 Ex vivo MRI of a healthy human brain, scanned at 7T using a 5-cm 1-channel surface-coil. The image is an average of four 1-hour runs of a 3D flash sequence (320 × 512 × 512, 120 µm isotropic voxel, TR/TE/flip 30 ms/4.5 ms/10 ms). The occipital pole and the superior part of the cerebellum are shown in great detail. In the occipital cortex, the stria of Gennari can be seen (arrowheads). The image quality and details give an outlook about future imaging possibilities, making it possible to detect even subtle pathologies. (Image courtesy of Lawrence L. Wald, PhD, A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Dept. of Radiology, Charlestown, MA.)

Electroencephalography

In general, the EEG plays only an ancillary role to identify the nature of the epileptogenic lesion. There is one report that found interictal epileptiform discharges in patients with mesial temporal lobe epilepsy due to hippocampal sclerosis to be highly restricted to the anterior temporal region while patients with mesial temporal tumors showed more widespread interictal discharges.[21] There is also evidence that continuous, rhythmic spiking on a slow background activity which is not associated with behavioral changes is characteristic although not pathognomonic for focal intrinsically epileptogenic cortical dysplastic lesions.[2,22,23]

Electroencephalography, however, is an essential tool to proof the epileptogenicity of a lesion seen on MRI (Figure 81.1). As mentioned above, the existence of a MRI-visible lesion in a patient with epilepsy does not proof its epileptogenicity. Video-EEG monitoring is necessary to demonstrate this relationship. Seizure semiology has to be consistent with the location of the lesion and the EEG defined irritative and seizure onset zone are usually required to overlap with the lesion or the immediate neighborhood. The same methodology is used when two or more lesions are detected in neuroimaging (Figure 81.1), such as patients with multiple cavernous hemangiomas or tuberous sclerosis. In selected cases invasive recordings are necessary to define the epileptogenicity of a lesion or the exact borders of the epileptogenic zone if the extent of the lesion is difficult to define by neuroimaging, such as in patients with MCD, or if it is unclear to what extent the adjacent cortex is responsible of the focal epilepsy.[24]

Magnetic resonance spectroscopy (MRS)

Magnetic resonance spectroscopy investigates cerebral metabolites, pH and some neurotransmitters. MRS provides an indirect, noninvasive tool to measure the integrity and function of neuronal tissue. Most clinical studies use ^{1}H-MRS at 1.5 T scanners with spatial resolutions between approximately 1 and 8 cc depending on whether multivoxel or single voxel techniques are applied. ^{1}H-MRS provides biochemical information about neuronal function (N-acetyl aspartate), membrane turnover (choline), total energy stores (creatine) as well as the presence of cerebral lactate.[25] The sensitivity and specificity of pathological findings in MRS in patients with temporal lobe epilepsy ranges from 60[26] to 90%[27] with higher spatial resolution spectroscopic imaging techniques reporting greater sensitivity and specificity.[28] Especially in patients with unremarkable structural imaging, MRS may be helpful to

delineate the epileptogenic lesion. However, it has been reported, that the ^{1}H-MRS signal may also be modified by recent seizure activity,[29,30] by antiepileptic medication or by metabolic interventions such as the ketogenic diet.[31,32,32] Therefore, results should always be interpreted with caution and in the clinical context. The usefulness of MRS in the presurgical evaluation has not yet been fully determined and its clinical application is still very limited.[25]

Positron emission tomography (PET)

Positron emission tomography using desoxyglucose (FDG-PET) demonstrates areas of reduced glucose metabolism, which are characteristic for the interictal state of the epileptogenic zone but usually extend beyond it.[33] It may be useful in temporal lobe epilepsy for lateralization. However, results in extratemporal lobe epilepsy have been less favorable.[4] FDG-PET has been applied as an ancillary technique to identify the epileptogenic lesion in a certain subset of patients, such as patients with MCD or tumors unseen by MRI at its present state.[34]

More promising than FDG-PET may be PET studies which explore various neurotransmission related with epileptogenesis and thus, delineate better the extent of the epileptogenic zone. Benzodiazepine receptor ligands, such as flumazenil (FMZ), are found to be reduced in the epileptogenic zone and FMZ-PET images were more sensitive than FDG-PET to define the epileptogenic zone.[4,35,36] FMZ-PET allowed lateralisation and localisation of seizure onset in MRI negative patients suffering from frontal lobe epilepsy.[37] Tryptophan PET was reported in one study to differentiate between epileptogenic and nonepileptogenic tubers in patients with tuberous sclerosis.[35] However, the lack of large multicentric and controlled studies, evaluating the impact of PET, represents a major limitation to a better understanding of the clinical role and utility of PET in epilepsy.[38]

Conclusions

MRI is generally the imaging technique of choice for identifying the structural basis of focal epilepsies. This is important for the diagnosis of focal epilepsies, the determination of therapeutic options and the prognosis in general[39] as well as in respect to epilepsy surgery.

Clinical and electrographic information on the possible location of the epileptogenic zone often helps to target imaging studies properly. Recent developments in MRI techniques and advanced postacquisition processing techniques further improved the sensitivity of MRI but there is still a subset of patients with focal epilepsy and unremarkable MRI.

Not every lesion seen on imaging studies is epileptogenic and the relationship between the structural abnormalities on MRI and the epileptogenic zone can be complex. Therefore, correlation with clinical and electrophysiological data is mandatory. In addition, MRS and PET can help to define this relationship. The usefulness of novel MRI, MRS and PET techniques for assessment of patients MRI-negative with standard techniques is not clear yet because only few studies have directly compared the different imaging techniques in large samples or related the findings to postoperative outcome.

Currently, a combination of different imaging modalities tailored specifically for each patient appears to be most appropriate to improve postoperative seizure control and reduce postoperative impairment through more accurate identification of the epileptogenic lesion, surrounding eloquent cortex, the epileptogenic zone, and vital connections between cortical areas. In addition to their use in the presurgical planning, these methods may reduce the need for invasive techniques in the future.

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82 Magentic resonance imaging in epilepsy: mesial temporal sclerosis

GD Cascino

Introduction

Partial or localization-related epilepsy is the most common seizure disorder.[1–3] Over 90% of the incident cases of epilepsy in adults experience partial seizure activity.[1,2] The most frequently occurring seizure type in the adult patient is a complex partial seizure of mesial temporal lobe origin.[1–3] Approximately 45% of patients with partial epilepsy will experience medically refractory seizures that are physically and socially disabling.[1] A minority of patients who fail to respond to first-line antiepileptic drug (AED) therapy will be rendered seizure free with newer medical treatments introduced in the past decade.[4–6] Less than 10% of patients will have a medically responsive seizure disorder if habitual seizures persist with the initial two or three AED medications. Epilepsy surgery is an effective and safe alternative form of therapy for selected patients with intractable partial epilepsy.[1,2,7–12] Patients with medial temporal lobe epilepsy and lesional epilepsy may be favorable candidates for epilepsy surgery and have a surgically remediable epileptic syndrome.[2,7,8] Surgical treatment compared favorably, i.e., more effective in reducing seizure tendency, to AED medication in a randomized controlled trial evaluating medical and surgical therapies in 80 patients with temporal lobe epilepsy. The majority of these patients experience a significant reduction in seizure tendency following surgical ablation of the epileptic brain tissue.[7–16] The hallmark pathology of medial temporal lobe epilepsy is mesial temporal sclerosis (MTS).[17,14,16–18] The surgically excised hippocampus in these patients almost invariably shows focal cell loss and gliosis.[13,14,16–18] This entity is also referred to as hippocampal sclerosis, although, the pathological findings characteristically extend to the amygdala, subcortical white matter, and entorhinal cortex. Patients with lesional epilepsy may have a primary brain tumor, vascular anomaly or malformations of cortical development (MCD).[10,11,14,15,18] The common surgical pathologies encountered in patients with lesional epilepsy include a low-grade glial neoplasm, gangliogliomas, dysembryoplastic neuroepithelial tumors (DNETs), cavernous hemangioma and focal cortical dysplasia.[10,11] Individuals with mesial temporal sclerosis and lesional pathology usually have an abnormal structural magnetic resonance imaging (MRI) study and the seizure types are classified as substrate-directed partial epilepsy.[2,10,18–20] Other MRI-identified structural abnormalities that may indicate the localization of the epileptic brain tissue include focal encephalomalacia related to a prior traumatic brain injury, cerebral infarction or intracranial hemorrhage. The MRI in these individuals may detect a specific intra-axial structural abnormality that may suggest the likely site of seizure onset and the surgical pathology.[20] MRI has a pivotal role in the selection and evaluation of patients for alternative forms of therapy.[7,10,13,16–18] The rationale for the presurgical evaluation is to identify the site of ictal onset and initial seizure propagation, i.e., epileptogenic zone, and determine the likely pathological findings underlying the epileptic brain tissue.[12,13] In patients with an MRI-identified foreign-tissue lesion or unilateral mesial temporal sclerosis the purpose of the electroclinical correlation is essentially to confirm the epileptogenicity of the structural abnormality.[13,15,16,18] The demonstration of concordance between the pathological substrate and the ictal onset zone indicates a highly favorable operative outcome in selected individuals. Approximately 80% of patients with a ganglioglioma, dysembryoplastic neuroepithelial tumor or cavernous hemangioma are rendered seizure free following surgical treatment.[2,7,11,13–16,18] The operative strategy in these individuals usually includes excision of the foreign-tissue lesion and the epileptogenic zone. Over 90% of patients with these pathological findings will experience an excellent surgical outcome, i.e., auras only or rare nondisabling seizures.[7] The operative outcome is distinctly less favorable in individuals with focal cortical dysplasia and other MCD.[19] The most common operative strategy in patients with intractable partial epilepsy involves a focal cortical resection of the epileptogenic zone with an excision of the surgical pathology.[10,11] The goals of surgical treatment are to render the individual seizure free and allow the patient to become a participating and productive member of society.[1,2,9]

This chapter will discuss the use of MRI in the evaluation of patients with medial temporal lobe epilepsy who are being considered for surgical treatment.

Magnetic resonance imaging

MRI has been demonstrated to be the most sensitive and specific structural neuroimaging procedure in patients with partial or localization-related epilepsy.[2,7] Importantly, MRI is a noninvasive technique that has no known biological toxicity and does not involve ionizing radiation.[18] The presence of an MRI-identified structural abnormality may suggest the localization of the site of seizure onset.[4–8] The high diagnostic yield of MRI to delineate foreign-tissue lesions, e.g., tumor or vascular malformation, has been confirmed.[13] MRI findings have

Table 82.1 Surgically remediable epileptic syndromes

Selected epileptic syndromes	MRI	SISCOM	Pathology
Substrate-directed			
Medial temporal lobe epilepsy	> 90%	–	MTS
Lesional epilepsy: tumor	100%	–	Ganglioglioma, glioma, DNET
Lesional epilepsy: vascular	100%	–	Cavernous hemangioma, AVM
Lesional epilepsy: malformation	80–90%	–	FCD
Non Substrate-Directed			
Neocortical (extrahippocampal)	0%	75%	Gliosis, focal cell loss, none

Adapted from Cascino GD. Advances in neuroimaging: Surgical localization. Epilepsia 2001; 42:3–12.

been used to select favorable candidates for epilepsy surgery, tailor the operative resection, and confirm the extent of corticectomy postoperatively.[16]

The sensitivity and specificity of MRI in patients with localization-related epilepsy has been confirmed.[13] The high diagnostic yield of MRI to 'reveal' the common pathological alterations, e.g., post-trauma, vascular malformation, tumor, MCD has been demonstrated in patients undergoing epilepsy surgery. The optimal technique in adult patients with partial epilepsy must include coronal or oblique-coronal images using T1-weighted and T2-weighted sequences.[15,16] The most common imaging alteration in the adult with intractable partial epilepsy is medial temporal lobe atrophy with a signal intensity change.[15,16] Fluid attenuated inversion recovery (FLAIR) sequences have been shown to increase the sensitivity of MRI to indicate a signal change (personal communication: Dr Clifford Jack). Both magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) have a high diagnostic yield in patients with temporal lobe epilepsy. These techniques may be most useful in patients with indeterminate structural MRI studies, e.g., no intra-axial abnormality of bilateral hippocampal atrophy.

Patients with lesional epilepsy may have a primary brain tumor, vascular anomaly or a malformation of cortical development (MCD). The common surgical pathologies encountered in patients with lesional epilepsy include a low-grade glial neoplasm, cavernous hemangioma and focal cortical dysplasia. Individuals with mesial temporal sclerosis and lesional pathology almost invariably have an abnormal structural magnetic resonance imaging (MRI) study and the seizure-types are classified as substrate-directed partial epilepsy. The MRI in these individuals may detect a specific intra-axial structural abnormality that may suggest the likely site of seizure onset and the surgical pathology.

The MRI seizure protocol at the Mayo Clinic Rochester includes:

1. Sagittal T1-weighted imaging with minimum echo time (TE) and 500 msec repetition time (TR) required for whole-head coverage with 5-mm thick contiguous sections;
2. Whole-head coronal three-dimensional volumetric spoiled gradient-echo (SPGR) acquisition is performed with minimum full TE and TR, 192 views, one repetition, 1.5 mm section thickness with 124 partitions, 22 cm field of view, and 45° flip angle; and
3. Coronal spin-echo (SE) imaging is performed with TE of 30 and 80 msec, TR greater than 2000 msec, 20-cm field of view, 4-mm section thickness and 2-mm intersection gap, and 192 views with one repetition. An oblique-coronal fluid attenuated inversion recovery (FLAIR) sequence is also obtained. The FLAIR sequence allows the pathological signal change to be differentiated from the physiological signal alteration related to cerebrospinal fluid. An enhanced study will be performed if a space-occupying lesion is detected in the unenhanced study.

Table 82.2 Presurgical evaluation

Performed invariably	Performed variably	At selected centers
History and examination	Video-EEG (intracranial)	SISCOM
Routine EEG	Electrocorticography	MRS
MRI head	FDG-PET	PET receptor studies
Video-EEG (extracranial)	Interictal-ictal SPECT	Functional MRI
Neuropsychology	Sodium amobarbital study	MRI volumetry

Performed invariably: almost always obtained prior to epilepsy surgery.
Performed variably: available at most epilepsy centers, used in selected candidates.
Performed selected centers: not widely available.
MRI: magnetic resonance imaging.
PET: positron emission tomography.
SPECT: single photon emission computed tomography.
SISCOM: subtraction ictal SPECT co-registered to MRI.
MRS: magnetic resonance spectroscopy.

Medial temporal lobe epilepsy

The three major categories of symptomatic partial epilepsy are as follows: (1) medial temporal lobe epilepsy; (2) lesional epilepsy; and (3) nonlesional neocortical epilepsy.[1] Approximately 80% of patients with partial epilepsy have temporal lobe seizures.[6] The epileptogenic zone in the temporal lobe involves the amygdalohippocampal complex in nearly 90% of patients.[21] The pathological hallmark of medial temporal lobe epilepsy is MTS.[5,7] Surgically excised pathology in approximately 65% of patients with intractable partial epilepsy is MTS associated with focal neuronal loss with or without gliosis.[5,7] A structural lesion underlying the epileptogenic zone is identified in approximately 30% of patients undergoing epilepsy surgery. Lesional pathology includes primary brain tumors, vascular malformations, and MCD.

Mesial temporal sclerosis

MRI findings in patients with MTS include hippocampal formation atrophy (HFA) and an increased mesial temporal signal intensity[5,7,11,13–15] (Figures 82.1–82.3). Inspection of MRI will allow detection of 80–90% of the cases of MTS.[5,7,11,13-15] The HFA atrophy is most obvious using the T1-weighted image in the oblique-coronal plane.[5,7] The signal intensity alteration can be identified using T2-weighted imaging or the FLAIR sequence in the oblique-coronal plane. The coronal or oblique-coronal planes are useful for MRI studies in patient MTS because of the capability to compare the two hippocampi for any side to side asymmetry.[5,7,11,13,14] Potential limitations of visual inspection of the MRI in patients with suspected MTS includes the following: head rotation, symmetrical bilateral HFA, subtle unilateral HFA or signal intensity alteration. Most importantly, visual inspection is a subjective determination that is strongly dependent on the inspector's expertise for appropriate interpretation. Three-dimensional SPGR images are helpful since they are reformatted into true anatomic coronal plane.

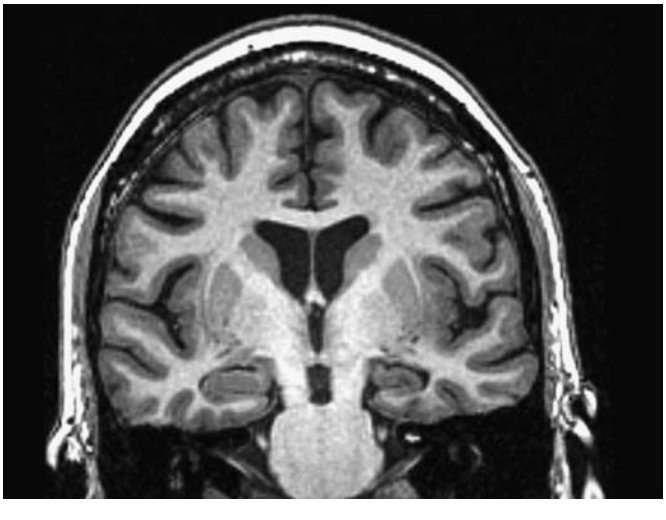

Figure 82.1 MRI head: 3-Tesla T1-weighted pulse sequence in the oblique-coronal plane revealing atrophy of the left hippocampus. The pathological findings showed hippocampal neuronal loss. (Note: the left hippocampus is on the right side of the figure).

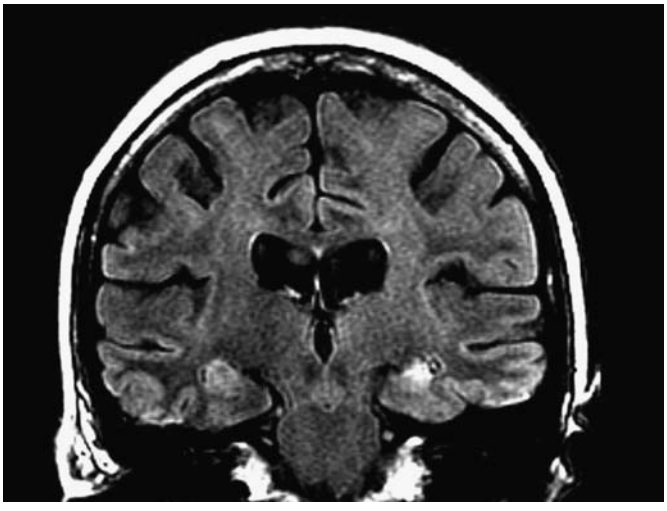

Figure 82.2 MRI head: 3-Tesla fluid attenuated inversion recovery sequence (FLAIR) in the oblique-coronal plane revealing a signal intensity alteration in the left hippocampus. The pathological findings showed severe gliosis. (Note: the left hippocampus is on the right side of the figure.)

MRI-based hippocampal formation volumetric studies have been developed to objectively determine the degree of hippocampal volume loss in patients with MTS.[13,14,16–18] Absolute hippocampal volume measurements are performed using a standardized protocol with the results being compared to age-matched normal controls to assign abnormal values.[13] A unilateral reduction in hippocampal volume has been shown to be a reliable indicator of the temporal lobe of seizure origin in patients with medically refractory partial epilepsy. Jackson *et al.* described T2 relaxometry to objectively determine the medial temporal lobe signal intensity.[17] Quantitative MRI studies have limited clinical application because of the high diagnostic yield of visual inspection. The most important use of hippocampal formation volumetry and T2 relaxometry is for research studies. HFA correlates with an early age of seizure onset, a history of a febrile seizure of childhood, and

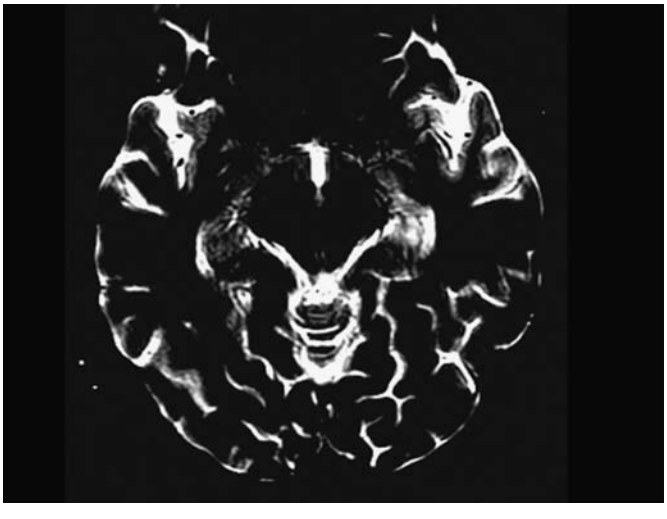

Figure 82.3 MRI head: 3-Tesla heavily T2-weighted pulse sequence in the axial plane shows unilateral hippocampal formation atrophy and a signal intensity alteration in the left hippocampus. The pathological findings showed hippocampal neuronal loss and gliosis. (Note: the left hippocampus is on the right side of the figure.)

Table 82.3 MRI and surgical pathology

	MRI				
Pathology	**T1**	**T2**	**FLAIR**	**HF atrophy**	**Gad-DTPA**
Tumor	+	++	+++	–	++/–
AVM	++	++	++	–	+/–
MCD	–	+/–	+	–	–
MTS	–	+/–	+	++	–

T1: T1-weighted imaging sequence.
T2: T2-weighted imaging sequence.
FLAIR: fluid attenuated inversion recovery sequence.
HF atrophy: hippocampal formation atrophy or volume loss.
Gad-DTPA: gadolinium enhanced study.
Tumor: primary brain tumor.
AVM: vascular malformation.
MCD: malformation of cortical development.
MTS: mesial temporal sclerosis.

Table 82.4 MRI and mesial temporal sclerosis

MRI Techniques	Sensitivity
T2-relaxometry	79%
IR	86%
Visual atrophy	90%
IR + visual atrophy	93%
Hippocampal volumetry	97%

Kuzniecky *et al.*, 1997

the diagnosis of medial temporal lobe epilepsy.[13,14,16–18] A history of a neurologic illness in childhood, e.g., febrile seizure, head trauma, or meningitis, appears to be an important risk factor for the development of MTS.[16] The duration of epilepsy and age at the time of surgery have not correlated with volumetric results in most studies.[13,14,16]

The identification of MTS in the surgically excised temporal lobe has been a favorable prognostic indicator of seizure control following epilepsy surgery.[12] Nearly 90% of patients with unilateral hippocampal atrophy have been rendered seizure free.[16] MRI is now recognized as being predictive of neurocognitive outcome in patients undergoing an anterior temporal lobectomy.[18] Patients with normal left hippocampal volumes are at greater risk for experiencing a significant decline in cognitive performance following a left medial temporal lobe resection than those with left HFA.[16–18]

Magnetic resonance spectroscopy

Proton (^{1}H) MRS has been shown to be a reliable indicator of the temporal lobe of seizure origin in patients with medial temporal lobe epilepsy.[28,29] ^{1}H MRS is highly sensitive in the lateralization of temporal lobe seizures by revealing a reduction in N-acetylated compound (NA) concentrations or abnormalities in the creatine (Cr)/NA or NA/choline ratios.[28,29] The underlying pathogenesis for the metabolic changes are likely to be complex and may relate to focal neuronal loss, gliosis, or a functional alteration intimately associated with the frequency of seizure activity. The diagnostic yield of MRS is similar to structural MRI in patients with medial temporal lobe epilepsy related to MTS[28]. The detection of metabolic abnormalities by ^{1}H MRS also correlates with the outcome following temporal lobectomy for intractable partial epilepsy.[28,29] Preoperative metabolic abnormalities in the contralateral temporal lobe were predictive of operative failure. ^{1}H MRS may be of particular benefit in patients with medial temporal lobe epilepsy and normal structural MRI studies.[28,29] Proton spectroscopy may also lateralize the epileptic temporal lobe in patients with bilateral hippocampal formation atrophy. There is limited information regarding the diagnostic yield of ^{1}H MRS in patients with neocortical, extrahippocampal, seizures. The potential benefits of proton spectroscopy in patients with nonlesional extratemporal seizures remain to be determined. At present, ^{1}H MRS is an investigative diagnostic tool that is restricted to only selected epilepsy centers. Despite observations of focal metabolic abnormalities in selected patients with nonlesional extratemporal seizures, it is doubtful that this diagnostic innovation will have widespread use to demonstrate a localized abnormality in patients with nonsubstrate-directed partial epilepsy.

Conclusions

The presurgical evaluation in patients with substrate-directed partial epilepsy is designed to determine the epileptogenicity of the neuroimaging alteration. The rationale for the electrophysiological studies is essentially *confirmatory* in patients with unilateral MRI-identified mesial temporal sclerosis or an isolated foreign-tissue lesion. Video-EEG monitoring is performed in these individuals to confirm the diagnosis of a partial seizure disorder, establish the seizure-type, and determine the disabling effect of the ictal behavior. Functional neuroimaging procedures may not be necessary in patients with medial temporal lobe epilepsy or lesional epilepsy in the presence of a structural MRI abnormality that is concordant with the remainder of the presurgical evaluation. Both MRS and PET have a high diagnostic yield in patients with temporal lobe epilepsy. These techniques may be most useful in patients with indeterminate structural MRI studies, e.g., no intra-axial abnormality of bilateral hippocampal atrophy. In patients with nonsubstrate-directed partial epilepsy there are significant concerns regarding the localization of the epileptogenic zone. Chronic intracranial EEG monitoring may prove necessary in these patients, especially with extratemporal epilepsy. Identification of a localized SISCOM *focus* may be a reliable indicator of the ictal onset zone. SISCOM may reveal a localized region of cerebral hyperperfusion or hypoperfusion in up to 80% of patients with intractable partial epilepsy. The SISCOM findings are also predictive of operative outcome. Ultimately, a decision regarding surgical treatment must be based on a convergence of the neurodiagnostic evaluation. Electrophysiological studies invariably need to be performed to localize the ictal onset zone in these patients. Resection of the SISCOM *focus* may be necessary to significantly reduce the seizure tendency in patients with a localized abnormality that is concordant with the epileptic brain tissue.

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83 Magnetic resonance imaging in neurocutaneous syndromes

D Moon and A Gupta

Introduction

Neurocutaneous syndromes are commonly associated with epileptogenic brain lesion(s) that could be surgically resected for relief from refractory epilepsy. Their clinical recognition is of critical importance before surgical epilepsy planning for several reasons. First, recognition of a specific neurocutaneous syndrome will help to anticipate the pathological nature of the epileptogenic lesion(s) such as hamartomas in tuberous sclerosis complex (TSC) or a leptomeningeal angiomatosis in Sturge Weber syndrome (SWS). Additionally, a possibility of multiple bilateral lesions, that may be subtle, could be recognized and special MRI protocols may be done to fully appreciate the extent of brain lesions and scalp EEG findings. Second, screening for other organ and system involvement may be necessary before epilepsy surgery. For example, patients with SWS may have glaucoma, choroid angioma and chronic visual loss that may impact surgical planning of a brain lesion that is usually in the posterior quadrant. Third, some neurocutaneous disorders are familial, and genetic counseling is of paramount importance. Fourth, basic science studies using characteristic pathological substrates on the resected brain tissue from patients with neurocutaneous disorders have enhanced our understanding of the epileptogenesis. Most neurocutaneous syndromes are identifiable by physical examination, and brain MRI helps in confirming the presence of anticipated lesion(s). In this chapter, we will focus on brain MRI and important clinical findings in neurocutaneous disorders that are commonly associated with epilepsy.

Sturge-Weber syndrome (SWS)

Sturge-Weber syndrome (SWS) or Sturge-Weber Dimitri syndrome is also known as encephalotrigeminal angiomatosis or encephalofacial angiomatosis. The majority of cases are sporadic mutations, and there is no clear inheritance pattern. Familial cases in which siblings have phenotypic presentation of SWS exist, but is estimated that these types of cases comprise less than 10% of all cases.[1] Prevalence of SWS is estimated in one study to be 1 in 50 000.[2] There is no known race or sex predilection. Seizures occur in 80% of SWS patients. Seizures usually begin in the first year of life, and are the most common presenting symptom of neurological involvement. Common clinical features include a facial capillary angioma (nevus flammeus or port-wine stain) suggesting a possibility of an underlying ipsilateral leptomeningeal angioma and ocular choroidal angiomas.

Skin findings in SWS

The facial capillary angioma is in the cranial nerve V distribution. Usually it is in theV1 distribution with variable V2 and V3 involvement. Patients with V1 involvement are at risk for neuro-ocular lesions. Some experts feel that facial angioma is not a sine qua non, and up to 5% of patients with SWS do not have facial angiomas.[3] In a minority of cases facial angiomas may be bilateral. Even when facial angiomas are bilateral intracranial involvement tends to be unilateral or dominant to one side.[4]

Eye findings in SWS

Glaucoma is diagnosed in 15% of SWS patients at birth, 61% in the first year of life and 72% by the age of 5 years.[5] Developmental anomalies in the anterior chamber and increased episcleral venous pressure are felt to be the inciting factors for glaucoma in SWS.[6] Dilated episcleral and retinal vessels are present with V1 involvement. There is increased incidence of retinal detachment secondary to hemorrhages from the choroidal hemangiomas. Eye involvement may result in acute or chronic or acute on chronic visual loss that may not be readily apparent in a young infant without an opthalmological examination by an expert.

Brain findings in SWS

Key neuroimaging findings are cortical calcification (Figure 83.1), cerebral hemiatrophy with patchy parenchymal gliosis, choroid plexus hyperplasia, and leptomeningeal angiomatosis. Facial angioma and intracranial lesions are usually ipsilateral.[7] The cortical calcifications show a gyriform pattern on unenhanced brain CT (Figures 83.1 and 83.2). This gyriform pattern, sometimes also referred to as 'tram line calcification', is best appreciated on bone window settings (Figure 83.1). In the normal brain windows the calcifications often appear as amorphous dense lesions (Figure 83.2).

On brain MRI, calcified lesions are best visualized on gradient or susceptibility sequences where they exhibit gyriform susceptibility artifact (low signal areas Figure 83.3) similar to the pattern seen on brain. T1 images (Figure 83.4 and 83.5) show encephalomalacia in the area of the lesions. On administration

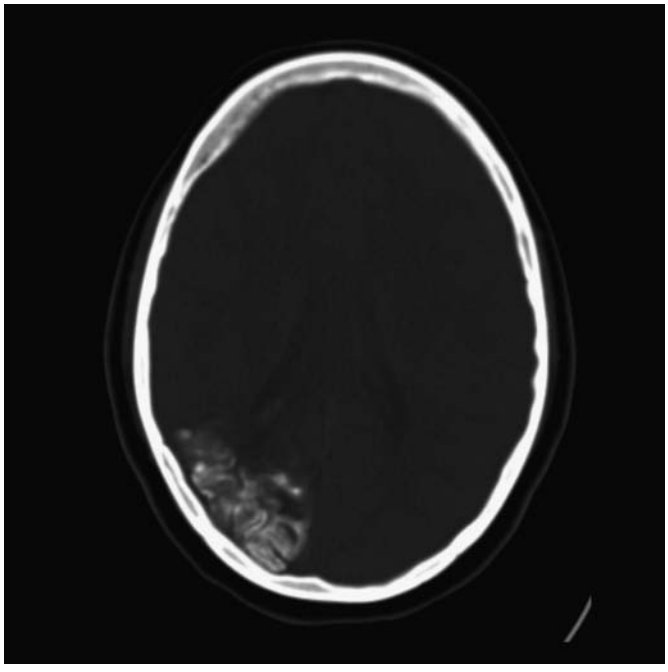

Figure 83.1 Dense occipital cortical calcifications on head CT, bone window in a child with SWS.

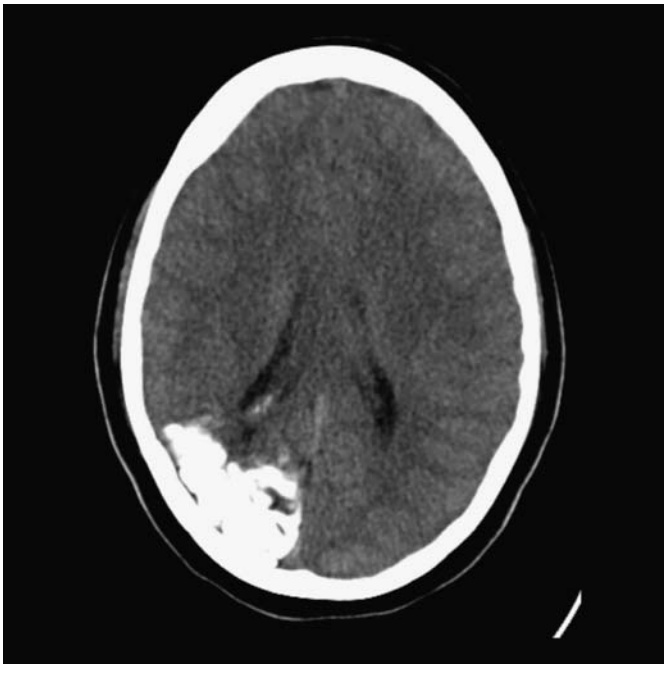

Figure 83.2 Dense cortical calcifications in same SWS patient on head CT, parenchymal window. Note that this is the same image as 86.1 but shows the appearance of more extensive calcifications because of windowing.

of the intravenous gadolinium, T1 contrast images shows enhancement in this area reflecting the underlying venous anomaly, and of the hyperplastic chroid plexus in the ipsilateral atria of the lateral ventricles. Contrary to what might be anticipated intuitively, neither MR venography or MR angiography is helpful in assessing SWS (Figures 83.6–83.8).

Neurological findings include hemianopsia that may not be appreciated or present at birth but tends to be recognized later in life. A subtle clue in a young infant may be gaze preference or ignoring the visual hemifield contralateral to affected size.[8] In SWS, seizures may be followed by prolonged or persistent hemiparesis in the postictal period, suggesting the diagnosis of transient ischemic attacks or cerebral stroke.[9] Fixed hemiparesis may develop. Hemianopsia is usually apparent by the time of hemiparesis.[10] Intracranial angioma may also be bilateral, but one side tends to be dominant. Also SWS patients have angiomas of visceral organs such as kidneys, spleen, ovaries, intestine, adrenals, thyroid, pancreas, heart, thymus, lungs, and extremities. The latter with hypertrophy of the limbs is similar to or may be a subset of Klippel-Trenaunay-Weber syndrome.

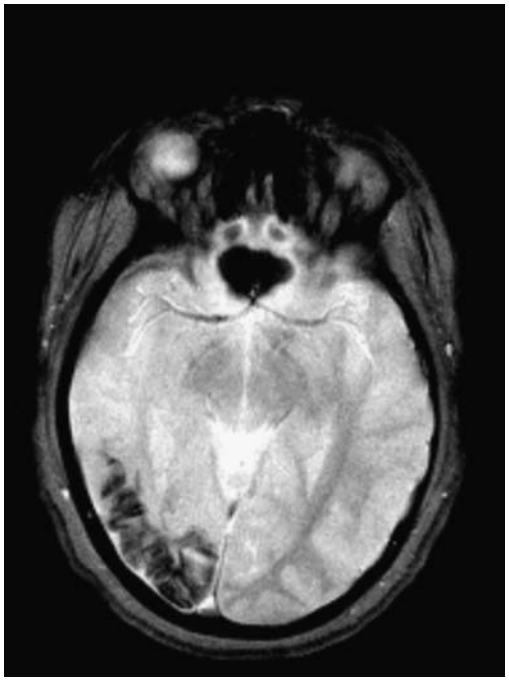

Figure 83.3 Cortical susceptibility artifact reflecting MRI appearance of calcifications in the same SWS patient as 86.1 on MRI gradient echo sequence.

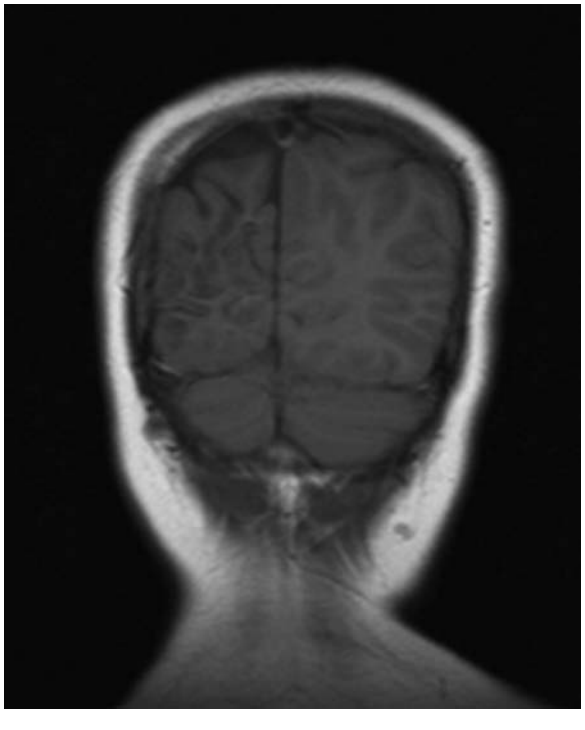

Figure 83.4 Noncontrast T1 weight coronal MRI in a child with SWS showing volume loss in the underlying brain parenchymal in the affected right parietal and occipital lobes.

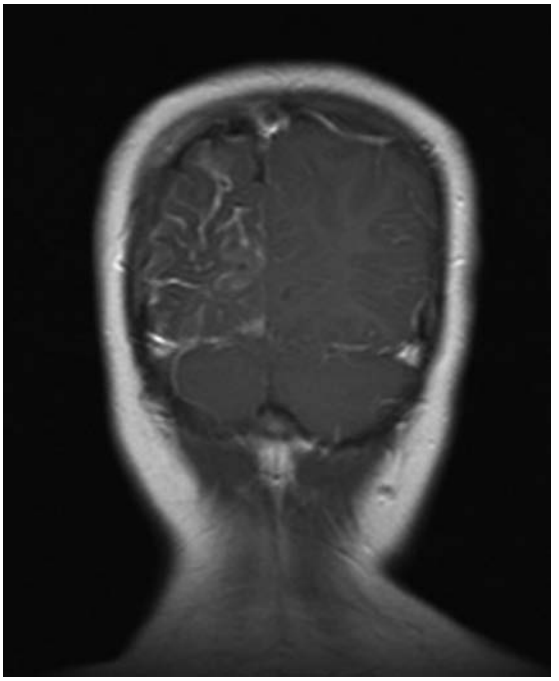

Figure 83.5 Post contrast coronal T1 images showing enhancing right pial angioma in the same patient as 86.4.

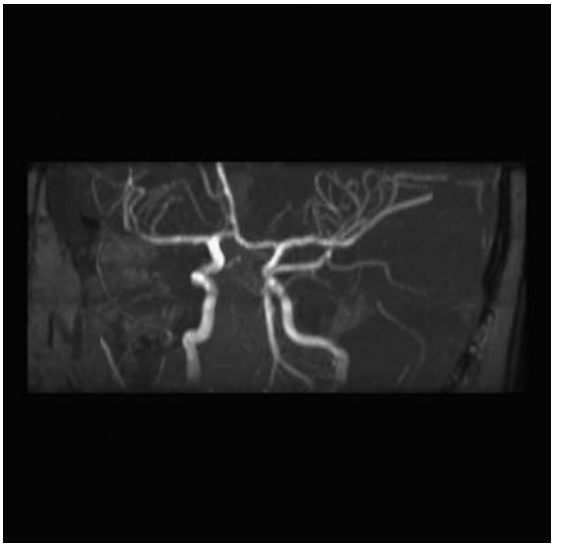

Figure 83.6 MRA maximum intensity images (MIP) shows no abnormal signal to suggest vascular abnormality.

Pathophysiology in SWS

The intracranial lesion is felt to be due to proliferation of leptomeningeal angioma in the subarachnoid space which causes shunting of blood away from brain tissue. Shunting and stasis of blood causes chronic ischemia resulting in gliosis, volume loss and calcification.[11,12] Leptomeningeal angiomas could be bilateral in up to 14% of patients in one series from Mayo Clinic.[13] Absence of superficial cortical veins and thrombosis of SSS has also been reported.[14]

Leptomeningeal angiomatosis is more obvious on gadolinium enhanced MRI than on a contrast enhanced CT.[15] Xenon-133 studies show decreased blood flow in the brain lesion even in patients without neurologic deficits suggesting chronic ischemia.[16] Calcification in SWS is intracortical and noncontrast CT can be used to evaluate cortical calcifications in the later stages. Plain films show the classic 'tram track' pattern on calcification outlining the cortical gyri usually by the age of 2 years. Angiography usually shows enlargement of the deep cerebral veins, decreased or absent cortical veins, or early filling in 82% of patients.[17]

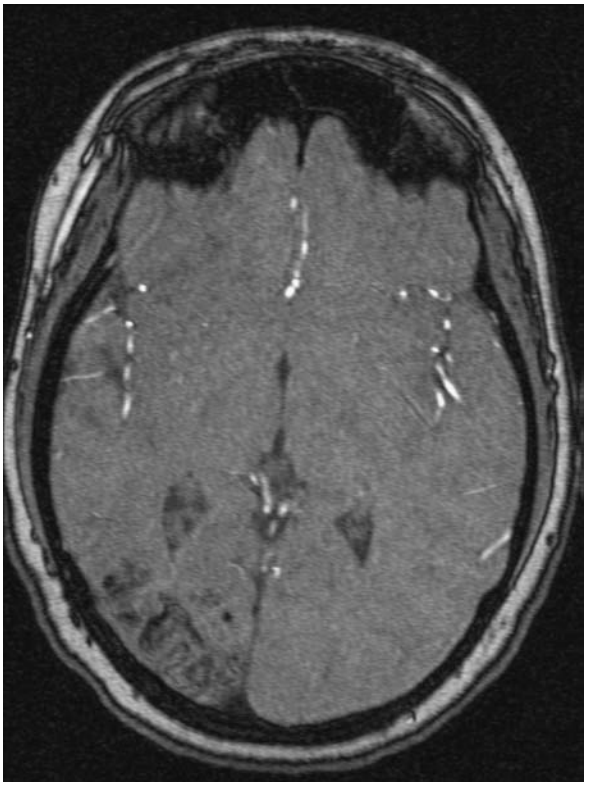

Figure 83.7 MRA individual source image shows no abnormal flow related enhancement (high signal) in the area of affected brain. There is susceptibility artifact in the area where there are gyriform cortical calcifications similar to the ones seen on the susceptibility scans.

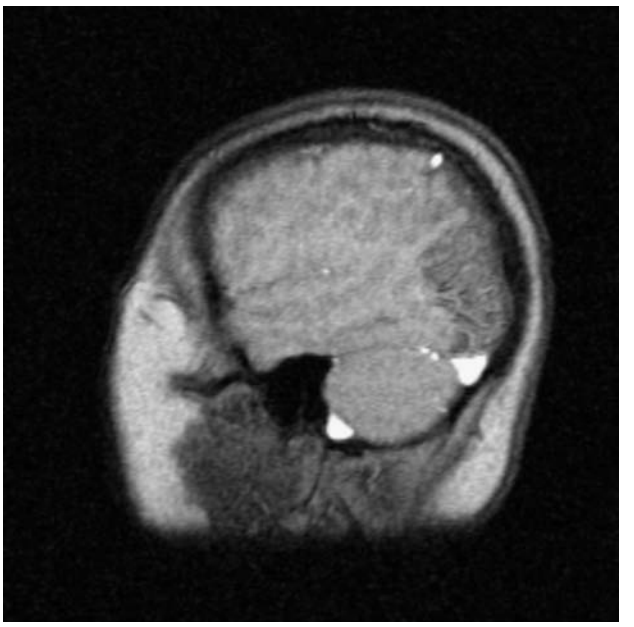

Figure 83.8 2-D time of flight MR venogram individual slice shows no abnormal flow related enhancement in the expected location of the cortical calcification in contrast to the normal high signal (bright) dural venous sinuses.

Neurological morbidity in SWS

Patients with SWS are more likely to have behavioral, social and intellectual issues than nonaffected siblings.[18] Of SWS patients, 60–80% have some degree of mental retardation, and 47–60% are reported to have severe mental retardation in two studies.[19,20] Bilateral hemispheric involvement usually shows increased severity of mental retardation.[21] Intensity of seizures rather than age of onset or hemiparesis as correlated with the presence and severity mental retardation.[22]

Seizures are also very common in SWS, and various studies quote the incidence of seizures to be 75–90% in children with SWS.[23–26] Of those SWS patients who will eventually have seizures, 75% develop seizures by the first year of life, and almost all by the age of 5 years. Only rarely, seizures may first present even in the second decade of life, as in a case report of one patient who presented with seizures at the age of 23 years.[27] Bilateral hemispheric involvement increases risk of seizures.[28] Seizures are usually partial motor (hemiclonic, hemitonic, or myoclonic) or secondarily generalized. Partial seizures involve contralateral extremeties to the intracranial (and usually the facial) lesion. A small number of patients may have primarily generalized tonic-clonic seizures. Some patients may experience a period of seizure remission but seizures may relapse later in life with increased frequency.[29] In one study, there is a 50% incidence of prolonged seizures or status epilepticus.[30]

Epilepsy in SWS is usually difficult to treat. There are some data to suggest that prophylactic antiepileptic drug therapy is useful, even before the patients present with seizures.[31] A trial of at least two antiseizure medications is usually given by most epileptologists before seizures are considered refractory.[32] In SWS with refractory epilepsy, surgical options are usually promising. Presurgical evaluation should be promptly done in these patients. Surgical options include lesionectomy with removal of tissue including generous margins around the lesion or hemispherectomy type procedure of patients of SWS, 70–80% may be seizure free or significantly improved with rare aura or brief seizure after surgery. Lesionectomy is usually reserved for SWS patients who have no motor deficits (hemiparesis), who show a unilateral well-demarcated angiomatous lesion in the parieto-occipital region posterior to the perirolandic region on the brain MRI, and the scalp EEG shows epileptogenicity over the lesion.[33] Hemispherectomy is usually recommended in patients with pre-existing severe hemiparesis that may be progressive, usually with an extensive lesion involving the sensory motor cortex on the brain MRI. The role of invasive recordings to salvage eloquent cortex or perform a more restricted surgery is controversial. Due to predominant posterior quadrant location of the lesions, a comprehensive eye examination and counseling for irreversible anticipated visual deficits is of great importance. Timing of surgery is important. A clinical course with worsening seizures, progressive hemiparesis, and relentless cognitive decline may occur in some patients with SWS. Early surgery is generally recommended for relief from catastrophic epilepsy and ensued encephalopathy from seizures and toxic doses of multiple antiepileptic medications.[34] There is also a possible positive effect on cognitive development with early surgery.[35]

Tuberous sclerosis complex (TSC)

Tuberous sclerosis complex (TSC) (Bourneville disease) is a multisystem genetic disease that is transmitted in an autosomal dominant pattern. Seizures are one of the most common presenting symptom in TSC, and most patients with TSC develop life-long refractory epilepsy. The prevalence is reported to be 1 in 10 000.[36,37] There is no race or sex predilection and spontaneous mutation rate is 60%.[38] Mutations in two genes have been identified in patients with TSC. TSC1 is located at chromosome 9q34 and encodes a protein called hamartin. TSC2 is located at chromosome 16p13.3 and encodes a protein called tuberin.[39] Although located on different chromosomes, the two genes appear to code two proteins that work in the same biochemical pathway involved in cell differentiation and proliferation. Although most patients have mutations localizable to either TSC1 or TSC2, 15% of patients in a study by Dabora *et al.* did not have a lesion localizable to either gene.[40] Sporadic mutations are more common in the TSC2 gene. TSC1 seems to have less severe phenotypic expression. Specifically, TSC1 patients appear to have fewer seizures, fewer intracranial lesions, and less severe mental retardation.[41] Those patients in Dabora's study who did not have a mutation localizable to either TSC1 or TSC2 had even a milder phenotypic presentation than the TSC1 patients.

The classic Vogt triad of mental retardation, seizures, and adenoma sebaceum is only found in only 29% of TS patients.[42] Diagnostic criteria for clinical diagnosis of TSC have been developed and are listed in Table 83.1. Interestingly, 7% patients with TSC1 or TSC2 mutation do not meet diagnostic criteria for TSC, and 15% of patients who meet the criteria for TSC do not have mutation in TSC1 or TSC2.[43]

Table 83.1 TS diagnostic criteria revised[44]

Major features
- Facial angiofibromas or forehead plaque
- Nontraumatic ungual or periungual fibromas
- Hypomelanotic macules (≥ 3)
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma, single or multiple
- Lymphangiomyomatosis
- Renal angiomyolipoma

Minor features
- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- Confetti skin lesions
- Multiple renal cysts

Diagnosis
- Definite tuberous sclerosis complex is diagnosed by the presence of either two major features or one major feature plus two minor features.
- Probable tuberous sclerosis complex is indicated by one major feature plus one minor feature.
- Possible tuberous sclerosis complex is indicated by either one major feature or two or more minor features.

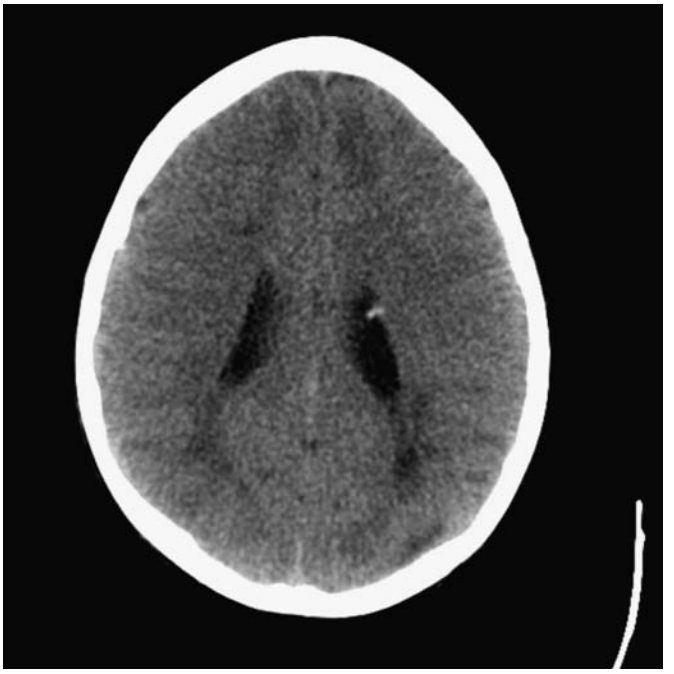

Figure 83.9 Unenhanced brain CT of an 11-year-old child with TSC. Cortical tubers and white matter changes are seen in the left parietal lobe.

Brain involvement and neuroimaging in TSC

This is associated with a variety of brain lesions, and these are: cortical tubers, white matter lesions, subependymal nodules (SEN), and subependymal giant-cell astrocytomas (SEGA).

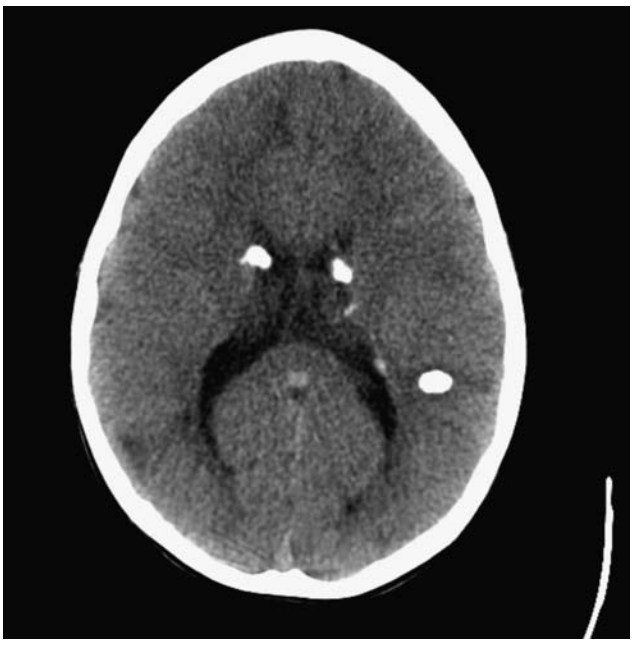

Figure 83.10 Same child as in Figure 83.9. Ventral cuts on unenhanced brain CT show subependymal nodules and subcortical calcification in the left posterior frontal lobe. Additional cortical and white matter lesions are seen in the right parietal and frontal lobe. Hypodense nature of cortical and subcortical white matter lesions in TSC may be mistaken for remote insult, however the presence of multiple lesions and associated calcified SEN usually clarify the diagnosis.

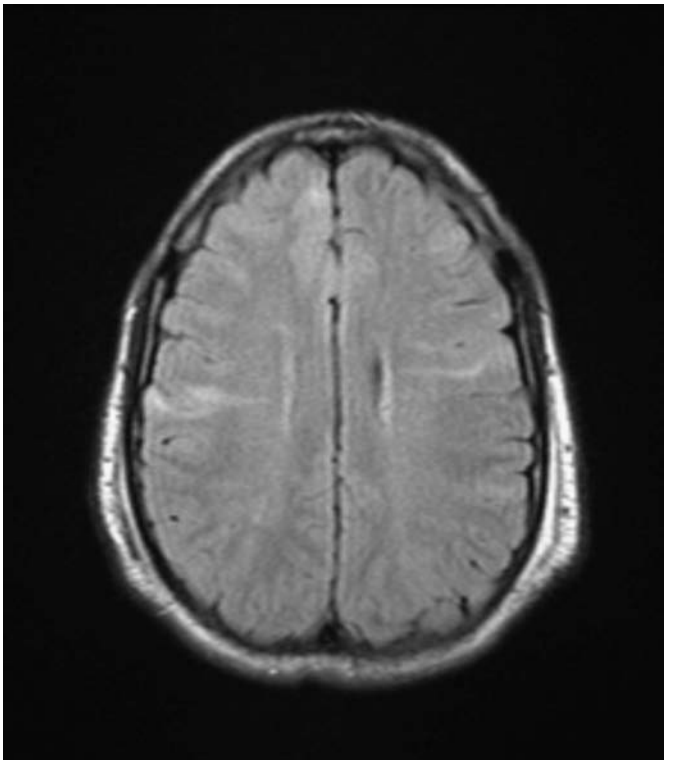

Figure 83.11 Brain MRI FLAIR sequence in a young adult with TSC showing multiple hyper-intense cortical tubers and linear and wedge-shaped white matter lesions.

Histologically, each of the four types of intracranial lesions are composed of clusters of giant cells with varying degrees of neuronal and astrocytic differentiation, and presence of cells that are transitional forms between these two types.[45]

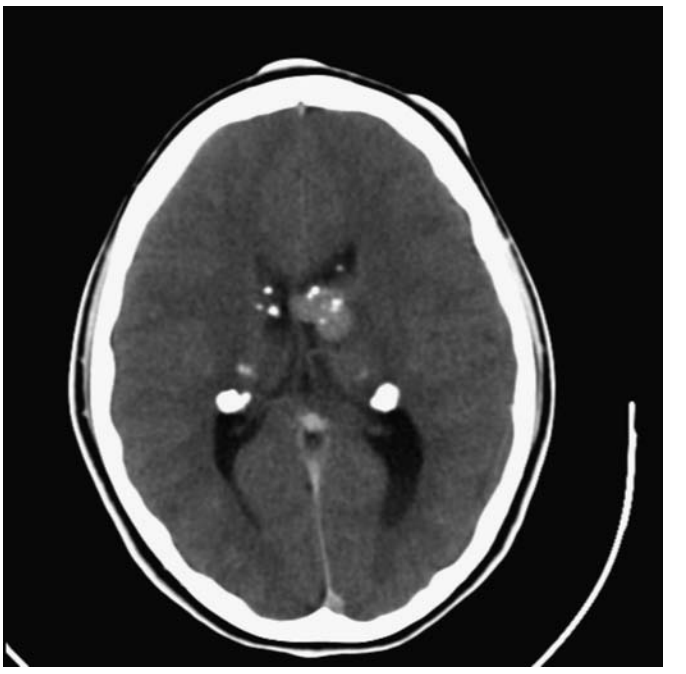

Figure 83.12 Brain CT after administration of contrast in a 16-year-old boy with multiple calcified subependymal nodules (SEN). In the left hemisphere, in addition to the calcified SEN, an enhanced soft tissue mass (SEGA) near the foramen of Monroe is seen. Note the lack of edema surroundings the intracranial masses. Also note the plaque-like areas of increased attenuation in the skin over the frontal bone compatible with cutaneous lesions.

While brain CT is helpful in noticing calcified lesions in TSC, brain MRI is recommended as the neuroimaging procedure of choice to elicit the extent of all lesions. Cortical tubers are hyperintense on T2 and FLAIR sequences, and hypointense on T1 sequences in patients with mature myelination. In newborn and infants with immature myelination, the tubers are hyperintense to unmyelinated white matter on T1 sequences and appear hypointense on T2-weighted images. This effect of immature myelination on the brain MRI findings in infants with TSC is felt to be secondary to the increased water content in unmyelinated regions of the brain.[46] Frontal lobe propensity for cortical tubers has been reported.[47] Cortical tubers usually show decreased uptake of radioactive agent on Tc99mHMPAO interictal SPECT imaging.[48] Similarly, there is hypometabolism on FDG (18-fluorodexy) brain PET.[49] Brain PET may not be as reliable in infants due to normal low glucose metabolism in the brain.[50] There is evidence to suggest that cortical tuber count and location is associated with increased risk of infantile spasms.[51] There also appears to be a correlation between increased number of tubers, development of early seizures, and developmental delay.[52] Magnetic resonance spectroscopy (MRS) shows decreased NAA/Cr ratio, increased choline to creatine ratio, increased myoinositol to creatine ratio, as well as lactate peak.[53]

There are three types of white matter lesions in TSC. These are, in the order of common occurrence; thin linear bands extending radially from the ventricular surface to cortical tubers, wedge-shaped bands with apices near ventricles, and amorphous lesions in the deep white matter. The white matters lesions also show predominance in frontal lobes.[54]

Subependymal nodules (SEN) are often near the caudate head or caudo-thalamic groove. They are variable in appearance. They do not usually obstruct CSF flow, but may uncommonly do so by mechanical pressure against the foramen of Monro. SEN may rarely enhance on gadolinium administration in a nodular or ring-like fashion, and enhancement is better appreciated at higher signal strengths.[55] SEN are better seen on CT than MR because of the presence of calcification.[56]

SEGA are slow growing tumors. They are typically located near the foramen of Monroe and are believed to originate from SEN or tubers.[57] However, rarely SEGA may also appear in other locations in the brain.[58,59] Typically, there is no edema in the brain parenchyma adjacent to the SEGA. Most SEGA are benign, although there are rare cases of malignant degeneration. The symptoms of SEGA are mainly due to their location. TSC patients with SEGA often present with acute or chronic increased intracranial pressure suggesting chronic or intermittent obstruction at the level of the foramen of Monroe. Incidence of SEGA in various studies on TSC is reported to be 1.7–26%. A recent series in a moderate sized group of patients reported 8.2%.[60] SEGA are generally iso- to hypo-intense to brain parenchyma on T1 and hyperintense on T2-weighted images. SEGA are heterogeneous in appearance. Flow voids may be identified within these lesions. They often have internal susceptibility artifact reflecting hemorrhage or calcification. They do show contrast enhancement, and in fact, SEGA should be suspected and periodic screening scans are indicated if SEN show enhancement.

Nonneurological lesion in TSC

Patients with TSC have many visceral lesions including: cardiac rhabdomyomas, phakomas in the eyes (retinal hamartoma), renal cysts and angiomyolipomas, hepatic cysts and pulmonary leioangiomyomatosis. TSC patients may also have a multitude of cutaneous lesions such as hypomelanic macules (ash leaf spots), adenoma sebaceum (facial angiofibromas), forehead plaques, shagreen patches, and ungul or subungual fibromas.

Epilepsy and neurological manifestations in TSC

Seizures are one of the most common presentation in TSC, and occur in up to 80% of patients with TSC.[61] Most patients of TSC with seizures tend to present early in life, and 70% TSC patients develop epilepsy by the age of one year.[62] Infantile spasms are most common type of seizures in infants with TSC. Depending on the location of the epileptogenic tuber(s), other types of seizures such as focal motor, grand mal, complex partial, and atypical absence seizures may occur.[63] Most infants with infantile spasms progress to complex partial to generalized tonic-clonic seizures later in life.[64] In rare TSC patients who develop seizures in later in teenage years or adulthood, partial seizures are most common.[65] Seizures in TSC patients are often difficult to control.

Of TSC patients, 50–65% have mild to moderate mental retardation. IQ appears to be bimodally distributed in patients with tuberous sclerosis.[66] On the good side of the spectrum are a few patients who have no, or infrequent, seizures beginning after infancy with no, or mild, learning disabilities and an IQ that is lower than siblings without TSC. On the guarded side of the spectrum are TSC patients who present with infantile spasms or catastrophic epilepsy with onset before 12 months of age who end with moderate to severe mental retardation.[67] Autism is commonly described in TSC patients, and is reported in 25–50% of patients.[68,69] Patients with TSC also have other neuropsychiatric morbidity in the form of a high frequency of hyperactive and aggressive behavior, and, rarely, self mutilation.[70] SEGA may grow and obstruct the CSF flow requiring tumor excision with or without placement of a ventriculo-peritoneal shunt.

The first line treatment for seizures is antiepileptic medication. Vigabatrin has been found to be especially effective in the treatment for infantile spasms in TSC.[71] There is a question whether it is more effective than ACTH treatment in the treatment of infantile spasms.[72] While ACTH has acute and chronic steroid-related side-effects, Vigabatrin may cause irreversible peripheral field visual defects after long-term use.[73] Besides other antiepileptic medications, ketogenic diet may be helpful in cases of otherwise intractable epilepsy.[74] Vagal nerve stimulation has also been used in a few refractory patients who are not candidates for surgery.[75] Surgery has proven to be an effective and promising option in many refractory cases of TSC. Detection of the solitary or predominant epileptogenic tuber(s) remains a challenge in patients with multiple closely located lesions, and is best achieved by carefully considering seizure semiology, scalp-EEG, and correlating with the brain MRI. Brain PET and ictal SPECT are less informative, although special radioactive PET agents have been touted to increase the yield to detect epileptogenic tuber(s).[76,77]

Epidermal nevus syndrome (ENS)

This is a sporadic neurocutaneous disorder without any known familial cases. Somatic mutation is postulated as the underlying genetic mechanism. The defining cutaneous features of ENS are congenital epidermal nevi that are usually raised skin lesions that may be band-like, round, oval, or linear in configuration. Cutaneous lesions may be subtle to detect due to their skin like color and velvety appearance in infancy, however, they may become verrucous orange or brown later in life. A wide variety of epidermal congenital lesions have been linked to ENS, such as linear sebaceous nevus (of Jadassohn), nevus verrucosus, ichthyosis hystrix, nevus unius lateris, and inflammatory linear verruous epidermal nevus. The cutaneous lesions may differ somewhat in histology.[78] Characteristically, the dermis is not involved, and there is thickening and hyperkeratosis of the epidermis with hyperplasia of the sebaceous glands.

Besides cutaneous manifestations, there is a wide spectrum of clinical presentation involving multiple organs and systems.[79] Pathogenesis of brain involvement is postulated to be vascular dysplasia and migrational anomalies.[80,81] There is no consistent relationship between side of nevus and CNS abnormality.[82] ENS patients may also have ocular, dental, and skeletal abnormalities.

Epilepsy in ENS

Various types of brain malformations and migration abnormalities are reported, however, classical involvement of the brain is in the form of hemimegalencephaly (17 out of 60 patients in Pavone's study).[83] Seizure onset is usually within the first year of life. Seizures in infancy are associated with significant hemispheric abnormalities.[84] Seizures are usually daily, catastrophic, and fail to respond to medical treatment. Hemispherectomy is the treatment of choice in patients with hemimegalencephaly. Important considerations before epilepsy surgery in ENS patients include careful examination and investigations to elicit the clinical severity and organ/system involvement in a given patient, scalp-EEG and MRI to locate epileptogenic zone and also look for evidence of bilateral brain involvement, parental counseling, and weighing benefits/risks of early surgery, whenever possible. A case of ENS with pictures is described in Chapter 170.

Neurofibromatosis 1 (NF1)

Unlike SWS and TSC, only a small percentage of patients with NF1 (Von Recklinghausen's disease) have seizures. The prevalence of seizures in NF1 varies from 4.2–7%.,[85,86] The lower figure is just twice the prevalence in the general population. Seizures were due to tumors (hamartomas), cortical malformations and mesial temporal sclerosis.[87] Other studies of NF1 patients with seizures report no structural lesions identified.[88] Mental retardation is often present in those NF 1 patients who have seizures. Age of presentation varied from 4 days to over 20 years.[89] There are occasional reports of seizures in NF2 patients which are likely due to the presence of localized effects of supratentorial meningiomas and meningioangiomatosis which occurs in NF2 patients.[90,91]

Neurocutaneous melanosis (NM)

This is a rare disorder in which patients have congenital cutaneous nevi and leptomeningeal melanosis leading to CNS manifestations. Precise incidence figure are unavailable, however, a 2.5% risk of developing NM with CNS involvement is quoted in patients with large congenital melanocytic nevi.[92] This disease may be lethal early in life but some patients survival into their 20's.[93,94] Most common MR findings in NM patients is T1 shortening (increased signal) in the temporal lobe and infratentorial brain on noncontrast examinations.[95] There is variable ventriculomegaly and there may be thickening of leptomeninges of brain and spine as demonstrated on contrast enhancement.[96] Leptomeninges may appear to be normal on T1- and T2-weighted sequences. Usually there is leptomeningeal enhancement, however cases have been described without the leptomeningeal involvement.[97] There may also be pachymeningeal (dural) involvement.[98] Dermatologically, patients have multiple congential nevi, the largest of which typically measures greater than 5 cm. NM patients usually present with seizures or increased intracranial pressure. Cranial nerve palsy, hemiparesis, myelopathy, or psychiatric disorders may coexist. NM is believed to be a sporadic neurocutaneous disorder, and is not transmitted as a single gene disorder and does not have any sex predilection.

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84 Magnetic resonance imaging in epileptogenic neoplasms

J Tamraz and Y Comair

Introduction

Refractory epilepsy is a consistent health problem worldwide, affecting almost 1% of the population from which more than a quarter present a medically refractory form. Since the preliminary essays of in vivo magnetic resonance (MR) performed 25 years ago, its efficiency took an increasing major role in the diagnosis and the management of intractable epilepsy demonstrating the underlying structural abnormalities.[1–3] Even in the idiopathic form of generalized epilepsy brain imaging may show related abnormalities. The Commission on Neuroimaging of the International League Against Epilepsy (ILAE) recommends[4,5] that '… the ideal practice is to obtain structural neuroimaging with MRI in all patients with epilepsy, except in patients with a definite electroclinical diagnosis of idiopathic generalised epilepsy or benign epilepsy of childhood with centrotemporal spikes'. It also recommends that '… epilepsy surgery should never be contemplated without an MRI examination'.

MR is actually a mature imaging technique and stands as the most accurate neuroimaging modality for the diagnosis of structural abnormalities related to epilepsy and the presurgical evaluation due to its inherent specific characteristics. In fact, MR due to its multiplanar ability allows the exploration of the patient in any oblique plane with a high-contrast resolution premitting to obtain an accurate differenciation of gray and white matter. The absence of beam hardening artifacts from bony structures such as those generated at the skull base vicinity, favors the exploration of tumoral processes located in the orbitofacial or temporal regions. The absence of ionizing radiation makes it the modality of choice for follow-up examinations, particularly in pediatric patients or post surgery or radiation therapy. MRI is a multiparametric technique that largely depends upon operator skills. It is an epilepsy specialist study. The choice of the appropriate pulse sequences contribute consistently to the final diagnosis. A minimum of T1- and T2-weighted sequences and a 3D-T1w volume acquisition with reformations and volume renderings are mandatory and recommended by the ILAE. The need for contrast administration, such as the paramagnetic Gadolinium chelates, is relatively limited usually restricted to the evaluation of intra-axial neoplastic processes and the leptom eningeal seeding and may be of some help in the differential diagnosis or in tumor grading.[6] The search for an optimal cost/efficiency ratio requires the prescription of the most informative examination. The well-established sensitivity of MRI in detecting structural abnormalities in refractory epilepsy averages (95% as compared to 32% for CT).[7] MR is superior for identifying both the focus and the histopathologic substrate found at surgery. A combined approach may be needed for the detection of minute calcifications. However, CT remains useful in patients presenting absolute contraindications to MR exams as patients with pacemaker, vascular clips, neurostimulators, or other ferromagnetic devices.

More sophisticated techniques, recently implemented on most available systems, may be used in addition to morphologic imaging: diffusion-perfusion to assess perfusion measurements and evaluate neovascularisation, diffusion tensor imaging (DTI) to obtain white matter tractography, functional imaging (fMRI) for mapping of brain functions, and in vivo spectroscopy (MRS), which may reveal subtle underlying biochemical abnormalities representing the effects or cause of the epileptic disorder. Note that fMRI activation is more widely available and of much higher spatial resolution than other functional techniques, improving particularly on higher field systems (3 Tesla magnets) and tend to become the powerful functional tool to detect metabolite disorders even supplanting PET for the localization of eloquent cortex most useful in the presurgical planning process.[8–20] In apparently normal MR exams, functional imaging techniques such as ictal SPECT and/or interictal FDG-PET may show regional dysfunctions.

Neuroimaging technique of brain tumors

In order to identify and recognize the underlying structural abnormality responsible for intractable partial epilepsy, a good knowledge of brain anatomy and the nature of the lesional processes that may potentially cause seizures, is necessary.[21–25] These lesions are frequently subtle and may be easily overlooked or misdiagnosed.[26] High spatial and contrast resolution thin coronal MR cuts off the brain and the temporal lobes should be performed on high field systems (1.5 or 3 Tesla).

Brain referentials essential for neuroimaging

Any precise topographical analysis of brain structures ought to be performed according to judicious and definite cerebral reference lines, based on reliable cutaneous, cranial and brain landmarks.[22] In order to facilitate the neuro-anatomical

approach and optimize biometrical studies using MRI, two brain reference lines, the horizontal chiasmato-commissural line (Ch-Cp line) and the vertical commissural-obex line (Cp-Ob line) perpendicular to the previous, are routinely used. These orthogonal reference planes suitable for multimodality imaging are used in brain imaging with highly reproducible anatomical results.[22,27,28,31] The anatomical landmarks defining these reference lines are very easily found on a mid-sagittal MR scoutview (Figure 84.1a).

The horizontal reference Ch-Cp line is defined as the line tangential to the superior border of the chiasmatic notch (Ch) anteriorly to join the inferior border of the posterior commissure (Cp) posteriorly. The consistency of the angle between this line and the bicommissural line serves to validate the choice of this pivotal line situated as it is at the mesodiencephalic junction. This plane has been shown to be truly horizontal oriented parallel to the parallel sulcus and consequently to the lateral fissure materializing a sylvian plane orientation of the brain cuts.[27,28]

The vertical reference Cp-Ob plane is defined as the line tangential to the anterior border of the posterior commissure (Cp) and joining the obex (Ob) at the caudal extremity of the calamus scriptorius on floor of the fourth ventricle (28) (Figure 84.1b). This Cp-Ob line materializing the great vertical axis of the brainstem has been demonstrated as the most reliable referential to obtain reproducible coronal cuts of the brain using MR.[27,31] Coronal cuts are therefore best obtained with the Cp-Ob reference plane due to its perpendicularity to Ch-Cp plane and thus to the anterior-posterior axis of the first temporal and the lateral sulci, becoming particularly most suitable for the coronal study of the temporal lobes, the inferior frontal gyri and the perisylvian speech areas.

Imaging protocol and methodology

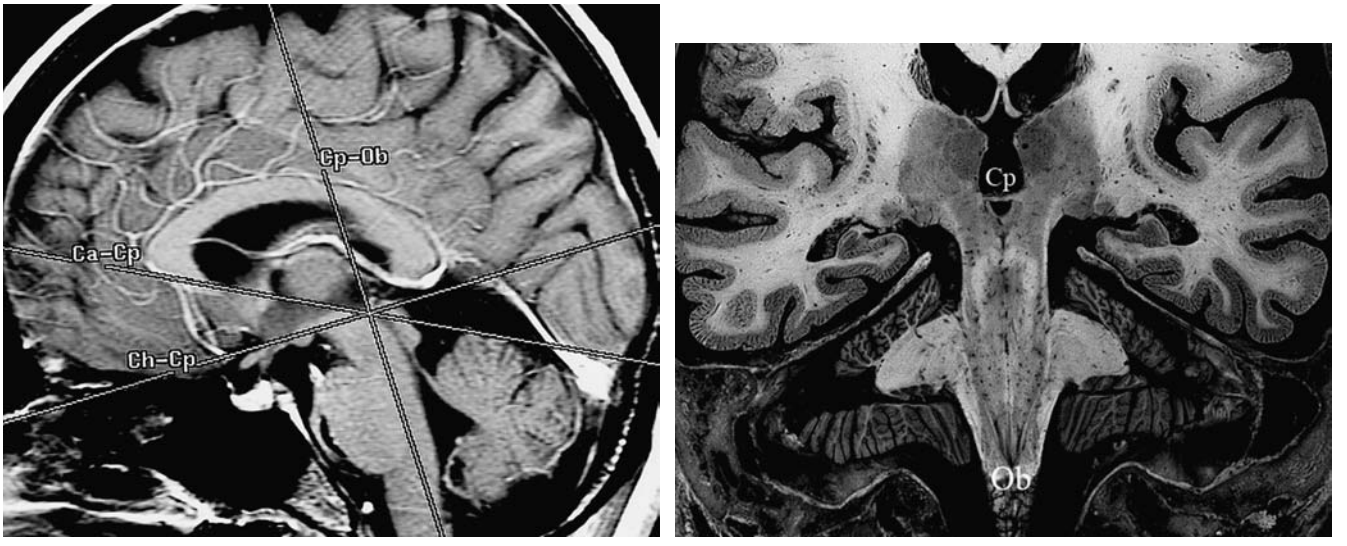
Accurate and reproducible brain reference planes as achieved using the Cp-Ob reference plane have to be used. The imaging protocol must include at least three pulse sequences: a sagittal T1-weighted gradient echo sequence useful for a morphological screening approach and for subsequent landmarking, followed by a coronal-oblique fast fluid attenuated inversion recovery (FLAIR) sequence according to PC-OB line and a 3D-T1 weighted volumetric acquisition with 128 partitions and 1.8 mm slice thickness. The near isotropic small voxel size obtained allow mutiplanar reformations and volume renderings with adequate spatial resolution. Additional T2-weighted and/or T2*-weighted pulse sequences in the axial or the coronal planes may be performed in special conditions.[32] Beyond the routine examination protocol, more sophisticated and powerful imaging modalities available may be used to improve sensitivity in the diagnosis and the staging of primary intracranial tumors and to optimize the presurgical planning. Post-surgical follow-up of resected tumors and evaluation of the effects of adjuvant radiotherapy or chemotherapy are also promising.

Functional aspects of MR

Functional imaging applies to any technique that acquires time dependent imaging data. This includes flow, diffusion, perfusion, brain activation and MR spectroscopy.[33–34] When combined and added to conventional MR technique these functional tools may increase the specificity of the positive diagnosis of brain tumors. A multifunctional approach may help to suggest the tumor grade, evaluate the tumor extension and the therapeutic response and precise the area to biopsy.[35–39]

Diffusion (DWI) and diffusion tensor imaging (DTI)

While MR angiography and flow measure the movement of spins from voxel to voxel, MR is capable of measuring microscopic translational motion within each voxel. This motion can be the molecular diffusion of water and the microcirculation of blood in the capillary network, referred to as perfusion.



(a) (b)

Figure 84.1 Cephalic reference planes suitable for neuroimaging. (a) Horizontal and vertical reference lines are used as referential coordinates for routine brain imaging: the chiasmatico-commissural line (Ch-Cp) joining the Chiasmal point to the Commissura posterior and the commissural-obex (Cp-Ob) line joining the Commissura posterior to the Obex, respectively. Both orthogonal orientations are compared to the bicommissural plane (Ca-Cp). (b) Anatomical correlation as obtained in the Cp-Ob coronal reference plane.

Diffusion is the process by which molecules and other particles mix and migrate due to their random thermal motion. DWI is acquired using a specific bipolar gradient with very high strength to detect the slow molecular diffusion in the body. This bipolar gradient will cause a signal loss in the diffusing spins which depends on the diffusion coefficient and the B value. The B value is determined by the strength and duration of the gradients. High B values can eliminate the T2 effect and improve the visualisation of the white matter fibers. It is therefore possible to obtain maps of diffusion in the three different orthogonal directions or combine the three images into a single map of overall diffusion. With specific research software it is possible to calculate the diffusion tensor and deduce the actual direction of the diffusion and even obtain the direction of the neuronal axons.

Diffusion is increased in area containing free water such as in edema and is decreased in case of hypercellularity as in solid tumors or in viscous necrotic areas found in an abcess, for instance. Increased diffusion appears as dark areas on DW images and as very bright on the ADC map. DTI may be useful to localize a tumor and evaluate its extent. This may be achieved either by the identification of an increase in diffusivity or a loss of anisotropy.[40–42] Interpretation of tractography is improving due to advances in technology and could be more reliable on higher-resolution images as obtained on higher field systems (3 T). The need to compare between normal and diseased hemispheres is helpful.[43] More work is still needed and the results are still debatable.

Perfusion imaging

Perfusion is the study of the net transport of magnetization into a volume of tissue. It can be performed either with endogenous or exogenous contrast agents.[33] One way of achieving this is by injecting a bolus of contrast agent like Gadolinium (Gd) and acquiring rapidly, usually with EPI a series of slices through the region of interest, and then repeating the multislice acquisition at a rapid rate of the order of one per second. This repetition is performed from before the injection until about 30 seconds after the arrival of the bolus. The images are then analysed to look for variations in the arrival of the contrast agent between the pathological and normal regions. The analysis can be made in several ways: the negative enhancement integral which produces a map of the susceptibility effect caused by the flow of blood containing contrast; the mean time to enhance which produces a map based on the time of arrival of the contrast in different regions; and the positive enhancement integral which produces a map of the contrast enhancement rates based on the increase in SNR due to increased concentration of contrast material.

Highly vascular high-grade gliomas usually show increased blood volume and blood flow with respect to normal brain. Conversely necrotic or cystic portions of the tumor show a decrease if not absence of perfusion.[44,45] Reduced perfusion is also found in the peritumoral edema. Although lacking specificity, perfusion imaging may help in some circumstances to approach tumor grade. Low-grade astrocytomas may also show increased blood volume.

Brain activation (fMRI)

Brain activation can be studied either by direct methods, those that measure directly the electrical activity of neurons like EEG (electrical effect) and MEG (magnetic effect), or by indirect methods, those that measure the hemodynamic response to the neuronal electrical activity, like ^{15}O PET (blood flow) and fMRI (BOLD effect).[33] The indirect method used by fMRI can be understood by following the chain of physiological events that describes it. When a set of neurons fire there is a local increase in glucose consumption which, in turn; produces an increase in oxygen consumption. This induces an increase in regional cerebral blood flow (rCBF) and an increase in regional cerebral blood volume (rCBV) with a consequent increase in blood velocity. In the blood there is a decrease in oxygen extraction fraction producing an increase in oxyhemoglobin and a decrease in deoxyhemoglobin. In this sequence of events the most common approach used in fMRI is the blood oxygen level dependent (BOLD) contrast. The decrease in deoxyhemoglobin, because of its high paramagnetism, produces a decrease in local microscopic field gradients which in turn produces an increase in T2*. This corresponds to an increase in signal which is measured by the MR equipment. The ideal sequence to use is a rapid sequence with T2* sensitivity which detects changes in magnetic field, usually a gradient echo EPI. fMRI has its own limitations both in spatial resolution and temporal resolution. To achieve optimal functional imaging it is important to have the highest possible magnetic field (1.5 T or 3.0 T), powerful and fast gradients and a powerful computer with adequate software to manipulate the image.

Magnetic resonance spectroscopy (MRS)

For almost two decades, in vivo magnetic resonance spectroscopy (MRS) has been a revolutionary technique in biomedical research. Today, it is a powerful tool in neurosciences giving noninvasive access to the chemistry of the human brain in health and in disease.[34] MRS is a unique and powerful technique that has been applied to a number of brain diseases. It can be correlated with imaging and other clinical data for confirmation. It enables tissue characterization on biochemical levels. It is useful in the diagnosis and prognosis of diseases and mostly in the evaluation of the noninvasive monitoring of the response to treatment.[46]

The spectroscopy technique routinely used to assess brain tumors is the multivoxel acquisition modality, performed both with an intermediate TE of 144 ms which evaluates the choline level, the major metabolic abnormality in brain tumors, and with a short TE of 30 or 35 ms in order to detect myoinositol which may help tumor grading.[51] The most salient findings are a decrease in NAA and Cr peaks and NAA/Cr ratio and an increase of Cho, lipids and lactate as well as Cho/Cr and Cho/NAA.[49,50] Both ^{31}P and ^{1}H MRS have been used for diagnosis and therapy monitoring of brain tumors.[47] Studying changes in tumor-type-dependent metabolites is an area of active research.[48–51] Lipids and lactate peaks correlate well with necrotic tumors.

In vivo MRS is a complex technology that requires the simultaneous optimal adjustment of multiple parameters during an examination. The most critical task in MRS, however, is not spectral aquisition but rather spectral analysis. This latter is time demanding and necessitates appropriate know-how in order to interprete the results, eliminate artifacts and quantitate data often by complex procedures and finally, statistically analyze the findings. The precise role of many identified metabolites is still unclear.

Neuroimaging of developmental tumors

Tumors are represented most frequently by gliomas of the astrocytic predominantly fibrillary but possibly protoplasmic type or of the oligodendroglial type, followed less commonly by the mixed neuronal-glial or neuronal tumors such as the ganglioglioma, gangliocytoma, and the dysembryoplastic neuroepithelial tumor (DNET). The majority of patients with DNETs or gangliogliomas are less than 20 years old. Tumor recurrence after surgery is usually low.

Dysembryoplastic neuroepithelial tumors (DNET)

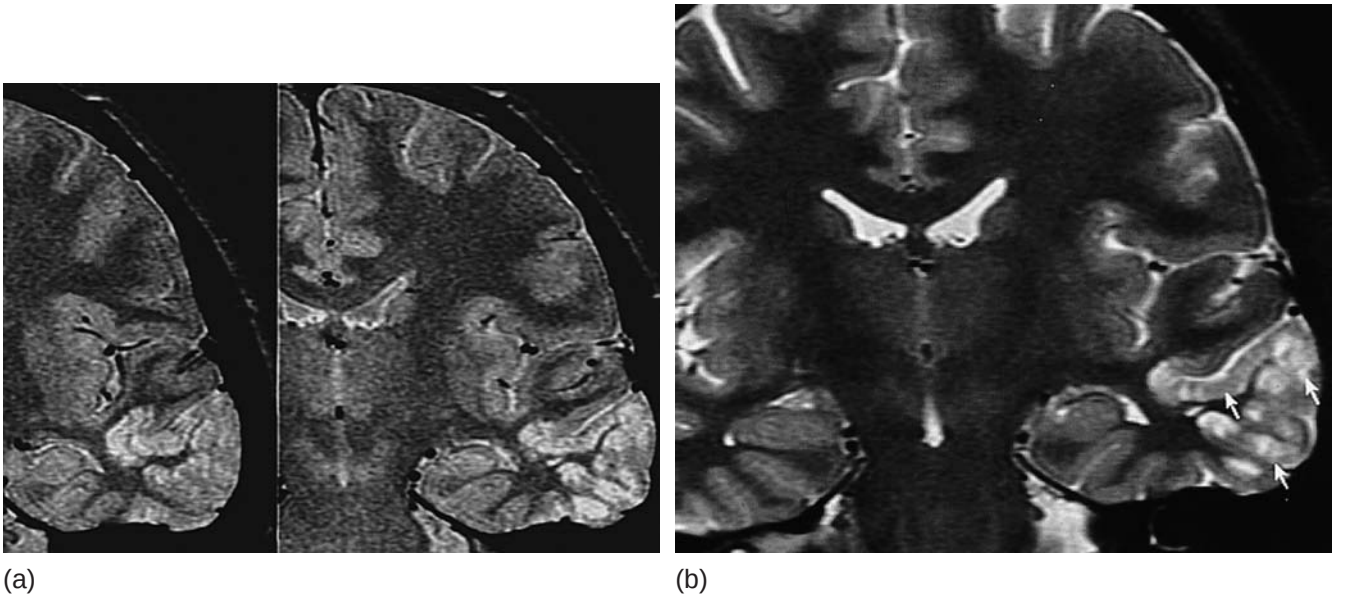
Described in 1988 by Daumas-Duport[52] and accepted into the 1993 WHO revision,[53] DNETs show characteristic histologic features consisting of three cell lines: neuronal, astrocytic, and oligodendroglial. These uncommon tumors are highly associated with long-standing intractable epilepsy with onset in early childhood, before the age of 15 years in 85% of cases,[20] with an average age of 9 years.[54,55] DNET has been indicated in about 20% of medically refractive epilepsy in children and adolescents.[52,56] Males are affected more than females. Diagnostic criterias include partial seizure activity before age of 20 with no associated focal neurologic deficits or congenital deficit, and a cortically-based tumor.

DNETs are benign hemispheric mixed glial-neuronal tumor, predominantly cortical, very rarely deep in location, causing seizures as their earliest manifestations. They correspond to WHO gradeI lesions. These tumors are relatively rare with more than 300 cases reported. All reported cases are supratentorial.[57,58] More than 60% of DNETs are found in the temporal lobes and involve the mesial structures preferentially and about 30% in the frontal lobes. Few are located in the parietal or occipital lobes, the basal ganglia, brainstem or cerebellum.

Morphology and imaging

Morphologically, these tumors are very superficially located, always involving and expanding the cortex despite a concurrent involvement of the subjacent white matter. The tumor gives rise to a macrogyriform aspect rather typically associated with a scalloping of the inner table of the skull vault in more than 50% of the cases.[59,60] These neoplasms are heterogeneous with a multinodular microcystic appearance (Figure 84.2), but true intratumoral cystic formation is uncommon. Actually two varieties may be differenciated, a 'macrogyric or megagyric' form that causes gross expansion of the cortical ribbon and a 'multinodular' form. In the case of associated subcortical extension the tumor appear triangular in shape on coronal cuts.[61] Associated edema is lacking and there is no mass effect. Calcifications are found in about 1/3 of the patients on CT.[54] DNETs show many of the features of gangliogliomas and oligodendrogliomas. DNETs may be associated with adjacent cortical dysplasias and may occasionally occur in neurofibromatosis type I. Because of its benign nature, total resection with complete cure may be obtained.

Hypodense to white matter on noncontrast CT, DNETs are hypointense to cortex on T1-weighted sequences on MR, becoming/hyperintense to adjacent cortex on PD-w and remaining hyperintense on T2-w and FLAIR, due to increased water content, but show no vasogenic edema. The characteristic microcystic architecture is demonstrated in almost 40% of cases on high resolution images using very long T1-w and T2-w sequences at high fields.[62] Cortical analysis and evaluation of DNETs and eventually associated cortical dysplasias may be highlighted using IR-T1-weighted sequence due to its higher contrast resolution. Subcortical extent of the lesion is observed in 30% of the cases.[60] DNETs usually do not show contrast enhancement in more than 2/3 of the cases and show a patchy pattern in 20–40% of the cases.[61] Peritumoral edema is almost absent. The differential diagnosis includes ganglion cell tumors and low-grade gliomas.[63]



(a) (b)

Figure 84.2 Dysembryoplastic neuroepithelial tumor. Coronal cuts showing a cortically based tumor involving the lateral temporal gyri and displaying highly suggestive multinodular appearance due to the presence of intracortical multiple tiny cysts (arrows), hyperintense to gray matter on PDw (a) and T2-w (b) images. The lesion expands the cortex with mild erosion of the inner table of the calvarium. There are no obvious mass effect, neither associated edema. No contrast enhancement was evidenced.

Gangliocytomas and gangliogliomas

Also called ganglioneuromas, most of these uncommon slowly-growing benign tumors are found in patients younger than 16 years old, affecting children and adolescents, but have been reported in patients ranging in age from a few months to 80 years old.[64] Their incidence is slightly higher in males.[65] The diagnosis is usually made in 80% of the cases before age 30 (20–30 years old) in patients presenting a long–standing epilepsy, most commonly partial complex seizures.[65,66] In the pediatric population, the average age at diagnosis is 10 years old with seizures as the most frequent presenting symptom.[65,67] Complete resection of the tumor usually cure seizures.[67,70]

Gangliocytomas are very rare mixed neuronal-glial tumors formed of neoplastic mature ganglion cells (WHO grade I). Gangliogliomas show the presence of mature ganglion cells with neoplastic glial cells (WHO grade I or II). The astrocytic component is either diffuse or pilocytic in nature. They represent together 1.3% of all brain tumors. The tumors may occur anywhere but are most commonly found in the temporal lobes and tend to spare the lateral neocortex.[66,69–71] The other lobes involved are the parietal, the frontal, and the occipital lobes. When superficially located, the tumor may cause thickening of the cortical ribbon and cause a scalloping of the calvarium. Although benign, an aggressive behavior is found in about 10% of gangliogliomas which may undergo malignant degeneration.[72,75] Association with cortical dysplasia may be found in 50% of the patients.

Morphology and imaging

Gangliogliomas and gangliocytomas are usually well-circumscribed small masses, solid or partly cystic in 25% of cases or almost cystic in about 50%. Intratumoral cysts are often multiple. There is usually no obvious mass effect and no or very mild, peritumoral vasogenic edema. In gangliogliomas, the tumor may involve the leptomeninges and the glial component of this mixed tumor may contribute to give a slight infiltrative appearance of the brain-tumor interface. Calcifications are common found in 40% of cases, sometimes of bizarre shape,[70] but remain less frequent than in oligodendrogliomas but more than in juvenile pilocytic astrocytomas or in pleomorphic xanthoastrocytomas.[70,71] It seldom presents as a brain 'stone' without associated soft-tissue neoplasm. They may be associated with mesial temporal sclerosis when located anteriorly. Peripheral tumors may erode the inner table of the skull as reported in about 5% of cases.[74] The tumors may be associated with mesial-temporal sclerosis. Differential diagnosis between gangliogliomas and gangliocytomas is made on histopathology.

Gangliogliomas are hypointense to cortex on T1-w sequences, but their cystic component may be isointense due to a high protein content. On PD-w images the solid portion of the ganglioglioma is hyperintense to the cortex with variable SI of the cystic component which may be even more hyperintense due to its high protein content. On T2-w images the solid portion of the gangliogliomas is mildly hyperintense to brain, less or equally to the cystic component and may show mild peritumoral edema (Figure 84.3). Calcifications may appear as areas of shortened T1 relaxation. IR-T1w sequence, due to its high contrast resolution, is a sensitive sequence, very useful in the investigation and the evaluation of cortical dysplasias, mesial temporal sclerosis and superficial tumoral conditions such as gangliogliomas or gangliocytomas. Cortical analysis is highlighted. On CT, the solid portion of the tumors are isodense or hypodense showing calcifications in about 30% of the cases and a variable contrast uptake.[75] Enhancement of at least the solid portion of gangliogliomas is variable either homogeneous or heterogeneous, usually mild and found in roughly half the cases, except in the case of malignant degeneration.[65,69–71] The wall of the cystic component may show contrast enhancement. In peripherally developed tumors, differential diagnosis with DNETs and oligodendrogliomas may be difficult.

Desmoplastic neuroepithelial tumors

The desmoplastic infantile gangliogliomas (WHO grade I) and the desmoplastic astrocytomas of infancy are tumors encountered in infancy and early childhood, mainly in boys, and presenting similar features. Histopathologically these tumors are composed of both ganglionic and astrocytic cells with a desmoplastic stroma.[76] Clinically, patients present with macrocephaly and partial complex seizures.[76–78] These tumors show a benign clinical evolution and their complete excision may be curative.[79]

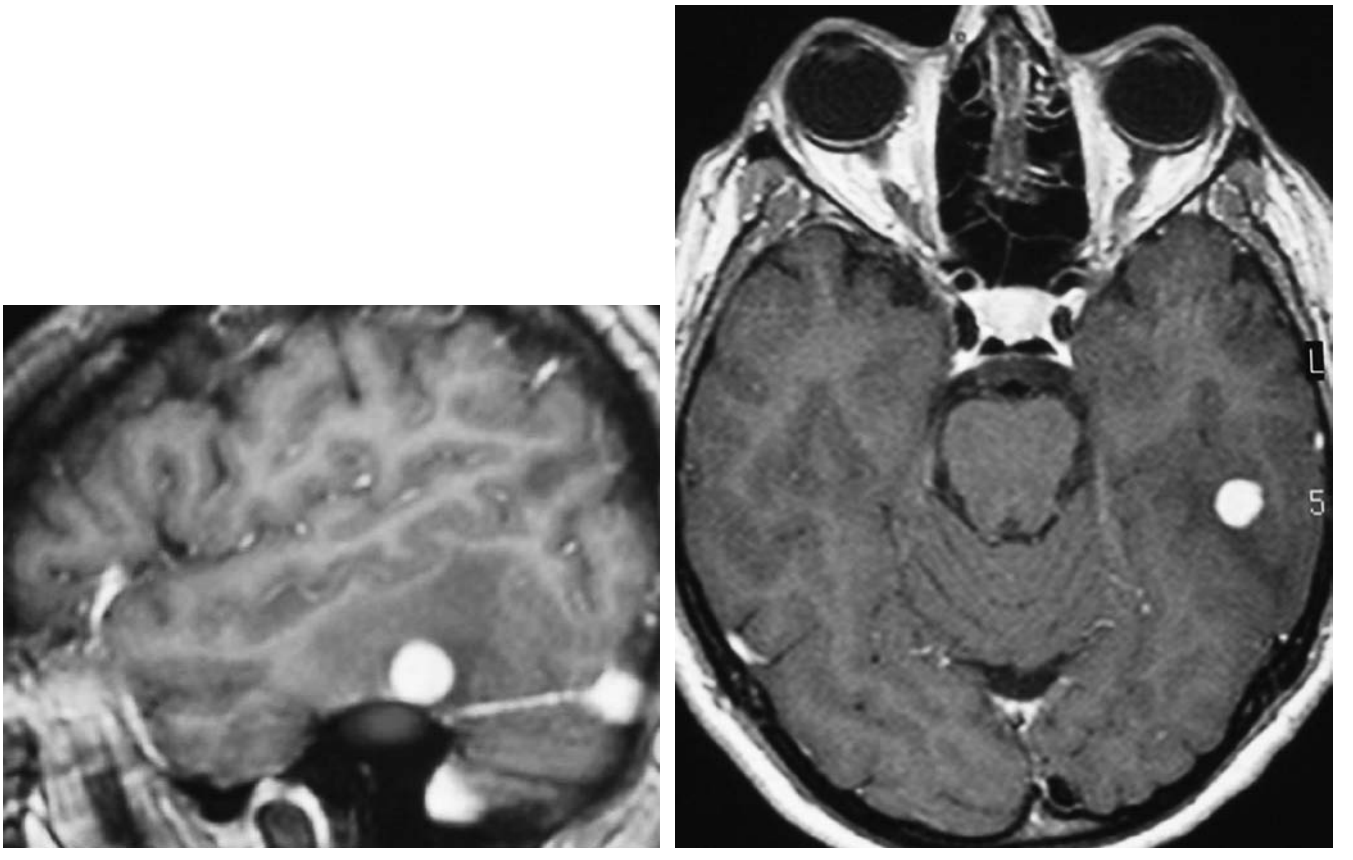
Morphology and imaging

On imaging, the tumor presents as a usually very large cyst with an associated solid component adjacent to the leptomeninges containing the desmoplastic tissue.[76,79,80] The mass shows a predilection to the frontal or the parietal lobes and tends to spare the occipital.[81,82] The solid portion is iso- to hyperdense to gray matter on CT and is isointense to gray matter on T1-w and T2-w images on MR, enhancing intensely after contrast infusion, except for the walls of the cystic component.[82] Desmoplastic neuroepithelial tumors should be differentiated from cystic astrocytomas and pleomorphic xanthoastrocytomas, the latter presenting similar imaging features but being found most frequently in adolescents and young adults, peripherally in the hemispheres and usually in the temporal lobe. Cystic astrocytomas are differentiated by the hypodense appearance of its solid component on CT and its long T2 signal intensity on MR.

Hypothalamic hamartomas

Hypothalamic or tuber cinereum hamartomas, are benign rare congenital slow-growing processes. Composed of disorganized heterotopic neuroepithelial cells, they are considered as non-neoplastic heterotopias. Found inferior to the hypothalamus originating usually from the tuberal region between the pituitary stalk and the mamillary bodies, or from the mamillary bodies.[83] There is no sex predilection.[84,86]

The clinical presenting signs, usually present when tumor size exceeds 10 mm, are most frequently isosexual precocious puberty observed before age 2, whose pathogenesis is unclear, and less commonly gelastic epilepsy and hyperactivity.[83,86–89] The characteristic gelastic seizures, although infrequent, result in spasmodic laughter. Many other types of seizures may be observed, partial complex, partial motor, atypical absences or even infantile spasms. Seizures would be mostly encountered with intrahypothalamic masses.[88,90–92] Interconnections



(a) (b)

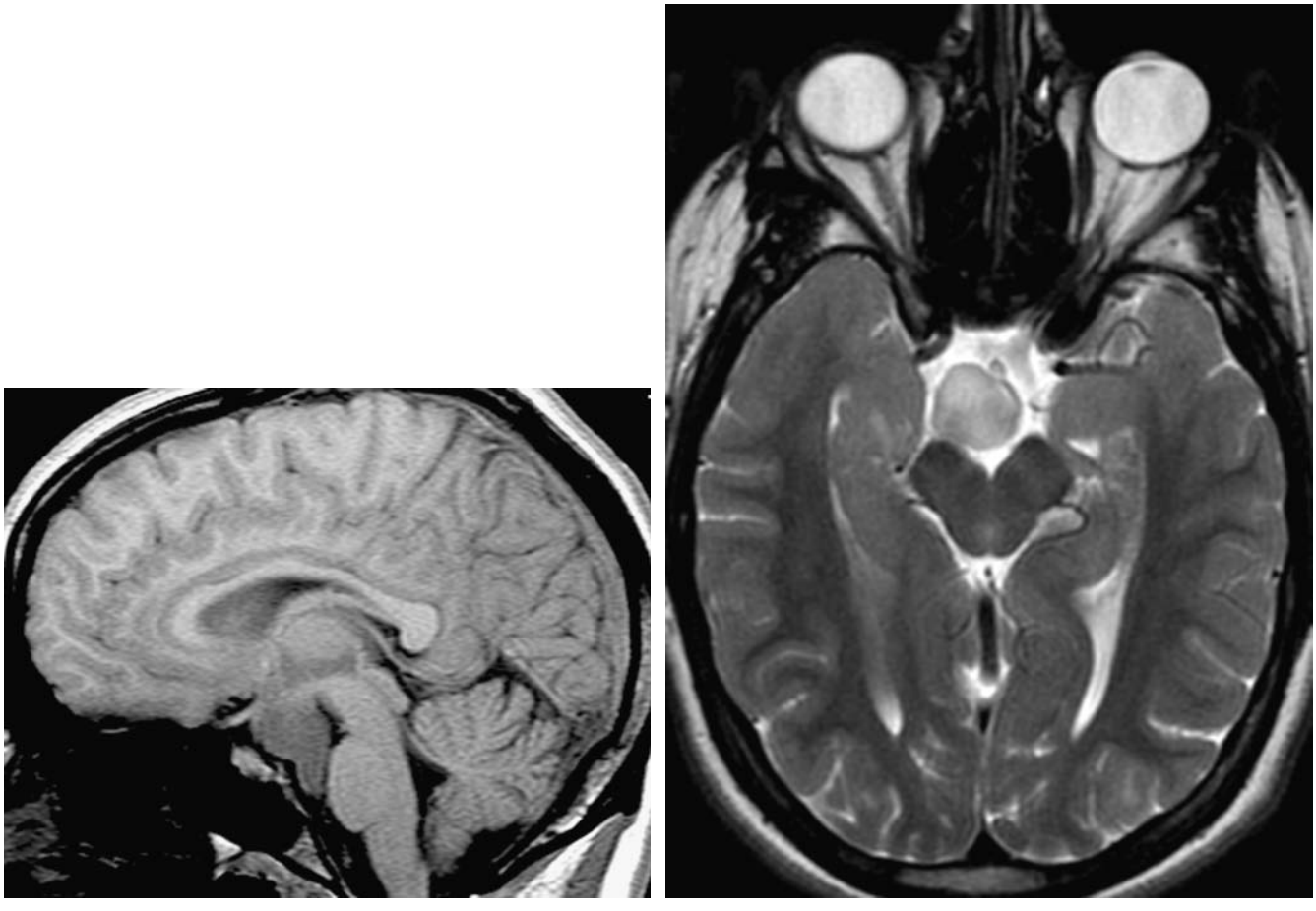
Figure 84.3 Ganglioglioma. Young adolescent male showing a well-demarcated rounded cortical-subcortical process involving the fusiform and inferior temporal gyri. The mass is homogeneously enhanced after contrast administration (a, b). Mass effect and edematous associated changes are mild (a) limited to an aspect of moderately expanded gyri with adjacent sulcal effacement.

between hamartomatous neurons to the limbic lobe could be one of the underlying causes generating seizure activity.[85] Precocious puberty was present in 2/3 of patients and almost 50% presented gelastic or generalized seizures and behavioral disorders.[83,87,89,92] Mental retardation is often associated in children.[86] Diabetes insipidus, growth hormone secreting pituitary adenomas and obesity may be associated.[83,93] Facial anomalies, heart defects or Laurence-Moon-Biedl syndrome have been reported as additional associated malformations. Presence of postaxial polydactyly suggests an autosomal dominant disorder, Pallister-Hall syndrome.[94,95] Tumoral excision may improve patients with medically refractory seizures.

Morphology and imaging

Hypothalamic hamartomas are solid well–demarcated neoplastic processes of neuronal tissue, attached to the floor of the third ventricle posterior to the pituitary stalk. They are usually pedunculated, best shown on coronal cuts or sessile demonstrated on midsagittal cuts. They usually extend toward the suprasellar or the interpeduncular cisterns. They vary in volume from several millimeters to few centimeters. Very rarely the mass appear calcified but show no intratumoral hemorrhage.[99] Typically the neoplasm does not infiltrate the adjacent neural tissues. Associated brain abnormalities may be found in the pediatric population such as callosal dysraphism, heterotopias, polymicrogyri.[86,87] A clinical-topographical classification proposed, with a type I (a and b) concerning small pedunculated masses attached to the tuber (Ia) or the mamillary body (1b), usually asymptomatic or presenting with precocious puberty, and a type II (a or b) in sessile hamartomas, larger than 1.5 cm associated with gelastic epilepsy.[100]

Axial CT usually fails to depict small sessile hamartomas attached to the floor of the third ventricle. Those visible are isodense to brain and well demarcated.[96] Sagittal and coronal cuts using MR improve the diagnostic capability even in very small tumors. MR shows more characteristic imaging features (Figure 84.4). The hypothalamic mass is well delineated, round or ovoid, attached to the floor of the third ventricle or extending into its cavity. Its signal intensity is roughly similar to gray matter. Hypothalamic hamartomas are homogeneously isointense to gray matter on SE-T1w sequences becoming slightly more hypointense on GE-T1w images with IR-preparation. The tumors appear slightly hyperintense to brain on PDw sequences. On T2-w images hamartomas are moderately hyperintense or may remain isointense to brain in about 1/3 of the cases.[85,98] The mass may appear heterogeneous, showing a hypointense central area on T1-w images and a hyperintense central area on T2-w images, surrounded by an isointense peripheral rim. MR spectroscopy tends to show a slight increase of the myoinositol peak and a small decrease of NAA peak, lower than within the thalami.[98] Large cystic formation may infrequently be found. Calcifications may be found. Hypothalamic hamartomas as a rule do not enhance.)[85] Hypothalamic glioma should be considered in the differential diagnosis.



(a) (b)

Figure 84.4 Hamartoma of the tuber cinereum. Huge well-delineated and pedunculated hypothalamic mass attached to the tuberal region of the floor of the third ventricle, between the pituitary stalk and the mamillary bodies as evidenced on the midsagittal T1-w cut (a) and developing within the interpeduncular and the upper prepontine cisterns. The tumor is homogeneous and roughly isointense to gray matter on T1-w (a) and slightly hyperintense on T2-w (b) sequences. The mass did not show any contrast enhancement.

Cortical hamartomas

Corticosubcortical hamartomas are formed of mature but disorganized ganglion and glial cells. Discovered in patients presenting epilepsy but with a normal neurological examination. Usually solitary, brain hamartomas are commonly located in the mesial temporal lobe and may involve the hippocampal formation or in the frontal lobe. They are well-circumscribed masses with no mass effect on the adjacent cortex or sulci. Cortical dysplasia is often associated.[17,18] The main differential diagnosis is the ganglioglioma. On MR imaging the lesion is usually homogeneous, isointense to gray matter on T1-w images, iso- to slightly hyperintense on T2-w images and becomes more or less hyperintense to gray matter on FLAIR sequences. A rim of hypointensity may be observed on T2-w surrounding the hyperintensity.[99] The tumors generally do not enhance.

Developmental cysts

Arachnoidal mesial temporal cysts of developmental origin are usually found incidentally and infrequently in patients referred for seizures. These smoothly marginated cysts are commonly found within the choroidal fissure which appear enlarged. The size of the cystic mass is variable and may be associated with variable mass effect upon the hippocampus. The cyst is well-delineated, ovoid in shape, fluid-filled, showing an homogeneous isointense signal intensity to CSF on all sequences. It never shows any peripheral contrast enhancement (Figure 84.5) but must be differentiated from cystic tumors arising in the mesial temporal lobe.

Neuroimaging of primary brain gliomas

The overall incidence of intracranial tumors is estimated to reach 5 individuals per 100 000 population per year. The rate of brain tumors is much higher in older patients reaching roughly 40% per year per 100 000 population after age 80. Primary brain tumors represented by the gliomas correspond to almost half of all primary intracranial tumors in adults and roughly two-thirds of these in children less than 15 years old. Metastatic tumors, rare in childhood, represent in adults roughly 1/4 of all intracranial tumors in autopsy series. There is a topographic difference between intracranial tumors found in adults, and children. Almost 70% of brain tumors are supratentorial in location in adults, whereas roughly 70% are found in the posterior fossa in children.

Elements of histopathology and classification

Gliomas may be divided into astrocytomas, oligodendrogliomas, and ependymomas corresponding respectively to the three types of glial cells, the astrocytes, oligodendrocytes, and the ependymal cells. Almost 5% of these neuroglial tumors are of a mixed type or 'mixed gliomas'.

Astrocytic tumors or 'astrocytomas' may be subdivided into five clinicopathological categories: 1) Diffuse astrocytomas representing more than 60% of all primary brain tumors are subdivided into three groups: low-grade diffuse astrocytomas (WHO grade II), anaplastic astrocytomas (WHO grade III), and glioblastomas multiforme (WHO grade IV); 2) Pilocytic astrocytomas (WHO grade I) found in childhood and usually circumscribed; 3) Pleiomorphic xanthoastrocytomas (WHO grade II) but showing some 'malignant' features on conventional criteria and usually circumscribed; 4) Desmoplastic astrocytomas, mixed neuronal-glial tumor, found in infancy; and 5) Subependymal giant cell astrocytomas typically found in tuberous sclerosis and usually circumscribed. The relationship with the neuroimaging aspect is critical as high grade astrocytomas show an enhancing core that may be necrotic centrally with surrounding edema. The enhanced part of the tumor correlates with neovascularity, hypercellularity and mitotic activity. Tumoral cells are found within the surrounding edematous area at least over 2 cm from the enhancing tumoral margin.

Oligodendroglial tumors or 'oligodendrogliomas' are subdivided into: (1) oligodendrogliomas (WHO grade II) and (2) anaplastic oligodendrogliomas (WHO grade III).

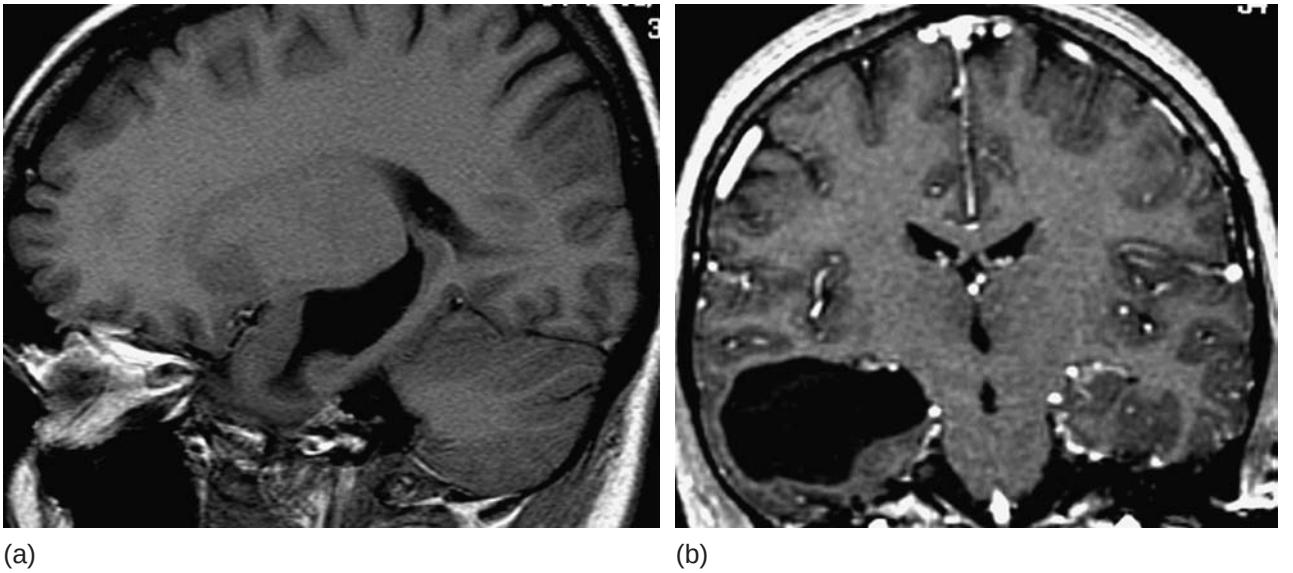
Mixed gliomas correspond to tumors showing a mixture of neoplastic astrocytic and oligodendroglial components. This pathological entity may be subdivided into two groups: (1) oligoastrocytomas (WHO grade II) more frequent of both varieties and (2) anaplastic oligoastrocytomas (WHO grade III).

Signs and symptoms

Patients with brain tumors may present variable neurological syndromes such as: generalized impairment of intellectual function with variable mental changes including emotional lability, inertia, psychomotor reduction, disturbance of memory, spatial disorientation and behavioral disorders; syndrome of increased intracranial hypertension with headaches usually mild, nocturnal and/or worse in the morning and of the pulsatile type, commonly bifrontal and bioccipital, accompanied by vomiting in almost 1/3 of the cases; generalized or focal seizures found in 20–50% of cases with the presence of an aura being suggestive and occurring most frequently in more than 2/3 of cases in slow-growing tumors as compared with fast-growing tumors in 30% of cases; specific neurological syndromes suggestive of specific tumors and localizations.

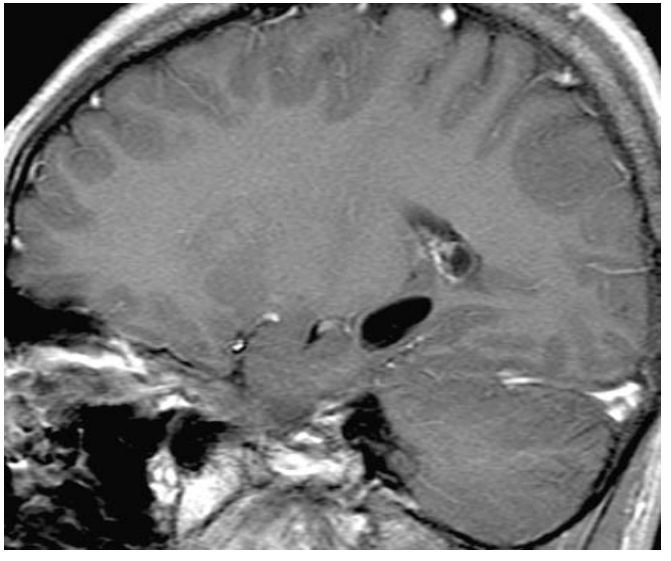
Low grade diffuse astrocytomas

Diffuse astrocytomas are poorly marginated neoplasms of varying potential which infiltrate the brain parenchyma. The appellation astrocytoma must be reserved to low-grade (WHO grade II) astrocytic tumors. These primary brain tumors account for 25–30% of all cerebral gliomas. The peak incidence occurs in young adults between ages 20 and 45 years in 60% of the cases (mean age of 34), after 45 years old it is about 30% and 10% before 20. They are unusual during the first decade and also in people older than 65. A slight male predilection is observed with a ratio M:F of 1.8:1. These are slowly-growing infiltrating tumors occurring anywere in the central nervous system but with a predilection to the cerebral hemispheres in adults following the path of white matter tracts without any associated significant damage, explaining the delayed symptomatology. These tumors are well-differentiated 'benign' but showing a great tendency for

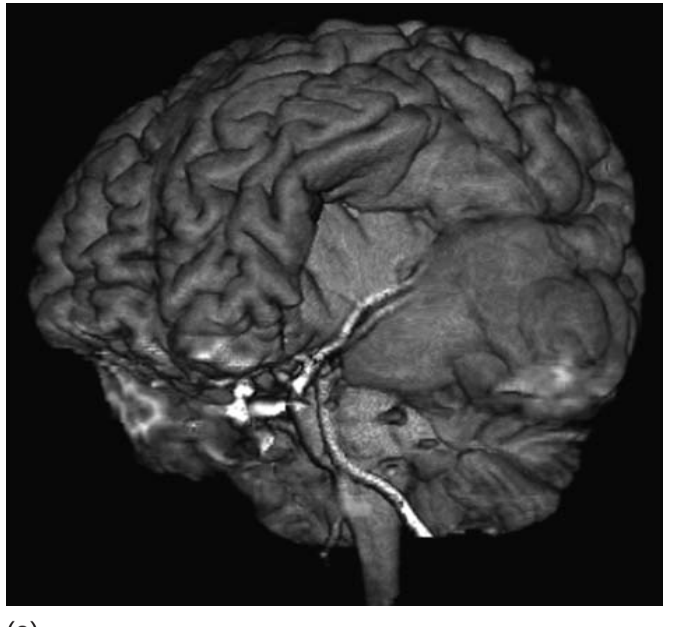


(a) (b)

Figure 84.5 Developmental mesial temporal cyst of the choroidal fissure. Usually found incidentally and of small volume, arachnoidal cysts are found within the choroidal fissure. Commonly of small size, the cyst may be huge, as in this case, with significant mass effect on the hippocampal formation displaced superiorly and effacing the temporal lobe sulci. The cyst is smoothly marginated and appears isointense to CSF on all sequences. No contrast enhancement of the cyst wall and no mural nodule associated (b) as compared to T1-w precontrast parasagittal cut (a). Such cysts have to be differentiated from other cystic lesions that may develop in the mesial temporal lobe, such as glial parenchymal cysts, found in another patient with intractable epilepsy, arising in the white matter core of the parahippocampal gyrus expanded, with upward displacement of the body of the hippocampus.



(c)



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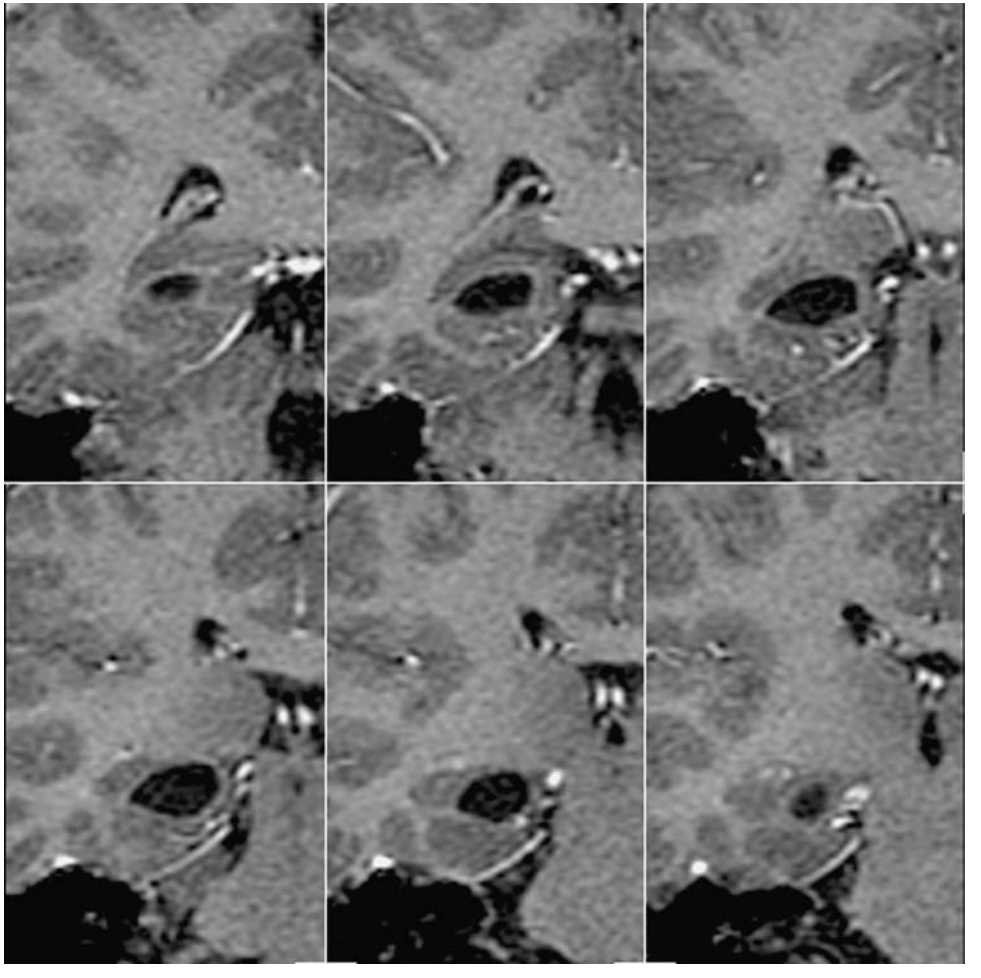


(d)

Figure 84.5 cont'd (c). The cystic mass lack of contrast enhancement (d). A huge temporal-insular arachnoidal cyst associated with adjacent dysplastic cortex (e) shown on a 3D image of the brain, explained in another patient seizure activity.

malignant transformation or anaplasia. Many of these tumors show areas of different degrees of anaplasia.[100,102]

Histopathologically the tumors are formed of neoplastic astrocytes which are increased in number and size. Three major variants may be distinguished with respect to the related neoplastic cell type: (1) fibrillary astrocytomas, the most frequent variety formed of fibrillary astrocytes, elongated cells with little visible cytoplasm expressing GFAP; (2) gemistocytic astrocytomas, composed mainly of gemistocytic neoplastic astrocytes, plump cells with eosinophilic abundant cytoplasm expressing GFAP; (3) protoplasmic astrocytomas, a rare variant of stellate cells with small cell bodies and showing few or no stainable fibrils.

Morphology and imaging

Low-grade diffuse astrocytomas are commonly homogeneous infiltrating tumors, developed in the cerebral hemispheres in young adults or in children. They are found anywere in the cerebral hemisphere except in the occipital lobe. Ill-defined, they do not show clear-cut demarcation from the adjacent normal parenchyma as demonstrated on pathological specimen. It has been shown that the tumoral process due to its infiltrating nature may extend beyond the abnormality evidenced on imaging. The tumors tend to expand the anatomical structure involved which appear bulkier than normal or may infiltrate these structures without marked morphological changes or distortion of the normal anatomy. Occasionally invasion of the subarachnoid spaces may be shown but it is usually observed in case of malignant degeneration.

These low-grade tumors usually lack of peritumoral vasogenic edema due to a normal blood–brain barrier. Presence of cytotoxic edema is unlikely as well. There are no vascular flow voids within the tumoral process and no evidence of intratumoral hemorrhage or necrosis. Calcifications which occur in about 15–20% of cases are seldom evidenced on MR as compared to CT. On CT such tumors tend to be isodense to hypodense. Using MR, the tumor is homogeneously isointense to hypointense to white matter on T1-w images becoming typically hyperintense to cortex and brighter than CSF, almost homogeneously, on PD-w images and hyperintense to white matter on T2-w and FLAIR images (Figure 84.6). Proton spectroscopy demonstrates an increase in Cho levels, a decrease in NAA levels and a mild elevation of Cr, but with nearly absence of lipid resonance peaks.[101] Note that the spectrum of low-grade gliomas may be similar to normal brain. Low-grade diffuse fibrillary astrocytomas (WHO grade II) usually do not show contrast enhancement and this may constitute the so-called 'paradoxical' diagnostic imaging feature. Note that enhancement is common in the circumscribed partly cystic pilocytic astrocytomas (WHO grade I) involving the mural nodule as in pleiomorphic xanthoastrocytomas and as in higher grade anaplastic astrocytomas (WHO grade III) or glioblastomas (WHO grade IV). Enhancement may be demonstrated during the course of the disease, mainly with tumor transformation. Note that recurrent low-grade gliomas usually show a more malignant form. Approximately 50% of glioblastomas show evidence of a pre-existing lower-grade astrocytoma. Note that enhancements do not correlate adequately with the histological grade of the tumor because anaplastic astrocytomas show variable behavior, including patchy enhancement or faint enhancement, or even no enhancement. Only half of the low-grade astrocytomas with characteristic imaging features prove to be low-grade tumors.[102–104] The prognosis is variable as well because of frequent transformation into high-grade tumors either spontaneously or in recurrent tumors.

Pilocytic astrocytomas

Pilocytic astrocytomas, are circumscribed low-grade (WHO grade I) benign tumors, also called juvenile pilocytic astrocytomas or polar spongioblastomas.[72] They represent 2–6% of all primary brain tumors and are as frequent as low-grade diffuse astrocytomas in epilepsy surgery series. Most astrocytic tumors of childhood are pilocytic astrocytomas. These tumors are relatively slow-growing neoplasms with a relatively favorable outcome. They are found primarily in childhood with a peak age of presentation between 5 and 15 years old and an equal incidence in both sexes in most series. A slight female predominance has been reported in a ratio less than 4:3. Seizures are a common presenting sign.

Morphology and imaging

Pilocytic astrocytomas are well-circumscribed yet encapsulated tumors which usually do not invade nor infiltrate the adjacent normal brain tissue as do most astrocytomas, but tend to expand the brain parenchyma. Most of these tumors tend to develop a cystic component and may show calcifications in almost 25% of cases. The overall suggestive gross aspect of the tumor is described as a fluid-filled proteinaceous cyst with a mural nodule. The mural nodule may be round or plaque-like. The wall of the cystic component is surrounded by a non-neoplastic gliotic tissue. Tumors with a pure solid component are infrequent. Multilobulated cystic mass is a more common finding. The tumors are most commonly located in the cerebellum, hypothalamus, thalamus, brainstem, and cerebral hemispheres.

On CT, the mural nodule is usually isodense with eventually associated cytic component and calcifications. On MR, the tumor is isointense to white matter on T1-weighted sequences and hyperintense on T2-w. MR spectroscopy may show in addition a reduced NAA peak and an elevation of lactate and lipid levels.[105,106] An intense homogeneous or heterogeneous enhancement of the tumor or its mural nodule is a characteristic feature and is invariably present. Note that the walls of the cystic component usually do not enhance (Figure 84.7). Contrast enhancement helps to differentiate it from a diffuse low-grade astrocytoma. Conversely it may lead to an erroneous diagnosis of a high-grade astrocytoma, especially in the cerebral hemisphere due to the possibility of associated vasogenic edema.

Oligodendrogliomas and mixed gliomas

Oligodendrogliomas are glial tumors arising from oligodendrocytes, usually slow-growing and developing in the cerebral hemispheres with a duration between symptoms and surgery ranging from 2 to 7 years. The presenting sign is most frequently a focal or generalized seizure found in 50–70% of cases. Signs related to intracranial hypertension with headaches are found in about 1/5 of cases. About 30% reduction in seizure frequency is observed after surgery.[107,108]

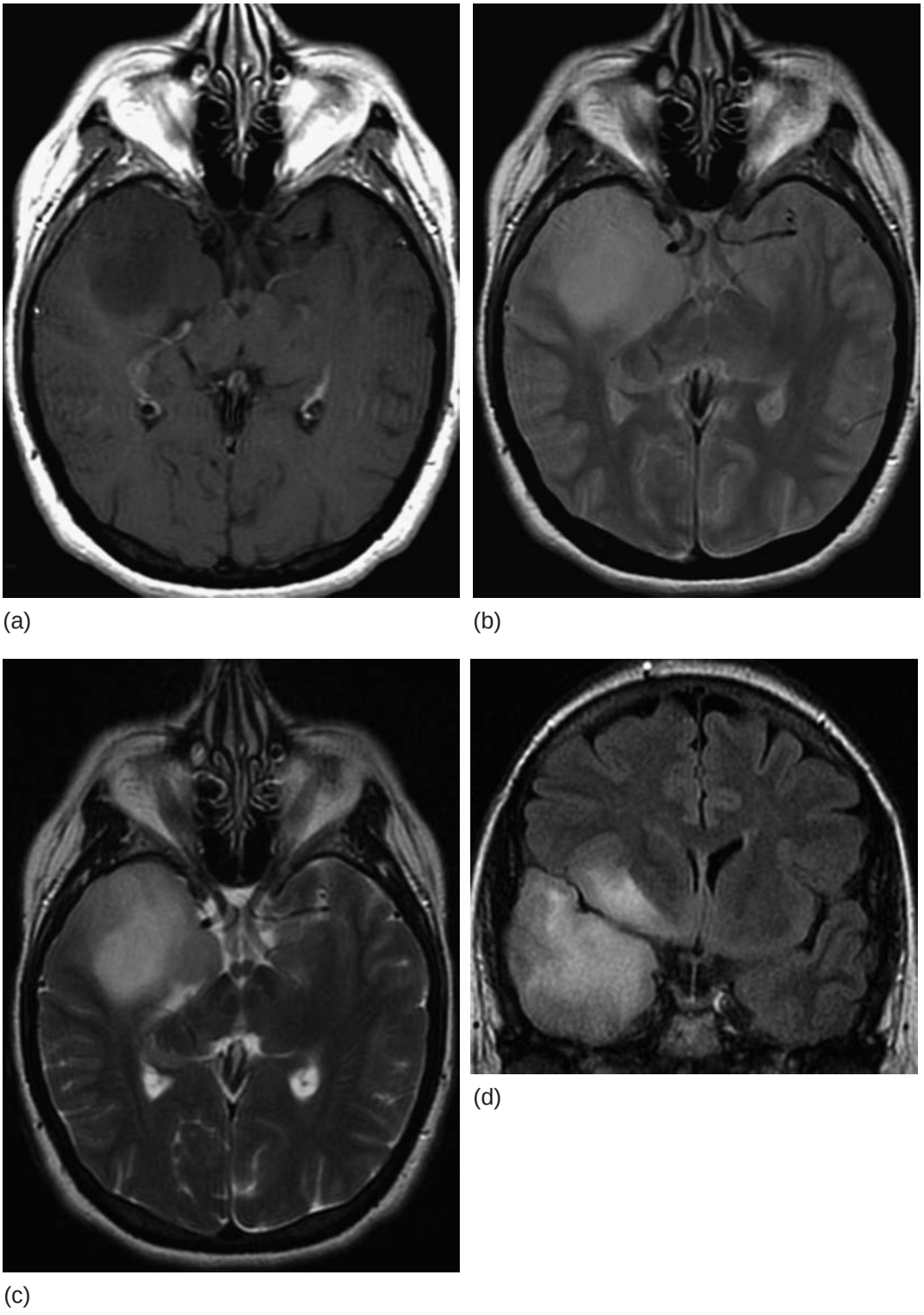
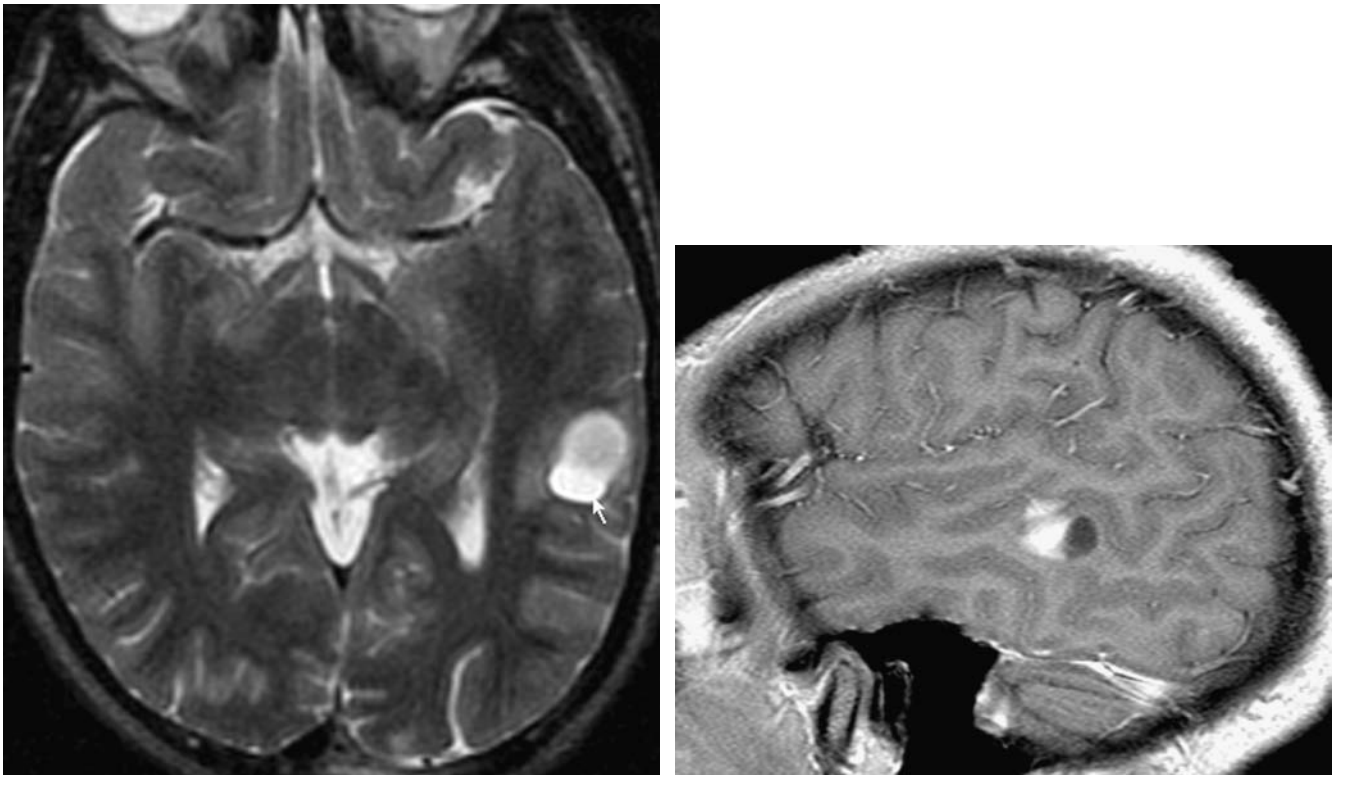


Figure 84.6 Low grade diffuse fibrillary astrocytoma (WHO grade II). MR shows a relatively well-demarcated temporal lobe mass expanding the pole with little associated edema and moderate mass effect on the mesial temporal region. The tumor is homogeneously hypointense to white matter on T1-w (a), hyperintense to gray matter on PD-w (b), T2-w (c), and FLAIR (d) sequences. The tumor infiltrates superiorly the sublenticular area and part of the insular lobe (d). No contrast uptake has been evidenced.

The overall 15-years, survival is about 25%[109] improving to reach almost 70% in the pediatric population.[108] Oligodendrogliomas are infiltrating usually well-defined tumors formed of cells resembling oligodendrocytes. Oligodendrogliomas account for 5–10% of all intracranial neoplasms and about 18% of all gliomas. They are found most commonly in adults in the fourth and fifth decades and are rare in infants or children found in about 6% of cases. A biphasic age distribution of 6–12 years and 26–46 years is found.[108,110] A slight male preponderance is observed with a 2:1 ratio.

Histopathologically, oligodendrogliomas correspond to WHO grade II in well-differentiated tumors and WHO grade III for anaplastic tumors. The Kernohan and Saint-Anne/Mayo classifications differentiate prognostically low-grade (1 and 2) from high-grade (grade 3 and 4) tumors. The classification is still debated. Oligodendrogliomas show a wide



(a) (b)

Figure 84.7 Pilocytic astrocytoma (WHO grade I). The tumor arising in the lateral temporal lobe demonstrates a characteristic cyst with mural nodule. The nodule is moderately hyperintense to the cortex on the T2-w axial image (a) and shows marked homogeneous enhancement on the T1-w lateral sagittal cut (b). Notice that the cystic component does not enhance with contrast.

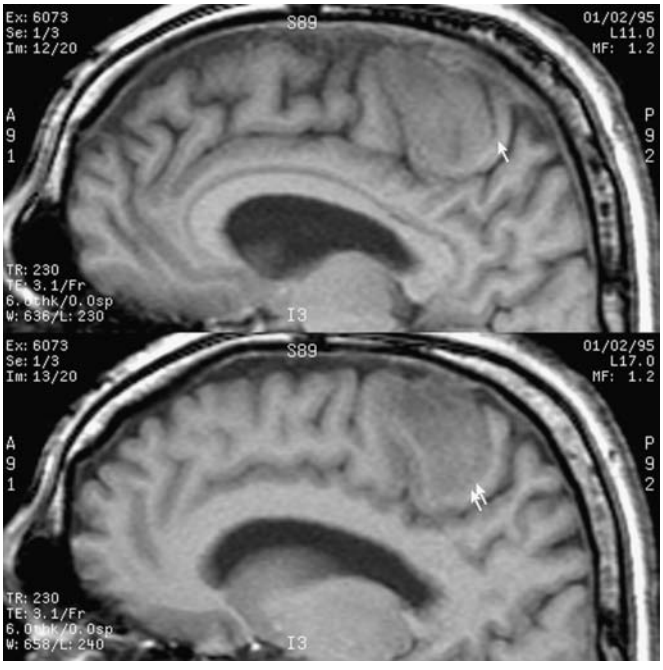
variation ranging from well–differentiated to highly malignant lesions.[111] Oligodendrogliomas are moderately cellular with a characteristic presence of intratumoral microcalcifications in 70% of cases which may also be found in the adjacent cortical area. Most neuropathologists require a preponderance of 75–90% of neoplastic oligodendrocytes within the tumor to be qualified as oligodendrogliomas, the remaining being considered as mixed gliomas.

Morphology and imaging

Oligodendrogliomas are supratentorial in location in 90–95% of the cases from which more than 50% up to 85% are located in the frontal lobe followed by the temporal, parietal and occipital lobes.[109,112,113] The tumors tend to progressively grow toward the cortex infiltrating and expanding the corresponding gyri in a nondestructive manner similar to low-grade astrocytomas rather than centrally infiltrating the corpus callosum. The tumors develop and spread similarly to astrocytomas through white matter which appears largely expanded before symptoms are produced. The importance of infiltration is usually more limited than in diffuse astrocytomas. Blurring of the gray-white matter interface is caused by the propensity to invade the cortex and even the leptomeninges with secondary desmoplastic reaction. This superficial extent and slow growth often causes a remodeling of the inner table of the skull observed in 17% of cases.[109] Meningeal gliomatosis and ventricular seeding are found in almost 10% of oligodendroglial tumors.[113] Oligodendrogliomas are commonly fairly well-circumscribed tumors with poorly defined boundaries, showing little peritumoral edema. Some may appear heterogeneous due to the intralesional presence of small cystic areas of degeneration (20%) and/or hemorrhages (20%) and / or calcifications (50–70%), the latter being best demonstrated on CT as dense or gyriform in shape commonly limited to the cortical areas and mimicking Sturge-Weber disease except that the brain is not atrophic. Calcifications may be to some extent depicted on MR using T2* gradient–echo sequences due to magnetic susceptibility, sensitive to the presence of iron frequently present within dystrophic calcifications. Most calcifications are isointense on T1-weighted and may become markedly hypointense on T2-weighted sequences.

Anaplastic oligodendrogliomas appear as diffusely infiltrating tumors much less demarcated than oligodendrogliomas, with increased associated edema and mass effect. Occuring in adults in their fifties, they are found in the frontal lobes in 60% of cases and in the temporal lobe in roughly 30%. Their estimated incidence is unsettled due to less defined criteria for grading ranging from 20–50%. A variable heterogeneous aspect is found owing to the presence of necrotic or cystic areas, hemorrhages and calcifications, similar to that observed in other anaplastic gliomas. This variety respond well to chemotherapy.

Mixed gliomas in which are demonstrated two neoplastic components are most frequently of the oligoastrocytic variety. These WHO grade II oligoastrocytomas are found in young adults with a mean age of 45 years, in the frontal and less frequently in the temporal lobes and show no significant imaging differences as compared to WHO grade II gliomas (Figure 84.8).



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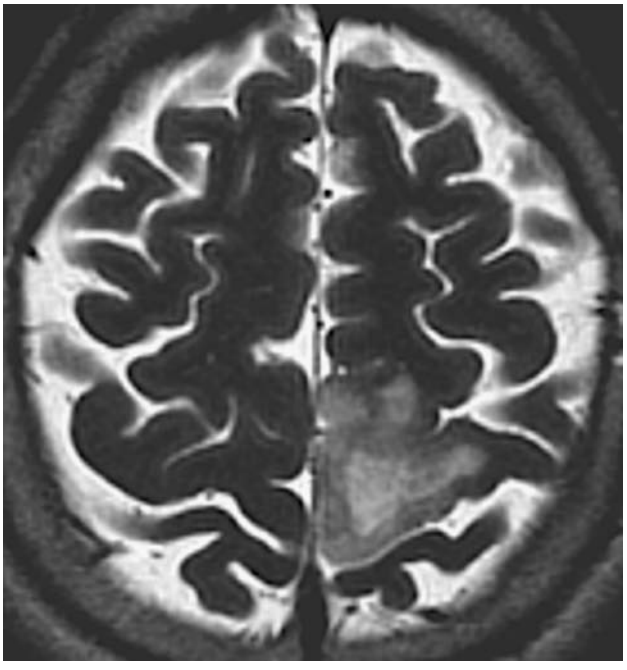

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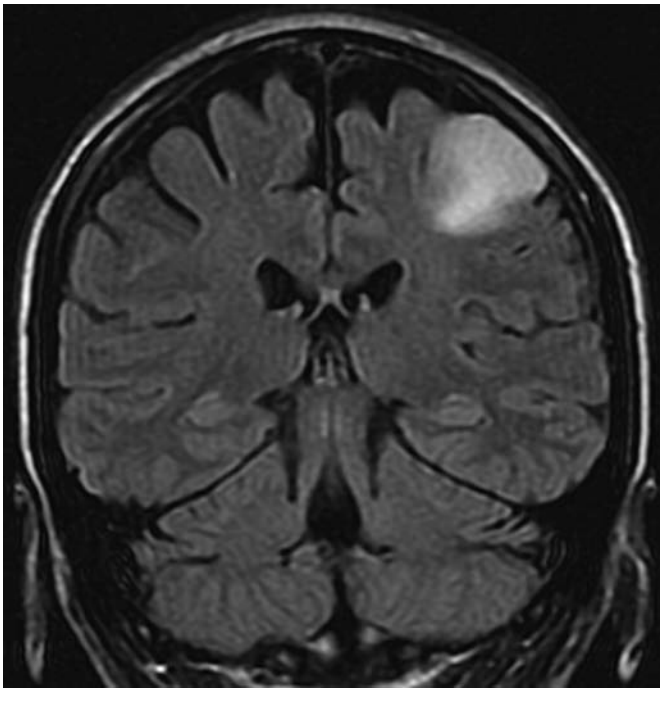

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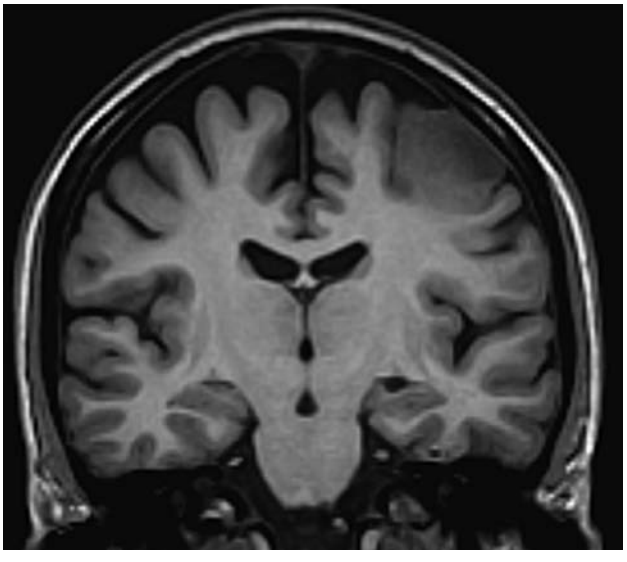


(d)

Figure 84.8 Mixed glioma (oligoastrocytoma, WHO grade II). Relatively well-delineated corticosubcortical tumor involving the superior part of the precentral gyrus extending medially into the paracentral lobule and anteriorly toward the superior frontal gyrus. The tumor is moderately hypointense to white matter on T1-w (a) images and appear roughly heterogeneous and moderately hyperintense on T2-w axial cuts (b). A slight sulcal effacement of the central sulcus is evidenced posteriorly. No associated edema not contrast enhancement were observed. The tumor is homogeneously hyperintense on FLAIR (c) sequence and best evaluated using 3D-T1w 2 mm contiguous slices acquisition (c) and volume renderings.

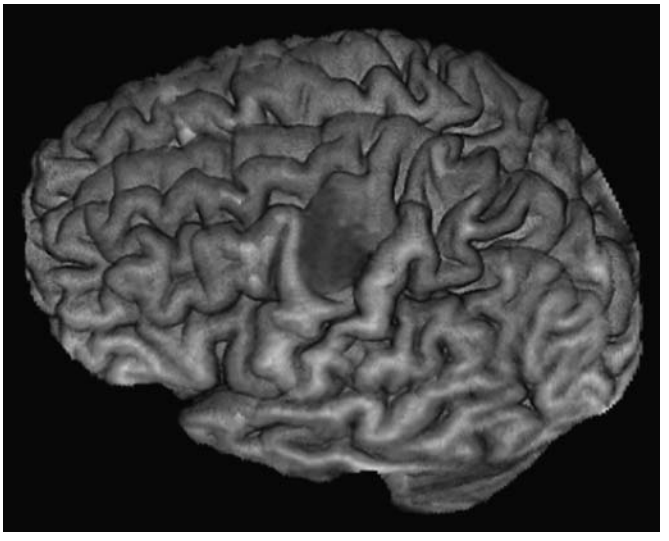


Figure 84.8 cont,d (e), Useful for presurgical planning, as shown in this other young patient with a mass expanding part of the hand unit of the precentral gyrus (c, d, e).

On CT oligodendrogliomas appear as well-circumscribed cortico-subcortical hypodense, partly calcified masses in about 40%, showing hemorrhagic areas in 20%, and presenting cystic formations in 20% of.[112,113] Sometimes a gyriform pattern of calcifications may mimic the changes observed in Sturge-Weber disease. On MR the tumor is remarkably hypointense to white matter or isointense to gray matter on T1-weighted images, hyperintense to cortex on PD-weighted images and hyperintense to white matter on T2-weighted or FLAIR images (Figure 84.9). In anaplastic oligodendrogliomas the aspect is more heterogeneous, showing small areas of necrosis. More infiltrating with a much less demarcated shape, they show a lower SI on T2-weighted sequences due to hypercellularity. Oligodendrogliomas may show contrast enhancement, usually mild and heterogeneous, reported in about 25% of cases on CT and almost 80% on MR.[111] Anaplastic oligodendrogliomas may show nonspecific irregular ring-enhancement patterns. Enhancement may have a negative correlation with patient survival.[114,115] In comparison with adults, oligodendrogliomas in children are less commonly calcified, enhance less frequently and show little peritumoral edema.[108]

Anaplastic astrocytomas and glioblastomas multiforme

Malignant astrocytic tumors are represented by the anaplastic astrocytomas (WHO grade III) nd the glioblastomas (WHO grade IV).

Anaplastic astrocytomas show a peak incidence in the fifth decade, with males more frequently affected than females with an almost 2:1 male-to-female ratio. They are slightly more frequent than low-grade fibrillary astrocytomas averaging 25% of gliomas. Almost 2/3 result from dedifferentiation of low-grade gliomas. The median survival averages 2.5 years. Histopathologicaly anaplastic astrocytomas are diffuse fibrillary astrocytomas of intermediate form showing on preparations focal areas of anaplasia involving roughly half the cells and focal or diffuse increased cellularity by 50% or more. They typically display mitotic activity. The microcystic changes found in low-grade tumors are lacking here. They may arise de novo or develop from low-grade tumors by malignant transformation.

Glioblastoma multiforme is the most frequent brain tumor in adults accounting for 50–60% of all astrocytic and 15–20% of all intracranial tumors. It is the most malignant of diffuse astrocytomas with a survival time of about 12 months. They usually arise as primary intracranial tumors but may develop as secondary tumors from low-grade diffuse or anaplastic astrocytomas. Glioblastomas are found at any age but most commonly in adults between ages 45 and 70 with/a mean of around 50 years old. They are rare in patients under age 30, with less than 3% reported.[117] The incidence in men is more frequent than in women, about 2:1. They are found most often in the cerebral hemispheres. Histopathologically the diagnosis of glioblastoma is based on the presence of anaplastic glial cells, frequent mitotic activity, endothelial proliferation and hypervascularity, found peripherally or around the necrotic zones. Frequent areas of necrosis are usually found in the center of the tumor. Apparent multicentric tumors are reported in as many as 5–15% of cases, presumably due to the presence of multifocal zones of anaplasia within a pre-existing low-grade diffuse astrocytoma.[116,118] Multiple glioblastomas are present as independent tumors in about 2.5–5% of cases.[118] Widening of the extracellular spaces through vasogenic edema facilitates spreading of the neoplastic cells.

Signs and symptoms: the clinical picture is similar in anaplastic astrocytomas to that presented in low-grade gliomas except for a shorter medical neurological history preceeding diagnosis and a higher mean age of 40 years old. The duration of the clinical history decreases dramatically in glioblastomas developed de novo, becoming as short as 3–6 months in almost half the cases as compared with those developing from pre-existing low-grade diffuse or anaplastic astrocytomas (4–5 years duration of the neurological history). In glioblastomas the symptomatology develops rapidly in a few weeks or months including generalized neurological symptoms and seizures followed by more definite lobar or callosal syndromes according to brain localization. The onset may even be sudden in 3–5%, pseudovascular in progression usually due to intratumoral hemorrhage or cystic formations within the tumor and leading to the development of focal cerebral signs. Glioblastomas show a very poor prognosis with less than 20% of patients surviving for 1 year and 10% beyond 2 years after the onset of clinical symptomatology. Younger patients, less than 45 years old, appear to have a better prognosis than the older presumably because of the higher frequency of secondary glioblastomas in such younger populations. Longer survival would be related to complete resection when possible.

Morphology and imaging

Anaplastic astrocytomas are morphologically often difficult to distinguish from low-grade astrocytomas but appear much more heterogeneous.[103,104] As in diffuse fibrillary astrocytoma the tumor shows tendancy to infiltrate the anatomical structures involved without obvious distortion except for a relative enlargement of the corresponding gyri or the basal ganglia. Vascular proliferation and necrosis are lacking. Occasionally proliferation of tumor vessels may be observed with flow void foci. Note that anaplastic astrocytomas are found in half the

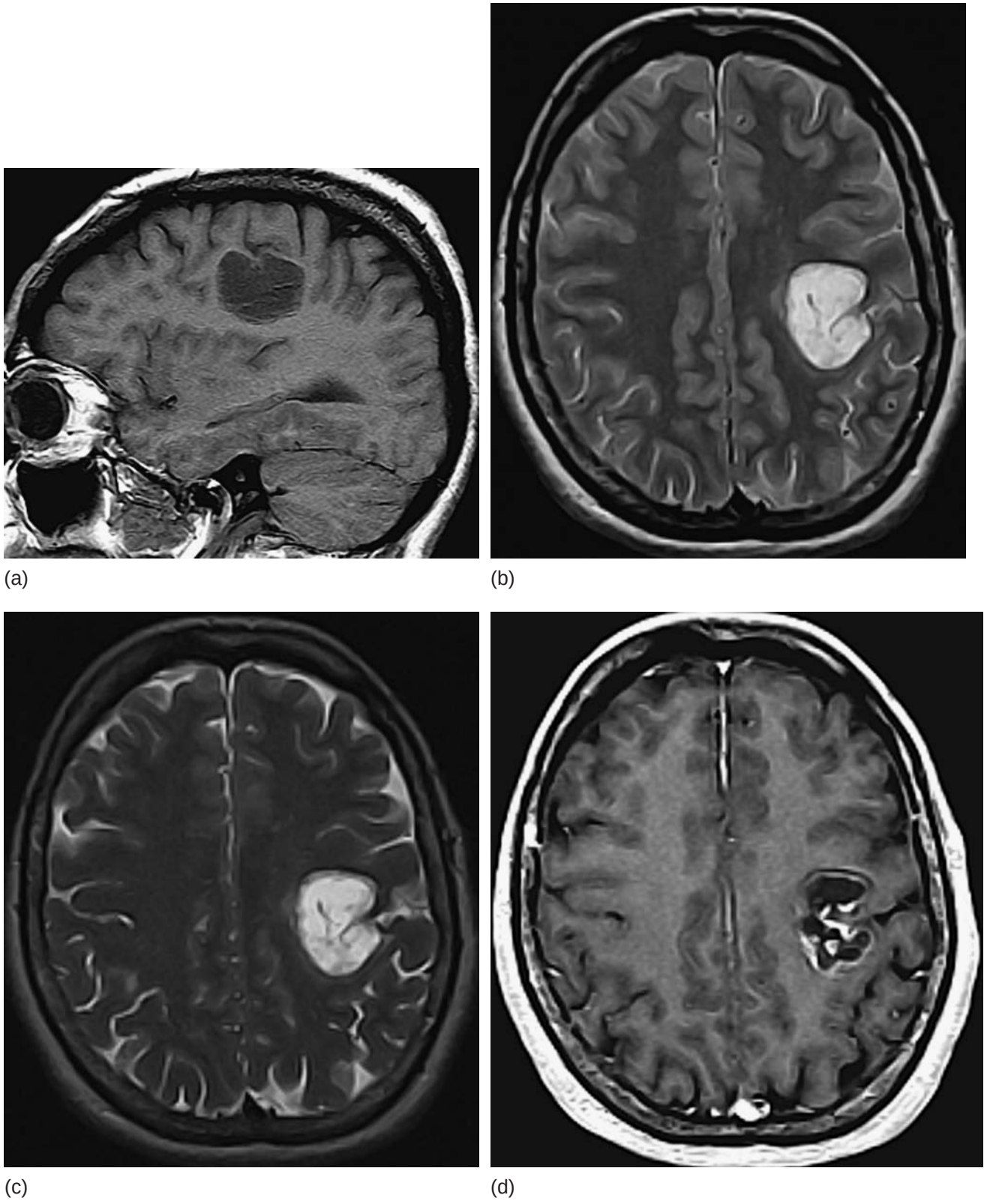


Figure 84.9 Oligodendroglioma (WHO grade II). Superficial fairly well-circumscribed mass developing in the central lobe within the subcortical white matter rand abuting the cortex. The tumor is hypointense to gray matter on T1-w sequence (a) and hyperintense on PD-w (b) and T2-w (c) sequences. Almost no mass effect, peripheral edema no intratumoral calcifications were evidenced. A peripheral contrast enhancement is noticed (d).

cases of recurrent tumors due to malignant transformation. Peritumoral edema and mass effect may be found but remain a feature of glioblastomas. Frank intratumoral necrosis is absent.

Anaplastic astrocytomas are usually heterogeneous tumors but may mimic a low-grade astrocytoma showing a homogeneous SI with slightly heterogeneous areas.[102,104] Hypointense to white matter on T1-w images the tumor is hyperintense to cortex on PD-w images and appear hetereogeneously hyperintense to white matter on T2-w images and FLAIR. Proton spectroscopy has been reported in anaplastic astrocytomas to show an increase of Cho levels, a decrease of NAA levels and presence of lipid resonance peaks. Anaplastic astrocytomas show variable patterns of enhancement ranging from homogeneous to even nodular or patchy (Figure 84.10). Very occasionally a 'ringlike' pattern is found. The latter is more suggestive of a glioblastoma and should not be observed in anaplastic astrocytomas.[103]

Glioblastoma multiforme, the most aggressive and least differentiated variety of gliomas, occur most commonly in the

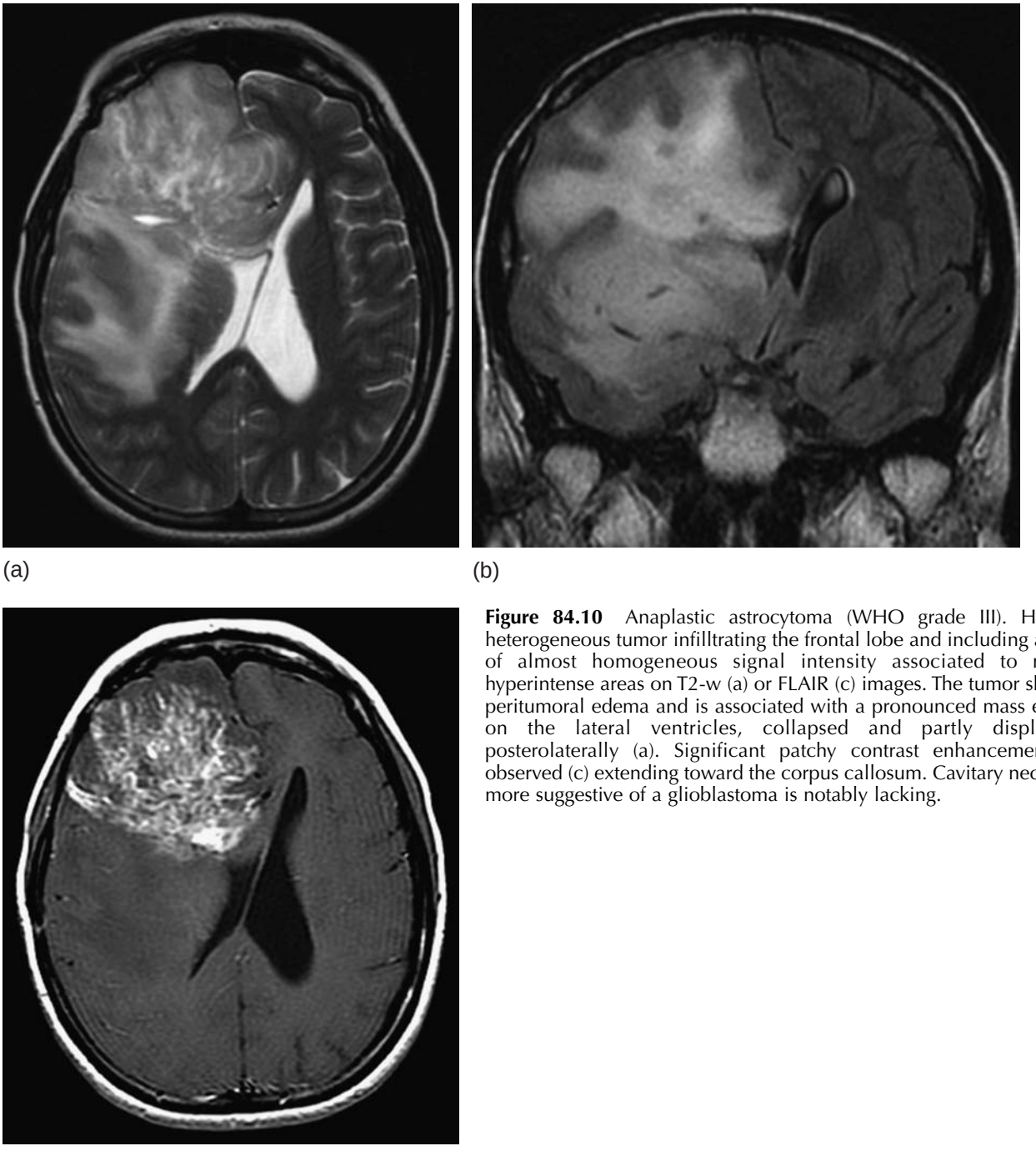
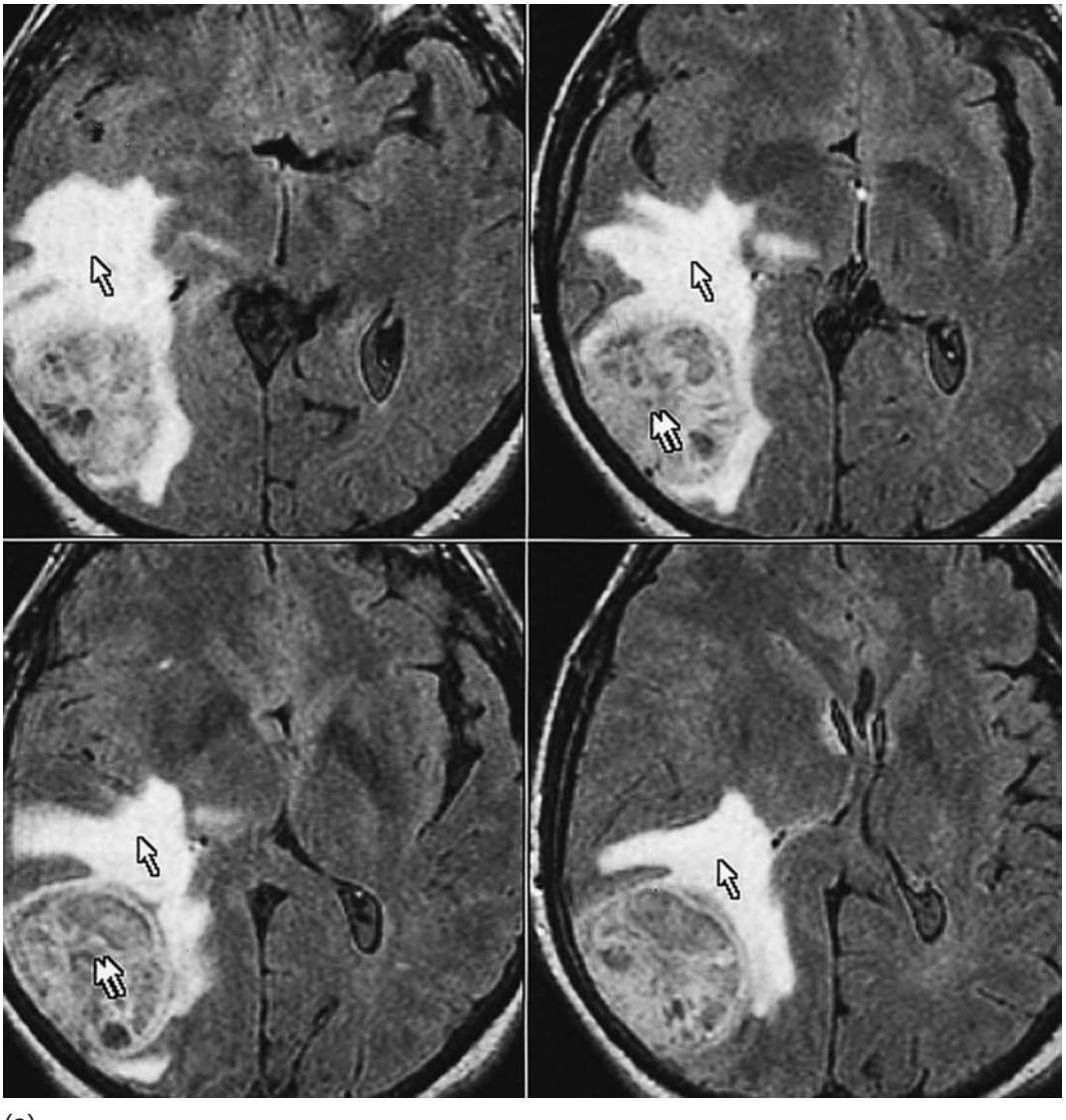


Figure 84.10 Anaplastic astrocytoma (WHO grade III). Highly heterogeneous tumor infilltrating the frontal lobe and including areas of almost homogeneous signal intensity associated to more hyperintense areas on T2-w (a) or FLAIR (c) images. The tumor shows peritumoral edema and is associated with a pronounced mass effect on the lateral ventricles, collapsed and partly displaced posterolaterally (a). Significant patchy contrast enhancement is observed (c) extending toward the corpus callosum. Cavitary necrosis more suggestive of a glioblastoma is notably lacking.

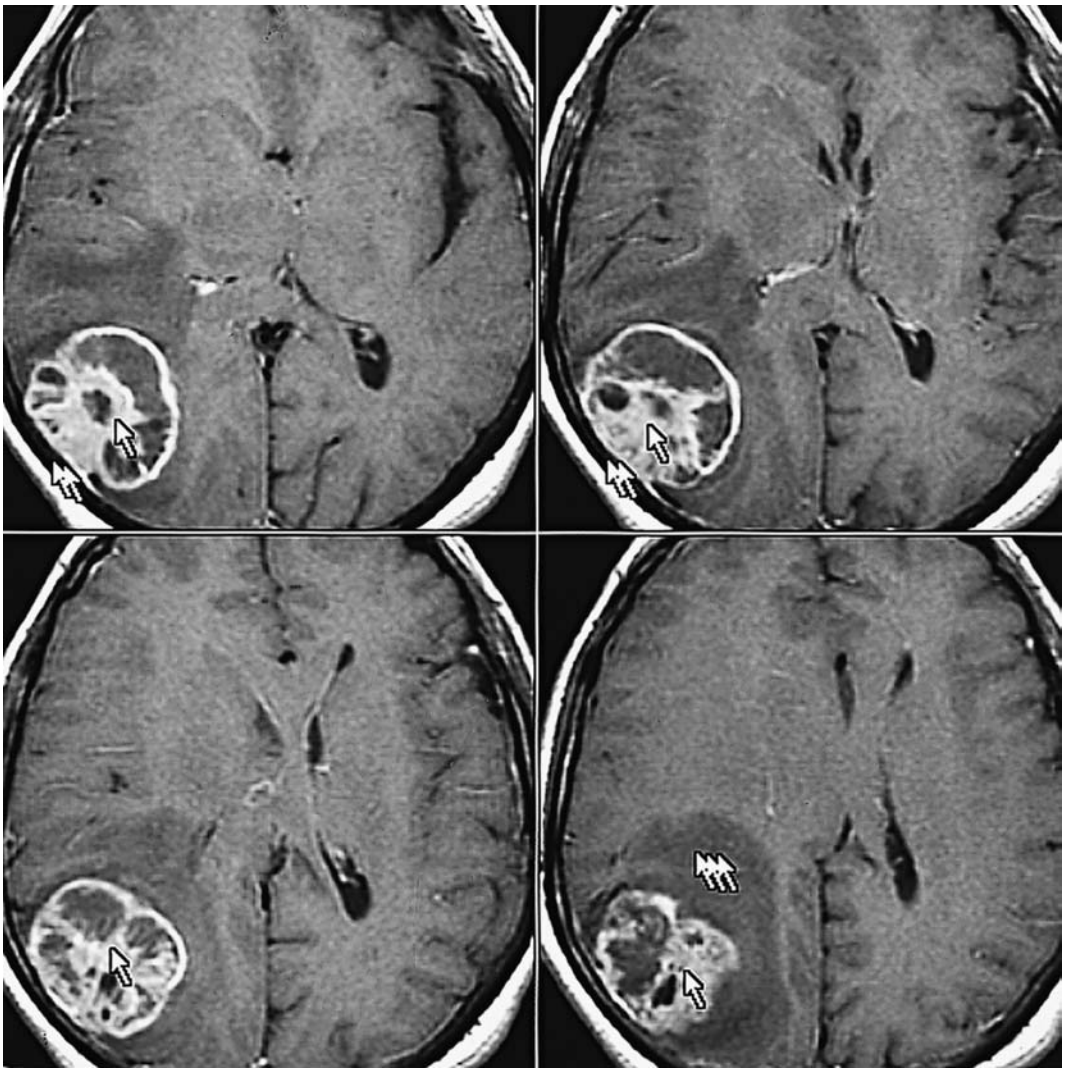
cerebral hemisphere located most frequently in the white matter, the epicenter of the tumor, of the frontal lobes, or temporal, and then parietal lobes. Some of these tumors are rather superficial in topography in contact with the leptomeninges and dura with possible subarachnoid seeding. Cortical infiltration may occur giving rise to a thickened appearance of gyri surrounding a necrotic area in the subjacent white matter. Glioblastoma commonly appear as an irregular almost well-circumscribed mass with highly suggestive central necrosis as compared to the anaplastic type, surrounded by relatively large areas of peripheral edema. The cellular peripheral zone is highly vascularized showing a microvascular proliferation corresponding to the zone of 'ring' enhancement. The large areas of intratumoral necrosis secondary to destruction of tumoral tissue may correspond to as much as 90% of total tumoral volume and appear as characteristic of primary glioblastomas, being absent in anaplastic astrocytomas. Hemorrhagic changes are common in the central portion of the tumor. Calcifications are very rare. Mass effect associated to peritumoral edema may be prominent with sulcal effacement or ventricular displacement or collapse. Sharply circumscribed tumors may be observed (Figure 84.11). Glioblastomas show a high propensity to rapidly expand along the white matter tracts to invade adjacent areas of the cerebral white matter or spread in the internal capsule or the fornix. This pattern of spread is facilitated by widening of the extracellular spaces through vasogenic edema. The tumor may also typically extend through the corpus callosum in almost 75% of cases and even cross the midline to reach the contralateral hemisphere with a 'butterfly' appearance. The latter aspect may also be encountered in lymphomas except that lymphomas exhibit a hypointense SI on T2 due to their hypercellularity. Glioblastomas may show subependymal or leptomeningeal spread in 5% of cases, best demonstrated after contrast enhancement.

Glioblastoma multiforme are markedly heterogeneous tumors showing on T1-w images a heterogeneously hypointense signal intensity to white matter with even more



(a)

Figure 84.11 Glioblastoma multiforme (WHO grade IV). Highly heterogeneous aggressive tumors, appearing as almost-circumscribed, arising in the white matter of the temporal lobe, including areas of cavitary necrosis, which is the hallmark of glioblastomas as compared to anaplastic astrocytomas (a,b).



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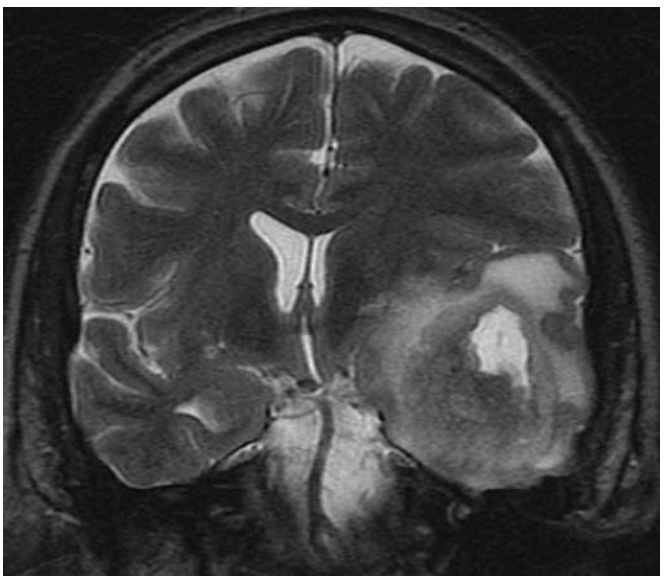

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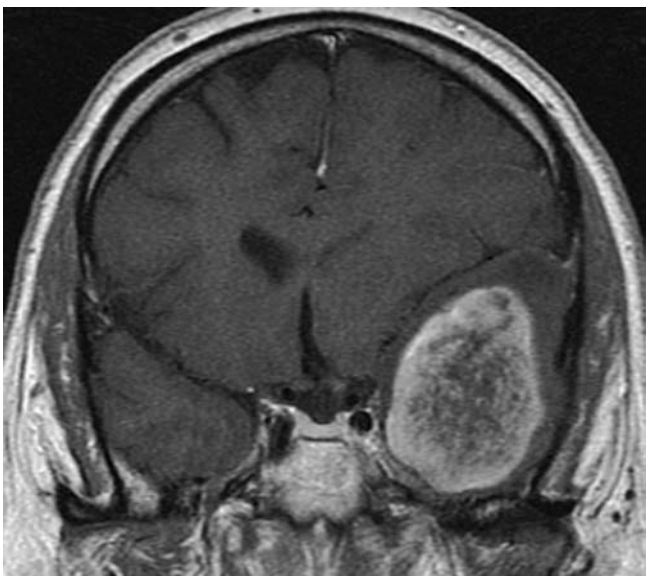


(d)

Figure 84.11 cont'd The tumor is heterogeneously hyperintense on FLAIR sequence (a, double arrows) showing a prominent enhancement (b, arrow) with an irregular ringlike pattern after Gd administration (b). Peritumoral vasogenic edema is pronounced (a, arrow and b, triple arrows) with important mass effect on the adjacent ventricular atrium almost collapsed and displaced anteriorly and medially. Extension to the leptomeninges (b, double arrows) and adjacent sulcal effacement may be observed as well. The tumor aspect may be misleading and appear as a well-circumscribed more homogeneous mass roughly well separated from the vasogenic edema as in an other patient (c,d).

hypointense intratumoral necrotic zones, unless including hemorrhagic areas which may be hyperintense due to the presence of paramagnetic methemoglobin. On PD-w images the tumor is hyperintense to white matter with areas of central necrosis that could show a more hyperintense SI than the solid part due to its high protein content and the presence of blood breakdown products such as extracellular methemoglobin, surrounded by extensive peritumoral vasogenic edema. T2-w images show a variably heterogeneous signal intensity of the solid portions of the tumor that may be mildly hyperintense to brain and/or may show iso- to hypointense areas due to tumoral hypercellularity. Serpentine fow void structures corresponding to vessels related to tumoral angiogenesis are also found. FLAIR sequence shows mild hyperintensity to normal brain tissue with variable intensity of the intratumoral necrotic areas associated to markedly hyperintense SI of the peritumoral vasogenic edema. Tumors may show a well-circumscribed appearance roughly well separated from the vasogenic edema (Figure 84.11). Proton spectroscopy has been reported in glioblastomas to show an increase in Cho levels, a decrease in NAA and the presence of peaks of lactate and lipids. A significant correlation has been observed between higher grade glial tumors and mobile lipid resonance peaks at 1.3 ppm. Glioblastoma multiforme always show a heterogeneous enhancement more sensitive with MR than with CT. Most commonly the enhancing pattern is irregular, ring-like, highly heterogeneous with variable thickness and a shaggy inner margin more conspicuously shown with delayed scans, surrounding the area of necrosis which do not enhance. Contrast enhancement correspond to the tumoral process but do not delimitate the outer tumoral boundary as shown on pathology. The nonenhancing surrounding edema has been demonstrated to include microscopic tumors. The extent of such microscopic adjacent peritumoral zone appear to be usually limited to 2 cm, an area which corresponds to the zone of tumor recurrence as observed in more than 85% of cases. It may extend to more than 2 cm and exceed 3 or 3.5 cm in 17–27% of cases according to imaging studies with pathological correlations to stereotactic biopsies.

The imaging aspect may mimic other malignant tumors such as anaplastic oligodendrogliomas, metastases, lymphomas, or other processes as radiation necrosis, cerebritis and abscesses. An abcess typically shows hypoperfusion as compared with high-grade gliomas which demonstrate a high perfusion. On diffusion-weighted images, abcesses show a bright signal intensity due to restricted diffusion, while necrotic areas of glioblastomas show a low or an isosignal on diffusion. On MRS the presence of a peak at 0.9 ppm corresponding to cytosolic amino acids is highly suggestive of an abcess. Note that Cho peak, the most specific marker of brain neoplasms may not be evidenced in tumors with significant necrosis. In lymphomas DWI shows similar high signal intensity. Hypoperfusion would be more suggestive of lymphoma probably due to elevated nucleus/cytoplasm ratios. MR spectroscopy will demonstrate the presence of suggestive significant high peaks in lipids associated to a decrease of NAA and Cr levels. Metastases may be differentiated and evidenced using MRS which demonstrates an almost absence of NAA and Cr peaks in the tumor and no elevation of Cho within the peritumoral area of vasogenic edema.[119] Conversely, high Cho levels peritumorally indicates infiltration of brain parenchyma by the tumoral process associated to edema. Radiation necrosis, eventually observed within 6 months, may demonstrate on multivoxel MRS similarly and with a greater sensitivity than PET, an increase in lipids and lactate peaks along with a decrease in Cho level or may show a normal spectrum.[47] Conversely in the case of elevation of Cho levels and Cho/NAA ratios in irradiated brain, tumor recurrence should be suspected.[46] Necrotic areas present in postradiation therapy or in postchemotherapy, show a drop in brain metabolites but an increase in lipids and lactate and disclose a large peak between 0 and 2 ppm related to cell necrosis. Note that administration of steroids may modify the absolute levels but do respect the ratio values of brain metabolites.

Pleiomorphic xanthoastrocytomas

Pleiomorphic xanthoastrocytomas, introduced in the 1993 WHO revision[53] are very rare circumscribed astrocytic tumors accounting for less than 1% of all gliomas and demonstrating marked cellular pleomorphism.[120] They are usually found in adolescents and young adults and children in the first or second decades with no sex predilection at a median age of 14 years old with a longstanding history of seizures, as in dysembryoplastic neuroepithelial tumors.[121–123] Pleiomorphic xanthoastrocytomas, classified as WHO grade II, are special variants of astrocytomas.[124] Considered as slow-growing low-grade tumors typically arising peripherally from the subpial astrocytes with predilection for a location within the temporal and parietal lobes, they may progress to a more aggressive behavior over time with transformation into a malignant glioma in more than 1/3 of cases.[125] Because of such potentiality the tumors are never better than grade II.

Morphology and imaging

Thought to arise from subpial astrocytes, the morphological aspect on imaging is suggestive. The tumor is characteristically a well-circumscribed peripheral mass showing cystic components with a solid mural nodule similar to the appearance of pilocytic astrocytomas and tends to develop at the surface of the cerebral hemisphere, often extending superficially to the pial surface of the brain which may show meningeal thickening and arachnoid spread in more than 2/3 of cases.[126] Cystic components, some of which very large, are found in 50% of the cases (Figure 84.12). Calcifications are infrequent. The neoplasm may be associated with a scalloping of the inner table of the cranial vault. Imaging features are suggestive, even if rarely diagnostic.[127–129] On CT, the mass is isodense to gray matter. On MR imaging, pleiomorphic xanthoastrocytomas show an isointense signal intensity or a mixed signal intensity to gray matter on T1-weighted and T2-weighted images and a hyperintense signal intensity on FLAIR. The solid portion of the tumor commonly enhances homogeneously or heterogeneously and may show a dural tail sign.[126] Cyst walls show variable contrast uptake.[130] Hemorrhagic foci and calcifications are rare and associated vasogenic edema minimal if not absent. These tumors may be differentiated from astrocytomas which are hypodense on CT and are more hypointense on T1-w and more hyperintense on T2-w images, due to their higher water content, but need to be differentiated from desmoplastic neuroepithelial tumors in infants and from gangliogliomas or oligodendrogliomas in children.

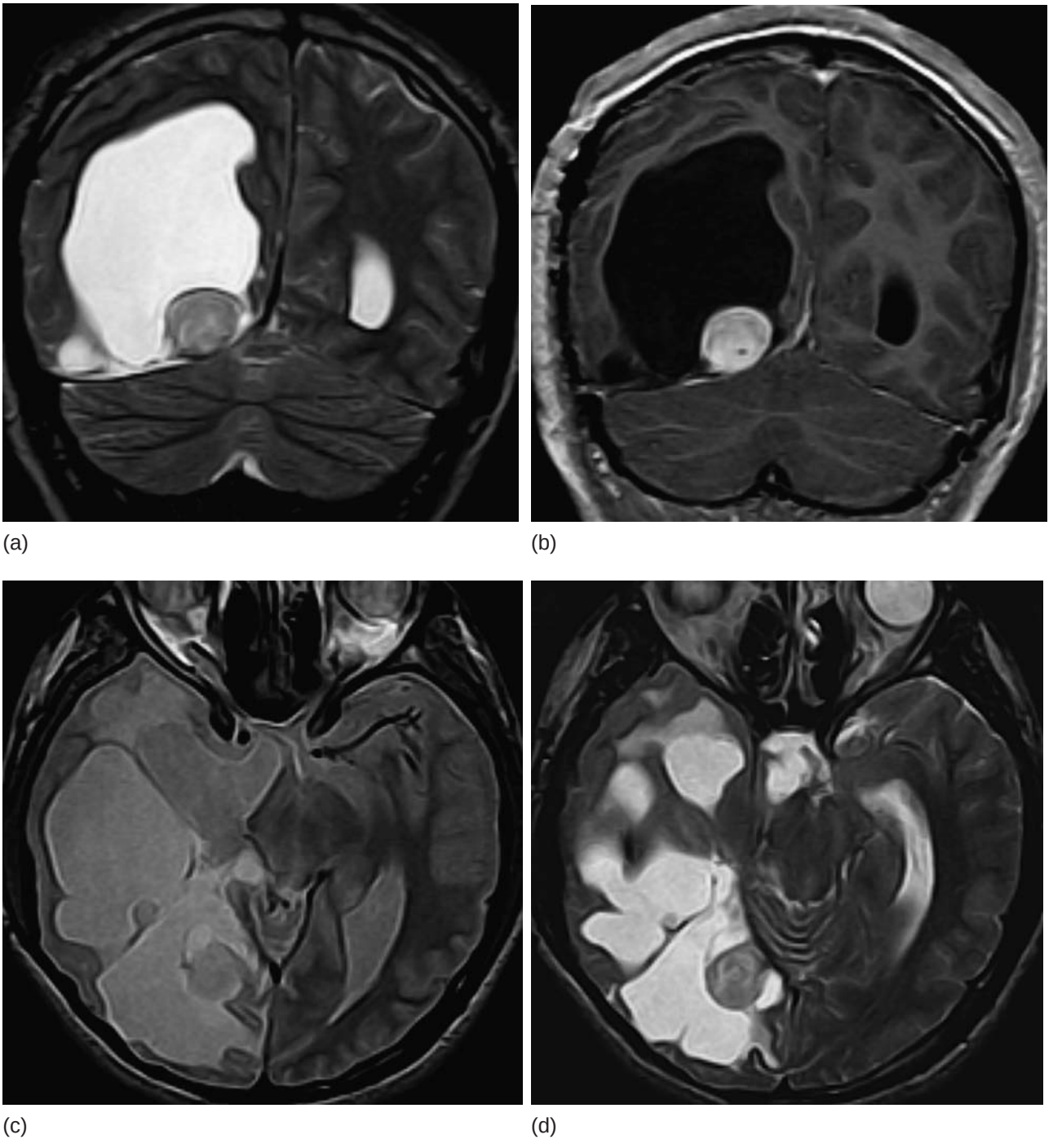


Figure 84.12 Pleiomorphic xanthoastrocytoma (WHO grade II). Huge multilobulated largely cystic fluid-filled mass with a relatively very small well-defined mural nodule superficially located adjacent to the cortical ribbon and showing a strong homogeneous enhancement (b) with a dural tail sign. Slight and limited contrast uptake involves the cyst walls. The morphological features are similar to pilocytic astrocytomas. The mass is isointense to gray matter on T1-w and PD w (c) or T2-w (a, d) sequences.

Gliomatosis cerebri

Recognized as a separate histopathological neoplasm by the WHO[53] most cases of gliomatosis cerebri are considered by most neuropathologists as representing an unusual extensive infiltration of the brain by a diffuse astrocytoma.[131,132] It is usually found in young adults with no sex predilection in their twenties to forties.

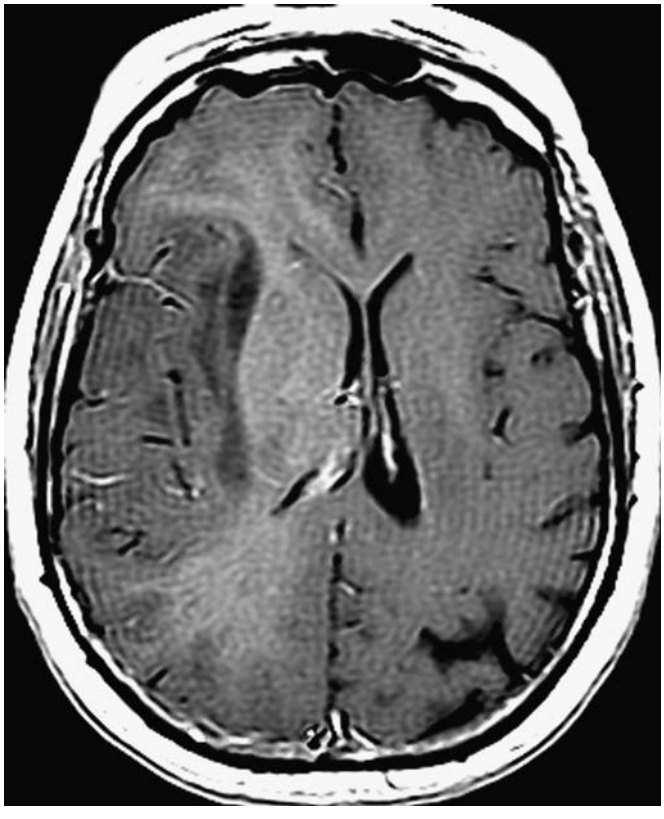
Morphology and imaging

Gliomatosis cerebri are very rare diffuse glial tumor (WHO grade III or IV) infiltrating the cerebral hemispheres in 2/3 of cases, uni- or bilaterally, and extending over more than one lobe which appear enlarged. The centrum semiovale is infiltrated in over 2/3 of cases and the cortex in less than 20%, followed by the brainstem in about half, the thalami in 40% and the basal ganglia in 30%. Leptomeningeal spread occurs in about 1/5 of the cases.[133] Age at diagnosis shows a peak incidence between 40–50 years old. Imaging features of gliomatosis cerebri include an isodense to hypodense appearance on CT but it is best imaged using MR, which is much more sensitive in depicting the neoplasm and evaluating its wide extension.[134] The neoplastic expansion along the anatomic

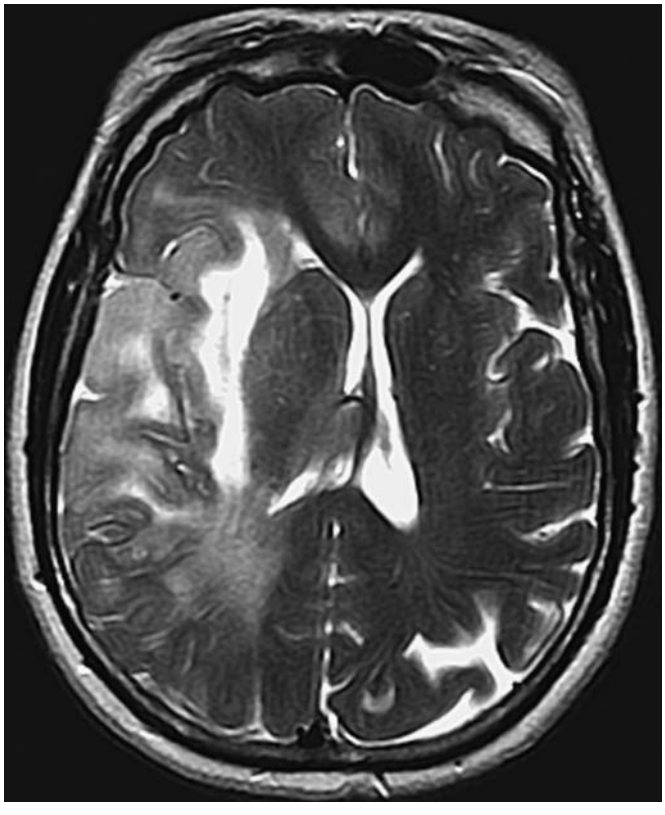
pathways is multilobar and often bihemispheric distorting rather than destroying the brain parenchyma in the manner of low-grade gliomas. Involvement of the white matter core is predominant with blurring of the gray-white matter junction (135). This ill-defined tumor is homogeneously isointense to hypointense on T1-weighted sequences and hyperintense on T2. Enhancement, usually faint, is observed in less than half of the cases and mass effect is usually moderate (Figure 84.13). Prognosis is poor.

Subependymal giant cell astrocytomas

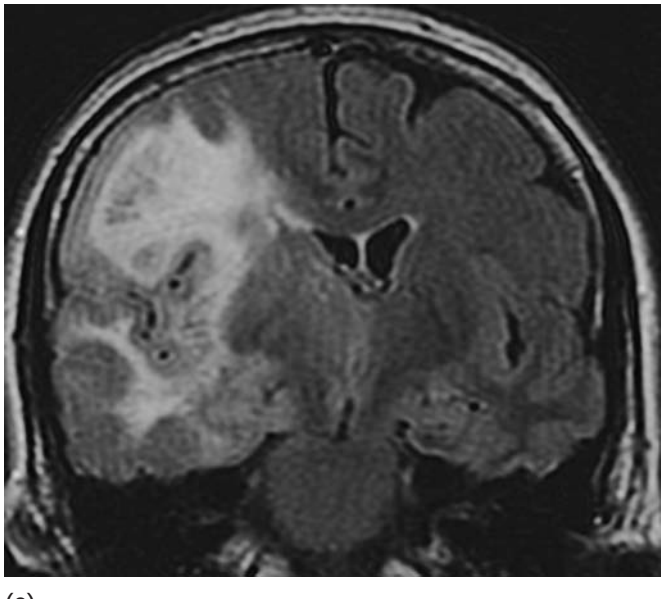
Subependymal giant cell astrocytomas are low-grade (WHO grade I) astrocytic tumors associated in more than 90% of



(a)



(b)



(c)

Figure 84.13 Gliomatosis cerebri (WHO grade III). Extensive tumoral process infiltrating the fronto-temporo-insular lobes in a young adult, associated with enlargement of the related gyri and moderate mass effect on the midline structures and the ventricular cavities displaced contralaterally. Note the predominant involvement of the white matter core with blurring of the gray-white matter interface (a,b) and the propensity to expand along the anatomical pathways such as the external and extreme capsules (b) or the temporal stem (c) in the manner of a low-grade glioma. This diffuse ill-defined glial tumor is hypointense on T1-w images (a), and hyperintense on T2-w (b) and FLAIR (c) images. Almost no contrast uptake is noticed (a).

cases with Bourneville's disease, a phakomatosis including cutaneous, visceral, and central nervous system manifestations. Almost 10–15% of these patients will develop, usually in their teens or twenties, the characteristic subependymal giant-cell astrocytoma.[136,137] The average age at diagnosis is 10 years old.[138] The clinical presentation is commonly hydrocephalus. Histologically, these tumors are similar to the subependymal hamartomas found in tuberous sclerosis[137] which is a genetically determined and familial disease transmitted in an autosomal dominant mode with low penetrance. Its incidence is evaluated as being 1:100–150 000 patients or may even be as high as 1:10–20 000. There is no sexual or racial preponderance. Clinically, patients with tuberous sclerosis present a classic triad of cutaneous angiofibroma (90%), appearing at 1–5 years old, in the nasolabial folds or extending to the cheeks and the malar region (butterfly appearance); myoclonic seizures and hypsarrhythmia (80%), and mental deficiency (about 60%) of variable severity. Tuberous sclerosis is characterized in the CNS by the presence of disseminated hamartomas or tubers consisting of nodules of disorganized cortical tissue containing atypical giant bizarre neurons and astrocytes. The subjacent white matter contains few myelinated fibers and fibrillary gliosis.

Morphology and imaging

The giant-cell astrocytoma is a slowly-growing well-demarcated tumor typically subependymal and almost always found in the lateral ventricle near the foramen of Monro, frequently causing an obstructive hydrocephalus with an ipsilateral or bilateral ventricular enlargement. This morphologic and topographic appearance is almost pathognomonic when associated with other features of tuberous sclerosis. The mass is fixed to the head of the caudate nucleus but does not infiltrate it or the adjacent parenchyma and does not show subarachnoid seeding (Figure 84.14). The tumor is covered by an intact layer of ependyma. Irregular calcifications may be commonly found. It may be rarely an isolated finding, a 'forme fruste' of Bourneville's disease.

The tumor is hypodense to isodense on CT showing calcifications. On MR the tumor is rounded or ovoid, presenting a heterogeneous signal intensity usually hypointense to isointense on T1-weighted images and hyperintense on T2-weighted images.[139,140] Associated subependymal nodules and tubers, best visualized on MR, are usually evidenced in Bourneville's patients. The tubers are centrally hypointense to white matter or isointense on T1-weighted images, but appear hyperintense in infants as compared with unmyelinated white matter. On SE-T2w or FLAIR images, the tumor is hyperintense to white matter. Note that in the case of associated calcified subependymal nodules or cortical tubers, GE-T2*w sequence is helpful for depicting the calcified portions due to the magnetic susceptibility differences with adjacent brain tissue. Calcifications may show a hypointense SI on SE-T2w and may even appear as bright areas on T1-w images. Subependymal nodules of more than 1 cm particularly if symptomatic should to be considered as subependymal giant cell astrocytomas.[140] Although cortical-subcortical tubers and subependymal hamartomatous and glial nodules within the white matter usually do not show contrast enhancement, subependymal giant-cell astrocytomas characteristically strongly enhance uniformly.[140] Note that enhancement of a subependymal nodule must be followed up with MR in order to rule out an eventual transformation into a giant cell astrocytoma. Regional parenchymal invasion or rapid growth is highly suspect of anaplastic transformation. Although benign, spontaneous intratumoral hemorrhage may occur leading to death.

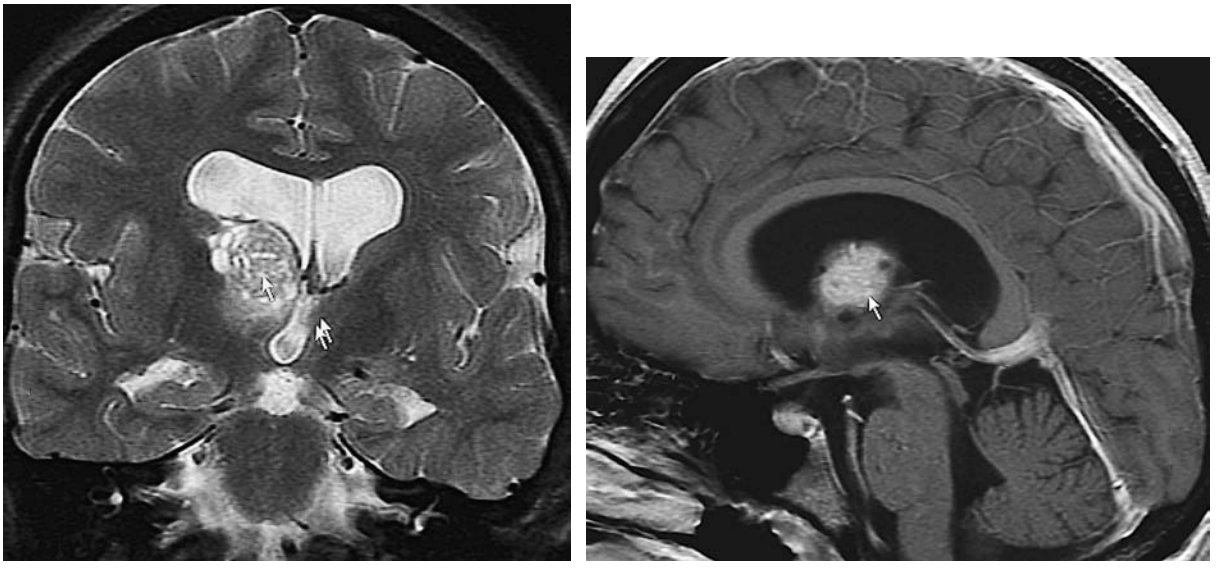


Figure 84.14 Subependymal giant-cell astrocytoma (WHO grade I). Intraventricular rounded mass found in association with tuberous sclerosis and developed in the lumen of the frontal horn of the lateral ventricle, at the foramen of Monro (arrow). It appears attached to the caudate nucleus which is not infiltrated. The mass is well demarcated including small cystic formations (a). It appears heterogeneously hyperintense to white matter on the T2-w coronal cut (a) and enhances intensely as shown on the parasagittal T1-w cut (b), overlying the interventricular foramen. Note the ipsilateral ventricular enlargement and the mass effect on the third ventricle (double arrows).

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85 Magnetic resonance spectroscopy in patients with epilepsy

MA McLean, M Koepp, and FG Woermann

Introduction

Magnetic resonance spectroscopy (MRS) offers a unique opportunity to assay noninvasively the concentrations of metabolites in the brain in vivo. In epilepsy, this information can be used to aid diagnosis of the epileptogenic lesion, optimization of the extent of a surgical resection, or prediction of postoperative outcome. MRS may give important insights into the mechanisms of seizure generation and termination, and into the pharmacodynamics of antiepileptic drugs, and may thus help in deciding which patients may tolerate particular drugs.

Principles of MRS

The principles underlying the technique are the same as for MRI discussed in previous chapters. A magnetic nucleus in an applied magnetic field can be induced to emit signal at a specific frequency, which depends on its electronic environment (specifically, on the electronegativity of the chemical bonds in which it takes part). These frequencies can be analyzed as a spectral fingerprint, to tell us what chemicals are present.

MRS is an insensitive technique: typically only metabolites present at concentrations of about 1 mM or higher are detectable in vivo. Not all isotopes are magnetic, and not all magnetic isotopes produce signal which is equally easy to detect. The most commonly studied isotopes in epilepsy are ^{1}H and ^{31}P.

Proton MRS

The ^{1}H nucleus (a single proton), although both abundant and relatively sensitive in NMR terms, initially presented problems to study via MRS: techniques needed to be developed to exclude the strong signals arising from water and macromolecules (lipids and proteins) in order to study the more interesting small metabolites (amino acids, sugars, etc.). Such techniques are now available to suppress the water peak,[1] and to reduce and/or spatially exclude the macromolecule signal. Spatial exclusion (known as outer volume suppression, or OVS) is needed because of the very intense lipid signals arising from the scalp. Macromolecule signals can also be reduced by taking advantage of their short T_2 relaxation (by acquiring at echo times >100 ms) or their short T_1 (by preceding the acquisition with an inversion pulse). If the delay between inversion and acquisition is short, the lipid signal may be nulled;[2] if it is long, the metabolite signal may be nulled, and the resultant macromolecule signal may be subtracted from a spectrum without inversion to yield a clean metabolite signal.[3]

Following these technical advances, ^{1}H has become by far the most widely studied nucleus in clinical MRS. The metabolites studied are shown in Figure 85.1. At long echo times, signal is primarily present from N-acetyl aspartate (NAA), creatine plus phosphocreatine (Cr) and choline-containing compounds (Cho). As described previously, at this echo time of 144 ms the macromolecule signal (MM) has decayed completely, giving a flat baseline from which metabolite peak areas can be measured. Following hypoxic insults, some seizures, or more rarely in normal brain, an inverted doublet signal can be observed from lactate at 1.33 ppm.

At shorter echo times (e.g., 30 ms as shown), the MM peaks interfere with quantification not just at the frequencies below 2 ppm, but throughout the spectrum. Additional interesting peaks can be detected from myoinositol (Ins) and glutamate and glutamine (Glx), but sophisticated modelling is necessary to distinguish them from the overlapping peaks,[4] and baseline determination remains a major source of error.

Localization techniques

Localization is needed for ^{1}H-MRS, not merely to exclude scalp lipid signal, but to compare different tissues and locations in the brain (e.g., left vs. right hippocampus as shown in Figure 85.2). Localization makes use of frequency-selective excitation, where the rf pulses are accompanied by gradients. In imaging, this is used to excite a single slice for 2D images. In spectroscopy, we often choose to do slice-selective excitation in three orthogonal planes to excite a cuboid volume at their intersection. This is called single voxel (SV) MRS. The three rf pulses used are chosen to create either stimulated echoes (STEAM) or spin echoes (PRESS).

The other common localization tool is phase encoding, as used in imaging. This is known as spectroscopic imaging (MRSI), sometimes called chemical shift imaging (CSI). Sometimes we use both 3D localization (e.g., PRESS) and MRSI, to acquire a spectroscopic image of a cuboid volume, rather than over the whole slice (Figure 85.3). This aids in the exclusion of the intense scalp lipid signal.

Analysis methods

Since the areas of metabolite signals are directly proportional to their concentrations in the tissue, we can use MRS to estimate

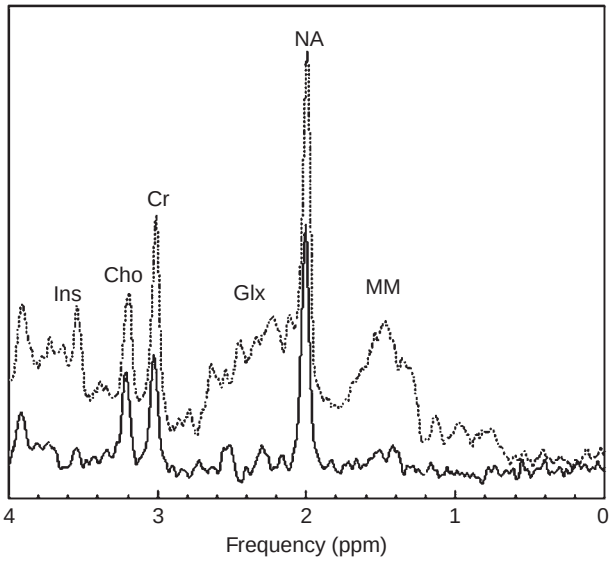

Figure 85.1 Sample proton spin-echo (PRESS) spectra from human frontal lobe in vivo, at long (144 ms, solid line) and short (30 ms, dotted line) echo times.

metabolite concentrations. However, since there are so many elements of the proportionality constant that are difficult or impossible to determine (e.g. characteristics of the coil hardware), we generally can only calculate a concentration relative to a known or assumed standard.

For example, we can scan a solution of 50 mM creatine and compare the area of the peak we measure to the area of the peak we measure in vivo. Then we can correct for differences in machine gains, the volume of tissue excited, relaxation properties, etc., to obtain an estimate for the concentration in vivo. Alternatively, sometimes only the ratio of one peak to another is reported, e.g., NAA/Cr, or NAA/(Cr+Cho). This has the advantage that any temporal, spatial, or inter-subject differences in machine performance cancel out. However, such ratios can vary in different tissues in the brain, or in disease, in ways that are not always easy to interpret.

Even the measurement of peak areas is not trivial, especially in short echo-time spectra, since many peaks of interest overlap with each other and with broad underlying macromolecule resonances. Therefore it is generally desirable to fit such spectra using automated routines which can take this broad baseline into account, and which incorporate information on the whole complicated spectral fingerprint of each metabolite of interest. The most commonly used spectral packages are LCModel[4] and MRUI (www.mrui.uab.es).

Finally, metabolite concentrations differ in gray matter, white matter, CSF and lesions, so it is desirable to estimate the proportion of each in the excited volume. Metabolite content of CSF can be assumed to be negligible,[5] and that of lesions would generally be expected to be lower than normal tissue for most metabolites. In gray matter, we and others have found significantly higher content of glutamate plus glutamine, creatine, and myoinositol than in white matter.[6]

Metabolite-specific spectroscopy

Only three to five metabolites are clearly visible in a conventional proton spectrum (perhaps up to seven can be estimated with spectral modelling at short echo times). If our metabolite of interest cannot be resolved from overlapping molecules, we must turn to more sophisticated methods.

One possibility is to perform 2D spectroscopic studies. If we collect data not merely at a single echo time, but at a series of incremented echo times, then we can perform a Fourier transform across this second time dimension to produce a second frequency dimension. Any coupled peaks in the spectrum are modulated at different echo times, so they appear spread out across the second frequency dimension. There are a number of slightly different techniques that use this approach: the most common are J-resolved PRESS[7] and localized correlation spectroscopy (L-COSY).[8] The main advantage of 2D techniques is that uncoupled signal is retained, so that, in theory, the entire metabolic content of the tissue can be determined from a single acquisition. The main disadvantage is that the spectral resolution in the second frequency dimension is often insufficient to fully resolve overlapping peaks.

Another approach with more potential specificity is spectral editing.[9] This is a difference technique: we collect one spectrum where we have manipulated a small range of frequencies, another spectrum where we have not, and we look at

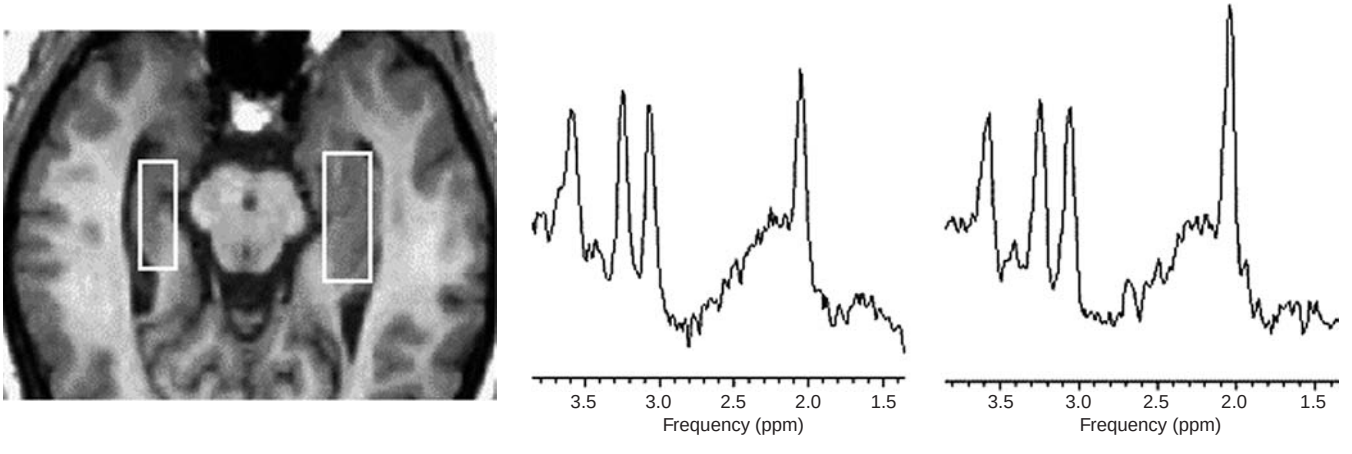

Figure 85.2 Proton spectra (using PRESS localization with an echo time of 30 ms and repetition time of 3 s) from the ipsi- and contralateral hippocampi of a patient with hippocampal sclerosis and epilepsy. Left: anatomic image showing the positions of the voxels studied. Middle: spectrum from ipsilateral hippocampus. Right: spectrum from contralateral hippocampus.

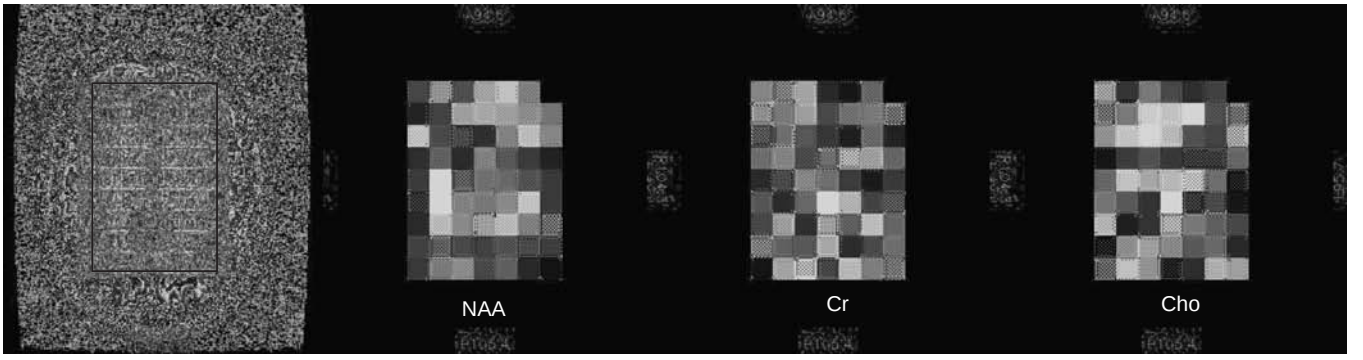

Figure 85.3 Long-echo-time (144 ms) MRSI in vivo at 3 Tesla: 20 × 20 phase encoding steps were acquired, but only those which fell inside the volume selected using PRESS are shown. The spectra from each voxel were fit using LCModel to obtain semiquantitative maps of N-acetyl aspartate, creatine, and choline.

the difference between them. There are still potential problems when multiple peaks in the same range pass through the spectral filter, or 'co-edit', but more complicated subtraction schemes can be developed to get around this limitation.[10] A more fundamental problem is motion: if it occurs, the subtraction will no longer cancel the unwanted resonances.

A final technique used to observe coupled peaks is multiple-quantum (MQ) filtration. If we create a MQ coherence, we can use gradients to filter out the uncoupled spins, which are not able to enter this state. The ratio between two gradients applied is chosen to select the desired coherence: the most common is a double quantum filter (DQF). This has been used to study GABA[11] and glutathione[12] in the brain.

Phosphorous MRS

^{31}P is the 100% abundant isotope of phosphorus, an important atom in biological systems. Its resonances can be detected by tuning the scanner into a frequency range roughly 60% lower than that of proton, although many clinical scanners are not equipped to transmit and receive signal over such a wide range ('broadband') of frequencies. The methods for studying ^{31}P are similar to those for proton, with two main exceptions.

The first is that the T_2 relaxation times are much shorter: about 10–30 ms. Therefore ^{31}P is unsuitable for spin-echo or stimulated-echo experiments, because the signal would have decayed away during the echo time. Instead, nonecho localization schemes such as ISIS[13] may be preferred.

The second major difference is that phosphorus signal is modulated by nearby protons. These heteronuclear splittings can complicate the spectral signal considerably, particularly the phosphomonoester (PME) and phosphodiester (PDE) peaks. Therefore, decoupling may be applied: this selectively saturates signal at the proton frequency, so that it no longer affects the ^{31}P signal.

Visible metabolites

The three resonances of adenosine triphosphate (ATP) are detectable in virtually every soft tissue in the body (Figure 85.4). They are not coupled with any protons, but they are coupled with each other: the gamma and alpha peaks are split into doublets by the beta peak, and the beta peak is split into a triplet with intensity ratios 1:2:1. The concentration of ATP tends to remain stable in living tissues, unless the bioenergetics are very severely compromised.

This stability is generally maintained by a store of phosphocreatine (PCr). This singlet (i.e., uncoupled) peak dominates spectra from skeletal muscle, and can be observed to radically reduce during exercise. In brain and other internal organs it is less prominent, but also less subject to reduction, except in hypoxic/ischaemic insults. It may reduce during seizures, as discussed below.

The singlet peak of inorganic phosphate (Pi) can also be detected. It has the interesting property that its chemical shift is dependent upon the local concentration of hydrogen ions, so that its distance from the PCr peak may be used as a noninvasive internal pH meter.[14] Similarly, the chemical shift of β-ATP can be used to monitor the concentration of free magnesium ions.

The other peaks visible in the phosphorus spectrum are broad signals assigned collectively as phosphomonoesters

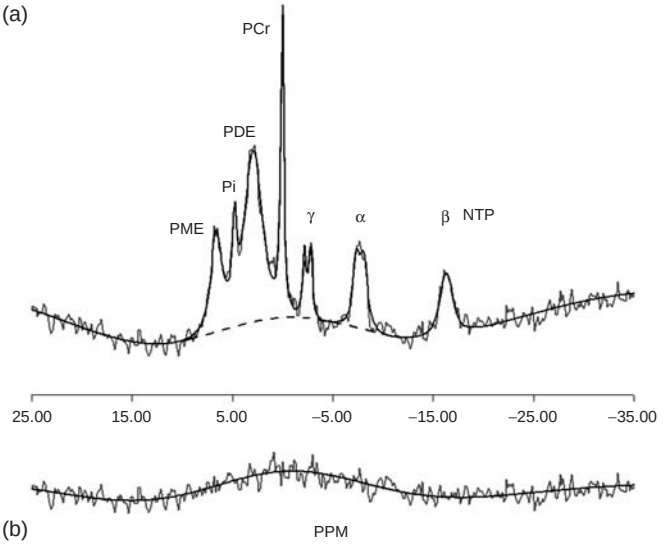

Figure 85.4 Seven peaks are characteristically identifiable in the ^{31}P-MR spectrum from a normal human brain. In order of decreasing chemical shift, these peaks are assigned to phosphomonoesters (PME), inorganic phosphate (Pi), phosphodiesters (PDE), phosphocreatine (PCr) and γ, α, and β nucleotide triphosphate (γ, α, and βNTP). These signals were quantified in the time domain using the AMARES algorithm included in the MRUI software program (a), with the residual shown (b) (courtesy of Prof B. Puri).

(PME) and phosphodiesters (PDE). These are thought to be associated primarily with membranes.

Clinical applications of MRS

MRS in temporal lobe epilepsy

In the presurgical evaluation of patients with TLE, the potential value of ^{1}H-MRS (or -MRSI) depends on the method's ability to detect lateralized metabolic changes not only in clear-cut cases of hippocampal sclerosis, but also in patients with normal MRI ('MRI-negative'); it depends on the method's ability to lateralize abnormality in the presence of bilateral EEG or MRI changes and to contribute to the detection of dual pathology; ultimately, the clinical value of ^{1}H MRS in this patient group is based on studies correlating presurgical measurements with post-surgical seizure and neuropsychological outcome.

Proton MRS in hippocampal sclerosis

In patients with hippocampal sclerosis, the typical finding in the epileptogenic hippocampus is a reduction of NAA and an elevation of Cr and Cho (or corresponding changes of ratios like NAA/Cr, NAA/Cr+Cho or Cr/NAA) relative to normal control subjects; the contralateral hippocampus may be normal or show a lesser degree of abnormality.

In a series of 100 consecutive TLE patients, the NAA/Cr values were abnormally low in at least one temporal lobe in all but one patient and were abnormally low bilaterally in 54%.[15] The asymmetry between right and left NAA/Cr ratios lateralized 92% of patients in concordance with lateralized ictal EEG findings. More abnormalities were detected using MRS than with MR volumetry, but only a few patients with postoperative outcome were reported in this study.

Prediction of postoperative outcome

The literature is discordant on the issue of predicting outcome with MRS. There is a restricted number of MR spectroscopic studies describing more than 20 operated adult TLE patients and providing individual MRS and outcome data.[16–22] A recent meta-analysis[23] aiming to assess the additional preoperative value of ^{1}H-MRS further included smaller studies (with 7–17 operated patients). Combining those studies on patients with TLE which allowed correlation of individual MRS data and seizure outcome according to the Engel Classification, unilateral MRS changes were reported to have a predictive value of 82% for good postsurgical outcome (Engel I+II). TLE patients with unilateral MRS abnormality had a markedly better chance of becoming seizure free compared to patients with bilateral abnormalities (odds ratio 4.891, CI = 1.965–12.172).[23] One study of 24 TLE patients included in this meta-analysis showed that unilateral abnormality in hippocampal ^{1}H MRS (in 61%) did not predict, and bilateral abnormalities (in about 30%) did not preclude, good surgical outcome.[16]

The predictive value of bilateral MRS abnormalities (for unfavorable outcome) is even less clear. Bilateral temporal MRS abnormalities have been observed to a varying degree in different studies in 0–70% of patients.[24] In 21 patients with bilateral hippocampal atrophy, discriminant ^{1}H-MRSI features associated with favorable post-surgical seizure outcome were: concordant ^{1}H-MRSI lateralization, a greater side-to-side asymmetry of NAA/Cr, and an absence of contralateral posterior NAA/Cr reduction.[18] However, in patients with preoperatively low NAA ratios contralateral to the seizure onset, a postoperative metabolic normalization on the non-operated side was observed.[25–27] It led to the view that a decrease of NAA does not necessarily represent neuronal loss, but that NAA might be a putative reversible, thus functional, marker.[28]

Bilateral MRS abnormalities might also affect neuropsychological prognosis. Patients with right sided TLE and with additional MRS abnormalities in the left temporal lobe performed worse on neuropsychological tests of episodic verbal memory compared to patients with right sided TLE and ipsi- and unilateral MRS changes.[29] Whether this particular combination of two independent markers for bilaterality has clinical significance remains questionable.

Proton MRS in temporal lobe epilepsy without MR abnormalities ('MR-negative')

Some TLE patients with apparently normal MRI ('MRI-negative') were the subject of feasibility studies[30] or part of studies correlating typical MRS changes (low NAA ratios ipsilateral to the seizure onset with a relatively low degree of contralateral abnormality) with good post-surgical outcome.[15,21,31–33] In 15 MRI-negative, but operated, TLE patients a single ^{1}H-MRSI study came to conflicting results.[34] This study curiously showed a greater degree of ipsilateral NAA/Cr changes in patients that were *not* seizure free after surgery. Extending this finding to the contralateral side, these results still confirmed the generally acceptable view that subjects with bilateral metabolic abnormalities might have seizure foci that extended beyond the ipsilateral hippocampus. Against all expectations, MRI-negative patients who were 'well lateralized' by NAA (i.e., ipsilateral NAA ratios lower than contralateral ratios) had worse surgical outcomes than patients who were 'poorly lateralized'.[35] A possible explanation for this solitary finding of a poor correlation between lateralization with NAA and surgical outcome, is that TLE patients with normal MRI may represent a different syndrome than TLE with hippocampal atrophy. In other studies, ^{1}H MRS described a metabolite profile in the hippocampi of MRI-negative TLE patients that was in fact different from patients with hippocampal sclerosis, with an increase in glutamate and glutamine and a less marked decrease in NAA than was seen in hippocampal sclerosis.[34,36]

Another explanation for a poor correlation between lateralization with NAA and surgical outcome in MRI-negative patients with TLE was put forward in a study correlating presurgical ^{1}H MRS, post-surgical histopathology and outcome.[19] In 13 patients with TLE, subtle histopathological signs of cortical malformations in the resected temporal lobes were found: six of them with concomitant hippocampal sclerosis (dual pathology) and seven without. The MRI-negative subgroup had a worse surgical outcome and showed more marked bilateral and/or contralateral MRS abnormalities possibly representing more widespread subtle developmental changes.

Proton MRS in dual pathology

These and other extrahippocampal or extratemporal abnormalities in patients with mesiotemporal/hippocampal sclerosis are called 'dual pathology'. Dual pathology is rarely

identified in a hypothesis-driven way allowing the targeted placement of regions of interest. ^{1}H-MRS/MRSI could only contribute to the detection of these changes when single voxels or single MRSI slices were placed outside the hippocampus and/or outside the temporal lobe or by the use of multislice ^{1}H-MRSI.[37] Making a virtue of technical necessity, some MRS studies placed their voxels outside the mesial temporal lobe due to the difficulty in sampling such small structures and the difficulty in achieving an adequately homogeneous magnetic field owing to the magnetic susceptibility effects at the tissue-air interface near the petrous bone. MRS measurements in the superior temporal lobes and inferior insular cortex lateralized 45% of TLE patients with a low extrahippocampal temporal lobe NAA/Cr.[21] Using multislice ^{1}H-MRSI in combination with tissue segmentation, significantly lower NAA in ipsi- and contralateral frontal gray and nonfrontal white matter compared with controls was found, although not correlated to outcome.[37] Further studies by the same group found that TLE was associated with extrahippocampal reductions of NAA/(Cr+Cho) in several lobes consistent with those brain areas involved in seizure spread and that temporal and extratemporal NAA/(Cr+Cho) reductions might be helpful for focus lateralization.[38]

Widespread abnormalities of ratios were found not only in TLE, but also in extratemporal lobe epilepsy.[39] Even in normal controls, large differences in metabolite concentrations were seen between posterior lateral temporal lobe (predominantly subcortical white matter) and the posterior mesial temporal lobe, most notably lower creatine, Glx, and myoinositol, and higher NAA/(Cr + Cho) in the lateral than mesial temporal lobe; this pattern was similar to that previously seen for gray/white matter differences in the frontal, parietal, and occipital regions.[40] It remains to be seen whether widespread MRS changes in TLE are specific and have prognostic value.

Brain GABA and glutamate-glutamine (Glx) in temporal lobe epilepsy

In adult patients with complex partial seizures, poor seizure control was found to be associated with low brain GABA levels measured with ^{1}H-MRS within a 14-cm^{3} volume in the occipital lobe, i.e., outside of the epileptic focus,[41] although other studies did not find a correlation between GABA and seizure control or recent epileptic seizures.[42] In one study, low GABA/Cr seemed even to lateralize the hemisphere with the seizure onset zone and predicted increases of the GABA/Cr signals after successful antiepileptic treatment with vigabatrin.[43] Acute and/or longstanding GABA increases were shown with different antiepileptic drugs, like gabapentin, lamotrigine, topiramate, and vigabatrine,[44–46] but not with carbamazepine, phenytoin, or valproate.[47]

Increased intracellular glutamate content in epileptic human hippocampus may also contribute to the epileptogenic nature of hippocampal sclerosis.[48] Short-TE MRS studies in patients with TLE showed an increase in the overlapping peaks of glutamate and glutamine in MRI-negative patients with TLE.[35,36]

Phosphorous MRS in temporal lobe epilepsy

Results from the few studies using ^{31}P-MRS in TLE are controversial. ^{31}P-MRS studies of the anterotemporal lobes of patients with medically refractory TLE showed that the pH was significantly more alkaline and the inorganic phosphorous concentration was greater on the side of the epileptogenic focus.[49–51]

Differences in intracellular pH between controls and patients were not observed in other studies, although some bilateral, but lateralizing, phosphorus metabolite abnormalities were found (e.g., the phosphocreatine/inorganic phosphate ratio was reduced in the epileptogenic temporal lobe).[52,53] The decline in energetics (reduced ATP/Pi, both ipsilateral and contralateral)[53] has been discussed as a seizure-mediated imbalance, because successful treatment of the seizures might reverse the contralateral impairment.[54] Further study is needed correlating presurgical ^{31}P-MRS with postsurgical ^{31}P-MRS and seizure outcome.

Summary: MRS in temporal lobe epilepsy

Although ^{1}H-MRS/-MRSI has been advocated as part of a cluster or a sequence of clinical tests prior to epilepsy surgery in TLE, its contribution to the overall validity of the cluster or sequence remains to be determined. Influential epilepsy surgery programs with early enthusiasm for ^{1}H-MRS/-MRSI ('NAA/Cho is an excellent marker for localizing the epileptogenic zone in TLE', Ng *et al.*, 1994) abandoned this noninvasive but tedious method as part of their presurgical evaluation of patients with TLE (H. Luders, personal communication). Is it time to reconsider?

MRS in extratemporal neocortical epilepsy

Studies correlating presurgical ^{1}H-MRS/-MRSI data with post-surgical seizure outcome in patients with extratemporal neocortical epilepsy seem not to be available in this increasingly important patient population. It remains to be seen whether ^{1}H-MRS/-MRSI can help to select those candidates whose extratemporal neocortical epilepsy can be treated successfully by epilepsy surgery.

Proton MRS in frontal lobe epilepsy

In the relatively large frontal lobes, the use of a restricted region-of-interest approach (single voxel or single slice) might reduce the sensitivity of ^{1}H-MRS/-MRSI for the localization or the lateralization of the epileptogenic region.

Mean NAA/Cr in the epileptogenic frontal lobe was found to be decreased compared to the contralateral homologous region;[55,56] however, widespread, even bilateral frontal lobe NAA/Cr changes have also been described.[57] 50% of patients with extra-TLE had NAA/Cr reduction outside the clinical and EEG-defined primary epileptogenic area.[18]

In individual patients, correct lateralization varied between 50 and 100%. Using reduced frontal lobe NAA/Cr, four out of seven patients were correctly lateralized.[58] Comparing MRSI in patients with MCD and in 'MRI-negative' patients with neocortical epilepsy, localization of the focus was correct in 70% of the patients with an MRI-visible malformation and in 60% of the patients with normal MRI.[59]

Phosphorous MRS in frontal lobe epilepsy

There are preliminary findings in patients with frontal lobe epilepsy awaiting replication in larger patient populations. Studying eight patients with frontal lobe epilepsy, interictal alkalosis and decreased phosphomonoester levels in the epileptogenic region compared to the contralateral frontal lobe were found.[60]

MRS in neocortical epilepsies due to malformations of cortical development

Some proton magnetic resonance spectroscopy studies have been performed in patients with malformations of cortical development (MCD), although without correlation to post-surgical outcome. A decrease in NAA (concentrations or ratios) was the most frequent finding in individual MCD and in group comparisons.[61–66]

Using quantitative short echo time ^{1}H-MRSI, abnormal metabolite concentrations in MCD, perilesional tissue and brain tissue remote from MCD were demonstrated in patients with localization-related epilepsy.[64] These findings support the concept of widespread abnormalities in patients with apparently focal MCD. Spectroscopic abnormalities do not necessarily represent widespread structural changes as described earlier in MCD,[67,68] but might demonstrate dysfunction.

Measurements of individual metabolites were abnormal in some malformations and normal in others, suggesting metabolic heterogeneity.[64] Even within a single MCD, metabolically normal regions were interspersed with metabolically abnormal regions.[66] Categorizing MCD based upon the step at which fetal cortical development was likely first disturbed (as proposed by Barkovich)[69] might reduce the variability of MRS results in MCD. NAA/Cr was shown to be most markedly reduced in MCD secondary to very early disturbances during stem cell formation.[62] This ratio was variably reduced in heterotopic gray matter (MCD due to a later developmental step, abnormal migration) and normal in polymicrogyria.[62,71]

Whether MR spectroscopy can contribute to the distinction between low-grade gliomas and focal MCD (especially FCD), remains unclear. Promising results from group comparisons (less NAA in tumours compared to MCD) await replication and prospective translation to clinical practice in individual patients.[71]

Prototypically in epilepsy patients with tuberous sclerosis, the presence of multiple bilateral lesions can make it difficult to identify a single lesion responsible for intractable epileptic seizures. Using MRS, a lactate peak was detected in the regions corresponding to an epileptic focus in some patients[72], but this was not a universal finding (Figure 85.5).

MRS in neocortical epilepsies without MR abnormalities ('MR-negative')

The usefulness of multislice ^{1}H-MRSI in combination with tissue segmentation for the identification of the epileptogenic focus, was extended from patients with MCD to MRI-negative patients with neocortical epilepsy.[38] MRSI correctly identified the lobe containing the epileptogenic focus as defined by EEG in 65% of the patients with neocortical epilepsy. MRSI localization of the focus was correct in 70% of the patients with an MRI-visible malformation and in 60% of the patients with normal MRI. Of the patients, 15% had metabolically abnormal brain regions outside the epileptogenic lobe, and 35% of the patients had evidence for secondary hippocampal damage.[38] It remains to be seen whether these changes have prognostic value and whether these widespread abnormalities are specific, as they are also found in temporal lobe epilepsy.[39]

Summary: MRS in extratemporal neocortical epilepsy

In contrast to the numerous ^{1}H-MRS of TLE, there are only a few reports in other types of localisation-related epilepsies. These studies suggest that the potential of correct seizure focus lateralisation is less than in TLE.

MRS in children with epilepsy

Metabolite concentrations change with early brain maturation, and this differs between different brain regions,[69] which complicates investigations of infants and young children. In older children and adolescents with TLE, ^{1}H-MRS of mesial temporal lobe regions showed similar results compared to adults. Abnormally low NAA/Cho+Cr was seen in 75%; 55% were correctly lateralized; bilateral abnormalities were seen in 45%.[73] These results were extended to young TLE patients who showed no abnormality on specialised structural MRI investigation.[30]

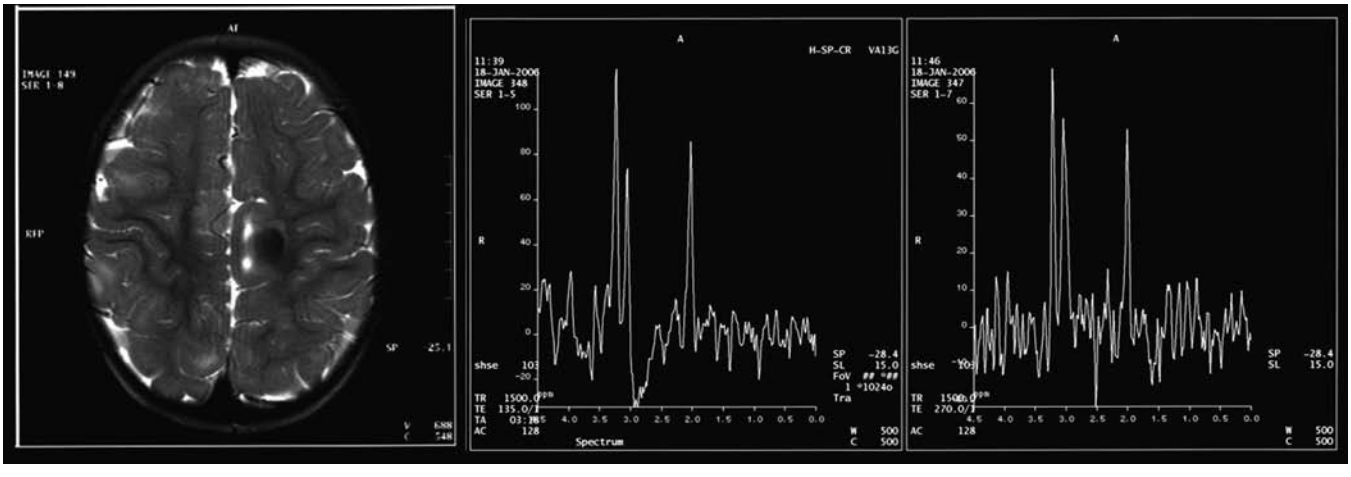

Figure 85.5 Left panel: MRI of a young patient with tuberous sclerosis with a large calcified tuber in the left pericentral region. Right panel: MR spectra (TR 1.5 s, TE 135 and 270 ms) showing low NAA and relatively high Cho as described recently in a larger series of patients with TS.[72] Note the presence of spectral distortion around 2.9 ppm, and that the SNR is lower than would be expected for a voxel of this size: both effects are presumed to be due to the presence of calcification, which degrades spectral quality.

Comparing children with TLE and a history of complex febrile convulsions and children without any history of complex febrile convulsions, changes in the metabolite ratios were detected to a similar degree (60%).[74] MRS-detectable neuronal dysfunction throughout the temporal lobes of children with TLE was already as severe at the time of diagnosis as it was in patients with long-standing intractable TLE.[75] Whether longitudinal MRS studies might help to clarify the role of febrile convulsions in the pathogenesis of TLE remains unclear.

The most frequent pathology in children undergoing epilepsy surgery is malformation of cortical development (MCD). Heterogeneous MRS findings in MCD have been reviewed in an earlier paragraph of this chapter. In pediatric epilepsy surgery, extensive resections (multilobar resections, hemispherotomies) are more frequent than in adults. Whether MRS can help to characterize the contralateral hemisphere and to define it as normal, remains unclear. In single cases of MRS investigations in hemimegalencephaly, the normal-appearing hemisphere was mildly affected (decreased NAA in white matter).[76]

There are case reports describing MRS results in catastrophic epilepsy, i.e., childhood epilepsy with very frequent seizures and the loss of neurological or neuropsychological function ('epileptic encephalopathy'). In these patients, MRS measurements at a single time point should be treated with caution considering the possibility of fluctuating metabolite profiles related to seizure activity. In an 8-year-old boy with Rasmussen's encephalitis, five MRS examinations were performed over 9 months.[77] Following complex partial status, MRS showed a reduction in N-acetyl aspartate, total creatine and choline. Subsequent scans showed complete resolution of these metabolite abnormalities, followed later by development of further abnormal metabolite values. In this case, lactate and Glx were elevated after status. In hemimegalencephaly, another cause of catastrophic epilepsy, a single case study reports signs of progression of MRS measures of glial proliferation after one year (reduced NAA and elevated myoinositol).[78] In Sturge-Weber syndrome, a vascular malformation underlying catastrophic epilepsy, NAA was reduced in the ipsilateral gadolinium-enhanced volume of interest compared to a similarly placed contralateral volume.[79] A focal area of elevated choline without significant alteration of NAA might characterize the early pathophysiological manifestation of Sturge-Weber syndrome.[80]

In pediatric neuroimaging, MRS has some role in diagnosis and follow-up of encephalopathies due to metabolic diseases,[69] which might be the cause of epileptic seizures. In the neuronal ceroid lipofuscinoses (NCL), probably the most common progressive metabolic encephalopathies of childhood associated with seizures, MRS might help to distinguish different subtypes. Infantile NCL was characterized by a complete loss of NAA, a marked reduction of Cr and Cho, and an elevation of myoinositol and lactate in both gray and white matter; reduced NAA and elevated Lac were also detected in gray and white matter of late infantile NCL; in contrast to the infantile forms, juvenile NCL exhibited normal metabolic profiles.[81,82] In late infantile NCL, proton MR spectra revealed progressive changes, with a reduction of NAA and an increase of myoinositol and Glx; myoinositol became the most prominent resonance.[83]

Decreased NAA, sometimes increased Cho and myoinositol, but mainly the presence of lactate can also be found in peroxisomal or mitochondrial disease. For example in Zellweger syndrome, a peroxisomal disease, widespread bilateral MCD might be associated with decreased NAA and an abnormal signal consisting of lactate and lipids.[84] Lactate has been detected in young patients with mitochondrial encephalopathies, but as with all other means used to diagnose rare disorders, MR spectroscopy does not depict elevated lactate in all cases.[85] Lactate is usually not seen in spectra of normal adult brain. Lactate was detected, however, in all 35 normal control infants at 31–42 wk of gestational plus postnatal age studied at 2.4 T, making the use of MRS to diagnose abnormal lactate in this very young age range difficult.[86]

Future research

MRS will benefit substantially from the increased availability of higher magnetic field strength scanners. The gain in SNR will allow shorter acquisition times, better spatial resolution, or a combination of both. The dispersion of individual peaks contributing to a spectrum will also increase, allowing separation of metabolite peaks that would otherwise not be distinguishable. These improvements should allow both more precise quantification of common metabolites, and assessment of a broader range of metabolites.

Future developments in MRS may enable the technique to benefit the investigation of seizure generation by correlating metabolite changes with interictal discharges or monitoring progression of neuronal damage due to ongoing seizure activity. In induced seizures in animals NAA ratios were reduced,[87] but have been observed to increase initially during the ictal phase.[88] Lactate/Cr ratios were observed to increase ictally, being elevated up to 24 hours after a seizure and returning to the baseline levels within 7 days in induced status in animals.[88] Increase in lactate ratios in kainic-acid treated rats was prevented by cycloheximide pretreatment, suggesting that in situ lactate increase is a marker of seizure-induced neuronal damage.

In human studies NAA levels were not changed after complex partial seizures and absences.[15] Significant increases in lactate/Cr during and soon after complex partial seizures were reported, but this was not seen during absence seizures. Castillo *et al.*[89] demonstrated increased lipids/lactate in the hippocampus of patients within 24 hours of their last seizure. The increase in lactate in these studies was maximal over the area of the seizure focus and this might explain the absence of change of lactate distant to the seizure focus. The rise in lactate seen following secondarily generalized tonic clonic seizures in two patients implies a spread of seizure activity into the frontal lobe.

In the first study using magnetization transfer (MT) MRS in patients with epilepsy, we recently observed that the MT effect on choline was reduced after seizures, while choline concentrations remained unaltered.[90] We hypothesise this is due to membrane perturbation as a consequence of seizure activity, possibly due to NMDA receptor activation, which has been shown to induce choline release from membranes by inhibition of phosphatidylcholine synthesis.

The future lies in the development of new MRS acquisition techniques and the refinement of existing ones. Increasing the

speed of MRS protocols would facilitate their validation in larger numbers of patients, which is an essential step in the more widespread application of the technique in clinical evaluation.

Conclusion

There is no doubt that MRS detects relevant metabolite changes in patients with TLE. There are indications that these changes are reversible with treatment. However, in children as in adults with epilepsy, 'the cornerstone of neuroimaging remains anatomic; the physiologic data (from spectroscopy, diffusion, or perfusion) should always be interpreted in association with anatomic neuroimaging, as well as knowledge of the patient's history, clinical exam, and laboratory data' (from the preface of Barkovich, 2005).[69]

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86a Post-processing of the magnetic resonance imaging to better define structural abnormalities

S Knake, F Rosenow, and PE Grant

Introduction

Magnetic resonance imaging (MRI) has become one of the most important tools in the pre-surgical evaluation of patients with medically resistant focal epilepsies. The importance of detecting a concordant lesion on MRI is reinforced by the impact it has on predicting surgical outcomes.[1,2] In many patients with medically intractable focal epilepsies that are MRI negative a focal cortical dysplasia (FCD) is later detected histopathologically. On MRI FCD are often characterized by a combination of increased cortical thickness, increased T2 signal within the dysplastic cortex and blurring of the gray and white matter junction. However, the visual identification of these abnormal characteristics may be difficult and time consuming, even for the experienced reader, because the changes on MR are subtle and the lesions may be only a few millimeters in size. Additional challenges include determining the full extent of the FCD and the secondary changes in brain structure and organization that may occur. New imaging techniques and post-processing methods have the potential to detect subtle lesions undetected in previously MRI-negative patients[3–5] and the ability to better define full impact on brain structure and organization. This chapter presents a brief overview of post-processing techniques currently in use, both clinically and experimentally, to diagnose, plan treatment, and increase our understanding of the neuropathology of focal epilepsies:

Advanced brain imaging technologies now provide a means to investigate disease specific morphological changes in their full spatial and temporal complexity. New imaging techniques have the potential to uncover patterns of altered structure and function that cannot be detected by visual inspection alone.

Analyzing the cortex

2D and 3D reformatting

Planar brain surface reformations

Curvilinear reformatting of the 2D images is used to reconstruct the images into thin, curved slices where the distance from the surface of the hemispheric convexities is kept constant.[6] These reformations ('pancake views') aid in the visual detection of subtle cortical lesions (Figure 86a.1). To create these images, isotropic 1 mm, three-dimensional (3D) MRI data sets are post-processed using a curved multiplanar reformatting technique.[3] These images preserve the spatial relation of adjacent cortex areas and surface structures in one view.[8] This technique can increase the reader's ability to detect cortical abnormalities compared to standard imaging planes.[9]

Surface rendering

Gyral folding patterns, although quite variable normally, can be significantly altered in a variety of diseases. Sulcal pattern anomalies have been identified in schizophrenia and epilepsy[10–12] and visually obvious gyral folding anomalies have been reported in patients with cortical dysplasias.[8] Subtle gyral folding abnormalities may not be identified on two-dimensional images. A 3D reconstruction of the cortical surface can aid in the identification of gyral folding abnormalities associated with cortical dysgenesis.[14]

Volumetric Analysis

Voxel-based morphometry

Voxel-based morphometry (VBM) can be performed as a semiautomated or automated procedure carried out on MRI data acquired at high resolution in a three-dimensional (whole-brain) format, typically a T1-weighted MRI volume data set (MPRAGE, 3DFLASH, 3DSPGR) that is normalized and segmented using algorithms from SPM99 (Statistical Parametric Mapping Software, Wellcome Department of Imaging Neuroscience, London). The distribution of gray and white matter is analyzed on a voxelwise basis and compared with a normal database of healthy subjects. The volumetric T1-weighted scans are used and a stereotactic normalization, segmentation, smoothing is performed before an automated statictic voxel-based comparison of T1-differences is performed.[15]

VBM has been used in previous studies in a variety of populations including healthy adults, patients with various forms of dementia, and schizophrenic patients to identify regions of cerebral abnormality as well as to determine how these regions correlate with neuropsychological function.[16] Some groups have used this methods to better define the epileptogenic lesion.[17–19] One of the advantages of this method is the automated, user-independent determination of gray-scale differences in each voxel that allows large amounts of data to be processed in a reasonable time frame. VBM analyses the whole brain voxel by voxel without the selection of predefined regions of interest that are based on a priori hypothesis.

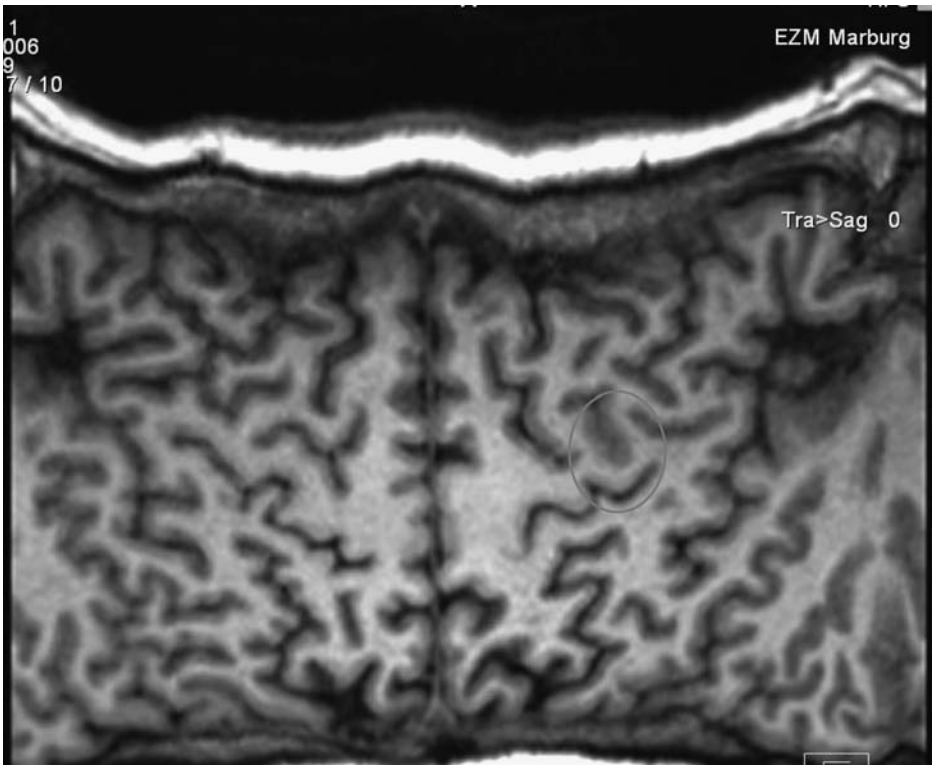

Figure 86a.1 Cortical flat map of a T1-weighted MR datatset of a 34-year-old right-handed woman with left frontal lobe epilepsy due to focal cortical dysplasia (FCD) (Taylor type 2). The area of FCD is represented by a difference in cortical folding and a subtle blurring of the sulci (see circle). We have used the technique in a 34-year-old patient with left central cortical dysplasia. Planar reconstruction images show the blurring in the depth of the cortical sulcus as demonstrated in Figure 86a.7.

The disadvantage of this method is that the accuracy is based on the voxel size and subtle differences, smaller than the voxel size cannot be detected. The performed stereotactic normalization is only a rough correction of global differences, subtle differences of individual brains might not be registered correctly and might have an influence on the result.

Atlas based segmentation

Fischl and Dale[22] have developed an automated technique for assigning neuroanatomical labels to each voxel in an MRI volume. The technique is based on probabilistic information that is estimated automatically for each voxel based on a manually labeled training set and is embedded in the Freesurfer program (CorTechs Labs, La Jolla, CA, USA). In contrast to several existing segmentation procedures the program assigns one of 37 labels to each voxel, including left and right caudate, putamen, pallidum, thalamus, lateral ventricles, hippocampus, and amygdala. The classification technique employs a surface-based registration procedure that seems robust to anatomical variability, including the ventricular enlargement typically associated with neurological diseases and aging.[23] The technique has to be comparable in accuracy to manual labeling, and of sufficient sensitivity to robustly detect changes in the volume and tissue of noncortical structures in epilepsy patients.[23,24] We have used the program to automatically label brains of patients with cortical dysplasia and periventricular heterotopia. The program labeled dysplastic cortex as 'cortex of unknown origin'. The technique therefore seems to be a useful approach to direct the eye of the radiologist reading the film (Figure 86a.2).

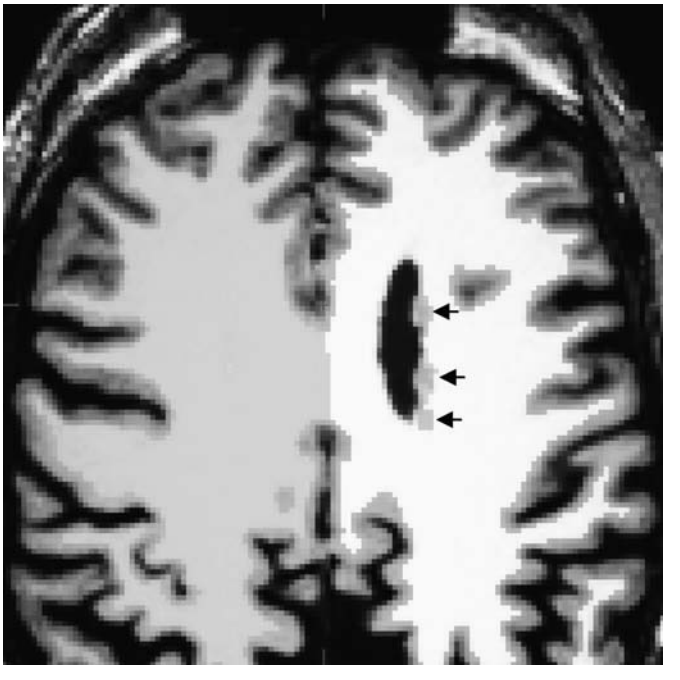

Figure 86a.2 Automated segmentation of a T1-weighted 3D MRI (mprage) of a 42-year-old right-handed patient with left periventricular heterotopia. The program detected the heterotopiua that were labeled as gray matter of unknown origin (see arrowheads).

Quantitative tissue characterization

Huppertz *et al.*[25] have used three novel VBM techniques in SPM for texture analysis of 3D MRI which may improve lesion detection by enhancing image properties not readily accessible by visual analysis. To better identify focal cortical dysplasia, they created 3D maps called 'thickness image', 'extension image', and 'junction image', which characterize three different features of FCD, i.e., abnormal thickness of the cortical ribbon, abnormal extension of gray matter into the white matter, and blurring of the gray-white matter junction (see Figure 86a.3). These methods were applied to the MRI data of 25 epilepsy patients with histologically proven FCD. In each of the new feature maps the locations of the five highest maxima (corresponding to the maximum deviations from the mean of the normal database) were automatically determined and compared with the sites of the lesions in the conventional MR images or – in case of cryptogenic epilepsy – with the resection areas in the post-operative MRI. This approach was able to identify 15/25 lesions in the thickness image and 18/25 lesions in the junction and extension image, respectively. With all feature maps combined, 23 out of 25 dysplastic lesions were identified. Among these cases there were also four patients in whom the dysplastic lesion itself or at least an essential part of it had not been recognized on conventional MR images despite acquisition and assessment in a tertiary epilepsy center.[25,26] These novel VBM techniques may facilitate the detection and localization of FCD and increase the diagnostic yield of MR imaging.

Another method of tissue characterization is to perform multiflip, multiecho FLASH sequences to quantitate T1, T2, and PD at each voxel in the brain. Combined with an atlas, this allows tissue classification and detection of differences that occur with disease.

Cortical thickness analysis

The human cortical surface is extensively folded so that two-thirds is in the sulci. Accurate manual determination of the

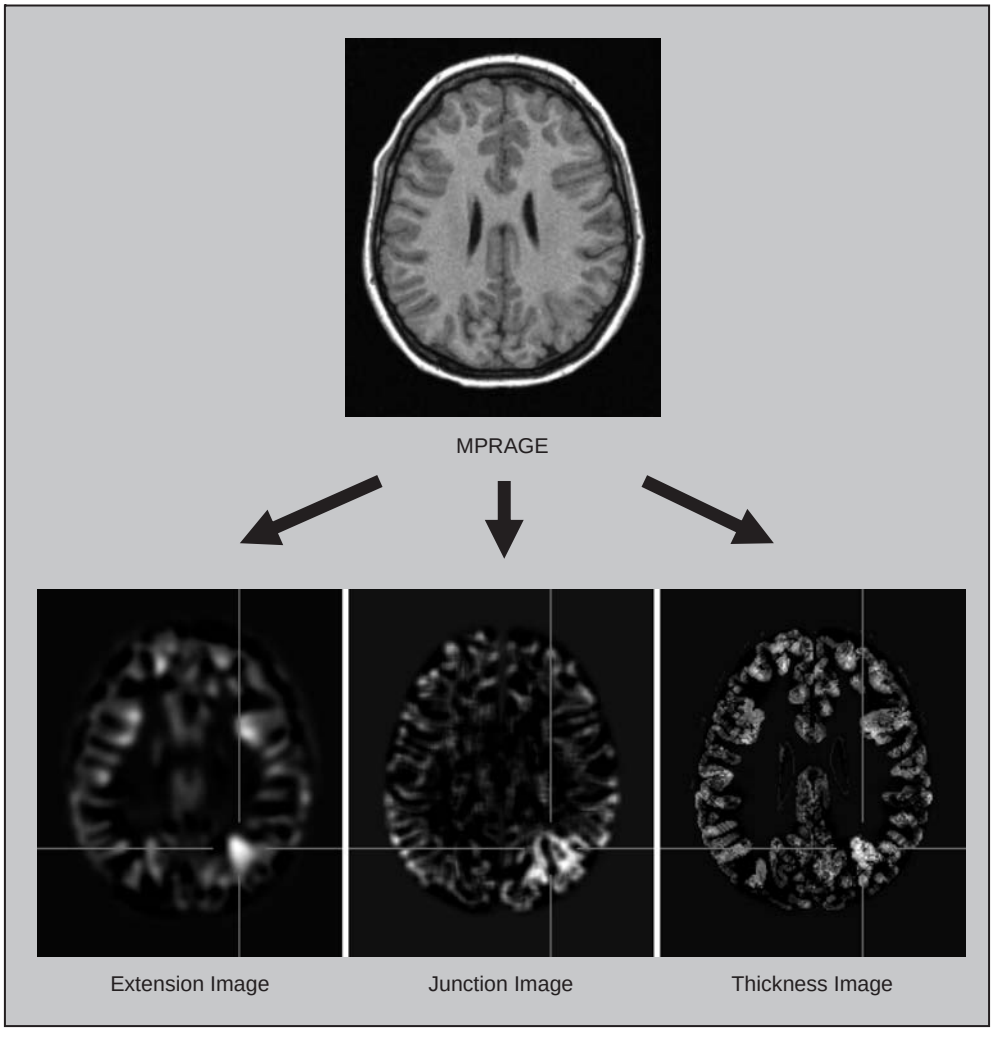

Figure 86a.3 Voxel-based 3D MRI analysis in an 18-year-old female patient with FCD Palmini 2b and SPS, CPS and SGTCS since the age of 2 years: Following the principles of voxel-based morphometry a T1-weighted MRI volume data set (MPRAGE) is normalized and segmented using algorithms of SPM2 (Statistical Parametric Mapping Software, Wellcome Department of Imaging Neuroscience, London). Then, the distribution of gray and white matter is analyzed on a voxelwise basis and compared with a normal database consisting of the MR images of over 50 healthy subjects. Based on this analysis, 3-dimensional maps called 'extension image', 'junction image', and 'thickness image', are created which characterize three different features of FCD, i.e., the abnormal extension of gray matter into the white matter (1), blurring of the gray-white matter junction (2), and slightly abnormal thickness of the cortical ribbon (3). (Courtesy of HJ Huppertz, Swiss Epi Center, Zurich.)

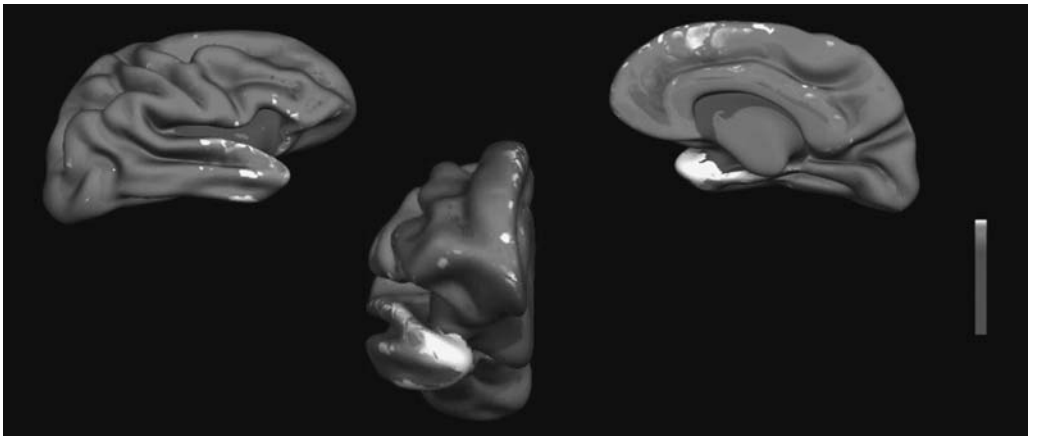

Figure 86a.4 Cortical thickness analysis of the cortex of a 38-year-old right-handed patient with right pericentricular heterotopia.

cortical thickness is labor intensive, time consuming and usually focuses on a priori selected regions of interest. In recent years, semiautomated techniques for analyzing cortical thickness have been developed.[23,27] Using this technique, disease-specific differences in cortical thickness have been detected in patients with Huntington's disease and in aging.[28,29] These intravoxel interpolation methods detect differences in cortical thickness that cannot be appreciated visually and are below the resolution of the image voxel. Cortical thickness measures have the potential to increase the diagnostic yield of MRI and to increase our understanding of the extent and location of cortical involvement associated with different epilepsy syndromes.[3] For example, in four patients with periventricular heterotopia we detected cortical thinning in the ipsilateral temporal lobe, concordant with the seizure semiology (see Figure 86a.4). Tools analyzing the cortical thickness may also help delineate the anatomical extent of epileptogenic cortical lesions. If validation is possible, this technique could provide a more accurate and regionally specific description of normal and abnormal cortex. Kotini *et al.* report the findings of increased cortical thickness in the affected cortex in a patient with unilateral perisylvian syndrom.[30] This technique may be especially beneficial for detecting unexpected widespread cortical pathology or in focusing the visual inspection for lesions in MRI-negative patients with focal epilepsies.[3] By using semi-automated tools, user-dependent inaccuracies are avoided. Currently, these cortical thickness measures rely on the ability to automatically detect a normal gray-white junction in a fully myelinated brain. Therefore, these measures are limited to subjects over approximately 2 years of age. Lesions with blurred gray-white junction are typically detected but the measured thickness of the cortex may be inaccurate due to the poorly defined gray-white junction.

Gyral folding

Quantitative analysis of 2D surfaces in 3D

Techniques like planar or 3D reformation of the brain focus on the visual detection of gyral and sulcal differences. However, the identifiation of subtle changes may require quantitative analysis of the brain curvature and comparison to previously established populations of normals. To perform quantitative analysis of surface properties a topologically correct 2D surface in 3D must be created. As it turns out, the cortical surface is folded in on itself in a way that makes it almost impossible to create a topologically correct surface from the existing volumetric MR data. This occurs because gyral surfaces touch, making it hard to resolve boundaries in an automated fashion. The gray-white surface in comparison does not have this property and therefore it is much easier to construct topologically correct 2D surfaces from this interface. The gray-white boundary is the surface area through which connections exit or enter from gray matter and therefore the characteristics of this interface have implications for cortical and white-matter organization. Only a few centers have begun to quantify properties of these surfaces. Quantities that are calculated include surface areas, local curvature and its components, local Gaussian curvature, local fractal dimension, and wavelet decompositions. Our preliminary data of normal neonatal brain development suggest that the gyri develop in a very regular manner, resulting in conserved curvature properties. We believe that these techniques hold great potential for defining normal growth trajectories and differentiating normal from abnormal brain development. It addition, these methods may improve our ability to detect global changes that occur with congenitial malformations or persistent seizures.

Different techniques have been used describe differences in cortical gyrification in patients with shizophrenia[31] and in Williams syndrome,[32] Ronan *et al.*[33] have used stereology. Quantitative examination of human cerebral gyrification has been applied to detect abnormal gyrification in schizophrenia on healthy brains using the isoperimetric ratio (IPR) as an index of cerebral gyrification. The IPR is a dimensionless ratio defined as surface area corrected for volume allowing for a robust and reliable quantification cerebral gyrification.[33]

Analyzing subcortical structures and white matter

Automated subcortical labelling and volumetry

Accurate manual segmentation techniques are labour intensive, time consuming and tedious. Automated techniques have the potential to make cerebral volumetrics part of a routine clinical assessment, but they currently require validation and standardization before this potential can be realized. The identification of anatomical substructures is based on tissue classification by classifying different gray-level intensities in different voxels. Fully automated analysis tools have been

developed to label different MRI substructures in an unbiased, user-independent fashion.[22,23,34]

Previous studies have shown that volumetry might help identifying the epileptogenic lesion. Especially in patients with temporal lobe epilepsy, volumetry seems superior to pure visual MRI inspection in correctly lateralizing the hippocampal pathology.[11]

We have used the technique developed by Dale and Fischl[23,34,35] to automatically segment the brain in patients with medically refractory epilepsies due to cortical dysplasia. Areas of cortical dysplasia were identified correctly and tissue was classified as 'grey matter of unknown origin' in the respective ares (Figure 86a.2).

Magnetic resonance diffusion imaging

Diffusion-weighted imaging and ADC maps

Diffusion imaging is based on changes in the diffusion properties of water molecues in diseased brain tissue: 'Diffusion' describes the random microscopic translational motion (Brownian motion) of water molecules.[36] Unrestricted diffusion of freely diffusing molecules is spherical, with the radius of the sphere increasing as the square root of the time of diffusion. Diffusion behavior in a highly organized system like the human brain is more complex and restricted and is determined by multiple variables such as fiber crossings, myelinization, ischemia, and neuronal cell density. Diseases of the central nervous system are often accompanied by changes in diffusion. The application of diffusion imaging on patients with epilepsies has been used to postictally identify areas of transient postictal changes.[35,37,38] Acute postictal changes have also been reported in areas distant from the EEG focus, often near the corpus callosum or the splenium.[39,40] Diffusion imaging has been used interictally to study patients with focal epilepsies: Wieshmann *et al.* showed significantly reduced diffusion in sclerotic hippocampi as compared to the nonsclerotic side.[36,41]

Diffusion tensor imaging

The phenomenon of a restricted diffusion is of particular interest to studies that evaluate the integrity of white matter and of fiber tracts. Like DWI, DTI uses the diffusion properties of water in the brain. With standard DTI, in addition to an ADC map from DWI, one also acquires a map that is a measure of the directional bias of diffusion. DTI therefore provides information about the rate, magnitude, and directionality of water diffusion in the brain. DTI contrast is associated with water diffusion and is influenced by microstructural factors such as myelin and other fiber components. A normalized metric of white matter integrity, termed 'fractional anisotropy' (FA) is computed from the diffusion properties within a voxel. Similar metrics have been used to detect white-matter pathology in epilepsy and neurodegenerative diseases.[42–46] Specifically, the more tightly packed and coherent the white matter tract, the more likely the diffusion is dominated by fewer versus many directions, the greater will be the FA value, resulting in a brighter signal intensity on an FA map. The signal abnormality in the DTI scan is presumed to reflect alterations in tissue properties, including decreased myelination or changes in the number of myelinated nerve fibers.[45] DTI is presently being explored as a research tool.

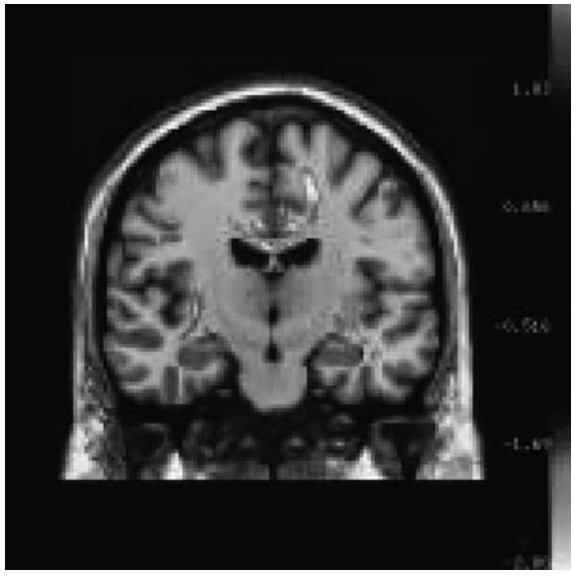

Figure 86a.5 Comparison of fractional anisotropy (FA) maps of 14 patients with left temporal lobe epilepsy due to hippocampal sclerosis and healthy normal controls. Statistically significalnt differences in white-matter organization, measured in FA, are presented co-registered on the anatomical T1-weighted image. Diffences mainly occur in the ipsi- and contralalteral temporal stem and the ipsilateral frontal lobe.

Information of WM integrity provided by DTI could be very useful in the characterization and quantification of epilepsy-associated brain damage and might be used as a marker of disease severity and progress. Our preliminary studies show decreased FA values in the ipsilateral and contralateral temporal stem as well as in the frontal lobe of patients with mesial temporal lobe epilepsy (TLE) (Knake *et al.*, unpublished data) (Figure 86a.5).

In addition to determining the coherence of white matter tracts, DTI can be used to estimate fiber orientation in the brain. To visualize fiber direction, images are color coded according to the direction of the diffusion and then superimposed on an image aquired without diffusion weighting (B0-image) (Figure 86a.6). The green codes for anterior to posterior vectors, blue for superior to inferior, and red for left to right.[48] Although it seems that DTI can identify networks and anatomical tracts, it is uncertain at present, if DTI is able to delineate relevant tracts with sufficient reliability. Voxel-size, artefacts and a variety of technical issues make it difficult to extract fiber directionality from water diffusion.[36]

Conclusions

Improved imaging technique and sequences as well as improved accuracy in data registration and the use of fully automated techniques will have a huge impact on standard MR imaging in the pre-surgical evaluation in future. However, most techniques are new and have to be validated in large, prospective studies.

It would be desirable to combine functional imaging techniques like EEG, fMRI and MEG with new structural imaging techniques to better define the epileptiogenic lesion, the irritative zone and the seizure onset zone, in respect to the eloquent cortex.

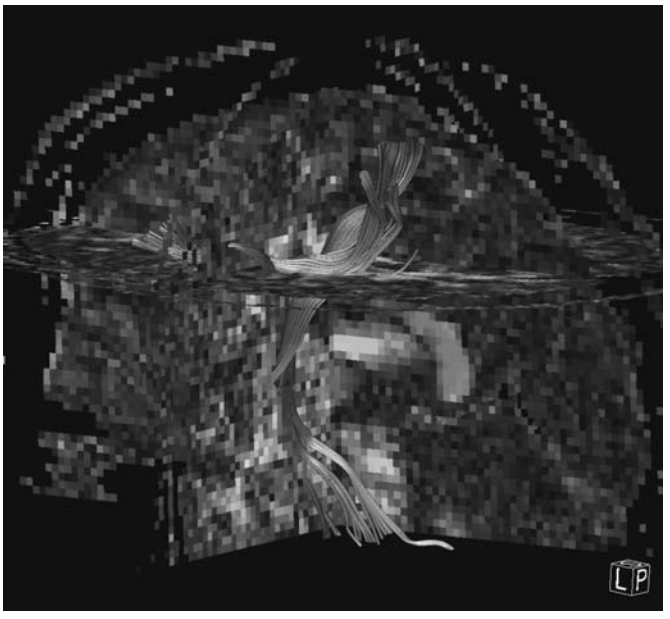

Figure 86a.6 Diffusion tractology image. Left corticospinal tracts (blue), interhemispheric connections (green), calculated from high-resolution diffusion tensor sequence at 3 T using custom built software by Drs Ruopeng Wang, Greg Sorensen, and colleagues at the HST A.A. Martinos Center for Biomedical Imaging. The directional bias of the diffusion can provide information about the structure of underlying white-matter tracts. Analysis techniques under development may enable statistical measures of connectivity which, in turn, may further our understanding of cerebral malformations and seizure propagation.

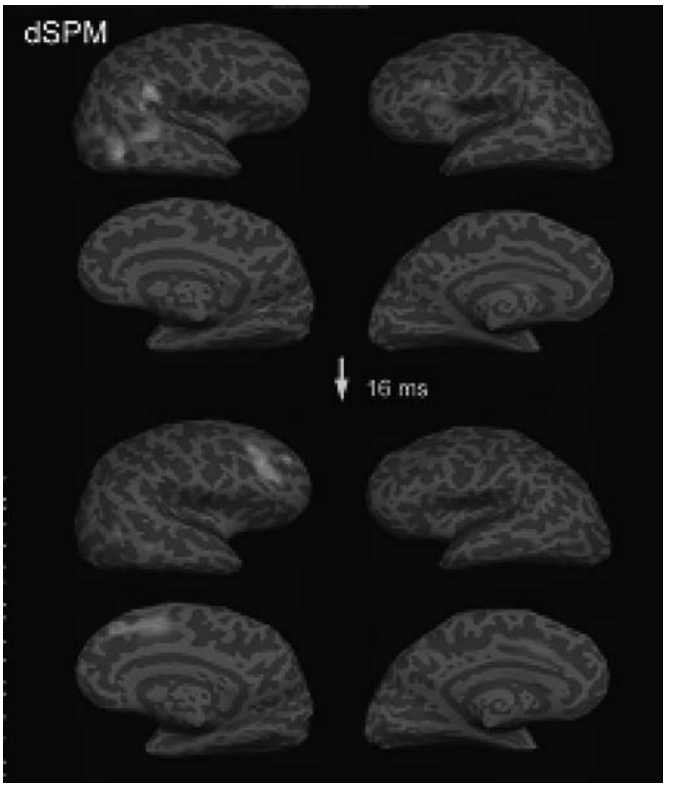

Figure 86a.7 MEG data of a 17-year-old right-handed boy suffering from right hemispheric epilepsy (referred by Dr G. Holmes, Children's Hospital, Boston). During the investigation several MEG-only spikes but no spikes were recorded on EEG. Magnetic source imaging of all recorded MEG spikes (right side) mapped the IED to the right posterior temporal lobe. Dynamic SPM of one IED shows that the spike is spreading from right posterior temporal to the right frontal region within 16 msec. (Image courtesy of Dr Hideaki Shiraishi, Department of Pediatrics, Hokkaido University, Graduate School of Medicine.)

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86b Multimodal image processing in pre-surgical planning

C Vollmar, S Noachtar, and PA Winkler

Introduction to the multimodal image processing approach

As described in Chapter 47, the definition of the epileptogenic zone is the key challenge in pre-surgical evaluation of epilepsy. The epileptogenic lesion and the seizure onset zone will typically be included in the epileptogenic zone. However, it is known that they may reflect only the core of the epileptogenic zone and that the irritative zone, the symptomatogenic zone or even the functional deficit zone can further contribute to epileptogenicity and can also define an additional part of the epileptogenic zone. In most chronic focal epilepsies, all these zones are partially overlapping, with different spatial extent and a complex mutual relationship between them. Additionally, most of these zones are not visualized directly by any imaging modality, but images reflect various physiological tissue characteristics and different aspects of epileptogenicity. Interpreting diagnostic images in the pre-surgical evaluation of epilepsy includes the task of assigning individual imaging findings to the theoretical zones described above: a regional hyperperfusion shown in an ictal SPECT study may reflect the seizure onset zone only, or spread to the symptomatogenic zone can already be involved. This judgment will be based on the exact time of injection in relation to seizure onset, EEG findings, seizure semiology and other information on the clinical context.

The presence of any structural lesion can further influence the regional perfusion. Facing the complexity of this mutual relationship between different imaging modalities, a precise topographic correlation of all available diagnostic modalities is helpful. Image coregistration and the combination with a three-dimensional reconstruction of the patient's individual cortical anatomy can assist the interpretation of each single modality and finally support a conclusive interpretation with the aim to individually define the epileptogenic zone for resection.

To transfer imaging findings from original or post-processed images into the operating theatre, it is necessary to provide some guidance, which allows a reliable correlation of images with the real brain.

The use of navigation systems is possible[1], however epilepsy surgery often includes large craniotomies, causing a significant brainshift, due to loss of CSF or distortions during the course of an extensive resection.[2,3] A significant brain shift also occurs after removal of a subdurally implanted grid, which is typically the occasion to proceed with the resection of the epileptogenic zone. To overcome this issue, we focussed on the topography of the cerebral venous system to provide anatomical landmarks for planning and tailoring cortical resections. The specific shape of the superficial venous anatomy is fixed to cortical anatomy via the arachnoid trabecular system.[4,5] This makes superficial cortical veins a reliable anatomical landmark, overcoming the trouble of brainshift. Finally this allows for a precise intraoperative localization of previously identified structures like subcortical lesions or the seizure onset zone or eloquent cortex, even in extensive craniotomies.

The aim of this chapter is to provide the reader with a short overview of techniques for multimodal image correlation, applicable in the pre-surgical evaluation of epilepsy. The specific contribution of multimodal image processing to the definition of the epileptogenic zone and for planning individually tailored cortical resections will be illustrated in several clinical examples.

Requirements

Increasing computing performance makes the technical basis for multimodal image processing available to a wide community. All the images in this chapter were created on a standard Personal Computer (Intel Pentium IV, 1.8 GHz CPU, 512 MB RAM), equipped only with an additional consumer class ('gamer') graphic acceleration card. Improvements in diagnostic imaging, like the invention of 3 T MRI scanners or multislice CT scanners, allows the acquisition of datasets with a higher spatial resolution, resulting in bigger image datasets being processed. However, this development coincides with a continuous increase in computing power and storage capacity of personal computers. In practical terms this means, a standard personal computer in the $ 1000 category has always been sufficient for multimodal medical image processing for the last few years, and most likely there will be no need for a higher investment during the next few years.

Searching the internet for 'medical image processing' will provide a broad bandwidth of possible software packages, including free and commercial products. The decision on which software to use should be based on previous experience in your department, since all available software packages require some period of time for training. It is important to mention, that most of the software is marketed for research

purpose only, and not for clinical patient care. This reminds us that every single step of image processing is a possible source of errors, and that clinical decisions should never be based on image processing results, without confirmation by the clinical context. The decision, how much image processing is allowed to contribute to clinical decision underlies the physician's responsibility. Typically, the involvement will increase over time, with more experience and confidence in the image processing procedures.

Another issue for image processing is the comfortable accessibility of digital image data. In a fully digitized hospital, employing modern network infrastructure and a PACS system, it will be easy to collect and process image data from several departments. However, with a less advanced infrastructure it is just a bigger effort, to export, convert, and transfer image data from different modalities and departments, yet image processing can still be performed.

Image acquisition

The basis for multimodal imaging is typically a T1-weighted, high-resolution volume acquisition MRI dataset. It serves as the primary dataset for all further image registration procedures, and also provides the anatomical basis for all further localizations, including the three-dimensional reconstruction of the patient's cortical surface. At the University of Munich Epilepsy Centre we use a sagittally acquired fast gradient echo T1 sequence, providing isotropic 1 mm^3 pixels ('mprage' on Siemens MRI-scanners or 'FSPGR' on General Electric scanners). An image matrix of 256 × 256 pixels and a slice thickness of 1 mm are entirely sufficient to depict the patient's individual cortical anatomy; however, the higher resolution that is becoming available with higher field strengths can further improve the image quality. Besides this anatomic basis dataset, a number of additional sequences will be acquired, following established protocols for epilepsy, or driven by specific questions from the clinical context. There are no specific requirements to allow further processing of additional MRI sequences. Limiting the slice thickness to not more than 4 mm warrants a minimum image quality after reformatting of images and will improve the reliability of image registration.

For visualization of the superficial cortical veins, we currently use a contrast enhanced 2D-Time-of-Flight-Angiography-sequence with a 512 × 256 matrix and 2 mm slice thickness. However, comparable results have also been achieved with different angiography sequences.

In nuclear medicine, SPECT and PET images can usually be acquired by routine protocols; most departments will create transverse datasets with isotropic pixels of about $3 \times 3 \times 3$ mm^3 which can perfectly be used for further image processing.

Image coregistration

The first step in multimodal image processing is image coregistration. This term describes the procedure of spatially aligning two different image datasets in a way that both studies show the same anatomic structure in every pixel. One dataset is defined as 'primary' or 'reference' and is left unchanged. The 'secondary' dataset is then transformed, to match the reference. Since the transformation and resampling of the secondary dataset requires interpolation, a modest loss of image quality is possible. For this reason, typically the higher resolution data like MRI is defined as 'reference', and the lower resolution data like PET is transformed to match the MRI.

The minimal necessary transformation to align two three-dimensional datasets from one patient is a 'rigid body' transformation, and uses six degrees of freedom: translation and rotation along the three perpendicular axes of a coordinate system. The scaling and internal configuration of both datasets remains unchanged. For image registration from different individuals or for the registration of an individual dataset to a normative template, a 'nonrigid transformation' might be necessary, which includes additional scaling or stretching of the datasets. These nonrigid transformations are based on complex algorithms and contain several sources of artificial influence on the image data. Currently this limits their use in clinical routine; nonrigid transformations are primarily applied for group comparisons in research settings.

In the pre-surgical evaluation of an epilepsy patient, the rigid body transformation of several imaging modalities will be sufficient to achieve the image registration, necessary for multimodal correlation of different imaging findings. However, even a rigid body transformation has to be verified to estimate the accuracy of the procedure, before its results are allowed to influence clinical decisions.[6] A rigid body image registration can be performed either automatically or manually.

Automatic image registration

All automatic methods are based on comparable principles, which will be illustrated briefly using the example of the 'pixel uniformity registration', also known as Woods' algorithm[7] as a representative method. The first step in this method is a classification of the primary modality, e.g. an MRI, into several groups of pixel values. The idea is that each of these pixel groups should represent an 'organ' or an anatomically defined structure. When matching this group of pixels with a second modality, e.g. a PET, it is obvious that the PET pixel values will be different in these defined 'organs'. Also there will not be a linear relationship between an 'organs' pixel values in each modality. However, at least the 'organ' is supposed to show homogenous pixel values, also in the second modality. With this assumption, the uniformity of pixel values in the second modality, within each pixel class of the first modality is analysed. An improvement of this uniformity is assumed to represent a better registration. Therefore, this uniformity is defined as a measure for the quality of a registration. The last step is now to optimize this measure of quality. The aim is to find the transformation of the secondary dataset that leads to the best possible pixel uniformity, according to the above definition. This is usually achieved with an iterative optimization process, which is a trial-and-error approach initially, changing the transformation parameters arbitrarily and recalculating the measure of quality. Parameter changes that improve the quality of the registration are recognized by the optimization algorithm and the next changes will be guided by previous achievements. This iterative procedure is repeated, until a predefined threshold is reached, or until a maximum number of iterations have been performed.

Most automated methods for image registration can be broken down into these three steps: First, some kind of classification or segmentation of the primary datasets is performed.

Secondly a measure of the quality of the registration is defined, typically including some correlation of pixel values between the two datasets. It is assumed, that an optimization of this error measure reflects an improved registration. Thirdly, this error measure has to be optimized, typically by an iterative approach. Each of these three steps can be modified and optimized independently, in order to improve automatic image registration.

However, despite all the major improvements in the field of automated image registration, all automatic algorithms are inevitably still prone to errors when used in the clinical setting of epilepsy surgery.

From a clinical point of view, divergences between different imaging modalities are exactly what we expect from a multimodal pre-surgical evaluation. In a patient with normal MRI, we perform a PET scan, because we expect the patient's pathology to be apparent by a change in glucose metabolism or receptor density, in spite of a normal MRI. This is the clinical reason why we perform the PET scan. For an automated algorithm this discrepancy will be regarded an error, worsening the measure of registration quality and the algorithm will try to correct this 'mismatch'. The possible work to identify those regions manually from an image dataset and exclude them from the automated registration algorithm is significant.

Manual image registration

On the other hand, there is the possibility to perform image registration manually. This typically means that a user interface is provided to the operator to perform the registration by hand. Usually the primary dataset is displayed as grayscale image in the background and is superimposed by the second dataset, using a transparent colour encoding, isolines or alternating display patterns. The user then has to shift and rotate the secondary dataset manually in all three orientations, until the best fit has been achieved visually. This is an interactive process, including a final visual control by scrolling through the whole dataset, to ensure an adequate registration quality.

This manual approach has several advantages, which is the reason why we only perform manual image registration in clinical routine at the University of Munich Epilepsy Centre.

Many 'automated' methods for image registration require a significant amount of user interaction to prepare the automatic procedure. The removal of the skull from images, or the manual identification of 'regions of interest', are often necessary tasks. The time spent in such preparations of the data quickly amounts to several minutes. Furthermore, one can hardly trust an algorithm blindly, and every automated image registration has to undergo some plausibility check by the physician. The minimum check a physician has to perform, is scrolling through the whole registered dataset to check the registration accuracy. This check will typically take a few minutes. Both of these steps are not necessary if the registration has been performed manually under permanent visual control of the user.

In the case of suboptimal image quality in either modality, the physician can identify the more reliable areas, or the areas of more clinical interest, and then focus on these areas during the manual image registration procedure. Not only technical artifacts, but also discrepancies in the imaging findings, can easily be detected and interpreted by the physician, who knows the clinical context. An automatic algorithm usually does not know how to handle such difficulties, and is likely to fail.

Finally, it could be shown, that the achieved accuracy of manual registration is superior to that of automated algorithms, when analyzing the registration of MRI and ECD-SPECT.[6] An accuracy of 1.5 mm could be achieved manually, and the effect of user- dependency could be shown to be negligible. Similar results have been achieved for registration of other modalities to an MRI dataset, namely PET, CT and MR-angiography, with errors between 0.9 and 1.5. Even the total processing time is lower for manual image registration, taking into account the above-described preprocessing and quality checks for automated algorithms. A manual registration can usually be performed in less than five minutes.

Image segmentation and 3D reconstruction

Image registration alone already allows a correlation of imaging findings from two different modalities. However, datasets are still only analyzed in 2D slices, not in the context of the patient's individual cortical anatomy.

Visualization of the cortical surface requires a three-dimensional rendering of an anatomical MRI dataset. Usually some manual image preprocessing is required before 3D rendering can be performed, namely the segmentation of the brain to separate it from skull and skin. This processing step can be performed automatically or manually. Our preliminary experience with automated segmentation algorithms showed that they work fine at the lateral convexity of the brain and can provide sufficient segmentation within minutes. However, in clinical routine, these algorithms are often limited by artifacts, e.g. skull base susceptibility artifacts or artefacts from eye movement, which typically appear at the level of the temporal lobes. Separating the dura from the cortical surface is also a challenge for automated algorithms, especially in images from patients with a history of previous neurosurgery or meningitis. Fully manual image segmentation, on the other hand, is the most time consuming step in 3D image processing. To manually segment a high resolution MRI of the brain, a trained user will need 15–30 minutes, depending on the characteristics of the dataset, software and user skills. Even the use of supportive tools, like interpolation of the segmentation or automated edge detection, barely reduces the total processing time. As with image registration, we also perform image segmentation manually at the University of Munich Epilepsy Centre. A time-saving compromise can be, to segment only the hemisphere of interest and leave the other side unsegmented. Other than segmenting the whole brain to display the patient's cortical anatomy, in some cases it is reasonable to also segment pathological findings from other MRI sequences or from other modalities. For example, FLAIR images can show focal signal increase in cortical dysplasia or may help to delineate the extent of structural lesions such as posttraumatic gliosis, and can reasonably be segmented for further visualization. In complex cases, the segmentation and colouring of anatomical landmarks such as the precentral gyrus can be helpful.

After the segmentation of the brain surface, we perform 3D volume rendering in order to display the cortical surface three dimensionally. Volume rendering applies for each pixel transparency settings, defined by a colour table, which is specifically adjusted to the underlying MRI sequence. Pixel values for gray and white matter will typically be displayed almost opaque, while lower values for CSF or higher values for fat will be displayed more transparent or completely invisible. This allows for some tolerance with the brain surface segmentation, because thin layers of dura will only slightly change the appearance of the underlying gyri. In case other image modalities show subcortical findings, then the overall transparency of the 3D rendering can be increased, to improve the view to the depth of the dataset. On the other hand, this procedure will reduce the quality of the superficial cortical anatomy.

For visualization of subdural or depth electrodes from a CT scan, no segmentation is necessary. Since the metal electrodes have a higher X-ray density than any tissue, a simple threshold technique with a cutoff at 2300 Hounsfield units can usually isolate the electrodes for further visualization.[8] Some subdural electrodes can be more difficult to display, if by chance the thin platinum contacts are positioned almost parallel to the CT slice orientations. This can happen to temporo-basal or fronto-orbital electrodes, typically resulting in lower pixel values in the CT scan which requires an adjustment of the threshold value. Once the invasive electrodes are visualized, all results from EEG recording and cortical stimulation can also be localized in the image data.

Image arithmetic

For some images, further processing has to be performed, before the final results can be defined and included in the multimodal visualization. The most common application of arithmetic calculations performed on image datasets is the subtraction of ictal and interictal perfusion SPECT, as described in the chapters on SPECT scans.[9] It is important to keep in mind, that such a subtraction is prone to different influences. The amount of injected activity may vary between both SPECT studies, requiring a normalization of the datasets' count rate before subtraction. After subtracting the interictal 'baseline' image from the ictal image, a 'difference' image is created, showing the specific change in perfusion at the time of injection. This image can now be displayed with different thresholds, modifying the extent of change that is visualized. Typically, the most prominent change in perfusion can be found in the seizure onset zone; however, areas of seizure spread, like the symptomatogenic zone or parts of the irritative zone may also be involved. A later time of 'ictal' injection might result in an actual postictal scan, showing a reduced blood flow. In this case, the postictal image would then be subtracted from the interictal scan. The knowledge of the clinical context of the tracer injection, is vital to handle the images adequately, and this requires a close interaction between different involved departments.

In some cases, the regional hyperperfusion can be prominent enough to be displayed without subtracting the interictal scan; in others, it might be beneficial to combine both and add the subtraction result to the whole ictal scan. Whichever way is chosen to calculate and visualize the relevant findings, it is important to always check the original data, to confirm the plausibility of any postprocessing result.

Illustrative case reports

After this technical introduction, illustrative case reports should demonstrate the relative contribution of each imaging modality, and of image processing, in the pre-surgical evaluation of epilepsy patients.

Patient 1

M.R. is a 32-year-old male patient, suffering from frontal lobe epilepsy since the age of 15. He suffers from tonic seizures of the face, evolving to left sided tonic and clonic seizures, eventually further evolving to hypermotor or automotor seizures and GTCS. At the time of pre-surgical evaluation, the seizure frequency on medication was 18 per month.

Initial MRI studies were normal, an FDG-PET scan revealed extensive right temporal and right frontal hypometabolism. Video-EEG monitoring with surface electrodes was performed, and showed interictal spikes and polyspikes, in the right frontal region, and continuous right frontal slowing. Ictal EEG showed consistent right frontal seizure patterns. Therefore, the patient was considered for epilepsy surgery and scheduled for implantation of subdural electrodes to prepare a right frontal resection.

Additionally, a Flumazenil-PET scan was acquired in order to localize the seizure onset zone. The scan showed a circumscribed reduction in GABA-A receptor density (white arrow) in the right frontoorbital cortex (coronal slices through the frontal lobes, Figure 86b.1a). The right frontal lobe was extensively covered with subdural electrodes, as shown in the right lateral view in Figure 86b.1b. Visualization of the electrodes was carried out by image registration of an anatomic T1-weighted MRI scan and a postimplantation CT scan and then combined 3D volume rendering. Figure 86b.1c is a combined image registration of the same MRI, the electrodes and the colour encoded Flumazenil-PET scan (inferior view to temporal lobes and orbitofrontal cortex). It shows the right fronto-orbital reduction in GABA-A receptor density (dark blue area) and its good correlation with the seizure onset zone as recorded from invasive EEG (black electrodes).

An ECD-SPECT scan was performed to visualize the regional hyperperfusion during a seizure, and it revealed a prominent hyperperfusion in the lateral right frontal lobe (Figure 86b.1d). Image fusion with MRI (Figure 86b.1e) allowed anatomic localization of the hyperperfusion (red spot). Figure 86b.1f shows the corresponding 3D rendering, localizing the hyperperfusion to the most posterior portion of the middle frontal gyrus. Since early spread of seizure activity and the maximal frequency of interictal spikes were also recorded from this area, it was decided to include this region in the resection. The detailed 3D view and corresponding equivalent intraoperative photograph (Figure 86b.1g and 1h) show a perfectly matching cortical anatomy. The posterior border of the frontal lobe resection was marked by a black cord intraoperatively and it includes the inferior portion of the central region(Figure 86b.1h). The photograph also shows a prominent artery and vein, crossing the border of the resection. Vascular anatomy was not included in the pre-operative imaging procedure at the time, but this example shows how helpful it would have been for the resection planning.

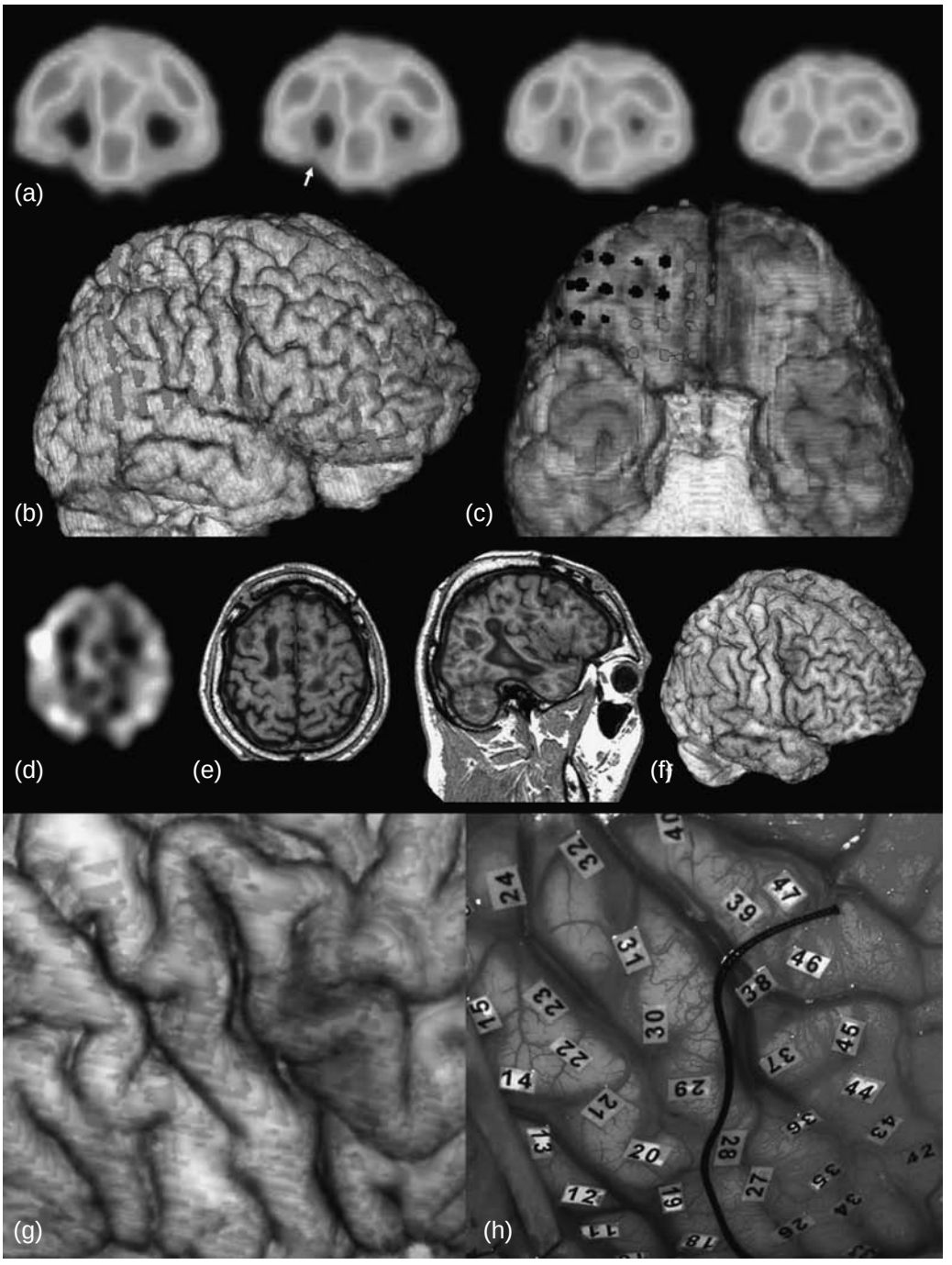

Figure 86b.1 Patient 1. Flumazenil-PET (coronal slices) showing reduced GABA-A receptor density in the right frontoorbital region (a). Subdural electrodes were implanted (b), confirming right frontoorbital EEG seizure onset (black electrodes), overlapping with the PET hypointense area (blue) (c). Ictal SPECT showed marked hyperperfusion (d) in the right middle frontal gyrus (e,f,g). This area was included in the resection (h). (See Color plates.)

Patient 2

A.F. is a 45-year-old female patient, who developed posttraumatic left temporal lobe epilepsy as a consequence of head trauma at the age of 17. Ten years after a car accident, she suffered from epigastric auras, dialeptic seizures, and automotor seizures with an increasing frequency (ten per month at time of admission). T1-weighted MRI showed a posttraumatic defect in the left temporal neocortex (white arrow, Figure 86b.2a, sagittal, transverse and coronal view). Video-EEG monitoring with surface electrodes confirmed left temporal origin of the seizures. Recurring postictal aphasia was indicative of a close topographic relation between the seizure onset zone and language relevant areas. Consequently, subdural electrodes were implanted, to localize the seizure onset precisely and to perform cortical stimulation for the identification of eloquent areas. Figure 86b.2b shows the implanted electrodes and their relation to the posttraumatic defect, which was labeled in orange (derived from FLAIR images). Figure 86b. 2c shows the results of the invasive evaluation, with a seizure onset zone (black electrodes) on the posterior border of the lesion, and an overlap with speech relevant areas (yellow electrodes). Because speech representation was very extensive in this case, and since we know, that inferior temporal language areas are usually accessory areas, it was decided to include this electrode in the resection. Motor responses were elicited from the red electrodes. The gray electrodes indicate

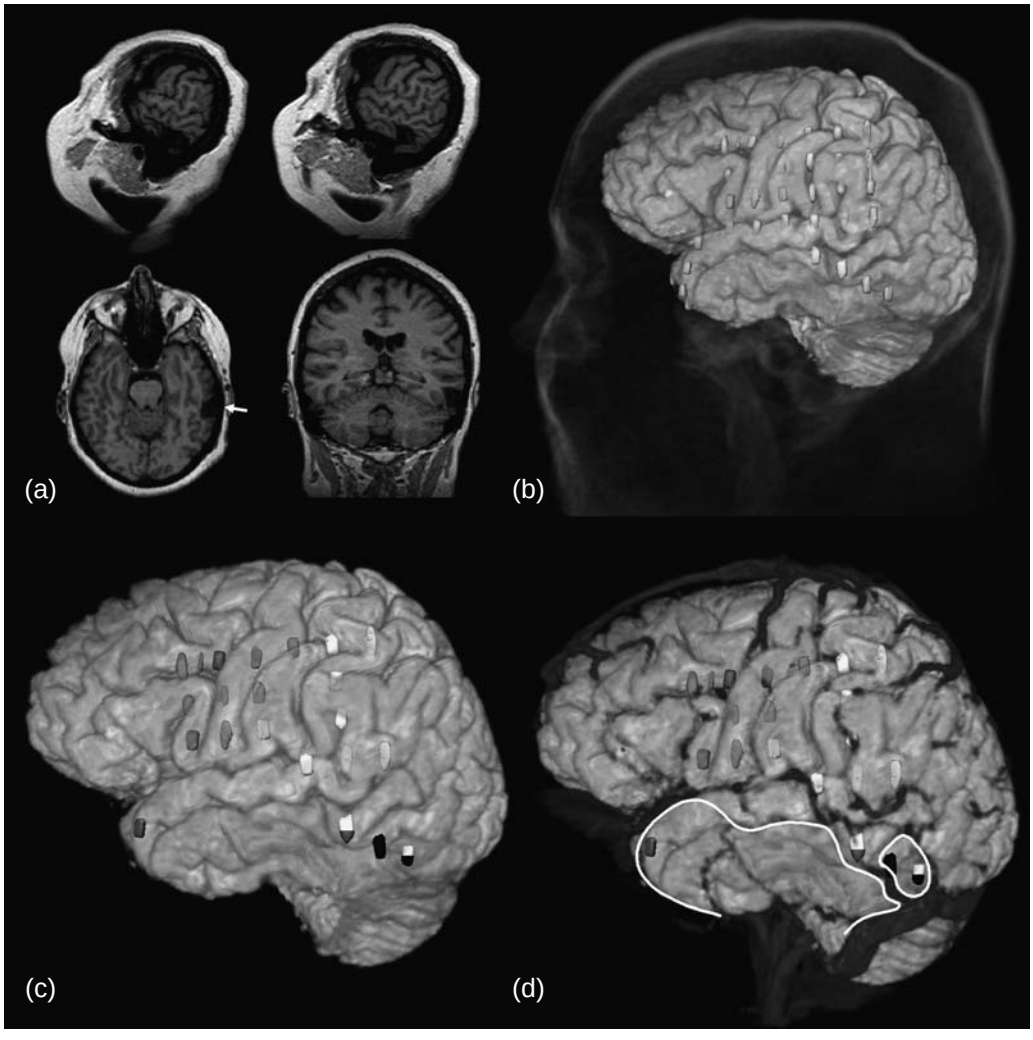

Figure 86b.2 Patient 2. T1-weighted MRI showed a posttraumatic defect in the left inferior temporal gyrus (a), with adjacent gliosis, apparent as FLAIR hyperintensity (orange in b,c,d). Subdural electrodes were implanted (b), localising the seizure onset (black electrodes) and language relevant areas (yellow electrodes, c). Venous MR-angiography revealed a prominent anastomotic vein of Labbé that had to be preserved during the resection (d). (See Color plates.)

interictal spiking. However, the maximum of interictal spikes was recorded from the mesio-temporal stripe electrodes (not visible in this lateral view), and justified a complete resection of the anteromesial temporal lobe. The newly developed technique to visualize the superficial cortical veins, showed a prominent anastomotic vein of Labbé, which had to be preserved, crossing the planned area of resection (Figure 86b. 1d). Additionally, an accessory duplicate vein of Labbé was present in this case, a common variation already described by Labbé in 1868.[10] Therefore, resection was limited to the part of the temporal lobe anterior to the vein. An additional topectomy of the seizure onset zone between both, the first order and the accessory veins of Labbé was also carried out (white resection line).

Patient 3

M.V. is a 44-year-old secretary, who suffered from short bilateral tonic seizures at night since childhood. Occasionally, she would also experience astatic seizures and GTCS. Initial MRI studies were normal, EEG showed rare interictal polyspikes in the right frontal region. At time of admission for epilepsy surgery, a new MRI was performed and 3 mm T1-weighted inversion recovery images (Figure 86b.3a) showed a circumscribed blurring of the cortical band with a corresponding slight increase in FLAIR signal (Figure 86b.3b) in the medial aspect of the dorsal superior frontal gyrus, close to the margin, on the left side. These findings confirmed the clinical hypothesis of a focal cortical dysplasia (FCD).

However, the reconstruction of the superficial veins (Figure 86b.3) showed a complex formation of draining veins over the FCD, making the implantation of subdural electrodes more difficult. From the venous topography, it was obvious that the craniotomy had to be extended towards the frontal pole, to allow for an implantation of electrodes in the medial surface of the frontal lobe, circumventing by the bridging veins Figure 86b.3d shows the localization of the medial electrodes, covering the FCD in a view to the medial surface of the left hemisphere. EEG Seizure onset in the region of the FCD could be confirmed (black electrodes). Cortical stimulation identified

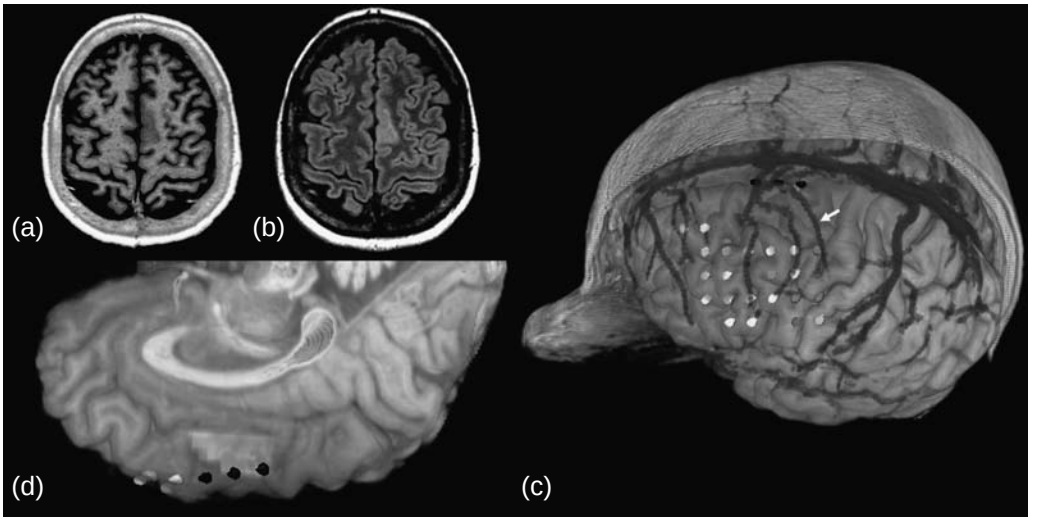

Figure 86b.3 Patient 3. Repeat MRI identified a focal cortical dysplasia in T1 (a) and FLAIR (b) images. Surgical access to the lesion (orange) was complicated by an intricate formation of cortical veins (blue), one of them also draining parts of the primary motor cortex (arrow). Preservation of this vein was crucial in order to avoid venous infarction. (See Color plates.)

motor (red), sensory (green) and speech (yellow) relevant eloquent areas.

A critical aspect of the venous anatomy is the drainage of the central region. A prominent vein (white arrow in Figure 86b.3c), draining the central region, which includes the right hand primary motor area was draining anteriorly and passing through the caput- medusa- like configuration of veins over the FCD. This vein had to be preserved, to avoid venous infarction of the central region. Part of the implanted grid electrode had already been cut off to avoid compression of this fragile venous configuration. The resection was a tricky surgical procedure, since it had to remove the complete FCD, reaching down to the cingulate gyrus, without sacrificing the adjacent lateral eloquent cortex, and without damaging the critical vein draining a part of the central region. This case shows how the reconstruction of superficial cortical veins helped in planning the implantation of invasive electrodes, as well as the resection itself. Also, the risk of a planned resection and the chances for complete removal of the target can be estimated more reliably. This combination of lesion localization and venous reconstruction allowed the veins to serve as robust anatomic landmarks, guiding the surgeon to the target region on the medial surface.

Summary

Defining the epileptogenic zone and defining the borders of a neocortical resection are the key challenges in epilepsy surgery. A wide range of different imaging modalities is included in the pre-surgical evaluation of epilepsy patients. It is beneficial to use all the available information from MRI, PET, SPECT, and CT scans. However, 2D images are usually not sufficient to precisely evaluate the topographic relationship between different imaging modalities. Multimodal image processing, including 3D reconstructions of the patients, individual cortical anatomy, allows a true anatomical correlation of all integrated relevant imaging findings. This approach is helpful for the interpretation of single imaging findings and in the individual planning of cortical resections.

The visualization of the superficial cortical veins can serve as brainshift-resistant anatomic landmark and therefore allows the transfer of diagnostic information into the operating theatre. Furthermore, the information about the venous anatomy can help to avoid complications such as venous infarction and improves the estimation of the individual risk benefit ratio of epilepsy surgery.

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SECTION 9

The functional deficit zone

87 The functional deficit zone: general principles

C Baumgartner and E Lehner-Baumgartner

Definition

The functional deficit zone is defined as the brain area that shows abnormal functioning in the interictal period. This abnormal functioning can be due to the effects of a structural lesion and/or due to the functional consequences of the persisting epileptic condition. The location and extent of the functional deficit zone can be assessed directly with the neurological examination and neuropsychological assessment (including the Wada test) and indirectly using surrogate markers of abnormal functioning including electroencephalography (EEG), magnetoencephalography (MEG) as well as functional neuroimaging tools like single-photon-emission-tomography (SPECT), positron-emission-tomography (PET), magnetic resonance spectroscopy (MRS) and functional magnetic resonance imaging (fMRI).

Neurological examination and neuropsychological assessment

In the early days of epilepsy surgery careful neurological examination was the only way to localize the epileptogenic lesion and the epileptogenic zone. However, even in the age of modern neurophysiology and neuroimaging, the clinical examination should precede the use of these techniques in order to exploit their full diagnostic potential. Careful neurological examination can reveal abnormal function, be it behavioral, motor, or sensory. Characteristics of the dysfunction often pave the way for a topographical diagnosis.[1] Nevertheless, neurological deficits are only present in a minority of surgical candidates because many cortical regions may be dysfunctional without causing abnormalities in the neurological examination, i.e. clinically silent.[2]

Several different causes can be responsible for neuropsychological dysfunctions in patients with focal epilepsy:

- A circumscribed structural lesion responsible for the patient's epilepsy, i.e., the epileptogenic lesion. Here, location and type of the lesion are decisive for the profile of neuropsychological impairment.
- Structural lesions remote from the seizure-onset zone, for instance in a patient with multiple lesions due to cerebral trauma. Approximately 10% of patients who survive severe traumatic brain injury will develop epilepsy. While memory and attention/information processing speed and efficiency are typically the cognitive domains most severely affected by head injury, intellectual, language, and perceptual skills tend to be relatively preserved.[3]
- Diffuse brain damage causing both the patient's epilepsy and neuropsychological impairment.
- Neuropsychological deficits can also occur in patients suffering from focal epilepsy with normal MRI scans. This patient-group constitutes about 20–30% of surgical candidates.
- Functional disturbances can arise remote from the epileptogenic lesion, i.e., lateral temporal or extratemporal dysfunctions in patients with mesial temporal lobe epilepsy.
- Functional disturbances can be caused by interictal epileptiform discharges, also referred to as 'transient cognitive impairments (TCI) caused by interictal epileptiform EEG discharges'.[4] While interictal epileptiform EEG discharges may cause additional and independent transient cognitive impairments, their incidence is as low as 2.2%[5] and their effect is usually small to moderate and limited to transient mechanistic cognitive processes (alterness and mental speed).[4]
- Functional disturbances can be the consequences of seizures, i.e., circumscribed postictal neuropsychological deficits.[6,7]
- Antiepileptic drugs can cause generalized, but also specific neuropsychological dysfunctions. Thus, topiramate can cause verbal dysfunctions which can be difficult to distinguish from dysfunctions as a consequence of the functional deficit zone in patients with seizures arsing adjacent to speech cortex.[8]

The concept of the functional deficit zone should be restricted to neuropsychological impairments caused either directly or indirectly by the epileptogenic zone. However, the segregation of the various causes of neuropsychological deficits can be difficult and requires an astute and experienced neuropsychologist.

Depending on the location of the epileptogenic zone several distinct neuropsychological profiles can be distinguished.[9–11] In patients with temporal lobe epilepsy, the most important neuropsychological symptoms consist of material-specific or even non-specific deficits in episodic memory due to hippocampal dysfunction.[9] While impairment of episodic verbal memory can be consistently found in left temporal lobe epilepsy, the relationship between figural or visuospatial memory deficits and right temporal lobe epilepsy is far less consistent. This could be explained by confounding of figural memory with

verbalization, sex differences, as well as by atypical language representation and suppression of right hemispheric functions due to crowding phenomena.[10] Within the temporal lobe a differentiation between mesial and lateral temporal lobe dysfunction is frequently possible by the assessment of verbal learning versus verbal memory. While lateral temporal dysfunction affects primarily verbal learning, mesial temporal structures are critical for verbal memory.[12] In addition, naming difficulties can be frequently found in patients with temporal lobe epilepsy. While deficits in visual confrontation naming indicate inferotemporal dysfunction, auditory confrontation naming requires inferotemporal and lateral temporal structures.[13] Finally, patients with temporal lobe epilepsy and more specifically patients with mesial temporal lobe epilepsy frequently suffer from considerable generalized cognitive impairments (intelligence, academic achievement, language, and visuospatial functions) indicating an extension of the functional deficit zone beyond the temporal lobes to frontal lobe structures.[14] Thus, frontotemporal dysfunctions frequently can be found in patients with temporal lobe epilepsy.[12] While prefrontal lobe functions such as attention and executive functions are frequently spared in patients with temporal lobe epilepsy, the occurrence of frequent secondarily generalized tonic-clonic seizures poses the patients at risk for global intellectual as well as specific impairment of prefrontal lobe functions. These neuropsychological deficits were associated with a prefrontal hypometabolism on [^{18}F]FDG-PET which therefore can be considered as a surrogate marker of the functional deficit zone.[15] Seizure-freedom after successful epilepsy surgery may lead to a normalization of this prefrontal hypometabolism and the corresponding neuropsychological impairments indicating the dynamic nature of the functional deficit zone.[16]

The complexity and diversity of frontal lobe functions and the intense connections between the frontal and the temporal lobes explain the variability of neuropsychological dysfunctions in patients with frontal lobe epilepsy. While frontal lobe epilepsy patients show little if any impairments of general intelligence and memory, some but not all patients show deficits in executive functions, psychomotor speed and attention.[17–19]

The neuropsychological characteristics of parietal and occipital lobe epilepsies have not been well characterized in larger groups of patients. Lesions of the parietal lobe may cause visual associative agnosia, hemineglect, visuospatial and constructive disorders, apraxia as well as linguistic deficits.[9] However, these symptoms are rarely found in patients with chronic epilepsies most probably due to compensatory mechanisms especially in patients with seizure-onsets early in life. More often impairments are diffuse and often mimic frontal or temporal dysfunction.[20] The neuropsychological profile of patients with idiopathic occipital lobe epilepsies does not systematically differ from that of normal controls.[21]

The intra-carotid-amobarbital procedure or Wada test

The goals of the intracarotid-amobarbital procedure or Wada test include language and memory lateralization.[22] In epilepsy patients, atypical language lateralization, i.e., right hemispheric or bilateral representation, is more likely than in normal controls.[23,24] The determinants for atypical language dominance include early injuries, lesions adjacent to speech cortex and finally the epileptic process *per se*. Thus, early left hemispheric injuries occurring before the age of 5 years result in an interhemispheric reconstitution of language functions to the right hemisphere,[25] while later injuries – when language becomes gradually lateralized – cause contralateral language reorganization more seldom.[24] In mesial temporal lobe epilepsy, left-sided speech occurred in 76% of left-sided and in 100% of right-sided patients. Atypical language representation was also associated with a higher spiking frequency and sensory auras representing an ictal involvement of lateral temporal structures indicating the influence of interictal and ictal epileptic activity on language lateralization.[26]

The rationale of the Wada memory test consists of anesthetizing mesial temporal structures which should simulate the potential mnestic effects of the proposed surgery in a crude way.[22] Injection of the hemisphere contralateral to the epileptogenic zone usually results in impaired memory performance due to the functional deficit of the affected temporal lobe. The functional status of the diseased temporal is also referred to as 'functional adequacy' and can be considered as a marker of the functional deficit zone of the ipsilateral temporal lobe. If the temporal lobe, which is planned to be resected, supports significant memory function (i.e., high functional adequacy), a greater memory decline should be anticipated because functionally intact tissue is removed. Anesthetization of the hemisphere ipsilateral to the epileptogenic zone, on the contrary, tests the functional integrity of the contralateral 'healthy' temporal lobe also referred to as 'functional memory reserve'. A poor performance after ipsilateral injection thus would indicate an extension of the functional deficit zone to the contralateral temporal lobe and also would suggest poor memory performance after surgery. Both functional adequacy and functional reserve are therefore important predictors for post-operative memory performance.[27] Patients with a strong asymmetry of memory performance, i.e., impaired memory ipsilateral to the epileptogenic focus and intact memory contralaterally, are those at the lowest risk for post-operative memory decline. In the case of symmetric Wada scores, functional adequacy will determine memory decline in patients with bilaterally good performance, whereas functional reserve will be decisive in patients with bilaterally poor performance. Especially in left temporal lobe epilepsy, high functional adequacy poses a major risk on post-operative memory decline. The highest risk for post-operative memory decrease is present in patients with unexpected asymmetry in Wada test performance, i.e., better performance after contralateral injection.[27] Some patients may fail the Wada memory component without developing a significant memory decline after surgery,[28] whereas others pass the Wada test and still experience a significant post-operative memory loss.[29,30] Nevetheless, failures of the Wada memory component can be considered as a risk factor for post-operative memory decline and always have to be viewed in the context of the results of other investigations.[27]

The Wada test was found to be a clearly superior predictor of seizure laterality in comparison to neuropsychological

testing.[31] Functional asymmetries as assessed by Wada memory scores were significantly correlated with structural asymmetries as measured by hippocampal volumetry on MRI.[32-34] Wada memory scores showed a significant negative correlation with the degree of hippocampal cell loss indicating that a severely damaged hippocampus could not support memory after contralateral amobarbital injection.[35–37] Furthermore, the Wada test has been used to predict post-operative seizure control.

Interictal EEG and MEG

Slow wave activity can be classified according to its distribution as focal or generalized, according to its persistence as intermittent or continuous and according to its morphology as rhythmic or polymorphic.[38] While continuous slowing (CS) on interictal EEG is usually caused by a structural lesion, intermittent rhythmic slowing (IRS) can be considered as the EEG/MEG marker of the functional deficit zone and often can be seen in the absence of structural lesions.

Temporal interictal rhythmic delta activity (TIRDA) – characterized by trains of 50–100 μV sinusoidal or saw-toothed 1–4 Hz activity localized predominantly over anterior temporal regions – was found in 45 of 127 recordings of patients with epilepsy with complex partial seizures. Because TIRDA often occurred in association with anterior temporal spikes or sharp waves particularly during sleep, TIRDA was considered as an accurate interictal indicator of epilepsy with complex partial seizures.[39] In a study reviewing 12 198 EEG recordings, TIRDA was present in 33 records of 27 patients and was associated with sharp waves either in the same record (23 patients) or on previous occasions (3 patients). All patients suffered from seizures and 23 patients from well-documented epilepsy with complex partial seizures.[40] Concerning its localizing significance, TIRDA was strongly associated with temporal lobe epilepsy, although it was infrequently seen also in extratemporal epilepsy. Temporal intermittent polymorphic delta activity (TIPDA), on the contrary, occurred at an equal rate in both temporal lobe and extratemporal epilepsy.[41] In a series on patients with medically refractory focal epilepsy undergoing prolonged video-EEG monitoring, TIRDA was present in 52 out of 129 patients (40.3%) and showed a significant correlation with mesial and mesio-lateral TLE, mesial temporal sclerosis, interictal epileptiform discharges localized over the anterior temporal regions and 5–9 Hz temporal ictal discharges. Therefore it was concluded that TIRDA can be considered as an EEG marker of an epileptogenic zone involving mesial temporal structures.[42]

The lateralizing significance of slow wave activity in temporal lobe epilepsy was investigated in several studies. In patients with unilateral seizure-onsets, exclusively or predominately unilateral delta waves occurred ipsilateral to the seizure-onset zone in 46 out of 56 patients (82%) and never were seen contralaterally.[43] Conversely, in patients with lateralized arrhythmic delta waves the concurrence with the side of seizure onset was 90% with delta waves in one EEG and 100% with delta waves in ≥ 4 EEGs.[43] In mesial temporal epilepsy, the lateralizing accuracy of delta waves was studied in relation to spikes and hippocampal atrophy as assessed by volumetric measurements in 56 patients – 35 patients had unilateral (group I) and 21 had bilateral hippocampal atrophy with lateralized predominance (group II). Unitemporal trains of delta waves lateralized the side of hippocampal atrophy with equal accuracy as interictal spikes (delta: 29 of 32 patients (92%) in group I and 12 of 19 of patients (63%) in group II; spikes: 85% or 28 of 33 patients (85%) in group I and 13 of 20 patients (65%) in group II). Delta waves and spikes occurred together in >85% of cases. Delta activity almost always occurred ipsilateral with unilateral spiking (19 of 21 of patients (90%) in group I and seven of eight of patients (88%) in group II) and bilaterally independently with bilateral spiking (six of nine of patients (67%) in group I and ten of ten patients (100%) in group II). Furthermore, spiking and delta activity were never in disagreement with respect to lateralization. It was concluded that intermittent delta waves are a reliable indicator of the epileptogenic focus and presumably reflect the epileptogenic process rather than the underlying structural pathology.[44]

The correlation of intermittent slow wave activity with other markers of the functional deficit zone, namely with hypometabolism on interictal [^{18}F]FDG-PET and functionality on fMRI was investigated in several studies. In the first study, 16 of 28 patients (57%) had lateralised IRS with a maximum over the temporal regions which was always ipsilateral to the resection and significantly correlated with hypometabolism in the lateral temporal neocortex on [^{18}F]FDG-PET, but not to mesial temporal sclerosis or any other pathology.[45] The authors suggested that IRS should be conceptualised as a distinct electrographic phenomenon directly related to the epileptogenic abnormality and that the lateral temporal hypometabolism may delineate a field of reduced neuronal inhibition which can receive interictal and ictal propagation.[45] In the second study on 40 patients with intractable temporal lobe epilepsy, the severity of temporal lobe hypometabolism on [^{18}F]FDG-PET was significantly correlated with the amount of delta activity in the interictal EEG, independently of MRI findings.[46] Therefore, common pathophysiologic mechanisms for metabolic and electrical dysfunction in temporal lobe epilepsy were suggested.[46] Finally, activation of malformations of cortical development (MCDs) by simple (sensomotor, visual) or complex (language, memory) functional magnetic resonance imaging (fMRI) paradigms was assessed in 28 patients with focal epilepsy and MCDs. Besides an influence of the type of MCD, both focal neurological signs and focal EEG slowing independently were correlated with MCD inactivity.[47]

Magnetoencephalography (MEG) which measures the weak magnetic field induced by neuronal currents has the advantage of a better spatial resolution as compared with scalp-EEG.[48] In one study, one or more sites of focal low-frequency magnetic activity (LFMA) were detected in 29 of 33 patients and showed a 48.5% specificity with respect to the presumed epileptogenic region. LFMA was in agreement with the final consensus as often as was ictal scalp-EEG, and was exceeded in specificity overall only by invasive ictal EEG.[49] In 29 patients with mesial temporal lobe epilepsy, LFMA with maximum amplitude over the temporal area was found in 17 patients (58.6%); it always occurred ipsilateral to the side of resection and the side of MEG interictal spike sources. Dipolar sources of LFMA were found in the posterior superior temporal region in the majority of cases and, occasionally, in mesial temporal structures.[50]

Functional neuroimaging with SPECT and PET

Functional neuroimaging techniques like SPECT and PET provide additional and independent information to structural neuroimaging during persurgical evaluation. While the recent developments of PET tracers aim to measure abnormalities of neurotransmission underlying neuronal hyperexcitability and thus could possible directly visualize the epileptogenic zone,[51] the classical SPECT and PET tracers measure regional cerebral blood flow, oxygen consumption and glucose metabolism associated with epileptic dysfunction and therefore can be considered as surrogate markers of the functional deficit zone.

SPECT ligands most commonly used in epilepsy, i.e., ^{99m}Tc-Hexamethyl-propyleneamine (^{99m}Tc-HMPAO) and ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD), are markers of regional blood flow. Both tracers are lipophilic, generally pass the blood–brain barrier on their first pass through brain tissue, become trapped and exhibit little subsequent redistribution. In temporal lobe epilepsy, interictal SPECT shows a regional temporal hypoperfusion ipsilateral to the epileptogenic zone in 40–50%, while 5–10% of studies are falsely lateralizing.[52] These results concur with PET studies demonstrating an uncoupling of glucose metabolism and blood flow resulting in significantly higher sensitivity and specificity of glucose metabolism for the lateralization of the epileptogenic zone in temporal lobe epilepsy.[53] Thus, interictal SPECT is of limited value and inferior to interictal [^{18}F]FDG-PET for the localization of the functional deficit zone.

[^{18}F]FDG has been the most widely used PET tracer used during pre-surgical evaluation. While [^{18}F]FDG crosses the blood brain barrier before phosphorylation in the cell compartment, unlike glucose-6-phosphate it does not enter into further steps of the Krebs glycolysis cycle, but accumulates in the intracellular compartment and thus directly reflects the energy demand of the brain cells.[51] The mechanisms underlying interictal glucose hypometabolism are not fully understood. While glucose consumption occurs primarily at the synapse, reduced regional metabolism appears to reflect a decrease in glucose influx from reduced glucose transport across the blood brain barrier which correlates with subsequent reduced phosporlyation.[54] Possible mechanisms of reduced interictal glucose metabolism include (1) atrophy and partial volume effects; (2) neuronal loss; (3) hypometabolic macro- or microscopic lesions; (4) decreased synaptic activity (diaschisis), (5) deafferentation due to reduced numbers of synapses, (6) postictal metabolic depression, (7) inhibitory mechanisms of seizures.[51]

Converging evidence has been accumulated that interictal hypometabolism represents a reversible functional state for several reasons. First, an increase of glucose metabolism can be observed during ictal PET scans in the interictal hypometabolic zone. Second, interictal hypermetabolism can be reverted by the application of a specific $GABA_A$ receptor agonist (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol), THIP. After THIP injection, the increase of glucose metabolism in the hypometabolic focus was larger than the mean increase in the whole brain. Within the hypometabolic focus, this increase was significantly higher in regions with the lowest basal metabolic levels. This metabolic response in the hypometabolic focus suggests that $GABA_A$ receptors are up-regulated or at least preserved in temporal lobe epilepsy. Furthermore, $GABA_A$ receptor mediated inhibition apparently increases the metabolic demand and therefore the hypothesis that hypometabolism is caused by increased inhibition becomes questionable.[55,56] Third, hypometabolic zones surrounding the epileptogenic zone pre-operatively showed a normalization of glucose metabolism after successful surgery.[16, 57, 58] This normalization of glucose metabolism was paralleled by an improvement in neuropsychological functioning.[16]

The sensitivity of [^{18}F]FDG-PET varies according to etiology and location of the epileptogenic zone.[51] In temporal lobe epilepsy, the sensitivity ranged between 65–90% in early studies encompassing patients with varying etiologies. This figure is closer to 60% in patients with normal MRI scans and closer to 90% in studies with newer scanners.[52] In a prospective study in patients with hippocampal atrophy on MRI, sensitivity approached 100%.[59] In frontal lobe epilepsy with normal MRI scans, abnormalities on [^{18}F]FDG-PET are found in only 50% of patients.[51]

The differing sensitivities of [^{18}F]FDG-PET according to the location of the seizure onset zone, the finding that hypometabolism on [^{18}F]FDG-PET was not related to the epileptogenicity of cavernous angiomas[60] and the low indicence of hypometabolism in new onset temporal lobe epilepsies,[61,62] indicate that hypometabolism is not directly related to the epileptogenic process itself, but rather may reflect the functional and maybe structural consequences of repeated seizures. This is in line with some studies which found a correlation between hypometabolism and epilepsy duration as well as age at epilepsy onset, although these results could not be replicated by other authors.[51]

Although the lateralizing value of [^{18}F]FDG-PET approaches 100% in temporal lobe epilepsy, bitemporal hypometabolism – which is usually less pronounced on the side contralateral to the epileptogenic zone – can be found in up to 32% of patients with unilateral temporal lobe epilepsy using statistical parameter mapping.[63] Conversely, bitemporal hypometabolism was indicative of bilateral independent seizure onsets in approximately 50% of patients, especially when involving the inferior temporal gyrus. Moreover, bitemporal hypometabolism was associated with a more rapid contralateral seizure spread, a longer disease duration and worse memory performance during the Wada test and therefore could reflect an advanced stage of the disease process, characterized by a breakdown of the inhibitory mechanisms in the contralateral hemisphere.[64]

The localizing significance of PET within the hemisphere or lobe of seizure onset is far less well-defined than its lateralizing value. In temporal lobe epilepsy, this is already intuitively clear from the usually widespread hypometabolism involving – besides the temporal lobe – also the ipsilateral frontal and parietal neocortex, ipsilateral subcortical structures such as the thalamus and the striatum as well as the contralateral cerebellum.[52] Recent studies suggested that lateral temporal hypometabolism is correlated with extrahippocampal structural changes including white matter changes in the anterior temporal lobe,[65] temporal neocortical microscopic cortical dysplasia[66] or temporal polar signal changes on MRI scans.[67] Furthermore, some specific patterns of hypometabolism may help to differentiate mesial from lateral temporal lobe

epilepsy. Whereas hypometabolism is more prominent in lateral than in medial structures both in medial and lateral temporal lobe epilepsy, a hypometabolism in the medial temporal structures is found less frequently in lateral temporal lobe epilepsy than in medial temporal lobe epilepsy. Furthermore, the extent of hypometabolism is significantly larger in medial temporal lobe epilepsy.[63]

Several studies correlated the functional deficit zone defined by interictal [^{18}F]FDG-PET with the irritative zone and the seizure-onset zone defined by EEG. A consistent unilateral spike focus concurs with a lateralized hypometabolism on PET in over 90% of the cases. However, bilateral independent spikes can occur in the presence of unilateral hypometabolism.[51] Several studies compared the location and extent of hypometabolism on [^{18}F]FDG-PET with the location of the irritative zone defined by EEG and MEG dipole modeling of interictal spikes.[68–70] While dipole sources usually were contained within the extended hypometabolic zone on [^{18}F]FDG-PET, dipole localizations did not concur with the degree of hypometabolism within this hypometabolic zone.[68,70] This is accordance with a study which found a poor agreement between stereo-EEG localizations of the irritative zone and [^{18}F]FDG-PET quantitative measures of regional metabolism.[71]

In temporal lobe epilepsy and lesional epilepsy, the seizure-onset zone defined by intracranial EEG usually is contained within the functional deficit or hypometabolic zone on [^{18}F]FDG-PET. On the contrary, in nonlesional neocortical and especially in nonlesional extratemporal epilepsy, the localizing value of [^{18}F]FDG-PET in comparison to intracranial EEG seems to be limited. In a series of 41 patients with nonlesional temporal epilepsy including 16 with frontal lobe epilepsy, 11 with neocortical temporal lobe epilepsy, seven with occipital lobe epilepsy, four with parietal lobe epilepsy, and three with multifocal onsets, [^{18}F]FDG-PET correctly predicted the lobe of seizure-onset zone on intracranial EEG in only 42.9% of the cases.[72] [^{18}F]FDG-PET analyzed by statistical parametric mapping correctly localized the epileptogenic lobe in 15 of 22 patients (68.2%) with nonlesional neocortical temporal lobe epilepsy, but only in three of 11 patients (27.3%) with nonlesional extratemporal epilepsy.[73] Furthermore the degree of hypometabolism does not correlate with the location of seizure-onset on stereo-EEG.[71]

The question whether the presence of hypometabolism on [^{18}F]FDG-PET and its restriction to the epileptic temporal lobe are necessary and sufficient prerequisites for a good surgical outcome after temporal lobectomy remains controversial. Whereas several studies identified a temporal hypometabolism as good prognostic sign independently of hippocampal atrophy on MRI,[74] other studies failed to verify such an association.[75]

Hypometabolism on [^{18}F]FDG-PET also has been correlated with other measures of the functional deficit zone, namely EEG and neuropsychological parameters. The correlation between slowing or background depression on stereo-EEG and quantitative measures of regional metabolism on [^{18}F]FDG-PET was poor.[71] Regional hypometabolism on [^{18}F]FDG-PET was associated with corresponding circumscribed neuropsychological deficits. Relative reductions in glucose metabolism of the left lateral temporal lobe and the left thalamus independently predicted verbal memory impairments in temporal lobe epilepsy patients.[76] Prefrontal hypometabolism which was more frequent in patients with left temporal lobe epilepsy and a history of secondarily generalized seizures correlated with impairments of neuropsychological 'frontal lobe measures', including verbal and performance intelligence measures.[15] The results of [^{18}F]FDG-PET – especially medial temporal metabolism – significantly correlated with Wada memory scores.[77,78] Finally, pre-operative [^{18}F]FDG-PET was predictive for post-operative memory performance in patients with left-sided temporal lobe epilepsy. Patients with no/mild asymmetry in temporal lobe metabolism exhibited significantly greater verbal memory decline compared with patients with moderate/severe hypometabolism.[79]

Proton magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) allows noninvasive in vivo detection and quantification of various brain metabolites.[80,81] ^{1}H or proton spectroscopy which measures N-acetyl aspartate (NAA), choline (Cho) and creatine (Cr) can be regarded as a surrogate marker of the functional deficit zone. NAA – a mitochondrial neuronal compound – is generally considered as a marker of neuronal density and viability. Cho which is bound to cell membranes, myelin and complex brain lipids indicates membrane damage and gliosis. Cr, finally, is used as an internal reference for other metabolites, because it is a relative stable compound and a marker for cell density of glial and neuronal cells.[82] In epilepsy, abnormalities of proton spectroscopy typically consist of (1) a reduced NAA/Cr or NAA/(Cho+Cr) ratio or (2) a reduced NAA signal without significant changes in Cho and Cr signals.[82,83] These MRS abnormalities reflect neuronal and glial dysfunction rather than neuronal cell loss as has been shown in a study comparing metabolic dysfunction measured by MRS and hippocampal volume loss detected by MR volumetry.[84] This concept is further supported by a recovery of the NAA signal remote from the epileptogenic zone after successful epilepsy surgery.[85–88]

Proton spectroscopy correctly lateralized the epileptogenic zone in 86% of patients with various forms of temporal lobe epilepsy[89], in 61% of patients with nonlesional temporal lobe epilepsy[90] and in 97% of patients with mesial temporal lobe epilepsy.[91] Proton spectroscopy can be used to differentiate patients with temporal and extratemporal epilepsies[92] as well as patients with mesial and neocortical temporal lobe epilepsy[93] although these discriminations were less accurate than lateralization. In neocortical epilepsy, multislice MRS imaging in combination with tissue segmentation correctly localized the epileptogenic zone in 70% of patients with an MRI-visible malformation and in 60% of patients with normal MRI.[94]

Proton spectroscopy is extremely sensitive for the detection of metabolic dysfunction. In one study on 100 patients with temporal lobe epilepsy, MRS was abnormal in 99 of 100 patients, while volumetric amygdala-hippocampal measurements were abnormal in only 86 of 98 patients.[89] These results were essentially confirmed in a subsequent study were no correlation was found between the degree of hippocampal volume loss and the NAA/Cr ratio indicating that the two techniques examine distinct pathophysiologic processes.[91]

Moreover, metabolic dysfunctions are usually found in widespread regions extending beyond the epileptogenic zone. In one study, 38% of patients with temporal lobe epilepsy and 50% of patients with extratemporal lobe epilepsy had NAA/Cr reductions outside the clinical and EEG-defined epileptogenic area.[95] In mesial temporal lobe epilepsy, comparisons between individual brain regions revealed trends toward lower NAA/(Cr + Cho) ratios in many areas of the ipsilateral and, to a lesser extent, the contralateral hemisphere outside the hippocampus and the temporal lobe, suggesting a diffuse impairment.[96] In patients with mesial and nonlesional temporal lobe epilepsy, reduced NAA/(Cr + Cho) ratios were found in the ipsilateral temporal and parietal lobes and bilaterally in the insula and the frontal lobes consistent with those brain areas involved in seizure spread.[97,98] Metabolic abnormalities of the contralateral temporal lobe were observed in 33% of patients with nonlesional temporal lobe epilepsy[90] and in 54% of patients with various forms of temporal lobe epilepsy.[89] MRS was more sensitive for the detection of bilateral involvement than MR volumetry in both studies.[89,90] Nevertheless, the reduction of the NAA ratios seems to be greater in the epileptogenic region as compared with nonepileptogenic regions.[99]

The MRS defined functional deficit zone was correlated with the irritative and the seizure-onset zone in several studies. One study found a moderate level of concordance between the distribution of proton spectroscopy and interictal EEG abnormalities, while proton spectroscopy identified abnormalities contralateral to the predominant seizure focus more often than EEG.[100] In nonlesional temporal lobe epilepsy, NAA/Cho was significantly decreased in the MEG spike zone indicating that functional abnormalities can be detected in vivo in radiographically normal-appearing cortex exhibiting abnormal excitability.[101] In patients with mesial temporal lobe epilepsy, there was a significant correlation between the asymmetry indexes of interictal epileptiform discharges recorded on foramen ovale electrodes with the asymmetry index of NAA/Cr ratios within medial temporal structures.[102] Finally, regional metabolic alterations on proton spectroscopy were correlated with electrophysiological abnormalities recorded by depth electrodes and with structural lesions in patients with temporal lobe epilepsy[103] and frontal lobe epilepsy.[104] NAA/(cho+cr) ratios were significantly lower in regions involved in SEEG electrophysiological epileptic abnormalities, while regions without electrophysiological abnormalities showed normal ratios. No differences between the metabolic profiles of the irritative and the seizure-onset zone were found. The metabolic alterations included, but also extended beyond, the structural lesions indicating that metabolic abnormalities are linked to interictal and ictal epileptiform activities rather than to structural alterations.[103,104] Proton spectroscopy was useful to predict seizure control after epilepsy surgery in temporal lobe epilepsy,[105] mesial temporal lobe epilepsy[106–108] and MRI-negative temporal lobe epilepsy.[109] Furthermore, proton spectroscopy may provide information on the individual best type of surgery.[108]

The relationship between metabolic dysfunction on proton spectroscopy and other methods assessing the functional deficit zone was addressed in several studies. There was no correlation between interictal background delta activity as assessed by quantitative EEG and abnormalities seen on proton spectroscopy.[110] Controversial results were found for the comparison of proton spectroscopy with [^{18}F]FDG-PET. While in one study [^{18}F]FDG-PET was more sensitive than proton spectroscopy for the lateralization of the seizure-onset zone in temporal lobe epilepsy ([^{18}F]FDG-PET: 87% vs. proton spectroscopy: 61%),[90] in two other studies [^{18}F]FDG-PET and proton spectroscopy showed an identical lateralization accuracy of 76%[111] resp. 85%,[112] although in general proton spectroscopy was more sensitive than [^{18}F]FDG-PET in depicting metabolic abnormalities.[111] In a recent study on patients with mesial temporal lobe epilepsy, hippocampal metabolic disturbances as measured by [^{18}F]FDG-PET and by proton spectroscopy did not correlate which was explained by differential effects of disturbed cellular energy metabolism on mechanisms of glucose use and biosynthesis of NAA.[113]

Several studies related proton spectroscopy to neuropsychological testing. In mesial temporal lobe epilepsy, material-specific memory deficits and memory performance during the WADA test were correlated significantly with hippocampal metabolic dysfunction, visual confrontation naming was selectively associated with left hippocampal metabolic function, whereas performance on a facial recognition task was correlated with right hippocampal metabolic function.[114–117] In patients with unilateral mesial temporal lobe epilepsy, reduced left hippocampal NAA/Cr ratios were more sensitive to predict verbal memory impairments than hippocampal volumetric measurements.[118] Furthermore, some studies indicate that pre-operative MRS findings may be useful to predict memory decline after epilepsy surgery.[115, 117, 119]

Functional magnetic resonance imaging (fMRI)

fMRI offers a unique technique for the assessment of the functional deficit zone because it not only allows to visualize areas of functional deficits, but also provides information where in the brain the remaining functions are actually represented. Thus, fMRI gives insights in mechanisms of compensation, shift and plasticity.

The primary contrast mechanisms used for fMRI are blood oxygenation level-dependent (BOLD) contrast and perfusion contrast obtained by using aterial spin labeling (ASL) which uses magnetically labelled arterial blood flow water as a flow tracer. Because BOLD contrast is easier to obtain and generally provides a higher signal-to-noise ratio for task-specific activation, it has been widely adopted as the method of choice for imaging regional brain activation.[120] BOLD contrast is based on the fact that brain areas actively engaged during functional activation experience a local increase in cerebral blood flow. The amount of blood flow increase exceeds the associated increase in local cerebral oxygen consumption resulting in a localized increase in the ratio of oxyhemoglobin (which is diamagnetic, i.e. its effect on T_2-relaxation is negligible) to deoxyhemogelobin (which is paramagnetic, i.e., it accelerates the rate of T_2-relaxation) which can be visualized using a variety of pulse sequences, including routine gradient-echo sequences and gradient-echo echoplanar sequences, which particularly emphasize T_2*-effects.[120, 121] For the assessment of

the functional deficit zone, fMRI language and memory lateralization and localization can be used.

Focal epilepsy can be associated with a disruption in normal language organization resulting in a high incidence of atypical language dominance (bilateral or right hemisphere) in epilepsy patients as compared to normal controls (epilepsy group: 78% left hemisphere dominance, 16% bilateral symmetric language representation, 6% right hemisphere dominance; normal subjects: 94% left hemisphere dominance, 6% bilateral symmetric language representation, none right hemisphere dominance) which was especially evident with early brain insults and weak right hand dominance.[24] In another study, 33% of patients with left-sided temporal lobe epilepsy showed bilateral or right hemispheric language lateralization which was significantly higher as compared to patients with right-sided temporal lobe epilepsy suggesting considerable plasticity of language representation in the brains of patients with intractable epilepsy.[122] However, it is difficult to infer intra- versus inter-hemispheric language reorganization on the basis of the vicinity of early pathology to classical language areas, because in a recent study lesions in or near Broca's area were not associated with inter-hemispheric language reorganization in four out of five cases, but with perilesional activation within the damaged left hemisphere. Paradoxically, lesions remote from the classical language areas were associated with nonleft language lateralization in four out of five cases.[123]

fMRI showed excellent agreement with the Wada test for language lateralization in several studies.[122,124–128] Concordance was usually best in left hemisphere dominant patients ranging from 91 to 100%, lower in patients with right hemisphere dominance (range: 67–100%) and worst in patients with bilateral hemisphere dominance ranging from 50 to 75% although the numbers in these latter groups were small.[122,125,126] Furthermore, agreement was better in left-sided temporal with 97% than in left-sided extratemporal epilepsy with only 75%.[127] fMRI was predictive for post-operative confrontation naming deficits after left anterior lobectomy showing 100% sensitivity and 73% specificity.[129]

fMRI also has been evaluated as an alternative to intraoperative cortical stimulation mapping for the localization of critical language areas in the temporoparietal region.[130] Correspondence between functional magnetic resonance imaging and intraoperative cortical stimulation mapping depended heavily on statistical threshold and varied between patients and tasks (i.e., verb generation, picture naming, verbal fluency, and sentence comprehension). Whereas fMRI correctly detected all critical language areas with high spatial accuracy (sensitivity of 100%), fMRI activity was found also at noncritical language sites with an overall specificity was 61%. Although fMRI cannot replace intraoperative cortical stimulation mapping at the present time, it can be used to optimally plan this procedure and increase its safety.

fMRI can be used to visualize asymmetries in the lateralization of memory activation in patients with temporal lobe epilepsy and therefore can serve as a marker of the functional deficit zone. While mesial temporal lobe structures are activated symmetrically in normal controls during various memory encoding tasks, a decreased activation was seen ipsilateral to the seizure focus in patients with unilateral temporal lobe epilepsy.[131–134] Verbal encoding engaged the right mesial temporal lobe in left mesial temporal lobe epilepsy, whereas nonverbal encoding engaged the left mesial temporal lobe in right mesial temporal lobe epilepsy.[134] In patients with left mesial temporal lobe epilepsy, an extensive left prefrontal activation was seen during memory encoding and retrieval which was not evident in normal controls.[135] In nonamnesic patients with left hippocampal sclerosis, verbal memory encoding was associated with reorganisation to the right hippocampus and parahippocampal gyrus, while it involved activation of the left hippocampus in normals. The additional presence of left amygdala sclerosis resulted in reorganisation for encoding of emotional verbal material to the right amygdala.[136] These findings indicate both a functional deficit of the diseased temporal lobe and a functional shift to the nonaffected temporal lobe or to extratemporal structures indicating a high degree of plasticity of medial temporal lobe functions.

fMRI memory lateralization concurred with the results of neuropsychological testing[133] and of intracarotid amobarbital testing.[132,134,137] The degree of verbal memory encoding activity in the left mesial temporal lobe was inversely related to the extent of verbal memory loss after left anterior temporal lobectomy and provided the strongest independent predictor of memory outcome after surgery in a multiple regression analysis.[138] In right mesial temporal lobe epilepsy, the pre-operative asymmetry index of memory-fMRI, consisting of retrieval from long-term memory induced by self-paced performance of an imaginative walk, significantly correlated with post-operative changes in memory retention: Reduced activation of the mesiotemporal region ipsilateral to the epileptogenic region correlated with a favorable memory outcome after right-sided anterior temporal lobectomy.[139] Finally, in patients with both left and right temporal lobe epilepsy, a greater post-operative memory decline was observed with increased pre-operative activation ipsilateral to the seizure focus using a complex visual scene-encoding task.[137]

MEG language lateralization and localization

MEG language lateralization obtained by various language paradigms including a word recognition task,[140] a silent reading task[141] as well as a verb generation and picture naming task[142] showed a high degree of concordance with the Wada-test ranging between 89 and 95%. MEG may also be used for intrahemispheric language localization where excellent agreement with direct cortical stimulations could be achieved in selected cases.[143,144] Finally, MEG was useful to study inter- and intrahemispheric language reorganization in patients with temporal lobe epilepsy.[145–147]

Conclusions

The functional deficit zone provides information on the functional deficits associated with focal epilepsies. These functional deficits manifest themselves as neurological and neuropsychological abnormalities. Surrogate markers of the functional deficit zone include interictal EEG and MEG as well as functional neuroimaging tools like SPECT, PET, MRS and

fMRI. When assessing the functional deficit zone mechanisms of neuronal compensation, shift and plasticity have to be taken into account, which in turn are influenced by epilepsy variables including age at insult and epilepsy onset, as well as duration, activity and severity of disease. Fixed and reversible functional deficits can be distinguished. The former are caused by structural lesions, most often the epileptogenic lesion; the latter represent consequences of the epileptogenic process per se, vary according to epileptic activity and can be reverted by successful surgical treatment. Thus, the functional deficit zone has to be considered as a dynamic concept. The various surrogate markers of the functional deficit zone measure different parameters of functional deficit and differ concerning their sensitivity. Therefore, the extension of the functional deficit zone varies according to the investigational technique applied. The functional deficit zone usually is spatially more extended than the epileptogenic zone. With the currently available techniques there is only a poor correlation between the local degree of functional abnormality and of epileptogenicity. Therefore, the functional deficit zone can only lateralize and localize the epileptogenic zone on a lobar, but not on a sublobar level. This could be improved by measuring dysfunctions more closely related to epileptogenicity. Nevertheless, the functional deficit zone provides important information during pre-surgical evaluation complementary to the five other zones (irritative zone, seizure-onset zone, ictal symptomatogenic zone, epileptogenic lesion, epileptogenic zone), can be used to derive prognostic information on post-operative seizure control and most importantly is critical to predict the post-operative functional status.

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88 Mesial temporal lobe epilepsy and positron emission tomography

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Introduction

Positron emission

Positron emission tomography (PET) is a molecular imaging technique that uses radiolabeled compounds to image molecular interactions *in vivo*. PET relies on the nature of positron decay. The positron was first conceived by Dirac in the late 1920s and discovered experimentally in 1932. The positron is the antimatter counterpart to the electron and has the same mass as an electron but a positive charge. PET scanners detect photons, which are released when a positron emitting radionuclide, such as fluorine-18, carbon-11, and oxygen-15 emit positrons, which then undergo annihilation after a collision with electrons. The commonly used positron emitting isotopes and their half-lives are shown in Table 88.1.

A key benefit of PET is the ability to quantify molecular events *in vivo*. This depends in part on the ability of PET to measure the tracer concentration in the region of interest, to account for photon attenuation by the body and to apply a mathematical model, which describes the kinetic behavior of the process of interest.

PET instrumentation

Positron annihilation is a unique form of radioactive decay where two photons (gamma rays with an energy of 511 keV) are emitted at 180 degrees to one another. Scintillation crystals (or detectors) detect these gamma rays and they are regarded as true events when they are detected simultaneously or 'coincidentally'. These detectors produce light output, which is detected and magnified by photomultiplier tubes. Logic circuits localize precisely where the annihilation event occurred. High-speed timing circuits provide temporal localization. This time window for coincidence detection is typically 6–12 nsec. Photons outside this time window are considered as single events and discarded by the coincidence circuit. Compared with most radioisotopes used in nuclear medicine, PET ligands emit photons with much higher energies. Hence, PET detectors require greater stopping power. The scintillation crystals may be made of sodium iodide (NaI), bismuth germinate (BGO) and more recently lutetium oxyorthosilicate (LSO) and gadolinium orthosilicate (GSO). The absorption efficiency of BGO is greater than LSO but the latter has five times more light output. Additionally, the decay time for LSO compared with BGO is lower at 40 nsec as opposed to 300 nsec. Consequently, it takes less a shorter period of time to obtain the necessary scintillation events (counts) for image generation with LSO.

The first human PET study was carried out in 1977 using 18-F-fluorodeoxyglucose (FDG) and was 'primitive' by today's standards.[1] These tomographs were generally restricted to large universities and devoted mainly to neuroscience research. They were slow and had poor spatial resolution but nevertheless they were regarded as a great advance because for the first time 'function' rather than just anatomy of the brain could be depicted. Instrumentation advances coupled with faster techniques to acquire data, corrected for attenuation and reconstructed the massive amounts of data that came with the addition of more than one image plane. This allowed the introduction of this technology into clinical practice rather than just basic research. The next major advance and arguably the most important advance in medical imaging over the past decade, was the development of the PET/CT scanner. Townsend[2] developed the combined PET/CT scanner in the late 1990s and the first commercial PET/CT devices were installed in 2001. The PET/CT combines a helical CT, which provides anatomical data and as well allows for correction of varying degrees of photon attenuation by different tissues. The PET device is attached to the 'back end' of the CT scanner. CT and PET studies are carried out sequentially and this allows for good registration between the anatomical (CT) and the functional (PET) data, such that the two images that are produced can be overlain to provide a 'fused' image (Figure 88.1). The introduction of the faster PET detectors (LSO, GSO) into these devices, volume acquisitions (3D) and CT attenuation has resulted in a dramatic shortening of scan time. At our institution prior to PET/CT a brain acquisition using FDG on a PET-only device took approximately 60 mins. The same study with our current PET/CT scanner (LSO Biograph Duo, Siemens, Hoffman Estates, IL, USA) takes only 10 minutes.

FDG

PET ligands are produced when ions are accelerated in a cyclotron to high speeds and directed to bombard a 'target'. The ensuing nuclear reaction in the target produces the positron emitter, which can then incorporated into a specific compound. In the case of FDG, fluorine-18 is incorporated into an analogue of glucose, deoxyglucose that can describe glucose metabolism in the body *in vivo*. FDG is the most commonly used PET isotope in the assessment of refractory epilepsy. In the early years

Table 88.1 Positron emitting isotopes

Radionuclide	Half life
^{11}Carbon	20.3 minutes
^{13}Nitrogen	9.97 minutes
^{15}Oxygen	124 seconds
^{18}Fluorine	110 minutes

of neuroscience research with PET, ^{15}O was also used; this ligand when attached to water (^{15}O-H_2O) labels blood flow but the signal to noise ratio with this ligand is far inferior to FDG and it is not routinely used in PET centers.

Patient preparation for FDG-PET

Patients are asked to fast for approximately 6 hours prior to the scan. They are instructed to avoid caffeine and caloric beverages but may drink water in this period. A clinical history is obtained before the PET procedures commence. It is important to determine the seizure frequency, in particular, the timing and type of the last. This is because seizures can induce postictal glucose hypometabolism, which can persist for many hours after a seizure. This hypometabolism can be focal or generalized and present outside the epileptogenic zone. In addition, it is important to determine the patient's medication history as sedatives, major tranquillisers and steroids can reduce cerebral glucose metabolism. Before injection of FDG, a blood sugar level is measured; a level of less than 150 mg/dL is desirable. An elevated BSL results in a technically poor PET scan because FDG uptake competes with glucose for the surface membrane protein (glucose transporter – [GLUT]), which facilitates glucose and deoxyglucose transport into cells.[3] An intravenous cannula is placed, usually in an arm vein prior to isotope injection. Typically, 10 mCi of FDG is injected intravenously. Patients then rest quietly and remain awake during the 'uptake period' as FDG equilibrates in the brain. This 'uptake period' is typically 45 minutes. Activity and speech are limited during this time to minimize physiologic uptake into 'active' areas of the brain. FDG is safe and there are no known contraindications or side effects. Imaging is initiated approximately 40 minutes following isotope injection. EEG monitoring prior to and after isotope injection is recommended to detect seizures, which at times may confound the interpretation of the scan.

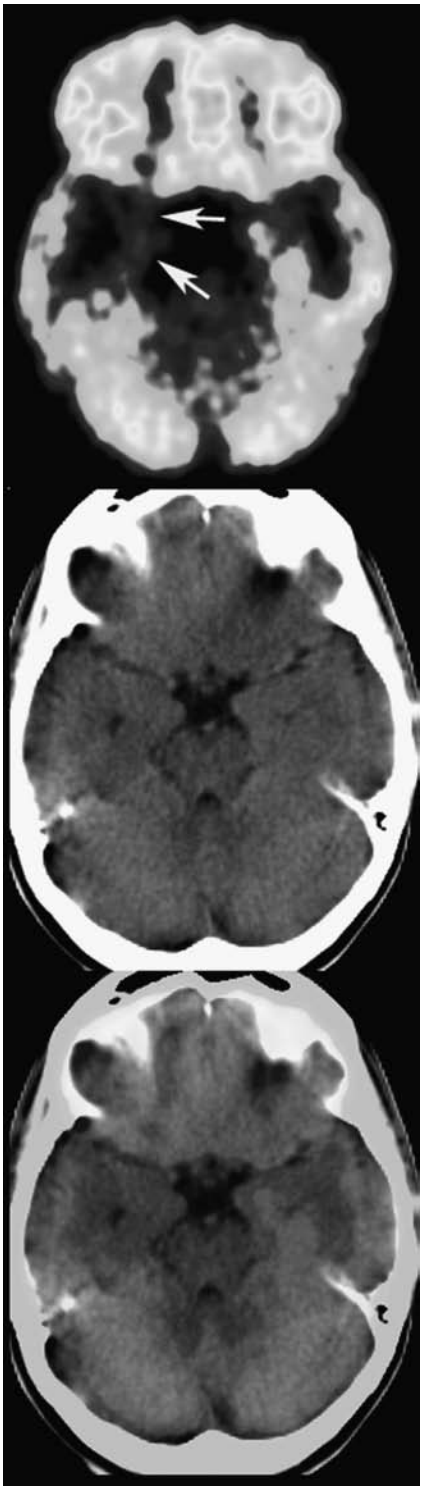

Figure 88.1 FDG-PET/CT of patient LS, a 23-year-old female with MTS. Top image, FDG-PET, middle image, co-registered CT, bottom image, PET/CT-fused images. Images show reduced glucose metabolism in the right anteromesial temporal structures including the amygdala, hippocampus and temporal pole (arrows).

Interpretation of FDG-PET studies

Interictal FDG-PET in mesial temporal sclerosis (mTLE)

The overall aim of functional imaging in mTLE is to map the site of seizure generation – the so-called 'epileptogenic zone'. FDG uptake in the brain represents synaptic activity [4] together with glutamate-mediated uptake of the ligand into astrocytes.[5] The first FDG-PET studies in epilepsy were done in the early 1980s and the typical findings that were reported by the early investigators were extensive and marked glucose hypometabolism of the involved temporal lobe[6–9] where severe mesial temporal sclerosis (MTS) was usually found (Figure 88.2). However, over the past decade the pattern of glucose hypometabolism in MTS appears to have changed.[10] The extensive glucose hypometabolism of the entire temporal lobe is now more commonly replaced by a more restricted region of glocose hypometabolism in to the anteromesial temporal structures, including the hippocampus, amygdala, temporal pole, entorhinal and anterior fusiform cortices (Figure 88.1).

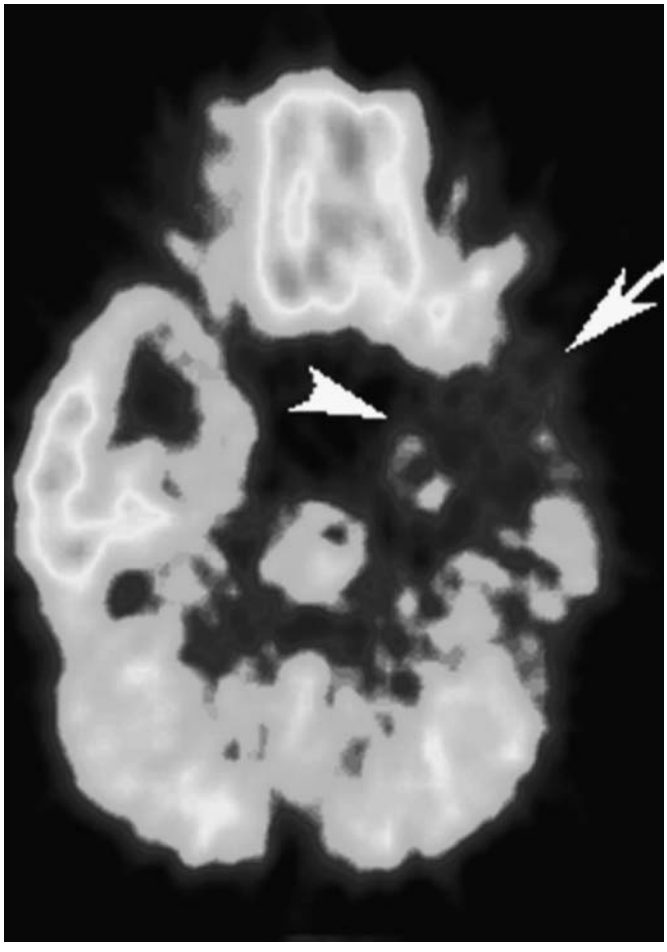

Figure 88.2 FDG-PET in a 35-year-old man with severe hipppocampal atrophy on MR and left temporal lobe seizures showing severe glucose hypometabolism in the entire left temporal lobe.

Subtle or marked glucose hypometabolism can also be seen in ipsilateral extra temporal structures including the thalamus, basal ganglia, frontal, parietal and occipital cortices and sometimes the contralateral cerebellar hemisphere.[11,12] These patterns of associated hypometabolism reflect the extra temporal connections of the seizure focus involved in the epileptogenic circuit. In the temporal lobe, the hypometabolic region involves the grey matter, which is involved in the initial ictal electrophysiologic discharges seen with intracranial monitoring.[13,16] Occasionally, glucose metabolism may be normal in the involved temporal lobe.[10] The reason for this is unclear but it may relate to differences in instrumentation and periscan ictal events that can increase glucose metabolism. In addition, the mesial temporal structures can be hypometabolic secondary to extra temporal neocortical epilepsy, in particular, due to seizure spread from the ipsilateral occipital lobe.[17,18] This change in pattern of involvement may reflect the earlier identification of patients with mTLE through the more widespread availability of surgical epilepsy programs and the advances in MR imaging.

Ictal FDG-PET

Ictal FDG-PET scans are difficult to obtain, in part, because of the half-life of FDG and the difficulty in predicting a seizure. Furthermore, they are problematic as there is always some degree of movement associated with all but simple partial seizures. Such head motion has its own problems for image interpretation but generally complex partial seizures (CPS) and generalized motor seizures will mean that the scan has to be aborted. Nevertheless, if the ictal event can be captured with imaging, the PET findings can be extremely valuable in seizure localization. The typical findings are focal, markedly increased glucose metabolism at the site of seizure onset [19,20] (Figure 88.3) and there may be ipsilateral increased metabolism in the basal ganglia and crossed cerebellar hypermetabolism due to increased efferent input to the contralateral cerebellar hemispheres via the cortico-ponto-cerebellar (CPC) pathway. The more problematic issue is when the patient has a seizure in the uptake period whilst awaiting the scan. If EEG monitoring is done prior to the scan acquisition it may provide valuable localising data but the practical issue is to whether to continue with the scan acquisition. Given that the static FDG-PET scan represents glucose metabolism over the entire uptake period and the study acquisition, a seizure produces a mixed interictal-ictal-post ictal scan where there may be regions of increased and decreased metabolism. However, the patient has already been injected with isotope and so our practice is to continue with the scan. If the scan results are problematic then we suggest that the study is repeated at a later date.

Visual versus quantitative analysis

Experience plays a large part in interpretation of PET scans and an extensive review of normal subjects is necessary to appreciate normal variation prior to the attempted interpretation of clinical cases. Co-registration programs that relate structural information to PET images allow a more precise anatomical localization of the lesion but this problem has been partially addressed with PET-CT. The limitations of qualitative visual analysis of PET images also apply to its quantitative analysis. With these limitations in mind, a few studies suggest that quantification enhances the clinical utility of FDG-PET[21,22] and may prevent misinterpretation of normal right and left variation.[23] However, in our experience quantification of studies, although a useful research tool, adds little to the clinical interpretation of PET studies. The routine quantification of clinical PET studies in every case of epilepsy is also tedious and is not practical in most centers.

Effect of blood glucose and anticonvulsants on FDG-PET

Endogenous molecules that compete with the ligand in the biological process can increase noise or reduce ligand tissue uptake. High blood glucose levels interfere with FDG uptake and lead to studies with poor signal-to-noise ratio. Antiepileptic medications produce a global reduction in cerebral metabolism in particular the deep nuclei and cerebellum[24–27] but this is not as marked as major tranquilisers and corticosteroids.[28] Chronically administered barbiturates, phenytoin, carbamazepine and valproate have all been shown to globally reduce absolute values of cerebral glucose metabolism but not to alter interregional ratios of metabolism.[29,30] Valproic acid reduces glucose metabolism by up to 10% and cerebral blood flow by up to 15%. The degree of glucose hypometabolism is not related to the serum valproate level and is similar to that of carbamazepine (10%) and phenytoin (11.5%). The reductions in cerebral glucose metabolism

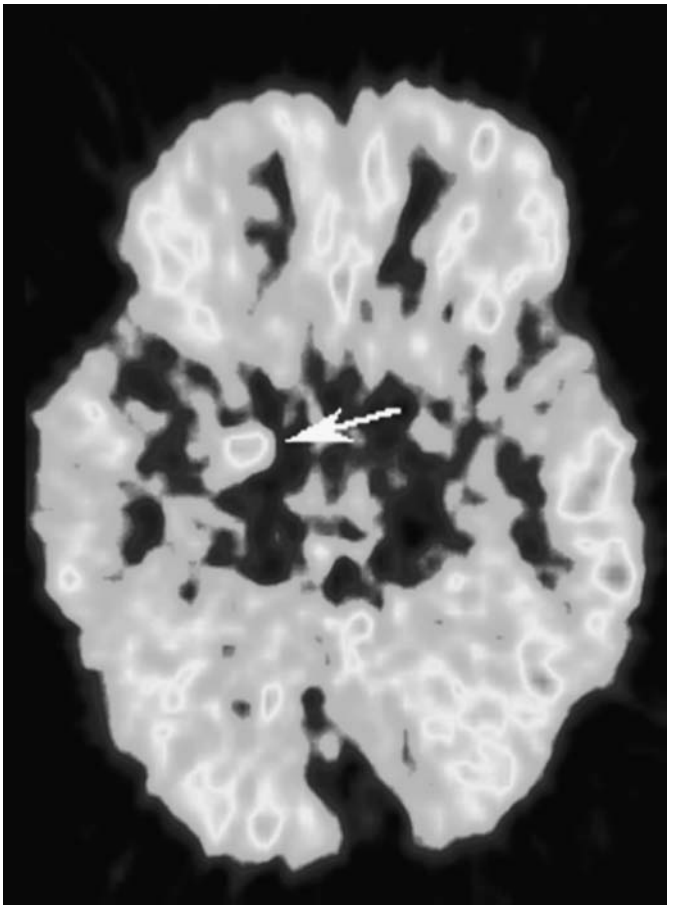

Figure 88.3 Ictal FDG-PET in a patient with right mesial temporal epilepsy who had a prolonged seizure in the uptake period showing markedly increased glucose hypometabolism in the right hippocampus (arrows).

is more pronounced with barbiturates (27%), diazepam (20%) or the combination of valproate and carbamazepine.[26,27,31,32]

Artifacts

Common artefacts that the reader should be familiar with may arise from partial volume effects, incorrect attenuation-correction, motion and seizures in the periscan period.

Partial volume is an artefact common to all tomographic imaging. If a structure is smaller than the detection threshold permitted by a scanner's spatial and contrast resolution, its functional activity will be averaged together with that of the activities of adjacent structures. Small structures may lose border detail if their contours are complex. Computer simulations show partial volume errors can cause up to a 15% change in the apparent size of an object in the PET image.[33] Incorrect attenuation correction can lead to false increases or decreases in the perceived tracer uptake. The most common mechanism for this in current PET-CT devices is head movement. The relationship of the scan to seizure activity is extremely important as discussed previously. Continuous EEG monitoring should be performed prior to the scan, during the uptake phase and when practical during scan acquisition to exclude unintentional ictal scanning which could lead to misinterpretation of FDG images.[34] However, it is important to note that surface EEG monitoring does not provide a complete solution to this problem, as subclinical electrographic seizures in small cerebral volumes or deep structures may not be detected with surface EEG.[35]

Current role of FDG-PET in assessment of mTLE

Interpretation of the literature on the role of FDG-PET in mTLE presents a formidable challenge to even experienced users of functional imaging. This in part relates to the different hardware/software methodologies, interpretation skills and variable emphasis on different investigation algorithms in the various centers. Further, local expertise across all facets (EEG, MR imaging, PET, SPECT) is usually not readily available in all centers. Although the studies in mTLE, which have compared FDG-PET to other imaging modalities, were done using older generation scanners, a number of reports have identified that interictal FDG-PET is more sensitive than volumetric MR imaging in identifying the temporal lobe of seizure origin.[36,37] FDG-PET also provides valuable information in patients with nonlocalizing surface ictal EEG, which can then reduce the need for intracranial EEG studies.[23] However, FDG-PET does not provide additional information when hippocampal atrophy is present on MR imaging.[38] The concordance between MR and FDG-PET is also associated with a better post-surgical seizure outcome.[39] However, false lateralization on FDG-PET, confirmed by depth EEG, can occur in a small percentage of patients.[6,22,40,41] Ictal HMPAO SPECT and interictal PET are probably equivalent for the lateralization of mTLE, although ictal SPECT generally requires hospital admission, cessation of medications and is more labor intensive and expensive when compared to an outpatient procedure.[42,43] In the comparison of FDG-PET to proton MR spectroscopy (MRS) there is little difference in lateralizing seizure onset according to the available data, although falsely lateralization is more common with MRS (6 vs. 3%) and expertise in MRS is restricted to only a few centers.[44,45]

Della Badia *et al.* has suggested that the combination of sleep EEG and MR imaging may be more cost-effective as outpatient screening tools.[46] It is our experience that the widespread availability of MR imaging at 1.5 T has meant that the need for routine FDG-PET scanning in mTLE has diminished. FDG-PET is now more directed to cases where there are discordant data and in this situation FDG-PET may be lateralizing and in this setting patients have a good post-surgical outcome.[47,48] FDG-PET may also be used to prognosticate on postoperative memory deficits (see below).

Pathophysiology of glucose hypometabolism with FDG-PET

Although it is over 25 years since the first interictal FDG-PET studies were done in the study of epilepsy the pathophysiology of the glucose hypometabolism in mTLE remains unknown. Various mechanisms have been suggested including neuronal loss, diaschisis, postictal depression and other epilepsy-related phenomena. There is no correlation between cortical metabolism on preoperative FDG-PET and neuronal density of resected hippocampi in mTLE.[49] There is also a lack of correlation between hippocampal volume loss and the degree of temporal glucose hypometabolism.[50] Diaschisis was described by Von Monakow over a century ago to explain a disconnection between functionally related parts of the nervous system.[51] In the 1980s the most common example of this was the reduction in blood flow and

metabolism in the contralateral cerebellar hemisphere ('crossed cerebellar diaschisis' – CCD), which was noted in patients with hemispheric or deep white matter strokes due to interruption of the cortico-ponto-cerebellar (CPC) pathway when PET scanning was used as a research tool.[52] However, despite the reduced metabolism and blood flow in the contralateral cerebellar hemisphere there were no obvious associated neurological signs. The most common example of CCD today is that seen with FDG-PET scans done in patients with brain tumors. Whilst this effect may in part explain the remote hypometabolism in extra temporal sites where there are known connections from the mesial temporal structures, it cannot be the sole mechanism and there is difficulty with this mechanism in explaining the marked neocortical temporal hypometabolism that is sometimes seen.

Dlugos *et al.* reported a correlation between hilar cell densities and the degree of glucose hypometabolism in the deep nuclei, which suggests that there may be functional changes in neurons and their associated circuits in relation to seizure spread.[53] Still other investigators have hypothesized that interictal spikes at sites inaccessible to surface EEG may explain the reduction regional glucose metabolism[54] and this is partly supported by depth EEG recordings.[55] These remote sites of regional glucose hypometabolism return towards normal after successful surgery for MTS.[56] But rather than an effect of diaschisis, Bartenstein *et al.* linked these findings to down-regulation of opiate receptors.[57]

The exact cause of glucose hypometabolism in mTLE remains unknown. The evidence so far suggests that it is due to a combination of factors and that neuronal loss does not adequately explain the reversible and functional changes seen with FDG-PET.

Interictal FDG-PET in early temporal lobe disease

Investigators have studied FDG-PET in early mTLE to understand the underlying cause for the glucose hypometabolism seen in focal epilepsy. There are conflicting data in the literature. There is evidence that temporal hypometabolism may already be present at the onset of mTLE. In a cross sectional study of pediatric patients with refractory mTLE, the incidence of FDG-PET hypometabolism was similar to that of the adult population.[58] These findings would also be in agreement with studies in adult patients that have failed to detect an association between the lifetime frequency of seizures and the severity of temporal lobe glucose hypometabolism on PET[59] or hippocampal atrophy on MR imaging.[60] There have been examples of patients with severe temporal glucose hypometabolism where hippocampal volumetric measurements were normal.[60] These data support the postulate that glucose hypometabolism represents the severity of the underlying epilepsy syndrome, rather than simply an effect of repeated seizures.

Other authors have argued that the degree of glucose hypometabolism may worsen with continuing seizure activity.[61] They cite prospective imaging studies[62] and studies done in children with new onset temporal epilepsy.[63] However, none of these studies have been longitudinal and the results may reflect a mixed cohort, some of whom may have a more benign epilepsy syndrome.

The evidence with FDG-PET in early TLE parallels that of clinical experience. That is, the natural history of refractory mTLE is different from mTLE which is easily controlled by anticonvulsants. It is not surprising that abnormal glucose metabolism may be present early in patients with refractory disease.

Clinical aspects of mTLE and FDG-PET

FDG-PET and seizure semiology

There is a weak association between seizure semiology and the pattern of interictal glucose hypometabolism. Early animal and clinical FDG-PET studies described temporal hypometabolism together with limbic auras, automatisms and posturing that are typical findings with mTLE.[8,64,65] A quantitative study by Savic *et al.*[18] confirmed that the topographical pattern of interictal glucose hypometabolism in mTLE was not only a reflection of regions involved in seizure generation but also included regions of the cerebrum involved in seizure expression. Limbic auras or staring spells without other motor manifestations were limited to the ictal onset zone. However, these authors found more widespread areas of glucose hypometabolism in patients with more complex motor behaviors during the seizure. Patients with motor automatisms, thrusting movements, head turning or swinging of the extremities had more widespread hypometabolism in the limbic structures, often involving the contralateral side. Posturing during the seizure was associated with hypometabolism in the dorsolateral frontal and/or motor cortex. In subjects with secondary generalized seizures there was cerebellar and parietal lobe hypometabolism in addition to the abnormalities described above.

The pattern of glucose hypometabolism in the temporal lobe may be also used to distinguish patient with mTLE from patients with neocortical temporal lobe epilepsy. Ipsilateral insular and temporal neocortical hypometabolism is more pronounced in patients with neocortical temporal lobe epilepsy when compared to mTLE.[66,67] Also patients with neocortical temporal lobe epilepsy who describe an acoustic aura can be differentiated from mTLE by reductions in glucose metabolism primarily involving temporo-perisylvian locations.[67]

FDG-PET and interictal epileptic abnormalities

There are conflicting reports on the relationship between the frequency of interictal temporal EEG spikes and severity of glucose hypometabolism on PET. This may be due to the different patient groups studied; evolution of PET technology; relative sophistication of MR imaging and PET equipment and the scanning protocols. Early studies did not find a relationship between interictal scalp and depth EEG spikes and the severity of temporal lobe hypometabolism[9] but this group may have been studied much later in the natural history of mTLE. In addition, continuous focal slowing or focal suppression of barbiturate-induced beta activity during the PET study did not correlate with the severity of temporal lobe hypometabolism.

More recent studies suggest that FDG-PET hypometabolism may reflect not only a permanent functional deficit but also a transient regional cerebral dysfunction related to the occurrence of interictal spikes.[68,69] Some researchers have found a relationship between interictal EEG abnormalities and the severity of glucose hypometabolism. In another study

there was a significant negative correlation between asymmetry in glucose hypometabolism in temporal lobes and total number of interictal spikes recorded.[55] Investigators have also shown a concordance between temporal lobe glucose hypometabolism and regional slow activity recorded over temporal electrodes [70] and the amount of delta activity in the interictal EEG that is independent of MR findings.[71] However, none of these studies accounted for the seizure frequency around the time of the PET study. This is an important issue because patients with more frequent interictal epileptic discharges often have more frequent seizures. Without controlling for seizure frequency around the time of the PET study, it is difficult to conclude that a reversible diaschisis from interictal epileptic activity results in neuronal dysfunction that in turn leads to abnormal glucose metabolism. At present there is no evidence that there is a strong relationship between interictal discharges and the severity of glucose hypometabolism on PET.

FDG-PET and ictal epileptic discharges

Early studies showed a good relationship between the site of focal hypometabolism and the epileptic focus determined by the combined results of all electrophysiological studies.[7] These findings then led to performing anterior temporal lobectomies without chronic intracranial recordings as a routine part of clinical practice provided there were no discordant data.[13] In mTLE, the zone of intracranially recorded electrographic ictal onset is almost always located in the region of glucose hypometabolism on FDG-PET.[72] This regionalization of the ictal onset zone has been borne out in more recent studies. The area of glucose hypometabolism is usually larger than the pathological abnormality and may even be present in the absence of any MR scan abnormality.[38]

There are also subtle differences between epilepsies of mesial temporal origin versus those from the lateral neocortex on FDG-PET.[72] Patients with mTLE as a group have the lowest FDG uptake in the entire temporal lobe when compared to patients with lateral or mesio-basal temporal seizure origin but there is no discernible correlation between the degree of hypometabolism and the location of EEG-defined epileptogenic zone.[21]

FDG-PET has superior sensitivity and specificity when compared to scalp EEG in mTLE.[13] These data are old and more recent studies have not been done but one would expect an improved performance with the new generation of scanners. FDG-PET is as accurate as MR imaging in identifying the temporal lobe of onset in patients with bitemporal epilepsy[73] and can provide lateralizing data in patients with a nonlocalized surface ictal EEG[23] or nonlateralized MR findings.[48] However, occasionally both metabolic and electrophysiological techniques can produce false positive as well as false negative results.[7]

FDG-PET and neuropsychological outcome and intracarotid amobarbital memory testing (ICAMT)

There are limited studies that have investigated the distribution of FDG-PET abnormalities, the temporal structures involved and neuropsychological measures. A number of general rules have emerged from these studies: patients with mTLE and left temporal hypometabolism perform poorly on verbal memory tasks and those with right temporal hypometabolism perform less well in visual memory tasks;[74,75] left thalamic and left lateral temporal hypometabolism are independently associated with impairment of delayed verbal recall[76] and more severe left hemispheric hypometabolism on FDG-PET is associated with poorer overall cognitive performance in patients with left hemisphere language dominance.[76]

FDG-PET has shown the mesial temporal region to be a dominant and leading area for lateralizing Wada memory dominance.[77] In one study 65% of patients with TLE and glucose hypometabolism on FDG-PET had impaired memory on the ICAMT and memory impairment contralateral to the temporal glucose hypometabolism was never found.[78,79] FDG-PET is also useful to help predict postoperative memory loss. Patients with mild to no glucose hypometabolism on the left side have a significantly greater verbal memory decline following a left temporal lobectomy when compared with those with findings of moderate to severe hypometabolism (89 versus 33%). However, there does not appear to be a significant relationship between the extent of PET hypometabolism and memory outcome for right anterior temporal lobectomy patients.[80]

FDG-PET and seizure outcome following surgery

FDG-PET can be predictive of postoperative seizure outcome and neuropsychological deficits following temporal lobectomy for mTLE but may be less useful in patients with bitemporal epilepsy. Studies that have examined the relationship of FDG-PET to outcome of temporal lobectomy independent of EEG findings have found that asymmetries in glucose metabolism in the temporal lobes of at least 15% can be predictive of good post surgical outcome.[22,81] The prognostic value of the exact location of glucose hypometabolism within the temporal lobe is more controversial. Some data suggests that patients with mesial temporal glucose hypometabolism on PET have a high probability of becoming seizure free postoperatively.[82,83] However, other studies have indicated that lateral[22,81] or polar temporal hypometabolism[84] are better predictors of a seizure-free postoperative course. Despite these conflicting results these studies provide us with a number of other important findings: (i) the high correlation between temporal hypometabolism and seizure outcome is independent of the pathologic diagnosis[83] (ii) a 100% lateralization by depth EEG, nonlateralized PET scan and MR imaging do not indicate poor surgical outcome;[6,73] (iii) unilateral temporal lobe hypometabolism is 'falsely lateralized' in approximately 1–2% of patients (iv) prior intracranial surgery, including depth electrode placement, can produce temporal hypometabolism that is falsely lateralized.[13]

Although bilateral temporal hypometabolism is a relative contraindication to surgery,[12] FDG-PET is as sensitive and specific as volumetric MR in patients with bitemporal epilepsy. However, in these patients, a lateralizing PET that is convergent with depth EEG recordings and MR imaging[73] does not increase the probability of successful postoperative seizure outcome.

FDG-PET and pathology

As described earlier cell loss in the mesial structures is only one component in the pathophysiology of glucose hypometabolism.

It is not surprising that reduced glucose metabolism on FDG-PET corresponds closely with the presence of a histologic lesion in the mesial temporal lobe that, rarely, may not be detected on MR imaging.[48] However, as already discussed, glucose hypometabolism on PET does not correlate with the degree of neuronal loss in surgical specimens[13,49,85–87] or hippocampal atrophy on MR imaging.[50]

FDG-PET is also very sensitive in patients with mTLE and a concomitant pathology located outside the hippocampus, i.e., 'dual pathology'. Alien-tissue lesions, including ganglioglial, oligodendroglial, and astroglial tumors, occur in 10–20% of patients who undergo surgery for temporal lobe epilepsy. Up to 91% of patients with dual pathology have abnormal PET scans[88] where they may also have a different distribution of glucose hypometabolism. For example in the subgroup of patients with dual pathology who have microscopic temporal cortical dysplasia and concurrent MTS there is more prominent lateral temporal metabolic dysfunction compared with isolated MTS.[89]

Other PET ligands

Several other PET ligands have been developed over the last two decades that have provided insights into the pathophysiology of epilepsy. These include ^{15}O-water, ligands that bind to benzodiazepine, cholinergic, opiate, serotonin, and monoamine oxidase receptors together with agents to identify protein synthesis and positron-labeled anticonvulsants.

[11C] Flumazenil (FMZ)

FMZ is a competitive central benzodiazepine receptor antagonist. Histopathologic and autoradiographic studies of surgically removed sclerotic hippocampi have shown reduced neuronal counts, central benzodiazepine receptor (cBZR) densities and a reduction of cBZR density per remaining neuron.[90] There is a reduction of available cBZR on remaining neurons in MTS detected *in vivo* by using FMZ-PET. After correction for grey matter atrophy there is reduced FMZ binding, which suggests that a reduction in cBZR binding is not solely due to hippocampal atrophy or neuronal loss.[91] These changes are not permanent and may be in part due to the effects of seizures on projection areas from the mesial temporal lobe.[92]

Comparison FMZ-PET with FDG-PET in defining the ictal onset zone

FMZ-PET studies when compared with FDG-PET have shown a less extensive reduction in cortical binding (Figure 88.4) but are as sensitive in localizing the temporal lobe of seizures onset.[93–95] It has been postulated that unlike more widespread glucose hypometabolism seen with FDG-PET, the FMZ-PET changes may be more specific to the epileptogenic zone (Figure 88.4). Ryvlin *et al.*[10] studied a series of patients with partial epilepsy the majority whom had temporal lobe epilepsy. An abnormal FMZ-PET was found in 94% of patients with temporal epilepsy in which 81% also had concordant MR abnormalities. There were a small number of patients who had a positive FMZ-PET with a normal FDG-PET and vice versa. False lateralization occurred rarely with FMZ-PET. However, as with FDG-PET where there are clear-cut MR findings of MTS, the more sensitive FMZ-PET does not provide any additional clinical information. By the same token, where hippocampal volumetry fails to show hippocampal atrophy, reduced binding on FMZ-PET as with FDG-PET, may provide evidence for functional impairment.[10,96] However it is important to note that transient and falsely lateralized abnormalities with FMZ-PET can occur in patients with normal MR imaging.[97]

Both visual and quantitative assessments of FMZ-PET are very sensitive where there is a coexistent cortical lesion in addition to MTS.[98,99] In patients with microdysgenesis where the MR images are normal, some authors have also found increased binding on FMZ-PET in the white matter and periventricular region and have postulated that it may represent benzodiazepine receptors on heterotopic neurons.[100–102] These authors did not confirm their postulate by a pathological study.

Opiate receptors

^{11}C-carfentanil PET binds to the mu opiod receptors, which are increased in the temporal neocortex, but decreased in the amygdala on the side of the epileptic focus.[103] On the other hand, ^{11}C-diprenorphine binding – that reflects mu as well as nonmu opiate subtypes – is not different among regions of affected and nonaffected temporal lobes in patients with unilateral TLE. One possible explanation of this increase in mu opioid receptors in the lateral neocortex without an overall increase of opioid receptor binding includes an up-regulation of mu receptors in response to epileptic activity and down-regulation or occupation of kappa opioid receptors.[104] This reduced binding of opioid receptors appears to persist after surgical removal of the epileptic focus.[57] The studies done so far in mTLE suggest that this ligand is of limited clinical value.

Cholinergic receptors

Cholinergic receptors have been imaged using [^{76}Br] 4-bromodexetimide (BDEX) or [^{11}C] *N*-methyl-4-piperidyl benzylate (NMPB). With mTLE BDEX there is a reduction in binding in the temporal lobe ipsilateral to the seizure focus.[105] Highly restricted zones of reduced activity in the anteromesial temporal regions are seen with NMPB[106] – similar to the distribution seen with FMZ-PET. These findings have also been reproduced using SPECT ligands.[107]

Monoamine oxidase type B (MAO-B) receptors

Deprenyl is an irreversible inhibitor of MAO-B with a very high affinity for the enzyme. In the brain, MAO-B is preferentially located in astrocytes and there is histological evidence for increased binding of MAO-B enzyme in sclerotic hippocampi. PET with ^{11}C-deuterium-deprenyl in patients with temporal epilepsy showed increased binding in its ipsilateral mesial temporal lobe.[108] However, ^{11}C-deuterium-deprenyl PET adds little to FDG-PET in patients with TLE.[109]

N-Methyl-d-Aspartate (NMDA) receptors

^{11}C-(*S*)-*N*-methyl ketamine that binds NMDA receptors in the brain may have a 9–34% reduction of tracer radioactivity in

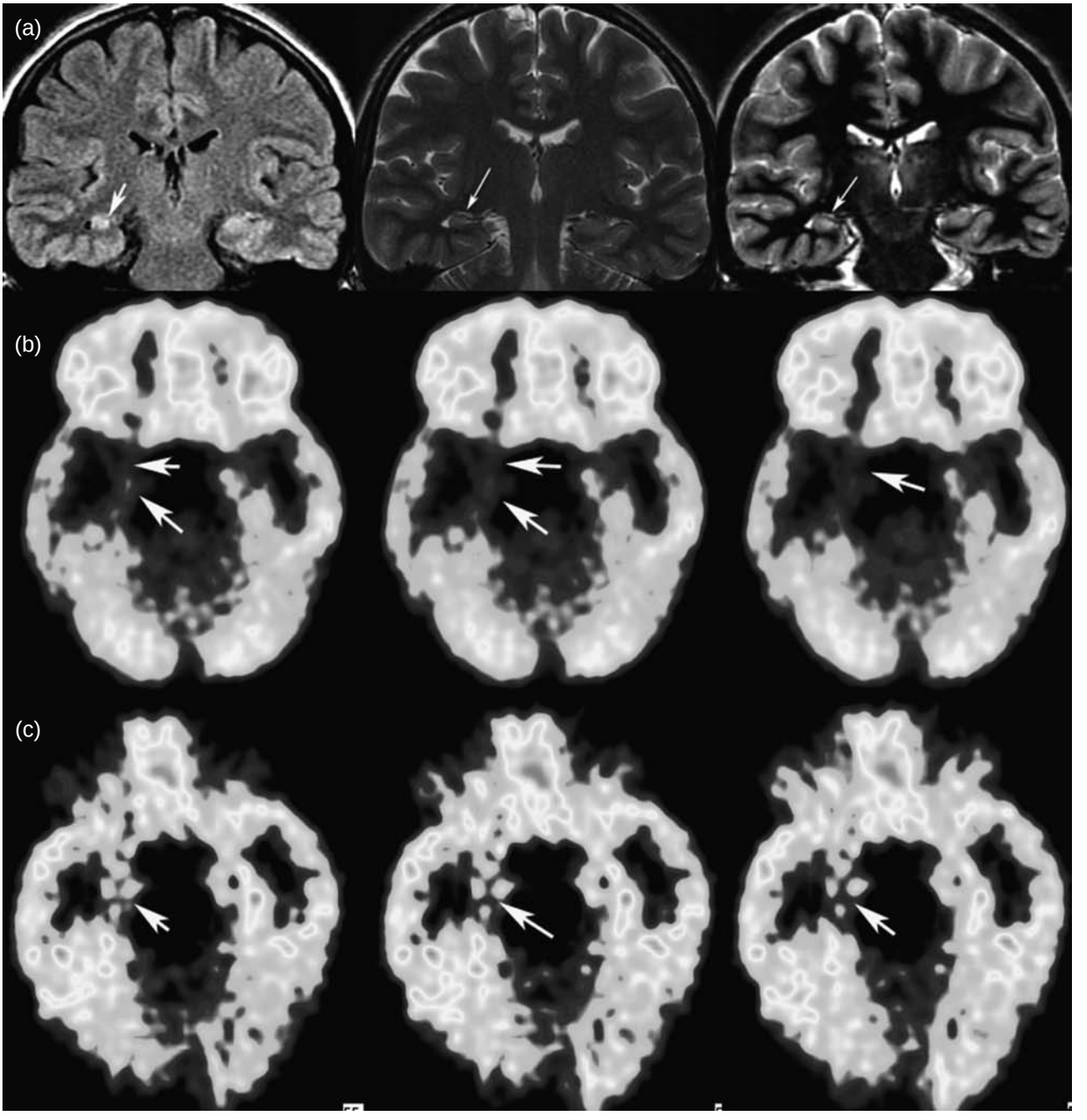

Figure 88.4 Patient LS from Figure 88.1. with left mesial temporal sclerosis and temporal lobe seizures. Row A,MR images. Arrows showing increased signal and atrophy in the right hippocampus on T2-weighted images. Row B,FDG-PET. Arrows showing marked anteromesial glucose hypometabolism. Row C,FMZ-PET. Arrows showing a more restricted area of reduced ligand binding in the right hippocampus when compared to the FDG-PET images.

the temporal lobes of ictal onset; very similar to the metabolic pattern seen on PET scans with FDG-PET.[110] However, only a few patients have been studied with this technique and its role in clinical assessment is at present uncertain.

Serotonin receptors and metabolism

Studies exploring the serotonergic mechanisms in animal models of epilepsy and human surgical specimens have shown increases in serotonin and its metabolites in epileptic tissue.[111,112] Patients with severe mTLE have reduced 5-HT1A serotonin receptor binding in the mesial temporal lobe and its limbic connections. There is decreased binding of the PET ligand [18F] FCWAY to the 5HT1A receptor in both mesial and lateral temporal regions ipsilateral to the epileptic focus[113] together with the ipsilateral anterior cingulate, insula and lateral temporal cortex, contralateral hippocampus and the raphe nuclei.[114] These findings have been echoed by another ligand that is an antagonist of the 5-HT1A receptor – 4-(2Vmethoxyphenyl)-1-[2V-(N-2-pirydynyl)-p-fluorobenzamido]-ethylpiperazine (MPPF).[115] Assuming that these findings are not due to the effect of anticonvulsant medications, they can be explained by increased endogenous serotonin release that results in agonist-mediated down-regulation of 5HT1A receptors in the hippocampus.

PET with alpha [11C] methyl-l-tryptophan (AMT) has been used to examine serotonin synthesis and has revealed an

increase in AMT uptake in the hippocampus.[116] The increased AMT uptake in the hippocampus has been speculated to be the result of serotonergic fiber sprouting.[117]

Although there have been limited studies of many ligands in temporal lobe epilepsy research in this area continues. None of the above ligands apart from perhaps FMZ have found a clinical place in the assessment of patients with mesial temporal epilepsy. However, even FMZ has not gained widespread clinical use due to its limited availability and little additional benefit when compared to FDG. This may reflect the fact that in temporal lobe epilepsy there is not only a change in the distribution of receptors but also altered function of the remaining receptors that will require new methodologies to investigate.

Conclusion

The current clinical role of FDG-PET/CT appears to be in the nonlesional cases of mTLE or where there is discordance between the MR and EEG data. Although instrumentation has improved markedly over the past decade and scan times are shorter, it should be emphasized that patients with mTLE are subject to dynamic changes in the periscan period. Accurate accounts of seizure frequency and EEG recordings around the time of the scan are essential to correct interpretation. Although many ligands have been used over the past decade, FMZ shows the most promise but in the extra temporal seizure disorders. A ligand that is able to map the seizure onset remains elusive.

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89 PET in neocortical epilepsies

HT Chugani, C Juhász, E Asano, and S Sood

Summary

- PET techniques have contributed to the clinical management of epilepsy.
- In extratemporal lobe epilepsy, glucose metabolism PET guides placement of intracranial electrodes. Dynamic metabolic changes occur with persistent epilepsy.
- Flumazenil PET is useful in detection of 'dual' pathology, more precise localization of the epileptogenic zone, defining perilesional epileptogenic cortex, and possibly identifying 'secondary epileptic foci'.
- α-[^{11}C]methyl-L-tryptophan (AMT) PET can differentiate between epileptogenic and nonepileptogenic tubers in tuberous sclerosis complex.
- AMT-PET can localize the epileptic focus in lesional and occasionally in nonlesional epilepsy.
- In cases of failed epilepsy surgery, AMT-PET may identify residual epileptogenic cortex for a second surgery.

Introduction

Positron emission tomography (PET) is a noninvasive functional imaging tool which can be used to measure regional uptake and affinity of ligands or metabolic substrates in brain and other organs. In epileptic disorders, PET scanning has been applied both in the clinical setting and also to investigate basic mechanisms associated with epileptogenicity and seizure propagation. The commonest clinical application of PET is in the evaluation of patients with intractable epilepsy for surgical treatment. In such instances, PET scanning can assist in the selection of appropriate surgical candidates, localize epileptogenic brain regions, evaluate the integrity of brain areas outside the epileptic focus, and even predict postoperative cognitive dysfunction in some patients. In this review, we summarize the findings of previous PET studies which have investigated clinical applications in patients with *neocortical* epilepsies with the aim of defining epileptogenic cortex for surgical resection. The application of PET in mesial temporal lobe epilepsy has been discussed in the previous chapter.

PET tracers used in neocortical epilepsy

The most widely available PET tracer for presurgical evaluation of both adults and children with intractable focal epilepsy is 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG), which is used to measure glucose utilization in various brain regions and, in the interictal state, shows decreased metabolism (hypometabolism) in the vicinity of the epileptic focus. It is important to monitor the EEG during the PET tracer uptake period, since an active focal epileptiform discharge present on the EEG may be associated with local *hypermetabolism,* even on the interictal PET scan. In such instances, the relative hypometabolism on the contralateral (normal) side may be mistakenly interpreted as an interictal epileptic focus, an interpretation that would lead to false lateralization of the focus.[1]

Of the receptor ligand PET tracers, the most commonly used in epilepsy is [^{11}C]flumazenil (FMZ) which binds to $GABA_A$ receptors.[2–8] It should be pointed out that in clinical studies with FMZ-PET, patients taking benzodiazepine drugs have generally been excluded, but the effects of drugs that result in allosteric interactions with $GABA_A$ receptors have not been well studied. Although quantification of FMZ-PET images can be performed using a three-compartmental model[9] or a simpler two-compartmental model,[10] a disadvantage is the requirement of arterial blood sampling to define the input function. However, experience has shown that visual as well as objective detection of focal cortical and subcortical abnormalities for clinical purposes can be reliably achieved using FMZ activity images that do not require arterial blood sampling. Comparison of focal FMZ abnormalities in patients with neocortical epileptic foci showed that summed FMZ activity images obtained between 10 and 20 min after tracer injection represented excellent agreement between FMZ activity and the quantitative 'volume of distribution' images.[11]

In our center, we also use alpha-[^{11}C]methyl-L-tryptophan (AMT) which measures tryptophan metabolism[12–14] for epilepsy surgery evaluation. AMT is an analog of tryptophan (the precursor of serotonin), and is converted in the brain to α[^{11}C]methyl-serotonin, which is not a substrate for the degradative enzyme monoamine oxidase, and therefore accumulates in serotonergic terminals. Obviously, patients taking medications that affect tryptophan or serotonin metabolism should not undergo AMT-PET scan.

Other PET tracers with the potential for detecting epileptic brain regions include radiolabeled ligands which bind to opioid receptors,[15] histamine H_1 receptors,[16] monoamine oxidase type B enzyme,[17] N-methyl-D-aspartate receptors,[18] peripheral-type benzodiazepine receptors,[19] and serotonin 1_A receptors.[20] Among these, only the few that have been applied in the study of intractable neocortical epilepsy will be described in further detail below.

Extratemporal lobe epilepsy

Unlike temporal lobe epilepsy, in which there is a 'standard' lobectomy procedure, extratemporal lobe resections are quite variable and range from small topectomies to unilobar or multilobar cortical resections. Defining the location and extent of *even the primary epileptic focus (let alone secondary foci)* can be quite challenging, particularly in frontal lobe epilepsy, which constitutes 20–30% of all partial epilepsies and the majority of extratemporal lobe epilepsy.[21–25] In a review of surgical outcome from 10 epilepsy surgery centers worldwide,[26] only 45% of 805 patients undergoing extratemporal cortical resections became seizure free. The success rate is even worse when no structural lesion can be identified on MRI.[27–29] For example, Schiller *et al.*[30] reported that of the nonlesional patients subjected to chronic intracranial EEG monitoring, only 22% became seizure free after surgery. Even with the many advances in neuroimaging techniques (reviewed in Kuzniecky & Knowlton, 2002,[31]) current success rates for extratemporal lobe epilepsy surgery remain modest at the 50–60% range.[32–34]

Nonlesional extratemporal lobe epilepsy

When the MRI scan fails to show a focal structural abnormality in extratemporal lobe epilepsy, the epileptologist is guided only by seizure semiology and scalp-EEG findings for the placement of intracranial electrodes, an approach that is fraught with sampling errors and may lead to surgical failure. In such instances, PET often provides important localizing data that can be compared to EEG localization and guide intracranial electrodes placement, thus increasing the confidence of the epilepsy surgery team (Figure 89.1). Using a high resolution PET scanner in a predominantly pediatric population, a sensitivity of 92% in the detection of frontal lobe epileptic foci with FDG-PET, and a specificity of 62.5% were demonstrated.[35] In an adult population with nonlesional neocortical epilepsy, however, the sensitivity was 42.9%.[36] Unfortunately, the consistent observation of large areas of glucose hypometabolism on PET extending beyond the primary epileptogenic region has precluded the use of FDG PET to define *precisely* the boundary of the epileptogenic zone for surgical resection, although it remains a very valuable tool for lateralization and *general* localization of epileptogenic brain regions.[37–39] This is supported by a recent study, which found that localization data obtained by FDG PET and interictal EEG tended to predict a seizure-free outcome.[34]

The large areas of glucose hypometabolism seen in patients with partial epilepsy are more often seen in cases of chronic epilepsy than in patients with recent onset epilepsy.[40,41] Indeed, in a PET study of 40 children with newly diagnosed partial epilepsy with normal MRI, only eight (20%) showed focal cortical hypometabolism on FDG-PET.[41] More recently, we measured changes in the extent of cortical hypometabolism defined by an asymmetry-based method and projected on the 3D-reconstructed cortical surface in 15 children who underwent two consecutive FDG-PET scans 7–44 months apart.[42] Change in seizure frequency between the two PET scans correlated positively with the change in the extent of cortical glucose hypometabolism ($r = 0.81$, $p < 0.001$; corrected for interval time between the two scans). Patients with persistent or increasing seizure frequency (≥1 seizure per day) showed extension of hypometabolic cortex over time (Figure 89.2). In contrast, patients whose seizures were characterized as <1 seizures per day during time interval between the first and second PET scan showed a decrease in the size of the hypometabolic cortex. These findings are consistent with our earlier studies, which found that in patients with an epileptogenic lesion, the extent of perilesional glucose hypometabolism increases with the number of seizures.[6] Together, these observations suggest that intractable epilepsy in children is a progressive disorder and that expansion of cortical hypometabolism may reflect a growing seizure network, i.e., an expansion of dysfunctional circuitry

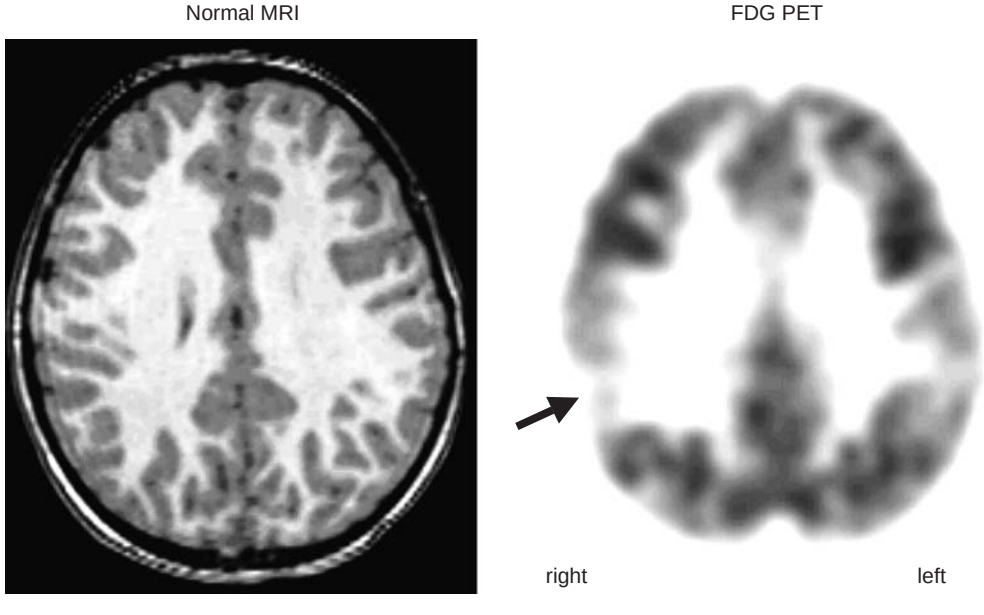

Figure 89.1 Focal cortical parietal glucose hypometabolism (arrow) on FDG-PET in a child with normal MRI and uncontrolled seizures. Video-EEG monitoring suggested ictal onset from the right centro-parietal cortex, consistent with the PET abnormality. High-resolution MRI was normal.

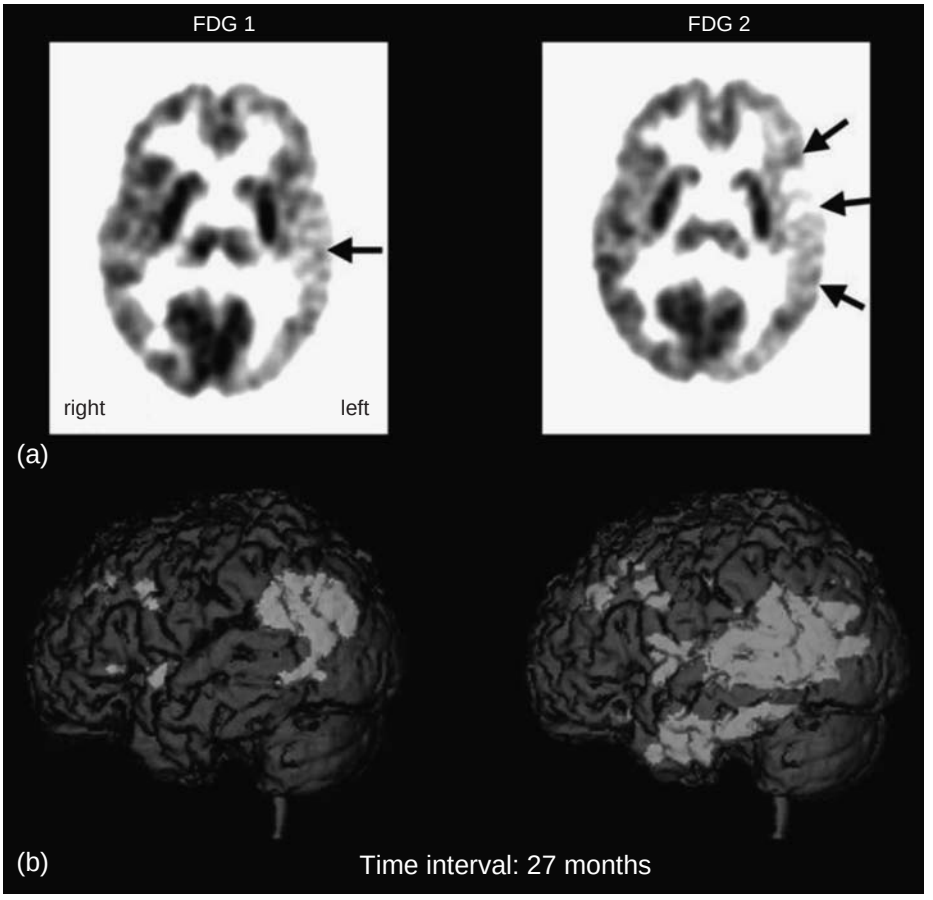

Figure 89.2 Expansion of cortical glucose hypometabolism in chronic epilepsy in a child with frequent seizures originating from the left hemisphere. The first PET scan (FDG1, at 15 years of age) showed left temporal hypometabolism which extended to the frontal cortex on the second PET scan (FDG2) performed 27 months later (see arrows on panel a). Panel b demonstrates the extent of cortical hypometabolism as projected to the 3D brain surface. Seizure frequency had increased between the two scans from 1 per day to more than ten seizures per day.

involving cortical (and subcortical) areas. It is tempting to speculate that the mechanisms associated with these dynamic changes may also play a role in the development of epileptic encephalopathy in children who experience repeated seizures during an early sensitive period when there is exuberant synaptic connectivity in the brain, but further studies are required to test this hypothesis.

Infantile spasms

Glucose metabolism PET studies in children with intractable cryptogenic infantile spasms have shown unifocal (Figure 89.3a) and, more commonly, multifocal (Figure 89.3b) cortical areas of hypometabolism interictally. Less commonly, increased focal glucose utilization may be seen if the study is performed ictally or in the presence of an actively discharging focus on the EEG. The EEG localization of focal ictal or interictal abnormalities corresponds well to the PET focus in most cases.[43,44] However, when hypsarrhythmia is present on the EEG, focal electrographic abnormalities either preceding or following the presence of hypsarrhythmia correlate best with the location of FDG-PET cortical abnormalities. When available, therefore, EEGs performed before the onset of spasms must be reexamined in conjunction with the PET study.

The discovery of these focal cortical metabolic abnormalities on FDG-PET has allowed some infants with refractory spasms to be treated with cortical resection. Thus, when a single region of abnormal glucose metabolism is present, and there is good correlation between the region localized with PET and the focus identified on the EEG, surgical removal of the epileptogenic region results not only in seizure control but also in complete or partial reversal of the associated developmental delay. Neuropathological examination of the resected tissue typically reveals cortical dysplasia.[43–45]

Unfortunately, about 65% of infants with cryptogenic spasms show more than one area of cortical hypometabolism on the FDG-PET scan[46] and are therefore not ideal candidates for cortical resection (Figure 89.3b). Within this group, there is a subgroup of infants with bilateral temporal hypometabolism (Figure 89.3c) and a typical clinical phenotype, comprising about 10% of all infants with cryptogenic spasms. The clinical features include severe developmental delay (particularly in the language domain) and autism.[47]

It is now recommended that all infants with intractable cryptogenic spasms undergo an evaluation with FDG-PET. In some cases, PET reveals bilateral symmetric or generalized cortical hypometabolism, with or without associated cerebellar involvement (Figure 89.3d). This pattern suggests an underlying genetic/metabolic condition, rather than cortical dysplasia, and strongly discourages pursuing of presurgical evaluation but may prompt more detailed metabolic and genetic studies.

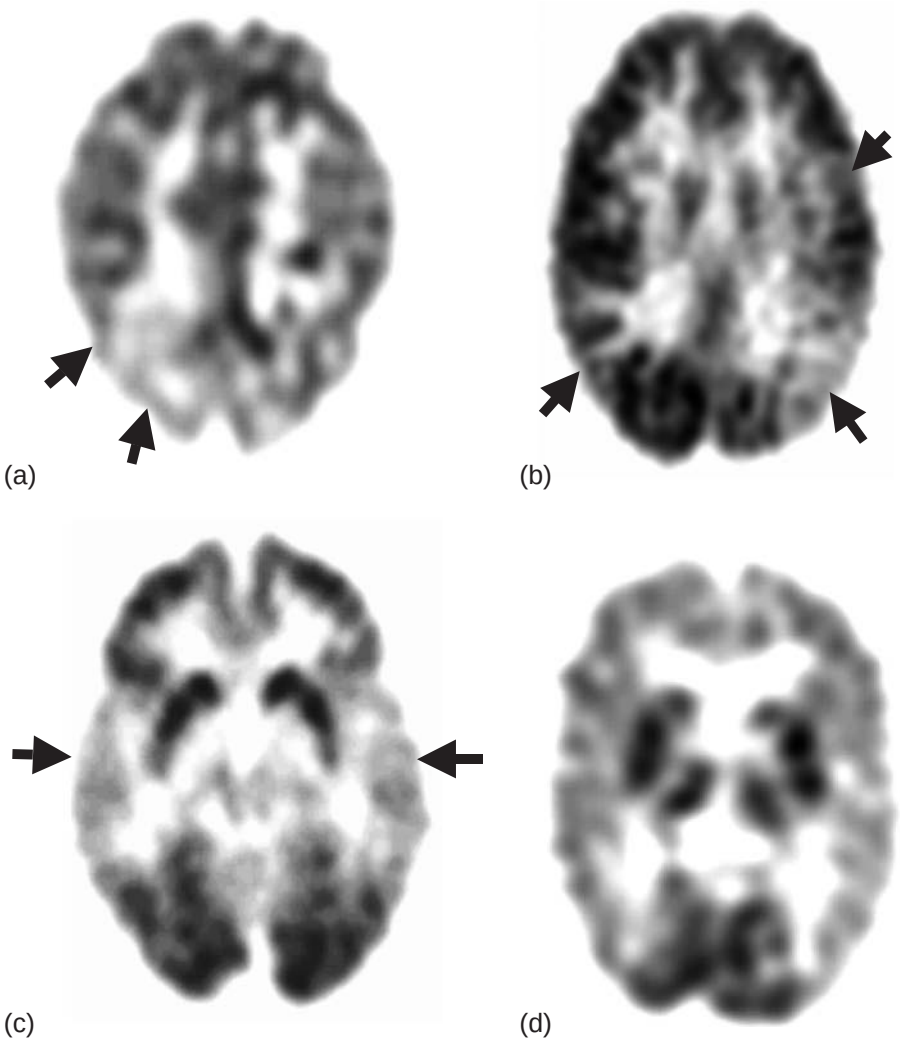

Figure 89.3 Various patterns of cortical glucose hypometabolism in infantile spasms. (a) Unifocal hypometabolism; (b) multifocal hypometabolism; both of these focal patterns are likely to be associated with focal cortical dysplasia. (c) Bitemporal hypometabolism, which is often associated with autistic features; (d) diffuse cortical hypometabolism, presumably indicating an underlying genetic and/or metabolic condition.

Other epilepsy syndromes

PET scanning has been used in the study of various other epilepsy syndromes occurring in infants and children. Studies with FDG-PET have provided a different classification of *Lennox-Gastaut* syndrome based on metabolic anatomy. Four metabolic subtypes have been identified: (1) unilateral focal, (2) unilateral diffuse, (3) bilateral diffuse hypometabolism, and (4) normal patterns.[48–50] These glucose metabolic patterns may be useful in determining the type of surgical intervention indicated for those patients with uncontrolled seizures. In children with *Sturge-Weber syndrome*, FDG-PET typically reveals hypometabolism ipsilateral to the facial nevus and thus allows the degree and extent of hemispheric involvement to be determined.[51,52] In addition, the rate of hemispheric deterioration can be determined by quantifying the degree of hypometabolism in sequential PET studies. PET has been useful both in guiding the extent of focal cortical resection (i.e., correlating better with intracranial EEG recordings than CT or MRI) and in assessing candidacy for early hemispherectomy in patients with Sturge-Weber syndrome. Paradoxically, children with mild but extensive glucose hypometabolism (confined to one hemisphere) often have worse cognitive outcome than children with early and severe unilateral hypometabolism;[53] this finding suggests that early and rapid demise of the affected hemisphere may be beneficial in allowing unaffected areas to take over lost functions (Figure 89.4a). In contrast, when the affected areas show slow deterioration, seizures tend to persist and plasticity may not be optimal; such patients may be good candidates for resective surgery in our efforts to prevent cognitive decline (Figure 89.4b). FDG PET scanning of glucose metabolism in infants and children with *hemimegalencephaly* reveals the expected, severe interictal hypometabolism of the affected hemisphere and, more importantly, allows the functional integrity of the better hemisphere to be evaluated (Figure 89.5). In a study of eight children with hemimegalencephaly, seven of whom underwent hemispherectomy, a general correlation was found between the degree of metabolic involvement of the less-affected hemisphere and overall prognosis.[54]

Flumazenil PET

In PET studies, flumazenil (FMZ) is usually labeled with the positron emitting isotope ^{11}C, which has a half-life of

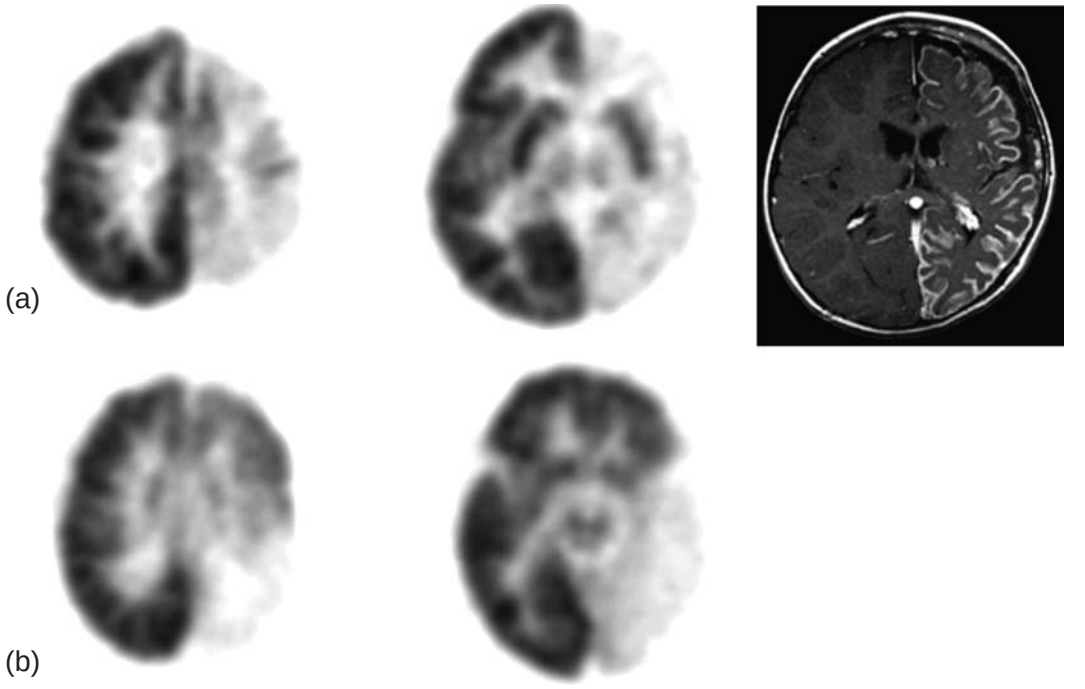

Figure 89.4 (a) Early, severe left hemispheric hypometabolism in a 2-year-old boy with Sturge-Weber syndrome (SWS). MRI with gadolinium showed extensive left hemispheric leptomeningeal angiomatosis, while the right hemiphere is not involved. Such patients typically show relatively preserved cognitive functions due to early reorganization and do not require resective surgery. (b) Lobar hypometabolism in a 1y 2m-old-boy with SWS and a left posterior angiomatosis. Note the severe hypometabolism in the left posterior quadrant (consistent with atrophy and calcification) and further, mild decrease of glucose uptake in the left frontal lobe. Seizures typically originate from the mildly hypometabolic cortex which needs to be resected to achieve seizure freedom.

20 minutes. Therefore, unlike FDG, which can be transported from another facility housing a cyclotron or purchased daily, the FMZ has to be synthesized on site using a cyclotron. FMZ binds to central benzodiazepine receptors and is useful in showing decreased receptor binding in medial temporal sclerosis, including that seen in association with an ipsilateral temporal or extratemporal lesion, so-called 'dual' pathology.[55] In neocortical epilepsy, FMZ-PET provides a better indication of seizure onset zones when compared to FDG-PET, an estimation of perilesional epileptogenic zones, and may also detect secondary epileptic foci in patients with chronic intractable epilepsy.

Seizure onset zone

Despite the very high sensitivity of FDG-PET in localizing the general area of seizure onset in patients with partial epilepsy, it is known that this hypometabolic area exceeds the epileptogenic zone and overestimates the extent of surgical resection in order to achieve seizure freedom. Glucose hypometabolism is relatively nonspecific and can be seen in patients even without seizures. For example, children born prematurely who have periventricular leukomalacia often show areas of cortical hypometabolism even when the MRI shows no overt abnormalities in cortex.[56] The situation becomes very complex when such children exhibit partial epilepsy because areas of glucose

Figure 89.5 FDG-PET in hemimegalencephaly shows gross structural and metabolic abnormalities in the affected hemisphere. Normal metabolism in the opposite hemisphere suggests relatively good cognitive outcome after hemispherectomy.

hypometabolism will encompass not only the epileptogenic zone, but also areas of hypometabolism related strictly to the periventricular leukomalacia. The extensive hypometabolism seen with FDG-PET may also include areas related to the primary epileptic focus, such as areas of seizure propagation, secondary epileptic foci, or areas of diaschisis, all of which are difficult to distinguish from the primary seizure focus.

Because the cortical regions showing hypometabolism on FDG-PET do not necessarily correspond exactly to the site of seizure onset, there has been an effort to develop PET tracers which are more specific for delineating the epileptic focus. Early studies using FMZ-PET in patients with intractable partial epilepsy showed very clearly that FMZ-PET was able to detect epileptogenic cortical regions and that the areas of decreased FMZ binding were smaller than the areas of decreased glucose metabolism.[2,4] Moreover, in patients with frontal lobe epilepsy, cortical areas of decreased FMZ binding showed good correspondence with the locations of seizure onset as determined with subdural electrodes (Figure 89.6).[3,57] Another study reported that 13 of 18 patients with normal MRI had regions of abnormal cortical FMZ binding, consisting of increases, decreases or a combination of both, and these tended to be concordant with at least the hemisphere of presumed seizure onset.[60]

In a study comparing the sensitivity and specificity of FDG and FMZ-PET to intracranial EEG data, we found that FMZ-PET detected at least part of the seizure onset zone in all patients studied, whereas FDG-PET failed to detect cortex showing seizure onset in 20% of subjects.[5] FMZ-PET was also more sensitive than FDG-PET in identifying cortical regions showing frequent independent spiking which are likely to be resected (Figure 89.7). Neither FDG nor FMZ-PET was sensitive in identifying cortical areas of rapid seizure spread.[5] In a subsequent study, in which we tested these findings against outcome in a cohort of subjects undergoing surgical resection for intractable neocortical epilepsy, we found that patients with large cortical regions showing decreased FMZ binding preoperatively had poor surgical outcome. Furthermore, there was a significant correlation between leaving behind (i.e., not resecting) cortical regions in the lobe of seizure onset showing decreased FMZ binding in the preoperative PET scan and a poor surgical outcome.[7] Stated differently, it appears that the entire area showing decreased FMZ binding in the lobe of seizure onset as revealed by intracranial electrodes should be resected in order to achieve a good surgical outcome and that leaving behind such areas is associated with a high risk of failed epilepsy surgery.

Perilesional epileptogenic zone

When medically-refractory partial epilepsy is associated with a cortical lesion visible on the MRI, and there is general concordance between scalp EEG localization and the lesion, surgical resection of the lesion is indicated. However, the extent of the epileptogenic zone is often underestimated by the MRI evidence of structural abnormality. In some cases, the lesion itself may be epileptogenic (e.g., cortical dysplasias), but additional epileptic tissue may lie in a concentric or, more commonly, eccentric location to the lesion. In other cases, the lesion may show little epileptogenicity (e.g., some cystic or glial abnormalities), and the seizures are arising from some adjacent site. A one-stage lesionectomy with intraoperative corticography or a two-stage surgery with invasive EEG monitoring are both reasonable approaches in surgical planning.

In such cases, FMZ-PET provides an alternative preoperative localization of epileptogenic tissue in and adjacent to the lesion. Richardson *et al.*[61] studied 12 patients with cortical dysgenesis identified on MRI, and found that regions showing abnormal FMZ binding frequently extended beyond the MRI-identified lesion, i.e., cortex that appeared normal on MRI often had abnormal FMZ binding. This has been confirmed in an FMZ-PET study of ten patients with malformations of cortical development following corrections for partial volume effects.[8] Interestingly, in this latter study, increased FMZ binding was found in several regions adjacent to some of the MRI detected malformations in apparently normal cortex. Similar findings were also reported in a study of 11 patients with various types of cortical lesions.[62] However, neither of these studies included correlations with intracranial EEG data. In a study of 17 patients with a lesion and intractable epilepsy undergoing resection, we found that the FMZ-PET abnormality (decreased binding) was significantly larger than the structural lesion, but smaller than the FDG PET hypometabolic area, which tended to be very large surrounding the lesion particularly in patients with a long history of epilepsy.[6] The extent of the perilesional FMZ PET abnormality showed an excellent correspondence with spiking cortex determined with intracranial electrodes (Figure 89.8). Resection of this zone of decreased FMZ binding in addition to the lesion itself resulted in a seizure-free outcome in 16 of the 17 patients. Thus, FMZ-PET may be a useful guide to the neurosurgeon during the surgical planning of lesional epilepsy surgery.

Secondary epileptic foci

One of the most challenging aspects in surgery for neocortical epilepsy is that the 'epileptogenic region' may include not only a focus of seizure onset, but also altered cortical regions, which are potentially epileptogenic, along the path or network of seizure propagation. These 'secondary' foci may be 'dependent' upon the primary focus, in which case they tend to disappear after removal of the primary focus, or they may be 'independent', in which case they may emerge as a new epileptic focus and, therefore, it is important to identify these 'epileptic networks'.[63,64] Patients with a prolonged history of seizures prior to epilepsy surgery have a poorer seizure outcome following resection of the primary focus when compared to individuals with a shorter history of seizures, suggesting that secondary epileptogenesis at sites located elsewhere in the brain may develop with persistence of uncontrolled seizures (e.g., Eliashiv *et al.*).[65] Secondary epileptic foci are defined as a 'trans-synaptic and long-lasting alterations in nerve cell behavior characterized by paroxysmal electrographic manifestations and clinical seizures' induced by seizures from a primary epileptic focus.[66,67]

Morrell[67] has described three stages in the formation of secondary epileptic foci. In the first stage, epileptiform activity in the new region is dependent on a trigger from the primary focus. In the next stage, epileptiform activity occurs spontaneously in the new focus, but removal of the primary focus results in a cessation of activity from the secondary focus with time. In the third stage, the epileptiform activity in the secondary focus is irreversible ('independent' secondary focus). This model is

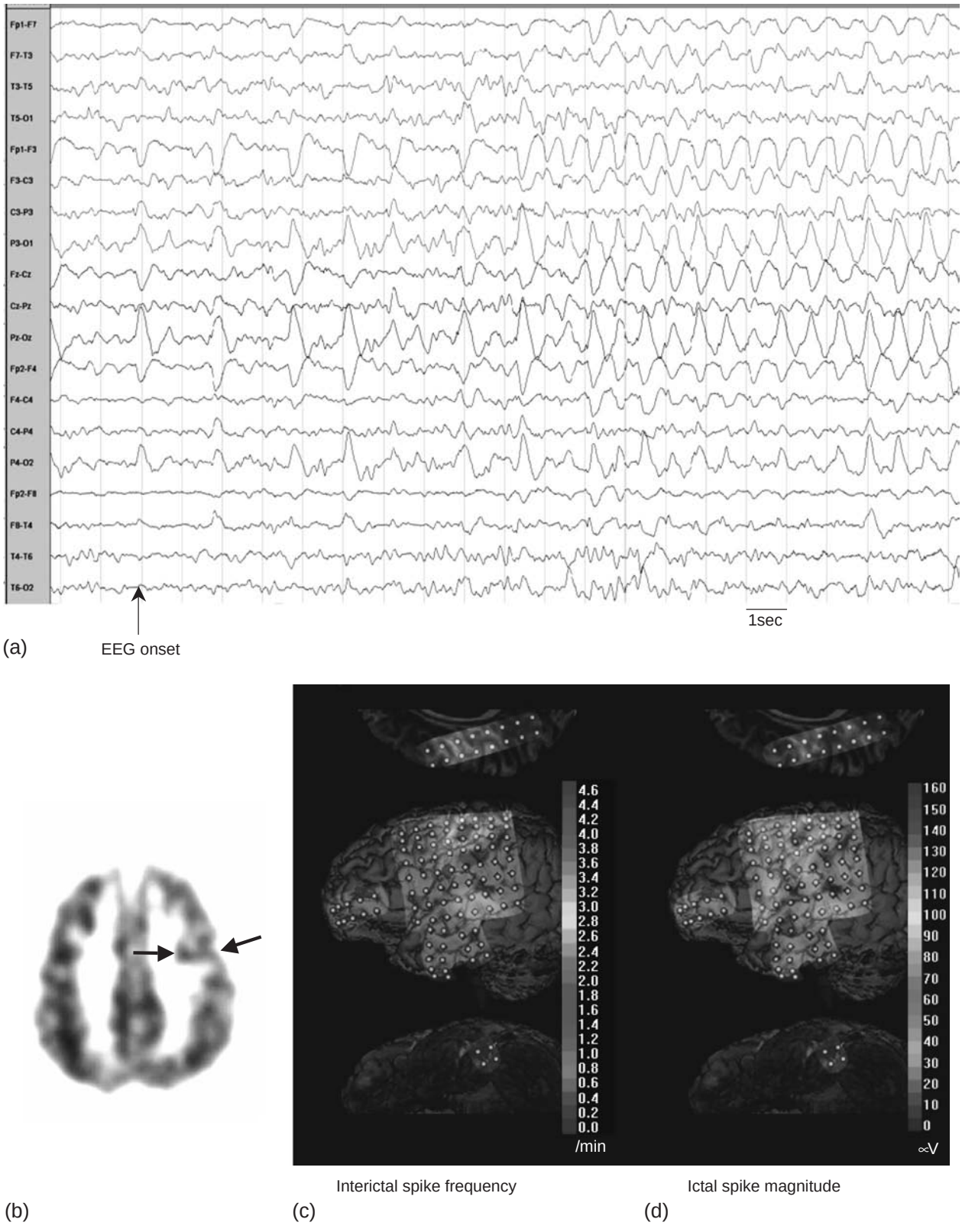

Figure 89.6 A 3-year-old girl with nonlesional neocortical epilepsy. (a) Ictal scalp-EEG on a bipolar montage showed a widespread periodic slow wave activity with frontal-central dominance, which was followed by a widespread continuous rhythmic slow-wave activity with higher amplitude in the left frontal-central region. Ictal EEG was diagnostic of focal seizures, but the exact location of epileptogenic zone was difficult to estimate solely based on scalp-EEG. (b) Decreased FMZ binding was seen in the left frontal region just anterior to the left precentral gyrus. (c) Quantitative interictal subdural EEG analysis[58] revealed that the frequency of interictal spike activity was highest in the left frontal region showing decreased FMZ binding. (d) Quantitative ictal subdural EEG analysis[59] revealed that the magnitude of ictal repetitive spike activity was highest again in the left frontal region showing decreased FMZ binding. The patient has been seizure free for 20 months since neocortical resection involving this region. (See Color plates.)

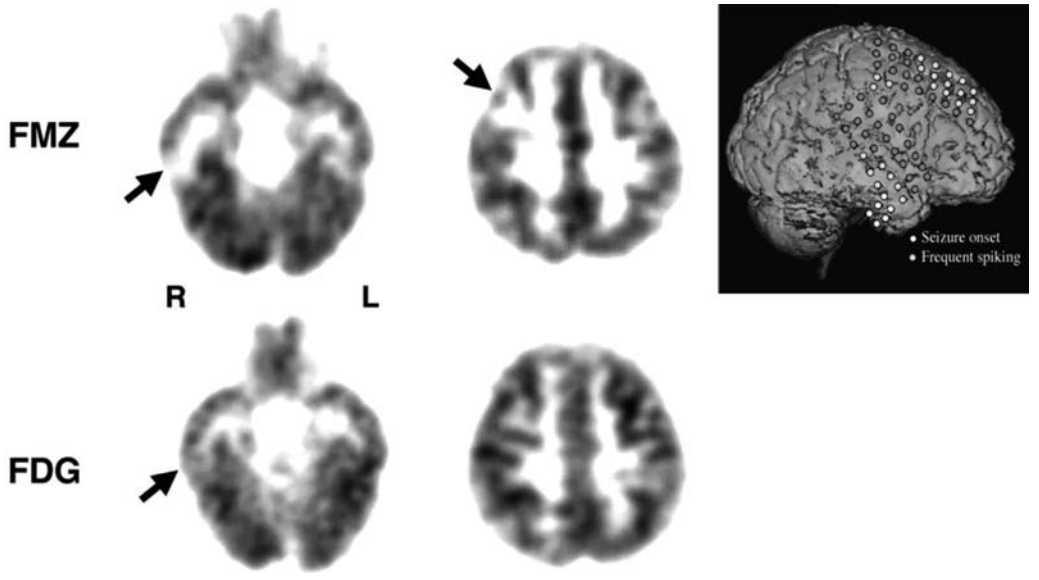

Figure 89.7 Flumazenil (FMZ) PET scan in a 7-year-old girl with neocortical epilepsy. MRI was normal. Decreased FMZ binding was seen in the right inferior temporal cortex, which showed seizure onset on subdural EEG; see electrode locations vs. PET abnormalities in red on 3D brain surface. An additional area of decreased FMZ binding was seen in the right frontal cortex, which showed independent interictal spiking on EEG (see again 3D surface). This latter area was not clearly abnormal on FDG-PET. (See Color plates.)

consistent with FMZ-PET data from Savic *et al.*[68] that some of the FMZ abnormalities outside the primary focus are *reversible* following surgical removal of the primary focus.

We have previously reported that FMZ-PET may detect cortical areas of decreased binding 'remote' from the presumed primary epileptogenic region as indicated by scalp EEG and seizure semiology; we believe that these 'remote' cortical areas represent secondary epileptic foci.[6] Unfortunately, it is not uncommon for secondary epileptic foci to remain quiescent on scalp and intracranial EEG during preoperative evaluation and to become manifest only after surgery to remove the primary focus has been performed. We made the observation that FMZ-PET identifies both primary and additional remote epileptic foci (i.e., secondary epileptic foci) in children with nonlesional epilepsy (Figure 89.9). Although we had reported similar results in patients with MRI lesions, our most recent analysis[57] considered only patients with nonlesional epilepsy in order to avoid the confounding effects of lesions on data interpretation. Of the 25 children (mean age 7.5 years) with normal MRI scans included in this study, cortical regions showing decreased FMZ binding were observed in the seizure onset area (determined by scalp EEG ictal localization and seizure semiology) in 18 children (72%). Of these 18 children, 13 showed *additional* cortical areas of decreased FMZ binding in remote

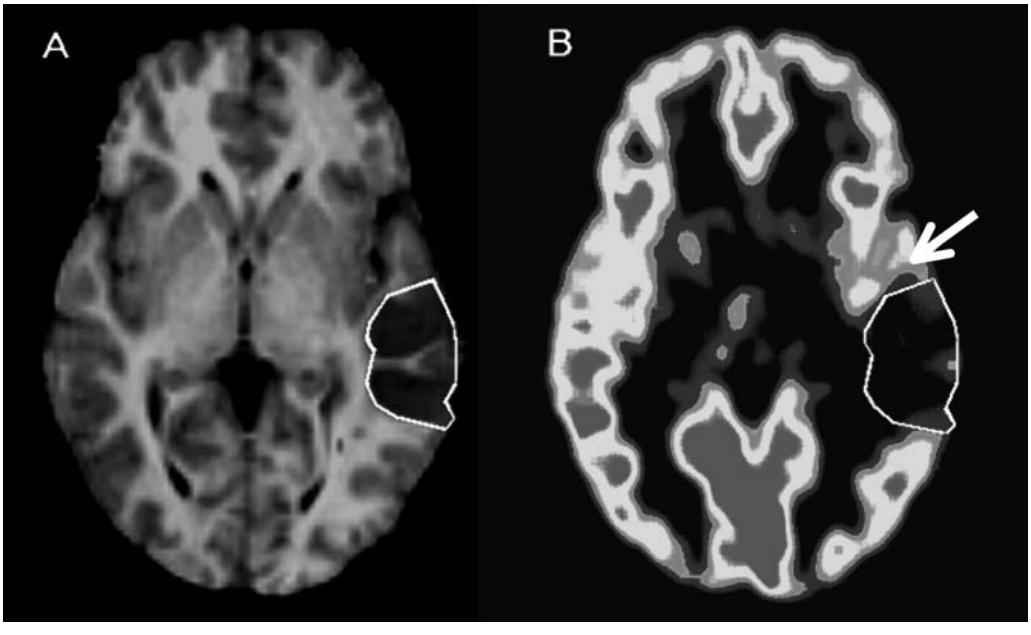

Figure 89.8 Flumazenil (FMZ) PET detects perilesional epileptic cortex. This patient had left temporal lobe seizures and a low-grade tumor (dysembryoplastic neuroepithelial tumor). The tumor mass itself did not show any FMZ binding, but decreased binding was seen in the peritumoral cortex (arrow), which showed frequent interictal spiking on intracranial EEG (reproduced from Juhasz *et al.*, 2000). (See Color plates.)

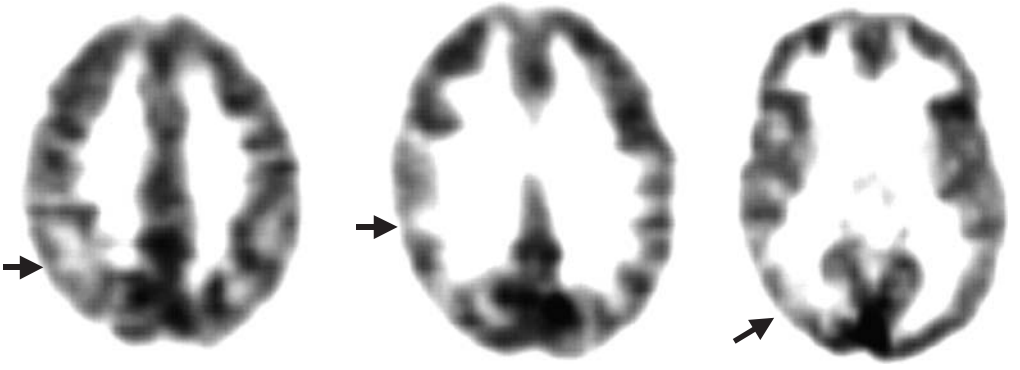

Figure 89.9 Multifocal decreases of cortical flumazenil (FMZ) binding (arrows) in the epileptic right hemisphere of a 14-year-old boy with daily complex partial seizures. Decreased FMZ binding in the right parietal cortex indicated the area of seizure onset (as shown by intracranial EEG), while rapid seizure spread occurred in the posterior temporal as well as central regions.

locations from the primary seizure onset region, and most of these remote areas (89%) were involved in rapid seizure propagation or showed frequent independent interictal spiking on subdural EEG recordings. Patients with complete removal of both perifocal and remote cortex showing decreased FMZ binding became seizure-free, and pathological examination of the resected tissue from remote sites typically showed gliosis. The concept that PET imaging with FMZ might identify secondary epileptic foci is novel and may play an important role in the future of epilepsy surgery evaluation.

α-[^{11}C]Methyl-L-tryptophan PET

The PET tracer α-[^{11}C]methyl-L-tryptophan (AMT) was originally developed for the *in vivo* measurement of the rate of serotonin synthesis,[69,70] but it now appears that what is actually measured is an 'index' of serotonin synthesis rather than the absolute rate; we have referred to this index as the 'serotonin synthesis capacity,[71,72] for an editorial discussion see Chugani and Muzik.[73] Our choice of the tracer AMT in studying epilepsy in children was based on several lines of evidence which implicated serotonergic mechanisms as playing a role in epileptogenesis.[74–80]

AMT PET in tuberous sclerosis complex (TSC)

Because AMT accumulates in the vicinity of the seizure focus, PET scanning of this radiotracer reveals an increased signal in the interictal state, as compared to FDG and FMZ which both reveal decreased uptake. This feature of AMT makes it an ideal PET tracer in patients with multiple lesions, not all of which are epileptogenic. Indeed, AMT-PET is able to differentiate between epileptogenic and nonepileptogenic tubers in patients with tuberous sclerosis complex (TSC): epileptogenic tubers show increased AMT uptake interictally whereas nonepileptogenic tubers show decreased uptake[12] (Figure 89.10).

The AMT PET method was used in the preoperative evaluation of 17 children (mean age: 4.7 years) with TSC and intractable epilepsy.[82] Fourteen of the 17 children had long-term intracranial EEG monitoring. Increased AMT uptake was found in 30 tubers of 16 patients and 23 of these tubers (77%) were located in epileptic foci as defined by intracranial EEG. In three of the 17 children, a 'palliative' surgery was performed because an optimal resection would have resulted in unacceptable consequences such as hemiplegia. Of the remaining 14 patients, 12 became seizure free. There was an excellent correlation between resection of tubers showing increased AMT uptake and good outcome;[82] see also editorial by Roach.[83] AMT-PET is particularly useful in localizing epileptogenic tubers that are close to the midline and EEG lateralization is difficult. Although clearly an advance in seizure focus localization in patients with TSC, cortical areas of increased AMT uptake are seen in only about 2/3 of subjects. The remaining patients, while their seizures are poorly controlled with medications, fail to show any areas of increased AMT uptake. It is not clear why this is the case and whether there are differences between TSC1 and TSC2 patients in this regard.

AMT PET in non-TSC subjects

Increased AMT uptake in epileptic tissue is not limited to patients with TSC, but may also be seen in other patients with epilepsy. Indeed, we recently reported increased uptake of AMT near the epileptic focus in approximately half of non-TSC patients with neocortical epilepsy[14] (Figure 89.11). Similar results had been reported in a study of 18 patients with cortical dysplasia ($n = 7$) or normal MRI and FDG PET ($n = 11$).[84] In that study, increased AMT uptake was found in seven patients (4/7 (57%) with cortical dysplasia and 3/11 (27%) of patients with normal MRI).

Kynurenine pathway of tryptophan metabolism

Analysis of resected brain tissue showing increased AMT uptake revealed *normal* serotonin levels but evidence of increased tryptophan metabolism along the kynurenine pathway. It appears that in addition to being converted into serotonin or incorporated into protein, tryptophan may, under some circumstances (e.g., ischemia, immune activation, epilepsy), be metabolized by tryptophan 2,3-dioxygenase[85] and indoleamine 2,3-dioxygenase[86] via the kynurenine pathway in the brain. Several metabolites of the kynurenine pathway, quinolinic acid, kynurenine and 3-hydroxykynurenine are convulsants through their action as agonists at N-methyl-D-aspartate (NMDA) receptors.[87–91] While quinolinic acid concentrations were not increased in the seizure focus as

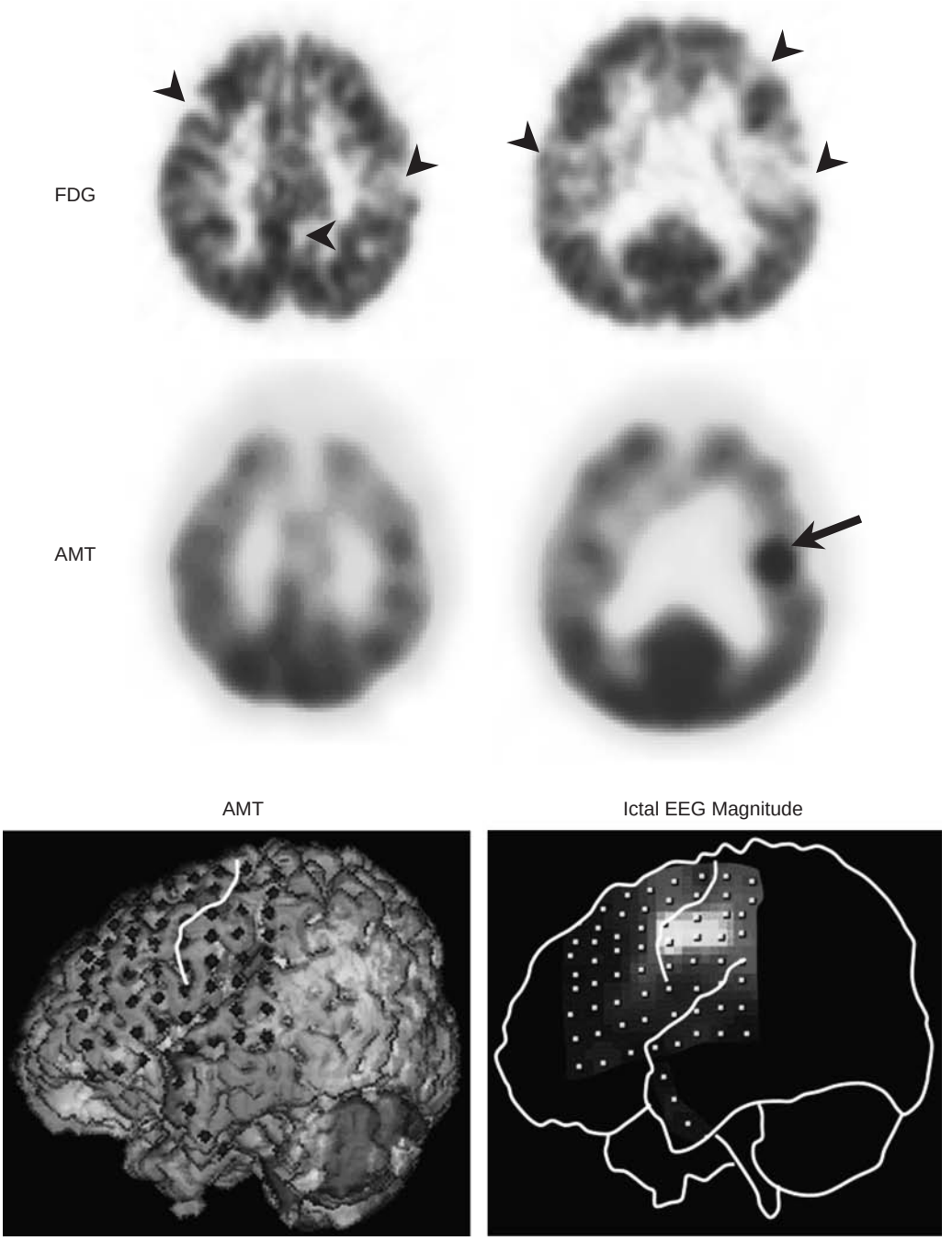

Figure 89.10 A 1-year-old boy with uncontrolled neocortical epilepsy associated with tuberous sclerosis complex. (A) FDG and alpha-[^{11}C]methyl-L-tryptophan (AMT) PET images are shown. Multiple tubers in both hemispheres were associated with decreased glucose metabolism (arrowheads) on FDG-PET, without indicating the epileptogenic tuber. In contrast, AMT-PET showed increased uptake in a single tuber (arrow) located in the left central region. (B) Increased AMT uptake (coded with red) was localized in the left inferior parietal region on a 3D-reconstructed MRI. (C) Quantitative ictal subdural EEG analysis[81] revealed that the magnitude of ictal rhythmic activity was highest in the superior margin of the cortical tuber showed increased AMT uptake. Neocortical resection involving this epileptogenic tuber resulted in a seizure-free outcome (follow-up period: 5 months).[82] (See Color plates.)

compared to nonfocus brain regions from adults undergoing surgery for temporal lobe epilepsy,[91] brain tissue showing increased AMT uptake on PET did indeed show much higher levels of quinolinic acid compared to adjacent brain tissue and tubers which do not show increased AMT uptake.[92] These findings suggest that, in at least some cases of epilepsy, including the epilepsy seen in TSC, the mechanism of epileptogenesis may involve activation of the kynurenine pathway leading to the production of endogenous convulsants.

Reoperation for failed epilepsy surgery

As alluded to above, the success rates (seizure freedom) in neocortical epilepsy surgery have not changed appreciably in the past several decades and remain in the 50–60%.[32,33] Some of these patients will be candidates for a second epilepsy surgery evaluation, since it is well documented that reoperation can achieve seizure control in a significant

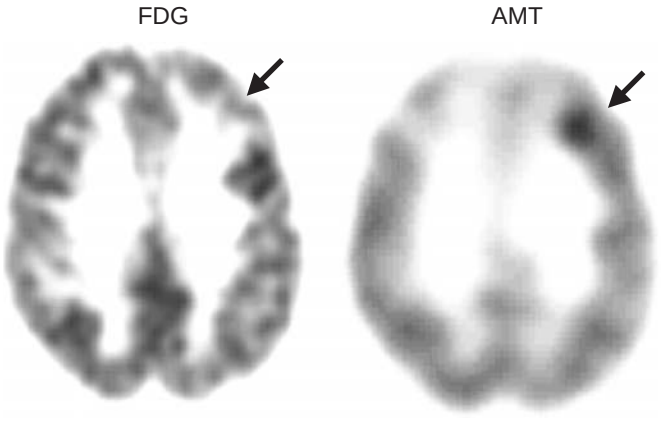

Figure 89.11 Increased uptake of alpha-[^{11}C]methyl-L-tryptophan (AMT) in an epileptogenic region of frontal cortex (as verified by subsequent intracranial EEG) in a patient with normal MRI. FDG-PET showed only a mild decrease of glucose metabolism in this region.

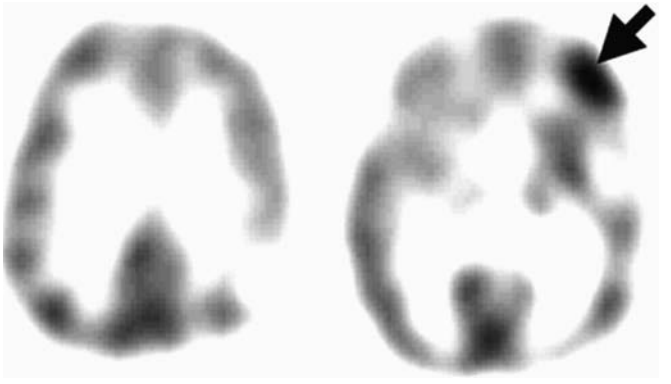

Figure 89.12 Detection of nonresected epileptic cortex by alpha-[^{11}C]methyl-L-tryptophan (AMT) PET. Increased AMT uptake was seen in the left frontal cortex (arrow) of a 10-year-old boy with a previous left parietal cortical resection. MRI was normal before surgery. Postoperative EEG monitoring suggested left inferior frontal seizure onset, consistent with the AMT-PET finding.

number of cases.[93,94] Yet, there have been remarkably few neuroimaging studies aimed at the localization of residual epileptogenic cortex. With the more widely used PET tracers FDG and FMZ, one typically looks for decreased glucose metabolism or $GABA_A$ receptor binding (i.e., a 'negative' signal) in epilepsy surgery evaluation, but both of these PET tracers are of little use in the setting of reoperation evaluation because the initial resection results in diaschisis or tissue damage which also appear as areas of decreased uptake. Ideally, a PET tracer which gives a 'positive' signal interictally (i.e., increased uptake) in epileptogenic cortex would be preferable in order to avoid the confounding effects of prior resection.

Juhasz *et al.*[95] used AMT-PET in 33 patients (mean age: 10.8 years; age range 3–26 years) who continued to have seizures following a neocortical resection. They reported that 10 (43%) of 23 patients scanned greater than 2 months, but less than 2.3 years of the failed resection manifested increased AMT uptake (Figure 89.12). These areas of increased uptake showed excellent concordance with the area of seizure onset on ictal EEG. Seven patients with localizing AMT-PET scans underwent a second resection and five became seizure free, while the remaining two showed considerable decrease in seizure frequency. Interestingly, if the AMT-PET scan was performed within 2 months of resection, a diffusely increased hemispheric uptake was found, presumably resulting from inflammatory changes.[95] While the sensitivity of AMT-PET in detecting residual epileptogenic cortex may not be great, the technique is useful in a considerable number of subjects undergoing reoperation and sets the stage for further research in this group of patients.

Other PET tracers for neocortical epilepsy

While FDG, FMZ and AMT have been the most widely used tracers for PET scanning in epilepsy surgery evaluation, a number of other tracers have also been studied and may have potential use for localization of neocortical epileptic foci.

[^{11}C]carfentanil

One of the first receptor ligands used in epilepsy was [^{11}C]carfentanil, which labels mu-opiate receptors.[15,96] The rationale for studying opiate receptors with PET is based on observations that recurrent seizures induce changes in the expression of opioid peptides and receptors[97] and that endogeneous opioid release play a role in termination of seizures in animal models of epilepsy.[98] Initial studies using [^{11}C]carfentanil PET reported *increased* interictal binding in temporal neocortex ipsilateral to the seizure focus in patients with temporal lobe epilepsy.[15,96] Interestingly, PET studies using the delta-receptor-selective antagonist [^{11}C]methylnaltrindole showed a different regional pattern of increased binding as compared to [^{11}C]carfentanil.[99] In contrast, there was a lack of overall asymmetry in studies using the ligand [^{18}F]cyclofoxy, which binds to both mu and kappa opioid receptors.[100] Together, these studies suggest a differential regulation of opiate subtypes in epilepsy, with greater involvement of mu and delta receptors. Although of potential clinical value, these PET tracers have not been validated for localization of epileptogenic zones in neocortical epilepsy.

[^{11}C]doxepin

Doxepin is an antidepressant medication with a high affinity for histamine H_1 receptors. Since histamine mechanisms in the brain are involved in termination of seizures, [^{11}C]doxepin PET was performed in order to study seizure mechanisms and provide localization data of epileptic foci. Indeed, patients with neocortical epilepsy showed areas of *increased* cortical binding where FDG PET showed decreased glucose metabolism.[16] Again, this PET ligand has not been adequately studied in relation to intracranial EEG data to determine its role in the evaluation for epilepsy surgery.

Conclusion

We have seen, in this chapter, how functional neuroimaging with PET continues to evolve as an important tool in the

diagnosis, monitoring, and eventual treatment of patients with neocortical epilepsy. In some cases, such as infantile spasms, PET findings have led directly to new treatment options previously not considered. In most cases, anatomic and functional neuroimaging, together with interictal and ictal EEG, provide complementary data and should be carefully used together for optimum management. Studies over the past few years have provided several examples of how application of new PET tracers (e.g., those for imaging benzodiazepine receptors or tryptophan meabolism) have led to more specific localization of epileptogenic brain regions. The synthesis of even newer PET tracers designed to evaluate various biochemical processes in the brain is proceeding at a rapid pace. These tracers will be applied in neocortical epilepsy to yield a wealth of new and specific information related to pathophysiology and therapeutic guidance.

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90 Pre-surgical neuropsychological workup: risk factors for post-surgical deficits

RM Busch and RI Naugle

Introduction

A comprehensive pre-surgical evaluation is essential to lateralize and localize the seizure onset zone and to determine whether the epileptogenic region can be safely resected without significant neurological or neuropsychological deficits.[1] Neuropsychological examinations have long been an integral part of pre-surgical epilepsy evaluations. The assessment of pre-surgical cognitive functioning can provide supplemental information about seizure lateralization and localization and help to identify patients who are at risk of cognitive decline following surgical treatment for intractable focal epilepsy. The purpose of this chapter is to discuss the factors that are related to cognitive outcome in adults following epilepsy surgery and to summarize existing literature on multivariate prediction of post-operative cognitive risk.

Pre-surgical neuropsychological patterns in epilepsy

Frontal lobe epilepsy

Frontal lobe epilepsy is the second most prevalent type of seizure disorder in adults. Studies have demonstrated that, when compared with patients with temporal lobe epilepsy, patients with frontal lobe epilepsy tend to perform more poorly on measures of attention, visuomotor and visuoperceptual speed, motor coordination, fluency, concept formation, planning, response inhibition, and language. However, these cognitive tasks have generally been unsuccessful in assisting with lateralization or localization of seizures within the frontal lobe. Motor impairment appears to be the most reliable method for assisting with lateralization and localization in patients with frontal lobe epilepsy.[2–5]

Although there has not been a great deal of research examining post-operative risk in this population, Helmstaedter and colleagues[3] found that frontal lobectomy patients demonstrated improvements in short-term memory when their seizures were successfully controlled. Examination of site of surgery revealed that patients with resections in the premotor/SMA or precentral/central area were at highest risk for cognitive declines following surgery, often demonstrating significant psychomotor slowing, initiation problems, and language difficulties (i.e., speech arrest or transcortical aphasia following dominant SMA resection). It has also been reported that, similar to findings in patients with temporal lobe epilepsy, cognitive outcome following frontal lobectomy is inversely related to pre-operative cognitive ability.[3]

Parietal and occipital lobe epilepsies

Because these types of focal epilepsies are relatively rare, descriptions of the neuropsychological characteristics of seizures originating from the parietal and occipital lobes have been based on rather small numbers of patients. Although the neuropsychological profiles of patients with parietal lobe epilepsy are variable depending upon seizure lateralization and localization, age of seizure onset, and age at first risk, parietal lesions have been associated with visual agnosia, hemineglect, apraxia, and visoperceptual/constructional difficulties.[6] Research on patients with occipital lobe epilepsy has failed to find any unique neuropsychological profile in comparison to other focal epilepsies.[7]

Temporal lobe epilepsy

Temporal lobe epilepsy is the most prevalent type of seizure disorder in adults, comprising approximately two-thirds of all surgical epilepsy procedures.[8] Patients with temporal lobe epilepsy often show deficits on neuropsychological measures of memory, particularly if the seizures are arising from the dominant temporal lobe. In individuals with typical language dominance, lesion studies have demonstrated the importance of right and left temporomesial structures for visuospatial and verbal memory, respectively.[9] Over the years, a large number of studies have investigated material-specific memory performance in patients with temporal lobe epilepsy. Patients with dominant temporal lobe epilepsy typically display deficits in verbal memory, whereas those with epilepsy arising from the nondominant temporal lobe show deficits in visuospatial memory, albeit less frequently.[9–13] In addition to memory dysfunction, patients with mesial temporal lobe epilepsy in the language dominant hemisphere often demonstrate confrontation naming problems, marked by word-finding difficulties.[6,14,15]

Risk factors for post-surgical decline

Given the high prevalence of temporal lobe epilepsy and the relative paucity of information pertaining to post-operative outcome following other focal surgeries, the remainder of this chapter will focus almost exclusively on findings pertaining to adults after temporal lobe resections. In light of the functional role of the temporal lobes in memory and language, most studies have focused on post-operative risk for decline in these two cognitive functions. Because memory decline is the most frequently observed deficit following temporal lobe surgery, the vast majority of these studies have sought to identify factors related to decline in memory.

Memory

Case studies published in the 1950s underscored the essential role of the mesial temporal lobe memory system, which consists of the hippocampal formation and adjacent parahippocampal region, in memory for new information.[16] Since that time, epilepsy researchers have sought to determine which patients are at greatest risk for memory decline following temporal lobectomy. Over the years, a number of predictors of post-operative memory decline have been identified.

Side of surgery

The dominant hemisphere of the brain has been associated with verbal cognitive functions while the nondominant hemisphere has been associated with nonverbal cognitive functions, although the former relationship is observed more consistently.[9,17,18] It is unclear why the relationship between nonverbal cognitive functions and the nondominant hemisphere is not always observed. Researchers have speculated that visuospatial memory functions may be less well localized/lateralized than verbal memory functions allowing the brain to more easily compensate following right temporal damage.[19–24] It may also be the case that the measures used to assess nonverbal memory functions are not as sensitive as those used to measure verbal memory. Nevertheless, neuropsychological tests are best at determining seizure laterality when dissociations are observed between performance on verbal and visuospatial measures.[25]

Material-specific memory deficits are readily observed in patients who have undergone temporal resections. The relationship between left temporal lobectomy and verbal memory deficits is a rather reliable finding across studies[26–30] whereas the relationship between right temporal lobectomy and nonverbal memory deficits has been less robust.[11,26,29–38]

Pre-surgical memory performance

Several studies have reported improvements in memory functioning following temporal lobe surgery, particularly with dominant temporal resections that resulted in seizure freedom.[36,39] Findings such as these led to the development of the *functional reserve* model, which posits that post-operative memory decline is largely a function of the capacity of the contralateral mesial temporal structures to support memory following resection of the ipsilateral structures.[21–24] However, more recent studies have demonstrated that persons with higher pre-operative performance on memory measures (average or above) are generally at greater risk for post-operative memory decline following temporal lobectomy than those with lower pre-operative memory scores.[8,40–44] This finding is most frequently observed following dominant temporal lobectomies, with observable declines in verbal memory among an estimated 10–60% of patients undergoing dominant temporal resections.[30,41,45] These studies support a *functional adequacy* model, suggesting that post-operative memory decline is inversely related to the functional adequacy of the resected tissue.[42] The majority of functional and structural studies to date provide support for the *functional adequacy* model.[41,42,45–47]

Language

In addition to memory dysfunction, patients with mesial temporal lobe epilepsy in the language dominant hemisphere often demonstrate confrontation naming problems, marked by word-finding difficulties.[6,14,15] Patients who undergo dominant temporal resections often show acute post-operative naming difficulties,[48,49] although this finding has not been universal.[50,51] An estimated 30–38% of patients who undergo dominant temporal resections show declines on confrontation naming measures, such as the Boston Naming Test or the Visual Naming Test from the Multilingual Aphasia Examination.[51,52] Similar to the findings with memory, patients with higher pre-operative scores on language measures appear to be at greater risk for post-operative decline in language functioning.[41]

Other important predictors to consider

Pre-operative evaluation findings

In addition to pre-operative neuropsychological test results, other data obtained during pre-operative investigations have been associated with cognitive outcome following temporal lobectomy including MRI and functional MRI (fMRI) findings, EEG results, intracarotid amobarbital procedure performance, event related potentials, and intraoperative mapping results. The extent of surgical resection has also been demonstrated to be related to post-operative cognitive outcome. These topics are addressed here only briefly. Interested readers are encouraged to review other chapters of this volume that address these topics in greater detail (MRI – Chapter 82; fMRI – Chapter 75; IAP – Chapter 93; event related potentials – Chapter 94; intraoperative mapping – Chapter 115; and surgical resection – Chapter 116).

MRI/pathology findings

Mesial temporal sclerosis (MTS), characterized by neuronal loss and gliosis in mesial temporal structures, is found in approximately 80% of patients with temporal lobe epilepsy.[47,53] MTS is often visualized as volume loss and signal change on MRI. The degree of MTS visualized on pre-operative MRI and the severity of MTS apparent on pathological investigation of the resected tissue have been shown to be inversely related to post-surgical memory decline. In other words, temporal lobe epilepsy patients without MTS are at greater risk for memory decline following surgery than those with MTS.[47,54–58]

Several recent studies have compared outcomes in patients with MTS and those with other pathologies. Findings suggest that patients with temporal lobe epilepsy and associated MTS demonstrate poorer memory performance both pre- and post-surgically than patients with other pathologies including tumor, DNET, cortical dysplasia, and vascular factors.[59–61] Furthermore, patients with MTS demonstrate more limited post-surgical memory declines following temporal lobectomy than patients with other pathologies.[61–63] Patients without MTS appear to be at increased risk for post-operative decline in naming ability[64,65] as well as memory. Many of these studies, particularly those involving children, have been conducted with small sample sizes. Nevertheless, it is promising that most of the studies that have been conducted to date have reported similar results.

Functional MRI

In recent years, fMRI studies have been conducted to determine their usefulness in the lateralization and localization of seizure onset as well as the lateralization of language and memory functions.[66–70] These studies have demonstrated that fMRI is useful in demonstrating hemispheric dominance for language.[71,72] More recently, studies have reported a significant relationship between pre-operative hemispheric asymmetry on fMRI during memory tasks and post-operative memory change. Patients with greater pre-surgical activation in the ipsilateral side showed declines in memory post-surgically, whereas those with greater contralateral activation showed memory improvements.[73–76] Functional MRI has also shown to be useful in predicting naming declines following left temporal lobectomy and to be even more predictive than pre-operative naming ability in the course of neuropsychological testing.[77] Specifically, research has demonstrated that patients whose fMRI results suggested greater language lateralization to the left hemisphere show greater declines in memory following left anterior temporal lobectomy than those whose fMRI results suggested language lateralization toward the right hemisphere.[77]

PET

Studies on F-fluorodeoxyglucose-positron emission tomography (FDG-PET) have reported that patients with no or limited PET asymmetries in temporal lobe metabolism are at greater risk for a decline in verbal memory following dominant temporal resections than those with notable asymmetries. This relationship has not been observed in patients following nondominant temporal resections, however.[24]

EEG

Neuropsychological deficits have been shown to be related to the level of EEG abnormality. Specifically, patients with generalized discharges tend to perform more poorly on neuropsychological measures than patients with focal discharges or no discharges at all.[78] Furthermore, patients with more frequent epileptic discharges demonstrate greater neuropsychological deficits than patients with fewer epileptic discharges.[78]

Intracarotid amobarbital procedure

Similar to neuropsychological findings prior to and following temporal lobectomy, lesions of the left temporal lobe often result in impaired verbal memory on IAP testing and right temporal lesions often result in nonverbal memory difficulties.[79,80] Many studies over the years have investigated the intracarotid amobarbital procedure (IAP) as a predictor of post-operative outcome in patients with epilepsy. In general, IAP results have been most predictive of verbal memory changes in patients with dominant temporal lobe epilepsy, but have not fared as well as a predictor of nonverbal memory changes after nondominant resections.[46,81] Three scores derived from IAP testing have been demonstrated to predict post-operative memory change. Several studies have reported that memory performance after ipsilateral injection (indicating memory ability associated with the structures to be spared) is a significant predictor of post-operative memory outcome.[23,81] Memory performance after contralateral injection (indicating memory ability associated with the structures to be resected) has also been demonstrated to be a significant predictor of post-operative memory impairment following temporal resection.[45,46] Finally, a number of studies have suggested that IAP discrepancy, or asymmetry, scores between performance after ipsilateral and contralateral injections are useful in predicting memory impairments following temporal lobectomy.[82] IAP asymmetries have also been shown to be useful in predicting naming declines following left temporal lobectomy, with patients showing left language lateralization on IAP demonstrating the greatest naming declines following left temporal lobectomy.[77] It remains unclear as to which of these three IAP indices best predicts post-operative memory decline following temporal resection, largely due to methodological differences among studies.[83] Nevertheless, the patients at greatest risk for post-operative decline based on IAP testing alone are those who have IAP scores demonstrating intact functional adequacy, limited functional reserve, and little discrepancy between contralateral and ipsilateral injection scores.

Event related potentials and intraoperative mapping

Recently, event related potentials have been shown to predict individual post-surgical memory with high precision.[21,84] It has also been reported that decline in verbal memory following dominant temporal resection can be predicted with relatively high accuracy (e.g., 80%) using results from intraoperative mapping of language and memory areas.[28] However, more research is required to determine the reliability and validity of this procedure in the prediction of post-operative cognitive decline.

Extent of surgical resection

Several studies have reported that selective temporal surgeries typically result in fewer memory problems than standard two-thirds temporal lobectomies,[85–88] although this finding has not been universal.[89–92] Furthermore, when studied in conjunction with other predictor variables, research has suggested that the functional adequacy of the tissue to be resected is more strongly related to post-surgical memory outcome than the extent of the resection itself.[42,91]

Demographic and seizure factors

There are a number of demographic and seizure variables that have proven to be very important in the interpretation of pre-operative neuropsychological test results and the prediction of

post-operative cognitive outcome. As such, a brief discussion of these variables is provided.

Age at seizure onset/first risk

Age at seizure onset has proven to be a very powerful predictor of cognitive outcome. Patients with earlier age at seizure onset often demonstrate more significant intellectual and cognitive dysfunction than patients who develop seizures later in life and are less likely to demonstrate significant cognitive declines following epilepsy surgery.[93–99] Studies have shown that age at onset and age at first risk (i.e., age at which the first risk factor for seizures occurred) are useful predictors of memory and language, particularly naming, decline after temporal lobectomy.[100,101] Patients with later age at seizure onset often show greater declines in memory and cognitive functioning following temporal lobectomy, particularly if the dominant temporal lobe is resected.[100–102] However, it should be noted that some researchers have suggested that age at seizure onset may simply reflect the likelihood of the presence of MTS, as MTS is strongly associated with early age at seizure onset.[53]

Duration of epilepsy

It has been suggested that the duration of epilepsy is related to cognitive performance. For example, it has been reported that patients who have had seizures for many years perform more poorly on intelligence tests than patients with shorter epilepsy duration.[10,96,97,103–105] However, this finding has not been universal,[17,94,98] and some have suggested that this relationship may be driven primarily by age at seizure onset rather than duration per se.[98] Alternatively, duration of epilepsy may not show a consistent relationship with cognitive functioning due to the manner in which seizure duration is defined (e.g., confound with seizure frequency).[94,104] For example, some patients may have frequent seizures and others may go years between events. As a result, Farwell *et al.*[104] have suggested that number of years with seizures may be a more appropriate measure than number of years since seizure onset.

Seizure frequency

Seizure frequency has been demonstrated to be related to cognitive test performance. Patients with more frequent seizures have been shown to have decreased scores on cognitive measures.[106–110] This appears to be more apparent in children with uncontrolled seizures than among adults.[111,112] It has been reported that recent seizure activity can affect a patient's profile on neuropsychological testing[113]; however, number of lifetime seizures appears to be more related to cognitive abilities than the recency of seizures (e.g., past month).[94,114] Further, patients with generalized tonic clonic seizures demonstrate more cognitive impairment than patients with partial seizures,[104,105] and a history of status epilepticus is associated with greater cognitive difficulties than observed in patients with frequent generalized seizures.[114]

Age at time of surgery

The risk for poor memory outcome following temporal lobectomy appears to increase with advancing age, at least on some measures of episodic memory.[102,115] There have been several studies that have reported that older individuals are at greater risk for post-operative declines in naming and verbal memory following dominant temporal resection than younger individuals.[50,52]

Drug therapy

There is a rather extensive literature on the cognitive side effects of antiepileptic drugs (AEDs). Although most AEDs have dose-related cognitive side effects,[116] these effects vary substantially with the type and number of medications being used. For example, barbiturates have been demonstrated to have the most adverse cognitive effects, phenytoin has been shown to slow response speed, and Topiramate often affects executive functioning.[117–120] In contrast, carbamazepine appears to have relatively few cognitive side effects.[94] Patients on multiple drug therapies over a number of years are more likely to demonstrate negative cognitive effects; however, it has been noted that all of these factors are likely affected by the severity of the epilepsy.[94]

Sex

Some research has suggested that males with epilepsy are at higher risk for intellectual difficulties than females, particularly with regard to verbal cognitive abilities.[98,121,122] Other studies have demonstrated that verbal memory is more bilaterally represented in women.[123] As a result, women tend to have better post-operative memory outcomes than men.[123,124] However, a subsequent study suggested that women may perform better than men both pre- and post-operatively with no significant interaction between sex and surgery.[125] It has also been reported that atypical language dominance, as determined via IAP, is not more frequently observed in women than men.[126]

Handedness and speech dominance

Studies have found that patients who are left-handed or have atypical language dominance demonstrate greater general cognitive impairments than those who are right-handed and have typical language dominance, particularly with regard to nonverbal functions.[17,98,127,128]

Psychopathology

Several studies have investigated memory performance in patients with temporal lobe epilepsy and comorbid depression, suggesting that patients with increased depressive symptoms demonstrate reduced auditory memory scores as compared to patients with fewer depressive symptoms.[129–131] However, this finding has not been universal.[132,133] This relationship appears to be most evident in patients with left temporal lobe epilepsy.[131,134] In addition to be ing associated with preoperative memory performance, preoperative depression has also been associated with declines in general and verbal memory following left temporal lobe resection.[135] Please refer to Chapter 100 for a more detailed discussion of psychiatric risk factors for post-surgical deficits.

Genetics

Recent studies have suggested that the apolipoprotein (APOE) e4 allele, previously implicated in the memory impairment observed in Alzheimer's disease, may be a risk factor for memory and cognitive impairment in temporal lobe epilepsy as well. The ε4 allele has been associated with reduced word-list learning performance in patients with newly diagnosed

partial epilepsy[136] and well-controlled, nonlesional TLE.[137] In fact, the latter study found that patients with an e4 allele were four times more likely to perform poorly on measures of verbal memory than patients without the allele.[137] A more recent study was conducted at our center with patients who underwent temporal resections for treatment of their seizures. An interaction was observed between e4 status and duration of epilepsy such that ε4-carriers with a long duration of epilepsy demonstrated the poorest memory performance on both verbal and nonverbal measures.[138] Interestingly, this relationship was observed both before and approximately six months after temporal lobectomy with little change in test performance over time.[138]

Multivariate prediction of post-operative cognitive outcome

Although the previously discussed studies provide very important information about individual factors that are related to post-operative cognitive decline, few studies to date have considered these risk factors simultaneously. In an attempt to facilitate the clinical utility of data obtained during pre-surgical epilepsy investigations, in recent years researchers have begun to develop multivariate regression equations that can use data from multiple sources simultaneously to predict post-operative cognitive decline.

Investigations using multivariate prediction

One of the earliest multivariate investigations was conducted by Chelune and colleagues in 1993.[139] They found that memory scores following contralateral IAP injection and baseline memory scores were significant predictors of change in verbal and general memory.

In 1995, Hermann *et al.*[102] examined multiple demographic and seizure variables simultaneously to determine their ability to predict change in verbal memory performance following temporal lobectomy. Later age at seizure onset, older age at time of surgery, and higher pre-operative memory performance were significant predictors of memory decline following left temporal resection. Pre-operative memory performance and chronological age were only significant predictors for change on select memory measures following right temporal lobectomy. Age at seizure onset was not a significant predictor of memory change in the right temporal group.

Davies and colleagues[142] examined the following predictors: age at onset, chronological age, sex, FSIQ, education level, and pre-operative memory scores. They determined that verbal memory decline following anterior temporal lobectomy could best be predicted using a multiple regression equation that included age, FSIQ and pre-operative verbal memory scores.

Helmstaedter and Elger[44] used multiple regression analysis to examine pre-operative memory performance (verbal and visual), extent of temporal resection, seizure outcome following surgery, presence of MTS, onset and duration of epilepsy, seizure type, age at time of surgery, and sex as predictors of verbal memory decline following anterior temporal lobectomy. In patients who underwent left temporal resections, memory decline was associated with high pre-operative memory scores, older chronological age, long duration of epilepsy, extensive resection, pre-operative visual memory deficits, and pre-operative secondarily generalized seizures. For patients who underwent right temporal resections, post-operative verbal memory declines were associated with higher pre-operative verbal memory performance and post-operative seizure outcome. For both surgical groups, pre-operative memory performance was the most significant predictor of post-operative memory decline.

In 1997, Jokeit and colleagues investigated prediction of change in prose recall following left temporal lobectomy. They examined a total of 15 independent variables including sex, age at epilepsy onset, probable age at temporal lobe damage, age at testing, lateralized frequency of sharp waves and slow waves, seizure frequency, left and right hemisphere IAP memory performance for verbal and nonverbal information, and immediate and delayed recall performance of two prose passages. They found that pre-surgical prose recall performance, in conjunction with discriminability score of the right hemisphere from IAP, explained up to 82% of the total variance. Specifically, patients with higher pre-operative memory functioning and impaired performance following left IAP injection were at highest risk for memory loss following left temporal resection.

These authors also investigated an alternative regression model in which age of probable temporal lobe damage (i.e., age at first risk) and age at epilepsy onset were used in place of IAP results. This regression equation was less effective than the first equation, explaining only 71% of the variance. Nevertheless, when age at first risk and age at onset were used in place of IAP results, patients with late age at first risk and early age of epilepsy onset were at highest risk for decline in prose recall following surgery.

Bell and colleagues[23] used a multivariate approach to examine the utility of IAP scores in predicting post-operative memory decline in patients with left temporal lobe epilepsy and left hippocampal sclerosis. They found that three variables, when examined in combination, were predictive of verbal memory decline following left temporal lobectomy: poor IAP recognition score following ipsilateral injection, high pre-operative cognitive ability, and late age at surgery.

Chelune and Najm[141] used a multivariate approach to predict memory decline following temporal lobectomy. They examined eight potential predictor variables: patient age, age of seizure onset, sex, baseline verbal memory scores, percent recall following IAP contralateral and ipsilateral injection, ratio of right to left hippocampal volumes on MRI, and side of surgery. They found that surgery in the dominant hemisphere, absence of ipsilateral MTS, and intact baseline verbal memory performance were all independent predictors of post-operative memory decline. Approximately 42% of the patients in this study demonstrated post-surgical memory declines. Using the three significant predictor variables discussed above, 71% of the patients were accurately classified with regard to absence or presence of memory loss with a sensitivity of 63% and a specificity of 76%. To facilitate clinical utility, the authors provided odds ratios for different combinations of the three unique predictors. They also provided odds for a nonsurgical control group.

In 2003, Stroup and colleagues[45] replicated and extended the findings of Chelune and Najm[141] in a larger sample.

They examined a total of five potential risk factors: dominant temporal resection, MRI findings other than unilateral MTS, intact pre-operative immediate and delayed verbal memory function, and intact IAP memory performance following contralateral injection. All five of these risk factors were found to be independently associated with memory decline following surgery. Side of surgery and MRI findings were the variables most strongly associated with memory change following surgery. Approximately 38% of the patients in this study demonstrated post-surgical memory declines. The combination of these five predictors accurately classified 78% of the patients included in the study with a specificity of 99%.

A recent study investigated the ability of fMRI, in conjunction with several other risk factors, to predict post-operative memory decline. Richardson and colleagues[75] examined three predictor variables: pre-operative verbal memory performance, volume of the dominant hippocampus, and encoding asymmetry evidenced on fMRI. All three of these variables were demonstrated to be independent predictors of post-operative verbal memory decline, with the difference between left and right hippocampal encoding activity providing the strongest independent prediction of decline in verbal memory.

Moderator/mediator variables

The studies presented in this chapter have provided very useful information in determining which patients are at highest risk for declines in cognitive functioning following epilepsy surgery. However, the majority of these studies have not directly examined the potential mediating and/or moderating effects[142] of demographic and seizure variables in the prediction of post-operative cognitive outcome. A moderating variable is a variable (qualitative or quantitative) that affects the direction or strength of the relationship between an independent predictor variable and the dependent variable. Mediator variables, in contrast, account for the relationship between the predictor and criterion variables. In other words, "moderator variables specify when certain effects will hold, mediators speak to how or why such effects occur."[142]

Clearly, many of the studies cited have provided evidence suggesting that the relationship between predictors and post-operative cognitive change is moderated by a number of factors, including side of surgical resection,[26–30] age at seizure onset,[100,143] and pathological findings.[47,54–58] However, few of the studies on post-operative cognitive outcome have directly assessed the moderating effects of these variables and the potential moderating effects of other factors known to be related to cognitive outcome (e.g., duration of epilepsy, seizure frequency, sex) and we are unaware of any studies that have assessed the potential mediating effects of these variables.

Recent studies examining the predictive ability of neuropsychological instruments in determining seizure lateralization have underscored the importance of considering potential mediators/moderator factors. For example, the relationship between confrontation naming measures and side of surgery has been shown to be moderated by intelligence, age at seizure onset, and duration of epilepsy,[144,145] suggesting that pre-surgical confrontation naming performance is best predictive of side of surgery in only a subset of patients. One would expect that similar relationships exist between the various predictor variables discussed in this chapter and cognitive change following epilepsy surgery. Careful consideration should be given to potential mediating and moderating variables in conducting multivariate predictions of post-surgical change. Consideration of such variables can only be expected to improve the predictive power of pre-surgical data in assessing risk for post-surgical cognitive outcome by accounting for more variance in the prediction of post-operative cognitive outcome.

Summary and conclusions

Over the last couple of decades, significant progress has been made in identifying the factors that are related to post-operative cognitive decline following epilepsy surgery. Information gleaned from pre-operative investigations as well as a number of demographic and seizure variables have proven to be rather consistently related to cognitive outcome following temporal lobectomy, particularly in patients who undergo dominant temporal resections. More recently, studies have sought to combine pre-surgical data in multivariate prediction analyses to improve the accuracy of identifying those patients at highest risk for cognitive declines following surgery. Additional studies are needed to determine which combination of pre-surgical and demographic variables result in the most accurate prediction of post-operative cognitive outcome. Consideration and identification of factors that may moderate and/or mediate the relationship between predictor variables and post-surgical cognitive outcome will only serve to improve the predictive ability of our pre-surgical variables in the future.

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91 Pre-surgical psychiatric evaluations: risk factors for post-surgical deficits

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Introduction

Psychiatric comorbidities are a common occurrence in patients with pharmaco-resistant epilepsy who are being evaluated for epilepsy surgery and their prevalence-rates are significantly higher than those of people in the general population.[1–7] Depressive and anxiety disorders are the most commonly diagnosed disorders in adults while Attention Deficit Hyperactivity Disorders (ADHD) take the lead in children. For example, various investigators have reported lifetime prevalence rates of depressive disorders ranging between of 30–55%, while ADHD has been identified in 20–30% of children with epilepsy, particularly those with seizure disorders of temporal and frontal lobe origin.[6,7] Typically these psychiatric disorders are chronic with a waxing and waning severity. The actual prevalence rates of ADHD in adults with partial epilepsy have not been investigated, however; yet, 50–70% of nonepileptic children with ADHD are expected to continue to be symptomatic in adult life.[8] Psychotic disorders are less frequent than the three other types of conditions, their prevalence rates are two- to fourfold higher in patients with epilepsy than in the general population.[9,10]

Post-surgical psychiatric complications have been recognized for the last 40 years, often presenting as *de novo, recurrence* or *worsening* of a previous mood, anxiety and/or psychotic disorder.[11–14] Given all of these facts, it is surprising that most patients being considered for epilepsy surgery do not undergo a pre-surgical psychiatric evaluation. After all, *pre-surgical* comorbid psychiatric disorders have significant impact on epilepsy surgery at several levels; these include: (i) a potential interference with the successful completion of the pre-surgical evaluation, including the ability to make an objective informed decision to proceed with epilepsy surgery; (ii) a potential risk for post-surgical psychiatric complications; (iii) an impact on post-surgical psychosocial adjustment, including the potential to obtain gainful employment; (iv) a potential impact on post-surgical seizure outcome. In this chapter we discuss the reasons behind the need to consider a pre-surgical psychiatric evaluation in every surgical candidate and review its content in the clinical and research domains, so as to identify patients at risk for post-surgical psychiatric complications and to ensure optimal adjustment to a life without seizures. We also discuss the circumstances under which epilepsy surgery should not be considered for patients with comorbid psychiatric disorders. The information presented in this chapter is complemented by that of Chapter 144, where we review the impact of epilepsy surgery on post-surgical psychiatric, psychosocial, and seizure outcome and discusses the disclosures that need to be made to patients and families with respect to potential surgical related psychiatric complications.

Surgical candidates: a population at risk of comorbid psychiatric disorders

Mood disorders

Mood disoiders are the most common psychiatric comorbidities in patients with epilepsy.[15–18] While the higher prevalence rates are typically found among patients with refractory epilepsy (and hence, potential surgical candidates), a recent population-based study has found that almost one in three patients with epilepsy had experienced a major depressive episode in their life.[19] Primary mood disorders comprise an *heterogeneous* group of conditions with respect to their clinical manifestations, course and response to treatment. Mood disorders in epilepsy may be identical to primary mood disorders that meet diagnostic criteria suggested in the Diagnostic and Statistical Manual of Mental Disorders (DSM), be it in its third, third revised, fourth, or fourth text revision (IV-TR).[20] These include major depressive disorders, dysthymia, minor depression, bipolar disorder, and cyclothymia. Yet, a significant percentage of mood disorders fail to meet any of the DSM-IV-TR diagnostic criteria in patients with epilepsy. That is, they present with atypical manifestations. This compounds the heterogeneity of mood disorders alluded to above in these patients.

Major depressive episodes (MDE) are the more severe expression of a mood disorders. Yet, MDE can occur as part of: (i) a major depressive disorder (i.e., multiple MDE); (ii) a bipolar disorder; and (iii) a double depression, in which recurrent MDE are intermixed with dysthymic disorders. Furthermore, establishment of whether an MDE is the first one is of utmost importance as the risk of subsequent MDE is of 50%, of 70% after two and almost 100% after more than two episodes.[20–22] Ten to 15 years after an index MDE, about 80–90% of patients can be expected to have a recurrence. Furthermore, several studies have highlighted the importance of also recognizing subsyndromal forms of depression, as these are associated with a risk of developing a major depressive episode.[22] Furthermore, in the setting of any MDE, clinicians must always look for risk factors of a bipolar disorder (i.e., family history, a MDE before the age of 18, hypomanic symptom triggered by the use of antidepressants) as spontaneous manic and/or hypomanic episodes can occur several years after an initial MDE.

As stated above, atypical mood disorders are relatively frequent in patients with epilepsy. Mendez *et al.*, found that almost 50% of depressive disorders in patients with epilepsy had to be classified as Depressive Disorder Not Otherwise Specified, or Atypical Depression, according to DSM III-R criteria.[23] A review of the psychiatric literature shows that in the early part of the 20th century two German psychiatrists, Kraepelin and Bleuler had recognized a form of depression that was associated with epilepsy.[24,25] Their observations were later on confirmed by Gastaut[26] and Blumer expanded on the work of these three investigators and coined the term of *Interictal Dysphoric Disorder* (IDD) to refer to this type of mood disorder.[27] He confirmed its relatively frequent occurrence in patients with TLE, an observation that has been supported by others and our own data. The predominant clinical manifestations consist of a chronic pleomorphic picture that includes symptoms of depression, anxiety, irritability, somatic symptoms, including pain, and intermixed periods of euphoric mood. It tends to mimic a *dysthymic* disorder, given the milder severity of symptoms and their chronic course with the exception of symptom-free periods that may last several days. Blumer considered that almost one-third to one-half of patients with epilepsy seeking medical care suffer from IDD. Likewise, in a study of 97 patients with epilepsy and depressive symptoms of enough severity to require pharmacologic treatment, we found that 69 patients had a clinical presentation mimicking a dysthymic disorder.[28]

Depressive disorders usually do not occur in isolation, both in patients with and without epilepsy. Rather they tend to occur in association with anxiety disorders. For example, in a study of 174 consecutive outpatients with epilepsy from five epilepsy centers, 73% of patients that met DSM-IV diagnostic criteria for a depressive disorder also met criteria for an anxiety disorder.[29] The comorbid occurrence of anxiety and depressive disorders is of great significance as the latter increases the suicidal risk of depressed patients. This problem is more worrisome in patients with epilepsy, as these are a population with a significantly higher risk of suicidality.[30]

Anxiety disorders

Together with mood disorders, anxiety disorders are the most common psychiatric comorbidity in patients with epilepsy.[31] Population-based studies have estimated the prevalence of anxiety in epilepsy patients to range between 15 and 25%.[32,33] In the study by Jones *et al.* cited above, a DSM-IV diagnosis of a current anxiety disorder was found in 30% of patients.[29] As in the case of mood disorders, the higher prevalence rates of anxiety disorders are more often identified in pharmaco-resistant patients.

The DSM-IV-TR has included 11 types of anxiety disorders.[34] Generalized anxiety disorder, panic disorder, phobias, agoraphobia without panic disorder, and obsessive compulsive disorder are the most frequently identified in patients with epilepsy and as stated above, often as comorbidities of a mood disorder. In addition, patients with epilepsy may often exhibit episodes of anxiety that fail to meet any DSM diagnostic criteria.

Attention deficit hyperactivity disorders and behavioral disturbances

As in the case of depression and anxiety disorders, ADHD and behavioral disturbances are significantly more common among children with epilepsy than in the general population.[1,6,7] Furthermore, in a population-based study done in the Isle of Wight in Great Britain, Rutter and collaborators found behavioral disorders in 28.6% of children with uncomplicated seizures, and 58.3% of children with both seizures and additional central nervous system pathology.[35] In a separate population-based study of children with seizures, cardiac disorders, and controls, McDermott and collaborators found that children with epilepsy had more behavioral problems than either the children with cardiac disease or the controls, who presented with higher rates of hyperactive behavior (28.1% vs 12.6% in cardiac children and 4.9% in controls), headstrong or oppositional behavior (28.1% vs 18.3% of cardiac children and 8.6% of controls), and antisocial behavior (18.2% vs 11.6% of cardiac children and 8.8% of controls).[36] Children with seizure disorders of temporal and frontal lobe origin are at special risk of this disorder, and particularly those with poorly controlled seizures. Hence, potential surgical candidates! As stated above, the prevalence rate of ADHD in adults with epilepsy is yet to be established.

Psychotic disorders

These are the less frequent than mood, anxiety, and ADHD, but their prevalence rates are still significantly higher than those of the general population.[9,10] Psychotic disorders are divided into interictal, ictal, and postictal psychotic episodes (PIPE). Consideration of epilepsy surgery in patients with comorbid psychotic disorders has been the source of great controversy among epilepsy centers. In a large number of programs, the presence of a psychotic disorder constitutes a criterion for exclusion from pre-surgical evaluation; other centers, on the other hand do not ruleout a surgical option, as long as the patient is able to cooperate with the pre-surgical evaluation and understands the risks of the surgical procedure and the benefits and limitations of this type of treatment.

Interictal psychotic disorders can be indistinguishable from primary schizophreniform disorders and present with delusions, hallucinations, referential thinking, and thought disorders. However, in a significant proportion of patients with epilepsy, interictal psychosis differs from that of patients with primary schizophreniform disorders. Slater coined the term of interictal psychosis of epilepsy (IPOE) to describe certain clinical characteristics, particularly, psychotic episodes seen interictally in patients with chronic epilepsy which are remarkable for *the absence* of negative symptoms, better premorbid history, and less common deterioration of the patients' personality.[37] This form of psychosis is less severe and more responsive to therapy. The 'more benign' clinical manifestations and course of IPOE acquires additional relevance for patients with refractory epilepsy who are being considered for surgery. Indeed, it makes it more likely that these patients can cooperate during a pre-surgical evaluation.

Postictal psychosis

Postictal psychosis (PIPE) can present in the form of isolated symptoms or as a cluster of symptoms mimicking psychotic disorders and represent approximately 25% of POE. The prevalence of PIPE in the general population of patients with epilepsy is yet to be established, but has been estimated to

range between 6% and 10%.[38] We estimated the yearly incidence of postictal psychiatric disorders among patients with partial epilepsy that are undergoing V-EEG to be 7.9%.[39] The majority or 6.4% presented as PIPE. In every case, the onset of symptoms lagged by a mean period of 24 hours (range 12 to 72 hours) relative to the time of the last seizure. The mean duration of the PIPE was 69.6 hours (range: 24 to 144) and they all responded well to low doses of antipsychotic medication or benzodiazepines. Other authors have reported similar findings with respect to clinical characteristics, course and response to pharmacotherapy.[39–44]

The occurrence of PIPE in potential surgical candidates is significant as several studies have found a greater risk of bilateral independent ictal foci.[39,41,42,44] In a study of 282 consecutive patients who underwent an ATL, Christodoulou *et al.*, identified three who developed denovo PIPE post-surgically.[45] In these patients, seizures were recorded predominantly from the contralateral (nonsurgical) site or had bilateral independent seizures; none of the patients who failed surgery but continued to have seizures from the site of the surgery developed de novo postictal psychosis. In a study completed at the Rush Epilepsy Center, the occurrence of PIPE was found to predict the presence of bilateral independent ictal foci with an 89% probability.[46] By the same token, patients with recurrent PIPE are at significant risk of developing interictal psychosis. To minimize this risk, clinicians must carefully weigh the option of 'palliative' surgery, particularly to patients with mesial temporal sclerosis (MTS), provided that most seizures originate from the side of the atrophic hippocampus and the neuropsychological data are concordant with the intended surgical target.

Clearly, patients with refractory epilepsy being considered for surgery are likely to be suffering from comorbid psychiatric disorders. In the next section we review the problems behind the limited use of psychiatric evaluations in surgical candidates.

Psychiatric consultations during pre-surgical evaluations

Use of psychiatric evaluations in major epilepsy centers

How do major epilepsy centers in the USA evaluate the existence of comorbid psychiatric disorders or risk factors for post-surgical psychiatric complications? To answer this question, we investigated the use of psychiatric and neuropsychological evaluations during pre-surgical work-ups of candidates for antero-temporal lobectomy (ATL) in a survey sent to the 88 epilepsy centers belonging to the National Association of Epilepsy Centers (Kanner AM, submitted). Forty-seven centers (53%) completed the survey. The survey consisted of seven questions (see Table 91.1).

Our results revealed that only 10 centers (21%) routinely perform a psychiatric evaluation in *every* patient who is being considered for ATL. Three centers (6%) perform a psychiatric evaluation only in case of a previous psychiatric history, 16% if it is recommended by the neuropsychologist and 45% use either of the latter two criteria.

The lack of available psychiatric consultants has been 'blamed' for the failure to carry-out psychiatric evaluations in all pre-surgical patients. This 'forces' the epilepsy team to rely on neuropsychological evaluations to screen for comorbid psychiatric disorders. Thus, the second question of the survey, enquired about the *availability* and *use* of psychiatrists in each center. Among the 47 centers, only 12 (26%) had a psychiatrist in their epilepsy team. Consultations were provided by the hospital's psychiatry liaison and consultation service (LCS) in the other 35 centers: in 10 (21%) the *same* psychiatrist was always available to do the consultation while in 24 (51%) consultations were carried out by *different* psychiatrists. In one center, consultations were done by the residents but the attending did not see the patients in person.

The concern among epilepsy teams of post-surgical psychiatric complications is another variable that accounts for the diversity in the use of psychiatric consultations in these centers. The third question addresses this issue by asking the epileptologists whether they believe that psychiatric complications following ATL are frequent enough to warrant a pre-surgical psychiatric evaluation. The survey's data indicate the absence of a consensus on this issue as 21 centers (45%) considered it to be a problem, while 26 (55%) did not. Clearly, the lack of consensus in this very important question among 47 of the leading epilepsy centers in North America is indicative of an urgent need to investigate this problem in a systematic manner.

The availability of an epilepsy team psychiatrist appears to make a significant difference on the concerns of post-surgical psychiatric complications and on the use of psychiatric evaluations in every patient. Thus, 75% of centers with an epilepsy team psychiatrist voiced a concern of frequent post-surgical psychiatric complications, while this was true in one third centers in which consultations were carried out by LCS psychiatrists. Of note, there was no difference among centers where the same (30%) or different (33%) psychiatrists performed the evaluation. These data suggest that psychiatrists with special expertise in psychiatric aspects of epilepsy are more 'attuned' to potential post-surgical psychiatric complications. These data also raise the question of the quality of psychiatric evaluations performed by psychiatrists that lack special expertise in the psychiatric problems of epilepsy patients. In fact, 35 centers (75%) voiced concerns on the failure to obtain in-depth psychiatric evaluations.

As suspected, the lack of an epilepsy team psychiatrist is associated with a reliance on neuropsychological evaluations to identify comorbid psychopathology. For example, among the 24 centers that rely on a different LCS psychiatrist for their evaluations, 23 (96%) based their decisions to order a psychiatric evaluation on the basis of the recommendations of a neuropsychologist or if the patient is known to have a psychiatric history, while this is the case in eight of the ten centers (80%) who have the same LCS psychiatrist available. In contrast only four of the 12 centers (33%) with epilepsy team psychiatrist relied on these criteria.

Whether neuropsychological evaluations are adequate to identify patients at risk for post-surgical psychiatric complications is the next question. In our opinion they are not! In fact, most neuropsychological evaluations rely on screening instruments aimed at identifying psychiatric symptoms occurring during the prior 1 to 4 weeks, depending on the instrument used; thus, these instruments are likely to fail to detect any past psychiatric history that may be in remission at the time of the pre-surgical evaluation and to capture the

Table 91.1 Survey on the use of pre-surgical psychiatric evaluation

Please check the answer that best reflects the practice at your center:

1. **Patients evaluated for an antero-temporal lobectomy:**
   - **(a) Only undergo a neuropsychological evaluation.**
   - **(b) Always undergo both a neuropsychological evaluation and a psychiatric evaluation.**
   - **(c) Only undergo a psychiatric evaluation if they are known to have a psychiatric history.**
   - **(d) Only undergo a psychiatric evaluation if suggested by the neuropsychologist.**
   - **(e) Either c or d apply.**

YOUR ANSWER:

2. **When requesting a psychiatric evaluation for our patients with refractory temporal lobe epilepsy undergoing a pre-surgical evaluation:**
   - **(a) We have a psychiatrist who is part of the epilepsy team and evaluates all of these patients.**
   - **(b) We can request a consultation from the Psychiatry Consult Service, but the same psychiatrist is always (or most of the time) available to see these patients.**
   - **(c) We can request a consultation from the Psychiatry Consult Service, but there is no one psychiatrist dedicated to evaluate the epilepsy patients.**
   - **(d) We can request a consultation from the Psychiatry Consult Service, but the attending psychiatrists rarely see the patient.**

A. In the following five statements, please check ***True*** *or* ***False****, according to your opinion*.

1. **Psychiatric post-surgical complications following a temporal lobectomy are frequent enough to warrant a pre-surgical psychiatric evaluation in every patient.** *True____ False____*
2. **Neuropsychological evaluations are adequate to identify any patient at risk for post-surgical psychiatric complications.** *True___ False____*
3. **Psychiatric evaluations are only** *necessary* **for patients in whom the neuropsychologist has suggested the use of psychotropic drugs.** *True_____ False_____*
4. **In my opinion, it is difficult to find psychiatrists interested in carrying out a thorough psychiatric evaluation in our epilepsy patients.** *True____ False_____*
5. **There is a need for more psychiatrists to be trained to evaluate the psychiatric comorbidities of Epilepsy.** *True____ False_____*

complexity of the comorbid psychiatric disorders that are so common in these patients, as discussed in the previous section. Indeed, only with a comprehensive psychiatric evaluation that investigates present and *lifetime* histories can clinicians have the necessary information to formulate a correct psychiatric diagnosis, recommend the appropriate treatment and make estimations on the risk for potential post-surgical psychiatric complications. Furthermore, family psychiatric history is one of the leading risk factors of mood, anxiety and ADHD. Unfortunately, these data are rarely investigated in a neuropsychological evaluation. In short, screening instruments do not identify the complexity of such psychiatric comorbidities.

Can epileptologists and neuropsychologists rely on a *patient's self*-report of past or concurrent psychiatric history? The answer to this question is also 'no'! Indeed, it is a well established fact that most frequent psychiatric comorbidities in epilepsy patients (depression, anxiety, and ADHD) are very often unrecognized by the treating epileptologist and that only severe forms of these disorders are reported by the patients to the physicians. In addition, patients may not volunteer information on a comorbid psychiatric disorder out of misinterpretation of such disorders being 'a normal reaction' to a life with epilepsy, while some patients may hide such history out of fear that such history would disqualify them from consideration for epilepsy surgery. Failure to recognize chronic depressive disorders is illustrated in a study of 97 patients with partial epilepsy with a depressive disorder severe enough to warrant the consideration of pharmacotherapy, 60% had been symptomatic for more than one year before any treatment had been suggested.[28] Only one-third of the 97 patients had been treated within 6 months of the onset of their symptoms.

What is the reason behind a failure of most epilepsy programs to incorporate a psychiatrist in their 'team'? After all, all programs have one or more than one neuropsychologist. The answer is ironically rather simple: lack of financial resources on the part of hospital psychiatry departments to provide a full- or part-time staff psychiatrist to a single service. Indeed, a careful analysis of the 12 epilepsy centers with an epilepsy team psychiatrist reveals that the epilepsy programs pay for part of the salary of their psychiatrist. Thus, epilepsy centers that wish to have a psychiatrist in their team will have to budget a fraction of the psychiatrist's salary in their operating costs.

Psychiatric complications of epilepsy surgery

This topic is reviewed in great detail in chapter 142; we present here the most relevant points. Post-surgical psychiatric complications can be identified in up to 30–50% of patients undergoing an ATL consisting primarily of *recurrence* or *exacerbation* in severity of pre-surgical depressive and anxiety disorders, and less frequently of de novo mood disorders.[11–14,47] Most of these complications occur within the first six months after surgery and tend to remit within the first 12–24 months. However, a subset of 10–15% of patients is expected to suffer from refractory depressive and anxiety disorders.[47] De novo

post-surgical psychotic disorders are relatively rare, reported in 1–10% of series.

What should a pre-surgical psychiatric evaluation consist of?

Clearly, the evidence presented in the previous sections suggest that patients who undergo epilepsy surgery are at risk for post-surgical psychiatric complications. Accordingly, pre-surgical psychiatric evaluations must seek to obtain the following:

1. *Lifetime* and *current* psychiatric history of mood, anxiety, attention deficit disorders and psychotic disorders and to identify any evidence of a personality disorder.
2. A detailed history of the temporal relation of psychiatric symptoms to seizure occurrence (i.e., to establish if all symptomatology was interictal or if it presented as preictal or postictal episodes solely or in addition to interictal disorders).
3. A family psychiatric history, since a genetic predisposition is a pivotal factor in the development of mood, anxiety and attention deficit disorders, the most frequent psychiatric comorbidities in these patients.
4. An assessment of family dynamics, and specifically, the role played by each spouse with respect to the decision making process in economic and family-related matters as well as an assessment of whether the patient's spouse is ready to adjust to a greater independence associated with a post-surgical seizure-free state. Indeed, it is not rare for spouses to have difficulty relinquishing the role of 'care taker' which inadvertently can lead to conflict, including divorce.
5. A vocational assessment and the need for referral to a vocational rehabilitation program.

Pre-surgical evaluations in research

The data obtained in the survey presented above clearly indicates the need of systematic research on the incidence and types of post-surgical psychiatric complications, the impact of pre-surgical risk factors on post-surgical psychiatric seizure and psychosocial outcomes. To that end, any methodologically sound study must include:

1. A structured psychiatric interview aimed at identifying lifetime DSM-IV-TR psychiatric syndromes and personality disorders. Various diagnostic interviews are available and can be administered by trained research assistants. It should be remembered, however, that these interviews were developed for patients with primary psychiatric disorders and not for patients with epilepsy with psychiatric comorbidities. The limitations of using these instruments are not known at this time. Furthermore structured interviews specifically developed for patients with epilepsy will need to be elaborated in the future.

   The most frequently structured interviews include: (i) the Structured Clinical Interview for Axis I and II DSM-IV Disorders (DISC).[48] (ii) the Composite International Diagnostic Interview (CIDI);[49] (iii) the Schedule for Affective Disorders and Schizophrenia (SADS);[50] (iv)the Diagnostic Interview Schedule;[51] (v) The Mini International Neuropsychiatric Inventory (MINI).[52]

   It should be said that these psychiatric interviews need not be given in their entirety. Indeed, depending on the question at hand of the specific study, special sections of a questionnaire can be administered. For example, in the case of a study on mood and anxiety disorders, investigators can decide to administer the section of these disorders of the SCID.

   Structured interviews have been developed specifically for the identification of psychiatric syndromes in children and adolescents. The most rigorous is the SADS, adapted from the adult version for this school-age children.[53]
2. We cannot emphasize enough the need to include an instrument that investigates the family psychiatric history. The Family History Screen for Epidemiologic Studies (FHE) is an user-friendly screening instrument that can be used in research.[54]
3. Self-rating *screening* instruments are the favorite methods to acquire psychiatric data in research studies of epilepsy patients because of the logistical ease and low costs.

Unfortunately, these instruments are designed to detect symptoms and not to establish a DSM-IV diagnosis, let alone the diagnosis of psychiatric entities with all their complexities and atypical manifestations encountered in patients with epilepsy. Thus, the sole use of these instruments represents the most frequent methodological error in psychiatric research studies in epilepsy. The argument for exclusively using screening instruments is that they have been validated to identify conditions such as MDE some with acceptable levels of sensitivity and specificity and the severity of the depressive episodes. Thus, proponents of the sole use of these scales might reason, *if a patient has a score of >30 on the Beck Depression Inventory–II, what can it be, other than a MDE?* While this statement is probably correct, a MDE may be the expression of more than one type of mood disorder, each with a different prognosis and treatment strategy (see the section on mood disorders in this chapter).

As in the case of structured interviews, most of the screening instruments were developed for the screening of symptoms in patients with primary psychiatric disorders and not in patients with epilepsy. The only exception is the *Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)*[55] (see below). In addition two screening instruments for the identification of symptoms of depression, the Beck Depression Inventory-II (BDI-II) and the Center for Epidemiologic Studies-Depression Scale (CES-D) have been recently validated in patients with epilepsy.[56]

Clearly, the use of screening instruments for psychiatric research in epilepsy must be *used in conjunction* with a structured psychiatric interviews designed to establish a DSM-IV-TR diagnoses; only then do these screening instruments yield meaningful data as they permit regular re-screening to measure changes in severity of symptomatology. The most frequently used screening instruments in adults include the following.

Screening of general psychiatric symptoms

Adult Self-Report Inventories-4: The Adult Self-Report Inventories are symptom inventories that can be used as a

guide for conducting clinical interviews.[57] They include the behavioral symptoms of more than two dozen psychiatric disorders described in the DSM-IV. There are parallel versions of the Adult Self-Report Inventories that are designed to obtain information from both patients and significant others. These inventories take approximately 15 to 20 minutes to complete. Items are grouped according to diagnostic categories.

Hopkins Symptom Checklist (SCL-90 Revised): The SCL-90 is used to evaluate a broad range of psychopathology. It consists of 90 items and usually can be completed in less than 30 minutes.[58] The scoring system includes nine symptom scales (somatization, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and three global indexes. This scale has documented validity and has been used in many treatment studies of mood disorders and schizophrenia.

Minnesota Multiphasic Personality Inventory: It consists of a self-report personality inventory with ten clinical scales (hypochondriasis, depression, hysteria, psychopathic deviance, male-female, paranoia, psychasthenia, schizophrenia, mania, and social introversion) and three validity scales. The administration time is about 40 to 90 minutes.[59]

Depressive symptoms

Beck Depression Inventory-II (BDI): The BDI-II is the most commonly used self-rating scale for depression.[60] There are 21 items scored on a scale from 0–3 according to how the patient feels at the current time. The scale is sensitive to change and has been used in clinical drug trials. As stated above, the BDI-II has been recently tested in 205 patients with epilepsy from five epilepsy centers and was found to have a high sensitivity and specificity as a screening instrument of major depressive episode.[56]

The Center for Epidemiologic Studies-Depression Scale (CES-D): It is a composite of 20 items, rated from 0 (rarely) to 4 (most or all of the time). It can yield scores from 0–60, with scores >16 being suggestive of depressive illness. This scale has also been recently validated for its use in patients with epilepsy.[56]

Neurological Disorders Depression Inventory for Epilepsy (NDDI-E). This is a new self-rating instrument that consists of only six items but which was *specifically* developed to screen for the presence of major depressive episodes in patients with epilepsy, while minimizing the risk of overlap with adverse antiepileptic drug effects or preexisting cognitive problems.[55] Completing this instrument only takes 3 minutes or less and a score >14 is suggestive of the presence of a major depressive episode.

Anxiety symptoms

Hospital Anxiety and Depression Scale:[61] This scale is specifically developed for use in patients with medical comorbidity, and consists of 7-item self-rated subscales for both depression and anxiety.

Beck Anxiety Inventory (BAI):[62] The BAI is a 21-item self-report measure of anxiety severity. The scale consists of 21 items, each describing a common symptom of anxiety over the past week on a 4-point scale ranging from 0 (*Not at all*) to 3 (*Severely–I could barely stand it*). The items are summed to obtain a total score that can range from 0–63.

Goldberg's Depression and Anxiety Scales:[63] The instrument consists of nine questions assessing mood and anxiety over the previous month, and the full set of nine questions need to be administered only if there are positive answers to the first four. The scales are devised specifically to be used by nonpsychiatrists in clinical investigations. Scores are from 0–9.

Hamilton Anxiety Rating Scale (HAM-A or HARS):[64] This scale is a 14-item clinical interview scale (not self-reported) measuring somatic and psychic anxiety symptoms. The responses include five degrees of severity ranging from 0 (*None*) to 4 (*Frequent and severe symptomatology*). This instrument should be used with caution in patients with epilepsy, given the large number of somatic symptoms included in this scale which in patients with epilepsy can result from adverse effects of AEDs potentially yielding false positive suggestions of more severe anxiety symptomatology.

Obsessive-compulsive symptoms

Yale-Brown Obsessive Compulsive Scale (Y-BOCS): This is the most widely used scale for rating obsessive-compulsive symptoms. It includes a symptom checklist as well as a ten-item scale that is rated by clinicians. It has been shown to be a highly reliable instrument that is sensitive for measuring changes in the severity of obsessive-compulsive symptoms.[65]

Self-Report measures for children and adolescents include:

Child Symptom Inventories (CSI-4): The Child Symptom Inventories are screening instruments for the behavioral, affective, and cognitive symptoms of more than a dozen DSM-IV childhood disorders. There are Child Symptom Inventories for three different age groups: Early Childhood Inventory-4 (ages 3 to 5 years), Child Symptom Inventory-4 (ages 5 to 12 years), and Adolescent Symptom Inventory-4 (ages 12 to 18 years). There is a self-report measure for adolescent patients: Youth's Inventory-4 (ages 12 to 18 years).[66]

Child Behavior Checklist (CBCL): Developed by Thomas M. Achenbach, this scale evaluates pathologic behaviors and social competence in children ages 4 to 16 years. Forms are available for teachers, parents, and children. It is one of the most widely used scales for both clinical use and research.[67]

Children's Depression Inventory (CDI): This is a 27-item self-report questionnaire that can be given to 7- to 17-year-olds. It is currently one of the most widely used instruments for monitoring depression in children. Each question includes three statements of increasing severity.[68]

Multidimensional Anxiety Scale for Children (MASC): This is a scale for children and adolescents designed to assess symptoms of anxiety. The 39 items are scored on a scale from 0–3 as follows: 0 = never true about me; 1 = rarely true about me; 2 = sometimes true about me; 3 = often true about me.[69]

Connors' Parent/Teacher Rating Scales: This scale identifies behavior problems through parent and teacher report and particularly symptoms of ADHD. It is available in three versions: a 93-item version, a 48-item version, and a ten-item screening version. It is used in children ranging in age from 3 to 17 years.[70]

Leyton Obsessional Inventory-Child Version (LOI-CV; Short Form): This questionnaire is a 20-item inventory with 'yes/no' responses adapted from the adult version to assess obsessive-compulsive symptoms.[71]

Should patients with pre-surgical psychiatric disorders be excluded from epilepsy surgery?

The short answer is *no, as long as they can cooperate with the pre-surgical evaluation and they can understand the risks of the surgical procedures and the likelihood of achieving a seizure-free state.* As discussed in detail in chapter 142, epilepsy surgery is associated with a significant improvement of pre-surgical psychiatric disorders, including remission of depression and anxiety disorders in approximately 50% of patients.[11,13,47]

A pre-surgical psychiatric evaluation is important in these patients as it can be predictive of the risk of developing post-surgical psychiatric complications (see chapter 142). Indeed, a pre-surgical lifetime history of depression has been identified as the strongest predictor of post-surgical psychiatric complications presenting as exacerbation or recurrence of latent pre-surgical psychiatric disorders. Various studies have also identified an association between pre-surgical psychiatric disorders and a worse post-surgical seizure outcome (see chapter 142). Thus, in the setting of a pre-surgical psychiatric disorder, discontinuation of AEDs post-surgically may be discouraged to avert seizure recurrence.

The biggest controversy centers on the consideration of epilepsy surgery in patients with psychotic disorders. In general, patients with chronic psychosis are less likely to be referred to epilepsy surgical programs because of the assumption that they cannot cooperate with the pre-surgical evaluation. This assumption, however, has been proven to be erroneous time and again. Also, there has been a concern that psychotic disorders may worsen following epilepsy surgery. As stated above, IPOE is more benign than the primary schizophreniform disorders and hence poses less problems for the patient to be able to cooperate with the necessary tests of the pre-surgical evaluation. A review of the literature in Chapter 144 shows that the impact of ATL on the post-surgical course of the psychotic disorder has varied from unchanged (in a majority of cases) to improved psychotic status and/or level of functioning. For example, among 74 patients who underwent an ATL, Jensen and Larsen found 11 patients who had experienced a psychotic disorder pre-surgically.[72] The surgical procedure had no impact on the course of psychotic disorder. On the other hand, in a small series of five patients with a chronic psychotic disorder who underwent an ATL, Reutens *et al.*, reported an excellent seizure outcome in all patients and while the seizure-free state did not modify the actual psychotic disorder post-surgically, it facilitated their level of functioning.[73] Marchetti *et al.* reported a series of six patients with pre-surgical interictal psychosis who underwent an ATL.[74] Five of the six patients achieved a seizure-free outcome and there was no worsening of their psychotic disorder, with relative improvement in the mental conditions of five patients. In summary, the presence of a comorbid psychotic disorder should not be an 'automatic' reason for exclusion for epilepsy surgery.

Concluding remarks

Pre-surgical psychiatric evaluations are of the essence to ensure that any psychiatric comorbidity has been properly identified and the appropriate treatment has been started to avert or minimize the development of post-surgical psychiatric complications. While most epilepsy surgery rely on neuropsychological evaluations to screen for comorbid psychiatric disorders, there is a great risk that comorbid psychiatric disorders will go undetected and untreated. As mentioned above, the psychiatric disorders of patients with refractory epilepsy are often atypical in their presentation and screening instruments are unlikely to provide an objective picture.

Epilepsy centers need to incorporate a psychiatrist into their epilepsy team. Unfortunately, the economic barriers of today's healthcare environment limits the availability of access to psychiatrists in general and epilepsy programs may need to cover the costs of having a psychiatrists available in their team.

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92 Pre-surgical neuropsychological workup in children and intellectually disabled adults with epilepsy

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Introduction

Due to several factors, children and intellectually disabled adult patients are more difficult to analyze neuropsychologically than other patients with epilepsy. There are similarities between both groups – for example behavioral problems often complicate the assessment of cognitive functions in both children and intellectually disabled adults – but there are also differences. For instance, the assessment of children needs to be sensitive to the developmental increases in cognitive skills, while floor effects in intellectually disabled patients can prevent an adequate mapping of performance changes. Therefore, children and intellectually disabled patients will be addressed in separate sections. The chapter summarizes technical problems of the neuropsychological assessment in children and intellectually disabled patients and provides an overview of test issues. First, special features that must be considered in the neuropsychological assessment of children and commonly used tests will be introduced and we will discuss matters of interpretation. Then, information concerning intellectual disability in patients with epilepsy will be provided as well as methods for the pre-surgical neuropsychological assessment. The final topic for discussion will address why a localizational interpretation of the neuropsychological profile in these patients is only of minor relevance in pre-surgical diagnostics.

Neuropsychological assessment of children

The goal of neuropsychological pre-surgical testing in children and adolescents is to provide a detailed assessment of the individual's cognitive functioning that serves as a basis for estimating and judging post-operative changes. The following objectives have been summarized by Oxbury.[1]

1. Confirmation of lateralization and localization of the epileptogenic area.
2. Prediction of risk to memory and other cognitive functions as well as long-term cognitive development.
3. Educational and rehabilitation issues and potential.

As we will see, the individual fit of these goals depends on the age and developmental level of the child. The neuropsychological assessment of pediatric patients is complicated by certain methodological and interpretational difficulties related to brain development and by patient intrinsic features which include lower cooperation and a frequent occurrence of behavioral problems. An overview of special features that have to be considered in the neuropsychological assessment of children is provided in Table 92.1.

Methodological aspects

Test selection

The components of a neuropsychological evaluation assess linguistic, attentional, memory, executive, sensory, perceptual, motor and higher cognitive functions. Table 92.2 lists commonly used tests well suited for the assessment of specific cognitive domains, academic achievement and behavioral problems in children and adolescents and provides information on the age range of their norms. Please note that the table is not comprehensive. Baron[2] recently provided a broad collection of tests and normative data in child neuropsychology. Other comprehensive test surveys that are not specifically designed for children were compiled by Spreen and Strauss,[3]

Table 92.1 Special features in the neuropsychological assessment of children

Methodological aspects
Test selection should consider the following aspects:
- Applicability of tests across a larger age range
- Suitability of tests for a specific age level
- Adequacy and topicality of age norms

Observation of the patient is a valuable additional source of information.
Anamnesis of parents or another caregiver is essential.
Interpretation of test results must relate to developmental expectations.

Patient intrinsic features
Ability-achievement discrepancy is likely because of
- Lower level of cooperation and motivation particularly in younger children
- Increase of behavioral problems

Brain development
- Increased potential for reorganization/ plasticity
- Possibility of a 'growth into the deficit'
- Possibility of functional changes during development

and Lezak.[4] A very useful overview is also given in Anderson *et al.*[5] Standardized neuropsychological test batteries such as the Halstead-Reitan Neuropsychological Test Battery for Children (9–14 years)[6]; the Luria-Nebraska Neuropsychological Battery – Children's Revision (8 years and older)[7]; and the NEPSY (3–12 years)[8] ensure a comprehensive assessment and usually rely on adequate normative data. However, their fixed format lacks the flexibility needed in order to tailor the assessment to the individual patient and often not all of the subtests are reliable for assessing the specific problems of patients with focal epilepsy. Many neuropsychologists therefore prefer a 'self-made' set of tests that are proven to be sensitive for the pre- and post-operative course of focal deficits in epileptic patients. When selecting a test, one must consider that test translations and culturally-specific, adequate age norms are not available for each country and that differences in the educational system may prevent the transfer of norm data between countries. A variation of the preferred tests is therefore found in the different countries. However, also within English-speaking countries, a great variety of tests was revealed by a comparison of the assessment methods used by neuropsychologists who work with children at different epilepsy surgery centers.[1] Neuropsychological tests should be selected in such a way that they are suited for a specific age level. Most abilities improve as the child grows older and it is essential to have tests that comprise adequate age norms. On the other hand, a test should be applicable across a larger age range in order to assess the course of illness and treatment effects in the individual child.

Table 92.2 Common neuropsychological tests for the assessment of different functional domains

Function	Test	Age range
Attention	Trail-Making-Test for Children (Reitan & Wolfson, 1993)	7–13 years
	Continuous Performance Tests (Conners' Continuous Performance Test, TOVA...)	Variable
	Visual Cancellation Tests (d2-Test of attention, Cancellation of Targets Test..)	Variable
	Test of Everyday Attention for Children (Manly *et al.*, 1999)	6–15 years
Language	Clinical Evaluation of Language Fundamentals-3 (Semel *et al.*, 1995)	6 years–adult
	Children's Token Test (Di Simoni, 1978)	6–13 years
	Peabody Picture Vocabulary Test-III (Dunn & Dunn, 1981)	2.5 years–adult
	Boston Naming Test (Kaplan *et al.*, 1983)	6–12 years
	Controlled Oral Word Association Test (Gaddes & Crocket, 1975; Anderson & Lajoie, 1996)	7–13 years
Learning/Memory		
General	Wide Range Achievement of Memory and Learning (Sheslow & Adams, 1990)	5–17 years
	Rivermead Behavioural Memory Test for Children (Wilson *et al.* 1991)	5–11 years
Verbal stimuli	Rey Auditory Verbal Learning Test, several parallel forms (Rey,1964)	7–13 years
	California Verbal Learning Test for Children, one alternate form (Fridlund & Delis 1994)	5–16
	Story Recall (Christensen, 1979; Anderson & Lajoie, 1996)	7–13 years
	Digit Span (Isaacs & Vargha-Khadem 1989; Wechsler 1991; Anderson & Lajoie 1996)	6 years–adult
Nonverbal stimuli	Rey-Osterrieth Complex Figure [a]: Recall (Rey, 1941; Forrester & Geffen, 1991; Anderson & Lajoie, 1996; Kolb & Wishaw, 1996)	6 years–adult
	Corsi Block-Span (Milner, 1971; Anderson & Lajoie, 1996)	7–13 years
	Benton Visual Retention Test, three parallel forms (Benton, 1982)	8 years–adult
Visuospatial functions	Rey Osterrieth Complex Figure: Copy (Kolb & Wishaw 1990)	6–15 years
	Motor free visual perception test-3 (Colarusso & Hammill, 2002)	4 years–adult
	Block Design and Object Assembly of the Wechsler Scales (Wechsler 1991)	6 years–adult
Executive and Motor Functions	Maze Tests (Porteus, 1965, Milner 1965, Wechsler 1991)	Various
	Tower of London (Shallice 1982)	7–13 years
	Digits backwards (Isaacs & Vargha-Khadem 1989)	7–15 years
	Trail Making Test (Reitan 1969)	7–13 years
	Wisconsin Card Sorting Test (Heaton 1981; Chelune & Baer 1986)	6–12 years
	Children's Category Test (Boll T 1992)	6–13 years
	Tests for manual motor sequencing and coordination	No norms available
	Purdue Pegboard (Gardner & Broman 1979)	5–15 years
	Finger Tapping (Finlayson & Reitan, 1976)	6–14 years
Academic functions	Wide Range Achievement Test (reading, spelling, arithmetic) (Jastak & Wilkinson 1994)	5 years–adult
	Wechsler Individual Achievement Test (Wechsler 1993)	5–19 years
Behavior and Mood	Achenbach Child Behavior Checklist (Achenbach 1991)	2–18 years
	Adolescent Psychosocial Seizure Inventory (Batzel *et al.* 1991)	12–19 years
	Conners' Behavioural Rating Scales–Revised (Conners 1997)	3–17 years
	Specific scales for the assessment of depression, anxiety, autism, conduct disorder,...	Variable
Family functioning	Parenting Stress Index (Abidin 1995)	3 months–10 years

[a] Full references and more detailed descriptions of the tests can be found in refs. 2,3,and 5. The Taylor Complex Figure as a parallel form of the Rey Osterrieth Figure is probably a bit easier.

It is important, that tasks are not too complex but yield information about functioning within specific functional domains. If possible, one should favor tests that include alternate versions, since neuropsychological testing in children treated with epilepsy surgery includes retesting after surgery. This is particularly relevant for tests that evaluate learning and memory. The type of assessment and the choice of instruments depends on the age as well as the maturational and cognitive level of a child. It can thus be adequate to evaluate a 10-year–old child with moderate intellectual disability using a test developed for preschool children.

Global intellectual functioning provides a background for the interpretation of the test profile in patients with focal epilepsy who are candidates for surgical treatment. Better than functions in individual domains, intelligence provides information about intellectual disability and this can be a clue in determining the etiology. Furthermore, intelligence is still the best predictor of school achievement. A measure of intelligence should therefore be included in the neuropsychological examination, although intelligence tests are usually insensitive indicators of common but subtle neuropsychological dysfunctions in these patients and they are largely insensitive to surgical effects. Table 92.3 provides an overview of tests for the assessment of intelligence or developmental level. The Wechsler Intelligence Scales are probably the most popular measures of general intellectual ability. There are versions for preschool children (WPPSI-III) and for school children (WISC-III) and these tests have been translated in to a multitude of languages. Abbreviated forms have been developed for screening purpose.[9] For infants, the Bayley Scales of Infant Development–II are probably the most popular method for assessing the current developmental level. For those patients who speak a foreign language or for language-impaired patients (e.g., deaf-mute or aphasic patients) tests of nonverbal reasoning (e.g., CPM, SPM) or nonverbal subscales of common intelligence tests (e.g., the performance scale of WISC-III) can be applied.

Table 92.3 Tests for the assessment of intelligence or developmental level

Test	*Age range*
Bayley Scales of Infant Development II (Bayley, 1993)	1–42 months
McCarthy Scales of Children's Abilities (McCarthy, 1972)	2 ½–8 ½ years
Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III, Wechsler, 2002)	2 ½–7 years 3 months
Stanford-Binet Intelligence Scale[a] (SB-IV, Thorndike *et al*., 1985)	2 yrs–adulthood
Kaufman Assessment Battery for Children[b] (KABC, Kaufman & Kaufman, 1987)	2 ½–12 ½
NEPSY (Korkman *et al*., 1998)	3–12 years
Coloured Progressive Matrices[c] (CPM, Raven 1995)	4–11 ½ years
Wechsler Intelligence Scale for Children[d] (WISC-III, Wechsler 1991)	6–16.11 years
Standard Progressive Matrices[c] (SPM, Raven 1996)	8–80 years
Kaufman Adolescent and Adult Intelligence Test[e] (KAIT, Kaufman & Kaufman 1982)	11–85 years.

[a] The SB-IV is particularly apt to assess gifted children.
[b] The KABC includes an achievement scale.
[c] The Raven's Progressive Matrices keep verbal instructions to a minimum and require nonverbal reasoning, they are relatively culturally unbiased.
[d] The WISC-III differentiates between verbal and nonverbal intelligence.
[e] The KAIT differentiates between fluid and crystallized intelligence.
Full references and more detailed descriptions of the tests found in refs. 2,3,and 4.

Interpretation of test results

In a child that is referred for the purpose of pre-surgical diagnostics, the neuropsychologist interprets the obtained data in the context of a comprehensive understanding of brain-behavior relationships. This interpretation varies depending on the age of the patient. In very young children or children with severe intellectual disability, the neuropsychological evaluation mainly aims to assess the global developmental level to set a baseline for follow-up. Answers to localization-related questions can normally not be given for those patients. In school children (6–12 years), neuropsychological patterns that exhibit specific profiles with strengths and weaknesses of localizing or lateralizing value can sometimes be recognized. Neuropsychological factors in the adolescent (> 12 years) are assumed to be very similar to those found in adults and neuropsychological patterns are often of localizing or lateralizing value. Specific deficits can be taken to strengthen or confirm or amplify other findings of the presurgical diagnostics, especially if an intracarotid amytal test has confirmed left hemisphere language dominance. General guidelines for a localizational interpretation are:

1. Selective deficits in language associated functions (e.g., expressive or receptive language, vocabulary, semantic fluency, verbal memory) point to impairments in functions of the language dominant hemisphere.
2. Selective deficits in visuospatial functions (e.g., visuoconstruction, visual perception, visual memory, mental rotation) point to impairments in functions of the nonlanguage–dominant hemisphere.
3. Predominant memory deficits are associated with temporal foci.
4. Predominant executive deficits are associated with frontal foci (see also Table 92.4).

The performance on psychological tests is reported in percentiles, standard scores or developmental/mental age scores. Mental age scores have a descriptive appeal, but it must be kept in mind that they are only on an ordinal-scale level and that the meaning of differences systematically shrink with age: a 5-year-old child functioning with a mental age of a 3-year-old might be quite impaired, while a 14-year-old functioning at a 12-year-old level might be only moderately behind. Percentile scores have an advantage over mental age scores because they maintain their meaning at different ages. However, they are also on an ordinal scale level and the unit of measure varies across the range (e.g., a 20-point difference is insignificant in the middle but very meaningful near the tail of the distribution). Standard score scales (e.g., z-, IQ-, T-Scores) report scores in standard deviation (SD) units from the

Table 92.4 Studies on cognitive functions in pediatric patients with focal epilepsy

Study	N	Measure	Results concerning group differences
Adams *et al.*[64]	16 LTLE 12 RTLE	WMS, RCFT, TROG/Grammar test, Shortened Token Test	LTLE declined in verbal memory after surgery.
Cohen *et al.*[65]	12 LTLE 12 RTLE	Comprehensive Children's Memory Scale	LTLE impaired in verbal memory. RTLE impaired in nonverbal memory.
Jambaque *et al.*[66]	14 ETLE 28 TLE; 18 IGE,	Signoret's Memory Battery Scale	LTLE lower performance in verbal tasks. RTLE defective visual memory.
Beardsworth & Zaidel[67]	13 LTLE 16 RTLE	Memory for faces	RTLE < LTLE in memory for faces.
Lendt *et al.*[47]	12 FLE 12 TLE	Verbal fluency, Mazes, VLMT, DCS-R WISC-R, Motor coordination Reaction times, Corsi Block Design Digits, Token Test, Letter cancellation	FLE more impaired in motor coordination, FLE higher IQ-level.
Culhane-Shelburne *et al.*[68]	12 FLE 15 TLE	TOVA, TOL, CVLT WRAML, Twenty Questions Test, Stroop Color-Word test, VABS	FLE deficits in planning and executive functions and mal-adaptive functioning. TLE deficits in memory.
Gleissner *et al.*[42]	26 LTLE 26 RTLE	VLMT, DCS-R	LTLE had a significant decline in verbal memory after surgery.
Hernandez *et al.*[69]	16 FLE 8 TLE 8 GEA	Purdue Pegboard, Self-ordered pointing task, motor coordination, WCST, TOL, Verbal Fluency.	FLE deficits in planning, impulse control, fluency, and motor coordination.
Hernandez *et al.*[70]	16 FLE 8 TLE 8 GEA	CVLT, CPT, WISC-III RCFT, CBCL	FLE were more impaired in attention, impulse control, working memory, perceptual organization, and behavior than the other groups.
Mabott & Smith[71]	17 LTLE 18 RTLE	CAVLT, RCFT face recognition	Significant post-operative difference in memory for faces (RTLE < LTLE).
Nolan *et al.*[72]	25 FLE, 32 TLE 13 GEA	WRAML	TLE more impaired in memory than FLE.

The table illustrates the fact that several studies observed functional deficits in children often associated with a focal epilepsy similar to those reported in adult patients. Therefore, the table is not comprehensive; it presents only a selection of studies on cognitive functions in pediatric patients with focal epilepsy. CAVLT = Children's Auditory Verbal Learning Test; CBCL = Child Behavior Checklist; CPT = Continuous Performance Test; CVLT = California Verbal Learning Test; DCS-R = Diagnosticum für Cerebralschädigungen-Revision; FLE = frontal lobe epilepsy; GEA = generalized epilepsy with absences; IGE = idiopathic generalized epilepsy; LTLE = left temporal lobe epilepsy; RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey Complex Figure Test; RTLE = right temporal lobe epilepsy; TOVA = Test of Variables of Attention; TLE = temporal lobe epilepsy; TMT = Trail Making Test; TOL = Tower of London; VABS = Vineland Adaptive Behaviour Scales; VLMT = Verbal Learning and Memory Test; WCST = Wisconsin Card Sorting Test; WISC-R = Wechsler Intelligence Scale for Children–revision; WISC-III = Wechsler Intelligence Scale for Children–third version; WMS = Wechsler Memory Scale; WRAML = Wide Range Assessment of Memory and Learning.

normative sample's mean. To understand and interpret standard scores, one must know the mean and SD of the scale on which it is based (e.g., 100 ± 15 for IQ-scores, 50 ± 10 for T-Scores). Standard scores allow for a more direct comparison of the different measures in the different age groups. A deficit is usually assumed if the test result is more than one SD below the mean. A deficit is specific if it is more than one SD below the test results in other functions. Thus, if a child exhibits memory problems, but also has difficulties in attentional, visuospatial and language functions, one would not diagnose a prominent temporal lobe dysfunction, but would rather assume diffuse functional damage. On the other hand, average verbal memory functions in an epileptic child with otherwise above average results might be considered as an indicator for a left temporal lobe dysfunction.

It should be kept in mind that neuropsychology never diagnoses epilepsy. Classifying test results into a cognitive pattern does not prove a causal relation with epilepsy. However, if a cognitive pattern with weaknesses and strengths is consistent with a focal deficit in the context of general assumptions about brain organization and if it is consistent with other, particularly functional findings (e.g. EEG, functional imaging), it is of course plausible to assume that the performance is influenced causally by the disease.

Intelligence tests usually do not localize or lateralize to specific brain regions or hemispheres. It is tempting, but not justified by empirical evidence, to interpret a difference of the verbal and performance IQ of the Wechsler Intelligence Scale for Children (WISC-III) or between the scales of simultaneous and sequential processing of the Kaufmann-Assessment Battery for Children (K-ABC) in terms of lateralization. Subtests of intelligence tests often cross multiple domains. However, if it is possible to decide the cause of a child's failure, this can provide valuable localizing information within the general context of the other tests. For instance, the 'picture arrangement' subtest of the Wechsler intelligence test requires that the child sorts cartoon pictures to make sensible stories. This can be impaired because of slow speed, a deficit in visual-motor integration, an impulsive mental style, or a comprehensional or conceptual deficit. Asking a child to tell the story helps one understand why a child fails the task. But please note that a real process approach during testing (i.e., determining what a child needs for successful performance as a means of determining which cognitive processes are not fully

operational) – although very useful in neuropsychological training and rehabilitation – cannot be applied in the field of pre- and post-operative evaluations because this would distort the results of the retest.

The observation in a face-to-face interaction provides indispensable additional information. For instance, as a basic function, an attentional problem can lower the performance in all of the other tests, but relevant attentional tasks can also be failed due to an impairment in the other processes. In practice, the psychologist will rely not only on the test results but also on his clinical observation of the child's alertness, his ability to focus on the task in hand, reactions to distracting stimuli, and the ability to sustain effort throughout time. The interpretation of performance will therefore rely not only on the profile of the test results but also on the observation of the child during the examination and on information given by the caregivers and other relevant persons (e.g., teachers).

Brain maturation

One of the main differences between an adult brain and that of child or adolescent, is that the child/adolescent brain is still engaged in significant developing processes. The enormous changes that occur, including an overproduction of dendrites and synapses and their consecutive pruning during the first years of life, are well known. The sequence in which the cortex matures shows parallels to the cognitive and behavioral development.[10] Regions subserving primary functions, such as sensory and motor systems, mature earliest. Temporal and parietal association cortices associated with basic language skills and attention mature next. Higher-order association areas, such as the prefrontal and lateral temporal cortices which integrate sensorimotor processes and modulate attention and language processes, mature last. However, it has become clear in recent years that the process of postnatal brain maturation is long and lasts at least into early adolescence. Although the total brain size is approximately 90% of its adult size by age six, the gray and white matter subcomponents of the brain continue to undergo dynamic changes throughout adolescence. Data from recent longitudinal studies which use modern imaging tools as magnetic resonance imaging (MRI), functional MRI (fMRI), and diffusion tensor imaging indicate that, while white matter volume increases in a roughly linear pattern until approximately young adulthood, gray matter has an inverted U-shaped pattern with a regional variation.[11] Developmental curves for the gray matter of the frontal and parietal lobes peaked at about age 12, the temporal lobe at about age 16, and the volume in the occipital lobe continued to increase through age 20. Ongoing maturation of the temporal lobes during adolescence is also indicated by electroencephalographic and postmortem studies.[12,13]

At least three possible implications of this immaturity for the neuropsychological evaluation of pediatric patients with epilepsy have to be discussed:

1. The function of a specific neural area may change over time. Several studies indicated that children recruit more diffuse prefrontal regions when performing executive tasks, and that the pattern of activity within brain regions with task-related activity becomes more focal or fine-tuned with age, whereas brain regions with task-unrelated activity decrease in activity with age.[14] However, similar results were obtained in adult learning studies.[15] Thus, it is likely that task-related activation of more extended or different areas in children is due to differences in training or strategy. A regional qualitative change of functions during development would not be economic and does not fit with the assumption that learning and experience guide cerebral development processes. Therefore, we regard it unlikely that functional brain organization is qualitatively fundamentally different in children.
2. Due to brain maturation, the extent of an impairment may not become obvious until the underlying brain structure is fully mature. Table 92.4 provides a selection of studies reporting neuropsychological results in children with focal frontal or temporal lobe epilepsy with functional associations similar to those reported in adults. Of course, this does not exclude the possibility that those functional deficits might strengthen when the children grow up. A deficit can also become more imposing when daily tasks become more demanding. The demands for self-organizational abilities, for instance, are relatively low at school because school provides a highly organized structure. The issue of a 'growth into the deficit' can be answered only in a longitudinal design. In their longitudinal study, Bjoernaes *et al.*[16] found some evidence that children may experience a greater decline of intellectual functioning than adults over the years of a severe epilepsy. However, the adult patients also had a significantly longer duration of epilepsy and started with a significantly lower performance at the time of the first test. There are a few single case reports about children with frontal damage, whose deficits were not apparent until they were grownup.[17] However, in the literature one gets the impression that this is the exception rather than the rule.
3. Brain damage in infants and children may produce different effects because it can alter the basic functional brain organization. When interpreting test results, it is essential to keep in mind that brain damage in infants and children can more easily alter the basic functional brain organization than in adults. The preservation of language functions seems to be particularly important for the brain. A reorganization of visuospatial functions with a suppression of language functions has not yet been described but a suppression of nonverbal functions in patients with an interhemispheric reorganization of language is a robust finding.[18,19] Language is usually thought to be lateralized by the age of 6 years. After the age of 5, the potential for language to reorganize from the left to the right hemisphere appears to decrease rapidly.[23] A high incidence of atypical (i.e., right- or bilateral) language representation in patients with early left hemisphere insult has been well documented.[18,20] Atypical language due to a damage beyond adolescence is very rare and probably reflects a genuine right hemisphere participation in language. In patients with epilepsy, it is presumed that not only lesions but also epileptic dysfunction can cause a language shift. Thus, a relatively small lesion which is not necessarily proximal to classic anterior or posterior language areas associated with epileptic activity can be sufficient for an interhemispheric transfer.[21] Characteristic features of adult patients with atypical language dominance are left-hemispheric

damage, an early onset of epilepsy, atypical hand dominance, a predominance of extratemporal lesions and a strong deficit in nonverbal memory. The same characteristics have been described also in children.[19,22,23]

The assessment of language representation can be more difficult in children than in adults. The determination of language representation by the IAT (Intracarotid Amytal Test) is more often applied in adults than in pediatric patients. The IAT temporarily inactivates one hemisphere by the injection of sodium amytal or, more recently, also with brevimytal by a catheter through the internal carotid artery. Difficulties in performing the angiographic portion of the procedure in conscious children are frequent and sedation interferes with language testing. Although IAT language testing has been successfully obtained in children as young as seven years of age,[24] children under ten years of age and intellectually disabled patients are sometimes not able to cooperate actively in the IAT situation.[25] The same is principally true for language assessment with fMRI, although there have been attempts to develop child-friendly functional magnetic resonance imaging paradigms for children too young or too impaired to execute an active task.[26] The baseline testing used to get the child familiarized with the procedure, and use of a pediatric protocol with simpler pictures and familiar words is recommended also in the IAT in order to maximize cooperation and the validity of the results. Near-infrared spectroscopy (NIRS), transcranial magnetic stimulation (TMS) and contrast transcranial Doppler sonography (CTCDS) provide interesting and valuable options for assessing language dominance in children, but these methods do not yet show a breakthrough.

It is still widely assumed that less dysfunction will result from a brain lesion if a child is younger at the time of a neurological insult, because plasticity processes can counterbalance the damage. This believe came up mainly because early hemispherectomized children often showed a respectable development and school achievement after surgery, but the general assumption is not true in light of the present data. An early cure of epilepsy can result in an impressive developmental catch-up, but early damage during the first two years of life in general is destructive for cognitive development and often results in global intellectual impairment.[27] Interhemispheric functional reorganization probably is an emergency solution for the brain. The resulting performance level for the rescued function is not unimpaired and it is not without cost as has been shown by the suppression of nonverbal functions in patients with an interhemispheric language reorganization.

Patient intrinsic difficulties

Behavioral problems

As both chronic illness and CNS disorders are risk factors for behavioral problems, the frequency of behavioral disorders is much higher for patients with epilepsy. The prevalence of behavioral problems is below 10% for the general childhood population. In pediatric patients with epilepsy, rates between 30% and 50% have been reported for behavioral problems, while rates of approximately 20% have been reported for children with other chronic physical illness not involving the central nervous system (i.e., diabetes mellitus or cardiac disease).[28] Behavioral problems include anxiety, aggression, oppositional behavior, autistic features, depression, and hyperactivity. Behavioral problems can already be observed in children with new-onset seizures.[29] Risk factors for behavior problems in childhood epilepsy include neurologic dysfunction, side-effects of antiepileptic medication, seizure variables as an early onset and a higher frequency and a stronger severity of seizures.[30,31] No significant associations have been found with the side and site of epilepsy.[32]

The family environment variables (e.g. family stress, family mastery, and extended social support) are also significant predictors of behavioral problems in childhood epilepsy.[33] Symptoms of depression, reported in approximately one-quarter of children and adolescents with epilepsy,[34] were correlated with a negative attitude toward seizures, lower satisfaction with family relationships and no internal locus of control. This points to the relevance of early educational programs that should support the family and the patient in order to reduce the risk of depression and anxiety.

Behavioral problems are diagnosed by a combination of the anamnesis of the patient and the parents, the observation of the patient during the examination and standardized questionnaires (see Table 92.3). The Child Behavior Checklist (CBCL[35]) and the Conners Behavioral Rating Scales[36] are among the most widely used instruments for assessing behavioral problems. They provide parent-, teacher-, and self-ratings. The CBCL is introduced as an example. It consists of 120 items that describe specific behavioral and emotional problems, plus two open-ended items for reporting additional problems. Also included are scales for measuring social problems, anxiety and depression, somatic complaints, attention problems, thought problems, delinquent and aggressive behavior. On a superordinate level, a score for Internalizing Problems (e.g., anxiety, depression), a score for Externalizing Problems (e.g., aggression, delinquent behavior), and a Total Problem score can be derived. The newest form (ASEBA) is for children between 1.5 and 5 years.[37] Children with epilepsy exhibit prominent problems, particularly in the scale of internalizing problems and in the subscale indicating attention problems (Figure 92.1, see also ref 29). It should be noted that for children with epilepsy, it is important to consider, that a few items describe the consequences of a chronic illness or aspects of

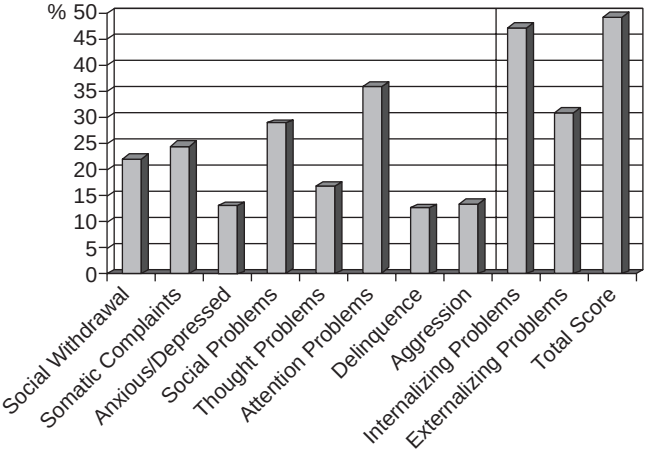

Figure 92.1 Child Behaviour Checklist : % with deviant performance (T-Scores ≥ 67 for the subscales, ≥ 60 for the superordinate scales) in our unselected clinical population of pediatric patients (in between 526 and 539).

seizure semiology rather than the behavior problems. Oostrom *et al.*[38] found that rescoring the CBCL by seven ambiguous items* reduced the percentage of patients trespassing the clinical cut-off score considerably in newly diagnosed patients while rescoring had no effect in healthy children. A recent study in pediatric epilepsy patients who were assessed pre-operatively and one year after successful surgical treatment indicated the CBCL as a valid assessment tool in children with epilepsy[73]. The parents of children with epilepsy should nevertheless be instructed that seizure should not be included in the ratings to avoid a confusion of behavior problems with seizure semiology.

Post-operatively, impressive improvements of behavioral disorders have been reported.[39,30] Post-operative behavioral improvements can often explain the positive changes in school and social life as reported by the parents despite no obvious improvements in the neuropsychological examination.

Guidelines for a valid neuropsychological assessment of children

A reliable and valid assessment implies that a child has put forth appropriate effort. Some guidelines that optimize a valid neuropsychological assessment of children are briefly outlined here; a comprehensive description is available in Baron.[2] Testing is often stressful for the child and produces anxiety especially at the beginning when the structure of the situation and the examiner are still unfamiliar. At the beginning of the test, informal conversations about a special interest or favorite activity increase the child's comfort level and allow the examiner to formulate initial clinical impressions. The purpose of testing should be explained as should information about what will happen during the session and how long it will approximately take. This will reassure the child. It should be emphasized that the child tries his best but failures are unavoidable, because some tasks are designed to push the test-taker to his limits and no child will always be correct. Children are often reassured when told that a hard item is actually intended for an older child. Praise should be given for the effort that the child made. Difficult tasks should not be given at the beginning, if it is compatible with a standardized sequence of the tests. Suitable first tests are drawings or simple verbal or motor tasks if they do not emphasize an expected weakness. A low level of cooperation and motivation can be expected particularly in children with conduct disorder, attention deficit disorder, and in younger children. In the latter, attentional persistence and tolerance to failure are limited and the children are less able to comprehend the relevance of the situation. This is probably one reason why intelligence measures during early childhood and preschool measures are far less predictive of later functioning than assessments taken during middle childhood. Highly active children require considerable structure and guidance from the examiner and it can be necessary to set firm limits for those patients. Informing the child that if the examination is not completed, there will be another visit might sufficiently motivate a defiant child to continue. If the child is extremely resistant, it might be appropriate to terminate and continue another time. It is absolutely crucial that the examiner adjusts to the individual child to optimize the child's motivation.

*The items are Nr. 13 "confused, seems to be in a fog", Nr. 17 "Daydreams", Nr 46 "Nervous movements or twitching", Nr. 80 "Stares blankly", Nr. 84 "Strange behaviour", Nr. 107 "Wets during the day", and Nr. 108 "Wets the bed".

Predictors of post-operative neuropsychological outcome in pediatric patients with epilepsy

As in adults, the location and extent of surgery in children influences the neuropsychological outcome. However, due to additional factors such as ongoing maturational changes and physiological and functional plasticity, the impact of epilepsy surgery on brain functions could depend also on the maturational stage of the child at the time of epilepsy onset and the time of surgery. Early surgery may prevent the disturbance of brain development by epileptic activity and enable the brain to recover more completely from the consequences of the surgery due to structural and functional plasticity. All in all, the available data indicate that early surgery in pediatric patients is beneficial.[40–43] It has been observed in individual patients that a cognitive decline was stopped or that development was advanced by successful seizure control after surgery.[44] However, group data on cognitive outcome after epilepsy surgery indicate that surgery is usually not followed by markedly improved intellectual development, but there seem to be fewer additional deficits induced by surgery and a better recovery than in adults.[45] With respect to temporal lobe resections, studies which have found no evidence of post-operative decline outweigh those studies revealing a loss.[46] Risk factors for a post-operative memory decline are a left-sided resection, a higher pre-operative performance, a shorter post-operative retest interval and a longer duration of epilepsy. One study investigating the cognitive outcome after frontal surgery observed improvements in measures of memory and attention. Seizure outcome was not a predictor of cognitive outcome in this study.[47]

After a hemispherectomy, the intellectual functions usually remain unchanged,[48] although more positive results could probably be obtained if the assessment of psychosocial features (e.g., level of integration in the family, at school or at work) would be assessed instead of the IQ. Etiology seems to be a relevant factor for the pre-operative level and the post-operative course.[49] Very favourable results have been obtained with regard to the post-operative cognitive development for patients with Sturge-Weber-Syndrome and an early epilepsy[74] Patients with hemimegalencephaly have a worse outcome than other etiological groups probably due to the presence of bilateral structural and epileptic anomalies.[43] An earlier age at the time of surgery has been shown to be prognostically good in patients with hemispherectomy.[43,40]

For those patients undergoing a callosotomy, behavioral improvement is one of the major surgical benefits.[50] In the series of Sauerwein *et al.*[41] only mild or moderate mental deficiency before surgery was the most reliable predictor of post-operative cognitive gains. The age at the time of surgery had an effect on the course of recovery from post-operative sequelae – patients younger than 13 years recovered more rapidly and more completely and had almost no disconnection deficits in simple tactile interhemispheric transfer tasks. All patients aged 13 years and older displayed permanent disconnection signs. Bilateral language and dissociated language dominance patterns can be considered an exclusion criteria for a callosotomy.

It should be considered that developmental gains may need longer periods to accumulate. Freitag and Tuxhorn[51] observed a significant increase in the developmental quotient after surgery for preschool children only after a follow-up interval of 2–3 years. Westerveld[52] reported that a longer post-operative retest interval (range 5–60 months) was a significant predictor for a gain in performance IQ.

Neuropsychological pre-surgical workup in intellectually disabled adult patients

Intellectual disability (ID) is found more frequently in patients with medically intractable epilepsy than in the normal population. Its prevalence has been estimated at 35% for those patients with an early onset of epilepsy.[53] It should be noted that the term 'mental retardation' has become stigmatizing and should be avoided. ID is pragmatically defined as a measured IQ of greater than two standard deviations below the mean (IQ ≤70), such that approximately 2 – 3% of the population would be defined as intellectually disabled. Further diagnostic criteria are according to DSM-IV, an onset of ID before age 18 and significant limitations in adaptive functioning in at least two skill areas (e.g., communication, home living, social/interpersonal skills).

According to the diagnostic manuals, there are four severity grades of intellectual disability (see Figure 92.2). Intelligence tests (see Table 92.2) are not suited for assessing more severe ID, since IQ test scores usually end between 10 and 50. Therefore, it is useful to also apply a measure of adaptive functioning, usually in the form of a semistructured interview with the parent or caregiver. Instruments which assess functional capacities in a wide array of domains including daily living skills, communication skills and socialization are the Vineland Adaptive Behavior Scales-II (VABS-II,)[54] and the second edition of the American Association of Intellectual disability Adaptive Behavior Scales.[55]

Pre-operative neuropsychological diagnostics refer not only to the absolute level of performance, but also to the diagnostic information given by the pattern of strengths and weaknesses in the cognitive profile. In the majority of intellectually disabled patients, many functions are equally impaired and the test results often indicate a diffuse functional impairment without a performance minimum of localizing value. More often, a performance maximum in a single function indicates relative functional integrity of a region, but this is, of course, of minor relevance from a pre-surgical diagnostic point of view. Finding tests for the assessment of specific neuropsychological functions in patients with ID is more difficult. Although most of the neuropsychological tests listed in Table 92.3; can be applied to patients with mild intellectual disability (e.g., Boston Naming Test, semantic fluency, recognition form of the Benton Visual Retention Test), the floor effects often prevent an adequate mapping of performance changes. Therefore, it might be more appropriate for the documentation of the post-operative course in patients with ID to compare raw scores rather than standard scores. Application of tests originally designed for children can be considered to quantify performance in intellectually disabled patients who can not cope with the test versions for adults. Behavioral problems are more frequent in intellectually disabled patients and can further complicate the neuropsychological examination. A health-related quality of life questionnaire (e.g., QOLIE-89)[56] should also be used, to optimize mapping of the post-operative outcome. A proxy report form can be used in those patients, who are not able to fill out the questionnaire themselves.

Patients with epilepsy and intellectual disability are often difficult to treat. Drug resistance is more frequent in patients with intellectual disabilities. In a long-term study conducted by Huttenlocher and Hapke,[57] 70% of the patients who had an IQ <70 and were studied for at least 18 years continued to have more than one seizure per year, while the rate was only 25% for those patients whose intelligence fell within the borderline or normal range. Surgical treatment could be beneficial for patients with intellectual disabilities, but intellectual disability is often associated with a bilateral or diffuse morphologic brain damage that increases the probability of a multifocal epilepsy or diffuse epileptogenic regions. However, there have also been reports of 9–30% focal lesions among intellectually disabled patients with epilepsy[58,59] and for these patients a surgical treatment is a valuable option. The assumption of a worse post-operative cognitive outcome for intellectually disabled patients due to lower compensational capacities of brain regions beyond the epileptogenic focus is not very well founded from an empirical standpoint. On the contrary, children with a low IQ can have substantial gains after surgery, that indicate a restart of development after a period of developmental stagnation or regression due to severe epilepsy.[30]

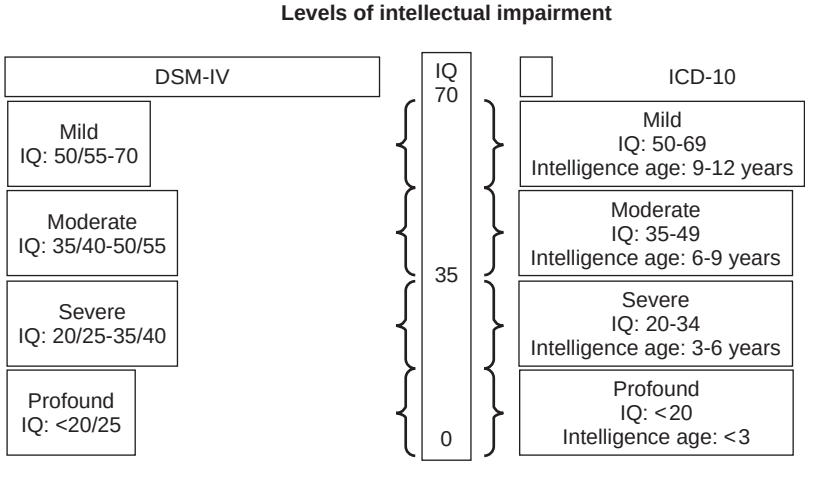

Figure 92.2 Severity grades of intellectual disability according to DSM-IV and ICD-10. Since IQ-test-scores usually end in the range of 40 – 50, it is useful to also apply a measure of adaptive functioning, e.g., the Vineland Adaptive Behavior Scales-II.

It has become clear through recent studies, that IQ alone is not a good predictor of the post-operative outcome. Bjornaes *et al.*[60] reported no significant post-operative cognitive declines in 31 patients with an IQ <70. The rate of seizure-free patients was 52% after temporal resection and 38% after extratemporal resection. A better outcome was found for those patients who underwent surgery at a younger age and displayed a shorter duration of epilepsy. In our series of 16 adult patients with an IQ <85, we observed no deteriorations in the cognitive and socioeconomic status after temporal and extratemporal focal resections.[61] The rate of seizure control was satisfactory one year after surgery (64% Engel Outcome Class I). In a large multicenter study, Chelune *et al.*[62] observed that adult patients with an IQ ≤75 were at a higher risk for continued seizures if structural lesions other than mesial temporal sclerosis were present. However, no influence of IQ was evident for the other patients. Freitag and Tuxhorn[51] recently reported in severely and profoundly retarded preschool children a complete seizure control in 46% and a worthwhile seizure reduction in another 39%.

Patients with a lower IQ often have a more severe epilepsy than those patients with normal intelligence. To further analyze the influence of the intelligence level, we matched pediatric groups with different IQ levels according to clinical and etiological criteria.[63] The comparison of intellectually disabled, learning disabled and pediatric patients of normal intelligence indicated no group differences with respect to seizure outcome and no dependency of the post-operative cognitive outcome on the pre-operative intelligence level. Behavioral improvements were observed in all groups independent of the intelligence level. As with patients of normal intelligence, the decision to operate on patients with a low level of intelligence should depend on the results of the pre-surgical workup. If the results of the neuropsychological examination indicate diffuse functional impairment, this should not hinder further steps if all other findings are consistent.

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93 Wada test and epileptogenic zone

DS Dinner and T Loddenkemper

Introduction

Main purpose of the Wada test is the lateralization of language and memory function. For that purpose, an anesthetic agent, usually amobarbital, is injected into the internal carotid artery producing temporary inactivation of the ipsilateral cerebral hemisphere.

It is important to know the lateralization of language when one is considering surgery of an epileptogenic zone or lesion located close to or possibly overlapping a potential speech area, Wernicke's area or Broca's area. In terms of memory function, the Wada test was initially used to predict postoperative global amnesia following unilateral temporal lobectomy. Subsequently the Intracarotid Amobarbital Procedure (IAP) has also been used to attempt prediction of selective modality specific memory deficits after surgery. The IAP may also assist in the lateralization of the epileptogenic zone as well as to predict seizure outcome following temporal lobectomy.

History

First description for language lateralization by Juhn Wada

The effects of injection of sodium amobarbital into the common carotid artery were first observed by Juhn Wada in 1948, when he described his findings in 15 right-handed patients the following year in Japanese[1] and later translated the original report into English.[2] The IAP was subsequently used to determine language lateralization in a series of 20 patients at the Montreal Neurological Institute being evaluated for focal surgical resection in the management of intractable epilepsy.[3] They then published a larger series of 123 patients being evaluated for epilepsy surgery which was the first large series of the relationship of speech lateralization and epilepsy.[4]

Gardner, a neurosurgeon at the Cleveland Clinic, previously reported the use of a local anesthetic agent to localize language areas (Figure 93.1). He injected procaine hydrochloride directly into the cerebral cortex through burr holes in order to functionally inactivate potential language areas to assess the possibility of a reversed hemispheric lateralization of language in the right hemisphere in two left-handed patients.[5]

IAP for memory lateralization

In the 1950s there were several reports of postoperative memory difficulties following unilateral temporal resection for intractable temporal lobe epilepsy (TLE).[6,7] Scoville and Milner described three cases with persistent global amnesia with bilateral mesial temporal resection.[8] It was also noted that patients who had undergone unilateral temporal lobectomy may demonstrate similar memory deficits if there was an unsuspected lesion in the contralateral temporal lobe.[9] Their hypothesis was that significant memory deficit in patients following temporal lobectomy was due to abnormally functioning tissue in the contralateral temporal lobe. The Montreal group subsequently modified the IAP to evaluate memory function in addition to language lateralization.[10] They hypothesized that unilateral inactivation of the ipsilateral hemisphere should not affect memory function during the procedure unless there was a lesion in the contralateral hippocampus. In their initial studies, they injected 200 mg of sodium amobarbital into the common carotid artery on the side contralateral to the side of the epileptogenic lesion and found memory disturbance in 11 cases. None of the patients developed postoperative memory loss. Subsequently, injection of sodium amobarbital was performed into the internal rather than the common carotid artery, allowing a smaller dose of sodium amobarbital, 125 mg, to be administered.[11]

The IAP later came to be referred to as the Wada test and has continued to be frequently referred to as such until the present. Besides amobarbital some centers have recently used alternate anesthetic agents including methohexital,[12–14] etomidate,[15] and propofol.[16–19]

Selection criteria and indications

Many centers perform the Wada test in the majority of candidates who are seriously being considered for surgical management of their epilepsy. However, some centers restrict the use of the Wada test to left-handed patients or those who demonstrate evidence of bilateral or contralateral hemisphere damage or unexpected or confusing findings on neuropsychological testing. In the past, the Wada test has most commonly been performed in candidates for temporal lobectomy. In these patients it was used for the evaluation of language and memory function. In patients with extra-temporal lobe epilepsy, the primary indication is the evaluation of language lateralization rather than memory function.[20]

Recently, indications and selection criteria have been changed due to advent of alternative language and memory lateralization techniques,[21–23] possible problems with memory lateralization, and due to recognition of complications during this invasive procedure.[24–26]

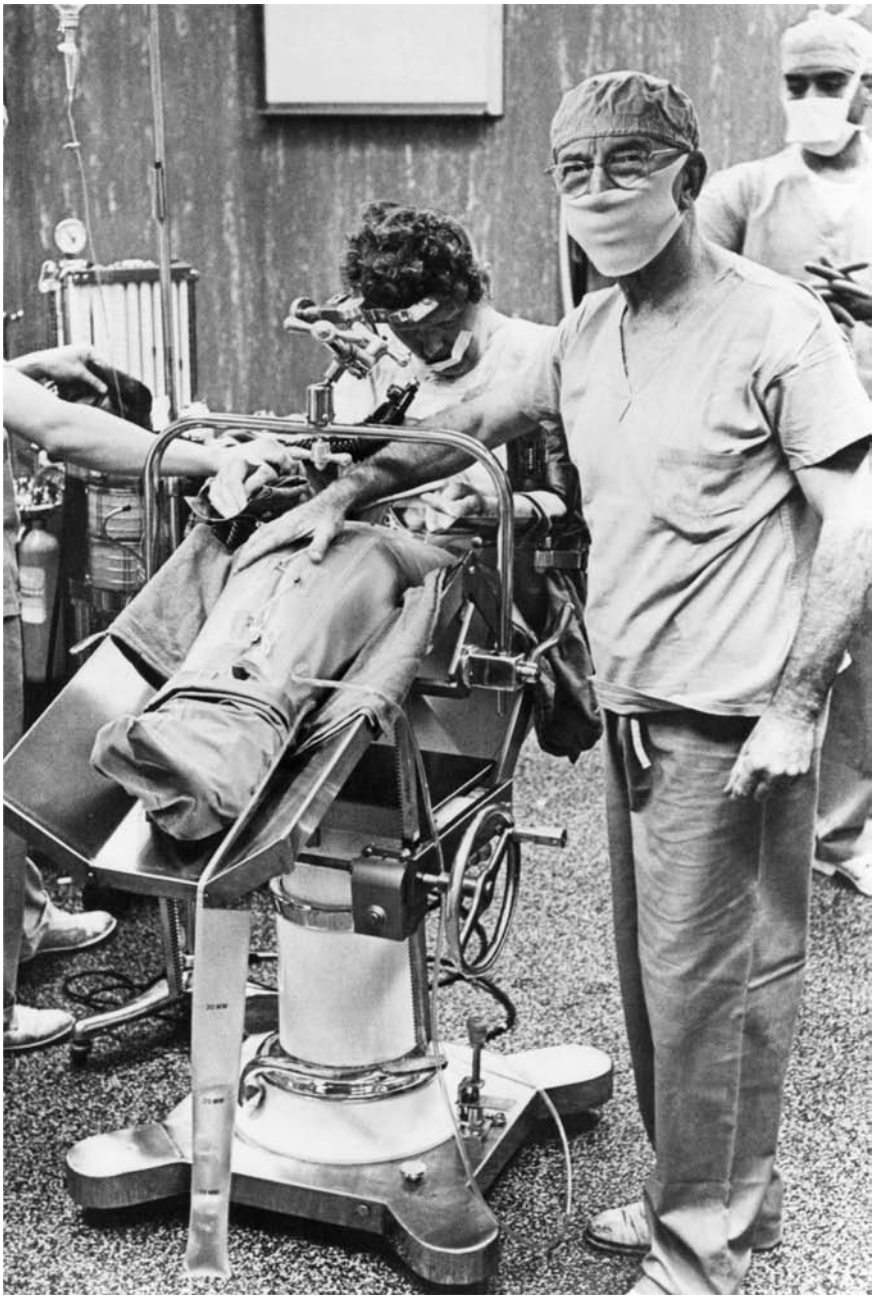

Figure 93.1 W. James Gardner II (1898–1987), photograph courtesy of Frederick K. Lautzenheiser, Cleveland Clinic Archives.

Risk of memory deficit

Neurocognitive morbidity, especially memory deficit is a significant and relatively common adverse effect of surgical resection in patients with intractable TLE.[27–30] Resection of the speech dominant temporal lobe has been associated with postoperative impairment in the ability to learn and retain verbal material.[21–36] Similarly a decrease in nonverbal memory after nondominant temporal resection has been reported by some investigators.[31,33,37–39] However other investigators have not found memory deficits after nondominant temporal resection.[32,34,36,40,41] Chelune and colleagues at Cleveland Clinic found that the rate of reliable decrease in verbal memory after left temporal resection was nine times higher than among nonoperated patients with intractable TLE and three times higher than among patients after right temporal resection.[42] Decrease in visual memory was only slightly higher than chance and no differences were noted between right and left temporal resection cases.

Model of hipppocampal memory function

The traditional model of hippocampal memory function suggested that memory decrement after temporal lobectomy was related to the capacity or functional reserve of the contralateral temporal lobe to support memory function. Support for the functional reserve model of hippocampal function was

based on the early observations of memory deficit following temporal resection as described above. It is also the reason why the group at the Montreal Neurological Institute (MNI) modified the IAP to study memory in the hemisphere contralateral to the proposed resection. The report of three cases of persistent global amnesia following bilateral mesial temporal resection demonstrated the critical role of the hippocampi in the the acquisition and retention of memory.[8] Subsequently in 1958 there was a report from the MNI of two cases with significant memory deficit following unilateral temporal resection.[9] They hypothesized that the patients had an occult lesion in the contralateral hippocampus which was not able to support memory. Among the factors that have been demonstrated to predict a decrease in memory after surgery has been the presurgical function of the mesial structures in the hemisphere to be resected. This is referred to as the model of hippocampal functional adequacy.[43] According to this model, postsurgical decline in memory is dependant on the functional adequacy of the tissue that is to be resected. This function in turn has been related to the presence of and degree of mesial temporal sclerosis. Support for the functional adequacy model of memory deficit after temporal resection comes from studies of both structure (histological analysis of neuronal cell densities and MRI volumetric studies) and function (neuropsychologyical evaluation and IAP memory testing).

Postoperative memory changes have been associated with histologic evidence of hippocampal pathology. The greatest decrease in verbal memory occurred in patients without evidence of significant hippocampal pathology.[33,44–46]

Patients with hippocampal sclerosis have poor memory prior to surgery as compared to those without widespread neuronal loss. The patients with relatively healthy hippocampi demonstrate marked memory loss compared to those with clear evidence of sclerosis following surgery.

MRI volumetric measurements are associated with hippocampal sclerosis.[47–50] MRI volumetry has also been shown to have an inverse correlation with the degree of verbal memory deficit after temporal resection in the speech dominant hemisphere supporting the functional adequacy model.[51] There is also a relationship that has been demonstrated between the neuropsychological measures of memory function and postoperative changes after temporal lobectomy. A decrease in cognitive ability particularly verbal memory was observed following left temporal lobectomy in patients with high preoperative baseline memory scores.[28] Other authors have found that good baseline memory preoperatively is a predictor for memory decline after left temporal resection.[33,32]

Findings on pathologic and neuroimaging studies also support the association of memory results on the standard IAP with hippocampal changes. Rausch and colleagues examined the relationship between memory performance and hippocampal damage in patients with TLE.[53] They found that patients with severe neuronal loss (>80%) throughout the hippocampus generally failed the IAP memory test following contralateral injection. In patients with less severe damage, IAP memory performance was not related to the degree of hippocampal damage. Sass and co-workers reported a subfield specificity with IAP memory results related to neuronal loss only in the CA_3 and hilar regions.[54] O'Rourke and colleagues provided further evidence of subfield specificity but noted that the degree of unilateral memory impairment was related to decreased neuronal density in the hilar and dentate granular regions and not in the CA_1 or $CA_{2–3}$ regions.[55]

In patients with unilateral hippocampal atrophy on MRI, significant asymmetries of IAP memory scores have been noted.[56] This has also been confirmed on volumetric measurements, although the relationship is not one-to-one.[57] It has also been shown that memory scores relate to hippocampal but not extrahippocampal volumes in TLE.[58] Salanova and co-workers investigated the relationship between interictal hypometabolism determined by fluorodeoxyglucose positron emission tomography (PET) and memory function with the IAP in 23 patients with unilateral TLE.[59] Ninety-five percent of patients demonstrated hypometabolism on PET scan or impaired memory on the epileptogenic side. No patient had impaired memory contralateral to the hypometabolic zone. Rausch and colleagues had also earlier noted that five of six patients with severe hippocampal sclerosis had asymmetric glucose hypometabolism on PET scan.[53]

Methodology

Although the IAP was first used over 50 years ago and the test is widely accepted, there is still no standardized protocol used. However certain basic aspects are common to most protocols. A trans-femoral arterial route is used to perform the cerebral angiogram immediately prior to the IAP to evaluate the vascular anatomy and also to determine the presence of and degree of crossover-flow to the contralateral cerebral arteries which may influence the effect of the amobarbital to be injected and subsequent interpretation of the study. Anomalous vascular patterns may affect the distribution of the amobarbital and impact on the subsequent interpretation of its effects. After the angiogram the catheter is kept in the internal carotid artery usually at the C3–4 cervical spine level and its position is confirmed by fluoroscopy.[60] Immediately prior to the injection, the patient is asked to keep both arms elevated to evaluate strength and then is instructed to start counting aloud. The anesthetic agent, usually sodium amobarbital is injected by a hand-push technique over several seconds. The contralateral arm drops as hemiplegia develops and if the speech dominant hemisphere is injected, the patient also develops global aphasia and stops counting. The patient is usually mute for 2–3 minutes and then speech returns, initially dysphasic with paraphasic errors being present for a few minutes before the speech returns entirely to normal. With injection of the nondominant hemisphere, the patient may continue counting, usually with a degree of dysarthria. However, the patient may become mute and this lasts for a much shorter time, 20–30 seconds, as compared to the dominant hemisphere.

Immediately after injection, strength is first evaluated to determine if adequate hemiparesis has occurred as an indicator that the injection has been sufficient to produce ipsilateral cerebral hemisphere inactivation. The patient's level of attention is then assessed by asking him or her to follow a simple one step command, requiring a nonverbal response such as 'close your eyes'.

Language and memory function are evaluated as long as the patient continues to demonstrate hemiparesis. Memory for the items presented during the period of hemiparesis is

tested approximately 10 minutes after the time of injection when strength and language function have returned to baseline. We also monitor the effect of the anesthetic agent on the EEG as a parameter of the effect of the EEG and wait for cessation of any slow and return of the EEG activity to baseline. We inject the hemisphere ipsilateral to the epileptogenic zone first and the contralateral hemisphere the same day a short time later, 30 minutes after initial injection if amobarbital is used and 10–15 minutes if methohexital is injected.

Variations in procedure

Baseline evaluation

At many centers, as well as in our protocol at the Cleveland Clinic, a practice test is performed prior to the actual Wada test in order to obtain an evaluation of the patient's baseline memory function and also to familiarize the patient with the procedure.[60] At certain centers only hand strength may be checked to gauge the degree of hemiparesis following injection or to perform a brief language assessment.[54,61] Baseline evaluation may be done either a day earlier or shortly before the procedure. We usually perform this baseline evaluation on the day prior to the Wada test.

Drugs administered: amobarbital

Sodium amobarbital is the standard drug used. The most frequently used dosage is 125 mg, but it may vary from 60–200 mg based on the patient's weight. When using amobarbital we most frequently inject 100 mg of amobarbital and if this did not produce an adequate hemiparesis, we would inject an additional 25 mg. The drug is usually diluted in several ml of solution and is injected by hand-push technique over 3–5 seconds. In a study of 72 patients, Loring *et al.* compared patients with lower doses (125 mg or lower) versus patients studied with high doses (greater than 125 mg). The group with higher doses performed significantly poorer than the patients with lower dose.[62] It was also suggested that the higher incidence of bilateral language and at-risk amnestic patients reported at some centers may be related in part to large amobarbital doses and that using lower doses such as 75 mg can improve the efficacy of the procedure.[63] Lower doses may not always produce adequate hemiparesis or be sufficient to produce transient global amnesia,[20] whereas too high doses may produce transient periods of confusion and thus impair the ability to evaluate the effect of the amobarbital.[25] One study investigated the relationship of dosage administered and memory performance during the Wada test.[64] The authors analyzed the effects of doses varying from 45–425 mg and found that dosage was not related to any of the measures of memory used in the test or to the final pass/fail outcome.

Alternative drugs

Although amobarbital was the standard drug for many years other drugs such as methohexital, propofol and etomidate have been used.[13,18,20,65] Several years ago when there was a shortage in the supply of amobarbital we began to use methohexital which has subsequently become the agent we routinely use.[66] We inject 3 mg initilally and if there is inadequate contralateral hemiparesis we inject an additional 2 mg after a 30 second interval. Ocassionally 5 mg is routinely injected. Of interest is the technique recently described by Jones-Gotman *et al.* They use etomidate injected as a bolus and then as a constant infusion to maintain a constant anesthetic effect during the testing of memory and language function.[15]

Time of injections

Most centers inject both internal carotid arteries to evaluate language and memory function.[20] Both hemispheres are usually evaluated on the same day with a period of time between each injection. This is more efficient in terms of performing the study and also subjects the patient to only one femoral arterial puncture. However injecting both sides on one day with a relatively short interval between the two injections may have an effect on memory evaluation particularly after the second injection. When injecting the epileptogenic zone first and comparing the effect of the timing of injection on memory one study showed that memory after the second injection on the same day was not as good as compared to testing on a second day.[67] They showed that memory for both verbal and figural material after intracarotid amobarbital injection was lower when injecting both hemispheres on the same day. If injecting amobarbital we usually wait 20–30 minutes from the time of the first injection to the time of the second injection. In some centers, the injections are performed on separate days. The centers using larger doses may inject the ipsilateral and contralateral injections on separate days because of the concern of obtundation associated with larger medication doses.[27]

Side of injection

The epileptogenic hemisphere is usually injected first.[68,69] However there is some concern that the order of injection may have an effect on memory evaluation. Grote and colleagues showed that memory after second injection on the same day was not as good as mentioned above.[67] The side injected first is usually the side ipsilateral to the epileptogenic zone in most centers. This is to mimic the effect of the proposed resective surgery in intractable temporal lobe epilepsy. The side of the epileptogenic zone is injected first in case it is not possible to subsequently inject the contralateral side. The group in Berlin compared a congruent patient population (where the epileptogenic side is injected first) with a noncongruent patients (where the nonepileptogenic hemisphere is injected first).[70] This comparison found that the congruent group demonstrated poorer memory function after injection of the nonepileptogenic hemisphere compared with injection of the epileptogenic hemisphere. The authors concluded that the commonly used method of injecting the epileptogenic side first results in a poorer memory recognition by the epileptogenic hemisphere than the nonepileptogenic hemisphere.

Arousal asymmetry

The effect of the injection on arousal may be asymmetric. Decreased arousal after left hemisphere injections has been demonstrated.[71,72] The Glasgow coma scale has been used in one study to objectively measure the level of consciousness.[72] Decreased arousal in turn may decrease the apparent memory

function of the opposite hemisphere being evaluated. This effect appears to also interact with the side of the epileptogenic zone, so that patients with left temporal lobe epilepsy are more likely to demonstrate poor memory related to the right hemisphere and may 'fail' the Wada test.

In the standard IAP, Lesser *et al.* showed that the initial confusion and muteness did not interfere with the ability of patients to form new memories since the patients remembered objects presented during this period.[73] Hart and colleagues compared the ability to comprehend the semantic relatedness between a picture and a word with the ability to name and read aloud individual items following dominant side injection.[74] They found that although almost all patients had severe impairment in reading aloud or naming pictures, 53% were able to match perfectly the same visually presented words to their corresponding pictures by their meanings or associations. These results suggest that some degree of comprehension, specifically complex auditory comprehension, is preserved following the standard IAP.

Crossover of drugs

Perrine and colleagues studied the relationship of behavioral, language, and memory variables during the IAP to angiographic evidence of the degree of ipsilateral posterior cerebral artery or contralateral anterior cerebral artery filling in 42 patients.[75] Contrast medium injection at the same rate as that of the later amobarbital injection was used to control for effects of different rates of injection. They found that ACA cross-filling was not related to any behavioral measure including the level of consciousness and mutism. The degree of PCA filling correlated significantly with the level of consciousness, but this was not significant after accounting for the effects of seizure laterality, injection side, and amobarbital dosage. Specifically, neither ACA cross-flow nor PCA filling correlated significantly with memory.

Stimulus timing

The timing of presentation of items for memory testing after injection is quite variable amongst centers. We usually present items after the first nonverbal response is obtained, performing a simple one step command to insure that we have the patient's attention,[76] even in the presence of aphasia. In some centers, presentation of items is performed only after return of speech.[10,60,77] With injection of amobarbital we found an initial period of muteness, confusion and unresponsiveness especially after injection of the language dominant hemisphere.[73] However stimuli presented early during this initial period of confusion could be recalled when memory was being tested.[73] Only left sided injections in left-hemisphere language dominant patients were used in this study. The London, UK, group investigated the influence of interference with language on memory. Their hypothesis was that memory function is dependent on language ability and that injection of the language dominant hemisphere will result in an artificially lower memory score.[78] In this study, however, patients did not display a better memory for items presented after return of speech than those presented while language was impaired. Thus language recovery and memory function were found to be independent. Nevertheless, result may be material specific.

At the Medical College of Georgia, Augusta, items are presented immediately after demonstration of hemiplegia, evaluation of gaze function and execution of a simple command by the patient before return of language. This is referred to as early presentation of items. Presentation of items after some recovery of language function is referred to as late presentation of items. Hemiparesis is usually evaluated by the grip strength of the contralateral hand and loss of strength in antigravity muscles of the arm.[20] The group in Georgia demonstrated that memory for objects presented early (beginning approximately 55 seconds after amobarbital administration) differed as a function of ipsilateral versus contralateral injection at a very high level of statistical significance. Items presented late (4 minutes and 30 seconds after injection) were also related to the laterality of the seizure focus but at a lower statistical level.[79]

The duration that each stimulus is presented is also quite variable from center to center and may also influence memory performance. In one report line-drawings were presented for 10–15 seconds[75] whereas in another report objects were presented for 4–8 seconds.[79]

Hemisphere speech dominance

After the injection of the speech-dominant hemisphere there is initially a profound aphasia and the duration is dependant on the drug and dose used.[20] Although the patient is unable to read or name objects, objects that are shown or tactually handled by the patients are encoded into memory and recognized after the drug effect has worn off.[11,73,80,81] Auditory verbal stimuli given in the early postinjection period are less likely to be recalled during subsequent testing of recognition memory.[82,83] Memory for three visual stimuli, pictures of common objects, words and abstract forms were used to investigate the effect of speech dominance on memory evaluation.[84] They demonstrated that injection of left speech dominant hemisphere compared to the right nondominant hemisphere resulted in an overall increase in errors. Long term memory testing following left hemisphere injection showed that fewer errors were made in regard to pictures of common objects during the early postinjection period as compared to the later long term memory testing. Thus pictures of objects could be adequately encoded for later recall. In contrast fewer errors occurred after right hemisphere injection and selective errors seen after left hemisphere injection were not found.

Stimulus type

A variety of test stimuli can be used to assess memory. Stimuli usually include actual objects, line drawings of objects, words and designs or photographs. A multicenter study including subjects from four centers studied the influence of the stimulus type in regard to memory lateralization in TLE.[85] They compared memory for actual objects and line drawings and determined that real objects were superior to line drawings in differentiating left from right TLE groups. Line drawing asymmetries incorrectly lateralized the temporal lobe memory impairment in left TLE subjects at a rate of 2.7 times greater than asymmetries based on object recognition. Similar findings were also reported by the same group in 152 pediatric patients aged 16 years and younger. In this study the use of real

objects (rather than using mixed stimuli, photographs and line drawings) discriminated the memory asymmetry better and lateralized the epileptogenic zone in a greater proportion of patients.[86]

At the University of Pennsylvania differential temporal lobe memory was demonstrated in relation to verbal versus visuospatial stimuli.[87] Patients with left temporal lobe lesions had poorer memory for verbal stimuli, whereas patients with right temporal lobe lesions performed more poorly for visual spatial stimuli during the IAP.

At our center, items are presented during the period of hemispheric inactivation, usually while the hemiparesis persists and while there is associated unilateral slowing in the EEG. Our current protocol involves three groups of items, a line drawing of an object, an object word and a function word (e.g., indeed, inspite). We previously also used abstract designs (Chinese pictograms) but dropped these from our protocol several years ago. After the initial injection and adequate hemiparesis is documented as well as adequate attention is obtained, one item of each of these three groups is then presented. Then strength of the contralateral arm and speech are re-evaluated. The next set of three items is then presented and language and motor function reassessed. The above pattern is repeated until full strength has returned. The time of presentation of items in the study is divided into three phases based on the contralateral hemiparesis. Phase one is the period from the time of injection to return of strength to grade 3/5; phase two is the period from the time strength reaches grade 3/5 until the return of baseline normal strength, grade 5/5; Phase three is the period after return to baseline or normal strength until presentation of all items is completed.

We evaluate memory for items presented 10 minutes after the injection of amobarbital providing full strength has returned and the patient's EEG has returned to baseline.[11,20,68,69,76,88–90] Since we have been injecting methohexital the duration of anesthetic effect is shorter and we are able to test memory sooner, but wait at least 5 minutes after injection.[66] We initially test memory for the items shown with spontaneous recall and then ask the patient to recognize the item shown on a flashcard, given a choice of the item and three foils.

Number of presented items

The number of stimuli that are presented in the test protocol is also quite variable at different centers. The Medical College of Georgia used eight early and five late items.[91] Harborview Medical Center in Seattle used 20 to 30 items.[92] UCLA used six items.[83] At Cleveland Clinic we initially used up to 20 items,[68,69] but now we use a maximum of 12 items.[66]

Language scoring

At our center, assessment of language lateralization is mainly based on speech arrest times. The hemisphere that displays the longest period of muteness after injection is usually defined as the language dominant hemisphere. However, if the interhemispheric time interval of speech arrest is shorter than 30 seconds, bilateral language is suspected. A protocol using different lateralization measures has been proposed by Benbadis *et al.*[93] In this paper three lateralization measures were suggested:

1. the absolute duration of the speech arrest after left and right intracarotid barbiturate injection, using a cutoff of 60 seconds;
2. the difference between speech arrest times after left and right injections using a cutoff of 30 seconds; and
3. the laterality index, definded as the difference between speech arrest times after left and right injections, divided by the sum of speech arrest times after left and right injection.

Other centers also use scoring of dysarthria and paraphasias during the language assessment.

Memory scoring

Memory score is calculated as the number of items correctly recognized as a percentage of the number shown during the period of hemiparesis, phases 1 and 2. The patient's memory score is not penalized for guessing. We inject the opposite internal carotid artery after an interval of 30 minutes from the initial injection if we are using amobarbital.[68,69,76,90] However if we use methohexital then we inject the opposite hemisphere 10–15 minutes after the first injection.

The initial major indication in evaluating memory function with the IAP was to determine the risk for postoperative global amnesia after unilateral temporal lobectomy, by determining if the patient failed the memory test with injection ipsilateral to the epileptogenic zone. In many centers memory scores of 67% or greater are classified as passing scores for the memory test and those with scores with less than 67% are classified as having failing scores on the memory test of the IAP.[53,54,68,69,76,94] A passing score of 50% or greater has also been used.[92] Additionally, a comparative method of evaluating memory with failure, defined as a retention score of at least 20% lower on one side compared to the other has also been used.[68,69] They defined failure on both sides when both scores were less than 50%, with neither score being 20% lower than the other.

Memory asymmetry scores have been devised to determine lateralization of seizure onset. This refers to inter-hemispheric differences in memory scores which may be calculated from left injection score minus the right injection score,[61] or right injection score minus left injection score.[75] An asymmetry of at least two is interpreted as indicating lateralized impairment of memory function. In addition, an IAP asymmetry ratio has been calculated by dividing the higher hemispheric score by the lower score.[95] We recently developed a scoring technique to account for patient guessing in the memory recall. In this study, memory function was based on identification of a minimum number of items (pass/fail). This number was determined by the probability to guess a series of results correctly in our multiple choice paradigm ($p < 0.05$ in binomial probability tables). For example, if the patient was tested with 12 items, a score of 8 or more would be achieved by chance or by guessing less than 5% of the time and was therefore used as the cut-off score to demonstrate functioning memory.[96,97]

Clinical applications

Prediction of language lateralization

Prediction of language lateralization has been the primary objective of the IAP. Despite obtundation language lateralization was robust and was easily confirmed on repeated intracarotid amobarbital testing.[96,97] Although language is usually unilateral, different methods to score language lateralization during the Wada test [93,98] and advances in functional imaging[99] indicate that language lateralization is not just left or right, but a continuum with different degrees of laterality. In biased epilepsy patient populations this continuum may be shifted more to the hemisphere contralateral to the lesion. Möddel *et al.* at our center analyzed 445 bilateral IAPs and found that patients without neocortical lesions on MRI are left-hemispheric-dominant for language. Right-handed patients with left-neocortical lesions were more likely right-hemispheric language-dominant or had bilateral language-dominance. Left-handed patients with left neocortical lesions were most frequently right- or bilateral dominant.[100] Due to possible bilateral language representation unilateral lack of speech arrest may not reliably predict language outcome after resection in selected cases.[101] Exclusively in patients with Rasmussen's encephalitis of the dominant hemisphere, transfer of language and subsequently change in language lateralization on Wada testing has been described up to teenage years.[96,102] This, however, does not question the validity of the Wada test language lateralization, as language itself switched in these patients.

Prediction of memory deficits

Prediction of memory deficits can be divided into prediction of global aphasia and prediction of selective memory deficits.

Predicting postoperative global amnesia following temporal lobectomy

Prediction of postoperative global amnesia after temporal lobe resection has been another objective of the IAP memory test since its introduction.[10] The majority of patients who pass the test, i.e., who have good memory after injection of the hemisphere ipsilateral to the epileptogenic zone, do not develop significant postoperative amnesia (true negatives).[10,11,77] However, there is no acceptable 'gold standard' with which to compare the results of the IAP except by producing the syndrome itself. It is not possible to know how many patients would become amnestic without operating on all of them, and there are ethical constraints to subjecting a patient determined to be at risk by the preoperative IAP results to surgery.[83] There are no true validation studies. The test is used as if its validity were beyond question.[60]

Validity of the test can only be estimated indirectly. The IAP can identify true-positives, i.e., patients who failed the test and subsequently became amnestic after unilateral temporal lobectomy. In the survey from the Palm Desert conference, six of these patients were reported.[20,103] In five of these patients, resection included mesial structures and were spared. MRI studies in one patient showed no obvious abnormality in the contralateral hippocampus.

On the other hand, there are rare instances where the IAP has missed patients at risk for postoperative amnesia (false-negatives). In the same survey,[20] six respondents reported such patients. One of these had transient amnesia, while confirmation and details of the remaining cases were unknown.[103]

There are also reports of patients who failed the IAP but underwent temporal lobectomy including the hippocampus and developed no postoperative amnesia (false-positives).[103] Loring and colleagues described ten patients who failed either the early or the late item recognition portions of their test following injection ipsilateral to the seizure focus.[91] All had satisfactory performance on other tests of hippocampal function (hippocampal stimulation or cooling) and underwent temporal lobectomy including hippocampal resection. On follow-up neuropsychological assessment, none of these patients had anterograde amnesia, although some had reduction in material-specific memory. The practical implications of these false-positive patients are that some patients may be needlessly denied surgery if only Wada memory results are taken into account and that, in those who are operated on, the hippocampus may be unnecessarily spared with poorer seizure outcome than if it was removed.[104] The methodological factors also need to be considered when analyzing false-positive cases.[105] With use of some protocols, a patient may be more likely to fail the injection ipsilateral to the proposed surgery. Rausch and colleagues found that the majority of centers reported a failure rate of greater or equal 5% and the percentage of patients showing consistent failure ipsilateral to surgery ranged from 0% to greater than 30%.[20] Also, at some centers only patients considered to be at high risk for amnesia undergo a Wada test, while other centers the test is performed on all surgical candidates.

Surgery is frequently denied to patients who fail the test or the extent of resection is modified to spare the hippocampus and the parahippocampal gyrus.[31] Other options include repeating the IAP at the same or lower dosage,[62,106,107] using information from other complementary tests such as neuropsychology or neuroimaging, and performing selective arterial amytal procedures. At the Medical College of Georgia, memory was further tested during localized hippocampal cooling during surgery [108] or by low-level electrical stimulation via depth electrodes with simultaneous memory testing,[109] but these procedures are no longer employed because of failures.[110]

McGlone and MacDonald reported changes in pass/fail rate in eight of 18 patients in whom the IAP was repeated.[107] However, in seven of these eight patients, the changes were due to extrinsic factors such as obtundation. We reviewed 15 patients with intractable TLE who underwent repeat IAP because they had poor memory scores following initial injection ipsilateral to the epileptogenic zone.[111] In these patients memory scores increased from a mean of 32.9–56.9, and this change was not related to the difference in duration of ipsilateral EEG slowing, contralateral hemiparesis or muteness, side of language dominance, age, or presence or absence of a lesion. Following temporal lobectomy none became amnestic. In another survey of 1249 consecutive IAPs at our center the IAP was repeated in 4% of patients due to unsatisfactory information on either language or memory lateralization.[96,97] Repeated memory test results were less consistent across tests, and memory lateralization was unreliable in 63% of the patients. However, these results may have been influenced by obtundation, varying dose of amobarbital, testing of both hemispheres on the same day, unblinded observers,

fluctuating cooperation of the patients and a biased sample of patients.[96,97]

In a group of patients who underwent modified surgery, sparing the hippocampus because of IAP failure Jones-Gotman found that the Wechsler Memory Scale memory scores were significantly worse before and after surgery than in patients who had passed the IAP.[104] Their results suggest that patients who fail the IAP have poorer memory and their memory remains disproportionately worse after surgery.

In summary, an accurate estimate of the usefulness of the IAP in predicting postoperative amnesia is difficult, and its validity for this purpose remains a concern. The considerable variation in patient characteristics, technique, and interpretation of results across centers is a major problem. Further studies investigating test reproducibility and the effects of methodological and patient differences are necessary.

Predicting selective memory deficits

The initial indication of the use of the Wada test in relation to memory was to predict who may be at risk to develop global amnesia after temporal lobectomy. However it was well recognized that postoperative global amnesia is rare after unilateral temporal lobectomy, and that a rather mild material-specific deficit commonly occurs.[76] Subsequently studies tried to extend the utility of the IAP memory testing to predicting more selective modality-specific deficits. Based on pre- and postoperative neuropsychological tests, decrements on verbally based tests following dominant temporal lobectomy have been found in several studies.[28,32,34,36,81,112,113] There appears to be an inverse relationship between the amount of verbal memory decrement and the preoperative level of functioning. Patients who are functioning higher preoperatively show greater decrements than those who are poorly functioning.[28] However, a similar decrement in visual memory scores has not been convincingly documented following nondominant temporal lobectomy.

In 1991 the Cleveland Clinic group reported that an absolute ipsilateral IAP memory value of <67% was not associated with a decrease in modality-specific memory after temporal lobectomy, but when ipsilateral failure was defined by a comparative method (retention score at least 20% lower after ipsilateral than contralateral injection), the results showed greater differences between groups.[69] Four patients with left temporal lobectomy who failed the IAP had a median postoperative decrease of the Wechsler Memory Scale-Revised (WMS-R) Verbal Memory Index score of 14%, while 16 patients who passed the IAP had a decrease of 7%. This difference was not statistically significant but suggested that patients with lower ipsilateral memory performances may be at greater risk for memory decline. Loring also found that memory asymmetries, but not absolute values, following left or right injection may be predictive of verbal memory decline following left temporal lobectomy.[114]

Although these studies examined material-specific postoperative deficits, they used global IAP memory scores, i.e., using a wide variety of items including objects, words, and designs. They made no attempt to correlate memory for material-specific items with material-specific postoperative scores. Rausch and Langfitt grouped their IAP items based on the amount of verbal encoding upon which they were presumed to depend.[83] An unfamiliar design was regarded as a nonverbal item, whereas a printed word was regarded as a verbal item. Their results suggested that left but not right temporal lobectomy patients who fail to remember the printed word following ipsilateral IAP have a worse postoperative verbal memory performance.

There are several studies that have investigated the importance of the contralateral injection in predicting material specific post-surgical memory changes.[42,76,91] In the study by Kneebone *et al.*,[76] 63 patients who passed their contralateral IAP subsequently underwent left temporal resection. The patients with a pass score on Wada, defined as equal or greater 68% correct recognition of early presented items when strength was <3/5, had a greater postoperative verbal memory deficit measured by the WMS-R than the patients with left temporal who failed the contralateral IAP. When the contralateral IAP recognition memory score was used as a continuous variable rather than pass/fail variable the contralateral memory IAP recognition score was significantly correlated with postoperative changes in the WMS-R verbal memory and Logical Memory. This relationship was not found in right temporal lobe patients with regard to visual memory and failure of the contralateral IAP. Similar to this Stroup also found that patients with left TLE and high memory scores on contralateral IAP were at a greater risk for postoperative verbal memory deficits.[115] This group studied the relationship of the material specific aspects of the IAP and the material specific changes in memory after surgical resection. They found that the IAP memory related to postoperative verbal memory but not to visuospatial memory change after injection ipsilateral to the epileptogenic zone when relying on the contralateral memory. This is consistent with the functional reserve model of memory.[116]

Sabsevitz investigated memory outcome in the expected asymmetry and unexpected asymmetry groups by IAP and found that patient with left temporal lobectomy and reversed IAP asymmetry have a poorer memory outcome as well as a poorer seizure control.[117] They concluded that patients with reversed Wada asymmetry were at greater risk for memory deficit after surgery. The reversed asymmetry group showed a significant decrease in the selective reminding test. This reversal may relate to two possible hypotheses. The ipsilateral hippocampus is minimally sclerotic or intact or secondly there is a reorganization of the verbal material to the right temporal lobe.

Contrary to that the group from the UCSF epilepsy center found a significant number of their patients with left TLE, 36%, had a reversed memory asymmetry and this did not predict a decline in postoperative verbal memory deficit. This may relate to the fact that they used mixed stimuli rather than real objects for memory testing. At Cleveland Clinic we found that patients with TLE who demonstrated a reversed memory asymmetry on Wada testing had a prolonged period of dysphasia after left internal carotid injection and this factor may be responsible for lowering of the right hemisphere memory scores with a subsequent reversal of memory asymmetry.[118] We concluded that reversed

memory asymmetry does not predict postoperative verbal memory change.[118]

Lateralization of the epileptogenic zone

Prediction of epileptogenic zone laterality by memory results

The IAP may also assist in lateralization of the epileptogenic zone in patients with TLE. Although the IAP was initially not used for this purpose, Milner noted that in 11 of the 12 cases with memory disturbance, injection was contralateral to the side of the epileptogenic lesion.[10] In 1981 Engel specifically proposed the use of the IAP to lateralize the epileptogenic zone in patients with TLE.[119] In 1989 Rausch subsequently demonstrated impaired memory performance on the IAP following contralateral injection which correlated strongly with the hemisphere from which the seizures were originating in 19 of 30 patients with intractable complex partial seizures.[53] None of the patients who underwent surgery failed the IAP following injection ipsilateral to the epileptogenic zone. At our institution similar results were found: in a series of 37 patients who underwent temporal lobectomy, memory was significantly lower following contralateral injection than ipsilateral injection.[68,69] The lateralizing significance of the IAP for the more epileptogenic hemisphere was greatest in patients with profound amnesia, with memory score from contralateral IAP of <33%. Additionally, the epileptogenic left temporal lobes showed worse memory function than epileptogenic right temporal lobes. Many other investigators have cnfirmed that the IAP, especially the contralateral IAP, is useful in defining the lateralization of the epileptogenic zone.[53,56,57,62,75,120–127]

Perrine studied the relationship of the IAP difference scores and the lateralization of the epileptogenic zone.[75] The IAP difference score was defined as memory score after right injection subtracted from the memory score after the left injection. This was performed for 70 patients with left-hemisphere language and TLE without an associated structural lesion. One point was added to the score after left-hemisphere injection to compensate for the effect of the dysphasia on memory. A difference score of <–1 indicated right memory better than left memory and was thought to predict a left hemisphere epileptogenic zone. A score of >1 indicated left memory better than right memory suggestive of a right-hemisphere epileptogenic zone. Scores in-between these two values was indeterminate in lateralizing the epileptogenic zone. This method classified 50 of the 70 patients (71.4%). Of these 50 patients, 100% of the right and 98.0% of the left were correctly lateralized.

The influence of timing of stimulus presentation after injection on correct lateralization of seizure foci has been studied by Loring *et al.*[128] They found that recall for items presented shortly after injection had greater lateralizing value than recall for items presented after partial return of language function.[129] In this study material-specific stimuli were used to assess the role of the IAP in lateralization of seizure foci in 45 left-hemisphere language-dominant patients with TLE. Patients with right TLE had significantly worse memory for verbally mediated stimuli (words, object drawings, colored shapes) with left as compared to right injection. Patients with left TLE had worse memory for a nonverbal stimulus (abstract design) after right injection than after left injection. They concluded that material-specific memory remains intact in the hemisphere contralateral to a seizure focus, but wider representation may occur for stimuli normally dominant for the hemisphere with the seizure focus. Other studies have shown similar results with memory for words and numbers being worse following the dominant side injection than the nondominant side injection and recognition of faces being better following left rather than right injection in patients with left TLE.[82,130,131]

Le Jeune compared three different techniques of IAP memory procedures, in defining lateralization of the epileptogenic zone [120] including the Montreal, Seattle, and Interview procedures. They found that the Montreal and interview techniques for right–left injections each significantly differentiated the patients into right and left seizure onset foci. They produced the correct lateralization in >70% in their original sample of 100 patients as well in an additional cross validation sample of 60 patients. However the Seattle method did not differentiate the patients correctly.

Pathology may influence the predictive value for the epileptogenic zone. The IAP correlated extremely well with the side of the epileptogenic zone in the group of patients with unilateral mesial temporal sclerosis (MTS) but not in the group without MTS.[132]

Determination of seizure laterality with neuropsychological test results and the IAP has been compared.[121,133] Brown found that seizure lateralization was correctly predicted by IAP in 83% and this was similar to standard neuropsychology 82%.[122] Kneebone found that the IAP was superior to the standard neuropsychology evaluation in predicting seizure laterality.[133] The results of discriminatory function analysis resulted in correct lateralization of the seizure onset in 59.3% for the WMS-R, 57.1% for the WRMT and 81.5% for the IAP. This analysis was significantly better than clinical analysis. However not all investigators have found the IAP to be superior to neuropsychological test results in defining seizure lateralization. Privitera found neuropsychology significantly more accurately.[121]

Use of intracarotid barbiturates in secondary hypersynchrony

Besides prediction of the seizure focus by calculation of memory asymmetroes, intraarterial injections of barbiturates may also serve as a tool for distinguishing independent epileptogenic zones in patients with bilateral hypersynchrony or generalized EEG patterns and a unilateral lesion on imaging.[134–136] In these cases, injection ipsilateral to the epileptogenic zone may interrupt 'generalized' of bisynchronous EEG discharges, whereas contralateral injection will only mask the injected hemisphere.

Predicting seizure outcome

All patients undergoing IAP are not operated on. Unless all patients undergo surgery, there is no 'gold standard' with which to compare the results of the IAP for correct lateralization of the epileptogenic zone. In those who are operated on, seizure freedom or significant reduction may be used as the 'gold standard'.[83,137] Rausch and Langfit studied two groups of

patients with TLE who underwent temporal lobectomy and had adequate follow-up.[83] One group underwent depth electrode evaluation, whereas in the other group, it was felt that seizure foci were well localized and depth electrode evaluation was not required. IAP memory scores were compared to the side of focus and seizure outcome. In the group of patients who underwent evaluation with depth electrodes, the IAP predicted good outcome (Engel class I and II) in at least two-thirds of cases in whom it confirmed the side of the epileptogenic zone. Similar results were seen in the other group but these were not statistically significant.

Perrine used a memory difference score calculated as right minus left hemisphere memory to predict seizure laterality and seizure outcome in 70 left-hemisphere language-dominant patients.[138] A difference score of >2, with 1 point added to the left hemisphere injection score to correct for aphasia, correctly predicted seizure laterality in 98% of patients and seizure-free outcome at 1-year follow-up in 80%.

Hamberger and colleagues proposed using the IAP to distinguish between mesial and neocortical TLE.[139] Using a memory assymetry score defined as the difference in memory scores after right and left injection, they found that the mean asymmetry scores were lower in a group of patients with neocortical TLE (<25%) than in a group with mesial TLE (≥25%).

Loring *et al.* investigated the IAP memory performance with seizure outcome following temporal lobectomy.[123] He examined the relationship of an asymmetry score to seizure outcome at 1-year follow-up in patients with no radiological evidence of structural lesions other than hippocampal sclerosis. In patients who were seizure free, asymmetry scores were greater than in patients who continued to have seizures. Patients with asymmetry scores of 3 or greater were more likely to be seizure free than patients with scores of < 3. Sperling *et al.* studied 117 patients and included concurrent factors that might affect outcome such as age at first seizure, presence or absence of tumor, and full scale intelligence quotient in their analysis.[140] They concluded that the IAP correctly predicted seizure relief independently of these factors.

At Cleveland Clinic Lancman and colleagues studied the sensitivity, specificity and the predictive value of the IAP for predicting seizure outcome after temporal lobectomy.[141] They studied 108 patients who underwent temporal lobectomy and who had at least 1-year follow-up after surgery. They found that at a 30% asymmetry of recall specificity for favorable outcome Engel class I and II was 100% (95% confidence interval). However the sensitivity was only 51% (95% confidence interval). The positive predictive value was 100% and the negative predictive value 34%. They concluded that asymmetric recall on the IAP was highly specific but not very sensitive and the positive predictive value was very high.

Sabsevitz and colleagues divided patients with left TLE undergoing resection into two groups: expected memory asymmetry where memory is better in the hemisphere contralateral to the proposed resection and the reversed asymmetry group.[117] They found patients with reversed asymmetry had a greater risk for memory difficulty as well as a poorer seizure outcome than the patients with IAP memory in the expected memory asymmetry group. All 12 patients with expected Wada memory asymmetry were seizure free at 6 months. In patients with reversed Wada memory asymmetry only four of nine patients met criteria for Engel class I.

Complications

A retrospective chart review of 447 patients undergoing the IAP at the Cleveland Clinic between 1993 and 1996 revealed four cases with clinically significant complications (0.96%). These complications consisted of a cerebral infarction, a transient femoral neuropathy, a temporo-mandibular joint dislocation and a left internal carotid artery spasm causing hemiplegia, hemisensory loss and hemianopia, which resolved within 15 minutes.[142] An additional study at our center in 677 patients covering the period from 1996 to 2002 found complications in 11.6%. During the procedure, encephalopathy (8%), seizures (1%), bleeding from the catheter insertion site (0.1%) and allergic reaction to contrast (0.1%) was seen. Interestingly, seizures were more frequently seen after methohexital than after amobarbital injections suggesting possible epileptogenic effects of methohexital.[143] After the procedure, 0.6% of patients were diagnosed with strokes, 0.6 % had transient ischemic attacks, and 0.4% had dissections of the carotid artery. Additionally, hemorrhage at the catheter insertion site and infection was seen.[25,26] Other studies also report behavioral and emotional reactions during and after the IAP.[144,145]

Conclusion

The IAP is a useful tool to determine language lateralization in selected patients undergoing epilepsy surgery. Additionally, the Wada test may also predict who is at risk for material-specific memory change particularly for verbal material after dominant temporal resection. There is preliminary evidence that IAP findings are predictive independently of other factors. Alternative speech lateralization techniques by means of functional transcranial Doppler ultrasound,[146] by functional MRI,[147,148] by PET,[149] by MEG[150,151] or by means of repetitive transcranial magnetic stimulation[152–155] have been described and may complement or even replace the Wada test for language lateralization. Additionally, memory lateralization has been attempted with alternative techniques such as functional MRI.[23,156,157] Noninvasive tests may eventually render an invasive procedure such as the IAP obsolete.[110,158,159] Although these tests may provide much of the same information as the IAP, they rely on activation of cognitive function, whereas the IAP, which is an inactivation procedure, more directly models the effect of surgery.[21,22] However, imaging techniques continue to be developed and refined. They may ultimately replace the IAP when an imaging paradigm for identification of language regions to be spared from resection, and for valid and reliable prediction of postoperative memory deficits can be established.

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94 Event-related potentials in patients with epilepsy

K Usui and A Ikeda

Introduction

Monitoring and evaluation of brain activities and functions are essential before, during, and after the surgery of patients with epilepsy. The pre-surgical evaluation incorporates the selection of candidates for surgery, characterization of seizure types, identification of treatable causes, and localization of the epileptogenic zone.[1] Intraoperative monitoring is performed to obtain accurate information of the extent of resection and to assess its completeness.[2] Post-operative evaluation is conducted to assess the outcome: seizure elimination or reduction in frequency.[3]

The goal of pre-surgical evaluation of candidates for epilepsy surgery is to identify the abnormal cortical region that generates seizures and to provide necessary information to remove or disconnect the region without precipitating any significant functional impairment. A variety of noninvasive diagnostic tests are used to help localize the putative seizure focus using electrophysiological and/or imaging methods.

In electrophysiological evaluation, the electroencephalogram (EEG) is the primary resource. In noninvasive recording, the simplest recording can be conducted with a pair of electrodes attached to the surface of the human scalp and connected to a differential amplifier. EEG is the output of the amplifier which shows a pattern of variation in voltage over time. While its original role is to detect abnormal electrical activities related to epilepsy, EEG is currently also applied to objectively evaluate specific brain functions using event-related potentials (ERPs). ERPs are based on the observation that the brain activities change in response to a stimulus given from the outside world. Voltage changes, or potentials, which occur time-locked to the stimulus, constitute the ERPs. In early studies, the term 'evoked-potential' or EP was employed because the potentials were believed to reflect brain activity strictly 'evoked' by the presentation of the stimulus, or activity associated with basic sensory processes. The more neutral term 'event-related' was later introduced because it was realized that the potentials reflected more than just evoked activity. ERPs, therefore, can be described as voltage fluctuations that are associated in time with some physical or mental occurrence. These potentials can be recorded from the human scalp and extracted from the ongoing background EEG by means of filtering and signal averaging. The time-locked nature of ERP recording along with their millisecond resolution make ERPs very useful for determining the temporal sequence/location of cortical events.[4–6]

The consensus among neurologists and electrophysiologists is that the ERP reflects activity generated within the brain. However, the relationship between what is occurring within the brain and what is observed at the scalp is not transparent. ERPs recorded from the scalp are the reflection of net electrical fields associated with the activity of large populations of neurons. The electrical fields can be measured at the scalp only when the associated neuronal population have a certain common geometric configuration (which is perpendicular to the cortical surface) and are activated synchronously. Biophysical and neurophysiologic considerations strongly suggest that scalp-recorded ERP waveforms are principally a reflection of post-synaptic (dendritic) potentials, but not of axonal action potentials.[7–10]

It is certain, however, that much neuronal activity is never apparent at the scalp. In many neuronal populations, activity might not be synchronous enough to generate an electrical field that can be recorded at a distance. In addition, the electric field distribution is inevitably distorted and dampened by the layers of skull and scalp. When the noninvasive methods of evaluation are inconclusive to determine the origins of the epileptic focus or when the epileptogenic zone must be defined with high precision in relation to nearby eloquent cortex, invasive measurement of epicortical EEG or electrocorticogram (ECoG) and epicortical ERP are indicated.

Since pre-surgical evaluation includes several methods and no single technique can provide complete information on which the precise neurosurgical decision is based, the best combination of techniques for evaluation has not been defined yet. There are different opinions about the specific surgical procedures that produce the best outcomes for different types of seizures.[11]

This chapter is intended to be a concise reference for practicing epileptologists and surgeons to help determine the appropriate evaluation methods and procedures among which a variety of ERP should be included as essential techniques. Since thorough and detailed description of ERP is out of its scope, this chapter will describe benefits and limitations of both noninvasive and invasive ERP measurement in relation to the phases of evaluation.

Terminology

The ERP waveforms contain components that span a continuum between the exogenous potentials (obligatory responses determined by the physical characteristics of the eliciting

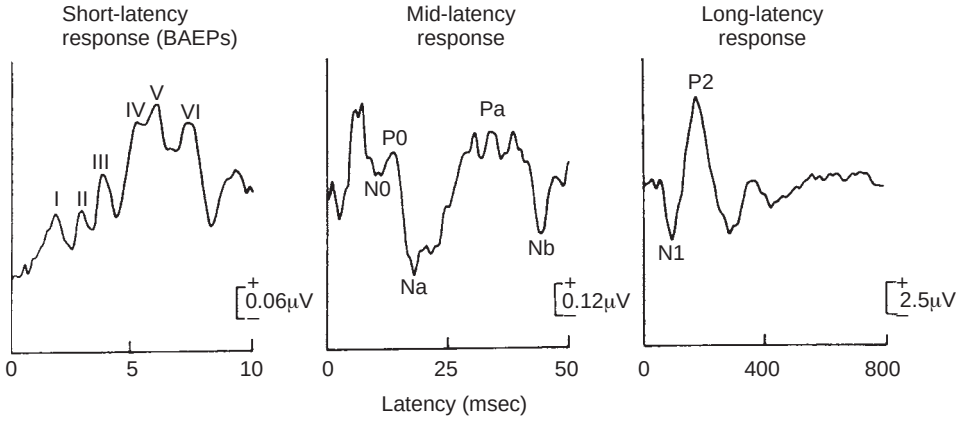

Figure 94.1 Auditory evoked potentials (AEPs) recorded from the vertex (Cz) in three sequential time periods. Early responses (also called brain stem auditory evoked potentials, BAEPs) and mid-latency components are regarded as exogenous. Long-latency components, N1/N100 and P2/P200, tend to be more endogenous (Reprinted with permission from Goodin DS, 1992.[5] Copyright 1992 Elsevier.)

event in the external world) and the endogenous potentials (manifestations of information processing in the brain that may or may not be evoked by the eliciting event). Principal factors that characterize ERP signals are their polarity and latency. Each ERP consists of a sequence of negative and positive voltage fluctuations. Each voltage fluctuation is labeled as component, and called by a name that denotes its polarity ('N' for negative and 'P' for positive) and characteristic latency after the stimulus onset. For example, P300 is a positive deflection occurring with a peak latency of 300 ms from the stimulus onset.

Potentials observed with the latency shorter than 100 ms from stimulus onset tend to be more exogenous and divided into three categories depending on their stimulus modality; visual evoked potential (VEP), auditory evoked potential (AEP) and somatosensory evoked potential (SEP). Strictly speaking, the terms EP and ERP refer to similar but not identical events. Considering the characteristics of the causes and/or origins, the potentials with latency shorter than 100 ms are usually called evoked potentials (EP) because they are believed to be 'evoked' by the presentation of the stimulus, or associated with basic sensory processes. The potentials with the latency longer than 100 ms, by contrast, are usually called event related potentials (ERP) because they tend to be more endogenous (Figure 94.1).

Numerous different components have been identified, such as N200, P300, N400, P600, CNV, and so on. Each component is evoked by a specific stimulus sequence, or paradigm, designed to produce the component. There has been much debate on each component with regard to its sensitivity to specific cognitive factors or its functional significance. In this chapter, only the components that have been investigated in relation to epilepsy will be discussed.

Noninvasive evaluation

In noninvasive pre-surgical evaluation, there are two clinical applications of ERPs. One is to use known components of ERPs to identify specific functional areas which should not be damaged by surgical procedures. Since some ERP components are confirmed to be generated in a specific functional area, the identification of the target area is more accurate with the help of ERP. The other is to use ERPs to detect functional abnormality. The abnormality may appear as changes in latency, amplitude, topography, and/or waveform of specific ERPs.

In many cases, crucial functional areas can be approximated by using anatomical landmarks.[11] In pathological brain, however, those landmarks are often distorted and the localization using them tends to be imprecise. In addition, functional areas may 'shift', which blurs the boundary of the targeted functional area.

SEPs obtained by electrical stimulation of peripheral nerves have come to be used for the localization of functional areas in an attempt to compensate for the inaccuracy of landmark study before surgery.[12] Historically, the first component of SEP, N20, was obtained by the electrical stimulation of the median nerve, and its characteristics are reported in the literature.[13–18] However, since noninvasive SEPs recorded at the scalp still do not have sufficient spatial resolution to localize the signal in a specific lobe or gyrus even with the insight obtained by invasive SEPs, the magnetic counterpart of ERP, event-related magnetic fields (ERFs), are also often used for noninvasive evaluation, which provides better spatial resolution. (Magnetoencephalography (MEG) is described in detail in another chapter of this textbook.)

In brief, MEG measures magnetic fields produced by electric current originating from synchronously activated neuronal populations using multiple channels of a superconducting quantum interference device (SQUID), a sensitive detector of magnetic flux.[19,20] Since it has as good temporal resolution as EEG and far better spatial resolution, the magnetic counterpart of N20, called N20m, is used to identify the SI cortex. Although MEG has a limitation, careful selection of target components will make ERF an efficient tool for pre-surgical evaluation.

As for the functional abnormalities, noninvasive ERPs have been used in research to identify the hemisphere from which epileptic seizures originate. In patients with temporal lobe epilepsy, P3 or P300 was recorded in pathological hemispheres

and compared with those in normal hemispheres.[21–25] The attempt to use scalp-recorded ERPs as a lateralizing tool of epileptic foci, however, has been mostly unsuccessful or at least not established as a standardized procedure. Although there is a possibility that the failure in the detection of signal difference between hemispheres might be partly due to insufficient coverage of the head with limited numbers of electrodes, the scalp-recorded ERP inherently has a limitation in separating neuronal activities between two hemispheres.

New techniques such as a topographic map[25,26] and a source localization using brain electrical source analysis procedure (BESA)[27] may broaden the applicability of scalp-recorded ERPs.

Invasive evaluation

Invasive evaluation is preferable when the highly precise identification and localization of specific functional area/areas in relation to the epileptic zone are necessary. Consideration of the type of disorder and possible surgical procedure is one of the essential factors to determine the methods for evaluation. If epileptic foci or other brain lesions that are to be resected are in the surrounding areas of the primary cortices for motor or sensory function, or crucial areas for higher cognitive function such as memory or language, pre-surgical and/or intraoperative localization of functionally important cortex is of utmost importance. Since the evaluation must provide crucial information for the decision of the extent of resection and the approach to the pathological area, noninvasive approach alone is not satisfactory in most of cases.

For invasive evaluation, surgically implanted electrodes are commonly used for a certain period of time, usually several days or two weeks, to localize seizure focus. The electrodes used for the evaluation include subdural grids or strips enmeshed in plastic, intracranial depth electrodes, foramen ovale electrodes, and others. Selection of electrodes depends on the type of seizures and the area that is most likely involved. When, for instance, signals from gray matter in deep areas are needed, depth electrodes are employed because no other electrodes provide access to that area. Subdural electrodes, by contrast, are directly implanted in the subdural space, hence they are less invasive than depth electrodes. All types of electrodes should be placed closer to the anticipated seizure foci based on the information obtained by noninvasive evaluation.

There are two main techniques in invasive procedures to investigate cortical functions; electrical cortical stimulation and epicortical ERPs. Since the former will be described in other chapters, this chapter is focused onto the latter. Compared with the noninvasive methods mentioned in the previous section, the most significant advantage of invasive ERPs is that they directly record neuronal activities occurring in the brain. Subdural electrodes monitor the activities beneath the electrodes, and depth electrodes detect the electric field from the contacted area.

Although invasive methods provide significant information that cannot be obtained by other techniques, attention has to be paid to the fact that invasive methods are not without problems. Monitoring using electrodes detects activities only in the areas where electrodes are placed. Even with the limited precision, whole-brain examination in general is conducted using scalp-based noninvasive methods.

Since invasive evaluation includes a wide variation in terms of the type of electrodes, techniques, as well as analysis and interpretation of data, which is not always straightforward, the detailed description of the whole aspect of ERPs would require an entire book. Instead of providing scant information of wide-ranging topics, this section will focus on some of the recent significant findings. The following subsections include new approaches using both subdural and depth electrodes, interpretation of memory-related component, language-related components, components associated with motor planning and with the integration of sensory information. As for the primary cortex for vision, audition and somatosensory sensation, identification is usually performed by using epicortical VEP, AEP, and SEP, respectively, details of which will be discussed in other chapters.

Temporal lobe epilepsy and invasive ERPs

Application of depth electrodes to mesial temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is the most common type of partial epilepsy.[28] Mesial temporal lobe epilepsy (MTLE) occupies a large portion in TLE and is often surgically treated.[29] In most cases, the epileptogenic zone is in the medial temporal structures, including hippocampus, amygdala, and adjacent neocortex. Precise localization before resection, therefore, requires invasive evaluation that provides information from deep areas where only intracranial depth electrodes have access. Since the objective of pre-surgical invasive evaluation is not only to localize epileptic foci but also to decide the extent of resection without precipitating any significant functional impairment, ERPs are used also to identify specific functional areas.

It should be noted in practice, however, that intracranial monitoring may involve greater risk than resective surgery itself and should be used only after appropriate noninvasive monitoring has been completed so that a hypothesis of seizure onset has been formulated and a clear goal of the investigation has been defined.[11]

Identification of memory-related ERPs

Research results suggest that memory is not just a storage of information in a specific area but coordinated functions among various regions in the brain as a sophisticated neural network.[30–32] It is generally indicated that the medial temporal structures play an important role in this particular cognitive function.[33–35] Clinical observation revealed that patients with MTLE, whose medial temporal lobes are involved in epileptic activities, show some memory impairment, although the severity varies depending on the patient.[36]

Among several ERP components regarded as memory-related, two components, P300 and 'N400 and P600 complex' are associated with the temporal cortex. Hence they are significant for pre-surgical evaluation of patients with MTLE and have been investigated using various experimental paradigms.

P300 is evoked in a relatively simple task of target detection, called an 'oddball paradigm', in which subjects are requested to react only to the rare target stimuli amongst the

frequent 'standard' stimuli. The rare target stimuli provoke a potential with a peak latency at around 300 ms from the stimulus onset.[37,38]

The anatomical localization of generators of P300 has been reported using invasive recording (Figure 94.2). Multiple generators have been identified, including in the hippocampus, frontal, and parietal lobes.[39–44] In medial temporal structures, bilateral hippocampi separately generate the P300. The clinical significance of P300 in the pre-surgical evaluation is also suggested in studies using depth electrodes sited in the bilateral hippocampi. Unilateral absence or decrease in amplitude of this component was reported to be predictive of the lateralization of epileptic focus and hippocampal sclerosis.[45–47]

In the case of scalp recording, it is difficult to conclude that the scalp-recorded P300 is the summation of the generators identified in invasive recording. The major contributor of scalp-recorded P300 is probably not the hippocampus but may be in an inferior parietal region[42] or midtemporal and inferior frontal area.[44]

P300 generally represents selective attention and information processing. Such detailed functional meanings as 'context updating'[48] and 'context closure'[49] are also reported, but the interpretation is not conclusive.

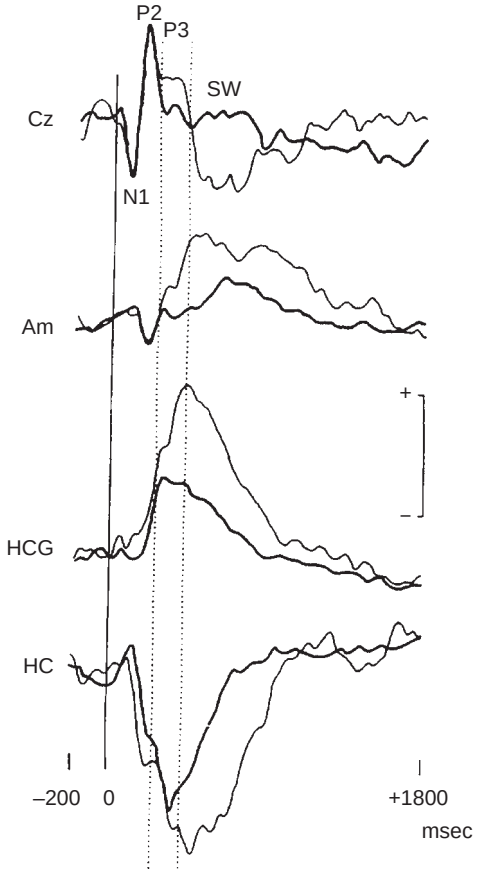

Figure 94.2 P300 recorded from scalp (Cz) and from the medial temporal structures by skin and depth electrodes, respectively. Thin lines show responses to rare stimuli and thick lines to frequent stimuli. Scalp-recorded P300 and responses from the medial structures present different waveforms. Am: amygdala; HCG: hippocampal gyrus; HC: hippocampus; SW: slow wave. (Reprinted with permission from Halgren E *et al.*, Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science* 210: 803-05.[39] Copyright 1980 AAAS.)

'N400 and P600 complex' was first recorded from depth electrodes placed in the medial temporal structures by using a paradigm to test recognition memory.[50] During the task of discriminating between novel stimuli and repeated (i.e., old one which is also in the memory) stimuli, a complex potential, consisting of a negative peak around 400 ms (N400) followed by a positive peak around 600 ms (P600) from the stimulus onset, is evoked. The complex varies in amplitude depending on the novelty of stimuli. The amplitude of N400 becomes larger in response to the novel stimuli than that are evoked by repeated stimuli. The amplitude of P600, by contrast, becomes larger in response to the repeated stimuli than that are evoked by novel stimuli. The phenomenon is called an 'old/new effect', which has been replicated in several other studies[36,51–57](Figure 94.3).

The N400 and P600 complex was indicated to have multiple generators in temporal, frontal, and parietal lobes.[58] Among these generators, ones in the medial temporal structures have been extensively investigated to assess the effect of epilepsy on this memory-related ERP component. Several researchers recorded the ERP complex from depth electrodes placed in the medial temporal structures. The results, however, varied between studies; some studies claimed that the ERP complex was sensitive to lateralize epileptic foci,[36,53,55] while others did not.[50,51]

In post-surgical states, the ERP component was also investigated. Groups of patients who had underwent left or right anterior temporal lobectomy and unoperated or normal controls performed the recognition paradigm. One study indicated that the old/new effect diminished in the patients with left-side lobectomy, while the patients with right-side lobectomy and unoperated patients showed the old/new effect.[59] There was, however, a contradictory result presented from other studies.[52]

Although the findings have contributed to the investigation of memory, the N400 and P600 and their old/new effect still need further evidence to be established as the evaluating method in epilepsy surgery.

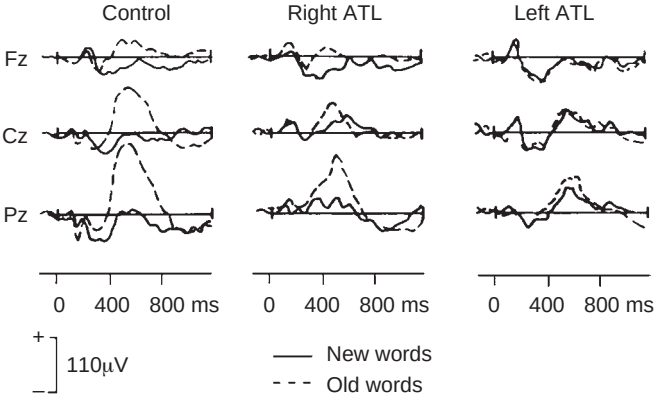

Figure 94.3 Memory-related N400/P600 complex and old/new effect. Grand-average ERPs from midline electrodes evoked by correctly recognized old and new words are shown. ERPs are presented separately for unoperated control subjects, and for subjects who had undergone right- or left-sided anterior temporal lobectomy. Old/new effects are exhibited in the ERPs of controls and right-sided patients but not in those of left-sided patients. ATL: anterior temporal lobectomy. (Reprinted with permission from Smith and Halgren, 1989.[59] Copyright 1989 APA.)

Application of subdural electrodes to the left basal temporal area

Among cognitive functions associated with the temporal lobe, language is one of the most important together with memory. The classical approach to studying the relationship between brain lesion and behavior identified Wernicke's in the posterior superior temporal area, as well as Broca's in the inferior frontal area. In addition to these classical language areas, recent studies using electrical cortical stimulation revealed the existence of another language area in the left basal temporal area (LBTA).[60–68]

Since the evaluation of the LBTA requires probes in the subdural space, strips or grids are inserted into the space and the technique is less invasive than depth electrodes. Subdural strips are made of flexible Silastic or Teflon strips with embedded stainless steel or platinum contact disks. Different types of electrodes with up to 10 contacts or more are used.[2]

Localization of the functions in LBTA is crucial in the surgical treatment of MTLE because LBTA is sometimes involved in resection due to insufficient pre-surgical evaluation, which occasionally results in the occurrence of post-surgical language impairment, mainly anomia.[63,69] Sparing of LBTA can be beneficial in this respect.[70]

Identification of language-related functions

In the basal temporal area, two language-related ERP components are known; N200 and N400.[71–74] Both of them are reported to be evoked by visual stimuli of written language but with different cortical localization. The conditions for them to be evoked are also different.

N200 is evoked by letter strings, both words and nonwords. The component is regarded as language-specific because other visual stimuli, such as pictures of objects do not provoke the potential. N200 was recorded on the electrodes located in the posterior portion of basal temporal area.[71] The existence of this ERP component indicates that the cortical area is involved in written language processing.

Localization of the areas that exhibit N200 is not straightforward because it was recorded bilaterally both in the language-dominant and nondominant hemisphere in several studies.[71,74] The combination with other methods, such as electrical cortical stimulation, is necessary for the final decision to confirm that the cortical area from where the N200 is recorded is crucial for written language processing.

N400, the most well-known language-related component, was first reported in a study using scalp electrodes.[75] In a landmark study, Kutas and Hillyard[75] showed that the amplitude of the N400 was a measure of 'semantic incongruity' (Figure 94.4). In particular, large N400s were observed for words that violated semantic context. Further research has suggested that the N400 amplitude is inversely proportional to the expectancy of the word in a sentence ('close probability').[76] N400 amplitude appears to decrease across word positions in a sentence.

An invasive examination of language function was conducted by employing intracranial depth electrodes inserted in the medial temporal lobe[72,73] using two types of sentences visually presented word by word; one ends with a word appropriate for the context and the other with a word that makes the sentence incomprehensible. A negative field potential with a peak latency around 400 ms was evoked only by incongruous sentence-ending but not by normal ending. The field was focally distributed in the anterior medial temporal lobe (AMTL), anterior to the hippocampus and near the amygdala in both hemispheres.[72,73] The potential was named 'AMTL N400'. In the recording using subdural electrodes placed on the anterior portion of the basal temporal region just inferior and lateral to the amygdala recorded a positive potential at the same latency (which is called 'AMTL surface P400'). The spatial distribution of the potential recorded from depth and subdural electrodes indicated the generators in the neocortex near the collateral sulcus and anterior fusiform gyrus.[72,73]

Although the anatomical localization of the component is achievable, identification and/or interpretation of language

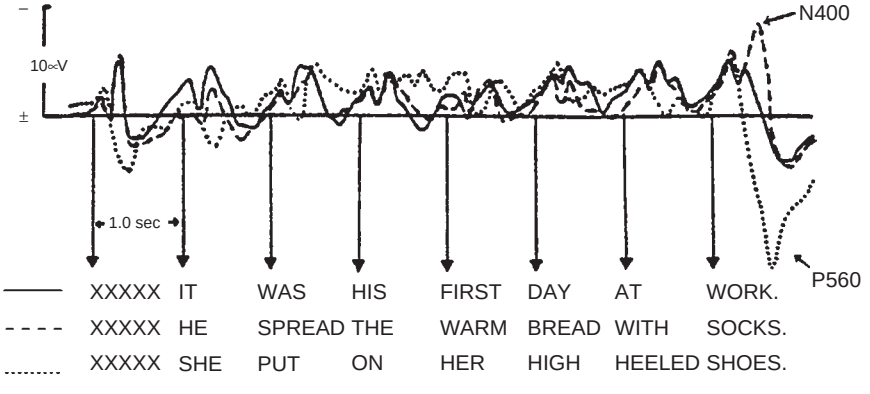

Figure 94.4 Language-related N400 recorded from midline scalp electrodes. Sentences with normal ending, with semantically incongruous ending and with physically incongruous ending are shown to subjects. Only the semantically incongruous final words evoke a large negative deflection. (Reprinted with permission from Kutas M and Hillyard SA, Reading senseless sentences: brain potentials reflect semantic incongruity. Science 207:203–205.[75] Copyright 1980 AAAS.)

function borne by each component is not conclusive. The potential was recorded bilaterally with no obvious interhemispheric difference in amplitude.[72,73] There was no report regarding the post-surgical evaluation of this ERP component, as well as the language ability of the patient, after the resection of this particular area. In pre-surgical evaluation, the existence of this ERP component and the results of electrical cortical stimulation must be compared for the final decision of the extent of the area to be resected.

Frontal lobe epilepsy and epicortical ERPs

Partial seizures of frontal origin are candidates for surgical treatment when the clinical manifestations and diagnostic evaluation localize an epileptic zone in a resectable area. Frontal resections range from localized topectomies to complete frontal lobectomies and must be carefully individualized. Identification of the primary and nonprimary motor cortices is essential to avoid motor deficits and of anterior language cortex to avoid speech difficulties.[4]

Nonprimary motor cortices

Since the primary motor area and its examination by movement-related cortical potentials (MRCPs) or Bereitschaftspotential (BP) will be discussed in another chapter, this chapter focuses on issues in nonprimary motor areas which are considered to be associated with motor planning. Previous sections discussed the ERPs observed after the stimulus onset, i.e., components that follow the events. Historically, however, a potential that precedes the event was also identified by Kornhuber and Deeke.[77] In their studies of voluntary movements, they found slow negative deflection of potentials that preceded the actual production of a voluntary hand movement.

Regarding the motor functions, another important potential in this category of 'event-preceding components' is contingent negative variation (CNV). CNV was first reported by Walter and his colleagues in 1964.[78] CNV is evoked in a paradigm using pairs of stimuli presented with an interval of one or several seconds. The first stimulus is a 'warning' stimulus (S1) served as a cue for the next 'imperative' stimulus (S2) to which subjects are required to make a movement as a response.

CNV is a slow surface-negative deflection observed between S1 and S2. A noticeable feature of CNV is that, when the interval between S1 and S2 is set to 1.5 s or longer, not one but at least two components appear.[79] Interpretation of these two components, 'early CNV' and 'late CNV', so far varies. Early CNV, or an initial portion of CNV, is claimed to be a response to S1[80,81] and an expectation of S2 to a lesser degree.[82] Late CNV, or the posterior portion, is supposed to be an anticipation of processing S2[83] and a preparation for a motor response.[77]

CNV using a conventional paradigm and S1-choice-go/no-go paradigm showed contrasting results (Figure 94.5). Early CNV consists of two subcomponents; one is a 'signal-related' potential evoked by stimuli after both S1 and S2, and the other an 'early set-related' potential recorded in the first half of the S1-S2 delay period. These constituents of early CNV are observed in both conventional and S1-choice-go/no-go paradigms. Late CNV, however, showed a contrasting result. Late CNV consists of a 'sustained set-related' potential occurring mainly in the second half of the delay period and a 'movement-related' potential. The subcomponents of late CNV are evoked only by S1-choice-paired stimuli which require motor response after S2. In addition, paired stimuli with no-go S1 in the variant paradigm did not evoke late CNV.[84,85] In the mesial frontal area, especially the presupplementary motor area (pre-SMA), decision-related potentials were also described in both S1-choice/S2-choice reaction time paradigms (Figure 94.6).

Application of subdural electrodes to frontal lobe area

Subdural EEG recording has revealed the cortical generators of CNV. In the studies using auditory stimuli, late CNV was

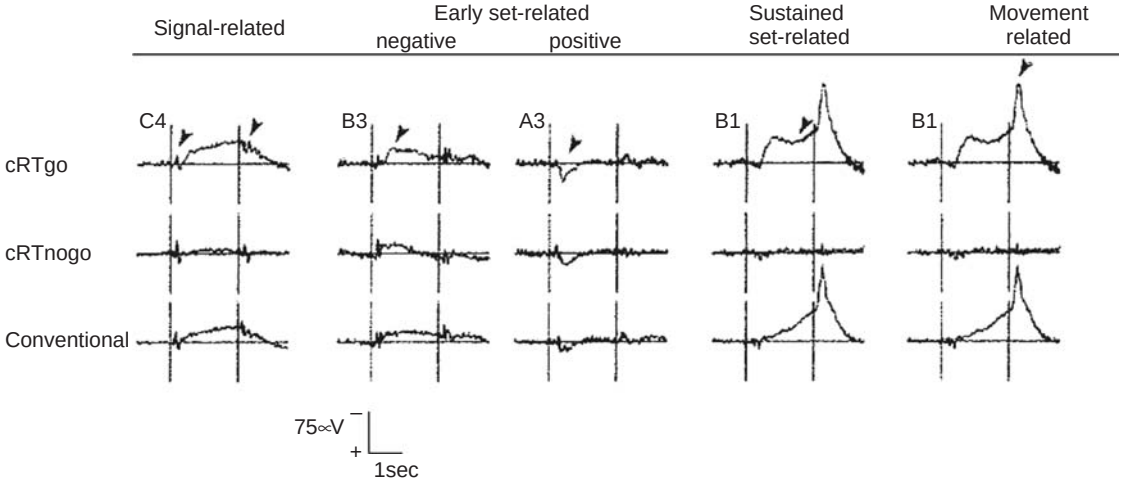

Figure 94.5 CNV recorded from subdural electrodes in two visuomotor tasks; (1) S1-Go/No-go-choice delayed reaction-time paradigm and (2) conventional S1-warning delayed reaction-time paradigm. Middle-finger extension was employed as a task response to S2 signals. The upper two rows show responses in the S1-Go/No-go-choice paradigm and the lowest shows responses in the conventional S1-warning paradigm. Arrowheads indicate each of the transient potentials occurring between S1 and S2. S1: green/red LED light; S2: yellow LED light; cRTgo: responses to choice delayed reaction to S1-Go signals; cRTnogo: responses to choice delayed reaction to S1-No-go signals. (Reprinted with permission from Matsumoto *et al.*, 2003.[85] Copyright 2003 Elsevier.)

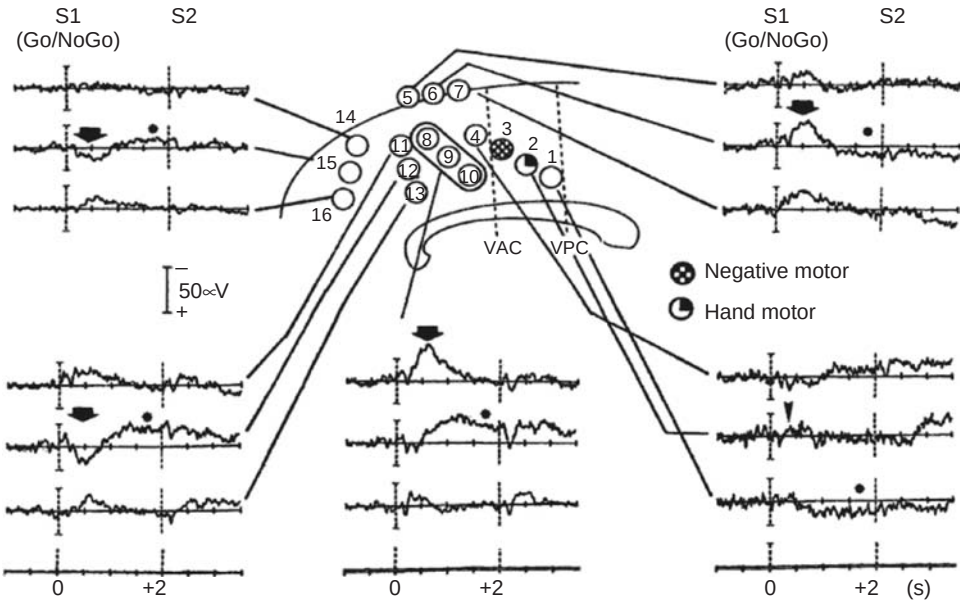

Figure 94.6 Decision-related potentials recorded from the medial frontal structures. Subdural electrodes are placed on the medial surface of the right hemisphere. In S1-Go/No-Go-choice and S2-reaction-time paradigm, transient potentials after S1 (indicated by arrows) are observed at pre-SMA, located rostal to VAC line. VAC line: a line on the anterior commissure perpendicular to AC-PC line. VPC line: a line on the posterior commissure perpendicular to AC-PC line (Reprinted with permission from Ikeda A *et al.*, 1999.[89] Copyright 1999 Oxford University Press.)

found to originate from the nonprimary motor cortices (pre-SMA, SMAproper, lateral premotor area), prefrontal area (mesial and orbitofrontal areas), and MI.[86–90]

In the 'go/no-go paradigm', the component was principally observed at the pre-SMA, starting around 200 ms and peaking at 600 ms from choice-related stimulus onset.[87] This may represent the characteristic function of cognitive motor control in pre-SMA. The generators of four components (two subcomponents of both early and late CNVs) were found to be located in a sequential manner from the rostal to the caudal part of the lateral premotor area.[85]

CNV may help to delineate the cortical functional area associated with motor planning or preparation. However, since late CNV has multiple generators including pre-SMA, SMA proper, the lateral premotor area, and MI, further delineation between the closely located, and yet distinct, structures (lateral premotor area versus MI, pre-SMA versus SMA proper) may require other methods such as electric cortical stimulation or vice versa.

Other functional areas and ERP components

Although parietal and occipital resections are performed much less commonly compared with the frontal lobe, patients with partial seizures from other extratemporal sites may also be candidates for surgical treatment when clinical manifestations and evaluation indicate an epileptic region in a resectable area. The results of resection for extratemporal epilepsy are variable depending upon patients and method of pre-surgical evaluation. Overall results are not so satisfactory for extra-temporal resections as for temporal removals. Nevertheless, extra-temporal resections including the frontoparietal and occipital regions can give excellent results.[11]

The basal aspects of the occipito-temporal area are known to be associated with face recognition.[91] Lesion studies suggested that the damage in this area causes prosopagnogia. Both invasive studies of animals and noninvasive imaging studies of humans indicated that, if the brain is intact, a specific region in this particular area selectively responds to visual stimuli of faces.

Reports using subdural electrodes placed on ventral occipitotemporal and lateral temporal cortex demonstrated that visual stimuli of faces selectively evoked a negative potential with the peak latency of around 200 ms.[92–94] The potential is recorded bilaterally. This N200 is the signal that is evoked by face recognition. Although the same peak latency, language-specific N200 that was previously discussed is totally a different one.

The inferior parietal area was found to cause asomatognosia, hemispacial neglect syndrome and visuo-spacial agnosia when damaged.[95–97] Since no noninvasive methods were applied for this particular function, there is no insight into the feasibility of electrophysiological evaluation of this cortical area by noninvasive techniques. As for invasive evaluations, by contrast, a study using subdural electrodes covering temporal and parietal area revealed that an ERP component has recorded potentials in response not to single but to cross-multiple modalities of sensory stimuli (i.e., visual, auditory and somatosensory) in a small area in the temporo-parietal junction within the inferior parietal area.[98] These findings indicate that the area is associated with multisensory integration in transforming perception into recognition.[99] If this particular area is intact, therefore, the function is supposed not to be specific to a single modality but multimodal.

Clinical role of ERPs

Since the eventual objective of pre-surgical evaluation is the precise localization of the epileptogenic zone and the identification of resectable area, a functional approach is essential

because anatomical localization by no means satisfies the necessity of exact delineation of vital cortical functions which include motor and language abilities. ERP reflects brain activation related to the preparation for, or response to, specific events. One of the advantages of invasive ERP is its high temporal and spatial resolution which localizes specific functional areas.

The utility of ERP can be increased when it is combined with other methods that would increase the accuracy of evaluation and provide sufficient data for surgical planning. Functional mapping using electrical cortical stimulation, for instance, allows accurate identification of crucial cortical areas that must be spared during resective epilepsy surgery to avoid or reduce post-operative functional deficits. On some occasions, however, ERP is solely employed without using electrical stimulation because the stimulation to the 'irritable' cortical area may induce epileptic activities.

While electrical stimulation directly stimulates the cortex with electric current, the ERPs record spontaneous cortical activities in response to peripheral sensory input. In addition, ERP recording and electrical cortical stimulation can be performed using the same set of subdural electrodes. The analysis of ERP generators, therefore, is clinically useful also as a complementary method for electrical cortical stimulation.

There has been steady progress in developing a variety of methods to address the issues of evaluation. However, none of them are perfect. Because the ERP signals are so small in amplitude or intensity, their recording requires a way to identify a very small signal from background noise. The most common technique is by averaging a large number of trials that all contain the same specific event.

Since particular areas in the brain and particular functions of cognitive processes are supposed to be activated in coordination, pre-surgical evaluation requires a combination of methods that will make information unambiguous in terms of correlation among functions of the brain, and procedures that will be determined to best fit each individual case. ERPs are a particularly powerful technique which clarifies the temporal aspects of cortical activities, which may lead to the understanding of the correlation among clinical signs. In patients with an unknown seizure origin, invasive ERPs are indispensable.

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SECTION 10

Pre-surgical evaluation of eloquent cortex

95 Eloquent cortex and tracts: overview and noninvasive evaluation methods

J Reis and F Rosenow

Preoperative evaluation for epilepsy surgery not only has to consider what to take out but also what to leave in
(Ron Lesser)

Definition and concepts of eloquent cortex and tracts

Epilepsy surgery is usually an elective procedure. Whereas the complete resection of the epileptogenic zone is of major importance, this aim is limited by the sparing of eloquent cortex in order to avoid new, unacceptable deficits after epilepsy surgery. Based on the findings of clinical and pathological studies of patients with brain lesions, it has been shown that different cortical areas are crucial for different functions and that some of the regions of cortex are indispensable for a defined cortical function.[1] These areas were referred to as 'eloquent cortex'. Furthermore, a high correlation between these eloquent cortical areas whose lesions produce a permanent functional deficit and the results of electrical cortical stimulation has been shown. During electrical cortical stimulation either activation or deactivation of a certain cortical function support the determination of eloquent cortical areas, while electrical stimulation of noneloquent areas does not elicit any symptoms. Examples of such areas are primary motor cortex, primary somatosensory cortex, essential speech areas (Broca's and Wernicke's area), primary visual areas, angular gyrus and mesial temporal regions crucial for memory. Many other cortical areas can be resected without obvious consequences for the patient, although detailed neurological or neuropsychological testing may reveal subtle deficits. These cortical areas may be considered to be partially dispensable eloquent cortex, as either the loss of function is clinically not significant or the loss of function is temporary with fully recovery over time. This might include the face primary motor area, primary auditory areas, the pre-SSMA and basal temporal region.

In pre-surgical planning also the determination of eloquent afferent and efferent subcortical white matter tracts (including pyramidal tract, corpus callosum and optic radiation) is important for preservation of function as these tracts carry information from and to eloquent cortex and therefore reproducibly connect a cortical function to the central and peripheral network. The disconnection of eloquent tracts was proven to result in similar neurological deficits than resection of the eloquent cortex area itself.

In the past decade, new imaging techniques were developed that can be used to define and localize these functional and structural cortical tracts in vivo. While diffusion tensor imaging is most helpful to illustrate structural connectivity, fMRI is used to depict functional connectivity. Matching of these data with a conventional 3D-CT or MRI allows the exact transfer of this information into the surgical field by neuronavigation.

The exact identification of eloquent areas in each individual is crucial, since the classical concept of a constant localization was proven to be incorrect and the spatial localization of these areas may show large interindividual differences.[2,3] Applying Intraoperative electrical stimulation of cortex sometimes necessitates the performance of surgery in the conscious patient. This can be a severe burden both for the patient and the operating team in a procedure that lasts several hours; in addition, electrical stimulation may evoke epileptic seizures which can be harmful to the patient in this setting. Therefore, non-invasive methods for pre-operative functional assessment (e.g., TMS, fMRI, MEG) should be applied if possible, which allow individual localization of eloquent areas.

This chapter will focus on noninvasive techniques to localize eloquent cortex by MRI, SPECT, PET, fTCD, TMS, MEG, and will describe the Wada Test as the 'gold standard', although it is an invasive method, for lateralization of speech and memory.

Methods used to define eloquent cortex and tracts during pre-surgical diagnosis of epilepsy

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is the neuroimaging modality of first choice in epilepsy. It is the gold standard in identifying epileptogenic lesions and their spatial relation to neighbouring cortical structures such as the precentral gyrus, which usually harbours eloquent cortex. The results of functional imaging techniques used to identify eloquent cortex are usually coregistered with a structural MRI in order to visualize the spacial relation between lesion and eloquent cortex at the time of resection planning or resection (neuronavigation).

Functional MRI

Functional MRI (fMRI) was introduced to investigate areas of altered regional cerebral blood flow (rCBF) and oxygenation

status of haemoglobin during task performance. The most frequently used method of fMRI is blood oxygenation level-dependent (BOLD) imaging.[4] BOLD fMRI employs hemoglobin as a convenient endogenous contrast agent, relying on the magnetization difference between oxy- and desoxy-haemoglobin to create the fMRI signal[5,6] and therefore measures neuronal activity indirectly via its assumed haemodynamic correlate. The accurate interpretation of the BOLD signal depends on the characterization of the underlying neural activity that gives rise to the haemodynamic response, known as neurovascular coupling. The exact nature of this coupling remains largely unknown, with regard to both the nature and origin of the communicating signal between neurons and vessels.[7,8] Other determinants of the BOLD response include the technical setup of the MRI scanner. The best current resolution of fMRI BOLD is at the level of one cortical column, which contains about 10^5 neurons.[9] Most fMRI scanning paradigms use shorter acquisition times with a lower spatial resolution of about 8–50 mm^3 (1–3 mm^3 dimensions), containing at least 10^6 neurons. Therefore, fMRI BOLD signal is able to reflect the hemodynamic status of a cell population, even within a single voxel. Beside its common availability, other advantages of fMRI are a beneficial cost value ratio, safety of the technique without need of radiation, a high temporal resolution (at the order of 5 seconds) and a good spatial resolution.[9–11]

Functional MRI has become a useful tool to investigate eloquent cortical areas and is now commonly available for presurgical diagnostics to delineate motor and sensory cortex from the areas of planned neurosurgical resection.[12–17] Simple motor and sensory tasks used to map primary sensorimotor regions can produce strong circumscribed BOLD signal activations in healthy individuals and patients (Figure 95.2).[18–20] Lateralization of language function may also be accomplished using fMRI.[18,20–23] However, additional activations (e.g., in the supplementary motor cortices or in the ipsilateral hemisphere) have often been described in patients with lesions or motor deficits and there is less information whether these 'unexpected' BOLD signals are relevant for normal preoperative function.[24] Some of these BOLD activations may represent movement artifacts (which may be compensated by image co registration), or haemodynamic responses of large veins remote from the relevant cortical area, but draining blood from activated cortex.[25] It is not clear yet if any of the fMRI paradigms developed can lateralize and localize memory functions reliably enough, to obviate the need for a intracarotid amobarbital test in candidates for a mesial temporal lobe resection.[20,26,27]

For the pre-surgical assessment of epilepsy, specific factors have to be considered before analyzing the fMRI results: Task performance may be decreased if the epilepsy is associated with cognitive impairment. This can also be secondarily related to anticonvulsive treatment. Furthermore, BOLD signal changes may be directly correlated with overall synaptic activity and changes were found in and around cortical lesions as well as in distant cortical and subcortical structures. Spike related changes of the BOLD signal as well as changes in the (peri-)ictal state in or near the epileptogenic zone may hamper the fMRI interpretation if the epileptogenic zone is in close spatial relation to eloquent cortex.[28–30]

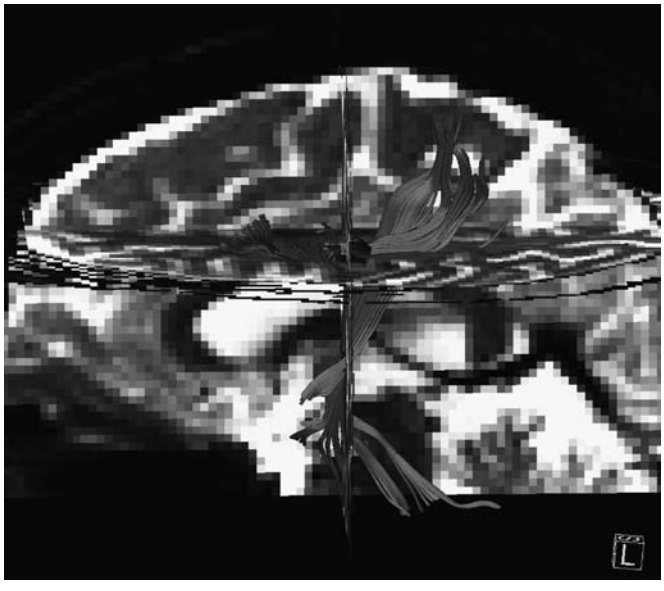

Figure 95.1 Example of pyramidal tract evaluation by diffusion tensor imaging. Images were obtained using the DTI-taskcard (Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard-MIT Division of Health Sciences and Technology, Boston, http://www.nmr.mgh.harvard.edfu/~rpwang/siemens/dti_taskcard) developed by G. Sorensen and R.Wang). Courtesy of S. Knake Marburg.

A further limitation of the fMRI technique for investigating epilepsy patients is the duration of the whole measurement (usually about 3 hours), which may be impracticable for epilepsy patients with very frequent seizures or a reduced attention span.

Diffusion tensor imaging (DTI)

MRI contrast mechanisms are based on variable physical and chemical properties of water molecules in different tissues and, thus, each pattern reflects different physiological and/or anatomical properties of the brain. In the late 1980s to early 1990s, a new MRI contrast scheme called, 'diffusion weighed imaging (DWI)', initially used for the identification of very acute cerebral infarction, was implemented and has subsequently been used more frequently in neuroimaging.[30–32] This contrast is sensitive to the structural orientation of axons. In DWI, the water diffusion process is used as a probe to investigate brain axonal organizations based on a fact that water tends to diffuse along axons. Based on this assumption, DWI can provide information about brain white matter anatomy. However, it is far from simple to mathematically describe complex neuroanatomy based on water diffusion process. Currently one of the most widely accepted models is based on a tensor model, thus called diffusion tensor imaging (DTI) (Figure 95.1). DTI allows the visualization of localization, orientation and anisotropy of white matter tracts. The diffusion of water molecules along the main direction depends on the parallel bundled architecture of axons, the myelin shield and other microstructural factors. Within each voxel a tensor is computed to describe the diffusion anisotropy (normalized metric), and the vector of the tensor main direction corresponds to the white matter fiber direction. This vector is usually color-coded to describe the tracts position and direction.

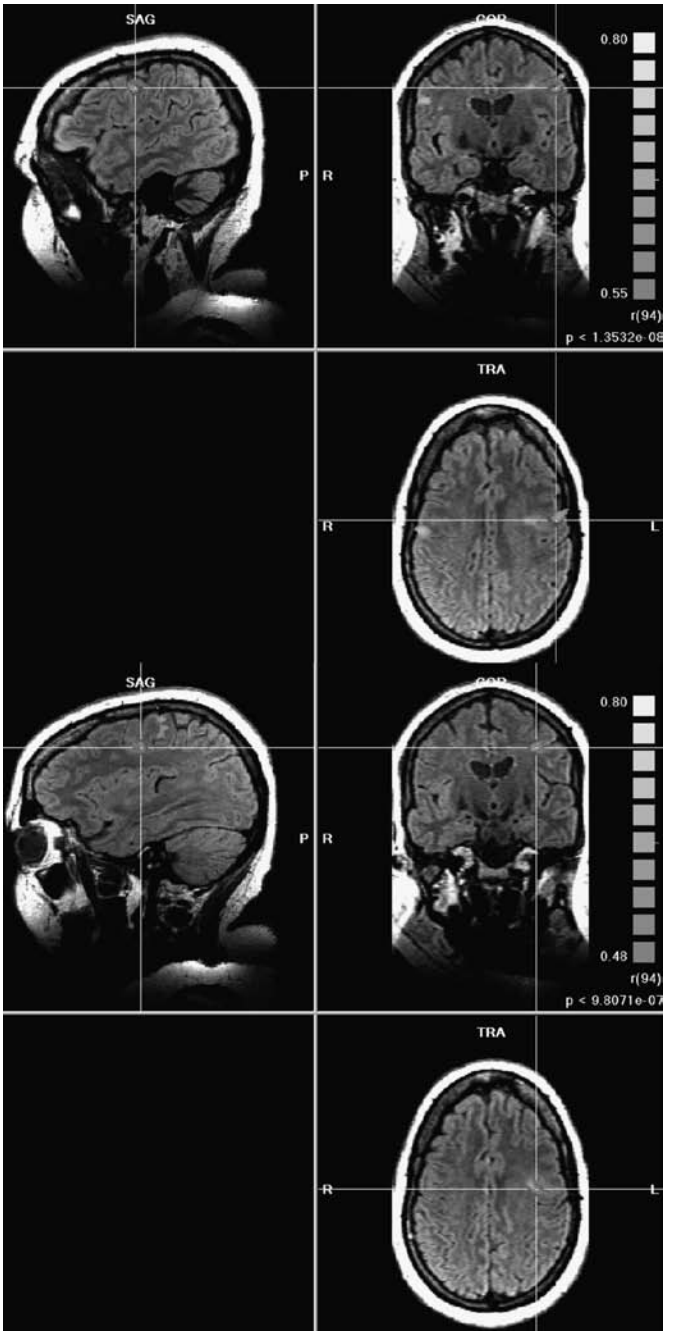

Figure 95.2 Evaluation of the tongue motor area (upper graphs) and hand motor area (lower graphs) by functional MRI.

DTI has been used to detect white matter abnormalities in epilepsy or neurodegenerative diseases.[33–35] However, as the method is based on mathematical post-processing techniques and clinical validation is lacking, DTI has to be regarded as an experimental method albeit with great potential for the localization and study of eloquent tracts in the future.

Positron emission tomography

While imaging methods such as CT or MRI isolate anatomical changes, Positron emission tomography (PET) is capable of detecting areas of specific cerebral function or altered biochemical processes even before changes in anatomy are apparent. For PET scans, short-living radioactive compounds are given intravenously to the patient. Commonly used isotopes are ^{15}O, ^{13}N, ^{11}C, and ^{18}F (^{18}F is used as a substitute for hydrogen). These radionuclides are incorporated into physiological compounds such as glucose, water, or ammonia. PET may also be used to demonstrate the binding of specific ligands to receptors, e.g., [^{11}C] flumazenil to the central benzodiazepine–$GABA_A$ receptor, or [^{11}C] diprenorphine and [^{11}C] carfentanil to opiate receptors.

The brain function studied during PET determines the used radiotracer. As increases and decreases of synaptic activity in the brain are accompanied by equivalent changes of glucose metabolism and cerebral blood flow,[36] the most frequent used PET techniques are the measurement of cerebral blood flow using labelled water ($H_2{}^{15}O$) and cerebral glucose metabolism using 2-[^{18}F]-fluoro-2 deoxy-D-glucose (FDG). Both measurements are based on the assumption that areas of high radioactivity are associated with brain activity.

For epilepsy surgery PET scanning is a useful tool which may help (i) to lateralize or localize the epileptogenic zone (usually hypometabolism during the interictal period and hypermetabolism during the ictal period in FDG-PET[37–39] and (ii) to evaluate eloquent cortex.

In comparison to the demonstration of the epileptogenic zone by measuring changes in glucose metabolism, PET scans to investigate a specific task are mainly based on changes of cerebral blood flow during 'functional activation' of brain areas. In healthy volunteers, the primary sensorimotor cortex, the visual cortex, language areas and cognitive functions have been mapped successfully with PET.[40–44]

Furthermore, the feasibility of PET for pre-surgical assessment has been shown by comparisons with direct cortical stimulation, Wada test and pre-operative outcome.[41,42,44–49] Most of these validation studies used language lateralization tasks. In one study PET showed an 88–91% positive predictive value for language lateralization compared to the Wada test.[41]

One problem with interpreting the data is that O_2-PET yields a map of all brain regions in which cerebral blood flow increases during task performance, although not all activated regions are critical to the investigated function. For example, some of the brain areas active during a language task may involve other functions such as attention and sensory or motor input. Passively visual observation of objects may produce activation in language areas and pre-motor areas comparable to naming objects.[48] Auditory activation in Wernicke's area appears identical to that in auditory cortex.[5] This problem is typically addressed by employing hierarchically-based subtraction studies, in which passive controls are subtracted from active conditions.[45,48,49] This method apparently works less well in controlling for cognitive tasks involving higher-order association areas, where activation patterns are more complex and controversial results have been reported. Thus, the choice of tasks, as well as the method of task comparison, profoundly influence the activation map, and clearly require more intensive study.

For pre-surgical epilepsy assessment PET has not become a standard procedure due to nearly universal availability of functional MRI, high costs for PET, and need of a cyclotron near the PET scanner due to the short half-life of the radiotracers (~2 min for ^{15}O, ~10 min for ^{13}N, ~20 min for ^{11}C, and ~110 min for ^{18}F). Beside this, PET is a semi-invasive procedure in that radioactive material is injected into the subject.

However, the total dose of radiation is usually small (~7 mSv, for comparison: ~0.02 mSv for a chest X-ray, ~ 8 mSv for a CT scan of the chest). Radioactivity may expose the foetus/child in pregnant or breastfeeding women, so that information gained from the PET should be considered in relation to the risk for the child.

In conclusion, PET scanning can be a useful tool to assess the epileptogenic zone as well as to determine eloquent cortex, but due to improvements of MRI in the last 10 years this has had two major consequences for the application of PET techniques to epilepsy. First, concordant MRI results may make PET data superfluous.[10]

Secondly, clinical and research PET data should always be interpreted in the light of high quality anatomical MRI to provide a structural–functional correlation. Fundamental to making these correlations has been the development of computer programs that may be used to coregister MRI and PET datasets on a pixel-by-pixel basis.[50]

Single photon emission computer tomography (SPECT)

Like PET, single photon emission computer tomography (SPECT) is a functional cerebral perfusion imaging technique. It is widely used in the noninvasive physiologic evaluation of intractable epilepsy to help define the seizure onset zone.[37,52] In comparison to the PET tracers, the SPECT radionuclides are not attached to physiological molecules. Therefore, the ^{99m}Tc-labeled lipophilic compounds hexamethylpropyleneamine oxime (HMPAO) and ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) have been frequently and successfully used for imaging of the regional cerebral blood flow.[53] Several receptor ligands like [^{123}I] iomazenil for benzodiazepine receptors are also available. The normal adult brain shows bilaterally symmetric tracer distribution, with higher activity in temporal, parietal, and occipital (primary visual) cortices, basal ganglia, thalami, and cingulate gyrus as well as reduced activity in the white matter and interhemispheric fissures. Changes in visual stimuli such as eye opening and closing may increase or decrease, respectively, the visual cortex activity by 30%.[54] Motor and sensory stimuli have similar but asymmetric effects.[55] Auditory stimuli effects are symmetric but less impressive. Abnormal findings include focal or regional areas of decreased or increased tracer uptake. Several studies of brain SPECT during functional activation have been performed in healthy volunteers to localize eloquent cortical areas for visual stimulation,[56] motor [40,55] and sensory stimulation,[57] memory tasks,[58,59] and the investigation of complex cognitive tasks.[54,59,61] Only a few studies are available describing the presurgical determination of eloquent cortex with SPECT. In a patient with a perirolandic low grade astrocytoma the validity of SPECT in pre-surgical assessment was proven by good post-surgical outcome after tumor resection. In 17 epilepsy patients, Borbely *et al.*[62] described a 100% concordance of the results of SPECT and functional transcranial doppler sonography to determine hemispheric language dominance.[62] Finally, three studies performed SPECT and Wada test simultaneously, but the aim of the studies was not the validation of SPECT for assessment of language or memory function, but the assessment of inactivation pattern after intracarotid amobarbital injection.[63–65] The major result of one of these studies was a lack of inactivation of the hippocampus in over 60% of the patients, suggesting a lack of accuracy of the Wada test to predict the risk for pre-operative amnesia.[64]

In comparison to PET, SPECT is less expensive and more frequently available than PET. Notwithstanding, SPECT still has the disadvantage of the use of radioactive tracers. While the PET tracers decay within minutes, the SPECT tracers have a longer half-life (up to 8 hours) and can therefore be used for patient-friendly accomplishment of functional tasks outside the scanner. As a consequence, the number of achieved images per scan is limited and images after a second tracer injection might be falsified by remaining activity generated by the previous injection.

While SPECT is not routinely used for the assessment of eloquent cortex, the ictal/interictal SPECT is widely used to determine the seizure onset zone in epilepsy patients.

Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is the measurement of the magnetic fields produced by electrical activity in the brain. The magnetic fields are analyzed by an equivalent-current dipole model to determine the location of the sources, e.g., epileptic discharges. The source locations can then be overlaid onto (functional) MRI images, a technique called magnetic source imaging (MSI).[37,66–68] These overlays can be used to show the spatial relation between MEG spike sources and a lesion or eloquent cortex revealed by MRI. Because the magnetic signals emitted by the brain are in the order of a few femtotesla (1 fT = 10^{-15} T), shielding from external magnetic signals, including the Earth's magnetic field, is necessary [66] and extremely sensitive devices based on superconductive technology are required for recording.[69] Modern whole scalp array systems have roughly 300 channels situated around the head to pick up intracranial activity. The MEG signals themselves derive through electromagnetic induction from the net effect of ionic currents flowing in the dendrites of neurons during synaptic transmission and in the axons during action potentials. These net currents can be thought of as current dipoles which are defined to have an associated position, orientation, and magnitude, but no spatial extent. According to the right-hand rule, a current dipole gives rise to a magnetic field that flows around the axis of its vector component. From the measured field distribution it is possible to calculate an inverse solution to determine the brain area where a set of neurons is synchronously active.

Clinical application of MEG in pre-surgical diagnostics represents a new modality for the localization of interictal epileptiform activity and seizures in patients with focal epilepsy.[67,70–73] The MEG spikes and seizure patterns have been shown to provide more accurate localization than surface EEG as they are not attenuated by skull and scalp. A comparison of MEG, MRI and EEG in pre-surgical localization of the epileptogenic zone showed that MEG was superior to both surface and intracranial EEG.[74]

Furthermore, the correct identification of eloquent areas, most frequently in respect to the sensorimotor system, has been reported.[68,71,72,75–78] Studying event related fields (ERF), the equivalent of evoked potentials, stimuli are presented in a time-locked mode to localize the primary sensory cortices. MEG and MSI have been established and validated for all primary sensory

modalities. As the temporal resolution of the MEG is within the millisecond range it is also possible to distinguish between early and late components of the ERF, which is crucial to separate activation of primary sensory and association cortex.[78–81] For the primary and secondary somatosensory cortex (SI, SII) MEG revealed a somatotopic organization of this areas after tactile stimulation in healthy and patients with perirolandic tumors.[82,83] The primary auditory cortex in the temporal lobe was localized by auditory evoked fields[84,85] and this was also validated for patients with intracranial lesions.[86] For the visual evoked fields, precise localization has been shown in healthy and patients with visual field deficits.[80] Additionally, motor-related fields were recorded to localize the hand area of the primary motor cortex.[77,78]

The reliability, validity and accuracy of language-localization by MEG as determined during simple language tasks was high[76,77] and a high correlation has been shown between the results of the MEG and the Wada-test (87–96% concordance).[76,88,89] The MEG findings were also in accordance with electrocortical stimulation results, even when atypical language representation was present.[90–92] Retest-reliability was investigated over several months and was found to be high.[93] Furthermore, MEG has been used to validate one imaging method with the other.[78,94,95]

In summary, MEG is a reliable, validated diagnostic tool to investigate eloquent cortical areas. With its high spatial and temporal resolution it bears several advantages compared to other imaging methods.

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) was first introduced by Anthony Barker and allows investigating the central motor pathway in a non-invasive and painless fashion.[96] TMS is based on Faraday's principles of electromagnetic induction. A pulse of current flowing through a coil of wire generates a magnetic field. If the magnitude of this magnetic field changes in time, then it will induce a secondary current in a nearby conductor. The rate of change of the field determines the magnitude of the induced current. For TMS a stimulating coil is held over a subject's head and a brief current is passed through it. This induces a magnetic field, which passes through the subject's scalp and skull with negligible attenuation (but exponentially decaying by the square of the distance). This time-varying magnetic field induces a current in the subject's brain, which stimulates the neural tissue. During time different stimulation protocols have been introduced. For example single pulse TMS evoked effects are similar to stimulating a peripheral nerve with a conventional electric stimulator. To date, single-pulse TMS appears to be completely safe when applied to healthy individuals. It is also possible to apply a train of pulses at rates of up to 50 Hz (repetitive TMS, rTMS). This procedure can cause seizures even in healthy subjects, therefore safety guidelines must be followed.[97]

TMS mapping of cortical motor representation

The scalp positions whose stimulation elicits responses in a target muscle can be reliably and reproducibly mapped by single-pulse TMS, using a focal figure-of-eight shaped coil.[98–100] TMS mapping provides several measures of the somatotopical cortical representation of the target muscle, such as the map area, the optimal position for stimulation, or the center of gravity of the map.[101] Magnetic resonance imaging (MRI) showed that the coil position that produces the largest MEP is located in M1.[102] The spatial validity of TMS-based mapping of the motor cortex has also been demonstrated by comparing the maps with the results of direct transcranial electrical stimulation (TES) of the exposed cortical surface in patients undergoing a neurosurgical intervention. Furthermore, the functional reorganization of the motor cortical maps after a central or peripheral lesion was investigated with TMS in patients with hemispherectomy,[103] spinal cord lesions,[104] limb amputation,[105] transient anaesthesia of limbs and fingers[106,107] and prolonged immobilization.[108] Aside from case reports,[109,110] TMS mapping has not been systematically used to define eloquent perirolandic cortex in pre-surgical epilepsy candidates. Recent advances in neuroimaging now allow coregistration of the position of the stimulating coil (TMS) and (functional) MRI data.[111,112] This multimodal approach could provide a valuable tool for pre-surgical planning in epileptic patients.

TMS and language lateralization

In addition to single- or double-pulse TMS, diagnostic use of focal rTMS was reported for the production of speech arrest or for determination of language laterality.[113,114] rTMS of the left fronto-temporal region led to a speech arrest in right-handed patients. The results of the rTMS intervention correlated with the results of the Wada test which showed left-hemispheric language dominance in all subjects.[113,114] In contrast, Michelucci *et al.*[115] revealed negative results in 50% of their patients and Epstein *et al.* showed that in one third of the epilepsy surgery candidates, 4–8 Hz rTMS effects did not correlate with the Wada test (apparent bilateral or right hemisphere lateralization).[116] One problem with these studies is that high-intensity rTMS could produce speech arrest by an effect on either the language processing or the jaw and mouth motor areas. Presumably, subthreshold stimulation over sites anterior to the rolandic area, which can dissociate the language components of speech from the motor ones,[117] should increase the specificity of rTMS to assess language laterality. A second problem of rTMS is discomfort or pain at the site of stimulation, depending on stimulation frequency (usually ranging from 8–30 Hz) and stimulation intensity (60–100% of the maximal stimulator output).[113,115] In conclusion, due to a lower sensitivity of the test and the frequently reported discomfort of the stimulation rTMS has not become a standard procedure to determine language laterality.

Functional transcranial Doppler sonography (fTCD)

Transcranial Doppler sonography has been widely used in clinical practice to detect intracranial stenosis of cerebral arteries. Additionally, the characterization of cerebral blood flow changes in relation to functional activation of brain areas was implemented as functional TCD.

Functional TCD, like fMRI, is based on the principle of neurovascular coupling assuming that neuronal activation increases cerebral perfusion in the corresponding brain area. The fTCD device measures the resulting cerebral blood flow velocity (CBFV) modulation in the corresponding larger intracranial arteries (M1-2, A1, P1-2); usually the medial cerebral arteries are investigated, and a difference between two different physical

stages (rest and activation task) is calculated. As CBFV increases bilaterally during task performance, a statistical procedure is used to calculate functional laterality indices which incorporate the difference between the relative CBFV changes in the right and left MCA over time of the task performance.[118,119]

During the last 10 years fTCD became a widely accepted tool to investigate changes in cerebral blood flow velocity (CBFV) during cognitive tasks.[19,119–125] In respect of the presurgical evaluation of eloquent cortex, lateralization of language has been most frequently investigated by fTCD.[23,121,123–126] While 'reading', 'silent word generation' and 'mental calculation' all increased the rCBF in the MCA bilaterally, a significant lateralization was only present in the word generation paradigm.[127] In patients, the results of language lateralization with fTCD using a word generation task matched with Wada test results in 100 %.[124,126] Furthermore, a 95% correlation between the results of fMRI and fTCD during a word generation task was shown for healthy volunteers.[22] Motor function (e.g., elbow and hand movement) was investigated in few studies.[128,129] The results have provided evidence that fTCD is capable to reveal a hemispheric lateralization of these functions.[21]

According to the CBFV modulation in intracranial arteries, fTCD has a poor spatial resolution, and provides only indirect information about the processes activated intracerebrally. Only statistical differences between two different physical stages (rest and activation) are evaluated. Therefore, the coactivation of several brain areas, that are not implicitly preconditioning performance of a specific task, has to be considered. Further restriction for fTCD is given by a lack of a temporal bone window in 10–20% of the subjects, ruling out recording of the Doppler signal.[130] Advantages of fTCD are the noninvasiveness, the high temporal resolution by continuous measurement of information about CBFV changes in relation to a cognitive task, the usefulness in children, disabled and patients with reduced IQ.[126]

Wada test, intracarotid amobarbital procedure

The intracarotid amobarbital procedure was first reported by Wada in 1949 for language lateralization and modified by Milner *et al.* in 1960 by including a memory task.[131,132] Since the early 1960s the Wada test is the gold standard to predict pre-operative amnesia, memory decline and language disability in pre-surgical evaluation of temporal lobe epilepsy patients. Nevertheless, for right-handed patients with right temporal lobe epilepsy, that do not have ictal or postictal aphasia as documented by video-EEG-monitoring is considered to be unessential in some centers.

The Wada test uses the functional inactivation of a single hemisphere by injection of sodium amobarbital into the ipsilateral internal carotid artery; during this temporary deficit, the language and memory abilities of the active contralateral hemisphere can be assessed in isolation. Usually, both hemispheres are tested successively with about 30 minutes waiting between injections. For the interpretation of the results it is necessary to keep in mind, that the intracarotid amobarbital procedure is only a lateralizing, but not a localizing procedure. Comparability of the results is limited, as different methodologies are used across centers (e.g. different dose of amobarbital, use of EEG, preinjection, delay between injection and testing). Especially the criteria used to test language and memory ability often varies between centers. There is a general consensus that over 90% of right-handed individuals show left hemispheric language dominance.[132] Thus, language can often be reliably lateralized by the Wada test.[20,124,126]

Results of memory testing may also be able to predict the likelihood of pre-operative memory dysfunction, though the significance is controversial. Several SPECT studies have shown that – due to the fact that vascular distribution does not supply the posterior three fourths of the hippocampus – the ipsilateral hippocampus is often not inactivated directly during the amobarbital procedure injecting the internal carotid artery,[63,64,133] and therefore interhemispheric comparison of memory dominance may be limited. Other studies suggested that perfusion of the hippocampus is not necessary for valid memory testing.

Due to its invasiveness the Wada test carries risks. On the one hand the cerebral angiography has a mean overall rate of 1.6% for neurological complications, ranging from 0.4–12.2% transient deficits, and permanent deficits in up to 5.4%.[134] The relative risk of death was reported to be 1.7%.[138] On the other hand the risk of misinterpretation of test results has to be considered prior to surgery.[139,140] The need to replace the Wada test with less invasive techniques of proven reliability has long been recognized. Several attempts have been made to substitute the Wada test in determining hemispheric language lateralization by noninvasive techniques such as fMRI,[18] functional transcranial Doppler sonography (fTCD),[124] PET,[43] SPECT,[144] magnetoencephalography,[124] or transcranial magnetic stimulation.[116] For example, fMRI showed comparable results for language lateralization (>90% concordance.[20] Furthermore, results of language lateralization in functional transcranial Doppler sonography (fTCD) matched with Wada test results (100%) with the advantage to be noninvasive and easy to use even in children, patients with low IQ and nonnative speakers.[126]

Summary and conclusion

During the last decade, several noninvasive techniques like fMRI, PET, SPECT, MEG, TMS, and fTCD have been investigated in respect of their validity to localize functional eloquent cortex (Table 95.1). Furthermore, the comparability of these results with the results of the Wada test as a gold standard has been addressed by several studies and a convenient consistency of results were found for fMRI, PET, SPECT, and fTCD. Therefore, it appears likely that the use of single or combined noninvasive evaluation methods could further limit the use of invasive methods such as the Wada test and invasive EEG recordings in the future. DTI may become a clinical tool to identify eloquent tracts.

Table 95.1 Summary of noninvasive methods to evaluate eloquent cortex and tracts

	fMRI, DTI	PET	SPECT	MEG	TMS	fTCD	IAP
Method of action	Functional imaging, based on BOLD effect, water diffusion	Functional imaging, cerebral blood flow, metabolism, radioactivity	Functional imaging, cerebral blood flow, radioactivity	Electromagnetic induction, evaluation of magnetic dipole sources	Magnetic stimulation of cortex, functional activation/inactivation (rTMS)	Functional evaluation of cerebral blood flow velocity changes	Pharmacological inactivation of cortical function by short acting barbiturate (amytal, brevimytal)
Availability (+ to +++)	++ (fMRI) + (DTI)	+	++	+	+++	++	+++
Spatial resolution	High	Medium	Medium	High	Med	Low	Low
Temporal resolution	fMRI medium, DTI low	High	High	High	High	High	Low
Advantages	Safe, painless, convenient to use	Biochemical image, even without anatomical changes	Available, biochemical image, even without anatomical changes	Very high resolution, evaluated reliability	Available, easy to use	Painless, convenient to use, useful in children, disabled, low IQ.	Inactivation paradigm, predicting pre-operative status
Disadvantages/ Limits	Task-related coactivation, bilateral activation, long duration of fMRI	Short-living radiotracer, radioactivity, false positive results in biochemical dysbalanced patients, limited detection of grey matter lesions	Short-living radiotracer, radioactivity, low special resolution	Special equipment, magnetic shielding, high costs, interference-sensitive	Risk of seizure induction (rTMS), need of clinical evaluation, poor reliability, discomfort	Lack of temporal bone window; only lateralizing tool, no localization	Invasive test, only lateralizing tool, no localization

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96 Noninvasive tests to define lateralization or localization of the motor area

R Matsumoto and H Shibasaki

Introduction

In the field of functional neurosurgery including epilepsy surgery, the areas of 'eloquent cortex' must be identified in order to minimize the risk of irreversible neurological deficits. Electrical cortical stimulation, first performed by Bartholow in 1874[1] and later developed intraoperatively by the Montreal group in the early 20th century,[2] has become a gold standard method to explore various cortical functions. The development of chronic intracranial encephalographic recordings with subdurally placed electrodes allowed extensive extraoperative functional cortical mapping of the brain.[3] This technique, however, is unable to be applied to the wide area of the brain due to the limited coverage with intracranial electrodes, and thus the region of implantation should be determined based on the noninvasive presurgical evaluation of the epileptic focus and functional cortical areas.

Owing to advancement of the anatomical and functional neuroimaging techniques that were originally developed to study normal brain functions in the early 1990s, a variety of mapping techniques are currently available for noninvasive evaluation of 'eloquent cortex'. In this chapter, we will focus on the mapping of the motor areas and introduce the state-of-the-art of available techniques.

Anatomical imaging of the motor cortex

Nomenclature of the motor cortex

The motor cortex is an agranular sector of the frontal lobe which occupies the caudal part of the frontal lobe and has been subdivided into two regions by Brodmann,[4] the primary motor cortex (MI), area 4 (BA4) and the nonprimary or premotor cortex, area 6 (BA6). According to recent proposals based upon comparison with the nonhuman primate findings,[5–9] the premotor cortex consists of the premotor dorsal (PMd) and ventral (PMv) areas in the lateral convexity and the supplementary motor area (SMA) in the medial wall (Figure 96.1). PMd is defined as BA6a-β and the dorsal part of BA6a-α, and PMv as the ventral part of BA6a-α and BA44. The boundary between PMd and PMv is physiologically set at the frontal eye field that is situated immediately rostral to the border of the face and hand portions of the motor strip.[10] The anatomical border between PMd and PMv, however, has not been established. Medially, the premotor area BA6, namely SMA, is located above the cingulate sulcus and is subdivided into the rostral (pre-SMA) and caudal (SMA proper) parts. The vertical anterior-commissural (VAC) line[11] is regarded as a landmark to differentiate between pre-SMA and SMA proper.[6]

The 'eloquent' motor cortex corresponds to the two motor homunculi described by Penfield.[2] One lies along the precentral gyrus with the face lying mostly ventrally and the foot most-medially, and the other situated in the medial frontal cortex along the rostro-caudal axis with the face lying mostly rostrally and the foot mostly caudally. These areas are determined by the positive motor response by electrical cortical stimulation, and thus mostly constitute the origin of spinal projection from the motor cortex. These positive motor areas likely correspond to the monkey motor execution areas with direct spinal projection, that is, the primary motor area and the caudal part of the premotor areas (caudal PMd, caudal PMv and SMA proper). Indeed, in humans these motor execution areas along the precentral gyrus cytoarchitecturally consist of BA4 and BA6a-α to a varied degree[12] (see Figure 96.1). In this sense, it is plausible to refer to them together as 'the precentral motor area' instead of 'the primary motor area (MI)' usually employed in the field of functional neurosurgery.

Identification of the motor cortex

Morphological identification of the central sulcus and the so-called 'hand knob' is the initial and most important step to identify the motor cortex. Three methods have been well-described to locate the central sulcus by means of structural MRI.

1. Lateral axial method[13]; identification of the intersection of the superior frontal sulcus with the precentral sulcus. The central sulcus is a sulcus immediately posterior to the precentral sulcus (Figure 96.2a).
2. Medial sagittal method[14]; identification of the ramus marginalis of the cingulate sulcus that reaches the midline cortical surface. The marginal ramus is located just behind the central sulcus (Figure 96.2b).
3. Lateral sagittal method[15]; identifying the course of the anterior horizontal and ascending branches of the sylvian fissure and the precentral sulcus. In the sagittal plane, the

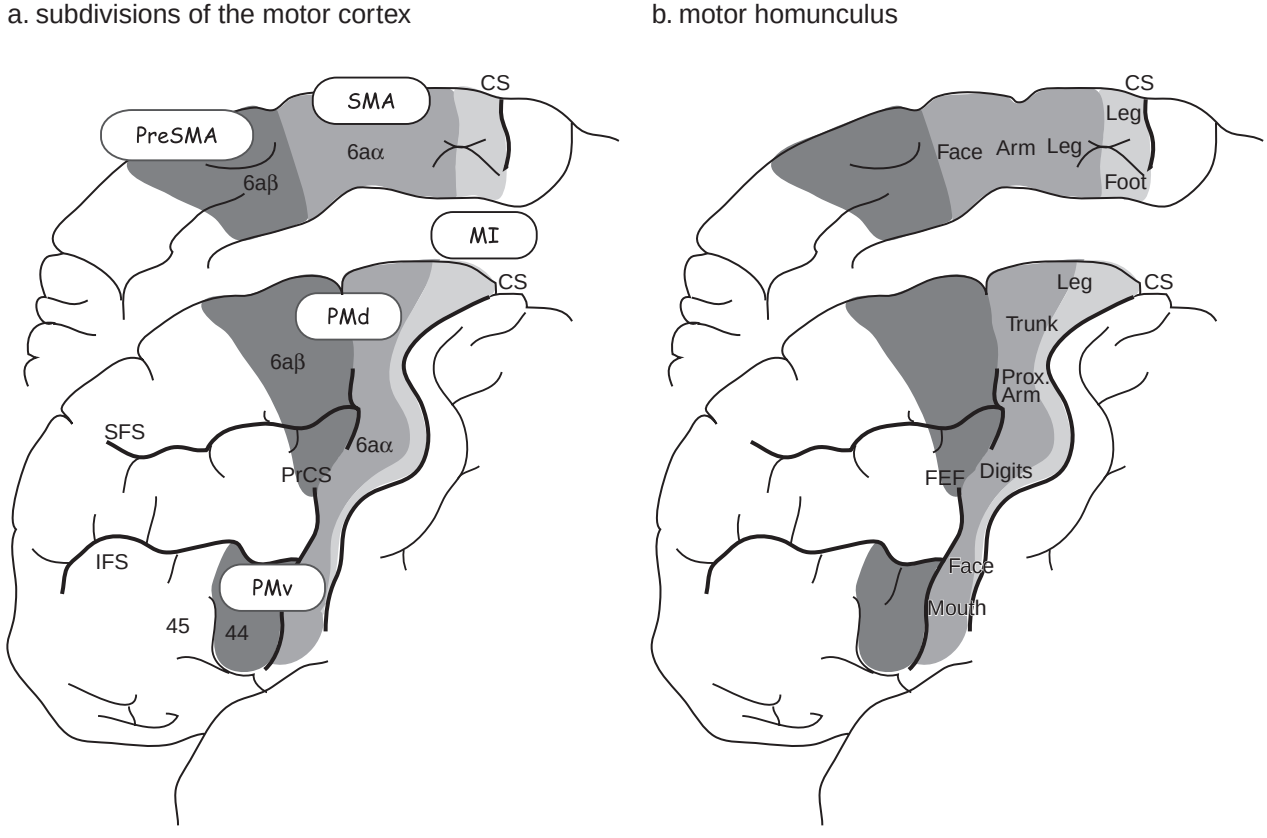

Figure 96.1 Diagram showing the human motor cortex. (a) Subdivisions of the motor cortex. Boundaries are based on recent proposals.[5–10] Note that the crown part of the precentral gyrus consists of Brodmann's area 6a-α(premotor area) and 4 (primary motor area) to a various degree; area 4 is situated more broadly in the leg area than the face area. SMA; supplementary motor area proper, pre-SMA; presupplementary motor area, PMd; premotor dorsal area, PMv; premotor ventral area, MI; primary motor area. (b) Motor homunculus. Two motor homunculi are present – one along the precentral gyrus and the other in the medial premotor area (SMA). The former motor strip consists of a mixture of area 6 and 4, and thus is better termed as 'the precentral motor strip' than the classical terminology of 'the primary motor area'.

zigzag shaped inferior frontal sulcus usually intersects with the precentral sulcus. The central sulcus is located immediately behind the precentral sulcus. The central sulcus typically does not unite with the sylvian fissure. Instead, in most cases, the lower end of the central sulcus is closed and detached from the sylvian fissure by the fusion of the lower ends of the pre- and postcentral gyri, which forms an arc of tissue, concave superiorly, called the subcentral gyrus. This fusion, closing off the central sulcus, also serves as the landmark (Figure 96.2c).

The relatively high variability of the central and surrounding sulcus pattern occasionally makes central sulcus identification difficult. With detailed MR and cadaver specimen analysis, Yoursey *et al.*[16] reported that a knob-like structure is a very consistent landmark to identify the precentral hand motor area in the precentral gyrus. This 'hand-knob' structure in the axial plane was defined as a knob-like, broad-based, posterolaterally directed structure of the precentral gyrus. It usually has an inverted omega shape and sometimes a horizontal epsilon shape with a mean diameter of 1.4 cm. On average it is located about 23 mm from the midline, just caudal to the junction of the superior frontal sulcus with the precentral sulcus and 19 mm from the lateral surface. It appears as a posteriorly directed hook when viewed on the sagittal plane. This anatomical knob-like structure corresponds well to the fMRI activation area by the hand movement.

Above the aforementioned methods, the omega-shaped knob of the central sulcus in the hand region seems to be especially useful for identification of the central sulcus; highlighting it in the 3D-MRIs would probably provide a useful starting point for intra- or extraoperative search for motor cortex, even without additional functional information (Figure 96.2d). Subsequently the other premotor areas can be located anatomically using landmarks such as the precentral sulcus, VAC line and cingulate sulcus. It is clinically important to note that no established methods currently exist to differentiate the foot portion of SMA proper from that of the primary motor area (BA4) in the medial frontal area.

Identification of the pyramidal tract

Until very recently, the knowledge of white matter pathways in humans has come from 'impoverished' dissection of the postmortem brain or from the extrapolation from the nonhuman primate invasive tracer studies. As for the pyramidal tract that constitutes an important part of the motor execution system, only a part of the tract could be traced by structural MRI (e.g., pedunculus cerebri, internal capsule). The fiber pathway in the deep white matter or corona radiata has not

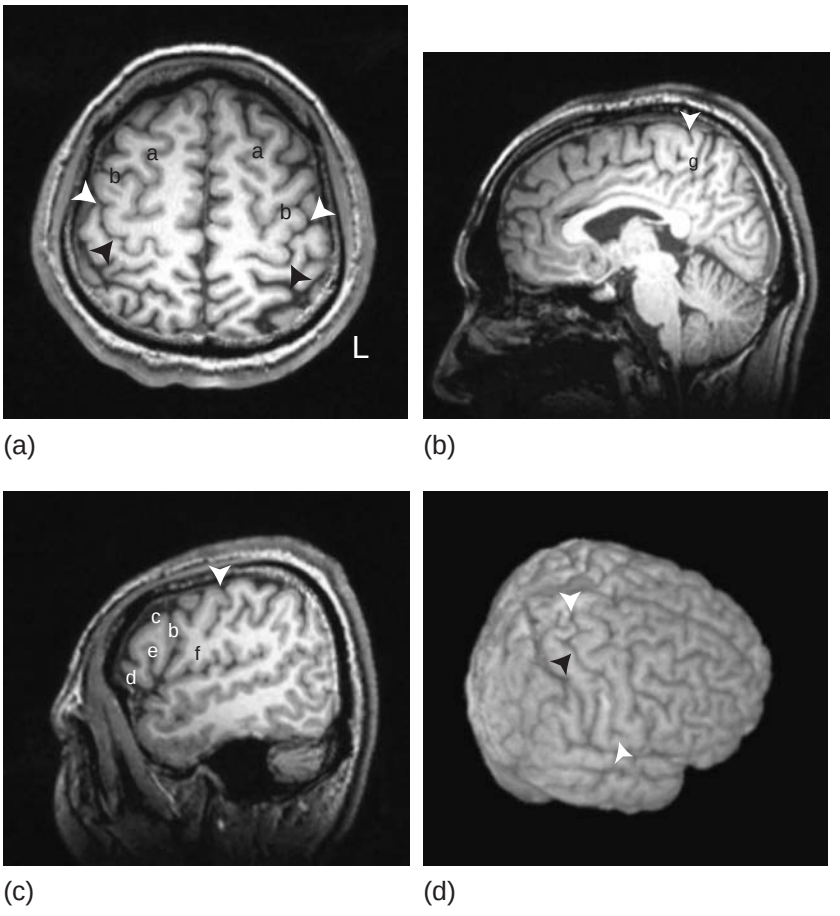

Figure 96.2 Identification of the central sulcus. (a) Lateral axial method. (b) Medial sagittal method. (c) Lateral sagittal method. (d) 3D MRI. MPRAGE sequence was taken and reconstructed into 3D image using MRIcro software (www.mricro.com). white arrowhead: central sulcus, black arrowhead: hand knob structure, a: superior frontal sulcus, b: precentral sulcus, c: inferior frontal sulcus, d: anterior horizontal ramus of the sylvian fissure, e: anterior ascending ramus of the sylvian fissure, f: subcentral gyrus, g: marginal ramus of the cingulate sulcus.

been visualized until very recently by a novel method of the diffusion weighted MR imaging (DWI).

DWI is a magnetic resonance imaging technique that is sensitive to mobility in the intravoxel water molecules and characterizes the local diffusion properties of water in tissue at a millimeter scale.[17] In tissue with a high degree of directional organization, the self diffusion of water is hindered more in some directions than others. With diffusion measurements in several noncolinear directions, the diffusion tensor imaging (DTI) computes the tensor matrix with principal diffusion direction at each voxel and enables fiber tracking of the major white matter fiber trajectories. DTI studies have enabled 'in *vivo* dissections' of major white matter tracts in normal subjects,[18,19] and its clinical application for tracing the pyramidal tract has progressed in the past few years (Figure 96.3). DTI, however, has limitation and should be used clinically with caution. The major limitation of DTI is that it can only resolve a single fiber orientation within each imaging voxel owing to the constraints of the tensor model. Therefore, DTI cannot resolve fiber crossing, bending, or twisting within an individual voxel. Because of this feature, the attempts to locate the pyramidal tracts have been more successful for those arising from the precentral hand and foot area than the face area. The white matter beneath the hand motor area contains the predominant unidirectional pyramidal tract fibers while that beneath the face area does less so, mixed with association fibers

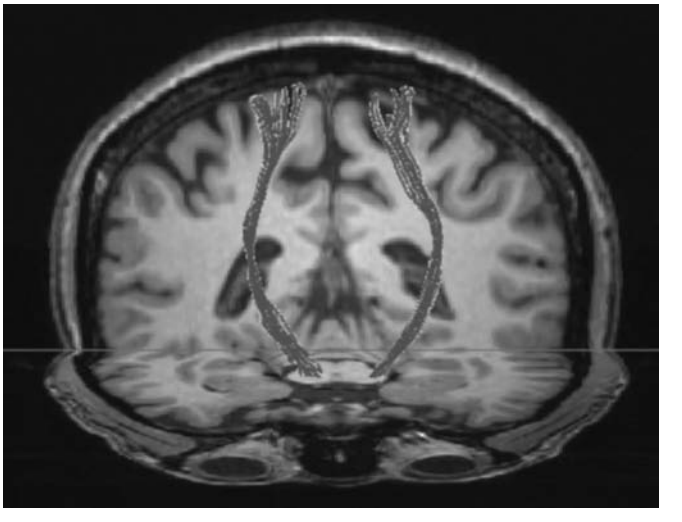

Figure 96.3 The pyramidal tracts revealed by diffusion tensor imaging (DTI). Diffusion-weighted images were taken in 12 noncolinear directions, and DTI was performed using DTIstudio version 2.40 software (H. Jiang, S. Mori; Department of Radiology, Johns Hopkins University).[19] Two ROIs were segmented on axial b=0 images for fiber tracking; the first ROI at bilateral cerebral peduncles, and the second ROI at bilateral precentral gyrus at the level of the hand knob. Results of fiber tractography are superimposed on MPRAGE. (Note that the majority of fibres were traced between the cerebral peduncle and the foot/arm motor area).

(e.g., superior longitudinal fasciculus) orienting in different directions. Nevertheless, this technique for the first time provided noninvasive evaluation of the pyramidal tract in the clinical settings.[20,21] Several theories have been proposed to solve the problem of intravoxel fiber crossing with or without tensor estimation, and further advancement will probably bring us the more precise and detailed analysis of the pyramidal tract and other motor-related pathways in the near future.[22,23]

Functional imaging of the motor cortex

The location of the motor cortex can be approximated using a priori knowledge of cortical anatomy as mentioned above, but considerable variations occur among individuals. In addition, the presence of local pathology can distort cerebral anatomy, making precise localization of the functional cortex difficult. This is not only the case with tumors but also with malformations of cortical development (MCD) that are currently recognized as one of the major etiologies of intractable partial epilepsy. Noninvasive techniques such as functional MRI (fMRI), magnetic source imaging and transcranial magnetic stimulation (TMS) can identify motor functions, if present, within or aside the dysgenic cortex as well as assess possible reorganization in the contralesional hemisphere, which is usually not explored during the invasive presurgical evaluation of patients.

Functional MRI

The basis of fMRI is that deoxyhemoglobin acts as an endogenous paramagnetic contrast agent. Therefore, changes in its local concentration lead to an alternation in the T2*-weighted MR image signal.[24] The physiological basis underlying the increase in signal intensity detected on fMRI is that, during neuronal activation, increase in the oxygen consumption by the neuronal group is accompanied by functionally induced increases in oxygenated blood flow and volume which becomes excessive for the required amount of oxygen consumption. This causes a decrease in the capillary and venular deoxyhemoglobin concentrations, producing a focal increase in the T2*-weighted MR signal. In other words, fMRI measures the blood O_2 level-dependent (BOLD) contrasts as the result of brain activity, and activation maps are derived from the BOLD images.

In order to investigate the accuracy of functional motor mapping by fMRI, several studies compared the results of fMRI activation with those of intraoperative electrical cortical stimulation in patients who harbored tumors close to or involving the precentral motor area. As for the precentral motor area, correlation between fMRI findings and the results of direct electrical cortical stimulation is high, ranging from 82–100%.[25–28] Although the correlation is relatively 'high', it does not necessarily mean that the area of fMRI activation is identical to that of the positive motor response elicited by electrical cortical stimulation. The following points are important to note for the interpretation of results.

1. fMRI is an indirect indicator of cerebral activation, because it measures changes in regional cerebral blood flow and not neuronal activity itself such as accomplished by magnetoencephalography.
2. Changes in blood oxygenation are characterized by a spatial and temporal dispersion that may cause errors in the accurate localization of activated areas (e.g., nonparenchymal deoxyhemoglobin changes in intraparenchymal capillaries or sulcal veins).
3. The area of fMRI activation does not necessarily define the 'eloquent motor cortex' which has a direct corticospinal output. Usually the activation involves the postcentral as well as precentral gyrus, even with simple abduction of the index finger.[29] The postcentral gyrus activation is most likely due to activation of somatosensory reafferents by positional changes of the hand and fingers during the performance of the motor task. In addition, even relatively simple movements (e.g., sequential finger tapping) elicit activation of the nonprimary motor areas (e.g., SMA or lateral premotor areas) as well as the parietal areas forming the premotor-parietal circuits[30] (Figure 96.4a).

Comparison of the fMRI findings and the results of direct electrical cortical stimulation in another motor homunculus at SMA is relatively scarce. Hanakawa *et al.*[30] reported such comparison and showed general, but not complete, agreement between the two modalities (Figure 96.4b).

With regard to the pathology, several fMRI studies have demonstrated that MCD can show various degrees of participation in motor functions ranging from corticospinal 'primary' motor control and putative participation as 'nonprimary' motor areas to absence of evidence for any functional participation.[31,32] The findings are consistent with the direct cortical stimulation study that showed variable motor functions in focal cortical dysplasia according to the degree of FLAIR signal abnormalities.[33]

Transcranial magnetic stimulation

TMS provides a noninvasive means of stimulating the cortex.[34] TMS is based on the principle of electromagnetic induction. The brief discharge of a capacitor induces a primary current within the stimulus coil. This primary current generates a magnetic field that passes painlessly through the scalp and skull nearly unattenuated and induces a secondary current within the conductive brain tissue. It is generally agreed that excitation of corticospinal neurons occurs within the cortex transsynaptically or, under some conditions, in the most superficial subcortical white matter.[35,36] In contrast to fMRI which visualizes both primary and nonprimary motor areas, TMS therefore can electrically stimulate the cortex and identify the positive motor areas having a direct corticospinal projection. In other words, elicitation of short-latency responses in a target muscle demonstrates the presence of monosynaptic corticospinal projections originating from the stimulated site. Using the figure-of-eight coil that can focally apply the current over the underlying cortex, motor representations that activate muscles at different joints of the upper extremity can be distinguished on the scalp and are shown to fall in the predicted somatotopic pattern.[37]

For functional motor mapping in patients with possible functional plasticity, TMS can identify the hemispheric specialization and laterality of corticospinal projections.

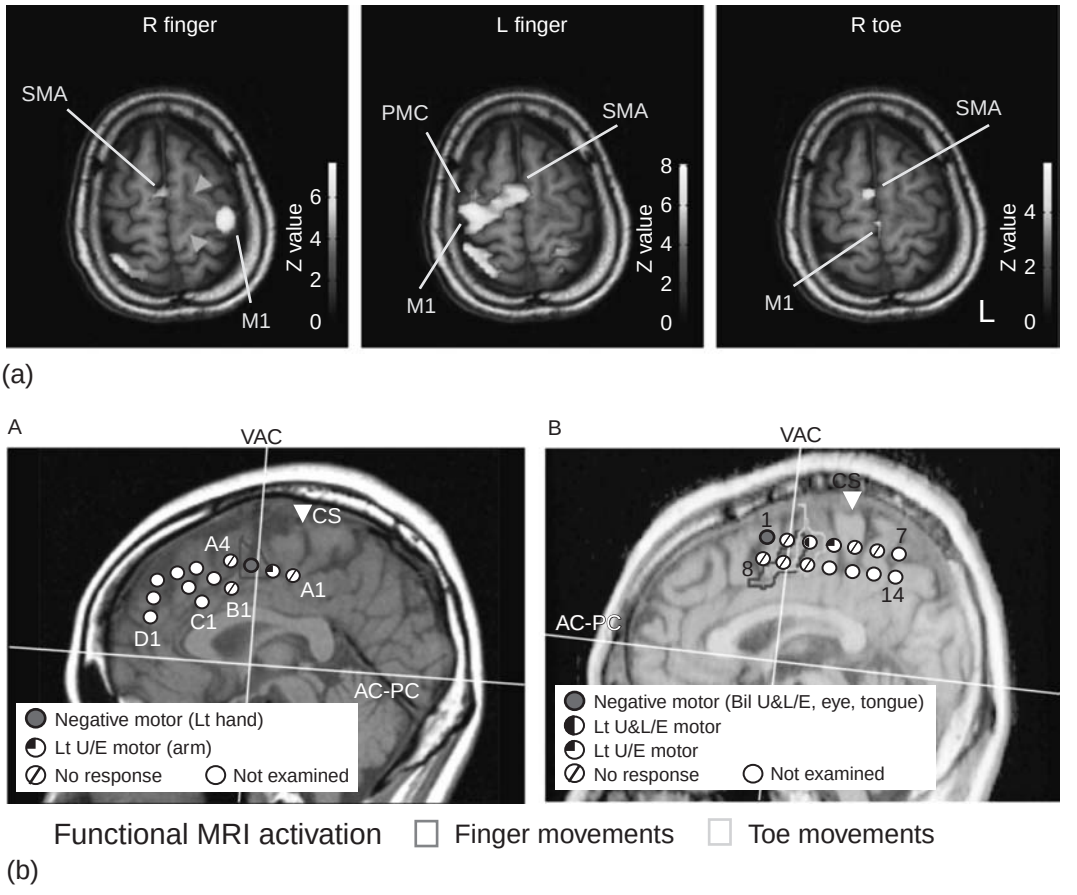

Figure 96.4 Comprehensive motor mapping by fMRI and electrical cortical stimulation. (a) Functional MRI activation in a patient with focal cortical dysplasia in the left superior frontal gyrus (green arrowheads), overlaid onto an axial slice of structural MRI. Simple limb movement task (finger tapping and toe movement) activates the lateral premotor cortex (PMC), the primary motor area (MI), the supplementary motor area (SMA) and the superior parietal lobule. Note the area of MI activation also involves the primary somatosensory area in the postcentral gyrus. Modified from reference 30 with permission. (b) The combined motor mapping by fMRI and electrical cortical stimulation for epilepsy patients with gliosis in the right medial frontal gyrus (A) and astrocytoma in the right superior and middle frontal gyri (B). The activated area of the functional MRI is shown in task-specific colors: finger-tapping task (magenta), and toe movement task (yellow). Icons indicate the cortical stimulation mapping, which are generally, but not completely, consistent with the functional MRI mapping. VAC: the line vertical to the anterior commissure-posterior commissure line (AC-PC) through the AC, CS: central sulcus, Rt: right, Lt: left, Bil: bilateral, U/E: upper extremity, L/E: lower extremity. Modified from ref. 30 with permission. (See Color plates.)

For example, in patients with polymicrogyri or schizencephalies, stimulation of the ipsilesional hemisphere may elicit normal MEP response in the contralateral hand muscle. Alternatively, stimulation of the contra-lesional hemisphere might show bilateral MEP responses suggesting the functional reorganization of both the contra- and ipsi-lateral corticospinal tracts originating from the normal hemisphere.[32]

Recent advances in frameless stereotactic surgery have refined current TMS mapping techniques by combining MRI with TMS using a 3D digitizer to measure the position of the stimulating coil and coregister this position on to a MRI data set. This 'stereotactic TMS system' combines the anatomical accuracy of structural MRI with the functional motor TMS map and provides accurate representation of the cerebral cortex immediately underlying the position of the stimulating coil on the scalp. By means of such a stereotactic TMS system, several studies attempted to locate the precentral hand area by combing TMS and fMRI.[38–40] These studies consistently reported discrepancies between fMRI and TMS maps with the maximum of fMRI activation 4~22 mm caudal to the TMS center of gravity (CoG). One plausible explanation is the presence of a somatosensory component in the BOLD activity during the hand movements. This is supported by the findings of Niyazov *et al.*[29] that maximum fMRI activation during imagined hand movements was located about 1 cm rostral to that during executed movements and corresponded well with the cortical projection area identified by the TMS mapping (Figure 96.5). In this study, all projected TMS CoGs lied within the precentral gyrus and on average slightly anterior to the hand knob. In summary, combined with the structural MRI, the stereotactic TMS mapping is capable of 'localizing' the precentral motor area and assessing the possible functional reorganization due to the underlying pathology.

Regarding the safety issue of TMS, single-pulse TMS apprears to be relatively safe even in patients with epilepsy. Even though the attempts to stimulate the epileptic focus with TMS have been made extensively in 1990s to improve and shorten the presurgical video-EEG monitoring of ictal events (see Tassinari *et al.*[41] and Ziemann *et al.*[42] for review), so far only one patient has been reported in whom seizures were

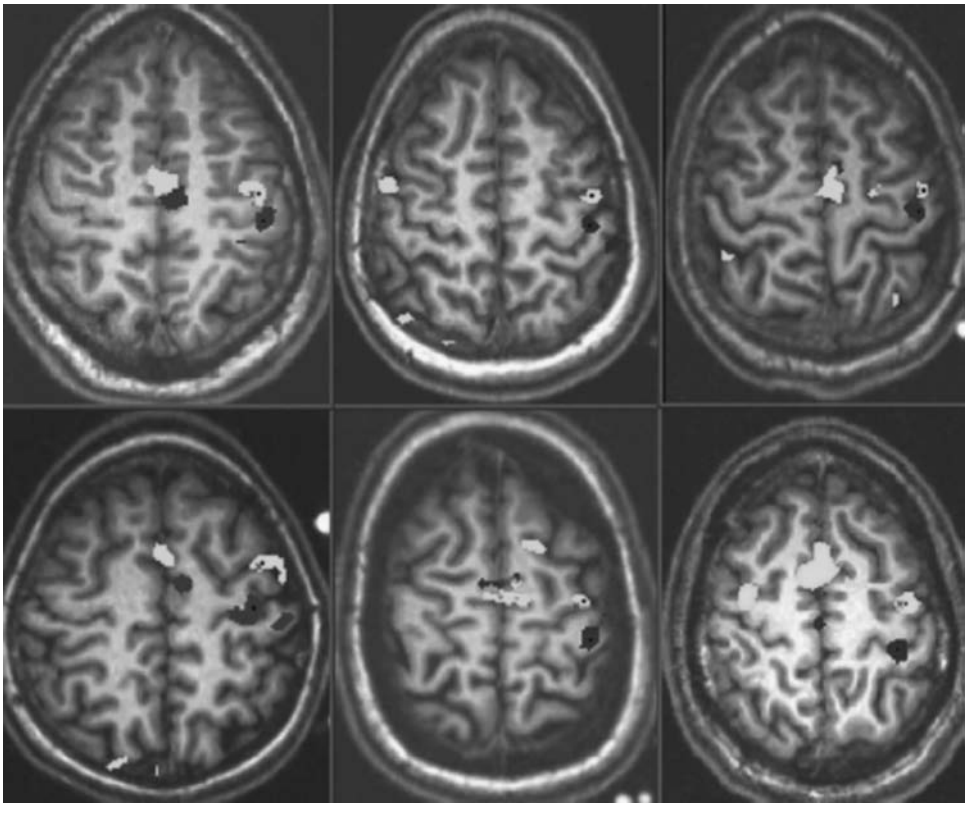

Figure 96.5 Comparison between the fMRI and TMS motor mapping. Blue and yellow activations correspond to the BOLD maps during executed hand movements and imagined hand movements, respectively. Red crosses represent the TMS CoG cortical projection points. Note that all projected TMS CoGs lie within the precentral gyrus and on average slightly anterior to the hand knob. The cortical projected area well corresponds to the fMRI activation for the imagined hand movements. From ref. 29 with permission. (See Color plates.)

triggered reproducibly and promptly by focal single-pulse TMS.[43] This patient had partial epilepsy arising from a documented epileptic focus in the left SMA, and the stimulation of SMA with an angulated figure-of-eight coil placed over the interhemispheric fissure reproducibly triggered the habitual seizure. Thus, careful observation is needed when the epileptic focus is situated close to the motor area.

Magnetic source imaging

With the development of the whole-head multichannel measurement system in 1990s, magnetoencephalography (MEG) has become one of the noninvasive useful tools to locate the motor area. In contrast to fMRI, MEG can record neural electromagnetic activity directly. Moreover, MEG has some advantage in evaluation of sources of brain activity over the more widely-used high-resolution EEG. Local changes in conductivity due to different tissues, for example burr holes from the previous operations, do not significantly affect magnetic fields, whereas electric potentials are clearly distorted.

To date, the following three methods seem to be clinically useful in localizing the motor or sensorimotor cortex; movement-related cortical field (MRCF), cortico-muscular (MEG-EMG) coherence, and somatosensory evoked field (SEF). MRCF usually starts about 1 sec before the movement onset, and it has contralateral predominance from the beginning as compared with Bereitschaftspotential in EEG which is a widely-distributed negative slow shift maximum at the vertex area, starting 3–4 sec before the movement onset.[44] The premovement magnetic fields presumably reflect neural activities originating only from the precentral motor areas, because those from the bilateral SMAs are relatively distant from the sensors and generate two tangentially oriented dipoles of opposite direction that cancel each other. Therefore, MRCF could be used to locate the precentral motor area although the recording of the slow components is occasionally hampered by patient's motion due to the relatively longer recording time (e.g., ~15 min for each muscle) compared with other methods.

Cortico-muscular coherence is evaluated by using correlograms beteeen spontaneous MEG and surface electromyograms (EMGs). The task usually employed is a sustained muscle contraction over 3–5 min for each muscle in the forearm and leg. The 15–30 Hz rhythmic activity of the motor cortex is coherent with the EMG during isometric muscle contraction, indicating that rhythmic cortical activity drives the descending motor commands at a similar rhythmicity.[45,46] In normal subjects, the generation sites of cortical MEG signals coherent with the surface EMG from the activated muscles indicate crude somatotopical organization in the precentral motor strip.[47] Makela *et al.*[48] applied this method to patients with brain tumors located in the vicinity of the sensorimotor region, and showed its efficacy in eight out of 12 patients (Figure 96.6).

The sources of SEFs to electrical stimulation of peripheral nerves accurately identify the posterior wall of the central sulcus with clear somatotopical representations of different

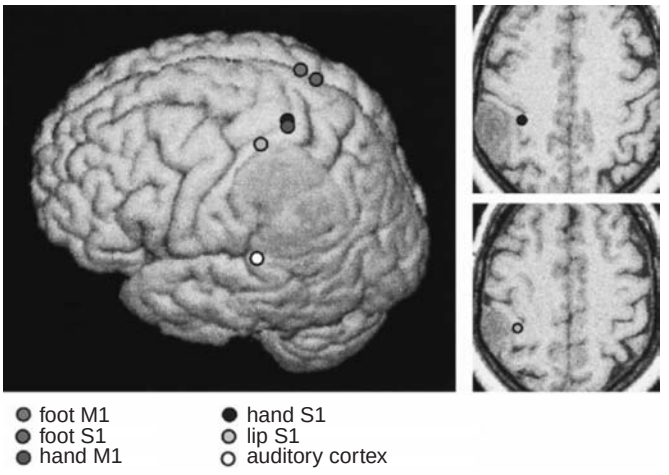

Figure 96.6 The equivalent current sources of SEFs to median nerve (shown as hand S1), tibial nerve (foot S1) and lip (lip S1) stimulation, auditory evoked field (auditory cortex), and MEG-EMG coherences for right wrist (hand M1) and ankle (foot M1) extensions are displayed on the 3D surface rendering of the brain. Sources of SEFs to median nerve and lip stimulation are displayed on two horizontal MRI sections. Note the distortion of functional cortical anatomy by the slowly growing tumor. From ref. 48 with permission. (See Color plates.)

body parts (for a review, see Hari and Forss).[49] Several literatures reported efficacy of SEF in locating the central sulcus in the functional neurosurgery.[50,51] In the aforementioned study of Makela *et al.*, the dipole analysis of SEF correctly identified the central sulcus in all patients, while useful corroborative information was obtained from anatomical landmarks in 11 and from cortico-muscular coherence in eight patients (Figure 96.6).

As reviewed in this chapter, MEG is generally useful for noninvasive mapping of the precentral motor area or the central sulcus. It is, however, important to note that the absence of MEG response does not necessarily imply the absence of function. This is because MEG detects almost exclusively tangentially oriented current source,[52] thus mostly picking up neural activity arising from the sulcal part of the cortex. Therefore, it is highly possible that some neural activation localized in the crown part of the cortex fails to be identified by MEG. Moreover, MEG is not suitable for the measurement of neuronal activities arising deep in the brain (e.g., SMA) because of the significant decay of the electromagnetic flux before reaching the MEG sensors.

Conclusion

Evoked potentials such as somatosensory evoked potentials and movement-related cortical potentials were the only methods available to 'lateralize' the sensorimotor cortex in the past. The recent advance in various technologies has provided clinically applicable means to 'localize' the motor cortex noninvasively. Because each method has its advantage as well as disadvantage, one should understand limitations of each technique for clinical use. Nevertheless, noninvasive functional mapping methods, when combined with the structural MRI analysis, will provide an important opportunity to assess, before surgery, location of the motor cortex and its possible functional reorganization due to the underlying pathology. This noninvasive approach greatly helps epileptologists and neurosurgeons to guide the placement of invasive intracranial electrodes. For the precise information for surgery, however, functional motor mapping data thus obtained should be confirmed by the gold standard of electrical cortical stimulation.

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97 Noninvasive tests to define lateralization or localization of memory

EB Geller and C Santschi

Introduction

In the 1950s it became apparent that bilateral temporal resection could cause severe anterograde amnesia, such as in the well-described case of H.M.[1] Additionally, unilateral temporal lobectomy patients who developed similar deficits were found to have contralateral hippocampal damage on later autopsy.[1,2] In an effort to better predict the risk of post-operative memory decline, Brenda Milner and the team at the Montreal Neurological Institute devised memory protocols to add to the intracarotid amobarbital test (IAT), already in use at the time for language lateralization. The notion was that patients at risk for amnesia following unilateral mesial temporal excision would incur a transient amnesia after administration of sodium amobarbital to inactivate the hemisphere ipsilateral to the proposed surgery. The IAT has been widely adopted among epilepsy surgery centers. Unfortunately, variations in technique have led to the lack of standardization and difficulty comparing results from different centers.

The task before us is to predict most effectively the risk of acquired memory deficits before performing epilepsy surgery, specifically temporal lobectomy. While the combined assessment of memory and language lateralization has come to be known as the intracarotid amobarbital test (IAT) or simply the 'Wada test,' this chapter will focus on data regarding the IAT test for prediction of postoperative memory deficits. IAT memory deficits have also been used as a predictor of seizure outcome. In addition, we will review newer, noninvasive tests of brain function that may add to or eventually replace the invasiveness of the IAT. While these newer techniques have provided insights into the functional neuroanatomy of memory, for the most part they have not been validated against post-surgical outcomes and are not yet ready to replace the IAT.

Throughout this chapter, we will use the term 'ipsilateral' to refer to the hemisphere determined to have the epileptic focus or that is operated, and 'contralateral' to the normal or unoperated hemisphere.

Chelune[3] has discussed a major theoretical issue involved in preoperative memory assessment, contrasting two models of memory function. One model has suggested that good memory function of the unoperated hemisphere will preserve memory after temporal lobectomy (the 'functional reserve hypothesis'). This model was in fact the basis for the initial use of the IAT. The 'functional adequacy hypothesis' suggests that preoperative memory is more related to the intrinsic abilities of the operated hemisphere, with better preoperative function creating a higher risk of postoperative decline. These models are an important framework for evaluating the IAT literature, and we will refer back to these concepts in the following discussion.

Methodological issues in IAT memory testing

The preoperative IAT evaluation of memory functions has been widely accepted and extensively utilized for over three decades as part of the pre-surgical evaluation of patients with intractable epilepsy expected to undergo temporal lobe resection. The original technique of intracarotid amobarbital injection was developed by Dr. Juhn Wada in 1949,[4] and the further development of the 'Wada test' has been reviewed by Snyder and Harris.[5]

Since no official standards or normative data exist governing the procedure, substantial methodological variability exists among centers employing this technique. The literature reports significant variations in IAT methods across centers and over time. This lack of consensus has been emphasized in several multicenter surveys of IAT protocol.[6]

Methodological variations exist in both the administration of amobarbital, as well as in the memory evaluation procedure. Administration variables include the dose of amobarbital (typically 80–120 mg per dose), the rate and method of injection (by hand or machine), which side is injected first, and whether EEG is recorded during the procedure. Memory evaluation variables include the number and types of test items, use of a baseline training procedure, and the timing of presentation, recall or recognition testing post injection. Scoring procedures have included evaluation of absolute scores, calculation of laterality indices, and have variably corrected for false positive recall. Other interindividual factors that may affect test results include cerebral perfusion patterns, duration of drug effect, and effects of antiepileptic medication on cognition.

Historically, a major methodological concern focused on the validity of the procedure itself. Given the invasive nature of the IAT, it is not surprising that few studies have been published regarding test-retest reliability, and those available are reviews of repeated procedures done for clinical rather than research purposes. McGlone and MacDonald reviewed

data on 10 patients who underwent 18 repeat injections in the same hemisphere.[7] There were major changes in memory results in eight of 18 injections; seven of these were attributed to difficulties with one injection. In eight cases with technically satisfactory first injections, seven had identical memory classification on repeat. They also examined 70 patients who had repeat bilateral injections, and found no evidence for a practice effect. Lodenkamper *et al.*[8] found 53 of 1190 patients (4%) had undergone a second IAT at the Cleveland Clinic, and only 3 (0.24%) had a third IAT. Language lateralization was always replicated, but memory results were inconsistent in 63% of patients.

Few studies have tried to assess whether the IAT protocol is truly predictive of global amnesia. McGlone *et al.*[9] used a four item adaptation of an IAT memory protocol, without drug injection, in patients with amnesia. Two with global amnesia failed, but 12 of 13 classified as having severe amnesia had good recall. Although this raises the possibility of poor predictive value for the IAT, it may be that using fewer items than the real IAT may have been too easy. Carswell *et al.* also found that amnestic patients failed their IAT memory protocol.[10]

Although IAT memory testing was presumed to assess hippocampal function, the question has been whether intracarotid anesthesia inactivates the mesial temporal lobe, which is served primarily by the posterior rather than anterior cerebral circulation. For this reason, the technique of selective posterior cerebral artery amobarbital injection was developed.[11] Urbach *et al.* used SPECT studies with HMPAO injected simultaneous with amobarbital to show that the selective posterior cerebral artery infusion is distributed to the entire hippocampus, as well as the occipital lobe and sometimes thalamus.[12]

Studies using SPECT agents co-injected with sodium amobarbital have shown a variable distribution of inactivation, typically more limited in area than the angiographic perfusion and involving the mesial temporal lobe in only a minority of patients.[13,14] This may possibly contribute to false negative results.[15] McMackin *et al.*[16] revisited this issue by performing the IAT in 10 patients with intracranial electrodes, and injecting HMPAO intravenously *after* amobarbital injection so as to assess the areas of functional inactivation, not merely the vascular distribution of the amobarbital. They found that the posterior hippocampus demonstrated significant hypoperfusion on SPECT as well as delta activity in the depth electrodes. This finding supports intracarotid amobarbital injection as a valid test of mesial temporal function.

Thus, although SPECT studies have not added clinical utility to the IAT, they have delineated and validated the physiological changes occurring during the IAT, and eliminated the theoretical need for the more difficult posterior cerebral artery injection.

Administration variables

Many of the IAT administration variables are not always amenable to strict control in the clinical setting, and have therefore been difficult to systematically analyze. One of the more studied methodological issues has been the timing of injections. Grote *et al.*[17] compared memory scores in patients who had received injections on the same day versus two consecutive days. They found better memory scores (approximately 1 point on a 0 – 9 scale) after the second injection when the language-dominant hemisphere was injected on a subsequent day than on the same day. This may have been due to persistent amobarbital effect; they used 125 – 150 mg for each injection, while some centers use less and may not encounter this effect. Grote *et al.* suggest using a correction factor if the dominant hemisphere is injected second on the same day. While there may be medical reasons to prefer both injections with a single catheterization, these authors note that the change in their protocol to same day injections had been caused by changes in insurance reimbursement, indicating the importance of non-scientific factors in medical practice.

Memory evaluation variables

Although no standardized protocol has been adopted for memory testing, most centers have utilized an approach modified from the original Montreal procedure in which discrete items are presented during the period of anesthetization and recall is tested after the drug effects have worn off. Memory is then assessed in a recognition paradigm which includes use of foil items, i.e., items not shown during the initial presentation. Failures to recognize items are scored as errors.

Loring *et al.*, in a large multicenter study, found that using real objects for memory testing is more accurate than line drawings in predicting the side of surgery.[6]

Loring *et al.* found that asymmetric memory was more predictive of verbal memory decline after left temporal lobectomy than absolute scores.[18] They also showed that asymmetric recall of items presented early after amobarbital injection may have greater lateralizing value than later items.[19] While there may be concern that memory for such early items may be confounded by confusion or inattention due to the injection, Lesser *et al.*[20] showed that many patients could recognize at least two thirds of the items presented during the confusional state.

Dodrill and Ojemann[21] compared three different memory protocols in 159 patients. They alternated items from the original Montreal protocol (five objects) with their own Seattle protocol (object naming, followed by reading a sentence, then recalling the object). After recovery from amobarbital, they performed the Interview procedure, in which patients are questioned about five aspects of their performance during the testing. There was little agreement among the three procedures. The Seattle procedure correctly predicted postoperative memory outcome in 76%, which was statistically significant, while the Montreal protocol (48%) and the interview procedure (52%) had no predictive value. The authors felt that the Seattle protocol was superior due to emphasis on verbal memory and testing of recall during rather than after drug effect, although there is dependence on speech recovery when injecting the language dominant side. They thought the Interview procedure suffered from potential interference by drug-induced neglect.

Interindividual variables

Finally, further limitations of IAT memory testing may be due to individual subject variables including age, cognitive status and medication regimen, affecting the patient's ability to comply with the testing procedure.

Children have been subjected to the IAT, but may not respond as adults do. Willams and Rausch[22] found that children

under 13 years old were less likely to pass the IAT when an epileptogenic left hemisphere was injected, although language lateralization was possible.

Antiepileptic medication may also potentially affect IAT results. McCabe *et al.* reported a patient who performed poorly on neuropsychological testing and IAT memory performance while on topiramate, an antiepileptic drug known to cause verbal and memory problems.[23] The patient's scores improved when tested on another drug regimen.

Memory outcome after epilepsy surgery can also be affected by subjective factors. Patients may mistake other cognitive impairment (e.g., verbal deficits) as a memory problem, depression may worsen perception of memory, and personality may also play a role.[24]

IAT for prediction of memory outcome after temporal lobectomy

Studies evaluating IAT efficacy in predicting memory performance postoperatively can be categorized into those which evaluate the IAT predictions against postoperative performance directly, and those which compare IAT performance with predictions of another noninvasive technique.

Direct IAT predictive studies

Avoidance of severe amnesia was the initial aim of the IAT. In 2003, Kapur and Prevett found only nine cases of amnesia after unilateral temporal lobectomy in the English literature, indicating that it is a rare occurrence despite likely underreporting.[25] IAT results were predictive of amnesia in the three cases in which they were available.

Wyllie *et al.*[26] used the Cleveland Clinic IAT protocol that included objects, drawings, pictures, and written and spoken words. Failure (<67% recall) after ipsilateral injection did not predict material-specific memory deficits postoperatively. There was better but not significant correlation using a >20% recall asymmetry. In a later study from the same center, Kneebone *et al.*[27] compared 32 left to 31 right temporal lobectomy patients. Left TLE patients who passed (≥ 68% recall) contralateral IAT injection had a greater decrement in verbal memory, but there was no similar decrement in visual memory for the right TLE patients. This suggested the functional adequacy model is relevant, but more for verbal than visual memory.

Chiaravalloti and Glosser[28] examined the value of the IAT in predicting material-specific memory outcome after temporal lobectomy in 70 left hemisphere language dominant patients. They found that total recognition memory scores and word memory scores were predictive of verbal memory decline, using either the injection ipsilateral to the epileptic focus or an asymmetry score. However, the visual test items were not predictive of visuospatial memory decline. Wieser *et al.*[29] found that the verbal memory performance after selective anterior choroidal artery injections of amobarbital was statistically identical to that found after left anterior temporal lobectomy, but visual memory was underestimated.

Jokeit *et al.*[30] compared a variety of prognostic variables in 27 left temporal lobectomy patients. Good preoperative verbal memory on neuropsychological testing and IAT recall after right hemisphere injection were the best predictors of memory decrement.

Stroup *et al.*[31] created a multivariate model based on the functional adequacy hypothesis to predict verbal memory decline, using five preoperative variables that had been shown to be useful in univariate studies. The variables used were: (1) whether the side of resection was language-dominant or not (based on IAT results); (2) presence or absence of exclusively unilateral mesial temporal sclerosis on clinical reading of the MRI; (3) IAT total memory score after injection of the hemisphere contralateral to the seizure focus (only objects and picture items were used); and preoperative verbal memory scores on (4) immediate and (5) delayed recall testing. Verbal memory scores were assessed using the California Verbal Learning Test and the Logical Memory subtests on the Wechsler Memory Scale-Revised. Using 132 subjects, they found that each of the variables was independently predictive of post-operative verbal memory decline, and they developed an equation to predict the risk of memory decline in individual patients based on these measures. When ipsilateral injection memory scores or asymmetry scores were included, they did not add to the predictive value of the IAT, supporting the functional adequacy hypothesis. This paper supports the continued use of the IAT (at least using this protocol) as an independent component of memory risk assessment for temporal lobectomy.

Sabsevitz *et al.*[32] compared 12 left temporal lobectomy patients with the expected memory asymmetry on IAT with nine who had a reversed asymmetry. Those with reversed asymmetry had poorer verbal memory outcome and worse seizure control.

Other studies have supported the functional reserve hypothesis. Bell *et al.*[33] found that right hemisphere memory on IAT was predictive of verbal memory decline in 22 patients with left temporal lobe epilepsy.

IAT comparison with other functional techniques

Positron emission tomography using fluoro-deoxyglucose (FDG-PET) is often used to evaluate focal dysfunction in epilepsy surgery candidates.[34] FDG-PET hypometabolism in the left hemisphere, particularly the lateral temporal lobe, correlates with lower verbal IQ and verbal memory scores.[35] FDG-PET has also been compared to the IAT as a measure of temporal lobe dysfunction. Salanova *et al.*[36] found 86% (20/23) patients had hypometabolism of the epileptogenic side, but only 13 of these 20 had ipsilateral memory impairment on IAT. Overall, 95% of the patients (22/23) had abnormality on FDG-PET or IAT, suggesting that while the tests are often in agreement, they provide complementary information. Griffith *et al.*[37] found left anterior temporal lobectomy patients with no or mild FDG-PET temporal lobe metabolic asymmetry had significantly greater verbal memory decline than those with moderate to severe hypometabolism, suggesting that FDG-PET may provide additional prognostic information regarding memory. IAT results were not included in this study.

Joo *et al.*[38] compared 36 patients with bilateral FDG-PET hypometabolism to 59 with unilateral hypometabolism, who were evaluated for temporal lobectomy. They found that IAT memory scores in those with bilateral hypometabolism compared to the unilateral group were more likely to be

symmetric (48% vs. 16%). When the score was asymmetric, the bilateral patients were more likely to have a reversed asymmetry (i.e., the ipsilateral side having better memory than the contralateral side) (31% vs. 3%). Overall, the mean memory score in the ipsilateral (operated) hemisphere was lower in the bilateral hypometabolism group (51 ± 20.9%) than the unilateral group (63 ± 24.5%). However, there was no significant change from preoperative neuropsychological scores after surgery in the two groups, except in four patients with left TLE and reversed asymmetry on the Wada, who did have significant worsening of postoperative memory. Although this study seems to suggest that the IAT was not useful in prediction of postoperative memory, only 26 of the 36 bilateral hypometabolism patients had surgery, and it is likely those most at risk of memory deficits were excluded.

Across studies and protocols, there is significant concern for the group of patients who 'fail' the IAT memory component bilaterally. This result raises concern for severe postoperative amnesia and such patients may be denied surgery. Bautista *et al.*[39] found that patients with bilaterally poor memory had no significant change in memory after nonlanguage dominant temporal resection, but that dominant resections caused similar verbal memory decline compared to those with dominant resections and unilaterally poor memory or bilaterally intact memory. This study again emphasizes the major cognitive risk of temporal lobectomy is verbal memory loss in language-dominant resections, no matter what the IAT results, and that temporal lobectomy might be possible in selected patients with bilaterally poor memory.

IAT memory for prediction of seizure outcome

Given that memory deficits suggest temporal lobe dysfunction, some researchers have evaluated the IAT memory results as another possible predictor of postoperative seizure outcome. Several studies have confirmed that the IAT memory results correlate with hippocampal neuronal loss histologically, using an IAT protocol including words, pictures and objects.[40–42]

Wyllie *et al.*[43] also showed that memory failure on IAT occurred in 80% of patients after injection of the contralateral side, versus 20% failure after ipsilateral injection.

Sperling *et al.*[44] evaluated memory results of the IAT in 117 patients who underwent temporal lobectomy. When the IAT showed worse memory in the operated hemisphere seizure outcome was better. The degree of difference was not predictive, nor was the absolute score in the operated hemisphere. Loring *et al.*[45] found similar results using a different IAT protocol, but in contrast they found that an asymmetry of three or more recalled items (out of eight) predicted better seizure outcome.

Kirsch *et al.*[46] assessed patients with an unexpected memory asymmetry (UA) on the IAT. UA was found in 36% of left-sided and 8% of right-sided surgeries. UA patients had worse seizure outcomes after right temporal lobectomy than those with the expected asymmetry, but there was no difference in the left temporal lobectomy group, in contrast to Sabsevitz *et al.*[32] as noted above. They did not find a difference in postoperative verbal memory for any group. A potential problem with this study was the use of verbal memory items, in which inactivation of language function may have confounded true memory assessment of the nondominant hemisphere. Even still, this study suggests that patients should not be denied surgery exclusively based on the results of Wada memory scores.

Alternatives to amobarbital for hemispheric anesthesia

Recurrent shortages of amobarbital have led some investigators to explore other agents for intra-carotid hemispheric anesthesia. While the acute effects of the agents are detailed in the studies cited below, they have not yet been validated against postoperative memory outcomes.

Sodium methohexital (SM) has been studied by several centers.[47] Compared to amobarbital, SM has a more rapid offset of action as assessed by clinical and EEG effects.[47] Buchtel *et al.*[48] used SM in 173 Wada procedures on 86 epilepsy surgery candidates, and compared it to their experience with amobarbital. The behavioral effects of the drugs were similar, but EEG recovery took only 4.8 minutes after SM compared to 7.8 minutes for amobarbital. They compensated for the briefer duration of action by performing two injections on each side, one for language testing and one for memory testing. We have had the opportunity to try SM in several patients and were impressed with the rapid recovery from drug effect. It is possible that using SM might reduce the same-day injection effects described Grote *et al.*[17]

Takayama *et al.*[49] evaluated propofol as an alternative to amobarbital for the Wada test, because of difficulty obtaining amobarbital in Japan. Propofol is an anesthetic agent with rapid onset and offset of action that is often used for intravenous conscious sedation as well as treatment of status epilepticus. They compared 55 patients tested with amobarbital to 12 tested with propofol. They found similar rates of satisfactory contralateral hemiplegia and ability to lateralize language and memory function. Time to full recovery of motor function was similar, but the propofol group had a somewhat longer time for speech recovery on the language-dominant side. In a later study the same group explored adverse effects of propofol in a larger group.[50] They tested 58 patients, including 32 with tumors, 13 with partial epilepsy, and 13 with arteriovenous malformations (AVM). Propofol was prepared as a 1 mg/mL solution in 10 mL of normal saline. Doses ranged from 5–32 mg to produce transient hemiplegia, with an average of about 20 mg across patient groups. They found a 33% rate of adverse reactions. Reactions included eye pain, shivering, face contortion, lacrimation, laughing and apathy (grade 1); confusion, involuntary movements, and head and eye version (grade 2), and increased muscle tone with twitching and rhythmic movements or tonic posturing (grade 3). The grade 1 and 2 reactions disappeared in 5 minutes and did not interfere with cognitive testing, but the grade 3 reactions faded more gradually, and were more likely to prevent valid cognitive assessment. Grade 3 reactions were more common in patients over age 55, with AVM, and with propofol doses >20 mg.

Jones-Gotman *et al.* evaluated etomidate, another anesthetic, in what they called the etomidate speech and memory test ('eSAM').[51] They assessed 16 epilepsy surgery candidates.

They injected a 2 mg bolus of etomidate via the internal carotid artery, followed by infusion at 6 mL/hour (0.003–0.004/mg/kg/minute). Infusion was continued until all cognitive tests were completed. Recognition was tested after clinical and EEG changes had returned to baseline, about 4 minutes. They found contralateral hemiplegia and ipsilateral EEG slowing in all injections. Side effects were frequent but mild; 46% of injections caused an upper extremity tremor, usually mild. Although similar in effect to the IAT, the eSAM allowed a more reliable period of cognitive testing due to continuous infusion. There is concern etomidate can cause adrenal suppression, seen in higher doses and in critically ill patients.[51,52]

Alternatives to the IAT

Because of the limitations of the IAT discussed above, noninvasive methods have been sought to replace it in the pre-surgical workup. Functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS) have been studied as tests of preoperative memory function. Each offers the advantages of being noninvasive and easily repeatable. It should be possible to better establish the validity of these tests in predicting postoperative memory deficits than it has been with the IAT. Their experimental nature would ethically allow their research use in a consecutive series of epilepsy surgery patients without the data influencing the surgical decision, as the IAT must. Each of these procedures has given insight into the functional neuroanatomy of memory, but they have yet to be established as reliable predictors in epilepsy surgery. The following section discusses the progress so far.

Functional MRI (fMRI)

Functional MRI is based on the finding that increased neuronal activity creates greater local blood flow, and changes in flow can be detected using the difference in MRI signal properties of hemoglobin and deoxyhemoglobin.[53] Images are obtained during two or more activation or rest states, and active areas are indicated by subtraction and statistical techniques. Assessment of hippocampal function may be difficult due to imaging difficulties in this region.[53] Functional imaging depends on detecting a difference between resting and activated states, which is more difficult in the hippocampus because memory is never truly 'at rest'.[53] Progress in fMRI for replacing the IAT was recently reviewed in detail by Gaillard[53] and Klöppel and Büchel.[54] In general, fMRI differs from the IAT in several ways. IAT is a regional inactivation procedure, which is performed rapidly and hard to reproduce. Behavioral abnormalities or sedation during testing can confound results. FMRI is an activation procedure, which may show areas *involved* in a function but cannot distinguish which are *essential* for that function.[54]

A number of studies have shown differences in fMRI activation by memory paradigms between controls and temporal lobe epilepsy patients. For example, Dupont *et al.* found that delayed verbal recall created weaker activation in left temporal lobe epilepsy patients than in controls.[55]

A small study of seven pre-surgical patients showed fMRI activations lateralized language consistent with IAT results (four left hemisphere dominant, three right hemisphere dominant).[56]

Verbal memory was assessed using learning and retrieval of a word list in seven patients with left mesial temporal sclerosis compared with normal controls.[57] All patients had left language dominance on the IAT. The patients showed significant differences in fMRI activation in both the encoding and retrieval states. They had less activation in the occipitoparietal and parahippocampal regions when encoding than the controls. During retrieval, the patients had much more extensive activation of the left lateral prefrontal region. Surgical results were not reported.

Deblaere *et al.* did a detailed comparison of their IAT protocol to memory activation using fMRI.[58] They found bilateral fMRI activation in the anterior/mesial temporal lobes in eight normal volunteers. The 18 pre-surgical patients studied included seven with a left-sided focus, nine with right-sided focus, and two determined only after depth electrode recordings. The IAT showed failure of the ipsilateral (epileptogenic) side in 7/16, bilateral passing for 9/16, while one patient passed the only injection in the ipsilateral side (i.e., testing the contralateral side), and one patient had a technically invalid test. Activation in the fMRI paradigm involved the hippocampus, parahippocampus, and fusiform gyrus, as well as other areas including thalamus and lateral temporal neocortex. Fifteen of the 18 patients had lateralized fMRI activation, and three had bilateral activation. The lateralized activations were higher in the contralateral (normal) hemisphere. Comparison of the fMRI and IAT results showed significant correlation only for the right TLE patients, not for those with left TLE. This was likely due to the differences between the two test protocols in memory modality. Their IAT protocol included 11 memory items, of which five were written words and seven were pictures, while the fMRI protocol included only five images and no words. This result lends support to the lateralization of modality-specific memory, and the importance of using appropriate testing paradigms in assessing patients. Further refinement of this fMRI memory protocol may indeed lead to a useful test that could replace the IAT.

Aldenkamp *et al.* used fMRI activated by language and memory items similar to those presented in an IAT, to assess which structures are activated by these procedures in normal volunteers.[59] Complex visual items, which could be encoded both verbally and visually, produced activation during encoding symmetrically in the bilateral hippocampus, parahippocampal and fusiform gyri, whereas recall produced activation more restricted to the posterior hippocampus as well as extratemporal (occipital and frontal) regions. They concluded that such memory items are useful and valid for activating both mesial temporal lobes during the IAT. This finding supports the validity of using complex visual items in the IAT even for assessment of the language dominant temporal lobe, as in the multicenter study of Loring *et al.*,[6] rather than combining visual and verbal items.

Deblarere *et al.*[60] created a semirandom fMRI memory paradigm, to try to incorporate more event-related type activations, which are harder to detect but show more anterior hippocampal activation than block design paradigms. This protocol produced agreement with the IAT laterality only in right temporal lobe epilepsy patients, not left-sided patients,

which they felt was due to more verbally-oriented items on the IAT protocol. Surgical outcomes were not reported.

Richardson *et al.*[61] more formally addressed the ability of fMRI memory testing to predict verbal memory outcome in left temporal lobectomy patients. They studied ten patients, and compared preoperative neuropsychological testing (List Learning and Story Recall subtests of the Adult Memory and Information Processing Battery), hippocampal volumetrics, and fMRI activation to postoperative List Learning and Story Recall scores. The fMRI memory testing was performed by presentation of 255 words. Subjects were asked to press a button to indicate if the word was 'living' or 'not living', and were not asked to memorize the items. Ninety minutes later a surprise recognition memory test was performed. The fMRI responses recorded during the encoding phase were categorized as to whether the items were later recalled, a left-right hippocampal activation difference was determined, and a recognition rate was calculated. While all these preoperative variables had some predictive value for postoperative memory, the fMRI asymmetry showed the highest correlation with memory outcome, with greater activation on the left predicting worse verbal memory outcome ($p=0.00027$). On an individual basis, fMRI showed 100% sensitivity, specificity and positive predictive value for >1 standard deviation decline in delayed list recall, with 40% specificity and 63% positive predictive value for immediate list recall and story recall. This study, while promising, was performed only in a small group of selected patients and needs to be repeated in a larger population. The authors also did not compare the fMRI results to IAT results, even though the stated intention was to develop a noninvasive replacement for the IAT. Even so, this study does provide an excellent start in developing protocols that are predictive of postoperative memory and could potentially displace the Wada test.

Rabin *et al.*[62] also developed an fMRI memory protocol to predict post-surgical memory outcome in 35 temporal lobectomy patients. They used 60 complex visual scenes, presented in ten scene blocks over 40 seconds each, and recognition was tested using 60 foils intermixed. Activation in a mesial temporal region of interest was symmetric in 30 controls, but asymmetric in patients. The degree of activation ipsilateral to the operated side was significantly inversely correlated with memory outcome, lending support to the functional adequacy hypothesis, while the contralateral activation was not correlated. However, the correlations were too weak to allow sensitivity and specificity predictions at the individual patient level, and further refinement in the procedure is needed. The authors did compare fMRI results to IAT memory results in 27 patients, finding only a mild correlation of asymmetry ratios on fMRI and Wada.

Janzsky *et al.*[63] used an introspective recall task during fMRI in 16 patients who underwent right temporal lobectomy. Reduced fMRI activation in the right temporal lobe correlated with better memory outcome after surgery, again supporting the functional adequacy model. IAT was not done in these patients.

Strange *et al.*[64] showed that there are different hippocampal fMRI responses to intentional learning versus passive encoding, suggesting that the different memory paradigms tested so far may produce varied results and be hard to compare directly.

Hwang and Golby,[65] in a recent review of fMRI and memory, note that fMRI is an activation procedure, which illuminates brain regions that may be involved in a task, but not those that are essential for the task. Inactivation procedures such as the IAT may still provide critical information for surgical outcomes. Additionally fMRI presents technical challenges in data acquisition and image processing, relying heavily on statistical analysis. These factors create time and personnel demands that may make clinical testing more cumbersome.

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) uses an external magnetic coil to noninvasively produce electrical currents in underlying cortex, thereby interfering with local cortical function. It has been used to study the distribution as well as relative timing of cortical processes. It is noninvasive, generally comfortable and can be performed repeatedly. TMS has been used to investigate memory function in temporal lobe epilepsy patients.[66] In a review of the literature up to 1998, Grafman and Wasserman[67] concluded that TMS could produce a 'modest, but reversible, negative effect on all components of memory' depending on stimulation parameters. As yet there has not been sufficient research into TMS and temporal lobectomy outcomes to comment on its potential utility.

Magnetoencephalography (MEG)

Magnetoencephalography (MEG) records the extracranial magnetic fluctuations produced by neuronal electrical currents. Like EEG, MEG offers the advantage of high temporal signal resolution (millisecond range), but unlike EEG it can localize the dipole activity source on the subject's own MRI scan. MEG has already shown utility in epilepsy surgery evaluations, for mapping both focal epileptiform activity as well as noninvasively localizing somatosensory, motor, auditory, and possibly language cortex.[68]

MEG has been used to probe the neurophysiology of memory in a number of studies, some of which are relevant to eventually incorporating MEG into pre-surgical memory evaluations. For example, Tesche and Karhu used MEG to probe stimulus-induced hippocampal activity related to a working memory (digit span) task.[69] With a stimulus-averaged evoked potential technique, they found that the memory task reset hippocampal theta (4 – 7 Hz) oscillations bilaterally, after the probe in the left hippocampus and prior to the probe (anticipation) in the right hippocampus. Kaiser *et al.* showed increased gamma-band activity in the left frontotemporal region during a verbal working memory task in normal controls.[70] Papanicolaou *et al.* found modality-specific MEG responses in the hippocampi, with verbal stimuli preferentially activating the left side and visual stimuli the right.[71] Breier *et al.* demonstrated excellent correlation between IAT language lateralization and lateralized MEG activations using IAT-type stimuli, however memory was not compared.[72]

Conclusions

The IAT has many flaws. It is invasive and expensive. IAT results may be unreliable and hard to replicate, and variations

in methodology make comparisons among centers difficult. Despite these drawbacks, the IAT has gained wide acceptance and has persisted for decades. The variability in the literature has led to significant controversy about the ultimate value of the IAT, however. Dodrill has argued that 'there is no convincing evidence that the Wada test is of any practical value, and especially so when its predictive capability is compared with other easily obtained variables,'[73] while Goldstein and Gilliam have suggested that the IAT may be deferred in right TLE patients.[74] Some of this controversy is related to the different IAT procedures used. It appears that the Medical College of Georgia procedure may be the most reliable.[6,18,19,45] Although this procedure uses real objects rather than verbal items, the Rabin *et al.*[62] fMRI study noted above showed that complex visual items activate the mesial temporal lobes symmetrically in controls and asymmetrically in TLE patients, lending support to using objects for assessing both temporal lobes. The use of objects also avoids the interference of drug-induced language deficits on memory testing.

It appears likely that the IAT can predict severe global amnesia, although such cases are rare. Its greatest utility may be in helping to predict risk of verbal memory decrement in language-dominant temporal lobectomy cases. We agree with Loring and Meador[75] that the IAT should not be scored as pass/fail, but should be interpreted in the context of other preoperative testing to suggest little, moderate or significant risk to memory.

Newer technology may eventually replace the IAT for both language and memory testing, with fMRI showing special promise so far. The research nature of these tests should allow their prospective scientific validation in a way that is no longer possible with the IAT. In order to truly replace the IAT, it will important for such techniques to be standardized as simply as possible for routine clinical use.

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SECTION 11

The epileptogenic zone

98 The epileptogenic zone: general principles

KM Klein and F Rosenow

Definition

The area of cortex that is indispensable for the generation of epileptic seizures is called the epileptogenic zone.[1–5] The goal in epilepsy surgery is to completely remove the epileptogenic zone while sparing the eloquent cortex. Unfortunately, there is currently no way to measure the extension of the epileptogenic zone directly. In patients who became seizure free after epilepsy surgery we can, by definition, conclude that the epileptogenic zone has been included in the resection. However, there is the possibility that the epileptogenic zone was much smaller than the resection and, therefore, a much smaller resection would also have led to seizure freedom.

By definition total removal or disconnection of the epileptogenic zone is necessary and sufficient to render a patient seizure free. The epileptogenic zone is a theoretical concept which would require permanent seizure freedom even after all antiepileptic medication was tapered. For practical purposes we would suggest to consider 1 year of postoperative seizure freedom even with the patient still on antiepileptic medication sufficient to conclude that the epileptogenic zone was removed completely/sufficiently, even though a proportion of patients will loose seizure freedom subsequently.

Relationship between the other zones of cortex and the epileptogenic zone

In order to generate an appropriate hypothesis regarding the localization of the epileptogenic zone one has to combine information about the localization of the other cortical zones which can be measured (ictal onset zone, irritative zone, epileptogenic lesion, ictal symptomatogenic zone, and functional deficit zone). When the localization of these zones is concordant there is a high possibility that a resection of this area includes the epileptogenic zone, and leads to seizure freedom.

Typically the epileptogenic zone consists of the *actual and the potential seizure onset zones*. The *actual seizure onset zone* is the area of cortex from which the seizures currently recorded arise. Even after complete resection of this area seizures may persist because neighboring or distant cortex that previously did not generate seizures starts generating seizures. In other words, this *potential seizure onset zone* reaches the threshold for seizure generation only after the actual seizure onset zone is resected.[4] This process may take time and can serve as a concept to explain that the rates of seizure freedom usually decrease over time in surgical case series.[6,7] Unfortunately, there is no way to measure these potential seizure onset zones prior to surgery.

A number further issues need consideration: a) using extracranial electrodes one has to keep in mind that at least about 6 cm^2 of cortex have to discharge simultaneously to allow detection of seizure activity.[8] When initially only small areas of cortex are involved and the seizure activity shows fast propagation, the onset zone of the recorded seizure may be more extensive or even be located differently to the real seizure onset zone. When using subdural electrodes one needs to consider that only a small part of the gyral cortex is covered and that the real seizure onset zone may frequently not be covered by the electrodes. In this situation a propagated seizure pattern might be mistaken for a focal or regional seizure onset occurring under the subdural electrodes.[3]

The location of the seizure onset zone measured with ictal SPECT depends on the time of injection. The seizure may have significantly propagated when the isotope reaches the cortex. Therefore, the epileptogenic zone may be smaller or larger than the recorded seizure onset zone.

The *irritative zone* which is the area of cortex that generates interictal epileptiform discharges must not necessarily be part of the epileptogenic zone.[1,9,10] Patients with temporal lobe tumors, for example, can achieve seizure freedom after resection of the tumor despite preoperative spikes in both temporal regions.[11,12] Furthermore, some patients with tuberous sclerosis, infantile spasms and multiregional spikes may become seizure free after focal resections.[13–15] On the other hand, in patients with mesial temporal lobe epilepsy caused by hippocampal sclerosis contralateral spikes are negative predictors for postoperative seizure freedom.[16]

In most cases the *epileptogenic lesion* is part of the epileptogenic zone. Complete resection of the epileptogenic lesion is correlated with a higher percentage of seizure freedom (Van Ness, 1992).[17] However, depending on the type of the epileptogenic lesion complete resection does not always cause seizure freedom. Brain tumors and cavernomas typically induce a perilesional epileptogenic rim restricted to the directly surrounding cortex.[4,18] In these cases the epileptogenic zone comprises the lesion and the directly surrounding tissue. Therefore, a topectomy is often followed by seizure freedom. On the other hand, in patients with cortical dysplasia frequently only a fraction of the dysplasia is visible on MRI.[19]

Consequently, the epileptogenic zone often comprises much more cortex than the lesion shown in MRI. Moreover, the complete epileptogenic lesion must not necessarily be included in the epileptogenic zone. This has been noticed in patients who became seizure free after epilepsy surgery despite only partial resection of the lesion because of its location in the eloquent cortex.[20]

The *symptomatogenic zone* gives additional information regarding the location of the epileptogenic zone. Depending on the semiology the information may be lateralizing and/or localizing.[21] In most cases the ictal symptoms did not start before a significant propagation of the seizure activity has occurred. Consequently, there is frequently no overlap between the symptomatogenic zone and the epileptogenic zone. Nevertheless, the epileptogenic zone is typically located close to the symptomatogenic zone. For example, a highly localizing somatosensory aura at the beginning of a seizure provides evidence that the epileptogenic zone is located in the vicinity of the corresponding primary sensory area.

The *functional deficit zone* which is defined as the area of cortex that is functionally abnormal in the interictal period is of limited value in the localization of the epileptogenic zone. Good correlation with the other zones supports the hypothesis of the location of the epileptogenic zone. Clear differences in the location often lead to additional tests such as invasive monitoring.[4] However, there may be disturbances of brain function at considerable distance from the epileptogenic zone. A typical example is seen in patients with pure mesial temporal lobe epilepsy due to hippocampal sclerosis where the epileptogenic zone is usually limited to the mesial temporal region. In these patients the FDG-PET often shows extensive hypometabolic regions outside the mesial temporal and even outside the temporal structures.[22]

In most cases some degree of discrepancy between the above-mentioned zones exists. Depending on the type of epilepsy, some zones are more and others less predictive for the epileptogenic zone. If there is no adequate explanation for the discrepancies of the different zones additional tests such as high resolution MRI, ictal SPECT, PET or invasive monitoring need to be performed. However, as invasive recordings are limited by their cortical coverage, a clear hypothesis regarding the location of the seizure onset zone should exist to make a well-founded decision about the placement of the intracranial electrodes.

The French and Italian concept of the epileptogenic zone

In the French and Italian school of epilepsy surgery there is a rather different concept of the epileptogenic zone. The epileptogenic zone is considered as a complex structure composed of separate pacemaker, relay and subrelay areas essential for producing ictal symptoms and signs.[23–25] According to this definition the contemporary presurgical diagnosis in France and Italy more frequently makes use of depth electrodes to define the more extensive epileptogenic zone[25] and tends to larger resections and more extensive disconnections.[4] Although there is detailed anecdotal evidence in the literature which supports this hypothesis[25] no systematic study has been performed to verify this concept.[4]

Conclusion

The epileptogenic zone is a theoretical concept. There is currently no diagnostic modality that could measure the epileptogenic zone directly. Furthermore, certain pathophysiological changes could act as an epileptogenic zone in one patient whereas another patient with the same pathophysiological changes never develops seizures. This may be due to a different seizure threshold of the remaining cortex presumably influenced by genetic factors. In order to develop future techniques to measure the epileptogenic zone directly we have to comprise genetic susceptibility factors influencing the seizure threshold.

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99 Future methods for the direct assessment of the epileptogenic zone

J Engel Jr

Introduction

At the second Palm Desert conference, held in February 1992, Lüders, Engel, and Munari[1] proposed that the localization of epileptogenic tissue for surgical resection could be defined on the basis of six different types of abnormalities (Table 99.1). Five of these: (1) the irritative zone, the area generating spontaneous EEG spikes; (2) the ictal onset zone; (3) the structural epileptogenic lesion; (4) the symptomatogenic zone, the area responsible for initial ictal manifestations; and (5) the functional deficit zone, can usually be easily measured, but none of these alone accurately define the epileptogenic zone, the area necessary and sufficient for spontaneous seizure generation. The goal of the pre-surgical evaluation is to identify the location and extent of the epileptogenic zone, because its removal or disconnection is necessary to achieve a seizure free outcome. Under the best of circumstances, the dimensions of the epileptogenic zone are merely approximated based on delineation of the other five abnormalities, using standardized electrophysiological and neuroimaging procedures, as well as observation of clinical seizures, the neurologic examination, and neurocognitive testing. A reliable, cost-effective means of directly identifying the epileptogenic zone would greatly facilitate surgical treatment. Unlike most medical disorders, there is currently no reliable surrogate marker for epilepsy that identifies either epileptogenesis or epileptogenicity.

In March 2000, a White House-initiated conference co-sponsored by the National Institutes of Health and the American Epilepsy Society established benchmarks for epilepsy research as a guide for researchers. The intention was to highlight the most important realizable objectives for the next decade, in order to better understand the mechanisms of epilepsy and to apply this knowledge toward the development of new treatments and cures.[2] The first benchmark (IA1) is to 'successfully develop a noninvasive dynamic imaging system or physiological monitoring system that reliably identifies an epileptogenic region in at least one form of human epilepsy.' The search for such a surrogate marker of epileptogenesis and epileptogenicity, therefore, has become a top priority; if found, it could be used to identify which patients would develop epilepsy after an epileptogenic insult; to assess the effectiveness of antiepileptogenic interventions (drugs or devices) in patients with active epilepsy without the need to wait for another seizure to occur; to screen potential antiepileptic compounds in animal models; and, most important for the purpose of this chapter, to delineate the epileptogenic zone for surgical resection.

Surrogate markers of epileptogenesis and epileptogenicity

Interictal EEG spikes

Although accurate delineation of the epileptogenic zone has been a goal of epilepsy surgery teams for over 100 years, very little research, until recently, has gone into the search for reliable surrogate markers of epileptogenesis and epileptogenicity. Interictal EEG spikes have for many years been considered the hallmark of the epileptogenic region, but it is well known that these interictal electrographic phenomena are often falsely localizing. On scalp EEG, they commonly occur bilaterally when the epileptogenic zone is unilateral. Intraoperative spike mapping during electrocorticography was commonly used in the past as an aid to tailored cortical resections, but has now been largely abandoned because these transients usually have a much wider distribution than the area responsible for seizure generation. The concept of *red spikes* and *green spikes* was introduced several decades ago by Theodore Rasmussen, a prominent neurosurgeon at the Montreal Neurological Institute, who noted that there must be some spikes that identify the epileptogenic zone, but that electrophysiologists are not able to recognize them. There have been many unsuccessful attempts to distinguish red from green spikes based on aspects of spike morphology such as rise time, sharpness, and after coming slow waves, as well as patterns of recurrence such as frequency, and response to suppression by drugs such as methohexital.

More recent studies have identified high frequency (150–500 Hz) oscillations, termed 'Fast Ripples,' superimposed on interictal spikes that appear to be unique to structures capable of generating spontaneous seizures in patients with mesial temporal lobe epilepsy, and also in animal models of this disorder (Figure 99.1).[3–13] It remains to be seen whether similar oscillations can identify the epileptogenic zone in neocortex. Nevertheless, at present, FR offer the most promising opportunity to develop a surrogate marker of epileptogenicity and epileptogenesis, but these events can only be seen with microelectrode recordings directly from the brain. Although it may be possible to utilize FR to delineate the epileptogenic zone intraoperatively, they would be more useful clinically if they could be measured noninvasively.

Table 99.1 Definition of abnormal brain areas

	Definition	Measures
Irritative zone	Area of cortex that generates interictal spikes	Electrophysiological (invasive and noninvasive)
Ictal onset zone	Area of cortex where seizures are generated (including areas of early propagation under certain circumstances)	Electrophysiological (invasive and noninvasive)
Epileptogenic lesion	Structural abnormality of the brain that is the direct cause of the epileptic seizures	Structural imaging and tissue pathology
Symptomatogenic zone	Portion of the brain that produces the initial clinical symptomatology	Behavioral observation and patient report
Functional deficit zone	Cortical area of nonepileptic dysfunction	Neurologic examination, neuropsychological testing, EEG, PET, SPECT
Epileptogenic zone	The area of brain that is necessary and sufficient for initiating seizures and whose removal or disconnection is necessary for abolition of seizures	Theoretical concept

From Lüders *et al*.[1] with permission.

Magnetoencephalography (MEG) has the ability to detect neocortical high frequency oscillations in the range of FR;[14] however, so far, it has not been possible to use MEG to identify such fast oscillations deep within the brain, as would be necessary to visualize these mesial temporal limbic events.

It is quite likely that the neuronal mechanisms responsible for interictal spikes associated with FR are substantially different from mechanisms responsible for interictal spikes that do not contain FR, e.g., spikes that are either projected or originate in areas incapable of generating spontaneous seizures. Therefore, the metabolic signature of FR-containing interictal spikes could be sufficiently unique to allow them to be identified noninvasively with EEG spike-triggered functional MRI (fMRI) averaging.[15]

Neuronal excitability

Electrophysiological approaches have been used to directly assess neuronal excitability of epileptogenic tissue, either intraoperatively during electrocorticography, or extraoperatively during chronic invasive monitoring. The epileptogenic hippocampus displays characteristic responses to paired-pulse stimulation, a technique that measures changes in neuronal excitability induced by a test pulse. The normal hippocampus displays paired-pulse facilitation on stimulation of the perforant path, its major afferent input from entorhinal cortex; that is, the test pulse causes a response to a subsequent stimulation to be increased. This effect is in part due to accumulation of calcium within presynaptic terminals following the first pulse, which increases the amount of neurotransmitter released in response to the second. Both animal and human epileptic hippocampus demonstrate paired-pulse suppression on perforant path stimulation, which can persist for hundreds of milliseconds; that is, the response to the second pulse is decreased (Figure 99.2).[16] This is believed to reflect enhanced inhibition induced by the initial response, either as a reflection of a homeostatic protective mechanism, or perhaps as an epileptogenic abnormality responsible in part for hypersynchronization. Paired-pulse facilitation is seen, however, with direct stimulation of hippocampal association pathways, indicating that the excitatory and inhibitory disturbances within this epileptogenic structure are quite complex.[16,17] Similar approaches to assessing neuronal excitability in neocortex have not met with consistent results. Recently, however, single-pulse electrical stimulation with intracranial electrodes in the frontal lobe have revealed delayed and repetitive responses that could be indicative of epileptogenicity.[18]

As with FR, electrophysiological indicators of neuronal excitability are so far only applicable to intraoperative and intracranial electrode recording situations. These concepts, however, could be more widely applicable if they could be measured noninvasively. Transcranial magnetic stimulation (TMS) is currently being investigated as a possible diagnostic, as well as therapeutic, tool for epilepsy at a number of laboratories. TMS, particularly paired-pulse stimulation, can be used to measure cortical excitability, as a potential surrogate marker of epileptogenicity.[19,20] It is conceivable that such TMS measures could eventually be employed as a noninvasive means to localize the epileptogenic zone.

Neuroimaging

Another potential surrogate marker of epileptogenicity and epileptogenesis is the positron emission tomography (PET) tracer alpha methyl tryptophan (AMT).[21,22] In patients with tuberous sclerosis who have multiple tubers and epileptic seizures, AMT PET preferentially accumulates in the tuber responsible for generating spontaneous seizures (Figure 99.3). Similar findings have now been published for mesial temporal lobe epileptogenic regions.[23] It is believed that AMT, a serotonin precursor, detects the presence of increased activity in the kynurenine pathway, which may play an important role in epileptogenicity.

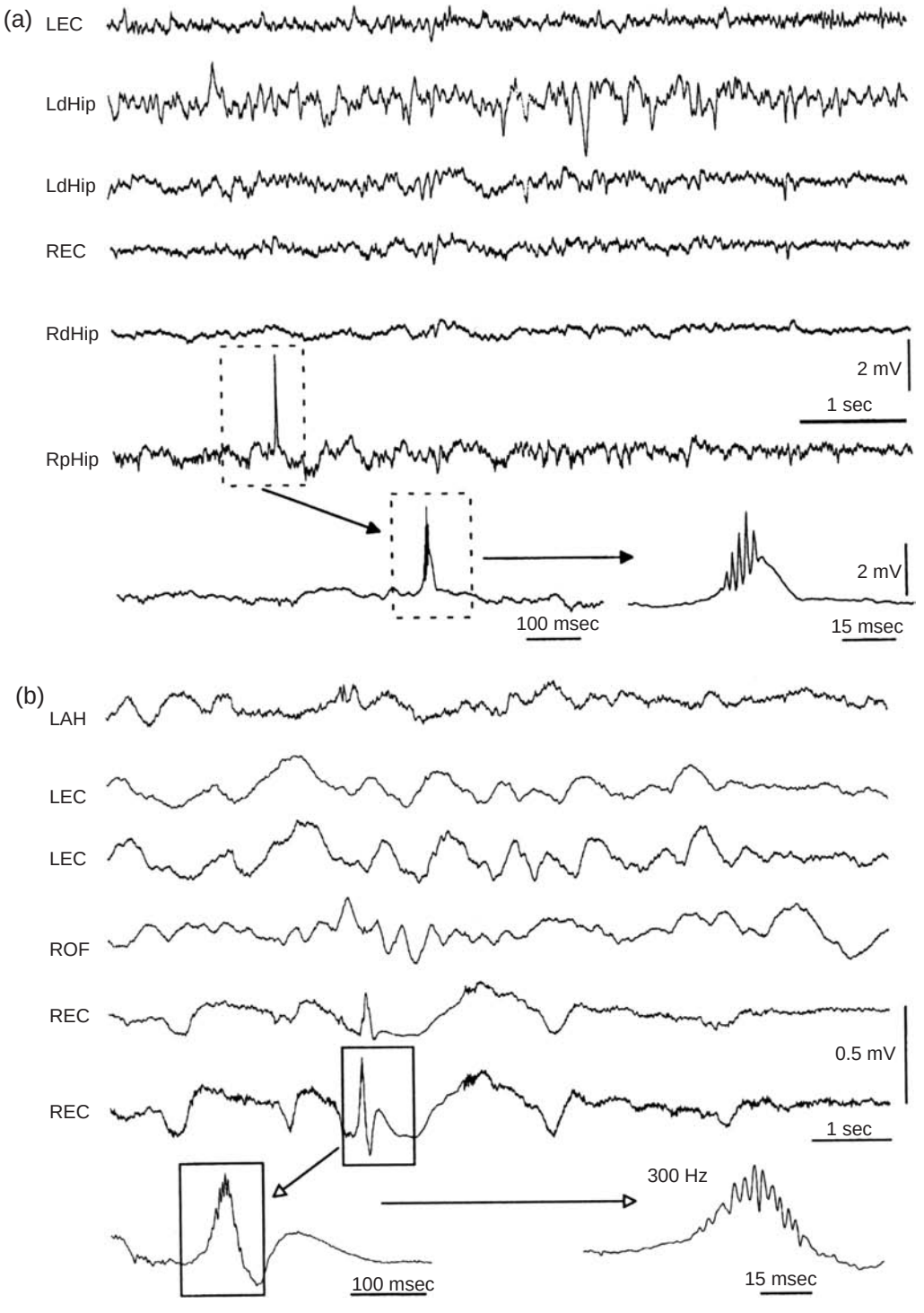

Figure 99.1 (a) Example of KA-rat EEG with interictal spike with superimposed fast ripples. Abbreviations: LEC and REC left and right entorhinal cortex; LdHip and RdHip left and right dorsal hippocampus; LpHip and RpHip left and right posterior hippocampus. (b) Interictal spike with superimposed fast ripples in the entorhinal cortex of a patient with mesial temporal lobe epilepsy. Arrows indicate extension of electrical activity in the box. Abbreviations: LAH – left anterior hippocampus; ROF – right orbitofrontal cortex; LEC and REC – left and right entorhinal cortex (two microelectrodes in each side). From Engel *et al*.[17] with permission.

The 5-HT1A receptor ligands [18F]FCWAY[24] and [18F]MPPF[25] show decreased binding in epileptic hippocampus, but it is not yet clear whether this reflects dynamic disturbances rather than static dysfunction similar to that demonstrated with fluorodeoxyglucose (FDG) PET.[26]

A potentially exciting new development for MRI is the use of magnetized nanoparticles (MNPs), extremely small magnetized particles that are visible on MRI, and that can theoretically be attached to virtually any bioactive molecule.[27–29] MNPs could potentially be used to measure such localized alterations as neurotransmitter activities that reflect brain excitation and inhibition, cerebral metabolism, immune responses, and antiepileptic drug (AED) distribution with extremely high spatial resolution. The latter is of interest in view of recent

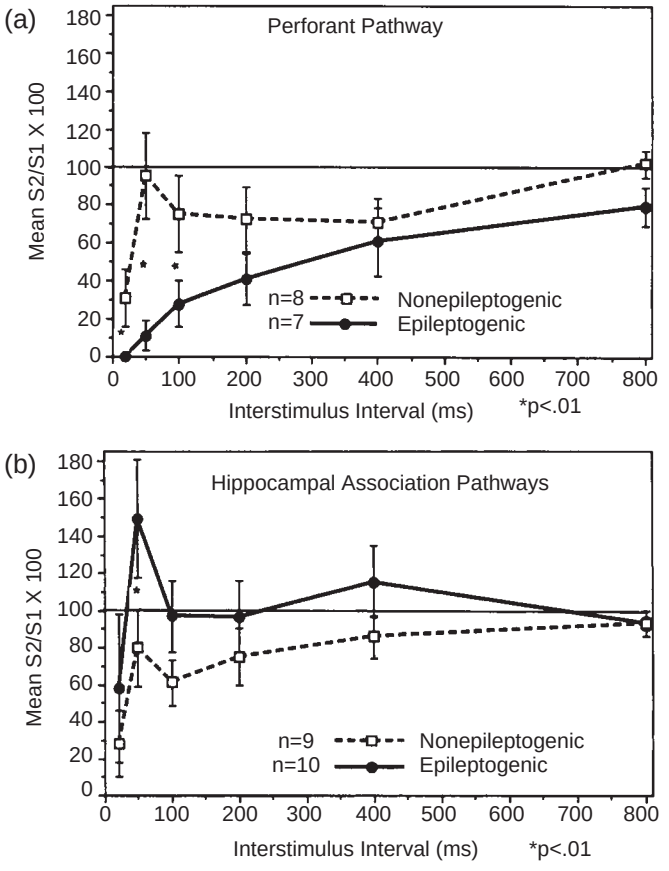

Figure 99.2 Mean differences in paired pulse excitability plotted for perforant path and intrinsic associational pathways of the hippocampus based on pPSP amplitude measurement. (a) Shows that mean suppression for the epileptogenic perforant path was profound up to 100 ms, while the nonepileptogenic perforant path showed significantly less suppression, particularly at 50 ms. The graph in (b) shows that the mean excitability of nonepileptogenic intrinsic associational hippocampal pathways was not significantly different than found in the nonepileptogenic perforant path (a), while the mean epileptogenic intrinsic hippocampal S2 response seen in (b) was significantly facilitated at ISI 50 ms. Although the epileptogenic associational pathways showed greater excitability at all interstimulus intervals than either the nonepileptogenic intrinsic hippocampal pathway or the epileptogenic perforant pathway, these differences were not significant, except at 50 ms (P <.01). From Wilson *et al*.[16] with permission.

evidence that the epileptogenic zone might be identified by lower AED levels due to up-regulation of blood-brain barrier efflux transporters.[30] The potential for application of this new technology to visualize surrogate markers of epileptogenesis and epileptogenicity is enormous.

Optical intrinsic signal (OIS) imaging is an invasive technique for measuring localized changes in cerebral activity.[31,32] Several investigators are applying this technique to animal models of epilepsy, and it has been used in patients during surgery. Research on OIS could yield results in future that would make it a potential surrogate marker of epileptogenicity, particularly if noninvasive measurements through the skull eventually become possible.

Gene expression

Microarray technology is now being widely employed to examine alterations in the profile of genetic expression in animal and human brain regions that could correlate with specific epileptic abnormalities. Individual gene expression can be up-regulated or down-regulated as a feature of the dynamic processes that cause, or result from, epileptogenic disturbances. The sum total of these alterations in individual gene expression make up a profile, or genetic fingerprint, which could possibly serve as a surrogate marker of epileptogenicity or epileptogenesis. If such genetic fingerprints are identified, it might be possible to construct tracers that would allow them to be visualized noninvasively with PET, or with MNP-MRI.

The future of pre-surgical evaluation

Because the field is moving so rapidly, it is premature to speculate on what pre-surgical evaluation might look like a decade or two in the future. Ideally, it should be based on a simple surrogate marker of epileptogenicity that would, noninvasively and interictally, identify the location and extent of the epileptogenic zone in three dimensions in the whole brain. This is much more likely to require a neuroimaging approach than a purely electrophysiological one, although advances in three-dimensional source localization, particularly with MEG, could permit the latter to be a valuable contributor to this analysis. As with the current pre-surgical evaluation, two or more different measures utilizing independent methodologies would be essential to ensure a high degree of reliability. None of these measures, however, would be concerned with delineating the irritative zone, ictal onset zone, structural epileptogenic lesion, symptomatogenic zone, or functional deficit zone. All would be direct measures of the epileptogenic zone.

The most promising candidate for a surrogate marker of the epileptogenic zone to date would be some mechanisms for identifying neuronal tissue generating FR. This could be achieved with MEG MRI fusion, or with EEG-fMRI averaging. Confirmatory tests would then involve a biochemical marker such as AMT, or perhaps a tracer based on gene expression profiles, that could be used with PET, or conjugated with a MNP to make it visible on MRI. Other confirmatory tests of the epileptogenic zone might be achieved through TMS measures of neuronal excitability and noninvasive approaches to image OIS.

Although the holy grail of this futuristic view of pre-surgical evaluation depends upon *noninvasive* measures of surrogate markers of epileptogenicity, the concept of the surrogate marker is that it measures the *potential* for seizure generation and, therefore, is present all the time, not just during seizures. Even if measurements of surrogate markers continue to require invasive monitoring, they could be carried out intraoperatively and obviate the need for ictal recording. This alone would greatly reduce the cost, and to some extent the risk, of pre-surgical evaluation. Such intraoperative invasive monitoring, however, would not likely achieve the same potential for three-dimensional localization as MEG and neuroimaging.

Continued basic animal, as well as human, research into mechanisms of epileptogenesis and epileptogenicity will not

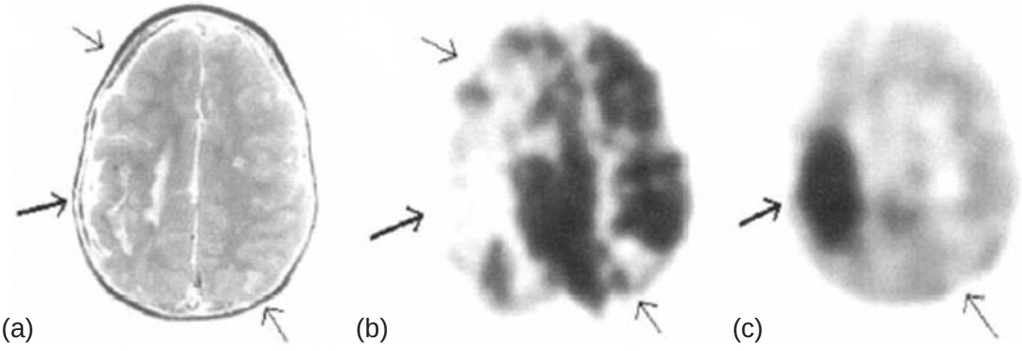

Figure 99.3 Magnetic resonance imaging (MRI) and positron emission tomographic (PET) scans in an 8-year-old girl (Patient 1) with tuberous sclerosis complex and intractable epilepsy. (a) MRI scan showing large tuber in the right central/parietal region (bold arrow) as well as other smaller lesions (thin arrows). (b) The glucose metabolism PET scan shows cortical hypometabolism in the same regions as the lesions seen on MRI (arrows). (c) α-[^{11}C]methyl-L-tryptophan ([^{11}C]AMT) standardized uptake value images display decreased tracer uptake in the location of small tubers compared with adjacent nonlesional cortex (thin arrow). The large right central tuber (bold arrow) shows a 110% increase in [^{11}C]AMT uptake. The left side of the image is the right side of the brain. From Chugani *et al*.[21] with permission.

only provide targets for novel treatments, but also for construction of surrogate markers that can delineate the epileptogenic zone. The latter should be a high priority, especially given that surgical resection of the epileptogenic zone remains the only curative treatment for epilepsy.

Acknowledgments

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SECTION 12

The patient management meeting

100 The patient management conference

M Carreño and HO Lüders

Introduction

All patients with intractable epilepsy who are being considered for epilepsy surgery should be discussed at the patient management conference. During pre-surgical evaluation, a considerable amount of information regarding a particular patient is gathered. At the Epilepsy Monitoring Unit, a detailed seizure history is taken, prolonged interictal and ictal EEG is recorded, EEG tracings and seizure semiology are carefully analyzed, and valuable information about seizure onset zone can be obtained.

Anatomic and functional neuroimaging techniques are also essential during pre-surgical evaluation, and should always include a high resolution MRI to detect possible epileptogenic lesions. In some cases, interictal SPECT and PET and ictal SPECT (specially if co-registered with MRI), may be necessary to localize the functional deficit and seizure onset zone respectively.

A thorough neuropsychological examination is also mandatory, as it may help to localize the functional deficit zone and, more importantly, to predict possible functional deficits after the planned cortical resection. Psychiatric evaluation is also routinely performed at our institution. It is very useful to detect and treat psychiatric comorbidity frequently associated to epilepsy and to assess psychosocial issues that may be relevant for the surgical management.

When the results of all these tests are available, the physician taking care of the patient (neurologist or epileptologist) should present the patient at the management conference. The conference brings together the different members of the epilepsy surgery team: epileptologists, neurophysiologists, neurosurgeons, neuroradiologists, nuclear medicine doctors, psychiatrists, neuropsychologists and nurses. Epilepsy surgery requires multidisciplinary collaboration, and the patient management conference permits review of all the data regarding a particular patient, interpretation of the results of the different tests in light of each other and exchange of opinions; it facilitates a consensus decision about surgical candidacy, surgical technique and possible risks the patient and his family should be counselled about. (Table 100.1)

The conference should be held at regular intervals, preferably in a standarized way, so several patients can be discussed in one session. A brief summary including seizure history, results of video-EEG monitoring, MRI, and functional neuroimaging tests, together with neuropsychological and psychiatric evaluation, is useful to introduce the different members of the team and guide the discussion.

The conference is also an excellent educational opportunity for students, residents and fellows; and multidisciplinary case discussions, especially of the difficult cases, is always a source of ideas for future clinical and basic research.

History

Every case discussion at the patient management conference should start with presentation of a detailed but summarized seizure history, including age at seizure onset, different types of seizures, seizure semiology, seizure frequency, and seizure duration. Handedness and any relevant findings in the neurological exam should be mentioned. Family history, risk factors for epilepsy, and possible etiologies should be discussed, together with medical treatments received in the past, their length, and side effects. At this point medical intractability should be clear. It is important to discuss also other medical conditions which may be relevant for the management of the patient. Most of these aspects may be adequately summarized in the five dimension epilepsy classification.

Video-EEG

Results of the prolonged video-EEG evaluation should be presented, either by the epileptologist taking care of the patient or by the epileptologist who was in charge of the patient when he was admitted to the Epilepsy Monitoring Unit. The epileptologist should discuss the following information: interictal nonepileptiform and epileptiform abnormalities (frequency and distribution), number of seizures recorded, seizure semiology, and ictal EEG. It is important to mention also the time interval between clinical onset and EEG onset, as the interpretation about location of seizure onset zone may vary depending on this time difference. Although information about interictal and ictal EEG is included in the final report of prolonged video-EEG, we usually display the actual tracings so they can be viewed and discussed by the different epileptologists and neurophysiologists attending the meeting. This can be done easily with the digital video equipments. We also find very useful to project digital videos to illustrate each seizure type. It is a good opportunity to discuss seizure semiology, postictal deficits and also to teach residents and fellows.

After the clinical history and the video-EEG evaluation have been presented, there should be a hypothesis about

Table 100.1 Patient management conference

Date:
Name:
Age:
Handedness:

History, physical exam:
Seizure description: age at seizure onset, seizure semiology, seizure duration, seizure frequency
Medications: current medications, medications used in the past (if possible, mention if maximal doses were reached, significant adverse effects)
Noninvasive video-EEG:
semiological seizure classification
interictal and ictal EEG
Invasive video-EEG
Neuroimaging:
anatomical: MRI
functional (if done): interictal SPECT, ictal SPECT, PET, functional MRI, MRS
Neuropsychological testing: IQ scores, memory scores
Psychological-psychiatric evaluation:

Summary: five dimension epilepsy classification
Epilepsy classification
Seizure classification
EEG classification:
Etiology:
Seizure frequency:
Related conditions:

cortical regions involved in seizure generation. This hypothesis should be compared with the results of neuroimaging tests and neuropsychological studies which are presented later on.

Neuroimaging

Anatomic neuroimaging

An essential exam during pre-surgical evaluation of a patient with medically intractable seizures is a high-resolution MRI, which includes all the specific sequences which are specially relevant to view epileptogenic lesions such as malformations of cortical development. The written report of a given MRI may have been done by a general neuroradiologist, but is important that a neurorradiologist with experience and an interest in epilepsy is present at the conference to review the digital images; special attention must be paid to the cortical regions which may be involved in seizure generation according to the clinical and video-EEG data. It is not uncommon that subtle abnormalities, considered 'nonspecific' when the MRI was initially reviewed, are reinterpreted as 'significant' during the meeting. The epileptologists and the neurosurgeon may also ask the neuroradiologist about the proximity of the epileptogenic lesion to eloquent brain areas, which may be relevant for the surgical planning.

Functional neuroimaging

Results of interictal and ictal SPECT should be presented by a specialist in nuclear medicine, as well as the PET scan if this was done during pre-surgical evaluation. In the case of ictal SPECT, it is very important for a correct interpretation to mention when the raidioisotope was injected respect to EEG seizure onset. Once again, the findings in MRI may help to consider clinically relevant subtle abnormalities which could have been dismissed otherwise.

Functional MRI (fMRI) is a technique increasingly used to localize eloquent cortex, especially motor and language areas. In some institutions, it is replacing Wada test to lateralize language dominance. Results of fMRI, if done, should be presented at this point.

Neuropsychological evaluation

Results of neuropsychological evaluation which should be presented at the conference include overall evaluation of intellectual function and assessment of memory. This information helps to lateralize and localize the functional deficit zone, but is most valuable for predicting possible functional deficits after surgery (mainly memory loss).

If performed, results of the Wada test should be presented also. In our institution, Wada test is not routinely performed in every patient. It is used mainly to lateralize language dominance when surgery close to potential language areas is planned. It is also used to assess risk of memory loss when planning resection of possibly dominant mesial temporal structures or when the MRI shows bilateral damage (for example, bilateral mesial temporal sclerosis) or there are signs of bilateral temporal dysfunction in the neuropsychological tests. Any incidence during the Wada procedure should be mentioned, especially those that may obscure the interpretation of the results, for example excessive sedation or incomplete paresis after the injection. Findings suggesting bilateral dependent or independent language should be discussed at length, because of their relevance in the management of the patient.

If a temporal resection is being considered, the neuropsychologists should give their opinion about specific risks of memory loss according to the results of the pre-surgical evaluation.

Psychiatric evaluation

All patients admitted to our Epilepsy Monitoring Unit undergo psychosocial and psychiatric evaluation. The psychosocial evaluation helps to understand the family, social and work environment of the patient, and the impact of persistent seizures in his quality of life. It helps also to clarify the patient and family's expectations about surgery, see if these are realistic and estimate the possible impact of the patient's personality and family and social support in surgical outcome. Psychosocial evaluation is essential to assess if the patient is able to fully understand risks and possible benefits of surgical procedure and give his/her informed consent.

We strongly believe also that psychiatric evaluation should be a routine part of pre-surgical process, given the high incidence of psychiatric disorders among people with epilepsy, its impact in the perceived quality of life of the patient, and its possible role in surgical outcome regarding quality of life. The psychiatrist involved in the epilepsy team should present the data regarding psychiatric comorbidity, suggested treatment, and possible evolution of the psychiatric disorder after epilepsy surgery.

Discussion of management issues

Once the different aspects of pre-surgical evaluation have been presented and the details discussed by the different specialists, the members of the team should be asked their opinion about further management of the patient. The main question to answer is: is the patient a surgical candidate? To be a surgical candidate, the patient must have medically intractable epilepsy; the seizures must be arising from one well-localized region that can be removed without inacceptable neurological deficits. If the answer is yes, the patient is a surgical candidate, and the best surgical procedure to achieve seizure freedom without neurological deficits should be discussed. The neurosurgeon should give his or her opinion about the planned cortical resection and specific surgical risks. Other risks involved in the planned resection, such as memory loss in case of temporal resections can also be discussed at this point, together with the patient's willingness to accept them.

If the members of the team feel that the suspected epileptogenic region has not been adequately localized but otherwise think there is a reasonable chance that the patient finally becomes a surgical candidate, more invasive studies including intracranial electrodes may be suggested. A clear hypothesis about location of epileptogenic zone to guide the placement of electrodes is essential to proceed. The areas to be studied with intracranial electrodes should be detailed, with the neurosurgeon having an active part in the surgical planning.

If the patient is not considered a candidate for resective surgery, other options could be mentioned, including vagal nerve stimulator placement and ketogenic diet.

The management discussion assists the neurologist/epileptologist and the neurosurgeon in their final decision regarding surgical candidacy of one particular patient, and reassures patients and families because all specialists involved and other epileptologists have participated in the consensus.

Case presentation

Case 1

J.M.G is a 24-year-old young right-handed young man. He was the product of a normal pregnancy and delivery, and had a normal psychomotor development. At the age of 18 months he had an uncomplicated febrile seizure, but otherwise he had no other risk factors for epilepsy. Seizures started at the age of 5 years, 3 days after chicken pox vaccination. Seizures consisted of repetitive, high amplitude movements of the four limbs, with lack of response, lasting approximately 2–3 minutes and occurring mainly during sleep, but also during wakefulness. According to the family, he recovered quickly, without postictal confusion or aphasia. Seizure frequency was 1–2 per day when he first was referred to us. The previous month he had been admitted to a local hospital because of increased seizure frequency without obvious precipitants (up to 100 seizures per day) The longest seizure-free period had been two years. Previous treatments included carbamazepine, valproic acid, levetiracetam, vigabatrin, gabapentin, phenytoin, phenobarbital, and lamotrigine.

When he was referred to our unit he was treated with oxcarbazepine (1800 mg per day), topiramate (500 mg per day), and clobazam (10 mg per day).

He studied until he was 16, but at that point he stopped going to school because of repetitive seizures. He was unemployed when he was referred to us.

He was admitted to the Epilepsy Monitoring Unit in November 2004. Interictal EEG showed continuous slowing in the theta range over the left fronto-central region, ocassionally rhythmic, together with bursts of generalized slowing lasting 2–3 seconds and seen every 5–10 minutes. Frequent polyspikes were seen either bifrontally, with a maximum over the left frontal region (FP1>F3>F5>Fp2>Fz), or more localized over the left frontopolar area (FP1>F5>F3). The frequency was once every 30–60 seconds during awake and once every 5–10 seconds during sleep (Figures 100.1 and 100.2). In addition, bursts of bifrontal, max left (FP1>F3>F5) paroxysmal fast activity, of 3–5 seconds duration, were seen during sleep, once every 10 minutes approximately.

Thirty seizures were recorded during EMU stay, mainly during stage I and stage II sleep. Seizure semiology was very similar in all seizures: the patient suddenly woke up, sat up in bed and displayed high amplitude movements of trunk and arms (as if he was trying to reach for objects) and repeated vocalizations, with lack of response. Seizures' duration ranged between 30–60 seconds. The patient recovered quickly, without postictal confusion. He was amnestic for all that happened during the seizures. Ictal EEG showed a generalized electrodecremental pattern, followed by fast paroxysmal activity (15 Hz/10 mV) over the left frontal region (max Fp1>F3>F5>Fp2>Fz). After 4–8 seconds, this activity evolved to a higher voltage theta rhythm (5–7 Hz/40-60 mV) which was lateralized over the left hemisphere, soon obscured by muscle artifact. After the seizures, focal continuous slowing was evident over the left frontal region.

Injection of radioisotope for ictal SPECT happened 22 seconds after seizure EEG onset. MRI showed a dysplastic lesion over the medial part of the left superior frontal gyrus and the polar portion of the orbital region, compatible with cortical dysplasia (Figure 100.2): Ictal SPECT co-registered with MRI showed increased perfusion over the more anterior and mesial part of the malformation of cortical development (Figure 100.3).

Neuropsychological study showed intellectual level in the low-medium range. There was some psychomotor slowing in fine visuomanual coordination tasks and execution of movement sequences, together with slowing and fluctuations in verbal learning ability.

Psychiatric evaluation showed mildly depressed mood without obvious need for antidepressant drugs.

All physicians attending the conference agreed that the patient had medically intractable left frontal epilepsy with hypermotor seizures due to cortical dysplasia over the left frontal region (Figure 100.4). It was clear that the patient had medically intractable epilepsy and that his seizures were significantly interfering with his daily life. The neurorradiologist and the neurosurgeon were asked about the proximity of the lesion to the expected location of Broca's area. Both concluded that the lesion was outside this area, and the neurosurgeon concluded he could safely resect the abnormal region on MRI.

The patient and his family were informed about the procedure, possible benefits, and risks of surgery. He was given an approximately 60% chance of seizure cessation. The malformation was resected. Pathology showed heterotopic neurons

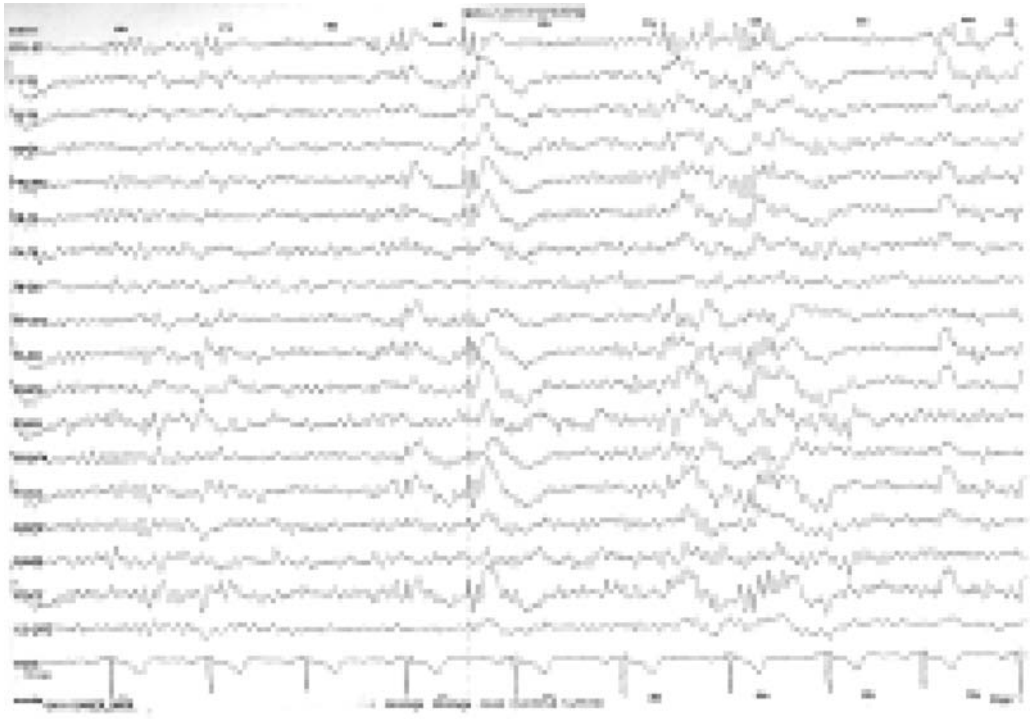

Figure 100.1 Repetitive frontopolar spikes.

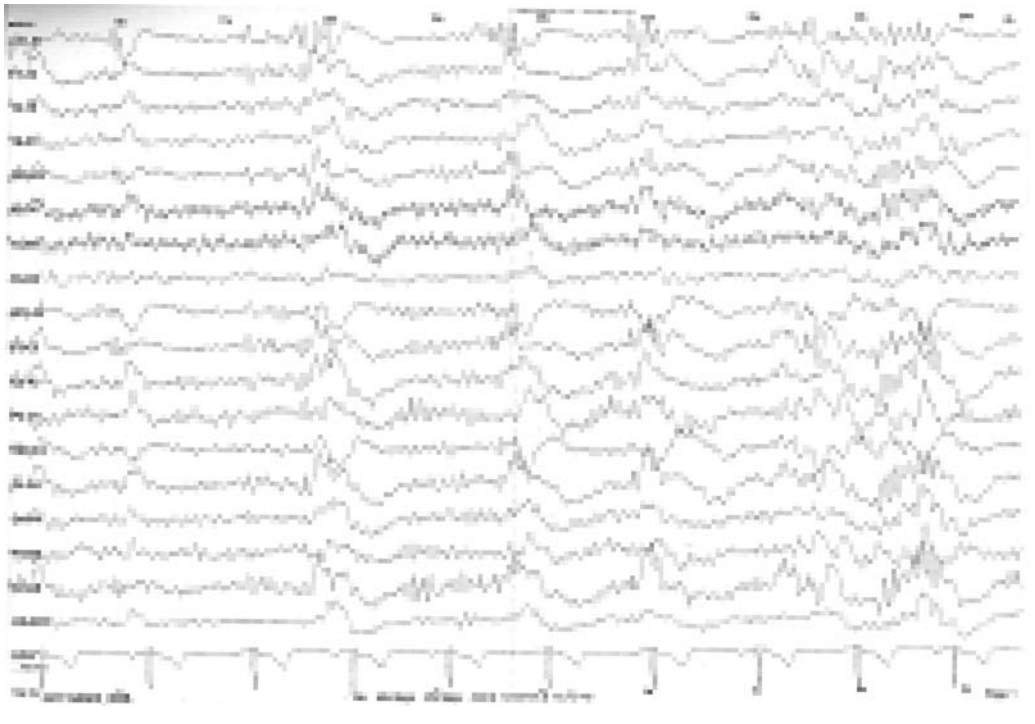

Figure 100.2 Repetitive frontopolar spikes.

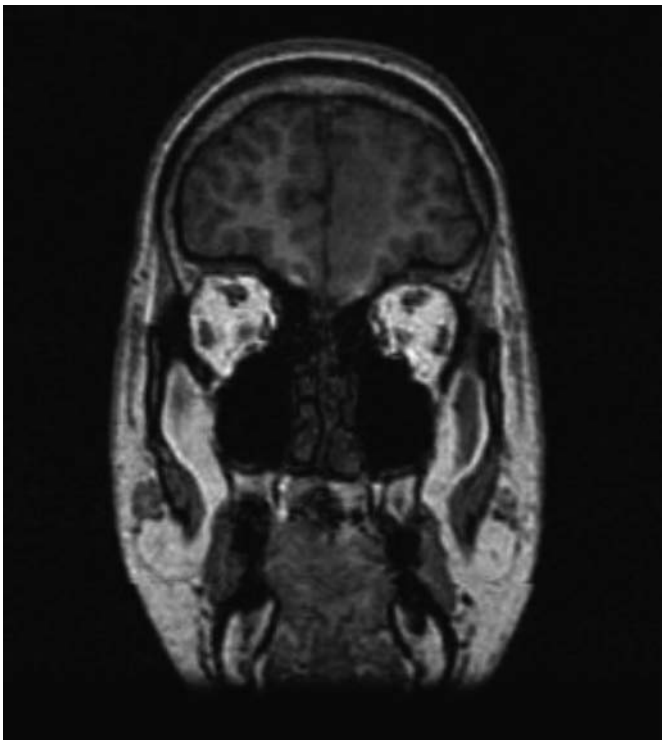

Figure 100.3 Coronal T1-W image showing malformation of cortical development over the left mesial frontal region.

and balloon cells. The patient has been seizure free since surgery. There was a temporary behavior abnormality (the patient was apathetic, with lack of inititative, and unwilling to get up and move) for 6 or 7 days after surgery. This seemed to resolve after discharge, and he has currently returned to his normal life.

Case 2

B.P.A. is a 32-year-old left-handed woman with seizures since the age of 27. She had no significant risk factors or family history of epilepsy. Seizures were characterized by an aura described as 'nervousness, together with a warm rising sensation'. Rarely she felt an auditory aura (beep in her ears, which she could not further localize). The aura was followed by a change in facial expression and clenching of both fists, without clear oral or manual automatisms. There was partial loss of awareness. At times, however, she was able to follow simple commands at the beginning of the seizure and the family stated that she was able to speak intelligibly during seizures, although sometimes the content of the sentences was inappropiate. Seizures lasted 1–2 minutes and thereafter she was slightly confused for another 4 minutes. She had never had a secondarily generalized seizure.

Seizure frequency was initially one every 10 days, but had progressively increased in spite of treatment with antiepileptic drugs. Seizures happened on a daily basis when she was first referred to us. She had failed treatment with carbamazepine, topiramate, and lamotrigine. She currently was treated with oxcarbazepine (1200 mg per day) and clobazam (20 mg per day).

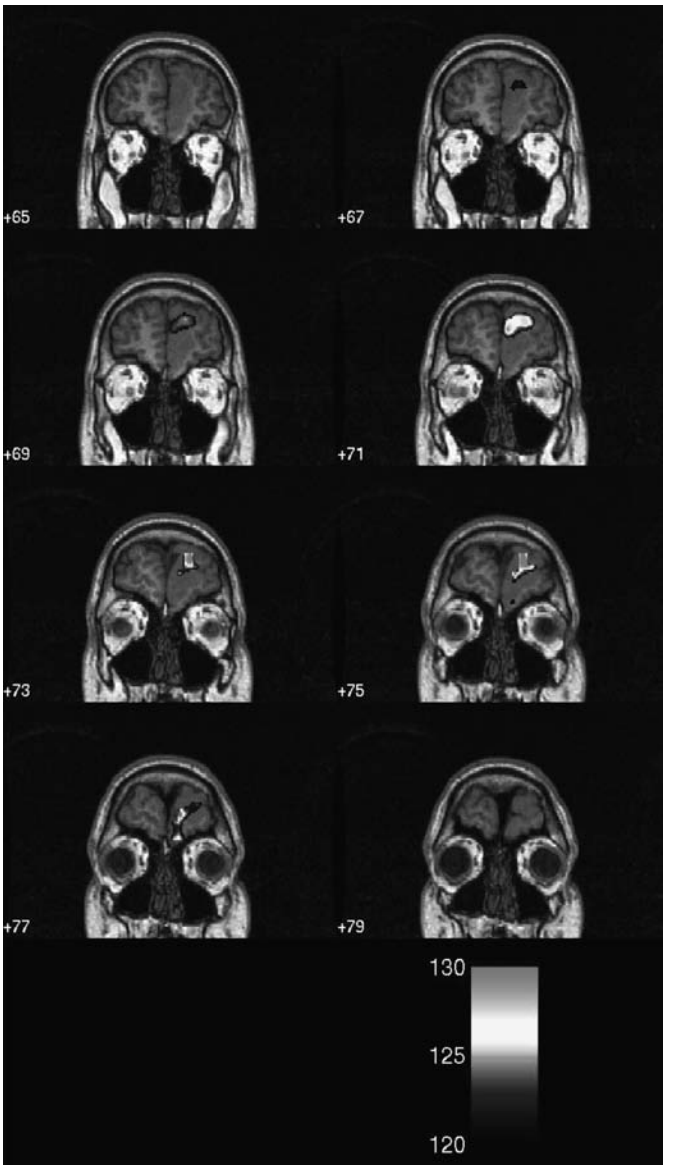

Figure 100.4 SISCOM showing hyperperfusion over the cortical dysplasia in the left mesial frontal region.

She was admitted to the Epilepsy Monitoring Unit in 2004. Right temporal sharp waves were seen, with a maxium over the middle temporal region (T4>FT8>FT10), once every 5 minutes (Figure 100.5). In addition there were left anteriotemporal sharp waves (max FT9>F9>T7, TP7), seen less frequently (once every 20 minutes of recording) (Figure 100.6). Five seizures were recorded, which were characterized by changing in facial expression, loss of awareness, and subtle oral automatisms, with ictal speech. There was no postical dysphasia. Seizures were nonlateralized on surface EEG, being characterized by irregular theta slowing over both temporal regions (Figure 100.7). Isotope for ictal SPECT was injected after 40 seconds of EEG onset.

The MRI showed a lesion in the white matter of the right temporal lobe compatible with cavernoma (Figure 100.8). There were no alterations in morphology or signal intensity of both hippocampi. Gradient sequence did not identify signs of bleeding in any other locations. Ictal SPECT co-registered with MRI showed increased focal perfusion over the mesial and basal region of both temporal regions, more pronounced on the left side (Figure 100.9).

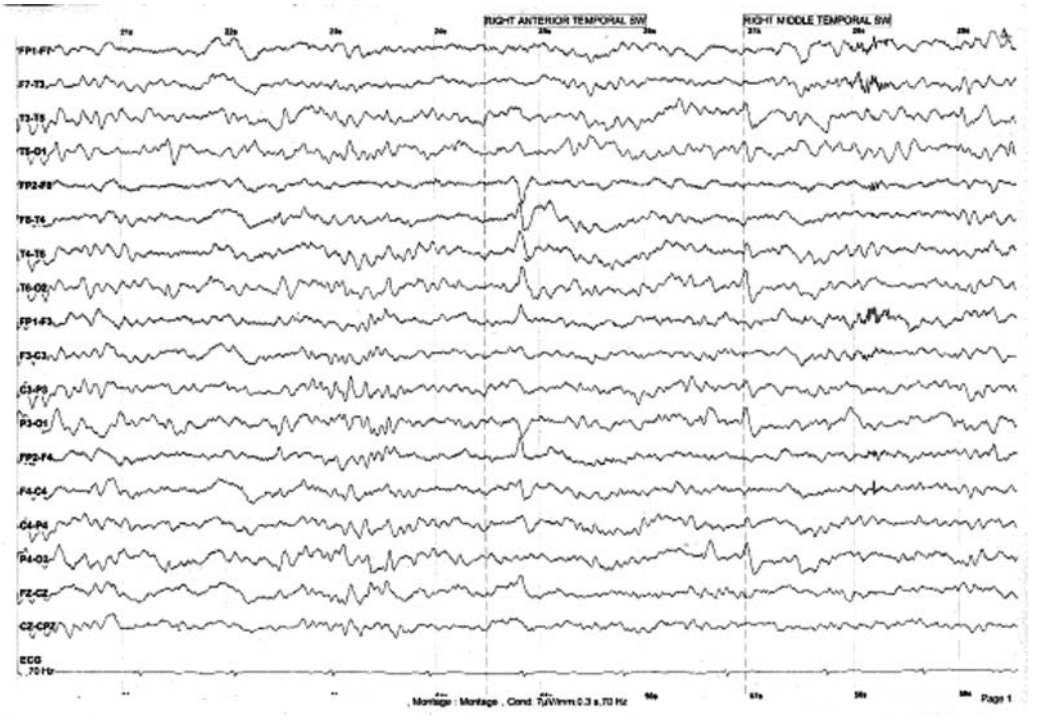

Figure 100.5 Right anterior and middle temporal sharp waves.

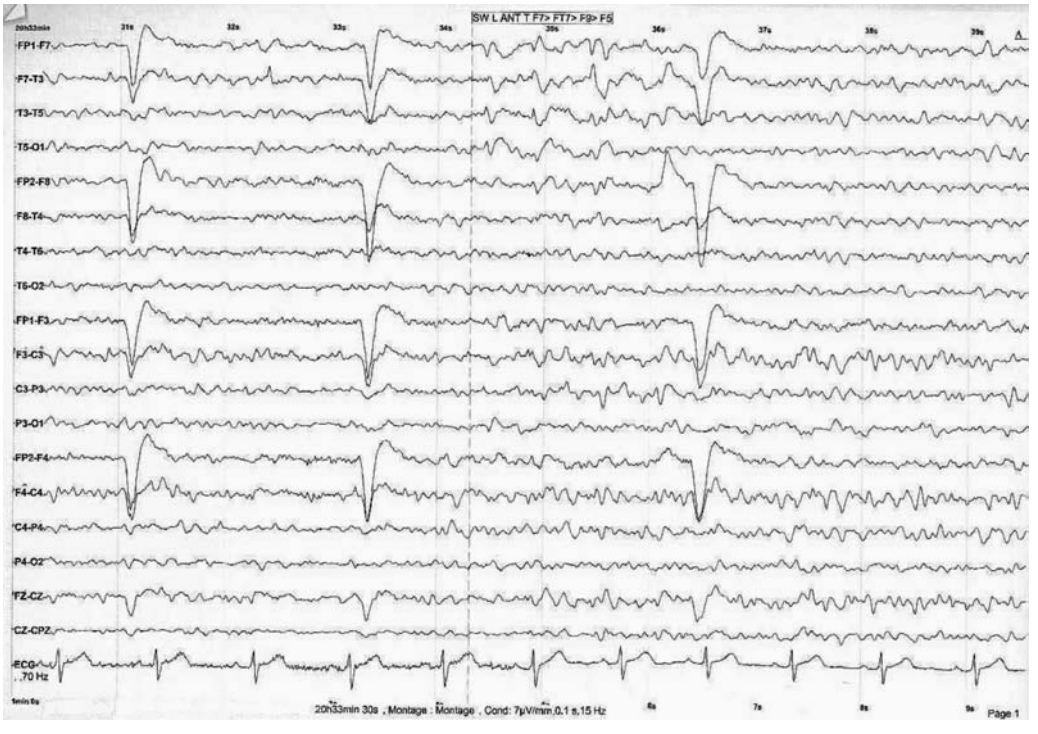

Figure 100.6 Left anterior temporal sharp waves.

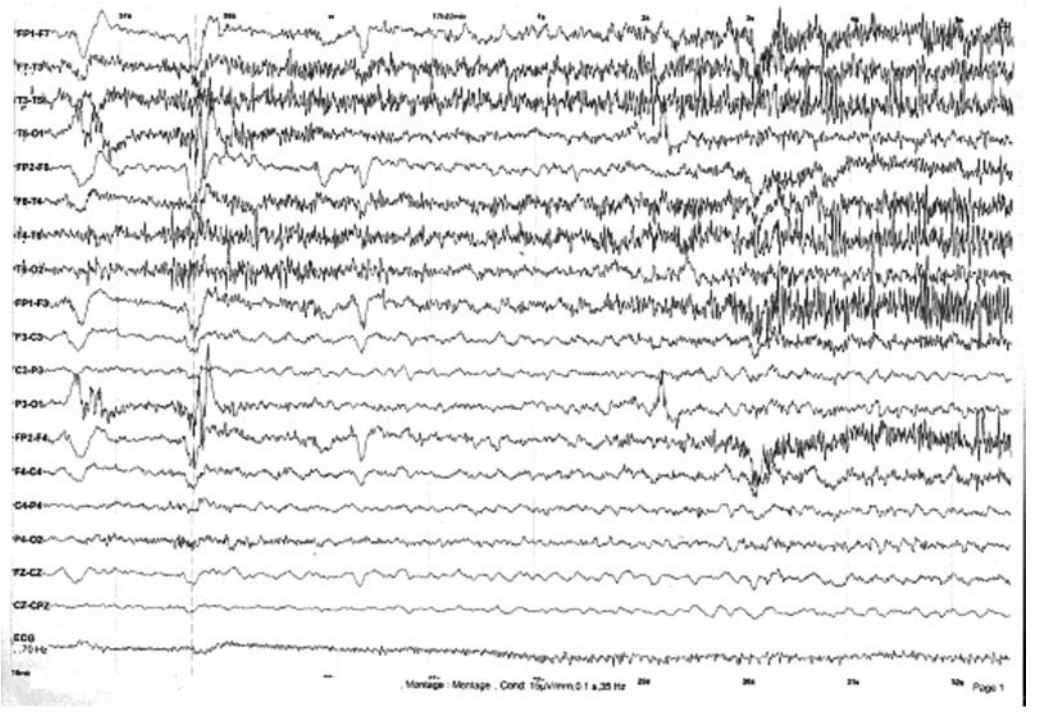

Figure 100.7 Ictal surface EEG. Nonlateralized theta.

Wada test showed right hemisphere dominance for language (she became mute after right carotid injection, while she continued to talk after left injection), with good functional memory reserve on the left side.

Neuropsychological study showed intellectual level in the normal range, with a subtle deficit in verbal fluency tasks (mainly with semantic clues), a slightly inferior than expected performance in naming and a slow verbal learning curve. No alterations in memory were seen. All these subtle difficulties suggested an initial involvement of dominant temporal structures. Psychiatric evaluation showed mild depression.

During the patient management conference it was concluded that the patient had medically intractable temporal lobe epilepsy, probably secondary to cavernous angioma located on the right temporal neocortex. However there was some concern that the seizure onset zone had not been adequately lateralized during the pre-surgical evaluation (the pattern on surface EEG was bitemporal, and also the ictal SPECT co-registered with MRI suggested a bitemporal ictal onset). In addition, ictal speech suggested seizure onset in the nondominant hemisphere which was discordant with the findings in the Wada test. After discussing risks and benefits, it was concluded that the patient would be offered video-EEG with placement of foramen ovale electrodes (FOE) to better lateralize the seizure onset zone. The possibility that seizure onset could not be accurately recorded with the FO electrodes if arising from the temporal neocortex was also discussed. The patient agreed to the semi-invasive evaluation. Interictal EEG showed abundant epileptiform activity over the contacts which were closest to the mesial structures on the right side (Figure 100.10). Seizure onset was also in the right temporal mesial region (Figure 100.11).

The patient was discussed again in another patient management conference and the best surgical technique was discussed. Everybody agreed that she should have a lesionectomy, leaving the right hippocampus in place, in view of its normal apperance in MRI, to avoid memory loss.

The patient underwent resection of the cavernoma in April 2005. She has been seizure free since then. Neuropsychological evaluation has shown no memory decline.

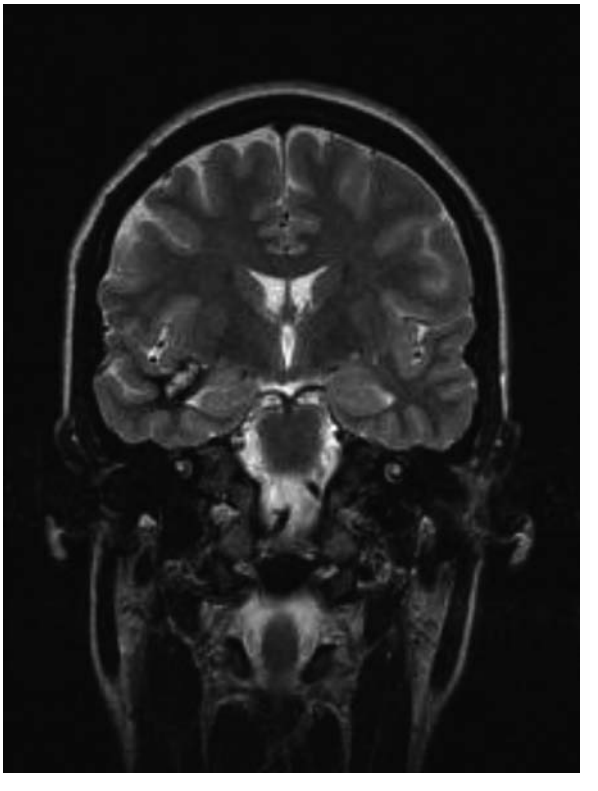

Figure 100.8 T2-Weighted coronal MRI image showing right temporal covernoma.

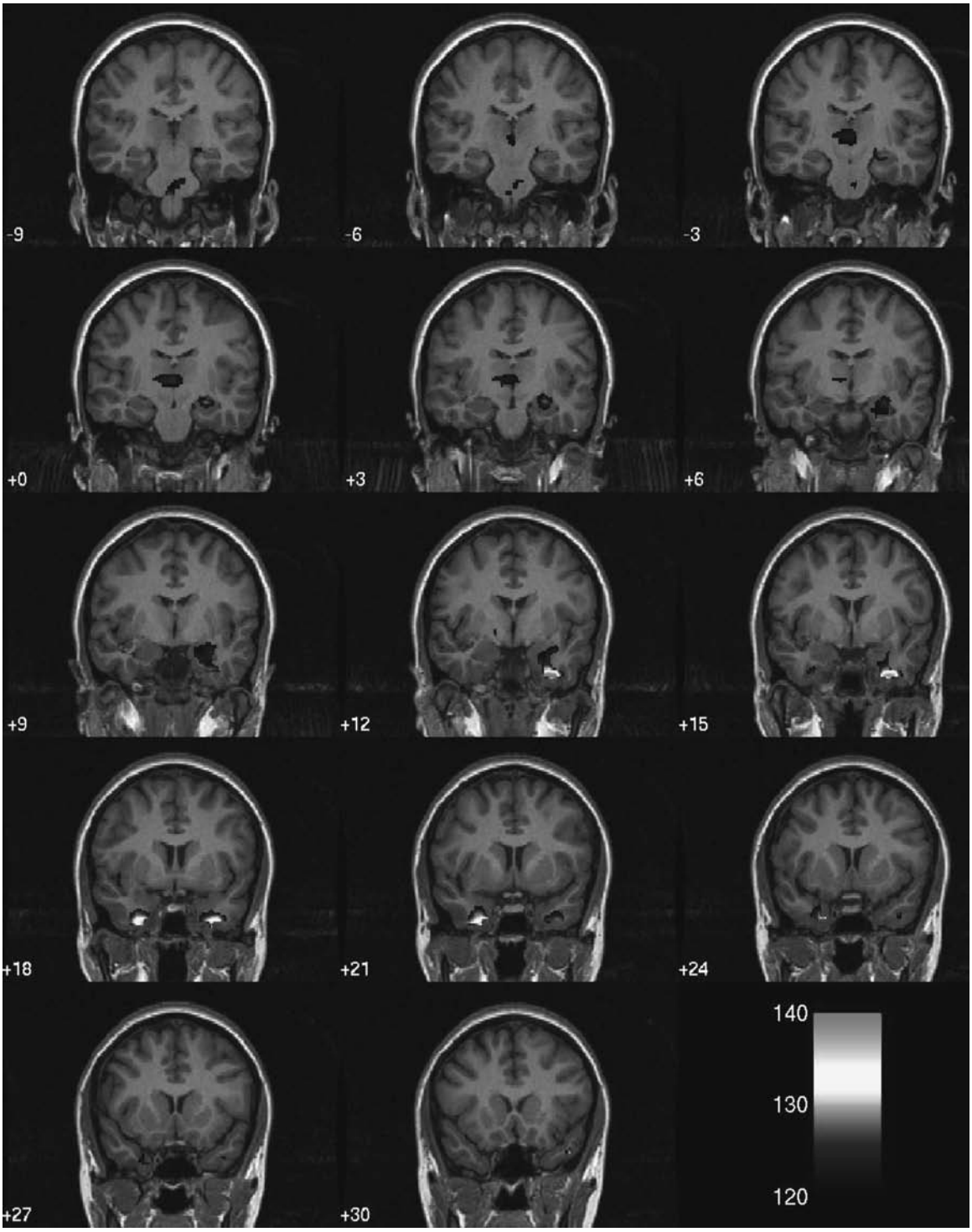

Figure 100.9 SISCOM showing increased perfusion over both temporal lobes, more pronounced on the left side.

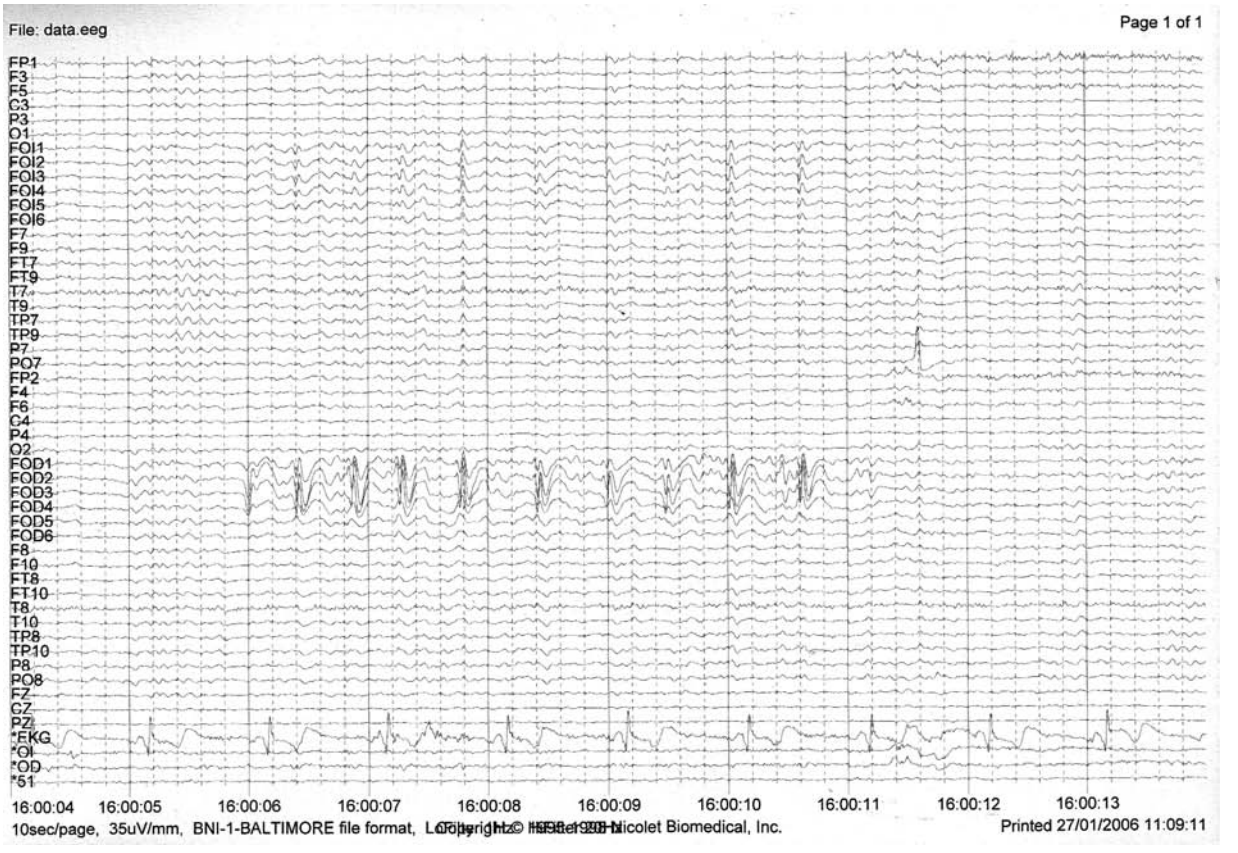

Figure 100.10 Interictal EEG with foramen ovale electrodes showing repetitive spikes over the right contacts.

SECTION 13

Surgical techniques for placement of intracranial electrodes

101 Anesthesia for epilepsy surgery

M Lotto and A Schubert

Introduction

Epilepsy surgery adds a level of complexity to the anesthetic care of the neurosurgical patient. Anesthetic selection significantly impacts surgical procedures which require intraoperative mapping of the epileptic foci or identification of eloquent tissue during resection of epileptogenic tissue. Designing an anesthetic that can produce varying depths of patient sedation and the patient participation necessary for speech and motor mapping requires forethought, skill and occasionally luck. In addition, anesthetic agents have a wide variation and sometimes confusing profile of proconvulsant and anticonvulsant effects that must be taken into consideration. There are also significant pharmacologic interactions between anticonvulsant medications and anesthetic drugs. Developing an anesthetic care plan that facilitates the patient's best interests and the intraoperative goals of the surgeon and neurophysiologist requires intimate knowledge of the pharmacology of the patient's antiepileptic medications and the anesthetic agents. Good communication between the anesthesiologist, surgeon and neurophysiologist is critical in achieving patient safety and a successful procedure. This chapter presents an overview of the anesthetic care of the epileptic patient undergoing epilepsy surgery, with a focus on the pharmacology of common anesthetic agents and how these drugs impact both epileptic surgical procedures and perioperative events in epileptic patients.

Pharmacology of anesthetic agents

Given the modification of neuronal transmission generated by anesthetic agents, it is not surprising that these drugs can have significant effects on CNS excitation events. However, the literature describing the pro- versus anticonvulsant effects of many anesthetic agents can be confusing and seemingly contradictory. One may produce reports which implicate the same drug in both precipitation and termination of seizure activity.[1,2] The mechanisms behind the conflicting convulsant effects of these agents are not completely understood. However, several authors attempted explanation by proposing that the ratio of affected inhibitory or excitatory neurons in both the cortical and subcortical brain structures varies with depth of sedation. EEG recording supports altering activation and inhibition of the cerebral cortex with administration of anesthetic agents. During light sedation reveals cortical activation with higher frequency beta activity which then progresses to slow wave activity as sedative/anesthetic depth increases.[3]

Some of the confusion may also be attributed to the method of documentation of epileptic activity used in the case reports of anesthetic drug related seizure activity. Several induction agents, such as propofol and thiopental, have been demonstrated to induce myoclonic activity not associated with EEG excitatory activity[4]; while others agents (etomidate, methohexital) have been shown to generate both myoclonus and EEG documented epileptiform activity in patients.[5]

Sedative hypnotic agents

As a group, these agents have the greatest variation and most confusing profile as far as effects on epileptogenic activity. Most of the agents can generate neuroexcitatory effects when used at low doses, and neurodepressive effects when used at higher doses. Motor stimulatory phenomena, such as myoclonus, opisthotonus, and tonic clonic activity may occur with varying frequency in both epileptic and nonepileptic patients during induction with these agents, however, only a few actually produce cortical electrical activity suggestive of seizures.

Methohexital, etomidate and ketamine are known to activate EEG seizure activity when administered to patients with a history of epilepsy.[6,7] Motor activity may not occur with the induction of abnormal spike wave activity. Both etomidate and methohexital have been used to assist with activation of ictal foci during intraoperative electrocorticography.[8,9] These agents may also generate nonepileptic myoclonic activity during induction which can be mistaken for epileptic convulsions.

Etomidate has a dichotomous effect on seizure thresholds, producing EEG confirmed epileptic activity when used as an induction agent in epileptic patients, as well as producing burst suppression and breaking status epilepticus when administered in higher doses.[10,11] Ketamine appears to have a dose dependent threshold for seizure generation, with most reported cases of clinical seizure activity occurring when doses greater than 4 mg/kg are administered.[12]

Despite an early report of seizure induction with propofol injection, propofol has demonstrated a good safety record and low epileptogenic potential when used in patients undergoing epilepsy surgery. The anticonvulsant properties of propofol are fairly well established, although the antiepileptic effect may be shorter acting after discontinuation of propofol than thiopental.[13,14] The short acting antiepileptic nature of propofol can be useful for sedation during epileptic procedures, generating fewer seizures in between monitoring periods than neurolept anesthesia.[15] However, propofol has also been observed to decrease the frequency of epileptogenic spikes and to quiet existing seizure foci, particularly in the lateral and

mesial temporal areas.[16] In addition, propofol may generate beta EEG activity obscuring spike wave activity for up to 20 minutes following discontinuation of the infusion.[17,18] See Figure 101.1. Therefore, propofol infusions should be discontinued 20–30 minutes prior to electrocorticography (ECoG) monitoring to facilitate successful location of the ictal foci.[19]

Barbiturates and benzodiazepines have substantiated anticonvulsive properties and are recommended for treatment of refractory status epilepticus.[20]

Volatile inhalational agents and N_2O

The epileptogenic potential of isoflurane, desflurane, and halothane appears low, and there have been no reported seizures when used in isolation.[21] However, there are rare reports of myoclonic activity with a normal EEG. Convulsions with spike and wave activity on EEG have been reported with combinations of isoflurane and N_2O.[22,23] Although N_2O has been associated with seizure generation when used to supplement other agents, it appears to be fairly inert in both the development and treatment of seizure activity in humans.[24] Both N_2O and isoflurane have been used for many years at multiple institutions with a good safety record in epileptic patients.

Enflurane, used either with or without nitrous oxide, has been the most frequent offender with reports of intraoperative and postoperative myoclonus and EEG demonstrated epileptiform activity in both epileptic and nonepileptic patient populations.[7,8,24–27] The incidence of EEG spike wave production with enflurane appears to be dose dependent. The end tidal concentration that triggers maximum epileptiform activity is reduced during hypocapnia. Enflurane has fallen out of favor as new inhalational agents have become available and it is currently rarely used clinically in the United States. Enflurane should be avoided in patients with a history of epilepsy, unless the desired effect is triggering seizures during ECoG. Sevoflurane, but not desflurane has been reported to generate convulsions as well as electrical spike waves in both epileptic and nonepileptic patients.[21,28] Similar to enflurane, the frequency of spike wave activity with sevoflurane increases with dose escalation and hyperventilation.

Analgesics

The effects of opioids on seizure threshold vary with opioid drug class. Synthetic opioids such as alfentanil, fentanyl, sufentanil, and the more recently introduced remifentanil are commonly used in neurosurgical anesthesia due to the short duration of action and ability to minimize cortical effects through continuous infusion. Synthetic opioids have been reported to have some proepileptic properties; however, the potency of seizure production is unclear. Bolus doses of synthetic opioids, such as alfentanil and remifentanil have been demonstrated to increase spike wave activity in the interictal foci of patients undergoing intraoperative EcoG.[29,30] In fact, bolus doses of these agents may be useful in ECoG to facilitate location of the ictal cortex through stimulation of spike wave phenomenon with concomitant depression of background EEG. Fentanyl has been associated with epileptiform electrical activity in subcortical nonictal cortical tissue, therefore the author prefers to avoid the dosing range in which epileptogenic properties have been observed (17–25 μg/kg).[31] The clinical history of the use of synthetic opioids in large numbers of epileptic patients undergoing ablative procedures suggest that synthetic opioids can be used safely in this patient population without significant increase in the risk of perioperative seizures.

The neurostimulatory effects of the long-lived meperidine metabolite, normeperidine have been well documented. Normeperidine can accumulate with chronic oral or parenteral administration of the drug. The normeperidine metabolite is renally excreted and can accumulate to neurotoxic doses more rapidly in patients with renal insufficiency.[32] Convulsions may occur in both epileptic and nonepileptic patients receiving repeated administration of meperidine. Concurrent administration of meperidine with anticonvulsants may increase the first pass metabolism of meperidine to normeperidine, making it a significant risk for epileptic patients treated with anticonvulsant medications.[33]

Morphine and hydromorphone used at clinically relevant doses do not appear to have significant proconvulsant activity.[24]

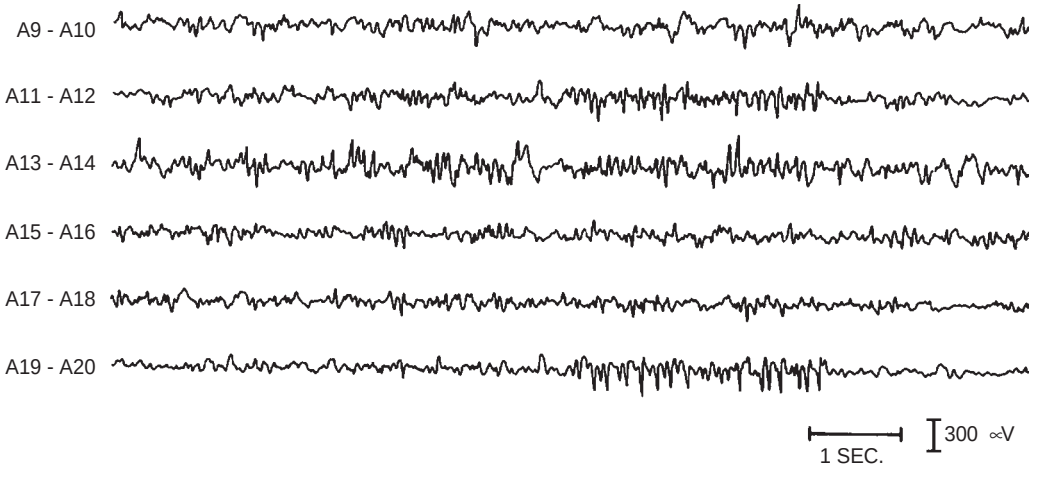

Figure 101.1 Beta-EEG activation 10 min after propofol injection (right temporal and central convexity). Reprinted with permission from Ebrahim ZY *et al*. Anesth Analg 1994;78:275–9.

Muscle relaxants

Chronic anticonvulsant therapy with phenytoin and/or carbamazepine can result in reduction of the duration of effect of nondepolarizing neuromuscular blockers, including pancuronium, vecuronium, rocuronium, atracurium, and cis-atracurium.[34–36] The etiology of the phenomenon was initially contributed to induction of hepatic enzymes leading to faster breakdown of muscle relaxant agents. However, the resistance to nonhepatically metabolized agents such as atracurium and cis-atracurium suggest additional effects on metabolism and possible competitive interactions between neuromuscular blockade and anticonvulsants at the neuromuscular junction.[37]

Anesthetic goals

Goals of anesthetic management

In providing perioperative care for the patient undergoing epilepsy surgery, the anesthesiologist aims to give a continuum of critical care throughout the perioperative period. Intraoperatively, the common goals of neurosurgical anesthesia apply, including adequate brain relaxation for surgical manipulation, good systemic blood pressure control, and timely emergence from anesthesia to allow for early postoperative neurologic examination of the patient. Procedures requiring seizure induction for epileptic foci monitoring require avoidance of inducing a prolonged epileptogenic event or patient injury during an intraoperative tonic clonic event. In treating unintentional seizure activity the anesthesiologist weighs the therapeutic goals of seizure control against the potential for oversedation or interference with critical electrocortical monitoring.

Preoperative evaluation and preparation

Seizure history

The nature and manifestations of the patient's seizures should be inquired about preoperatively. Epileptic activity can occasionally be difficult to discriminate from psychomotor behavior sometimes displayed during emergence delirium. Familiarity with the patient's seizure pattern promotes recognition and awareness of perioperative seizures. In all cases, the anesthesiologist should maintain a high degree of suspicion for an epileptic etiology in a patient who has prolonged emergence, poor responsiveness, or repetitive motor movements in the postoperative period.

Associated medical conditions

Most patients presenting for epilepsy surgery are relatively young and fit from the cardiovascular and respiratory standpoint. Any patient with a significant end organ dysfunction or complex past medical history should have a comprehensive preoperative anesthetic evaluation prior to surgery. Open craniotomy is considered a moderate risk procedure (indicating a less than 5% risk of cardiac events) with regards to its taxing effects on the cardiovascular system of the patient.[38]

Several rare medical conditions associated with epilepsy may present significant challenges to the anesthesiologist. Patients with neurofibromatosis may have intracranial tumors, airway compromise from tumors involving the respiratory tract or from cranial nerve involvement. Pulmonary status may be compromised from chronic aspiration syndrome, pulmonary fibrosis, and pulmonary hypertension.

Medication history

Medication history is important for preoperative laboratory test selection and predicting intraoperative drug interactions. Antiepileptic agents have been demonstrated to have significant impact on the dose response curve for both nondepolarizing muscle blockers and opioids. Both phenytoin and carbamazepine are associated with resistance to nondepolarizing neuromuscular blockade[37] and elevated liver function tests. The direct relationship between the number of anticonvulsants a patient receives, and the dose of fentanyl required for intraoperative anesthetic maintenance[39] further suggests that anticonvulsant therapy predisposes resistance to opioids. Elevations in hepatic enzymes are prevalent (gamma-glutamyl transpeptidase is elevated in 75% and alanine aminotransferase in 25% of patients receiving anticonvulsant therapy).[40]

Asymptomatic laboratory abnormalities should not cause cancellation of the surgery, since elevated liver function tests are almost always a predictable result of anticonvulsant therapy. Sedation and lethargy are common side effects of many antiepileptic agents including newer therapies such as Lamotriqine and oxcarbazepine and may potentiate the central nervous system (CNS) depressant effects of anesthetics. Carbamazepine may cause a severe depression of the hemopoietic system and cardiac toxicity in rare cases. This drug's metabolism is materially slowed by erythromycin and cimetidine, drugs which may be administered during the perioperative period. Valproic acid therapy results in dose related thrombocytopenia and platelet dysfunction.[41] A bleeding time obtained preoperatively is indicated to assess the potential for increased perioperative bleeding. Phenobarbital, phenytoin, or valproic acid may theoretically increase the possibility of halothane hepatitis since they induce its hepatic metabolism.[42]

Recent craniotomy

Small case series suggest significant pneumocephalus may be seen in post-craniotomy patients for up to 1 month after surgery.[43] Avoidance of nitrous oxide in patients who have had recent placement of intracranial electrodes would thus be prudent.

Psychologic preparation

Preoperative consultation and discussion of expectations has a significant impact on the anxiety of the patient undergoing neurological surgery. Planned intraoperative corticography or awake craniotomy should always be preceded by a realistic description of what the patient will experience including expected discomforts, level of cooperation and tasks that will be performed for speech and memory testing, and the possibility of events that may require rapid interventions including conversion to general anesthesia. It is important that the anesthesiologist develop an excellent rapport with the patient during the preoperative period. The interview should include

an assessment of the patient's ability to cooperate during a planned awake procedure. Patients who are too young, are mentally impaired, have personality disorders, behavioral problems, or difficult airways should not be considered for 'awake' craniotomy. The age cut-off utilized at the authors' institution is variable based on the adolescent's maturity. Children under 14, however, rarely tolerate this procedure awake.

Because intraoperative electrocorticography commonly requires significant reduction in the dose of sedative hypnotic agents for adequate EEG monitoring, patients should be prepared for the possibility of intraoperative awareness even when this procedure is performed under a general endotracheal anesthetic technique. The patient should be reassured that this experience is usually described as a painless awareness of voices or other sensations. Patients and their families need to understand that this is expected and that other risks such as perioperative seizure, nausea, vomiting, and airway compromise exist.

Intraoperative anesthetic approach

Diagnostic surgical procedures for intractable epilepsy

Placement of epidural ('peg') electrodes requires multiple burr holes and can be a lengthy procedure depending on the number of electrodes to be placed. 'Depth' electrodes exploring subcortical regions of the brain require stereotactic placement. The procedure is usually uneventful and not associated with significant bleeding. A general anesthetic is most frequently used at the authors' institution. Unless otherwise indicated for medical co-morbidity, only routine noninvasive monitoring is employed.

Implantation of subdural grid electrodes requires a full craniotomy. In our institution, this procedure does not generally involve EEG recording or stimulation as this is done postoperatively in the epilepsy monitoring unit. Therefore, we employ a standard anesthetic technique without special consideration for suppression of EEG components. As with any full craniotomy procedure, significant bleeding may occur from dural sinuses. This requires good IV access (two large-gauge IVs) and an arterial cannula. The anesthetic regimen should be constructed to allow rapid emergence for timely neurologic assessment. The electrode plates to be implanted are quite bulky and require brain shrinkage with mannitol and hyperventilation. One should be aware, hyperventilation to facilitate surgical exposure may precipitate seizure activity. It should be used only as necessary, with increased reliance on ancillary measures such as mannitol and/or loop diuretics. Furthermore, patients with complex partial seizures may have reduced CO_2 reactivity of cerebral blood flow when compared to normal controls.[44]

Resection of epileptogenic brain regions under general anesthesia

The anesthetic goals for these surgeries will depend upon the need to use intraoperative ECoG for seizure foci localization. Resection of epileptic foci under general anesthesia without the use of ECoG has goals similar to those of most open craniotomy procedures. These goals are to ensure lack of awareness, immobility and hemodynamic stability, to facilitate brain relaxation, ensure rapid emergence so that neurologic status can be assessed and to avoid perioperative seizures. Benzodiazepine premedication can be given if EEG recording is not planned. Multiple studies have investigated the potential benefits of one anesthetic technique over another for providing hemodynamic stability, good brain relaxation and rapid emergence for evaluation of the patient's neurologic examination. Many anesthetic combinations have been used with success. Recent studies suggest total intravenous anesthesia (TIVA) with propofol may have the benefit of providing lower intracranial pressures and better brain relaxation when compared to isoflurane or sevoflurane administered at >0.5 minimum alveolar concentration (MAC) in patients undergoing craniotomy with intracranial mass lesions.[45] However, these benefits may be less clinically significant when lower MAC doses of volatile agent are used.[46] Use of the ultra-short acting opioid remifentanil more consistently allow for rapid emergence and early neurologic examination than other opioids.[47–50] Remifentanil has also been associated with better brain relaxation than fentanyl; however, this has not been a consistent finding in comparison studies.[51–52] No prospective studies have been adequately powered to determine the impact of anesthetic technique on neurologic outcome after craniotomy.

Additional goals for anticipated use of intraoperative ECoG include avoidance of drugs that will interfere with monitoring of seizure spikes and preventing unwanted generalization of interictal spike wave activity. Barbiturate and benzodiazepine premedication should be avoided as seizure threshold may be elevated, making EEG recording of epileptogenic activity more difficult. Antihistamines can activate seizure foci in these patients and should likewise be avoided as premedicants. Despite an isolated report of N_2O-related diminution of epileptic foci during intraoperative electrocorticography,[44] N_2O can be used for these procedures. The use of low concentrations of isoflurane, sevoflurane (for induction of pediatric patients) or desflurane is permissible, provided these agents can be eliminated well before the onset of corticography. When no potent inhaled anesthetics are in use, scopolamine or droperidol can be substituted to prevent intraoperative recall with virtually no effect on the EEG. Alternatively, narcotic dosing is increased. Mild to moderate hypocapnia ($PaCO_2$ = 30–35 mmHg), however, is often necessary to assist in brain volume control and brain relaxation.

Isoflurane may decrease the frequency and spatial distribution of epileptogenic spikes, although it is unclear whether this effect persists at low concentrations.[53] An intubation dose of short-acting barbiturate during induction is not contraindicated, but should be avoided later in the case, as should intravenous lidocaine.

If cortical motor area stimulation is necessary, particular attention to the management of neuromuscular blockade and anesthetic dosing is appropriate. As a general rule, neuromuscular blockade must be minimal to allow motor stimulation. If moderate residual neuromuscular block persists, a small dose of anticholinesterase can be administered to achieve complete reversal.

Occasionally, intraoperative EEG recording fails to reveal seizure spikes. After consultations with a surgeon and an electroencephalographer, doses of methohexital (10–50 mg increments),[8,25] alfentanil (50 μg/kg)[26] or etomidate (0.2 mg/kg)[7]

may be administered to help activate dormant foci. However, controversy exists over the correlation of seizure spikes elicited with these drugs to pathologic epileptogenic foci.

Awake craniotomy for epilepsy surgery

Awake craniotomy for resection of seizure focus is performed when tissue resection requires mapping of eloquent cortical tissue located proximal to the ictal foci. The technique may also be used to avoid anesthetic related interference with intraoperative ECoG. The anesthetic technique for awake craniotomy is more aptly described as variable depth anesthesia with periods of wakefulness. Various institutions and anesthetists have reported on favored techniques for 'Awake' craniotomies including periods of general anesthesia using a laryngeal mask airway or endotracheal intubation, or deep sedation with discontinuation of anesthesia for the period of speech or memory testing.[54,55] Despite the development of multiple approaches to the problem, the awake craniotomy remains one of the more challenging anesthetics to provide and no method is without its pitfalls and limitations. Factors which support a successful procedure include: selection of a patient appropriate for the procedure, preoperative psychologic preparation of the patient, positioning which will be comfortable for the patient for an extended period of time, and a short surgical duration. There is no prospective data to suggest one approach is preferable to another. The following techniques represent the favored technique of the authors. Regardless of the anesthetic technique used, excellent scalp local anesthesia is required for patient comfort. Escalating the patient's sedation to supplement an inadequate scalp block should be avoided as this will needlessly increase the risk of airway obstruction and oversedation during cognitive testing. Girvin described the technique which is utilized for local scalp anesthesia during craniotomy.[17,27]

Patients are best placed in the full lateral position to allow adequate access to the airway and avoid back or pressure point pain after prolonged positioning. The authors common approach to positioning these patients is to administer bolus doses of short acting sedation titrated to patient comfort levels (propofol 10–20 mg) during the placement of the local block and Mayfield head holder (if used) then allowing the patient to become conscious enough to cooperate in finding the most comfortable head and body position for the procedure. Although some surgeons choose to use a pin-type head holder to minimize head movement, the holder is not attached to the bed but is placed on a foam doughnut for comfort. Sudden movement is certainly undesirable during craniotomy, but it must be an anticipated event during awake craniotomy even with the best anesthetic technique. Patients may have confusion while emerging for the testing portion of the procedures and seizures may occur from mapping or from the patients' underlying condition. Immobilization of the head may be dangerous in these situations. Excellent access to the patient's face and extremities is required. The drapes need to be appropriately tented to allow a clear view of the patient's face for both patient safety and adequate sensorimotor and speech and memory testing. Pillows are placed between the patient's legs, between the back and the back support and in front of the patient allowing them to 'hug' the pillow. Potential pressure points are padded with foam or soft blankets. Drapes are carefully taped out of the way to allow good access to the face. Figure 101.2 demonstrates a configuration for operating room setup which the authors have found useful to facilitate the process.

The development of short acting, rapidly titratable intravenous agents has made total intravenous anesthetic (TIVA) a more popular choice over the traditional neurolept anesthesia for the awake craniotomy procedure.[56] Until recently the authors used a combination of propofol (75–150 μg/kg/min) and alfentanil (0.25–0.75 μg/kg/min) or fentanyl (0.5–1 μg/kg/hr). These agents were then discontinued

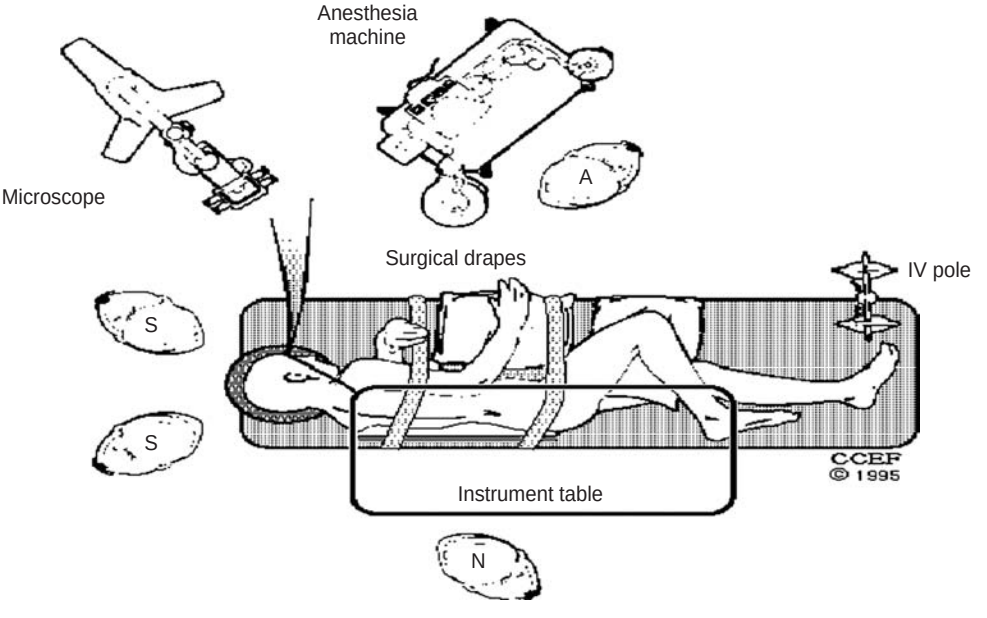

Figure 101.2 Operating room setup for right-sided craniotomy performed for the awake patient. Note the arrangement of the surgical drapes, which ensures access to the patient's face. Reprinted with permission from Schubert A. Clinical Neuroanesthesia Boston, MA: Butterworth-Heinemann Publishers, 1997;4,66.

15–20 minutes prior to the testing period. During testing, the authors preferred to reduce, but not eliminate the opioid infusion to maintain an analgesic background.

For the last several years a newer anesthetic agent, dexmedetomidine has gained some favor due to its unique property of inducing a sedation more akin to natural sleep with minimal respiratory effects.[57] Dexmedetomidine is given as a loading dose of 1 mcg/kg over 10 minutes and then infused at 0.6 mcg/kg/hr for the remainder of the procedure. A second agent is often required for adequate sedation during cranial flap opening and then discontinued for the testing period. The authors prefer to use a low-dose propofol infusion (25–75 mcg/ kg/min) that can be titrated to the desired sedation depth to supplement dexmedetomidine. Other authors have reported good experience with remifentanil combined with dexmedetomidine.[58] Propofol is discontinued 15–20 minutes prior to intraoperative stimulation of motor, and speech areas to allow adequate time for patient emergence. Experience with dexmedetomidine has demonstrated that some patients require more intense effort to be roused from dexmedetomidine sedation (a physical stimulus such as sternal rub and calling of their name). However, once roused and engaged, the patient remains able to cooperate with cognitive testing. At least one institution has reported difficulty with cognitive testing in patients receiving dexmedetomidine during Wada testing. It is possible the excessive sedation was due to the use of additional sedative agents, such as benzodiazepines in combination with dexmedetomidine. Dexmedetomidine is known to have a significant second drug effect and the sedative effect will be greater when used in combination with other sedative agents.[59]

Frequently, surgical resection proceeds while the patient completes verbal tasks or reads from a large-print book (speech area assessment) or squeezes the tester's hand (motor area assessment). Resection is stopped or modified at the first sign of speech difficulty or weakness. During cortical stimulation, the patient may be distressed by strange sensations and involuntary movements. Reassurance and comforting words go a long way, but occasionally mild sedation is also provided. More seriously, a seizure may be precipitated which requires prompt termination as well as assurance of a patent airway and adequate ventilation.

Following the completion of the cognitive testing, sedation is then again deepened to the point of unresponsiveness as necessary.

Adverse events

Sedation techniques for 'awake' craniotomy are associated with a significant incidence of complications, which can be managed safely under the management and close scrutiny of the experienced anesthesiologist. The traditional neurolept sedation regimen was associated with a 16% rate of convulsions, an 8% incidence of nausea and vomiting and at least a 2% rate of conversion to general anesthesia.[54] Contrary to neuroleptanalgesia, propofol sedation techniques are almost completely devoid of intraoperative seizure risk. Yet, transient respiratory depression is much more prevalent with propofol compared to neurolept or dexmedetomidine-based techniques, where it is virtually absent.[54]

Seizure activity (especially with direct cortical stimulation) can be treated with propofol (0.75–1.25 mg/kg), or thiopental (1.0–1.5 mg/kg) depending on the need for subsequent EEG recording. At the end of the procedure, benzodiazepines and phenytoin may also be used.

Cerebral hemispherectomy

On occasion, the seizure foci are so diffuse as to require resection of substantial portions of an entire cerebral hemisphere. Frequently, this procedure is performed in children and can be associated with significant morbidity and mortality, related to massive blood loss, electrolyte and metabolic disturbances, coagulopathy, cerebral hemorrhage, and seizures. Hemispherectomy requires a very large craniectomy, which increases the chance of bleeding and tearing of dural sinuses. Air embolism also has been reported and may lead to serious morbidity. Recently, three different surgical techniques (anatomical, functional, and lateral) for hemispherectomy were compared. Lateral hemispherectomy was associated with the lowest intraoperative blood loss, the shortest intensive care stay, and the lowest complication rate. Functional hemispherectomy had the highest rate of reoperation, while patients undergoing anatomical hemispherectomy had the longest hospital stays, greatest requirement for CSF diversion and highest postoperative fever. Patients with cortical dysplasia had the largest intraoperative blood loss.[60]

Continuous monitoring of blood pressure by arterial catheter is required, as is central venous access and monitoring of cardiac filling pressure. Brian *et al.*[61] report a series of ten patients, ages 3 months to 12 years, whose intraoperative blood replacement amounted to 1.5 blood volumes, on average. Seven of ten patients developed a coagulopathy intraoperatively, requiring administration of platelets and/or fresh frozen plasma. Progressive hypokalemia requiring replacement occurred in 40%. Hypothermia and metabolic acidosis was observed in 50%. Urine output was a poor indicator of volume status because of frequent massive glycosuria. Zuckerberg *et al.*[62] report several children under 5 years who developed severe decreases in cardiac index, bradycardia, increased systemic vascular resistance (SVR), and an alveolar to arterial gradient suggestive of neurogenic pulmonary edema after hemispherectomy with extensive subcortical resection. Removal of the endotracheal tube at the conclusion of the case is fraught with the danger and should be carefully reconsidered in each patient. Postoperative hemodynamic instability is common and the airway may be compromised by seizure activity. Early postoperative recovery is best accomplished in an intensive care environment. As has been reported in adults,[63] children undergoing major brain resection become hypercoagulable as early as during dural closure.[64] While the clinical significance of this finding is debated, thrombotic complications should be anticipated.

Emergence and postoperative management

The incidence of complications after intracranial neurosurgery remains substantial.[65] Nausea and vomiting occur in 30–50%,

the incidence of neurologic deterioration is 8–10%, of which approximately one-half is permanent. Respiratory morbidity occurs in 3–8%, while cardiovascular complications were found in 5–19% of patients. While epilepsy patients are generally healthy from the cardiovascular perspective, seizures, impaired mental function and the effect of large craniotomy procedures with substantive brain resection can combine to put patients at significant postoperative risk.

Because of preoperative tapering of anticonvulsants and perioperative drug interactions, patients may be at higher risk of developing postoperative seizures.

Anticonvulsant blood levels need to be checked frequently and doses adjusted accordingly to continue appropriate maintenance of anticonvulsant therapy postoperatively. When a seizure occurs, adequacy of oxygenation and ventilation must be assured by appropriate measures to secure airway patency. The first step should be ventilation with 100% oxygen via bag/mask. If necessary, the airway is secured by tracheal intubation. In adults, the seizure may be stopped with a small (1–2 mg/kg) dose of thiopental, lorazepam 2–5 mg, diazepam 5–10 mg administered over 2–3 minutes, or midazolam 2–4 mg. If seizure activity recurs, phenytoin is begun at 50 mg/minute to a total dose of 20 mg/kg, assuming the patient has not previously been treated with phenytoin. Intractable status epilepticus is treated with general anesthesia using isoflurane, barbiturates, or propofol.

Antiepileptic medications are associated with drowsiness and lethargy. It is our clinical experience that epilepsy patients emerge from anesthesia more slowly than neurologically normal individuals. Intraoperative loading of phenytoin for treatment of seizures may increase the risk of delayed emergence from general anesthesia. This tendency can be exacerbated in epilepsy patients with mental handicaps who are also on therapy with the anticonvulsants mentioned. During the course of aggressive medical therapy and in the postoperative period, phenytoin and carbamazepine blood levels may increase into the toxic range.[66]

Intracranial bleeding occurs in a small percentage of patients, so that neurological status must be closely and continuously monitored during recovery. Coughing and systemic hypertension should be avoided and promptly treated so as not to precipitate or aggravate intracranial bleeding. Prophylactic administration of antinauseants is effective[67] and advisable. Other postoperative neurologic complications of temporal lobe surgery include memory and visual field deficits. Patients with temporary subdural grid electrode implants may suffer cerebral edema[68] occasionally necessitating emergency re-exploration.

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102 Placement of subdural grids

F Salazar and WE Bingaman

Brief history

It is often said that the history of epilepsy surgery began on 25 May 1886, when Victor Horsley operated on a patient of John H. Jackson at the National Hospital for the Paralyzed and Epileptic at Queen's Square in London. This patient was a man of 22 years with focal motor seizures that were caused by a depressed skull fracture, the consequence of a trauma he had suffered 15 years earlier.[1]

The first cortical electrical stimulation studies in humans can be traced back to work done by Robert Bartholow in Ohio. In 1874, he had in his care a patient with a large cranial defect exposing her cerebral hemispheres. Needles were inserted into the dura mater and, upon closing the circuit, right arm and leg muscular contractions were observed.[2] In 1893, Krause performed the first documented case of intraoperative electrical stimulation of the human cerebral cortex to determine locations of cerebral function and epileptogenic foci as a guide to cortical resection.[2]

The first intraoperative electrocorticogram was produced by Foerster and Altenburger in 1934. By the early 1950s, direct electrical activity measurement from the human cerebral cortex during surgery was extensively used and considered an indispensable technique in the evaluation of surgical candidates to define the irritative zone[2]. However, chronic intracranial recordings were not reported until 1939 when Penfield used epidural single contact electrodes in a patient with an old left temporo parietal fracture and whose pneumoencephalography disclosed diffuse cerebral atrophy[3]. The use of subdural grid arrays became more popular after several publications during the 1980s demonstrated their safety and efficacy[4–6]. Before that time most invasive techniques involved epidural electrodes or intraoperative recordings.

Materials and design

Subdural electrode grids consist of stainless steel or platinum contacts embedded in a thin matrix of biologically inert but flexible material such as Silastic® or Teflon®. By design, each contact and its connecting wire are electrically isolated so as to provide precise anatomic localization of seizure foci.[7,8] These wires extend to insulated cables that attach to an extracranial amplifier. The shape and size of each subdural electrode grid varies from simple strips, consisting of a single row with usually four to eleven contacts to rectangular or square arrays of 16 to 64 electrodes. The distance between electrodes is approximately 10 mm. The diameter of the electrode contact varies between 2 and 5 mm. It is very important that the material in which the electrodes are embedded is flexible and thin permitting the array to adopt the shape of the brain it is covering.[9] The embedding material should be clear in order to facilitate its placement over specific brain areas and also to define the relationship of the contacts with the underlying vessels and other anatomical landmarks such as sulci and gyri. Minimizing the total volume of the electrode array is essential to avoid increased intracranial pressure from mass effect.

Variability in shape and size of the electrodes permits tailoring their use to the specific clinical situation. Custom designed arrays of subdural electrodes have been configured for placement in specific anatomical locations. For example, to record from interhemispheric brain regions, rows of electrodes arranged in curvilinear fashion were designed to follow the average curvature of the corpus callosum. The plate is designed with contacts on both sides to record from the ipsilateral mesial cortex and the contralateral mesial region through the falx.[7]

Indications and advantages

Epilepsy surgery is based on the principle that resection of an epileptogenic focus can result in seizure freedom. The epileptogenic zone is defined as the area of brain necessary and sufficient to generate seizures.[9] Accordingly, accurate localization of the epileptogenic zone and its relationship to eloquent cortex is crucial for the success of epilepsy surgery.[10–18] In certain clinical situations, invasive electrode recordings allow for accurate localization of the epileptogenic zone and mapping of functional cortical regions.

The most common indications for intracranial electrodes include lateralization or localization of epilepsy and localization of functional/eloquent cortical information. In the first case, preoperative noninvasive studies and semiology often suggest focal epilepsy but scalp electroencephalography (EEG) is unable to adequately localize or lateralize the epileptogenic zone.[14,19] Subdural grids have particular advantages: they can be in place long enough to record both spontaneous seizures and interictal activity during various stages of arousal, and they have applicability for mapping of cerebral function extraoperatively.[9,20,23] These characteristics allow tailored cortical resections around areas of higher function while minimizing

Table 102.1 Major indications for implantation of subdural grids

Determination of extent and distribution of the epileptogenic zone.

- Normal imaging data.
- Epileptogenic zone that is more widespread than the structural lesion.
- Absolute noncongruence of preoperative data.
- Epileptogenic zone versus structural lesion.
- Multiple lesions or multifocal interictal epileptiform activity.

Determination of the relationship of the epileptogenic zone to eloquent cortex.

- Cortical stimulation
- Somatosensory evoked potentials.

the risk of permanent neurological deterioration.[21,22] Intraoperative electrocorticography, as compared with chronically implanted subdural grids, is a limited option because it only provides information restricted to interictal activity. When used in patients under general anesthesia, it is believed that anesthetic agents may influence EEG activity by altering the thresholds of after discharges and motor responses creating a misleading electroencephalographic picture. Additionally, intraoperative functional mapping often requires a cooperative patient that can tolerate being awake during surgery under local anesthesia. This is particularly difficult in the pediatric population.

Indications for invasive video-EEG monitoring can be divided in two overlapping groups (see Table 102.1[11–15]).

Disadvantages and limitations

Disadvantages of subdural invasive monitoring include increased surgical risks, financial costs, and limitations in the ability to access deep cortical regions. It requires two surgical procedures, the first to implant the electrodes and the second for removal of electrodes followed by resection of the epileptogenic zone. The amount of cerebral cortex exposed is often extensive requiring larger craniotomies and increasing the risk for complications. Implantation of a foreign body in the brain has increased potential of causing intracranial mass effect and infection. Additionally, hospital cost and length of stay are increased. Because of these factors, invasive monitoring should not be routinely undertaken as an 'exploratory procedure' to identify a focal epilepsy (the noninvasive preoperative evaluation should identify a focal epilepsy and approximate location of the epileptogenic zone). Subdural grids should be used if it is believed that their use will alter the ultimate surgical strategy and outcome. An attempt must be made to place adequate electrodes so that the predicted site of seizure origin and its boundaries are sampled.

Limitations in both the area and regions of cortex to be covered exist. In specific cortical areas such as the interhemispheric, basal temporal, and basal frontal surfaces the grids are placed without direct visualization. This makes precise cortical coverage difficult and more risky. The use of intraoperative stereotaxis can improve the accuracy by displaying the grid's implanted position on the 3D reconstruction of the cortical surface. This allows the surgeon to adjust grid position intraoperatively. The relatively common presence of bridging veins in these regions is a limiting factor for safe implantation of grids. Additionally, in the interhemispheric region it is common to find adhesions that makes grid placement difficult. Finally, subdural grid coverage of the mesial temporal lobe structures is not optimal since the grids/strips are placed in the subtemporal region without direct visualization and likely record from the parahippocampal gyrus and not the hippocampus directly.[24]

Other limitations of subdural grid implantation are the number of available channels for recording with the EEG system in the hospital. Some systems can handle only 64 channels unlike other systems record up to 200 channels thus allowing the implantation of more electrodes over wider cortical areas. Despite this, only limited coverage of cortical regions can be sampled and preoperative surgical planning is necessary to maximize the chances of covering the ictal onset zone with the electrodes.

Surgical technique

Video of subdural grids placement (DVD)

Placement of subdural grid electrodes is carried out by means of a standard neurosurgical craniotomy under general anesthesia.[20] Our preference is to use mannitol (0.5–1.0 gr/kg), hyperventilation, and optimal head positioning at the beginning of skin incision in order to obtain adequate brain relaxation and sufficient subural space for placement of the plates. Before prepping, the skin incision should be planned to allow adequate brain exposure and room to tunnel the electrode wires. Localization can be performed with simple craniometric measurement in accompaniment of magnetic resonance imaging (MRI), or frameless navigation can be used as a localizing aid.[25] The scalp and bone flaps should be of generous proportions, exposing areas of cortex needing coverage and taking into account the requirements of any definitive surgical procedure.[26] The use of stereotactic navigation and direct inspection of cortex and identification of gyri allows optimal grid placement according to the preoperative plan. The goal of surgery is to maximize the chance of fully documenting seizure foci and to be able to identify functionally important cortex by brain mapping techniques. Thus, the location of electrodes is a synthesis of the preoperative information and the surgical limitations on the amount of cortex that can or needs to be covered.[27]

Once the brain is exposed, the plates are inserted with smooth bayonet forceps, directing them towards the desired cortical region using a steady stream of irrigation allowing it to slide smoothly over the surface of the brain and preventing trauma. The grids can be 'slid' beyond the edges of the craniotomy to cover adjacent areas, including basal temporal, basal frontal and interhemispheric regions. Areas of resistance may include bridging cortical veins or adhesions that should be avoided to prevent hemorrhage. Whenever possible the electrodes should be placed under direct visualization to prevent this complication. Occasionally, when large plates are used over the convexity, there is a tendency for them to buckle. This can be overcome by dividing the grid along lines of electrodes to give a better fit over the brain. If the grids are cut to a smaller size to fit in the region of interest, edges should be carefully trimmed to avoid electrode injury and cortical laceration.[28]

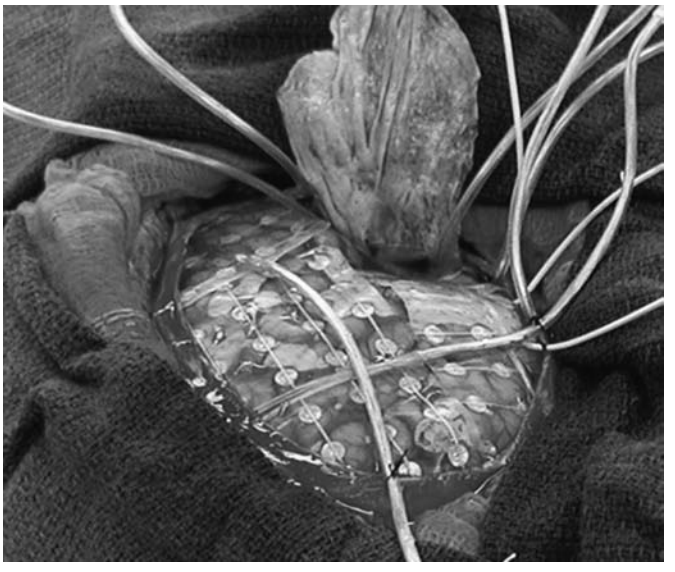

Figure 102.1 Intraoperative photography showing subdural grid electrodes after implantation before closing the dura.

Care must also be taken to ensure that the edges of large grids do not compress and impede the outflow of major draining vessels such as the vein of Labbe or Trolard as they enter the dural venous sinuses.[29] Care should be taken when implanting electrodes in patients with mass lesions, in reoperations (there are usually adhesions of the dura to the cortex), and in areas of encephalomalacia (grids may be difficult to secure). Prior to closure the electrode positions should be confirmed with the neurologist. Once in place, the electrode cables are secured to the dura with suture. A digital photograph of the brain is taken; this provides a reference between gyral anatomy and electrode placement that cannot be obtained with three dimensional reconstructed scans (Figure 102.1). A watertight dural closure around the electrode cables reduces the possibility of cerebrospinal fluid leakage. Hitch stiches are used to reduce the risk of extradural bleeding. The leads should exit without kinking in the bone edges. Electrode leads are tunneled a minimum of 10 cm from the craniotomy margin and attached to the skin with a purse-string suture. The bone flap is replaced and secured to minimize the risk of electrode movement during seizures. It is important to appropriately identify each plate and record the intended position in the patient's chart.

Computer software has been developed to aid the surgeon intraoperatively in the placement of the subdural grids. A standard preoperative stereotactic volume acquisition MRI with scalp fiducial markers in place is obtained, and co registered to the patient intraoperatively after positioning with rigid head fixation. The pointing tool is then used to register the positions of as many exposed electrodes as possible, and using specialized computer software the grid is displayed as pseudocolored spheres on the volume surface reconstruction of the brain. This allows the surgeon to have immediate intraoperative feedback demonstrating the anatomic position of the subdural grid.[30,31]

Postoperative management

The patient is sent to a neurosurgical intensive care unit (ICU) for the first postoperative night. The next day the patient is transferred to the Epilepsy Monitoring Unit where the electrodes are connected for continuous digital EEG recording along with video imaging. Intravenous antibiotics are prescribed throughout the entire monitoring period. Following removal of the subdural grids at least one of the plates is sent for culture (even in the absence of signs of infection). In cases of positive cultures, antibiotics are continued based on these results and the clinical condition of the patient. Corticosteroid therapy is administered during the first 48 hours after surgery to reduce cerebral swelling and help with postoperative pain. In some patients severe headache can develop after surgery requiring use of intravenous analgesics. Postoperatively, any change in the level of consciousness or neurological function is evaluated with computed tomography (CT) scanning. The period of implantation is variable with a range between 9–26 days and an average of 12 days.[21] In general, patients with extra temporal seizure foci require more recorded seizures than patients with temporal foci.

Traditionally, the method of localizing implanted electrodes is based on a skull X-ray after implantation and from this an electrode map is drawn on a standard hard-copy template of the brain. In this map, electrodes involved in interictal epileptiform activity, ictal onset, and spread patterns can be marked along with the functional brain map obtained during cortical stimulation and evoked potentials (Figure 102.2). The main limitation of this method is the difficulty correlating the electrode positions to precise sulcal and gyral cortical surface anatomy. The clinical value of subdural electrodes can be further enhanced by postimplantation MRI co-registration and 3D visualization of the electrode position in relation to the cortical surface on the MRI.[32] This allows a more precise understanding of the anatomic relationships between the ictal onset zone, eloquent cortex, and the underlying brain anatomy. For this, a stereotactic computed tomography (CT) scan is obtained immediately postimplantation to verify electrode location and to supplement drawings or photographs made intraoperatively. The preoperative MRI is fused with the postoperative CT scan in order to obtain a 3D reconstruction of the brain and the relationship of the grids with the particular anatomy of the patient.[33] Postoperative MRI is avoided because of safety concerns as it has been shown that the oscillating magnetic field can induce electrical currents in any metallic implants and potentially cause heating and/or electrical damage to the brain cortex.[34] Unfortunately, CT scan images show extensive streak artifact which is especially pronounced with alloy grids. Although MRI imaging allows for better visualization of the electrodes, the risk of possible complications outweigh the benefits.[8]

Upon return to the operating room, the surgeon must be careful to avoid movement of the subdural grids as they are exposed. Once exposed, the cortical resection takes place using the grids as a reference with the interictal, ictal, and functional cortex information. Additionally, stereotactic navigation can be used to further correlate electrode position based on post implantation CT.[35]

Complications

Subdural monitoring with grid electrodes has historically been shown to have low permanent morbidity (0–3%) compared

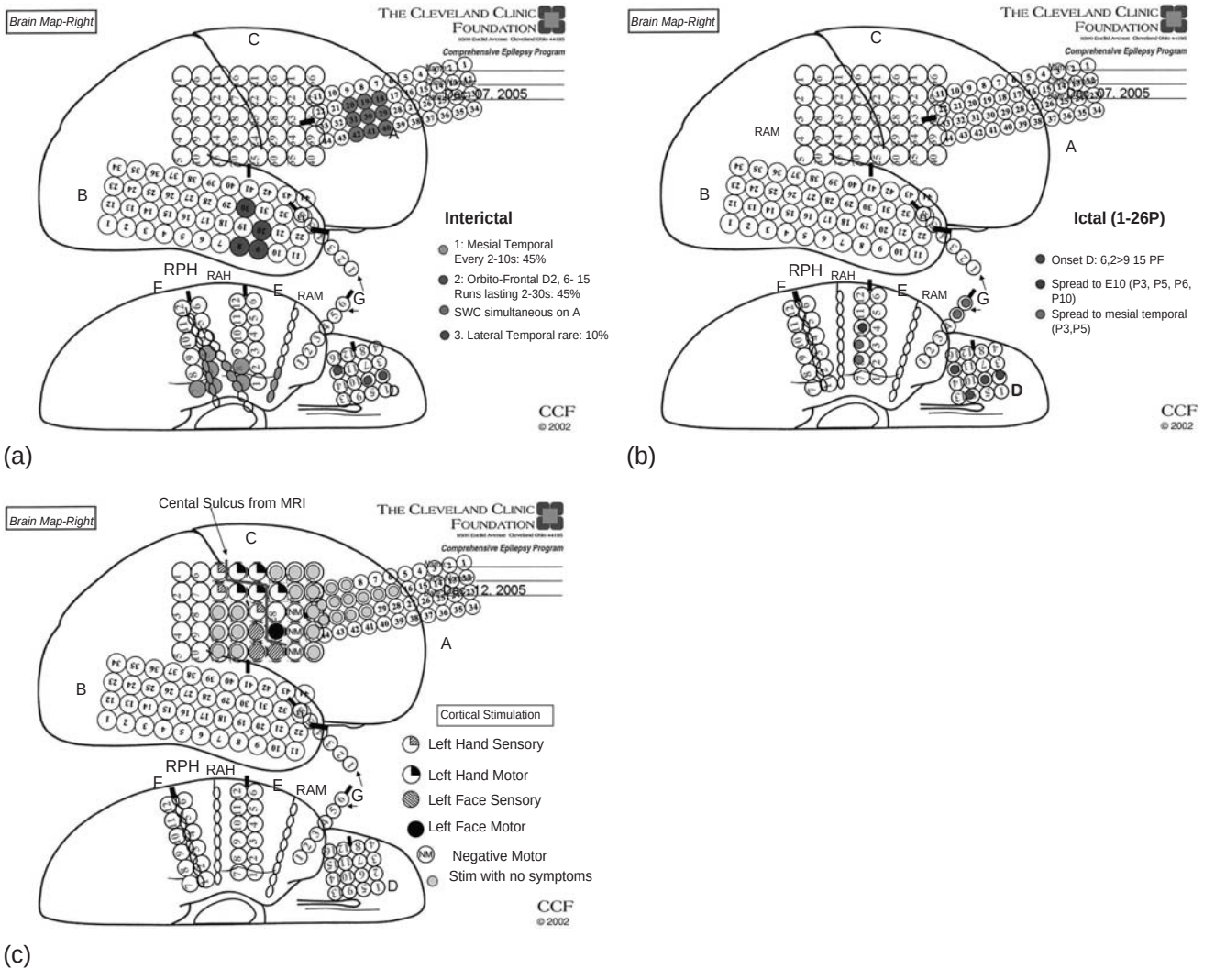

Figure 102.2 (a) Brain map showing the relative position of the subdural and intracerebral electrodes and the recorded interictal activity. (b) Brain map showing the relative position of the grids and the recorded seizure activity of its electrodes. (c) Brain map showing the cortical stimulation map.

with depth electrodes (3–6%) since, as mentioned previously, there is no intraparenchymal passage.[36] Adverse events caused by subdural grid implantation can be categorized as either surgical or neurological. For purposes of this chapter, emphasis is placed on the surgical and neurological complications related to the implantation of the grids separate from the resective stage. Resections performed after the monitoring period can also cause neurological complications, either transient or permanent. These sequelae can be variable depending on the amount of cortex resected, and are predicted based on the information obtained during the stimulation period. Risk factors for complications are: greater number of implanted electrodes, longer duration of monitoring, dominant side grid insertion, and earlier age at time of monitoring.[37]

One of the most common complications is cerebrospinal fluid leakage. Transient cerebrospinal fluid (CSF) leakage through the electrode exit site has been reported to be between 13 and 31% of the patients despite careful watertight dural closures, adequate subcutaneous tunneling, and tight skin closure.[29,38,39] This occurs most frequently after motor seizures or bouts of vomiting. Our current practice is to check the dressing regularly for any signs of cerebro spinal fluid leakage, to suture any active leak at the bedside, and to apply topical sterile skin adhesive, though the clinical utility of this practice is unknown. Use of a lumbar drain has been reported to significantly reduce the incidence of CSF leak,[40] although not routinely used at our institution due to concern of downward cerebral herniation.

Infectious complications are also reported in several invasive monitoring series. Postoperative wound infections after clean neurosurgical procedures have been quoted to range from 0.6–11%. Meningitis has been reported in 0.34–2% of patients.[41] Considering these percentages, a 6–8% rate of infection is not unrealistic for a procedure that leaves several foreign bodies implanted with cables exiting the scalp for seven or more days. Factors that have been reported to increase the incidence of infection are greater number of electrodes, exiting cables, or exit sites. The duration of recording following implantation is also found to correlate significantly with infection rate; duration exceeding 14 days is more likely to result in an infectious complication.[38] This can occur acutely during the monitoring period or chronically after

removal of the grids. During the invasive video-EEG evaluation period, wound infection, meningitis or epidural abscess can appear. Except for cases with superficial localized wound infection, the grids should be removed and aggressive intravenous antibiotic treatment initiated immediately. Subsequently, the treatment plan is modified based on culture results and clinical response. Osteomyelitis is a rare complication that has been described in 3% of the patients;[29] it usually is a late infection, occurring weeks or months after the initial surgery that requires removal of the bone flap and treatment with intravenous antibiotics. Brain abscess has also been described as a potential complication, but its incidence is very low.[42] Bacteria that have been isolated in patients with clinically relevant infections have included different species of *Staphylococcus, Streptococcus, Bacillus,* and *Diptheroid* mainly.[37]

Cerebral edema and intracranial mass effect is a potentially serious complication. Factors that favor its development are patients with multiple plates, presence of intracranial mass lesions, and pediatric patients.[37] Its precise incidence is not well defined because many times the only manifestation is headache with or without nausea that is successfully treated with analgesics and antiemetics. Severe cases leading to somnolence or stupor, focal neurological deficit, brain shift, or impending herniation are infrequent and require immediate removal of the electrodes. Large duraplasties and hinging the bone with sutures have been reported to prevent clinically significant cerebral edema in some patients. Also, some centers report on leaving the bone flap out during the monitoring period to avoid this complication.[43]

One of the most concerning complications with invasive monitoring is intracranial hemorrhage. As opposed to depth electrodes, intracerebral bleeding is a rare occurrence during placement of subdural grids. It is related more to venous occlusion or laceration of cortex caused by the edges of the plates. Subdural hematomas can be more frequently encountered and its incidence has been described around 8%; they can lie between the cortex and grids or superficial to the electrodes.[42,44,45] These could be a cause of deficient recording, may induce seizures or change the epileptiform activity, and also can contribute to intracranial mass effect and neurological deterioration.

As a result of the requirement for large craniotomies and two surgical procedures these patients have a significant risk for blood loss during surgery and may require blood transfusion. This is more frequently observed in patients with interhemispheric electrodes implanted where its location in relationship to venous structures enhances the risk of bleeding.

Accidental removal or displacement of grids is a potential complication that can be seen more commonly in patients with severe motor seizures or during periods of postictal confusion were the exiting cables can be pulled. If there is any suspicion of displacement, an immediate skull X-ray and a CT scan should be performed in order to evaluate movement of the grids or possible hemorrhage.

When the information obtained during the monitoring demonstrates that the ictal onset zone is at the edge of a grid or is suspected to be in an area not covered by the grids, repositioning of the plates may be necessary in order to obtain adequate coverage of the area of interest. In selected patients where invasive monitoring fails to identify the site of seizure origin, reinvestigation can sometimes achieve localization of the seizure onset and allow a successful surgical treatment.[46–48]

Due to the relatively prolonged period of reduced activity in these patients, other serious complications such as deep venous thrombosis, pulmonary embolism, pneumonia, and other sequelae of immobility can develop. Appropriate diagnostic and therapeutic measures should be initiated.

Outcomes

In evaluating outcomes after application of subdural grids, several important factors should be mentioned. First, it has been reported that patients selected for intracranial monitoring with subdural grids are less likely to have excellent outcomes because of their inherent complexity (non concordant preoperative data, non lesional MRI, and/or close relationship with eloquent cortex).[49–53] Second, this population of patients is heterogeneous and the analysis process itself is dynamic and changes over time. Third, in many cases, the invasive monitoring is a combination of subdural grids and strips, depth electrodes, and scalp electrodes which makes comparison of techniques difficult.[54,55] Another important variable is the amount of resection performed: resection of the ictal onset zone plus interictal epileptiform abnormalities, only the ictal onset zone, or limited resection of the ictal onset zone. The area of resection is often limited by the presence of eloquent cortex or by dominant draining veins.

Because of these factors, reported outcomes after subdural grid evaluation are difficult to interpret. In a recent Cleveland Clinic series of patients with normal preoperative MRI no differences in outcome were identified with or without the use of subdural grids, but the authors suggest that the invasive testing helped to devise a surgical strategy and allowed surgical treatment to patients who would not otherwise been candidates.[56]

Despite adequate and prolonged invasive monitoring with subdural grids, up to 10% of the patients are found not to be candidates for surgical resections. In most of these cases, the epileptogenic zone is overlapping with eloquent cortex that if resected will cause severe permanent neurological deficit. At other times, it is found that the ictal onset zone is widespread or cannot be localized thus impeding surgical treatment.

Conclusions

Subdural grid placement is a useful technique that helps to localize areas of epileptogenicity and to map functional brain cortex in order to aid in the planning of cortical resections for the treatment of medically resistant epilepsy in patients whom otherwise will not be candidates for surgical intervention or patients with increased risk of neurological deficit.

Despite its usefulness, it is a costly and risky procedure that should be limited to highly selected patients with severe refractory epilepsy and should be attempted in tertiary centers with the appropriate experience in video-EEG monitoring and by a surgeon with experience in these techniques.

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103 Placement of depth electrodes

L Mulligan, K Vives, and D Spencer

Background

The first step to eradicating chronic seizures is to accurately identify the seizure focus. Although imaging has improved dramatically in recent years, there are still patients whose seizure focus defies noninvasive localization as described earlier in this text, and who must proceed to intracranial electrode evaluation. Intracranial recordings can be done by a variety of means, including subdural grid and strip electrodes, epidural electrodes, and depth electrodes. Depth electrodes, electrodes that actually enter the substance of the brain and pass to deep structures, were first used for the evaluation of epilepsy in 1950 and then more consistently in the United States since the early 1970s.[1] They are still used now either alone or, more commonly, in concert with subdural strip electrodes (SDSEs) and subdural grid electrodes (SDG) for chronic recording for as long as a month if necessary to capture an adequate number of ictal events. The electrodes are also useful for recording interictal activity and studying the pattern of seizure spread. Depth electrodes offer the advantage of being able to record from deep structures (i.e., the hippocampus, hypothalamus, deep frontal lobes) where there is inadequate coverage provided by subdural electrodes. They can also be used to record activity from the neocortex through which they pass, though the sampling area is quite limited. Similarly, they can be stimulated to map for function, although are usually far less useful than subdural strip or grid electrodes for that purpose.

Materials

Over the years, the structure and materials for depth electrodes have evolved substantially. While the early electrodes were rigid, most electrodes implanted currently are flexible (Figure 103.1), usually with a semi-rigid stylet to help prevent errant placement. They are often implanted through a guide cannula to further improve the accuracy of placement. The electrodes, usually 1–1.5 mm in diameter, come in a variety of configurations with arrays of 4–10 individual contacts with spacing from 5–10 mm between the center of each. The most commonly used material now for the contacts is platinum, though stainless steel, nickel-chromium and gold have all been used.[2] Silver and copper are toxic to brain tissue and cannot be employed. The outer casing is usually polyurethane which houses the individual wires for each contact. The electrodes can also be configured to allow for the performance of microdialysis, useful for research applications.

Planning

There are several common scenarios where depth electrodes prove useful (Table 103.1), however, the frequency and extent of their use varies from institution to institution. Their use in focal versus survey studies, temporal versus frontal studies and in re-operative cases will be discussed below. The special cases of sampling from other deep structures will also be discussed.

Temporal lobe studies

Patients that have temporal lobe epilepsy confirmed on scalp-EEG with MRI findings of mesial temporal sclerosis, appropriate semiology, and concordant PET and neuropsychological data do not require invasive monitoring. Those patients can usually go directly to resection with a high degree of success. Patients that do require invasive monitoring fall into one of several categories. The most common scenario is a patient that appears to have apparent temporal lobe epilepsy but has a normal MRI or discordant phase I and II evaluation data that do not confirm location or laterality or imply bilaterality. In that instance, one reasonable approach would be to place depth electrodes in both hippocampi and subdural, subtemporal strips around both temporal lobes. This can be performed through 2–4 burr holes or small troughs. The depth electrodes can be placed in one of two principle orientations: either longitudinally or orthogonally. Longitudinal electrodes are passed posteriorly to anteriorly starting from a paramedian occipital start point and traversing the long axis of the hippocampus. Orthogonally placed electrodes are passed perpendicularly to the cortical surface via the middle or inferior temporal gyrus into the mesial structures. These orthogonal approaches are typically designed utilizing one anterior electrode placed into the pes/amygdala area and another into the body of the hippocampus. Either method can be combined with subdural strip or grid electrodes and the purpose of the intracranial study largely determines the best approach.

Two other common scenarios involving the temporal lobe are (1) patients that are suspected to have extrahippocampal temporal lobe epilepsy or (2) patients with well lateralized epilepsy, but the lobar location of the seizure is still in question and the medial temporal lobe remains suspect. In these cases, a detailed study is usually designed to find the extent of the epileptogenic zone and its relationship to critically functional cortex. A large grid is often used over the cortex in combination with subdural strips and depth electrodes (Figure 103.2). This type of study usually requires a large craniotomy.

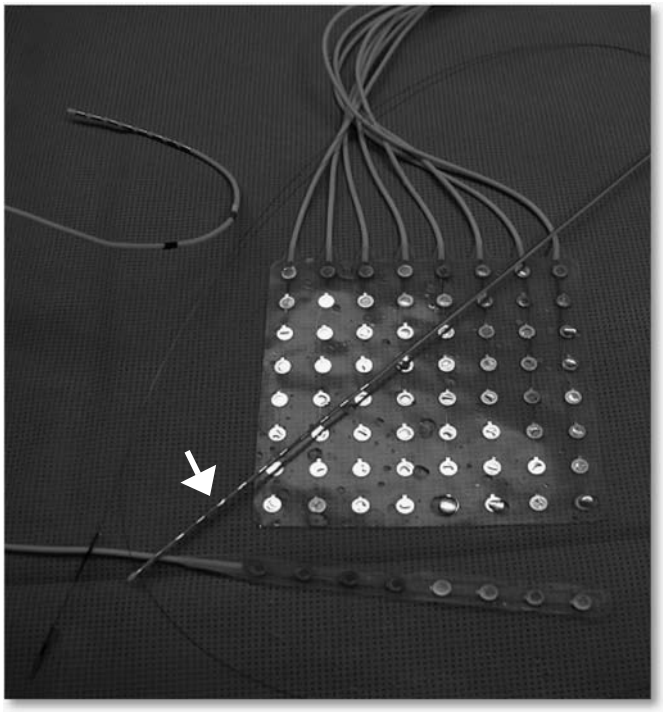

Figure 103.1 Intracranial electrodes. Arrow – depth electrode with microdialysis membrane.

Rather than making an additional burrhole to pass the electrodes from an occipital approach, depth electrodes are typically passed in an orthogonal orientation often by making a small hole in the grid though which the electrode(s) can be passed. Multiple electrodes can be passed into different portions of the amygdala and hippocampus to further refine localization as described above.

Extratemporal epilepsy

Another common category is patients with nonlesional extratemporal epilepsy. The placement of depth electrodes in these patients is usually done in order to sample areas where subdural strip coverage is either difficult or unreliable. In patients with frontal lobe epilepsy where there is a high suspicion that the medial frontal lobe is involved, interhemispheric subdural strip coverage is typically planned. Due to draining veins, these strips typically cannot reliably be placed without directly exposing and dissecting the interhemispheric fissure. In other patients, the suspicion of medial frontal onset may be lower, but a limited sampling of the interhemispheric ares is indicated; in this situation, depth electrode coverage of the anterior cingulate and supplementary area can be utilized (Figure 103.3). Care is taken to avoid primary motor and language cortices when planning the entrance sites – often coregistration of preoperative fMRI can be utilized to further define these areas. Subdural strip coverage of the orbitofrontal and fronto-polar areas is also unreliable. Depth electrodes can easily be used to provide coverage of these areas as well (Figure 103.4). Fortunately, medial occipital coverage can typically be gained by directing posterior subtemporal strips posterior to the collusum and pineal area.

Table 103.1 Common scenarios where depth electrodes prove useful

Study type	Structures sampled
Temporal lobe studies	Hippocampus and amygdala
Frontal lobe studies	Anterior cingulate, orbitofrontal and supplementary motor areas
Reoperative studies	Areas where adhesions prevent subdural strip monitoring
Deep lesions	Hypothalamic hamartoma, periventricular gray heterotopias

Deep structures

Several groups have reported successfully recording both ictal and interictal activity from hypothalamic hamartomas[3,4] and from periventricular gray matter heterotopias.[5,6] An example of this type of case is illustrated in Figure 103.5. The technique and placement of electrodes in this situation is not different that in others. Gray matter heterotopias may also be an indication that the overlying cortex may be abnormal thus making subdural cortical recordings in these corresponding areas, important. Likewise, it is often the case that depth electrode recording can supplement surface recordings in cases of large cortical dysplastic lesions, even those that come to the surface.

Technique

There are several viable techniques for inserting depth electrodes: framed stereotaxis, frameless neuronavigation, freehand passage, and endoscopically assisted. Framed stereotaxis is certainly the time-honored standard. Any number of systems are useful, including the Brown-Roberts-Wells (BRW), the Cosman-Roberts-Wells (CRW), the Leksell frame and others. Pillay *et al.* studied the accuracy of the BRW and CRW systems and found them to be consistently within 2 mm of the target.[7] Similarly, Ross *et al.*[8] reported 100% accuracy of electrode placement with the Leksell frame using MRI. Framed stereotaxis is particularly useful for bilateral survey studies. It allows for the placement of bilateral longitudinal hippocampal electrodes without the need for repositioning.

To perform a framed placement of hippocampal depth electrodes, the frame is usually placed the morning of surgery under local anesthesia and possibly light sedation. The patient is then scanned usually with fine cut MRI often using SPGR sequencing. MRI gives a more detailed anatomical image than CT and allows better visualization of blood vessels along the proposed trajectory, but CT has also been shown to be a viable alternative. CT theoretically introduces less error and is more rapidly acquired. Van Roost *et al.*[1] placed 212 longitudinal hippocampal depth electrodes using CT guided framed stereotaxis followed by postoperative MRI for evaluation of placement. They found that 97% of hippocampal head contacts and 96% of hippocampal body contacts were in or

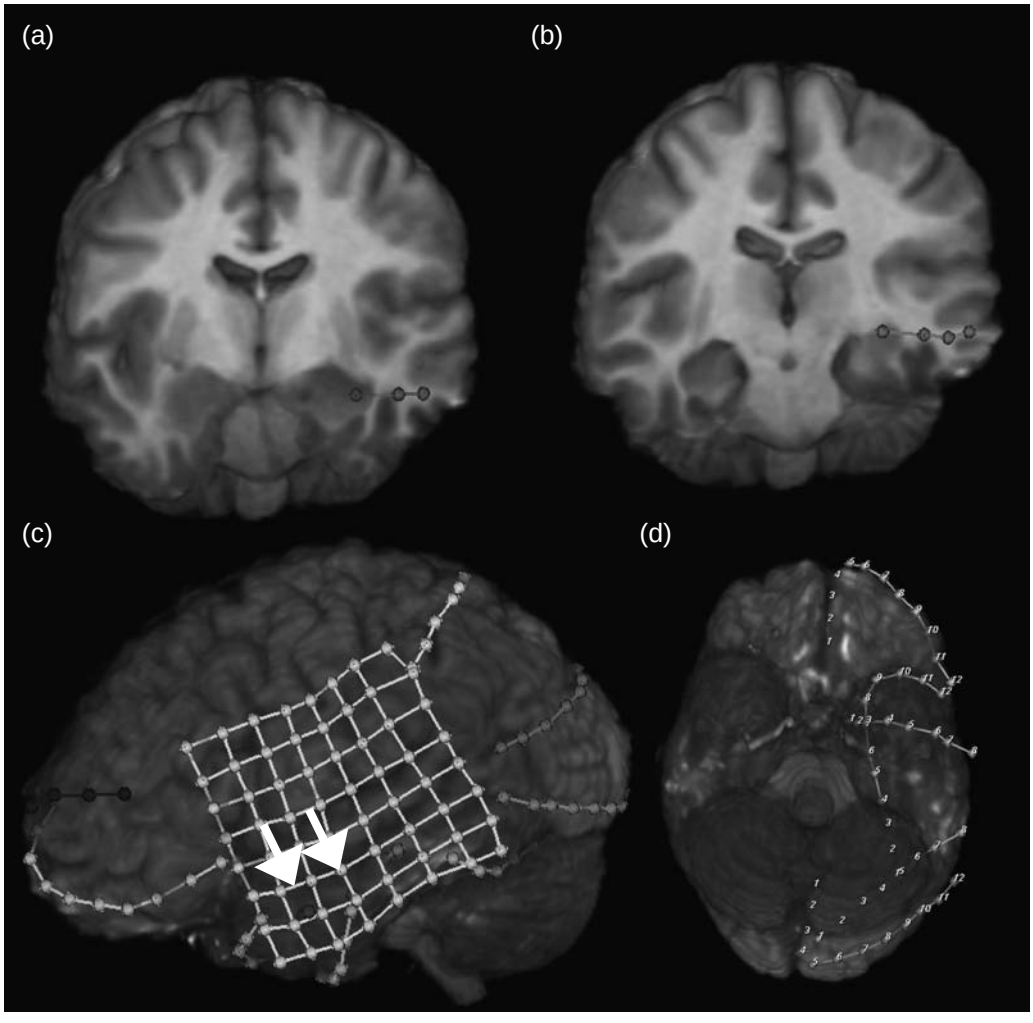

Figure 103.2 Reconstructions of electrode positions superimposed on preoperative MRI scans. A – anterior medial temporal depth electrode. B – posterior medial temporal depth electrode. C – electrode entrance sites (arrows) in context of the rest of the study on a lateral view. D – a view from below of the subtemporal strip electrodes.

immediately abutting the target.[1] Others have performed fusion of the two modalities in an effort maintain the excellent detail afforded by MRI while reducing any error introduced by magnetic reasonance.[9]

Once the scan is obtained, the patient is taken to the operating suite and the surgical planning can be performed on a navigation system. Great care is taken to define a trajectory that avoids major blood vessels and brings as many contacts as possible through the length of the hippocampus and into the amgydala. A 10-contact electrode is often chosen for this purpose. A burr hole is recommended, rather than a twist-drill hole, so that surface vessels can be identified and avoided. A rigid cannula is usually passed along the proposed trajectory, sometimes several millimeters short of the final target, and then the electrode is passed through that with its stylet still in place. Once it has reached target, the cannula and the stylet are removed and the electrode can then be tunnel several centimeters from the insertion site and secured with a stitch to the scalp. Once the depth electrodes are placed, burr holes can be made in the temporal areas to pass subdural strip electrodes. If only depth and strip electrodes are inserted, those can actually be removed at the bedside upon completion of monitoring without returning to the operating room.

Frameless systems can be employed with some minor customized adaptations to perform the same procedures. Mehta *et al.*[10] and Murphy *et al.*[11] both report on their experience with commercially available systems. Longitudinal and orthogonal electrode placement was performed and found to be accurate. Mehta *et al.*[10] showed with postoperative imaging that the electrodes were on average 3 mm from the intented target site, but only 0.4 mm ±0.9 mm from the anatomic structure of interest. Not surprisingly, they also found the orthogonal electrodes to have a lesser degree of error than the longitudinally oriented electrodes. Frameless navigation is particularly useful for detailed studies when orthogonal electrodes are to be placed can be placed through the grid at to target various locations within the amygdala and hippocampus. Using a stabilizing arm, the electrodes can be passed through a cannula in nearly identical fashion to a framed system. If the depth electrodes are passed through a large subdural grid, the electrode is typically secured to the grid and the patient must return to the operating room for their removal. Frameless navigation offers a great deal more flexibility in the design of a cranial flap as there is no frame to hinder the approach. There are several other benefits as well. First, the scanning can be done the day before the surgical procedure. Imaging can be

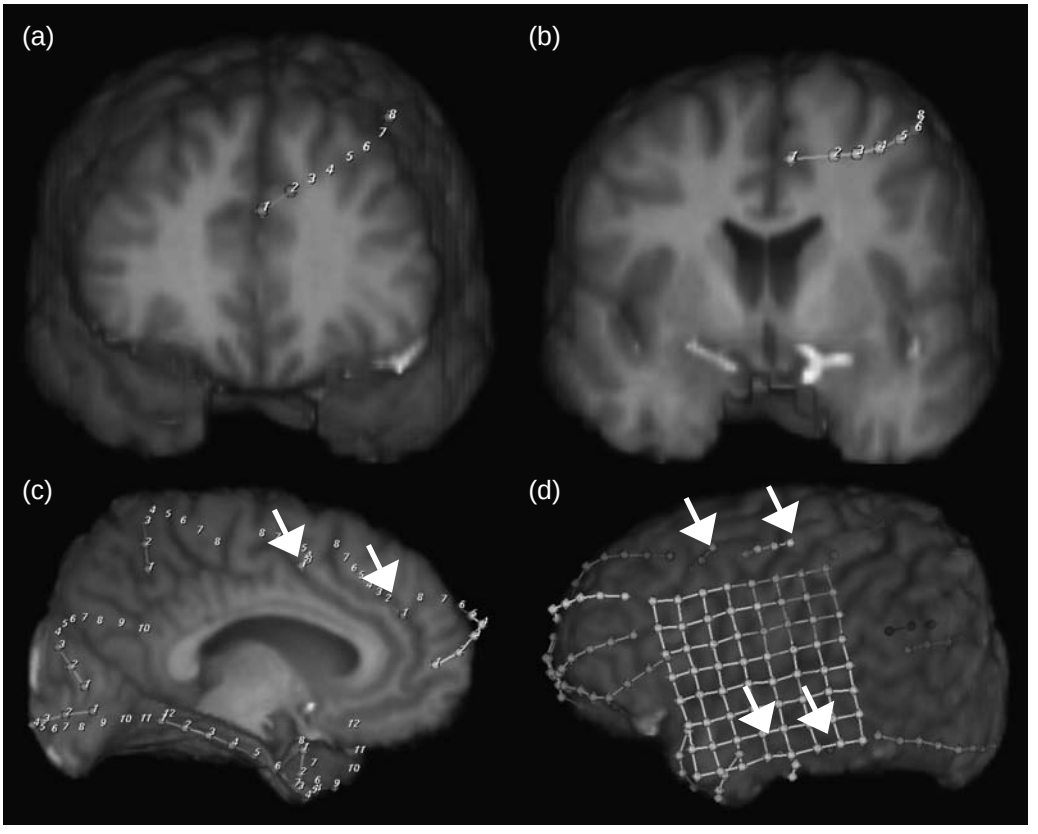

Figure 103.3 Reconstructions of electrodes trajectories for medial frontal monitoring. A – coronal reconstruction of a left anterior cingulate (AC) depth electrode. B – coronal reconstruction of a supplementary motor area (SMA) depth electrode. C – interhemispheric reconstruction of the above mentioned electrodes. Arrows point to the SMA and AC depths. D – left lateral view of the same depths. Upper arrows indicate the AC and SMA depths. Inferior arrows also demonstrate the medial temporal lobe depths.

acquired and a surgical plan devised prior to taking the patient to the operating room. This allows for a rapid start of the case on the day of surgery. Furthermore, application of the frame can be quite distressing to the patient and this step is obviated.

Freehand application of orthogonal depth electrodes has also been reported with acceptable accuracy. Davies *et al.*[2] placed 15 electrodes in 12 patients and found that their average closest contact was 0.8 mm from target, with 11⁄15 actually being in or abutting the hippocampus and all were capable of capturing ictal events. It is not a viable technique, however, for longitudinal placement and theoretically has a higher risk of hemorrhage as vessels along the trajectory cannot be accounted for. It does, however, reduce operative time and the need for additional imaging.

Finally, Song *et al.*[12] describe a combination of frameless navigation and neuroendoscopy for the placement of longitudinal hippocampal depth electrodes. Using frameless stereotaxis, a trajectory is developed for introduction of the endoscope into the atrium of the lateral ventricle. Then, under endoscopic visualization, the electrode is passed into the temporal horn along the hippocampus, without actual penetration of the tissue. Plain film radiography is used intraoperatively to

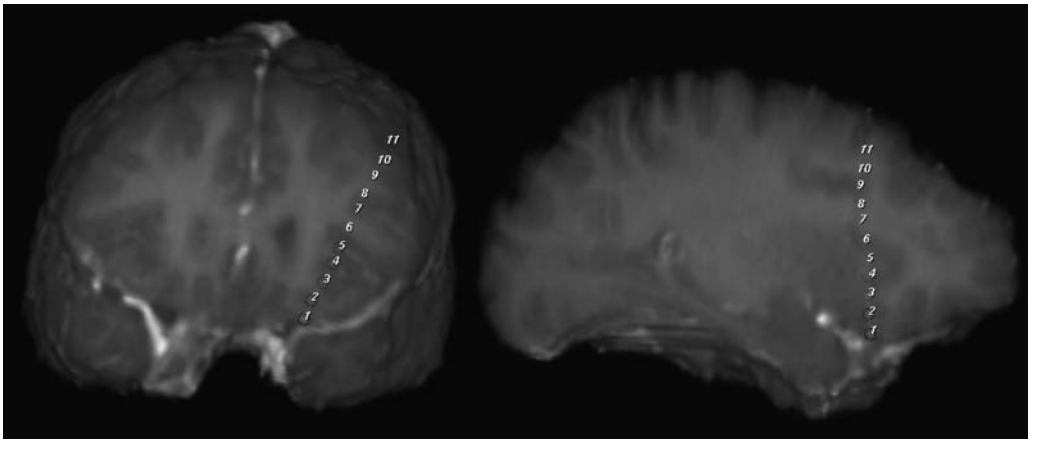

Figure 103.4 Coronal and sagittal reconstructions of an orbitofrontal depth electrode.

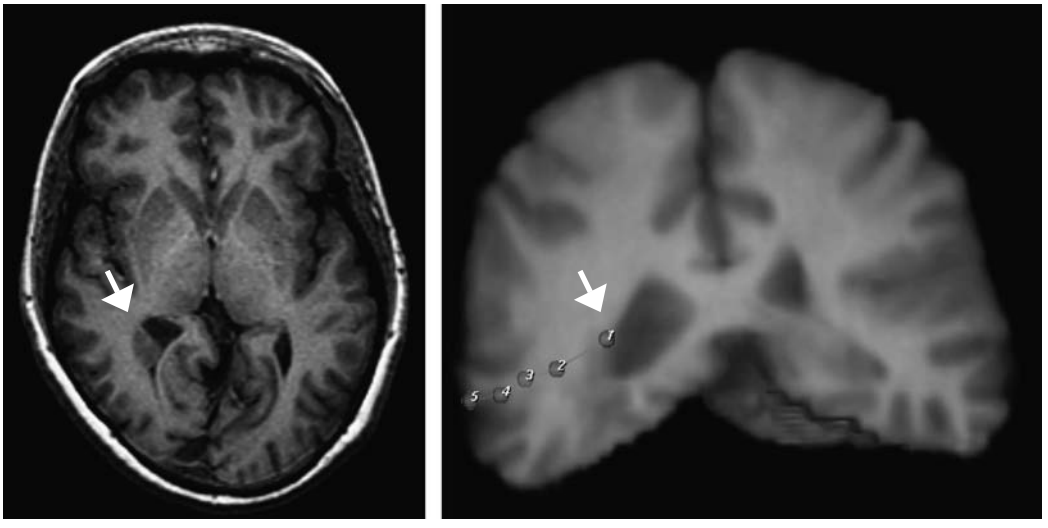

Figure 103.5 Use of depth electrode monitoring of a periventricular heterotopia. A – axial T1 weighted MR with arrow pointing to the heterotopia. B – reconstruction of the path of the depth electrode used to monitor electrographic activity.

verify an appropriate trajectory. CSF pulsations do not appear to degrade the recordings. Because the electrode does not actually traverse tissue, this method offers the advantage that the non-resected hippocampus is not injured. Although the clinical significance is not known, it certainly confers a theoretical advantage.

Once the electrodes are placed, they are tunneled several centimeters and secured by a suture to the scalp. Purse string sutures are also placed around each electrode to decrease the leakage of CSF. A generous head wrap is applied and the patient is taken to the ICU for overnight observation. Postoperative imaging is usually obtained the next day to document the actual location of the electrodes. Post placement imaging is routinely performed to assess the accuracy of the electrode placement. While plain film can certainly demonstrate at least gross localization, MRI yields the most detailed information and lends itself to three dimensional reconstruction programs. Davis *et al.*[13] performed a study to verify the safety of MRI with respect to the scanning of electrodes made from stainless steel, platinum, and nickel-chromium alloy. Placement of 143 depths, 688 subdural strips, and 38 subdural grids was evaluated on a 1.5 T MRI unit. T1, T2, and spoiled-gradient sequences were obtained and no patient had an adverse neurological event.

The patient is typically maintained on antibiotics only for 24 hours and steroids are tapered off over 3–4 days. On postoperative day 1, the patient is transferred to the epilepsy monitoring unit to continue recording.

The above discussion was directed mostly at the placement of depth electrodes into the hippocampus. Depth electrodes can be used in a number of different locations including in perilesional areas, deep frontal lobes, the hypothalamus, the thalamus, and the subthalamic nucleus. The technique for insertion remains essentially the same just with different targeting. Most experience with these alternative locations, especially the deeper locations is with framed systems.

As with any surgery, the decision to proceed must weigh the potential gains versus the potential risks. The overall risk associated with depth electrode placement is 1–4% with most risk falling into one of two categories: hemorrhage or infection. In preparation for surgery, aspirin and nonsteroidal anti-inflammatory medications are stopped and for patients on valproic acid, a bleeding time is assessed. If it is prolonged, the medicine is stopped, due to its documented adverse influence of platelet function. Specific surgical technique may also reduce the risk of hemorrhage. Using a burr hole where the cortical vessels can be adequately visualized and coagulated is safer than using a small twist-drill hole. Improved intraoperative imaging and guidance is beneficial as well. The entire tract along which the electrode is to be placed can be assessed for the presence of vessels. Additionally, limiting the number of electrodes to that which is truly essential reduces the numbers of passes through the brain and thus reduces the risk of hemorrhage as well. The risk of hemorrhage with permanent sequela ranges from 0–0.8% and hemorrhages without permanent deficit occurred approximately 0–4%.[9]

With regard to infection, the rate is approximately 0–4%.[9] Some institutions prophylax their patients with intravenous or oral antibiotics for the duration of implantation. However, there is not convincing data to support that practice,[14] so many simply perform standard perioperative dosing, and discontinue antibiotics after twenty four hours. Another technique that reduces infection is ensuring that each lead is individually tunneled several centimeters from the incision and a purse string suture is placed around the lead to minimize CSF leak. Most infections can be successfully treated with removal of the leads coupled with intraventous antibiotics. Cerebritis and abscesses are extremely rare. Of note, two cases of Jakob-Creutzfeld have been reported, so electrodes should not be reused.

Some controversy does exist about the ability of depth electrodes to provide information that subdural strip electrodes cannot. Spencer *et al.*[15,16] noted that 168 of 181 temporal lobe seizures presented in the hippocampal depth electrode in advance of presentation in the subdural strip, sometimes by as much as 70 seconds. It was further noted, however,

that 21 of 105 events captured with the hippocampal electrode, never appeared in the SDSEs. Twelve of those events were simple partial seizures, but even nine complex partial events were missed. Based on that they reported that depth electrodes were approximately 20% more sensitive that subdural strip electrodes in detecting mesial temporal seizures.[15] Seizures from patients with bilateral strip and depth electrodes were also analyzed for spread pattern and it was noted that the pattern of spread never showed epileptiform activity in the contralateral neocortex prior to the ipsilateral neocortex, thus in their data, the SDSE never provided falsely lateralizing data.[15–18] Ultimately, they felt a combination of subdural strip and depth electrodes were most effective as the sdse were useful in detecting the uncommon patient with neocortical temporal lobe or extratemporal lobe epilepsy and they were useful for studying spread patterns that are sometimes prognostically relevant. Sperling and O'Connor[19] did report rare instances of falsely lateralizing data from SDSEs when compared to depth electrodes.

Davies *et al.*[2] however, found that although the depth electrode may detect mesial temporal seizures slightly earlier by 2–3 seconds, that no novel information was gleaned from the depths and that every seizure did appear in the SDSE.[2] Eisenshenck, *et al.*[20] noted that false localization did occur between depth subdural electrodes in approximately 15% of seizure events, but was seen when the subdural electrodes were placed suboptimally and specifically, lateral to the collateral sulcus. With regard to SDSE placement, Cohen-Gadol and Spencer[21] note that a newer technique for placement may provide more accurate information. Instead of placing the strips subtemporally perpendicular to the long axis of the lobe, placement is in the anterior-posterior axis around the temporal pole just underneath the lesser wing of the sphenoid. This passage provides extensive mesial coverage. It has yet to be confirmed that this SDSE provides sufficiently similar data to hippocampal depth electrodes to be used in their place.

To justify the use of invasive monitoring, there has to be a substantial number of patients that have localizable seizure foci and that ultimately go on to have excellent seizure control following resection. Ross *et al.*[8] reported on their results over three years comparing their temporal lobe epilepsy patients that did and did not require invasive monitoring. They found of 50 patients on whom they performed invasive monitoring with combined depth and subdural electrodes, 37 were found to be good candidates for temporal lobectomy, 36 underwent the surgery, and 69% were seizure free following resection. In comparing that to their patient population who underwent lobectomy without invasive monitoring, 70% of that group was seizure free. So the results of resection were nearly identical and because of intracranial monitoring, they were able to offer resection and ultimately seizure control to a substantially larger group of patients.

Although most studies comparing subdural and depth electrodes involve the mesial temporal structures, there are case reports of extratemporal lobe epilepsy where depths were critical for detection. Privitera *et al.*[22] report the case of a patient with MRI occult focal cortical dysplasia that was not detected by subdural electrodes that was subsequently detected by depth electrodes. The patient was found to have an epileptogenic area approximately 2 cm below the sensory cortex with depth electrodes that did not demonstrate abnormalities on the overlying subdural electrodes. Following resection of the area detected by the depth electrode, the patient experienced a 95% reduction in seizures.

More recently, depth electrodes have been used in less conventional ways. With interest in deep brain stimulation for epilepsy management increasing, depth electrodes have found new used. Dinner *et al.*[23] performed a study on four patients by implanting bilateral subthalamic nucleus (STN) depth electrodes and simultaneously recording scalp and STN activity. They found that activity, both interictal and ictal, recorded from scalp EEG was also represented in the ipsilateral STN which may ultimately lead to novel treatment options.

Future

Currently, depth electrodes, or perhaps more properly probes, sample the electrical activity of structures with the brain or are also used for microdialysis in order to examine the concentrations of substances in the CSF. Centers are looking at a number of different devices to add to these probes to gather other types of information about the tissue of interest. Probes for pH, oxygenation, calcium and enzyme-linked probes for a number of different molecules are either being designed or are being used in investigations. Additionally, research is being done to provide 'smart' electrodes that house their own pre-amplifiers, analog to digital converters, wireless broadcast mechanisms and power sources. Phase 3 studies are also underway for implantable devices that continuously sample EEG activity and provide electrical stimulation to interrupt seizure activity through both subdural strips and depth electrodes (Neuropace, La Jolla, CA). Until an efficient means becomes available to monitor the electrical, magenetic and/or chemical changes in 3D space from a remote location, it is likely that depth electrodes will continue to play an instrumental role in the investigation of patients with epilepsy.

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104 Stereoelectroencephalography

D Hoffmann, GL Russo, and M Cossu

Historical aspects of stereoelectroencephalography (SEEG)

The first successful attempts to record intracerebral electrical activity date back to the first half of the past century. In those decades, during which the technique of intraoperative recording from the cerebral cortex in epileptic patients had been developed by Penfield and Jasper,[1] intracerebral electrodes began to be placed with the aim to record from subcortical structures, mainly in order to elucidate the role of basal nuclei in 'petit mal'[2,3] as well as to investigate cases with presumed 'centrencephalic' seizures.[4,5] In several studies electrodes were placed using a rough 'free hand' technique, which resulted in largely imprecise targeting of intracerebral structures.[6–8] Furthermore, despite a trend towards chronic recording was progressively developing, the primary goal of inserting intracerebral electrodes was to record interictal stationary spike discharges, in this way depending on the same concepts established for intraoperative electrocorticography.

Some new essential issues were addressed by two crucial methodological landmarks in the development of presurgical evaluation of epileptic patients, namely the employment of stereotactic approaches for the targeting of intracranial structures and the introduction of the concept of Epileptogenic Zone (EZ).

Stereotactic devices for use in humans were designed in 1947 by Spiegel and Wycis,[9] and their employment in recording from deep brain structures is reported since 1950.[10] Stereotactic placement of intracerebral electrodes gained popularity and it was reported for the evaluation of temporal lobe epilepsy in the early 1960s.[11] Meanwhile, in the Neurosurgical Unit of the Saint-Anne Hospital in Paris, France, stereotactic investigations of epileptic patients with intracerebral electrodes were inspired to a newly elaborated concept: epileptic seizures were regarded to as a dynamic process, with a spatial-temporal, often multidirectional, organization, which is best defined referring to a 3-dimensional arrangement.[12–15] The site of origin and of primary organization of this dynamic process in focal epilepsies, whose surgical removal results in control of seizures, was defined as the EZ.

With these premises, the Saint-Anne group developed the methodology of stereoelectroencephalography (SEEG),[16,17] which enabled to address the complex requirements of defining in the 3D space and time the organization of the ictal discharges by tailored 'explorations' (arrangements of intracerebral electrodes). These were aimed to the verification of a previously formulated coherent hypothesis as to localization of the EZ, based upon available anatomo-electro-clinical findings peculiar of each single case (see also Chapter 78, Kahane-Francione). For these purposes, several needs should be satisfied: the electro-clinical definition of epilepsies must rely on the recording of spontaneous seizures, and not be limited to recording of static interictal electrical abnormalities; the structures presumed to be involved in the ictal electrical onset and in the primary and secondary organization of the ictal discharge should be previously defined, included in the plan of exploration and surgically reached with the precision of the stereotactic technique; unlike the early studies with intracerebral electrodes, a primary role was assigned to the exploration of cortical structures, since the dynamic organization of the ictal discharges was presumed to follow cortical trajectories. For this latter purpose, owing to the interindividual variability of cortical anatomy, the stereotactic localization of different cortical areas required an approach based on a statistically built up proportional reference system which used the intercommissural line, as identified by contrast ventriculography, as the baseline landmark. This approach enabled to incorporate the anatomy of each single patient into a flexible anamorphotic reference system.[18] Furthermore, stereotactic and stereoscopic tele-angiography provided excellent definition of the gyral and sulcal anatomy of the brain,[19,20] and allowed to plan avascular trajectories for electrode placement through a double grid mounted on the custom-made Talairach's frame.[21]

Since the pioneering experience of the Paris group, the development of modern neuroradiology and of image-fusion techniques have progressively increased the safety of the methodology and the accuracy of stereotactic targeting of intracerebral structures.[22,23] Nevertheless, the baseline concepts of a single 'stereotactic environment', where electrophysiological, morphological and functional information may be imported and entered in a dynamic process of correlation to define the 3-dimensional organization of an epileptic discharge, are still topical in the current era of SEEG and they have been relevant for the development of modern epilepsy surgery and stereotactic neurosurgery.[24–26]

Indications

In our centers, approximately 40% of resective surgical procedures in patients with drug-resistant focal epilepsy have been performed so far after chronic intracranial EEG monitoring with stereotactically implanted intracerebral electrodes (SEEG). Nevertheless, this proportion is progressively decreasing, and in the last two years it has dropped to less than 35%. This is the result of the growing experience of the teams

dedicated to selection of patients and of the refinement of available diagnostic tools, mainly in the field of neuro-imaging, which enabled to reduce the indications to invasive diagnostic procedures.

From a general point of view, invasive recordings are indicated whenever the non-invasive investigations fail to correctly localize the epileptogenic zone. This is the result of a varying degree of incoherence among anatomical, electrical and clinical findings, which is peculiar for every given patient. Although this means that indications to a SEEG exploration are usually customized to the requirements of single cases, a retrospective analysis of our experience allows to group the indications into different patterns of anatomo-electro-clinical incoherence that configure the need for invasive monitoring.[27] This issue is extensively detailed in Chapter 76 by Kahane–Francione.

Planning

General principles

The available noninvasive anatomo-electro-clinical data are reviewed to formulate a coherent hypothesis of localization of the EZ and to plan a consistent tailored strategy of exploration. This decisional process requires a good experience in the interpretation of electro-clinical patterns of focal seizures, as well as a detailed knowledge of the functional anatomy of the brain, including that of both intra- and interhemispheric connections. Furthermore, one has to take into account the intrinsic peculiarities of multilead intracerebral electrodes, which, despite a limited coverage of the cortical surface compared to subdural strips or grids, enable an accurate sampling of the structures encountered along its trajectory, from the entry site to the final impact point. In this way, the investigation may include lateral and mesial surface of the different lobes, fissural and deep-seated cortices, as well as different kinds of lesions (Figure 104.1).

The implantation strategy should be addressed to record from the regions considered the most likely origin of the discharge (including the lesion, if present) as well as from all the structures possibly involved in the organization of the discharge through the more common pathways of propagation, as suggested by available electro-clinical findings. Furthermore, one should arrange the exploration taking into consideration also possible alternative hypothesis of localization, with number and sites of additional electrodes consistent with the likelihood of these hypothesis. The aim to obtain all the possible information from the SEEG exploration should not be pursued at the expense of an excessive number of electrodes. The possible involvement of eloquent regions in the ictal discharge requires their judicious coverage, with the twofold goal to assess their role in the seizure organization and to define the boundaries of a safe surgical resection.

Patterns of explorations

The SEEG methodology emphasizes a tailored strategy of exploration, which results from the anatomo-electro-clinical features of every case, therefore rejecting a standardized arrangement of electrodes. Nevertheless, a posteriori, a number of typical patterns of coverage are clearly recognizable, and some illustrative examples of the more frequent of them will be herein detailed.

Cases of temporal lobe epilepsy with consistent anatomo-electro-clinical findings are usually operated on after noninvasive investigations. SEEG recordings may be required in patients in whom the supposed epileptogenic area, though probably involving the temporal lobe, is suspected to extend also to extratemporal areas (so called 'temporal plus' epilepsies).[28] In these cases, the main implantation patterns point to disclose a preferential spread of the discharge to the insulo-opercular complex,[29,30] to the temporo-parieto-occipital junction (Figure 104.2), or to the anterior frontal cortex. Sampling of extratemporal areas must be wide enough to provide

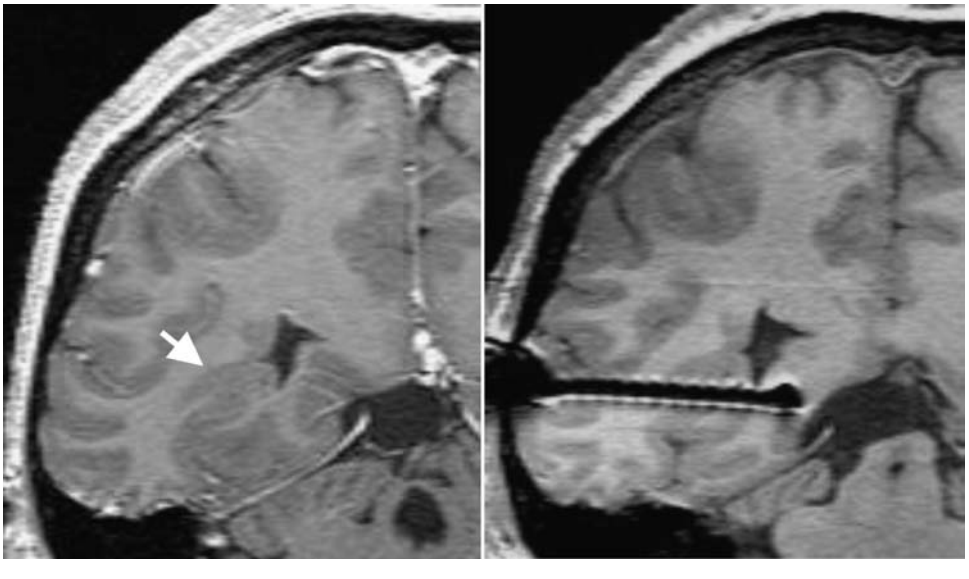

Figure 104.1 Left: pre-implant Gadolinium-enhanced T1-weighted coronal slice showing a nodular heterotopia at the right temporo-occipital junction (arrow). Right: T1-weighted 3D post-implantation MRI, coronal slice at the same level, showing an intracerebral electrode sampling the lateral cortex, the lesion and the cortex mesial to ventricular trigone. The electrode artifact generated in this sequence (as well as in the MRIs appearing in the following figures) is three-fold thick (2.5 mm) compared with the actual thickness of the electrode (0.8 mm). Single contacts on the length of the electrode are easily recognizable.

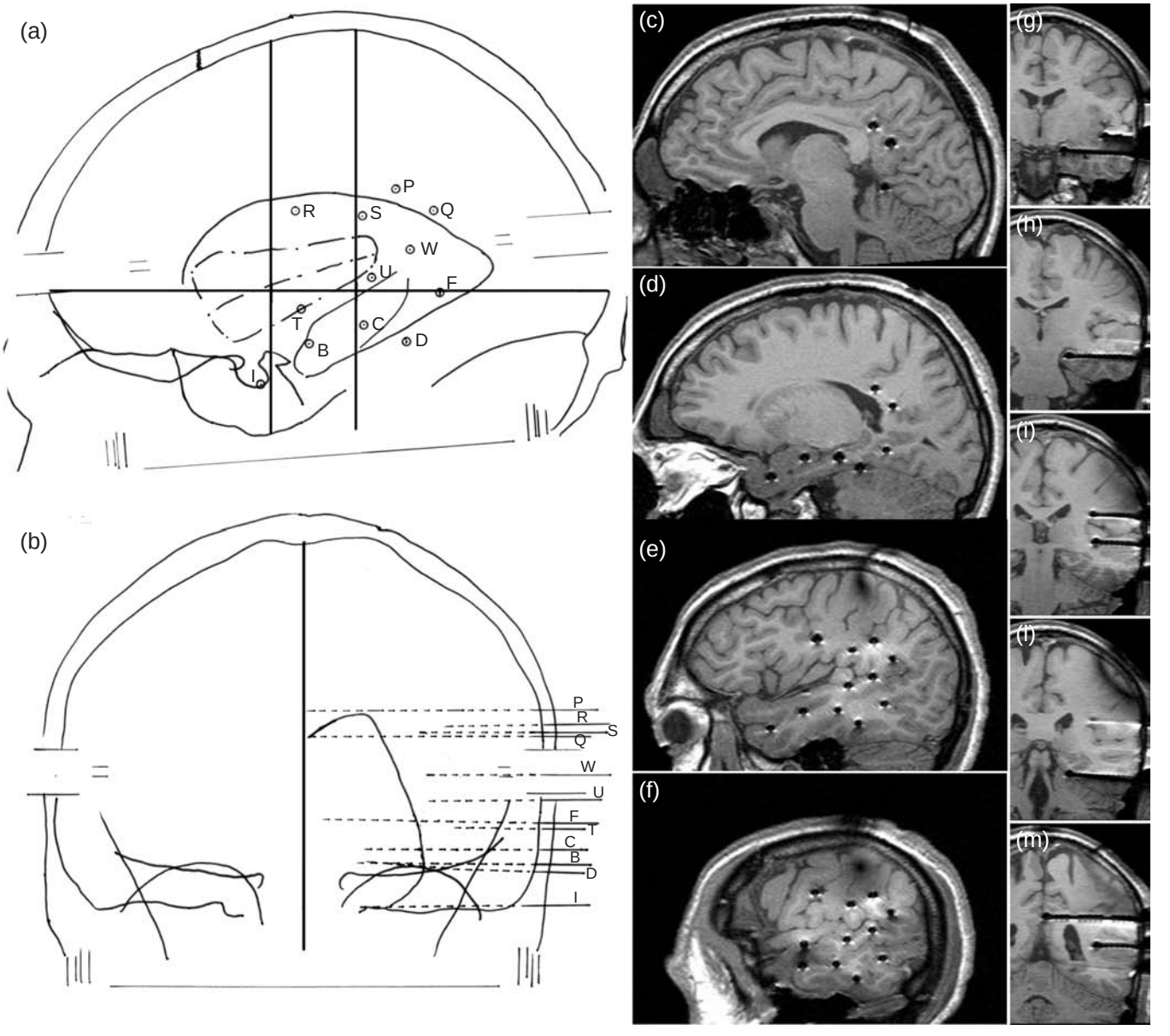

Figure 104.2 Lateral (A) and antero-posterior (B) views of the stereotactic sketch, according to the bicommissural reference system, of a left inferior temporal-parietal SEEG exploration. Electrodes are indicated with either circled dots or dashed lines labelled by upper case letters. C-F: T1-weighted 3D post-implantation MRI, where the arrangement of electrodes is shown in some sagittal slices. G–M: same MRI, coronal slices.

information also to identify a possible extratemporal origin of the seizures that could not have been anticipated with certainty according to scalp EEG and clinical findings.

Owing to the large volume of the frontal lobe, one can expect that a high number of electrodes is required for an adequate coverage of this region. In most patients, however, taking into account ictal clinical data and the related surface EEG expression, such a very large sampling can be avoided, and the exploration is focused on (but not restricted to) a more limited portion of the frontal lobe. The suspicion of an orbito-frontal epilepsy, for instance, often requires to investigate both the gyrus rectus and the orbital cortex (using oblique electrodes that also evaluate the frontal pole), the lateral fronto-basal cortex, the anterior cingulate gyrus (including Brodmann areas 32 and 24), and the anterior portion of the temporal lobe (Figure 104.3). In the same way, seizures that are thought to arise from the mesial wall of the premotor cortex are evaluated by targeting at least the rostral and caudal part of the supplementary motor area (SMA), the pre-SMA, different portions of the cingulate gyrus, as well as the primary motor cortex, mainly for functional mapping purposes (Figure 104.4). Proceeding this way, hypothesis-based sampling often allows localization of the seizure onset zone in the frontal lobe, and in some cases may allow to identify very small epileptogenic regions.[31] Occasionally, frontal lobe explorations may be bilateral, but almost always very asymmetric, because the question of the 'affected side' is usually addressed to before placement of electrodes.

Rolandic electrodes are placed when MRI shows anatomical abnormalities within or close to this region and/or when its involvement in the EZ may be suspected, with the aim to evaluate the rolandic participation to the ictal discharge and to obtain a functional mapping by intracerebral electrical stimulations. This is not infrequently required when seizures

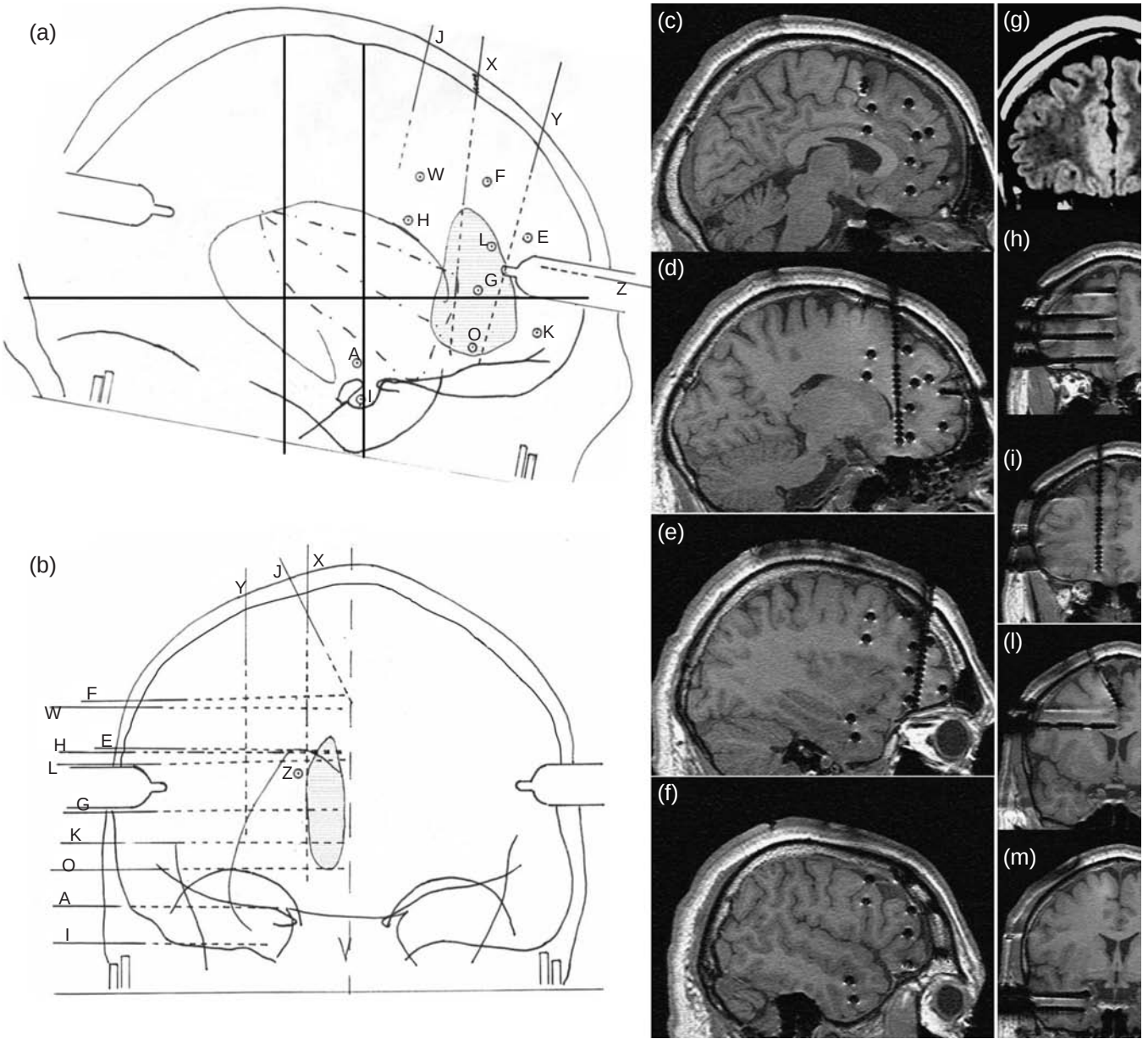

Figure 104.3 Lateral (a) and antero-posterior (b) views of the stereotactic sketch, according to the bicommissural reference system, of a right fronto-orbital and anterior temporal SEEG exploration. Electrodes are indicated with either circled dots or dashed lines labelled by upper case letters. The contoured and shaded area corresponds to a focal cortical dysplasia detected at MRI, incorporated into the stereotactic space by co-registering the 3D MRI to the stereotactic angiography. c–f: T1-weighted 3D post-implantation MRI, where the arrangement of electrodes is shown in some sagittal slices. g: pre-implant coronal T2-weighted FLAIR MRI image, showing the hyperintense dysplastic lesion on the mesial aspect of the anterior portion of right frontal lobe. h–m: coronal slices of post-implantation 3D MRI. Box h shows sampling of the lesion by the internal contacts of electrodes 'L', 'G' and 'O' (see the stereotactic scheme).

are suspected to start in the frontal or parietal lobes and to propagate subsequently to the perirolandic areas. In the central region, intracerebral electrodes are particularly helpful to sample the depth of the rolandic fissure, as well as the descending motor and ascending sensory pathways.

In the posterior quadrant of the hemisphere, placement of electrodes limited to a single lobe is extremely uncommon, due to the frequent simultaneous involvement of several occipital, parietal and posterior temporal structures, as well as to the possible multidirectional spread of the discharges to supra- and infra-sylvian regions. However, though multidirectional, posterior discharges often show a preferential spreading pattern that has to be adequately assessed by employing implantation strategies which mainly focus on parietal, occipital and temporal areas (Figure 104.5).

Technical aspects

Stereotactic neuroradiology

In all patients a cerebral stereotactic stereoscopic teleangiogram,[20] by injection of the appropriate vessels through catheterization of the femoral artery, is obtained after placement of the Talairach frame by transosseous pins and under general anesthesia.

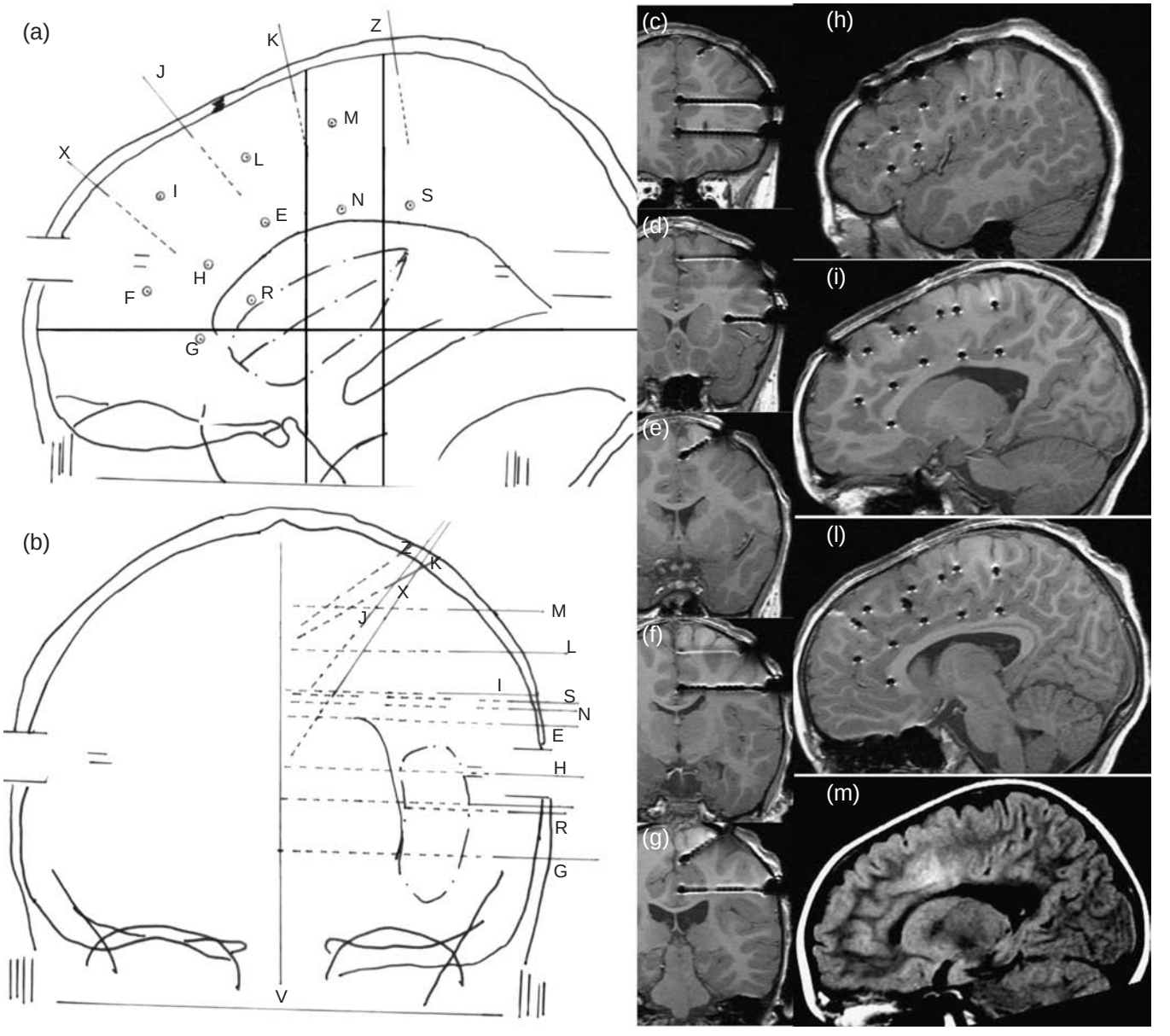

Figure 104.4 Lateral (a) and antero-posterior (b) views of the stereotactic sketch, according to the bicommissural reference system, of a left fronto-parietal SEEG exploration. Electrodes are indicated with either circled dots or dashed lines labelled by upper case letters. c–g: T1-weighted 3D post-implantation MRI, coronal slices, showing the arrangement of some of the intracerebral electrodes. h–l: same MRI, sagittal slices. m: preimplant T2-weighted FLAIR sagittal sequence, showing a precentral mesial focal cortical dysplasia, which was sampled by internal contacts of electrodes 'E', 'J' and 'L'.

The X-ray sources are placed at 5 m distance from the patient's head in order to obtain nearly distortion-free images in the lateral and anterior-posterior views. Two series of angiograms are obtained by both an orthogonal and a slightly oblique incidence (±6 degrees) of the X-rays. The coupled vision of corresponding phases of the two series enables a stereoscopic 3-dimensional effect, which is particularly helpful to distinguish vascular structures in different anatomical planes. Furthermore, 3D MR images (spoiled gradient echo T1-weighted gadolinium-enhanced sequence, slice thickness 1 mm, no gap, matrix 512×512) are imported in a computer-assisted neuronavigational module (STP 4.0, Leibinger/Fischer, Freiburg, Germany, or Voxim, IVS, Chemnitz, Germany) and co-registered with angiographic images. In this way, a stereotactic diagram may be plotted, which includes arterial and venous vessels, anatomical structures and possible lesions within the same geometrical referential space (Figure 104.6). This direct stereotactic localization procedure is employed in order to plan avascular trajectories for electrodes intended to reach well defined intracerebral structures.

Placement of electrodes

Placement of intracerebral electrodes is performed usually in a separate procedure (in order to dedicate all the time required to the accurate planning of trajectories), under general anesthesia and following refixing the frame exactly in the same position as for the previous stereotactic arteriographic study.

Several thousands of commercially available, platinum-iridium, semiflexible multilead intracerebral electrodes

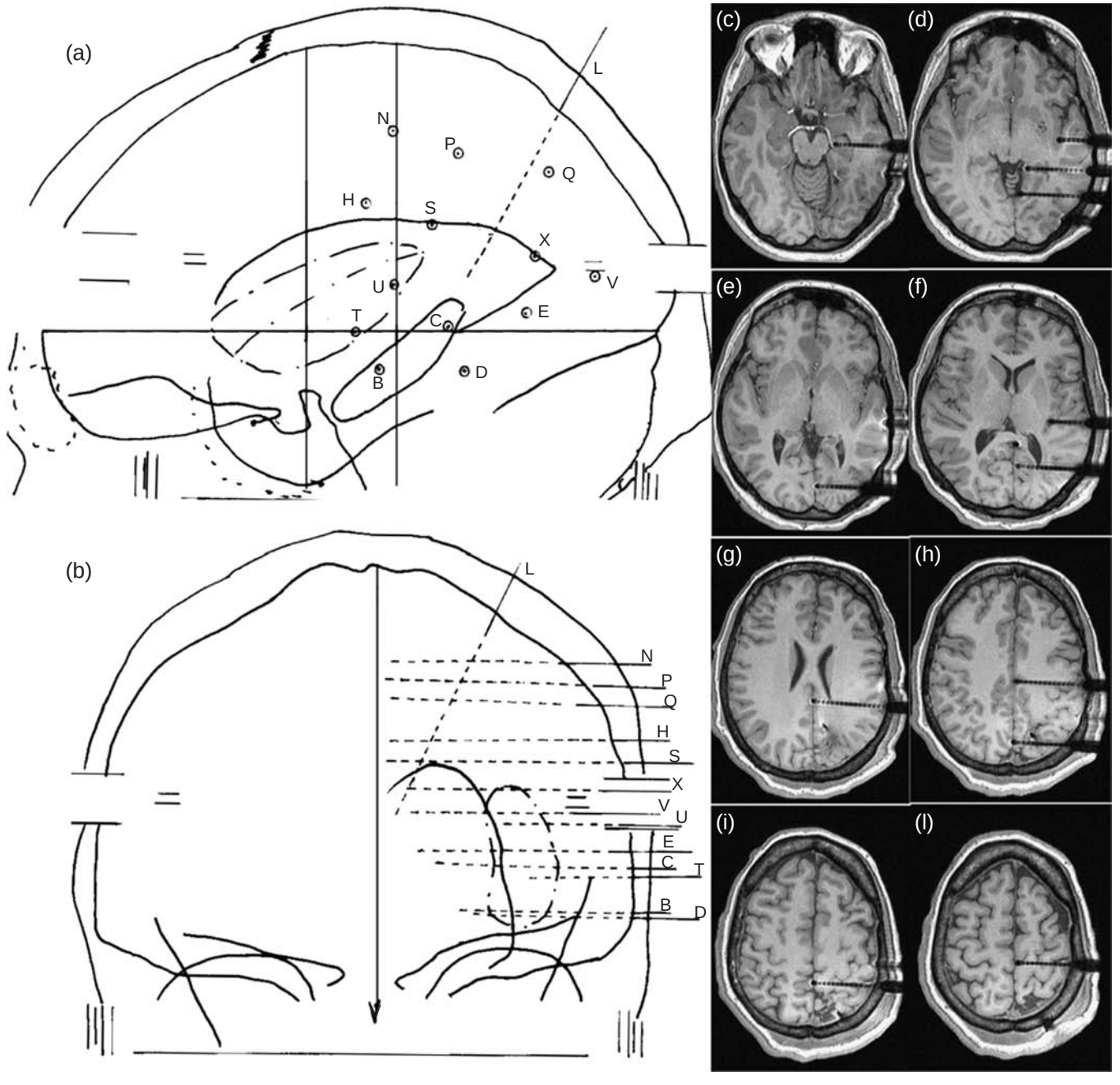

Figure 104.5 Lateral (a) and antero-posterior (b) views of the stereotactic sketch, according to the bicommissural reference system, of a left temporo-occipito-parietal SEEG exploration. Electrodes are indicated with either circled dots or dashed lines labelled by upper case letters. c–l: T1-weighted 3D post-implantation MRI. The electrode arrangement is shown in eight axial slices.

(diameter 0.8 mm; 5–18 contacts of 1.5 mm length, 2 mm apart) have been implanted so far in our Centers, the number of electrodes per patient ranging from 3 to 20 (mean 12 ± 3 electrodes/patient). The exploration is unilateral in most cases; bilateral (but not symmetrical) explorations account for less than 20% of the procedures.

Antibiotics (cephamezine, 1–2 gr i.v. depending on patient's weight in a single bolus) are routinely administered at anesthesia induction.

Electrodes may be successfully placed by either orthogonal (i.e., perpendicular to the frame 'midline' plane or, less frequently, to the 'coronal' plane of the frame itself) or oblique trajectories in all the cerebral lobes. Targeting of deep-seated or mesial structures such as the amygdala, hippocampus, cingulated gyrus, calcarine cortex is feasible, as well as excellent sampling of the insular cortex by electrodes inserted through the supra- or infra-sylvian opercula or by a retro-insular trajectory with a fronto-polar entry point (Figures 104.7–104.10).

For the implantation of each electrode, a skull percutaneous trephination is performed with a 2.3 mm twist drill, guided through metallic double grids. Alternatively, a computer-assisted robotized tool holder fully dedicated to stereotactic procedures (NeuroMate, Integrated Surgical Systems, Davis, CA, USA) which enables practically infinite degrees of freedom, is employed to insert electrodes with complex obliquities.

Figure 104.6 The lateral view of this stereotactic scheme shows several anatomical structures incorporated into the stereotactic space. The different structures are imported from the stereotactic skull X-ray film (bone profiles, black lines), from the stereotactic angiograms (profile of the insular vessels and of the sylvian fissure, dotted and dashed red line; some mesial and dorso-lateral arteries, red lines; a mesial vein, blue line) and from a co-registered 3D MRI (profiles of the ventricular cavities, violet; profile of the hippocampus, pink). The bicommissural referential system (thick black lines) has been drawn on the sagittal midline MRI slice and imported in the stereotactic space as previously described. (See Color plates.)

The dura is perforated by low-current monopolar coagulation. Minor leakage of cerebro-spinal fluid is often observed at this stage, but it does not require particular attention. Titanium hollow pegs (external diameter 2.5 mm), for the insertion and the fixation of the electrodes, are then screwed to the skull. A rigid stylet (diameter 0.8 mm) is then advanced through the peg as far as the established target under fluoroscopic control, in order to trace the intracerebral track of the electrode. After removal of the stylet, the electrode is inserted and advanced to the target. A plastic cap fixes the electrode to the peg and prevents possible CSF leakage. EEG signal provided by all implanted electrodes is checked in the operating room, enabling replacement of malfunctioning electrodes, which is however an uncommon occurrence. The cables are sutured to the skin and a sterile medication is applied. The patient is then awakened from anesthesia and moved to the recovery room.

Intensive video-EEG monitoring usually starts the day following implantation, with the purpose of recording patient's habitual ictal manifestations. After an adequate number of seizures is obtained, the patients undergo the sessions of intracerebral electrical stimulations (see below). Mean duration of video-SEEG monitoring approximates 10 days.

An MRI with implanted electrodes is obtained in all cases, in order to define the actual position of each electrode contact. Nevertheless, local artifacts generated by the electrodes may prevent the accurate anatomical location of each individual electrical contact. This technical problem can be overcome by image fusion of post-implantation MRI or CT scan and preoperative 3D MRI investigation.

Removal of electrodes

Once monitoring is completed, electrodes are withdrawn. In most patients local anesthesia is employed, though sedation may be required in less cooperative patients and children. The plastic caps are removed, then each electrode is gently withdrawn and accurately inspected in order to check its integrity. Once all the hollow pegs have been unscrewed, a skin suture is applied to each electrode entry site and a sterile medication applied. The patient is usually discharged the day after.

Functional mapping

High- and low-frequency intracerebral electrical stimulations, delivered to pairs of contiguous contacts, have the two-fold goal to induce habitual ictal manifestations and to provide a functional map of the implanted regions.[32–34] For these issue see also the chapter by Minotti.

Intracerebral electrical stimulations performed for functional purposes enable the identification of regions related to different critical functions: primary somatomotor and somatosensory, visual, acoustic, and speech. Positive responses consist of either objective clinical events (e.g., clonic jerks of circumscribed body districts, errors in naming or reading, tachyphemia) or subjective manifestations (dysesthesic sensations, positive or negative visual and acoustic phenomena) concurrent with electrical stimulations. For primary sensory-motor functions low-frequency stimulations (frequency 1 Hz, duration of single stimulus 2–3 msec, current intensity 0.4–3 mA) are preferred.[32] In most cases, positive responses may be obtained from stimulations both in grey and white matter, thus allowing to map critical pathways extensively. Speech and visual areas are mapped using a combination of low and high-frequency (frequency 50 Hz, duration of single stimulus 1 msec, current intensity 1–3 mA) stimulations. Low-frequency stimulations are usually adequate in inducing subjective acoustic changes, the effect of high frequencies resulting often unpleasant for the patient.

Chronic intracerebral seizure monitoring coupled with functional mapping is crucial in distinguishing between patients with early ictal involvement of highly eloquent regions, who should be excluded from surgery, and those with later spread of the discharge to these structures, who can be operated on with limited surgical risks and with predictable benefit on seizures. Functional mapping allows to anticipate potentially acceptable postoperative deficits, such as visual field defects in posterior temporal, occipital and parietal resections, as well as to evaluate the risk-to-benefit ratio of excisions close to more critical regions, such as sensory-motor and language areas. Though similar functional information can be obtained also from acute intraoperative electrical cortical stimulation, the following points must be stressed. First, chronic SEEG intracerebral electrical stimulations makes mapping of both cortex and fibres feasible, allowing to plan safer resections also in potentially critical subcortical areas. Second, availability of functional information before and not during surgery allows the patient to participate in the discussion of the risk-to-benefit balance in a relaxing and comfortable setting. Third, intraoperative electrocorticography only exceptionally results in spontaneous seizures recording, which is essential in evaluating the actual ictal involvement of eloquent areas.

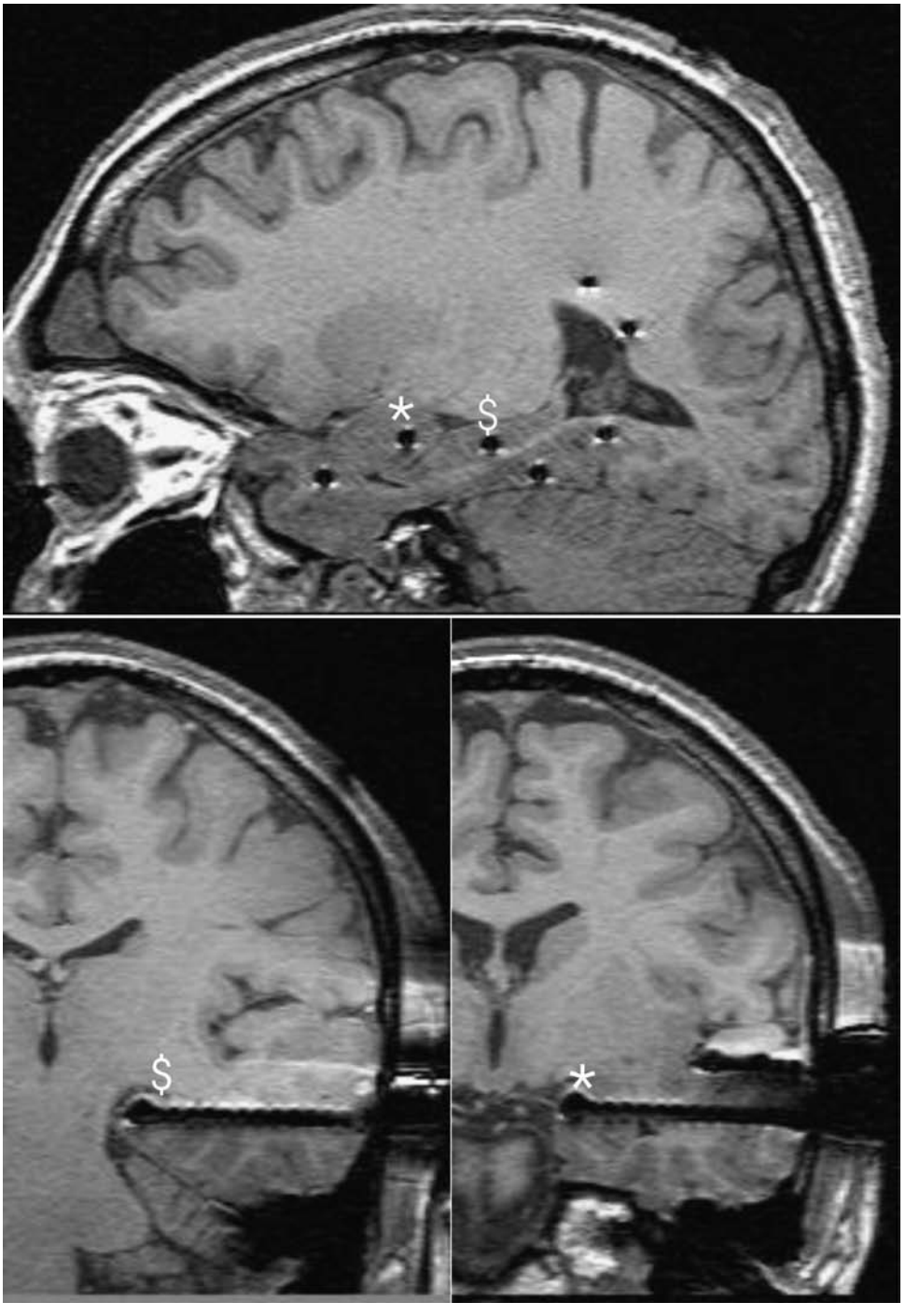

Figure 104.7 T1-weighted 3D post-implantation MRI. In the sagittal slice at the level of the left mesial temporal structures electrodes sampling the amigdala (*) and hyppocampus ($) are highlighted. The coronal slices are parallel to the trajectories of the two electrodes.

SEEG-guided thermo coagulation

Though SEEG is merely a diagnostic tool, the employment of this technique for possible therapeutic purposes has been suggested.[35] Following a complete SEEG monitoring, intracerebral electrodes may be used to generate focal lesions of the SEEG-defined EZ. A thermocoagulation with a diameter of 5–7 mm is produced by a radiofrequency generator connected to adjacent electrode contacts. By these means, a variable number of lesions may be produced in the cortical areas selected according to the SEEG data, with no relevant morbidity. Preliminary results are encouraging, with 15% of patients seizure free and 40% with significant improvement after the procedure.[35] This technique, though deserving further evaluation in order to assess its feasibility, safety and efficacy, has been proposed as a possible option in cases with a limited and well-confined EZ, or when resective surgery is contraindicated.

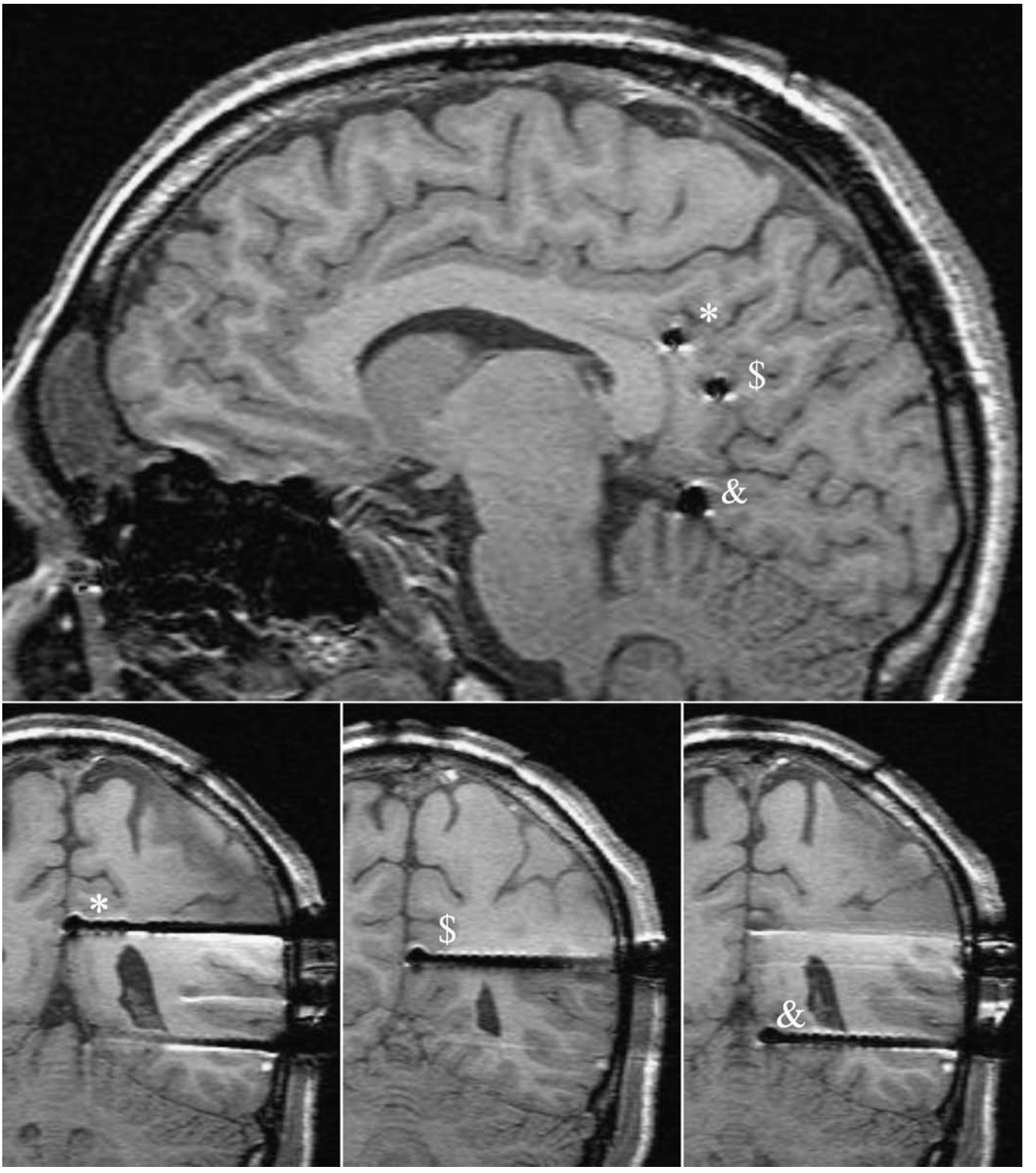

Figure 104.8 The sagittal slice of the T1-weighted 3D post-implantation MRI details electrodes sampling the parietal portion of the cingulated gyrus (*,$) and the anterior portion of the lingual gyrus (&). In the lower row the same electrodes are shown in coronal slices.

Morbidity

Severe intracerebral hemorrhage is the most feared complication of intracerebral electrode placement.[36] Talairach and Bancaud,[16] in a series of 560 cases, report three cases (0.5%) operated on for removal of intracerebral hematomas which developed after SEEG implantation. It is not clear whether these authors observed other cases with intracranial bleeding which did not require surgical treatment, but it is unlikely that such cases were diagnosed by the neuroradiological techniques available in the pre-CT scan or MRI era, even if mild neurological impairment was evident following implantation

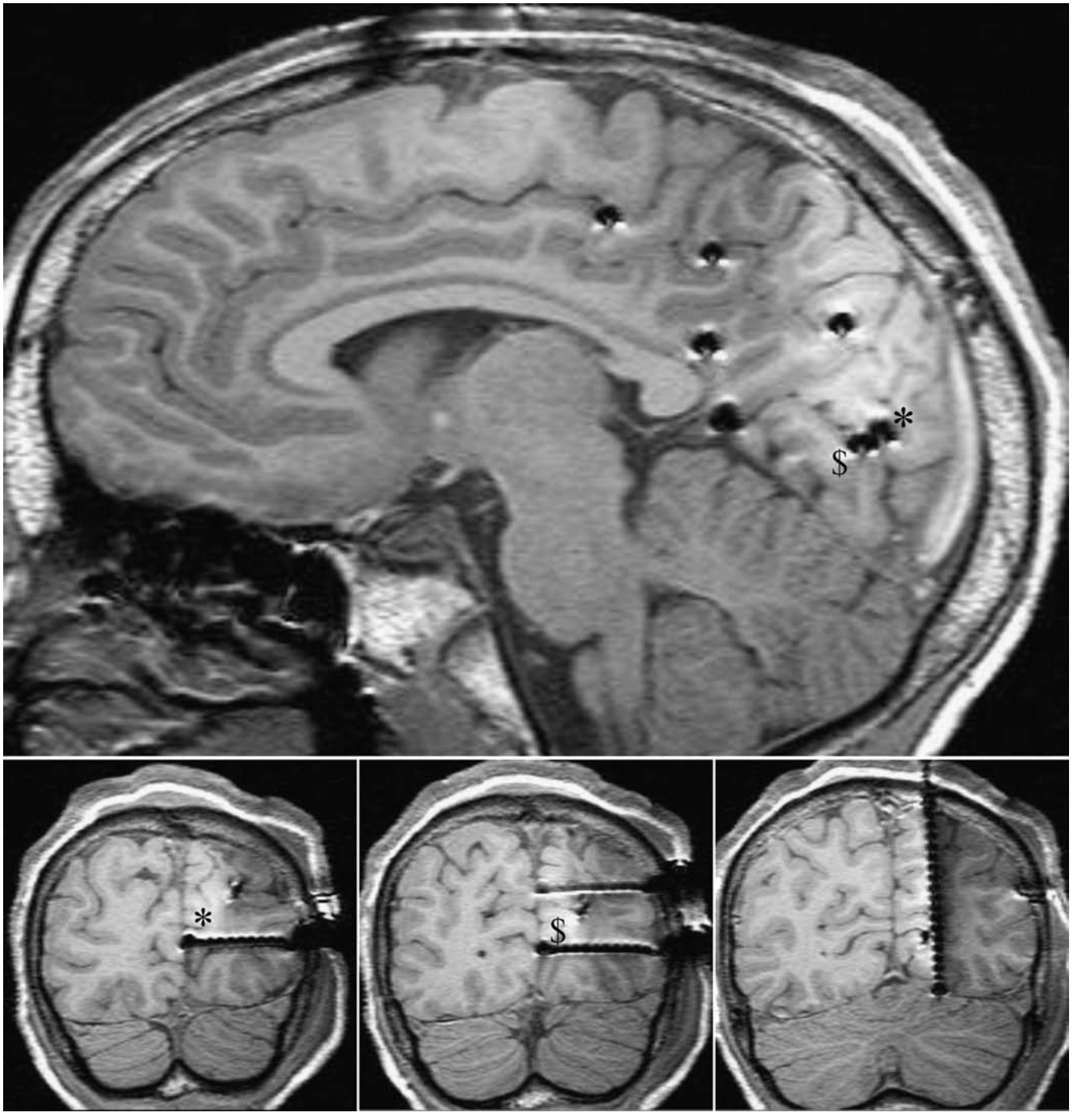

Figure 104.9 The sagittal slice of the T1-weighted 3D post-implantation MRI details electrodes sampling the superior (*) and inferior ($) lips of the left calcarine fissure. In the lower row, the same electrodes are shown in the coronal slices (left and centre). A different trajectory has been employed for an additional electrode which encroaches the calcarine fissure with an entry point in the parietal parasagittal cortex (right).

of intracerebral electrodes. The MNI group experienced one subdural bleed out of 170 cases (0.6%) investigated with intracerebral electrodes.[37] Mortality has also been associated to such complication. Engel *et al.*,[38] in a series of 140 patients, reported two deaths (1.4%) from intracerebral hemorrhage. In a series of 100 SEEG cases one death secondary to an intracerebral clot (1%) has been reported in a patient under anticoagulant treatment for deep vein thrombosis.[39]

The morbidity associated to the SEEG technique described in the present chapter has been recently reported.[27] Out of 215 procedures in 211 patients, complications of different nature occurred in 12 SEEG procedures, for an overall incidence of morbidity as high as 5.6%. There were three acute symptomatic intracerebral hemorrhages which required emergency surgical evacuation, five asymptomatic intracranial bleedings detected at postimplantation MRI, one obstructive

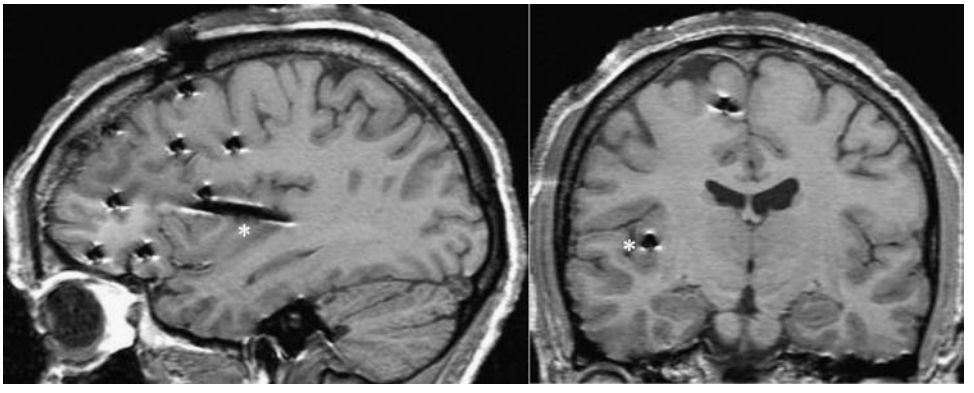

Figure 104.10 Sagittal (left) and coronal slices of a T1-weighted 3D post-implantation MRI, showing an electrode (*) placed in the insular cortex with a fronto-polar entry point.

hydrocephalus due to a clot in the aqueduct in a patient with a platelet disorder, one symptomatic brain abscess, one focal cortical edema and one retained broken electrode. In two cases (0.9%) a permanent motor deficit resulted from massive intracerebral bleeding. No death occurred in that series.

SEEG-guided resection

The contribution of SEEG in addressing the decision whether to operate or not, the choice of an adequate surgical strategy, and the results of SEEG-guided resections may vary among different epilepsy surgery teams.

The results of resective surgery performed relying on the SEEG methodology described in this chapter have been previously reported.[27] Temporal lobe resections have been performed in approximately 25% of the studied patients. In several of these cases the indication to SEEG recording was formulated in the previous decade and, as experience of the teams has increased with time, the rate of temporal lobe resections performed after SEEG has currently dropped to 16%, with invasive tests having been reserved to temporal lobe cases with atypical ictal clinical features[40] (or with poorly localizing ictal EEG. In most patients (75%) SEEG indicated an extratemporal or multilobar ictal onset, a proportion which is comparable to other studies,[41,42] though several reports on invasive EEG tests show a preponderance of temporal lobe epilepsies over other localizations.[43–46]

Overall surgical results on seizures show that 56% of our patients operated on after SEEG investigation are in Engel's[47] class I, with 44% of them being completely seizurefree (Engel's classes Ia and Ic). These proportions conflict with the much more favourable results obtained in patients operated on after noninvasive evaluations (in our experience, 83% in class I and 69% completely seizure-free). It has been reported that employment of invasive EEG predicts a non-favourable outcome on seizures, compared with surgery performed after a noninvasive workup,[48] a finding which probably reflects the particular complexity of patients who need intracranial monitoring.

In a number of patients, ranging close to 13% in our centers, SEEG findings may provide contraindications to resective surgery for different reasons. First, bilateral or multifocal ictal onsets of the epileptic discharge may be detected, a situation which per se does not match a fundamental prerequisite of the surgical treatment of focal epilepsies by resective procedures. Second, coupling electro-clinical monitoring to functional mapping may disclose that not-resectable highly functional cortex is involved by the ictal onset or by the early spread of the discharge. Third, SEEG may fail to define the EZ, indicating that the previously elaborated hypothesis of localization was incorrect. The literature reports a 10–20% rate of poor localization after invasive recordings.[49,50] In this regard, no consensus exists on whether such patients should be considered for repeated invasive tests or not. In our experience, the few patients who received a double exploration before surgery had, at their first evaluation, ictal SEEG evidence of an EZ partially covered by the exploration at the margins of the electrode arrangement, which was therefore corrected in the second step.

Clinical example

This 22-year-old man with a negative familial history of epilepsy was born after a complicated pregnancy with repeat threats of miscarriage. Seizures started at 6 years of age, and prevailed during wakefulness. Administration of carbamazepine resulted in control of seizures for 2 years. Ten months following withdrawal of therapy seizures relapsed, and they persisted despite attempts with different antiepileptic drugs. Progressively, seizures became more frequent during sleep, occurring during wakefulness only occasionally. The patient was awakened by a subjective manifestation of discomfort at his left upper limb associated to a feeling of constraint at his throat which prevented him from speaking. Stiffening of the left upper limb, apnea, bilateral eyelid blinking and a complex hyperkinetic behavior occurred after the subjective phase. Postictally, no focal deficits were observed. A high seizure frequency was reported, with many episodes every night. Neurological examination was normal. Scalp video-EEG monitoring disclosed a possible right anterior onset of seizures.

Brain MRI demonstrated a possible focal cortical dysplasia in the right frontal lobe (Figure 104.11). According to anatomo-electro-clinical considerations, which suggested an early ictal involvement of areas exceeding the anatomical limits of the lesion, a tailored SEEG exploration was indicated. In particular, the presence of early subjective symptoms

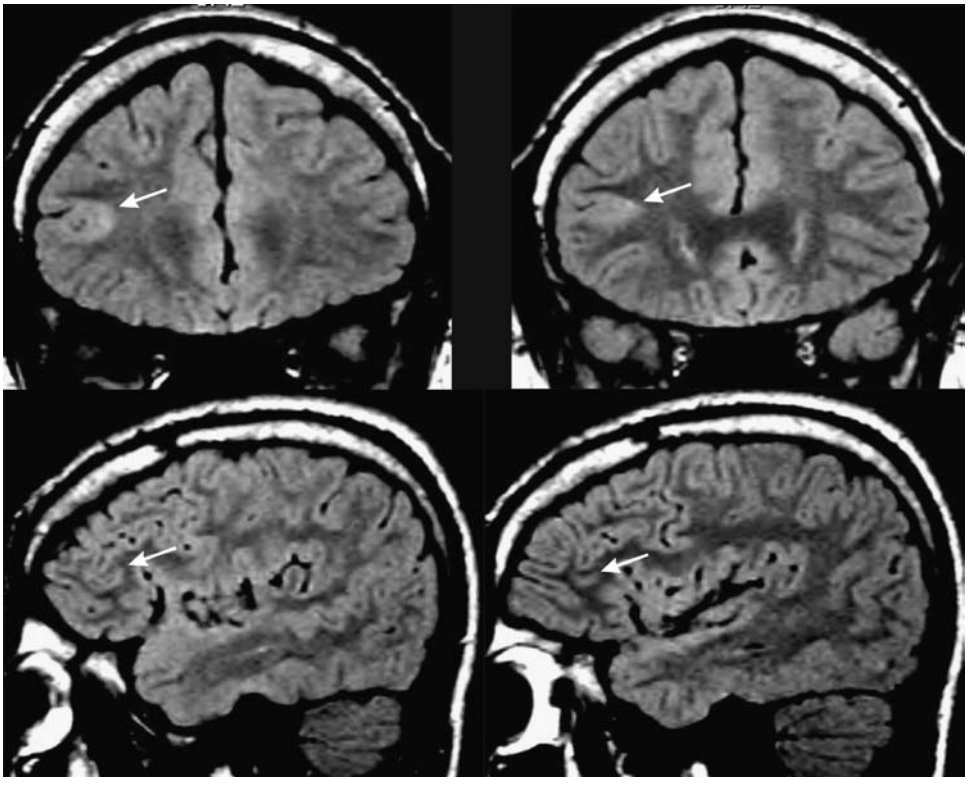

Figure 104.11 T2-weighted FLAIR MRI sequence shows a hyperintense cortical lesion in the anterior portion of the right inferior frontal sulcus (arrow) in both coronal (top) and sagittal (bottom) slices.

pertaining to the visceral domain suggested the possible involvement of the opercular-insular region. In this tailored SEEG exploration intracerebral electrodes covered dorsolateral, mesial (including different portions of the cingulated gyrus), polar, opercular and orbital aspects of the right frontal lobe, the anterior and posterior portions of the right insular cortex and the lesion disclosed at MRI (Figure 104.12). Epileptiform interictal activity, often consisting of rhythmic paroxysmal discharges with no clinical correlates, was recorded from the insular and fronto-opercular cortices (electrodes I and R, deep leads of electrode Z). Ictal discharges, recorded during 18 spontaneous seizures, originated in the same regions, with subsequent spread to the anterior cingulated gyrus (internal leads of J) and posterior-mesial superior frontal gyrus (supplementary motor area, internal leads of M) (Figure 104.13). The lesion showed only a delayed and marginal involvement in the discharge. Intracerebral electrical stimulations of the internal leads of electrode R (opercular cortex) and of insular leads of electrodes I and Z evoked symptoms identical to those experienced during habitual fits, with concomitant electrical discharges in the same sites of the spontaneous seizures.

Therefore, surgical resection of the fronto-central operculum, extended as far as the posterior aspect of the lesion, and of the suprasilvian portion of the insular cortex was performed (Figure 104.14). Histology of the 'lesional' specimen was positive for a cytoarchitectural focal cortical dysplasia, with no relevant alterations having been found in the opercular and insular specimens. It should be stressed, however, that removal of the insular cortex resulted in fragmentation of the specimens, which probably did not allow an adequate histological evaluation. One year after surgery, the patient is seizure free.

Summary

- Stereotactic placement of intracerebral multilead electrode for chronic EEG recording of seizures (SEEG) was introduced in the second half of the last century by the group of Saint-Anne Hospital in Paris, France, for the presurgical evaluation of patients with drug-resistant focal epilepsy.
- SEEG explorations are indicated whenever the noninvasive tests fail to adequately localize the Epileptogenic Zone (EZ). Currently, approximately 35% of our operated-on patients require a SEEG evaluation.
- Arrangement of electrodes in SEEG explorations is tailored according to the peculiar needs of each patient, and it is therefore customized to verify a predetermined hypothesis of localization of the EZ based on pre-SEEG anatomo-electro-clinical findings.
- Multilead intracerebral electrodes are designed to sample cortical structures on the lateral, intermediate and mesial aspect of the hemisphere, as well as deep-seated lesions.
- Planning of avascular electrode trajectories is performed employing stereoscopic teleangiograms of the pertinent vessels obtained in stereotactic conditions, co-registered to 3D T1-weighted gadolinium-enhanced MRI to improve

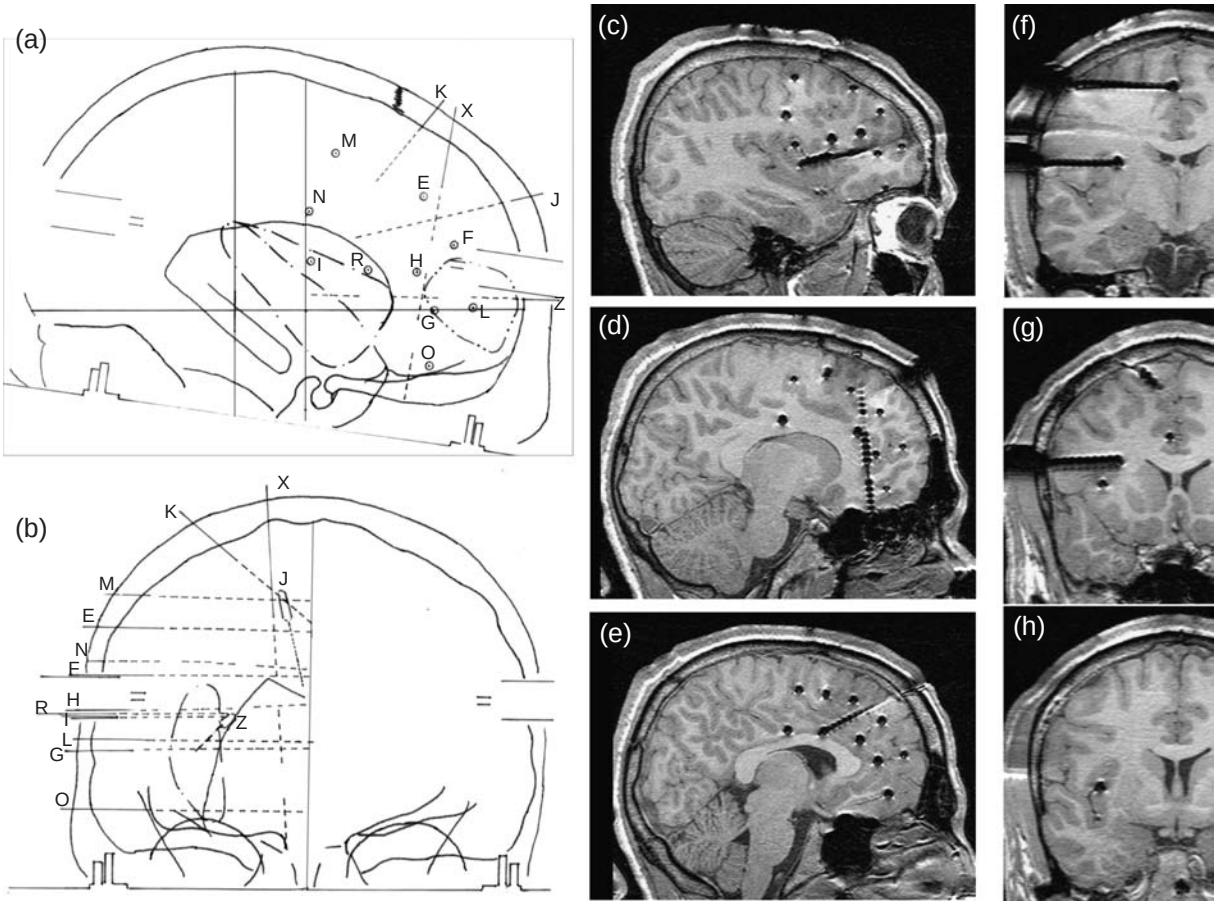

Figure 104.12 a–b: stereotactic scheme showing the electrode arrangement in this SEEG exploration. Electrodes are indicated with either circled dots or dashed lines labeled by upper case letters. The contours of the lesion, incorporated in the stereotactic space by co-registering the stereotactic angiogram and the 3D MRI, are detailed in the lateral view (double-dotted line). Electrodes 'L', 'G', and the external contacts of 'Z' sample the lesion. The insular cortex is sampled by the internal contacts of electrodes 'Z', 'I', and 'R'. In the post-implant 3D T1-weighted MRI, sagittal (c–e) and coronal slices (f–h) provide further details on the structures explored by intracerebral electrodes.

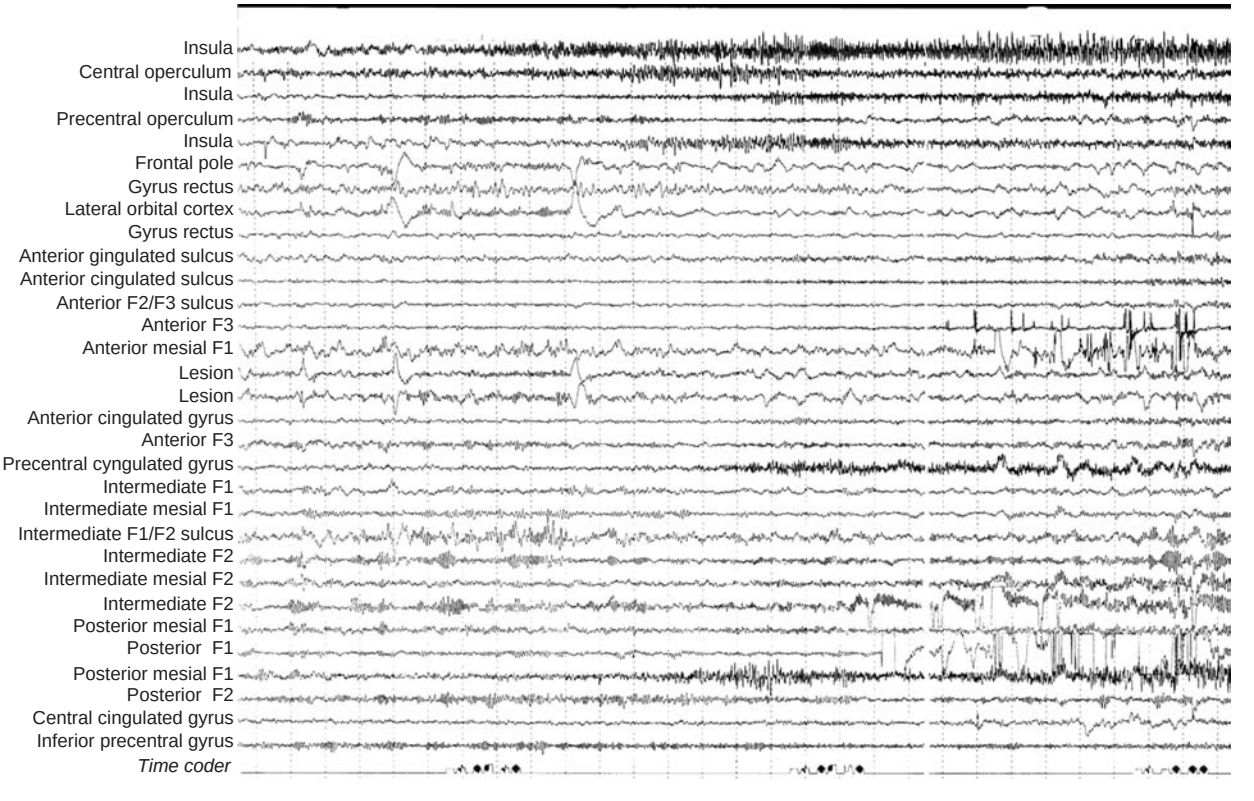

Figure 104.13 Early electrical activity during a spontaneous seizure in a synthetic montage of intracerebral EEG traces. The ictal discharge originates in the insular and opercular cortices, with subsequent involvement of the postero-mesial portion of the superior frontal gyrus (F1) and of precentral cingulated gyrus. The lesion does not show prominent ictal involvement. F2 = middle frontal gyrus; F3 = inferior frontal gyrus.

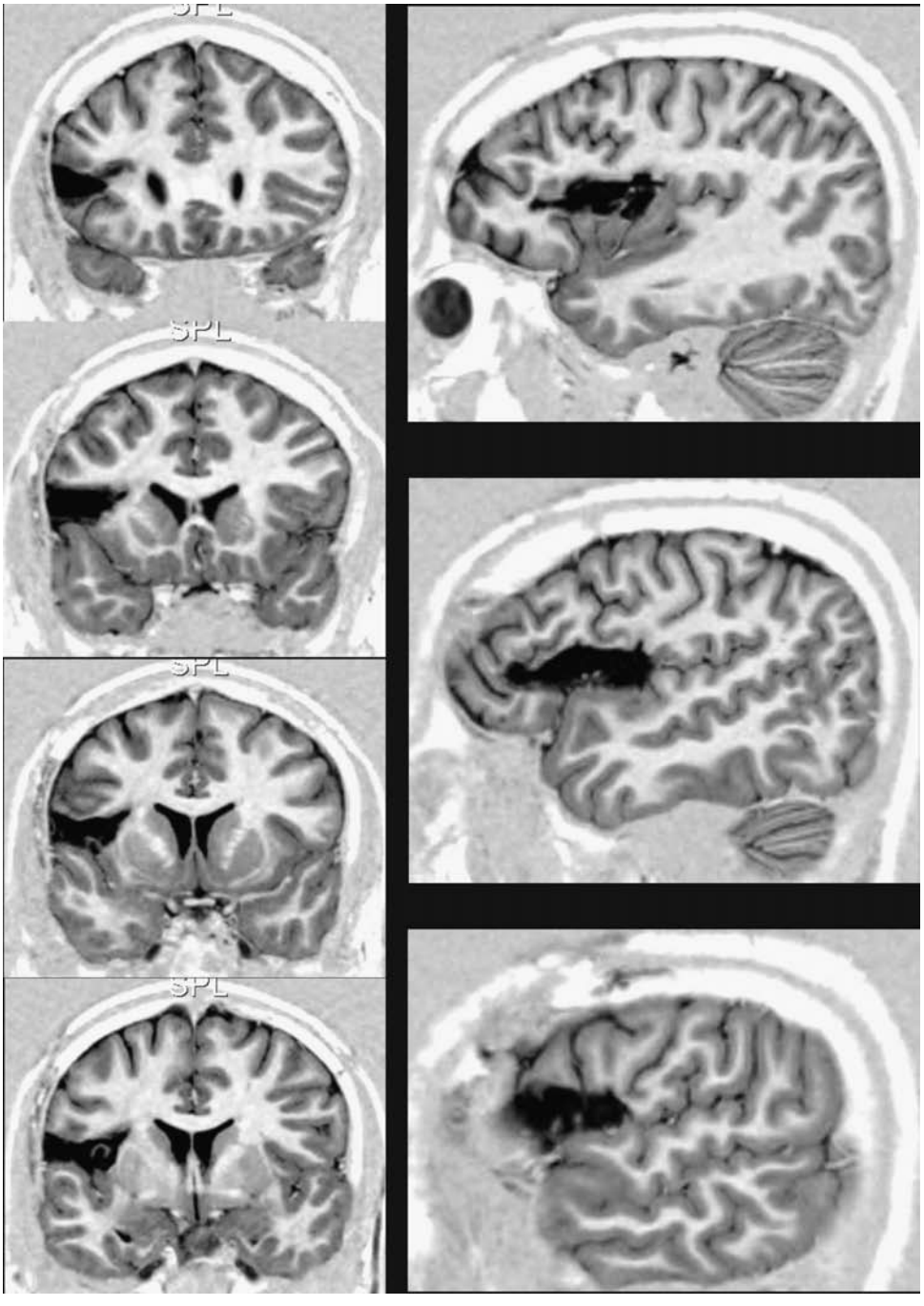

Figure 104.14 Postoperative T1-weighted Inversion Recovery MR images, coronal (left row) and sagittal (right row) slices, obtained six months after surgery, demonstrating resection of the right fronto-central operculum and of the suprasylvian portion of the insular cortex.

the targeting of the desired structures. Pre-SEEG stereotactic neuroradiology and electrode implantation are usually performed in separate procedures. Electrodes are removed once video-SEEG monitoring is completed.

- Intracerebral electrical stimulations are used to better define the EZ and to obtain a detailed functional mapping of critical cortical and subcortical regions, which enables to perform safer surgical resections in eloquent areas.
- Surgical morbidity of SEEG is reasonably low, and it mainly consists of intracerebral bleeding. Permanent post-SEEG neurological impairment is observed in less than 1% of the procedures.
- In approximately 75% of cases, SEEG evaluation enables to guide extratemporal or multilobar resections. SEEG-guided resective surgery may yield excellent results on seizures, with 56% of operated on patients in Engel's Class I.

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SECTION 14

Cortical mapping and electrocorticography

105 General principles of cortical mapping by electrical stimulation

SU Schüle, C McIntyre, and HO Lüders

Introduction

History of electrical stimulation of the human brain

The modern objective of resective epilepsy surgery is the complete removal (or disconnection) of the area of cortex indispensable for the generation of clinical seizures without causing a permanent neurological deficit.[1] Electrical cortical stimulation (ECS) has been one of the essential tools not only to instigate the beginning of epilepsy surgery but also to develop the concepts of modern epilepsy surgery.

The localization of brain function with ECS heralded the first brain surgeries and at the same time the idea that seizures may arise from an identifiable 'discharging lesion'.[2] Until the first half of the nineteenth century, the brain was believed to function as a single unit.[3] Opposing views, introduced by Frank Joseph Gall, who observed that a patient with a fencing coil wound in the frontal lobe of the brain suffered from speech disturbance, were dismissed.[4] In 1861, Pierre Paul Broca, a prominent French surgeon, reported that a localized lesion in the third convolution of the left frontal lobe of man was responsible for expressive aphasia.[5,6] John Hughlings Jackson (1864), influenced by the work of Bravais (1827) and Todd (1856) on postictal hemiparesis, supported Broca's observation and introduced the concept of focal epilepsy as a 'discharging lesion' of the brain.[2,7–9] Jackson conceived that during a focal motor seizure there is a discharge in the gray matter of the brain which begins at a local point and spreads from that point, producing a march of outward phenomena.[10] Experimental evidence to Jackson's ideas was provided by Fritsch and Hitzig (1870) who performed the first direct electrical stimulation of mammalian cortex. When they applied galvanic current through bipolar electrodes to the anterior half of the canine cerebral hemisphere, they obtained movement of muscle groups in the opposite half of the body.[11] Fritsch and Hitzig used voltaic current, i.e., direct current, polarizing the nerve cells and producing undifferentiated twitches. A few years later, Ferrier employed Faradic stimulation, i.e., alternating current, thereafter used by all investigators, and provided incontrovertible evidence for functional localization.[12]

In the following decades, animal studies using electrical cortical stimulation revolutionized the understanding of brain function and allowed the description of the supplementary motor area,[13,14] the primary auditory and olfactory cortex,[12,15] and the visual area, corroborated by the results of experimental lesions.[16] Grünbaum and Sherrington were able to separate the pre-Rolandic area for motor function from the post-Rolandic area for sensory function in anthropoids and discovered the frontal eye field.[17] Direct stimulation of the human brain to produce sensory or motor responses was first performed in 1874. A 'feeble minded' American woman in Cincinnati, Ohio, granted her neurosurgeon, Roberts Bartholow, permission to insert wires through the granulation tissue overlying the crater of an abscess in the left cerebral convexity.[18]

The ability to map human brain function with electrical stimulation revolutionized brain surgery and led to the first resective epilepsy surgeries by Macewen, Bennett, and Horsley.[19–22] However, epilepsy surgery remained focused on the symptomatogenic motor cortex and was associated with significant postoperative deficits, and consequently fell more and more out of favor when Bromide (1857) and Phenobarbital (1912) became widely available as an effective medical treatment for epilepsy.[23–27] At the beginning of the 20th century, Feodor Krause in Berlin was the only surgeon who continued to perform craniotomies on Jacksonian epilepsy in a larger number of patients.[28,29] Krause introduced faradic stimulation to map the human cortex during surgery, which until then had been used only in animal studies. His work continued to focus on the central motor area and he published the first detailed map of the primary motor area (Figure 105.1). His goal was not only to define and resect the symptomatogenic area with the help of ECS but to delineate the cortex from which the habitual (motor) seizures could be induced with weak current. He thought the area of increased irritability to stimulation represented 'das primaer kramfende Zentrum' (the primary convulsing center) which should be included in the resection.

Advancements in anesthesia permitted Cushing to perform an awake craniotomy eliciting a sensory response from the postcentral region in humans.[30] In Breslau, Ottfried Foerster continued the detailed mapping of the human cortex using local anesthesia so that the patient could report subjective responses during the operation (Figure 105.2).[31–34] He was the first to describe 'erregbare' (excitable) or 'epileptogenic' regions outside the central area, and reported on stimulation induced somatosensory, auditory, olfactory, gustatory, visual, and prefrontal symptoms. (Figure 105.2). Foerster operated in various areas of the brain and correlated the results of ECS with the immediate and 'nachhaltigen' (long-term) deficits after resection.[32,34] Foerster's seminal work coincided with the discovery of the EEG[35] and he reported the first series of intraoperative cortical EEG records together with Altenburger in 1935.[36]

Wilder Penfield, after spending time with Sherrington, Cushing, and Foerster, extended the work of Foerster through

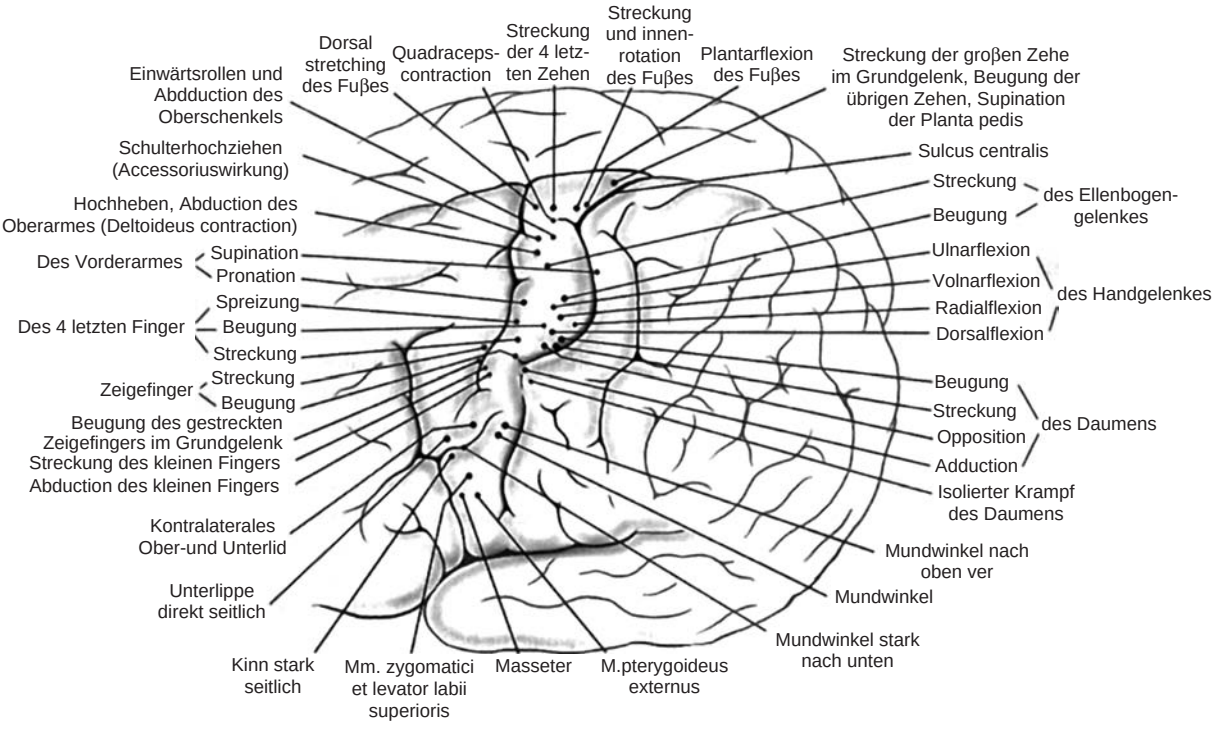

Figure 105.1 The first published map of the human motor cortex by Feodor Krause, 1911.

a more detailed mapping of cortical areas subserving speech, hearing, vision, and further refined cortical representation of sensory and motor function. The work of Penfield lead to the mapping of a posterior and superior language area, the vestibular cortex, the secondary sensory area, autonomic areas, simple, and complex psychic responses, and negative motor areas.[37,38] 'Dreamy states' associated with stimulation of the uncus were first described by Jackson. Penfield realized the high prevalence of intractable epilepsy arising from the temporal lobe and pioneered temporal lobe surgery for these patients.[39] His initial limited antero-lateral approach was influenced by the perioperative interictal EEG findings using intraoperative electrocorticography with grids over the lateral temporal region.[40] Clues from experimental animal studies and stimulation responses during surgery, however, began to point to the mesial and inferior parts of the temporal lobe as

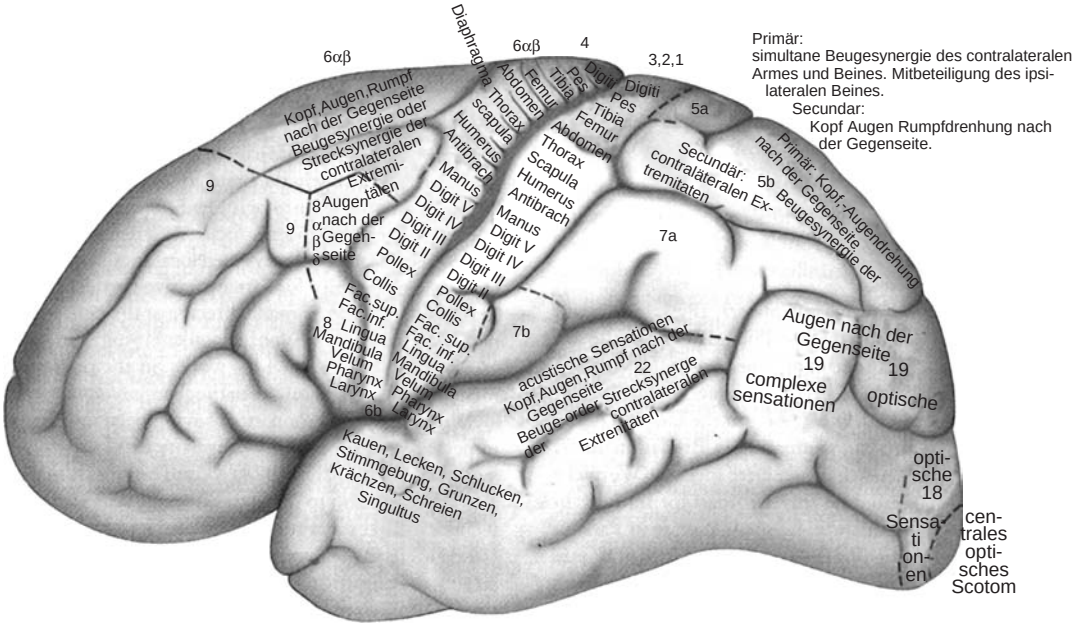

Figure 105.2 Foerster and Penfield's map of the human cortex, 1930.

the origin of the epileptic attack. Subsequent surgical series included the mesial structures in the resection improving the outcome significantly.[41–43]

In the minds of Talairach and Bancaud in France, Penfield's localization approach could only be truly applied through EEG recording directly from the involved brain structures allowing not only interictal but also ictal recordings. This goal was accomplished in 1959 when Talairach introduced a stereotactical method to accurately place numerous intracerebral electrodes which could be left in place for several days, followed by recording of electrical activity from involved cerebral structures during the course of a seizure.[44,45] Similar to Krause, Foerster, and Penfield, the French school emphasized the usefulness of electrically induced seizures to delineate the epileptogenic network to be included in the resection. In North America, extraoperative ictal recording became feasible by the work of Ajmone-Marsan and Van Buren who introduced subdural strip electrodes in temporal lobe epilepsy.[46] Epidural grid electrodes were introduced by Goldring, but proved to be less useful for simultaneous cortical mapping.[47,48] Subsequently, large array subdural plates which permitted not only invasive ictal recording but also detailed extraoperative mapping were developed.[49,50] The extraoperative mapping with ECS allowed the verification of Penfield's intraoperative results, and, with less interference by anesthesia and time constraints, lead to a revised map of eloquent language areas, and a more detailed description of the supplementary sensorimotor area, the negative motor area, and the secondary sensory cortex.[51–54]

Definition of eloquent cortex by electrical stimulation

Epilepsy surgery is based on the assumption that human functions are localized in discrete anatomical modules and that there are areas of the brain which can be resected without causing noticeable deficits.[55] Historically, electrical cortical stimulation was the first experimental technique which established the concept of functional brain localization. Based on the results of ECS the human brain was divided in 'eloquent' and 'silent' areas and it became soon apparent that the effect of stimulation was able to predict functional outcome after surgical resection.

Response to electrical stimulation includes not only positive (motor) signs which can be readily observed, but also subjective symptoms reported by the patient and negative signs which become only apparent to the patient and the examiner while testing specific functions.

Classical areas of eloquent cortex defined by electrical cortical stimulation include:

- Primary motor area (Figure 105.3)
- Primary sensory area
- Supplementary sensory motor area
- Secondary sensory area
- Language areas (Figure 105.4)
- Visual cortex
- Auditory cortex
- Negative motor area

Additional areas of functional localization based on ECS have been described but are not predictably obtained: the cortical representation of olfactory, gustatory, vestibular, autonomic, and nociceptive function.[56] Elementary emotional

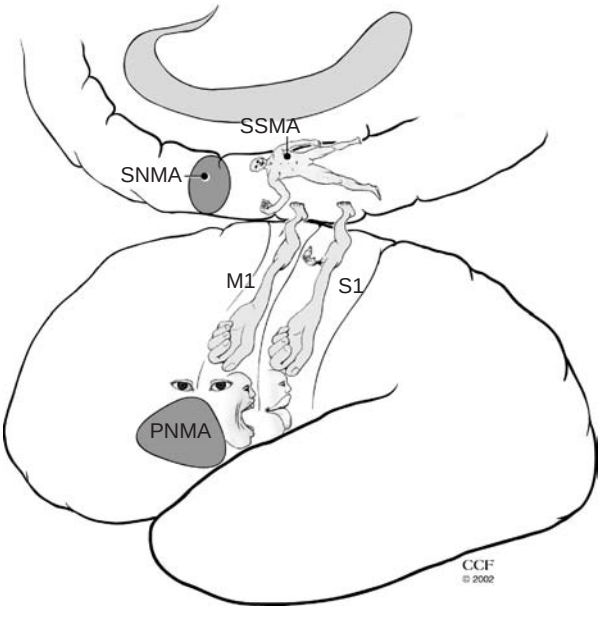

Figure 105.3 Diagram showing the location of the primary motor area (M1), the primary sensory area (S1), the primary (PNMA) and supplementary negative motor area (SNMA), and the supplementary sensorimotor area (SSMA).

responses, e.g., fearful sensations, are well localizable to the amygdala and bilateral resections are associated with noticeable impairment in the perception of fear.[57] More complex psychic responses seem to occur predominantly in patients with epilepsy including the déjà vu and deja vecu experience seen during stimulation of the temporoparietal association cortex.[37]

Negative signs associated with the localization of discrete cognitive functions have been mapped with electrical cortical stimulation, e.g., Gerstman syndrome over the dominant angular cortex.[58] However, except in unusual situations, it is impossible (because of time constraints) to check at any given electrode for interference of more than two or three specific functions. In other words, in the absence of a positive response, the possibility that stimulation of an electrode interferes with a function that was not tested for cannot be excluded. Absence of a response does not exclude functional localization for other reasons: the stimulus intensity may be insufficient to interrupt function or the area stimulated is too limited to interrupt function in larger functional networks. Notably, memory in the temporal lobes and executive function in the frontal lobes cannot be predicted by ECS and intracarotid amobarbital injection, neuropsychological evaluation, and functional MRI seem better tools for predicting preoperatively cognitive outcome in resective surgeries involving these areas. However, despite its shortcomings, electrical stimulation remains the gold standard for presurgical functional mapping, particularly in patients requiring invasive evaluations, providing the surgeon with the most accurate correlation of ictal onset and eloquent cortex.

Dispensable versus indispensable cortex

Eloquent cortex as defined by ECS may have the highest correlation with postoperative functional outcome but has to be validated with the results of surgical resections. The resection of eloquent areas may lead to no recognizable or only a temporary deficit, or may provoke a permanent, noticeable impairment for the patient or the physician during testing.

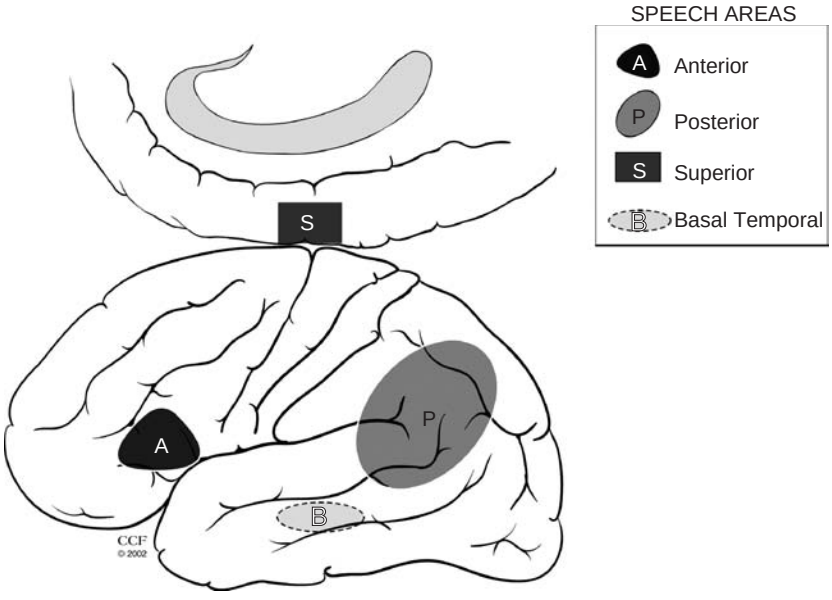

Figure 105.4 Diagram showing the location of the anterior, posterior, basal temporal language areas and Penfield's superior language area.

The benefit of neurosurgical resections often outweighs the risk of a minor or temporary deficit, but permanent deficits are usually not acceptable for most adult patients. Influenced by Foerster, Penfield introduced the terms 'dispensable' and 'indispensable' eloquent cortex to differentiate between these areas of the brain.[37,59]

Indispensable eloquent cortex:

- Primary motor area (corresponding to the distal portion of upper and lower extremity)
- Primary sensory strip
- Primary visual area
- Anterior and posterior language areas

Resections involving the primary motor, sensory and visual cortex are mostly associated with a permanent and functionally significant deficit.[59] These areas can be reliably mapped with ECS and show a well-defined contralateral somatotopic response. The language areas seem to safely allow resection up the gyrus adjacent to the functional sites based on ECS. However, there are reports that for the posterior language cortex resections closer than 1 cm to sites with stimulation-induced naming errors may increase the risk for a postoperative deficit.[60] We have not been able to confirm these observations.

Other motor areas with a positive response during ECS, the premotor cortex (possibly also including the frontal eye field) and the supplementary motor area, can often be resected without significant permanent impairment and in the context of intractable epilepsy or tumor surgery may be considered dispensable.[61,62] However, resection of these areas may produce significant acute deficits and more detailed postsurgical testing may reveal permanent but subtle changes in motor coordination or eye movement control.[63–65] Besides, most reported cases only refer to partial resections and it is unclear if more extensive resections could result in more significant permanent deficits.

Besides, resection of the face motor area which has a bilateral cortical representation has mostly a good recovery of function on long-term follow-up.[66,67] The basal temporal language area in the dominant hemisphere can lead to a temporary naming deficit which usually resolves long-term.

Dispensable eloquent cortex:

- SSMA
- Primary auditory cortex (Heschl's gyrus)
- Brodman's area 6 (probably including the frontal eye field)
- Face area of Brodman's area 4
- Secondary sensory cortex
- Basal temporal language area

Subjective factors may play a role of what constitutes a dispensable eloquent area: unilateral resection of the primary auditory cortex will not lead to any noticeable deficit for many of us, but certainly impair an orchestra conductor depending on the ability of dichotic listening. The permanent deficit after resection of the supplementary motor cortex may be subtle, however, the immediate consequences with contralateral weakness and mutism are dreaded by patient and surgeon. Age-dependant cortical plasticity has a strong impact on recovery and may allow extensive hemispheric resections with at least partial recovery in children and may become a consideration in catastrophic hemispheric epilepsy.

Predicting postoperative functional deficits in areas silent to cortical stimulation is even more complex. Most of the frontal lobe cortex, except for motor and premotor cortex, the anterior language area in the dominant and the negative motor area in the dominant and non-dominant hemisphere show no response to electrical stimulation.[66] The same is true for the parietal lobe caudal to the postcentral sulcus in the nondominant hemisphere. Experience has shown that limited surgical resections of these silent cortical areas are usually not associated with any neurological deficits.[68,69] Resection of the 'nociferous' epileptic brain, a term used by Penfield, may actually lead to improvement in cognitive function.[37,70] However, it is less defined to what extent larger surgical resections

of silent cortical areas are permissible without behavioral consequences.[71] Whereas limited unilateral frontal resections are well tolerated, bilateral lesions of the frontal lobes will produce a typical frontal lobe syndrome.[72–74] In other words, so-called silent areas most probably are involved in functions for which the brain has extensive capacity for compensation either by using adjacent cortex (when only small areas of cortex are resected) or due to bilateral representation of these functions. The fact that no deficits are detected even when the brain is inactivated acutely by electrical stimulation implies that these silent areas of the brain have extremely flexible compensation mechanisms that are immediately effective. In addition, whatever defect the excision might have produced in a completely normal individual can not to be determined. Therefore, the risk of cognitive decline can only partially be predicted by the size, location, dominance, and preoperative functional deficit.

Neurophysiological effect of electrical stimulation of the cortex

Electric field generated by cortical stimulation

The electric field generated by clinical cortical stimulation electrodes is a three-dimensionally complex phenomenon that depends on the stimulation parameters and the electrical conductivity of the surrounding medium. Experimental measurements of the field are difficult to perform, but detailed theoretical models can be constructed to study both the potential distribution in the brain and the neural response to the stimulation.[75,76] These studies show that the strength of the field directly transmitted to the brain is strongly regulated by the relative position of the electrode contact to the cortical surface, and the presence of CSF between the contact and the cortex. The high conductivity of CSF can shunt current flow around the brain, instead of through the brain, thereby increasing the stimulus amplitude necessary to generate a behavioral response.

The voltage distribution generated in the brain is the starting point for understanding the neural response to extracellular stimulation. The first derivative of the voltage distribution is related to the current density. The second derivative of the voltage distribution is related to membrane depolarization and hyperpolarization.[77,78] The stimulation induced membrane polarization interacts with voltage-gated ion channels, and given the appropriate conditions, can result in the generation of propagating action potentials that underlie the clinically observable behavioral response. The electric field is applied to the complex three-dimensional geometry of the surrounding neural processes (i.e., axons and dendrites). Each neuron (or neural process) surrounding the electrode will be subject to both depolarizing and hyperpolarizing effects from the stimulation.[77–81] As a result, a neuron can be either activated or suppressed in response to extracellular stimulation in different ways and in different neural processes depending on its positioning with respect to the electrode and the stimulation parameters.

Neural response to cortical stimulation

When electrically stimulating the brain, three general types of neurons can be affected by the applied field: local cells, afferent inputs, and fibers of passage. Local cells represent neurons that have their cell body in close proximity to the electrode (i.e., cortical pyramidal neurons). Afferent inputs represent neurons that project to the region near the electrode and whose axon terminals make synaptic connections with local cells. Fibers of passage represent neurons where both the cell body and axon terminals are far from the electrode, but the axonal process of the neuron traces a path that comes in close proximity to the electrode. Each of these classes of neurons can be activated by stimulation with extracellular sources. And, experimental measurements indicate that local cells, axon terminals, and fibers of passage have similar thresholds for activation when stimulating with extracellular sources.[82] However, activation of each different class can result in substantially different physiologic and/or behavioral output. Therefore, it is important to understand the factors that regulate the neural response to applied electric fields so accurate inferences about anatomical structures or physiological mechanisms involved in stimulation can be made.

Most work addressing the neural response to extracellular electric fields concentrates on the direct effects of the stimulation on individual neurons. When neurons are directly activated by extracellular electric fields, action potential initiation takes place in the axon because it is the most electrically excitable part of the neuron.[80,81] However, the threshold for indirect, or trans-synaptically evoked excitation (or inhibition) of local cells, is similar to the threshold for direct excitation of local cells. Indirect excitation (or inhibition) of local cells is the result of stimulation induced release of neurotransmitters from the direct activation of afferent inputs by the stimulus pulse. This stimulation induced trans-synaptic activity can be predominantly excitatory, predominantly inhibitory, or any relative mix of excitation and inhibition depending on the types and numbers of afferent inputs activated. Therefore, the interpretation of the effects the stimulation on the neural output of local cells is made up of two components: 1) The direct effect of the extracellular electric field on the local cell, and 2) The indirect effect of the stimulation induced trans-synaptic excitation and/or inhibition.

In general, the indirect effects of extracellular stimulation of local cells result in a biphasic response of a short period of depolarization followed by a longer period of hyperpolarization. This biphasic response is the result of the interplay between the time courses of the traditionally fast excitatory synaptic action and the traditionally slow inhibitory synaptic action. The role of indirect effects on the output of local cells can be enhanced with high frequency stimulation. If the interstimulus interval is shorter than the time course of the synaptic conductance, the indirect effects will summate. Because inhibitory synaptic action traditionally has a longer time course than excitatory synaptic action the effect of this summation is hyperpolarization of the cell body and dendritic arbor of the local cell. This hyperpolarization can limit the neuronal output when stimulating at high frequencies. However, because action potential initiation takes place in the axon of local cells in response to the direct effects of the stimulation, local cells can still fire action potentials in response to each stimulus pulse given that the stimulus amplitude is strong enough.[76,83,84]

Effects of stimulation parameters on cortical stimulation

The complexities of the neural response to applied electric fields are further complicated by the vast array of stimulation hardware and stimulation parameter options available. Stimulation pulse generators are either current-controlled or voltage-controlled. Voltage-controlled pulse generators are more simplistic in design, but the current delivered to the tissue is regulated by the electrode impedance, which may be variable.[85] And, the shape of the stimulus waveform transmitted to the tissue under voltage-controlled stimulation is distorted by the electrode capacitance.[86] Therefore, current-controlled stimulators are suggested for scientific investigation or clinical situations where long-term consistency of stimulation delivery is required.

Once a stimulus pulse has been generated, the physical dimensions of the electrode contact can substantially impact the shape of the resulting electric field and subsequent neural response to stimulation. Microelectrodes enable focal stimulation of targeted populations of neurons, but their small surface areas limit the amount of charge that can be safely delivered to the tissue.[87,88] Macroelectrodes enable stimulation of large volumes of tissue and are commonly used in clinical contexts, but their neural and spatial specificity of stimulation is limited. However, the focus of stimulation can be manipulated by simultaneously activating multiple contacts. Detailed computer models of the electric field generated by clinical epidural, subdural, and deep brain electrode designs have been generated.[75,76,84,89] These results show that bipolar stimulation or current steering with any number of anodes and cathodes can substantially change the shape of the electric field in the tissue.

The stimulus waveform plays an important role in the neural response to extracellular stimulation. Square waves are typically used in clinical settings; however, sinusoids or any other arbitrary waveform can also be implemented. One of the fundamental requirements of a clinical stimulation device is to use biphasic stimulus waveforms to limit stimulation induced tissue damage.[87,88] In addition, the axon represents the most excitable part of a neuron, so extracellular stimulation of fibers of passage, afferent inputs, and local cells are all regulated by the response of the axon to the stimulation.[80,81] In turn, the strength-duration properties of extracellular stimulation have a relatively short time constant of ~100 μs. Therefore, to maximize the stimulating influence of the injected charge, a pulse duration of 100–200 μs is suggested. Typically, anodal stimulation preferentially excites neural elements perpendicular to the electrode surface, and cathodal stimulation excites those with a direction component parallel to its surface. When stimulating bipolarly, the excitation of neural elements parallel to the bipole axis is additionally facilitated.[84] Manipulating the shape of the stimulus waveform can also be used to improve the neural selectivity of the stimulation. In general, local cells will be preferentially activated with anodic pulses, and fibers of passage will be preferentially activated with cathodic pulses.[90]

Comparison of stimulation with subdural and depth electrodes

Both subdural and depth electrodes, are usually made of nonferromagnetic platinum electrodes which allow postoperative verification of placement not only with two-dimensional X-ray or CT scanning but also postoperative MRI imaging. Postoperative CT and MRI can be co-registered to a (preoperative) volume-rendering 3D-MRI. Subdural electrodes have an interelectrode distance of 0.5–1 cm and are available in variable sizes, from 1×6 strips to 8×8 grids. Depth electrodes with four up to 15 contact leads are available from various vendors, with interelectrode distances of 3.5–10 mm.

Table 105.1 Stimulation parameters: Subdural and depth electrodes

	Subdural	*Depth*
Polarity	Biphasic	Biphasic
Stimulated electrode	Monopolar or bipolar	Bipolar
Stimulus intensity	1–15 mA (Grass S88) 1–17.5 mA (Grass S12) 1–20 mA (Ojeman)	1–3 mA
Duration of stimulus	0.3 ms	1–3 ms
Frequency	50 Hz	50 Hz
Duration of train	5 s	< 5 s

For subdural grids, we use stimulus pulses of 0.3-ms duration of alternating polarity at a rate of 50 Hz using a monopolar stimulating electrode to a remote reference over non-eloquent cortex. The testing is routinely begun at low intensity of 1.0 mA and increased gradually by 0.5–1.0 mA until afterdischarges, a clinical response or maximum stimulus strength of the instrument is reached (15 mA with Grass S88 stimulator, 17.5 mA with Grass S12 stimulator, and 20 mA with an Ojeman stimulator). The duration of the stimulus train is usually 5 s for the initial screening. When afterdischarges occur, one can usually repeat testing at the same or lower stimulus intensity without the recurrence of afterdischarges. Subsequently, a gradual increase in the stimulus intensity much beyond the initial threshold for afterdischarges can usually be attained, without continued afterdischarges. It is important to bear in mind that the afterdischarge threshold can vary even within adjacent electrodes and from one day to the other, and hence one must establish the afterdischarge threshold for each area tested for every testing.[91] We are usually screening for negative responses by testing reading and alternating hand and tongue movements. Subdural cortical stimulation is no longer used to induce restricted afterdischarges or habitual seizures. However, stimulation induced auras without the occurrence of afterdischarges seem to overlap with the ictal onset zone in a significant portion of patients and may be useful in surgical planning.[92,93]

Stereotactic electrodes used in centers in France and Italy are 0.8 mm in diameter and include 5,10, or 15 leads, 2 mm in length and 1,5 mm apart (Dixi, Besancon, France) depending on the target region. Stimulation is delivered in bipolar mode through adjacent contacts only 3.5 mm away from each other (center to center) and not located on the pia-arachnoid (as for subdural electrodes), thus avoiding shunting of the current through cerebrospinal fluid.[75] Electrical stimulation is performed using bipolar contiguous contacts at 1 Hz (pulse width: 3 ms) and 50 Hz (pulse width: 1 ms) by delivering biphasic rectangular stimuli.[94,95] Stimulation intensity ranges from 0.2–3.6 mA. The duration of the stimulation, usually fixed (40 s for 1 Hz stimulation and 5 s for 50 Hz stimulation) can be shortened, depending on the type of manifestation induced[96,97] Stimulation is stopped at the onset of a clinical response or the

appearance of afterdischarges. Spatial sampling around the stimulated electrodes is mostly reduced to the neighbouring leads, and limits the ability to assess for afterdischarges and systematic delineation of functional cortex. Electrical stimulation with stereotactic depth electrodes has been used primarily to explore the epileptogenic network following the concept of Talairach.[98] Single shock, 1 Hz stimulation has been found to be more specific in eliciting the habitual aura or seizure semiology, whereas 50 Hz stimulation seems more effective to detect eloquent regions.[97] However, evidence to support the usefulness of electrically induced seizures in defining the epileptogenic zone remains limited. Wieser reported on 133 patients with bilateral temporal depths and compared the concordance of electrical and chemical induced seizures with spontaneously recorded events, demonstrating a concordance of 77% for electrical and 60% for chemical induced events.[99] On the other hand, depth electrodes may allow mapping in the depth of the rolandic fissure and the associated subcortical motor and sensory pathways to guide surgical resections close to the central white matter tracts.

Mesial structures in the temporal lobe and deeper structures in the insula and opercular regions may be only accessible with depth electrodes. Electrical cortical stimulation and ictal recording with stereotactic depth electrodes in these areas have widened our understanding not only of the ictal onset zone but also of the functional anatomy of man.[37,94,100–109]

General correlation of eloquent cortex defined by electrical stimulation and eloquent cortex defined by non-invasive methods

Mapping of human brain function can be divided into two conceptually different methods.[55] One method uses interference of brain function to deduct localizing information. These include the study of brain lesions, electrical cortical stimulation (for higher cortical functions), transcranial magnetic stimulation (TMS), and intra-arterial amobarbital injection (WADA test), with varying degrees of spatial accuracy. The other method measures the activation of the human brain at rest or during a specific task or event and includes fMRI, nuclear imaging with positron-emission tomography (PET) and single-photon-emission computed tomography (SPECT), magnetoencephalography (MEG), and event-related potentials (ERP).

Brain interference methods are based on the assumption of a 'modularity' or localized segregation of function. The concept of functional modularity is crucial for any form of brain surgery and implies that although any brain region has functional importance in that it can theoretically be activated by the appropriate task, some regions are less dispensable than others. In that sense, interference methods allow in many cases a better prediction of postoperative outcome than activation methods.

Table 105.2 Methods for functional brain mapping

Interference methods	Activation methods
Brain lesion (including surgical resection)	fMRI (high spatial resolution)
Electrical cortical stimulation	PET/SPECT
Transcranial magnetic stimulation	MEG (high temporal resolution)
WADA	ERP

Traditionally, functional mapping aside from ECS has been largely limited to Wada and Neuropsychological testing to determine preoperative language lateralization and functional reserve and adequacy of memory.[110–115] Hypometabolism in the temporal lobe on Fluro-deoxyglucose (FDG-) PET seems to correlate with the memory results of Wada testing.[116–118] In the last two decades, additional non-invasive mapping methods have been developed which offer a similar spatial accuracy as ECS to localize sensory and motor function as well as language, but with less specificity and without the ability to correlate function directly with the ictal onset zone obtained during the invasive recording.

Magnetic source imaging (MSI) is a technique in which the equivalent current dipole sources of the magnetoencephalography (MEG) are coregistered to an MRI image of the brain. MSI can have a resolution on the order of millimeters.[119] Moreover, when spatially separate predominant sources are sequentially activated, MEG allows temporal resolution (milliseconds) that is not possible with other modalities. The time course of neuronal language processing can be imaged noninvasively with millisecond resolution.[120] There is relatively good correlation between intraoperative ECoG and MEG,[121] although direct measures of differences in localization cannot be performed because of the intrinsic tendency of sulcal localization with MEG versus surface maps with electrical stimulation. Detailed homuncular maps have been reported in normal subjects generally following the Penfield homunculus.[119]

fMRI has the advantage that it can produce functional and anatomic maps and is equally sensitive to superficial and deep regions. However, a criterion to determine what statistical thresholding should be used to obtain a map of 'true' activation is not feasible. Simply varying the magnitude of the correlation coefficient will result in apparently striking different activation maps. Activation of the primary sensory and motor areas yields robust BOLD signals (5% signal change in a 1.5 T scanner), and it is relatively easy to determine precise boundaries of functional tissue of these regions with fMRI. Motor cortex representing tongue, hand, finger, arm, and foot areas is readily identified with tongue movement, finger tapping, and toe wiggling,[122–126] including demonstration of the somatotopic organization of these regions.[123,127,128] Analogous sensory areas are identified with brushing or an air puff. With more complex motor paradigms, the supplementary motor area and cerebellar areas are also activated. Motor cortex localization with fMRI is generally highly concordant with intraoperative electrocortical stimulation mapping.[129–136]

Numerous studies have demonstrated that fMRI is able to identify hemispheric language dominance reliably. However, the areas of language processing vary markedly in different studies, likely related to use of different linguistic activation or control tasks, imaging, and postprocessing techniques, among other factors. The most common types of tasks successfully used for lateralization purpose are word-generation tasks (also called verbal-fluency tasks) and semantic decision-making, the former tending to show relatively consistent activation of anterior language areas and the latter demonstrating a more widely

distributed network including anterior and posterior hemispheric regions.[137,138] In addition to information on lateralization, fMRI has the potential to provide detailed maps of the intrahemispheric localization of critical language areas. There are a number of studies suggesting a close spatial relationship between fMRI activation and intraoperative electrocortical stimulation.[139–146] A recent study by Rutten *et al.* compared the results of fMRI quantitatively with intraoperative electrocortical stimulation mapping in 13 patients with temporal lobe epilepsy.[147] In eight patients, critical language areas were detected by ECS, and in Seven of eight patients, the sensitivity of fMRI was 100% (i.e., fMRI correctly detecting all critical language with high spatial accuracy). This indicates that areas not activated by fMRI could be safely resected without the need for intraoperative electrocortical monitoring. However, a combination of three different fMRI language tasks (verb generation, picture naming, and sentence processing) was needed to ensure this high sensitivity, as no single task was sufficient for this purpose and only 51% of fMRI activations were confirmed by ECS stimulation, resulting in a low specificity of fMRI.

Noninvasive preoperative assessment of brain function can support or obviate the need for invasive mapping and several indications for noninvasive functional activation studies have emerged:

1. In patients with a single epileptogenic lesion with predictable borders, e.g., cavernous angioma or low-grade tumors non-invasive preoperative mapping may obviate the need for invasive mapping.
2. Malformations of cortical development may or may not harbour eloquent cortex and preoperative noninvasive mapping can assist in the decision-making if invasive studies and surgery should be pursued.
3. Interference method can be of limited usefulness to predict outcome of cognitive functions organized in larger networks, e.g., memory. fMRI may be used to detect clinically relevant asymmetries in memory activation in patients with temporal lobe epilepsy.[148–150]

Safety issues

Two principle safety concerns have to be considered when subjecting a patient to electrical cortical stimulation.

The first concern should be the risks associated with placing invasive subdural grid or intraparenchymal (stereoencephographic) depth electrodes. The morbidity in patients undergoing subdural electrode implantation is probably not greater than that for neurosurgical patients in general when proper care is taken. The complication rate has decreased over the last two decades probably related to grid technology, surgical technique, and postoperative care. Complications include infection, (mostly transient) neurological deficits, epi- and subdural hematoma, increased intracranial pressure, status epilepticus, and death.[151] Depth electrodes can lead to breakages of electrodes and intraparenchymal hemorrhage.[152–154] The rate of complications seems associated with a greater number of grids, longer duration of monitoring, older age of the patient, left-sided insertions, and burr holes in addition to the craniotomy.[151] The risk of infection can be minimized by observing strict intraoperative and postoperative antiseptic techniques and by tunneling the wires for a distance under the scalp before their final exit. Antibiotics are routinely given, either continuous or as a single postoperative dose.[50] The infection risk is higher in patients with previous craniotomy or reimplantation.[155] A decreased level of awareness postoperatively without signs of infection can be related to raised intracranial pressure either due to brain swelling and a disproportionate high number of electrodes, or an intracerebral hematoma, but also caused by nonconvulsive status epilepticus. Intravenous corticosteroids are routinely given postoperatively to reduce brain edema and close monitoring with video-EEG and CT imaging is paramount. The overall complication rate with stereoencephalographically placed depth electrodes which do not require a craniotomy may be even lower according to a recent larger series (5.6%) with only a 1% risk of intraparenchymal hemorrhage related to the placement of the depth electrodes.[153,156]

The second concern involves the safety of electrical stimulation itself. Intermittent cortical stimulation for mapping with the current protocols does not result in cortical damage and is felt to be safe in adults and children.[157–159] A case report of a patient who had received occipital cortical stimulation over a period of 10 years for the purposes of artificial vision reproduction failed to show pathological changes when the electrodes were removed.[160] The concern of kindling with repetitive electrical stimulation has been raised, which the potential to render the brain more epileptogenic. Although the afterdischarge thresholds may vary over a tested region of the brain with recurrent electrical stimulation on different days, there is no evidence to support any progressive decrease in the afterdischarge threshold which would be expected with a kindling phenomenon.[91,161]

Symptomatology induced by electrical stimulation of the cortex

1. General principles

As previously outlined, eloquent cortex defined by electrical cortical stimulation includes an area of the cortex, the stimulation of which leads to a reproducibly demonstrable change in neurological function. This change of function can be either a positive or a negative phenomenon. Positive phenomena can be either verified by direct observation or can consist of subjective phenomena reported by the patient. Negative phenomena are unnoticed by physician and patient unless appropriate and often task specific testing is performed.

2. Positive effects

The following areas have been extensively studied in stimulation studies and have demonstrated a relatively stable and reproducible positive response:

- Primary motor area
- Supplementary sensorimotor area
- Primary sensory area
- Secondary sensory area
- Auditory cortex
- Visual cortex

Primary motor area

Brodmann (1909) cytoarchitectural map distinguishes between a primary motor area (area 4) encompassing the anterior bank

of the precentral sulcus and a premotor area (area 6) in the precentral gyrus and the posterior portion of the superior frontal gyrus. (Figure 105.5)[162,163] In 1937, Penfield and colleagues noted that it was impossible to confine functional representation within Brodman's areas 4 and 6.[164] Their results revealed a disproportionate somatotopic map of the body as depicted by Penfield's famous figurine or homunculus [37] Motor responses are not limited to the precentral gryus and may be found as much as 4 cm anterior to the central sulcus and up to 2 cm posterior.[165–167] Stimulus duration, frequency and intensity alter the type of motor response with distal muscle groups being activated first. Mapping of the motor cortex is performed to maximize resection in patients with nonlesional frontal lobe epilepsy and in patients with lesions encroaching the precentral area or distorting anatomical landmarks. A number of case reports suggest that small excisions, even of cortex directly adjacent to the Rolandic fissure may be followed by surprisingly limited functional deficits. It is not known, however, what the size limits of a 'safe' perirolandic excision might be.[168]

Supplementary sensorimotor area

The mesial aspect of the superior frontal gyrus, just anterior to the primary motor area for the lower limbs, was known to elicit motor responses in monkeys more than a century ago.[13] The difficulty in accessing this area of the cortex limited systematic studies on humans until the later half of the 20th century when implantable depth electrodes and subdural grid electrodes were available.[169–171] It became apparent that this area has both sensory and motor representation, and hence the preferred use of the term supplementary sensorimotor area (SSMA).[170] There are some patterns of responses that are more likely to be obtained upon stimulation of SSMA and are referred to as SSMA-type responses. While stimulation of PMA gives rise to predominantly distal and clonic responses, the SSMA leads to predominantly proximal and tonic responses. Bilateral asymmetric tonic movements of lower or upper extremities, head and eye deviation, vocalization are some other SSMA-type responses. Sensory responses consisting of numbness, tingling or pressure can be elicited contralaterally or bilaterally. The somatotopic organization of SSMA is posterior to anterior with the representation of lower extremity followed by the upper extremity followed by head. A supplementary eye field which causes conjugate contralateral eye deviation is located within the area of the head representation.[170]

Various studies have shown that resection of the SSMA produces a temporary state of contralateral weakness with mutism and intact comprehension.[61,172–174] Forced grasping in the contralateral hand has also been described in the acute postoperative period.[37] On long-term follow-up of patients who had partial resections of the SSMA unilaterally, no gross motor deficits were noted. It is not known if complete unilateral SSMA resection could lead to significant and lasting neurological deficits. In this sense it is important to emphasize that the SSMA is not only rostral to the mesial frontal MI area, but also extends caudally immediately ventral to the MI and SI area of the foot.

Sensory areas

Somatosensory sensation can be elicited from the human brain by electrical stimulation, from three areas – the primary sensory cortex (SI) in the post central gyrus, the secondary somatosensory cortex (SII) in the frontal and parietal operculum and the supplementary sensorimotor area in the mesial surface of the frontal and parietal cortex.

The primary sensory cortex (SI) can be defined as the postcentral or anterior parietal region consisting of areas 3a, 3b, 2, and 1 (Figure 105.6). The clear somatotopy of SI corresponds to that of the motor strip with the exception of the representation of the genitals that is only found in the postcentral cortex.[37,38,164] SII is located on the superior bank of the sylvian fissure in the region of the planum infraparietale of the operculum.[37,38,164] Stimulation effects in this area consist of sensations of the whole body on the contralateral side and quite often also on the ipsilateral side. The sensations are not different from those obtained by stimulating SI with the exception that there is a whole body representation in SII. Sensory responses obtained from the supplementary sensorimotor area consist of a mixture of bilateral, ipsilateral and contralateral sensations. The sensory responses are mixed with motor responses. The mesial cortical areas of precuneus, paracentral lobule, superior frontal gyrus and cingulate gyrus have shown supplementary sensorimotor type responses upon electrical stimulation. Resection of the primary sensory cortex leads to permanent cortical sensory deficits in the corresponding contralateral body part. These deficits affect primarily the position sense and fine touch. Vibration and pain sensation is not affected by SI resections.

Visual cortex

Following Munks' work on hemianopia after unilateral parieto-occipital lesions and Henschen's original description of the primary visual cortex in the calcarine fissure,[16,175,176] Brodman divided the visual cortex into areas 17, 18 and 19.[177–179] Area 17 corresponds to the striate cortex defined by the presence of the striae of Gennari which is identified histologically by a distinctive myelin band. It receives input from the lateral geniculate body and is considered the major gateway for visual information to the cortex. Areas 18 and 19 are visual association areas and are difficult to identify histologically. Three categories of responses can be obtained in the surrounding of the primary visual cortex and correspond well with the visual auras seen during spontaneous epileptic seizures. Simple visual hallucinations consisting of unformed circles of flashing light which may be white or colored can be obtained during stimulation of the area just above and below the calcarine fissure.[179] More elaborate geometric shapes such as diamonds, triangles, or stars, which can be white or colored and flashing are seen with stimulation of the fusiform gyrus and the lateral temporal or temporo-occpitial cortex.[179] Visual illusions leading to distortion of the image in a localized visual field consist of micropsia, macropsia, and metamorphopsia and can be produced in the basal temporo-occipital region. All these responses are localized to the upper or lower quadrant of the contralateral visual field. The switch from upper to lower quadrant corresponds to the calcarine fissure. A considerable proportion of patients with occipital lobe epilepsy may already present with a visual field defect. In patients with intact visual fields, surgical resection in the occipital lobe is mostly associated with a persistent postoperative visual field defect.[180]

Auditory cortex

Ferrier first noted a peculiar head turn in monkeys after stimulation of the contralateral superior temporal gyrus and was

able to confirm the presence of the auditory cortex by inducing deafness with bilateral lesions.[12,15]

The primary auditory cortex (area 41) lies in the posteromedial aspect of the gyrus of Heschl. The secondary cortical auditory areas include the contiguous areas of the transverse gyrus of Heschl, which extend dorsally into the planum temporale and ventrally in the region of the superior temporal sulcus (areas 42, 52, and 22). Electrical stimulation is carried out, and the patient is asked to describe the subjective symptoms during and after each stimulus. The stimuli should be separated by a sufficient time interval (5–10 min) such that the local background electrical activity has returned to the prestimulation status before the next stimulus is delivered.[181–183] Penfield divided the auditory sensations in elementary crude sensations or auditory hallucinations and termed the altered interpretation of heard sounds auditory illusions. Stimulation of the primary auditory area of the Heschl's gyrus (area 41) gives rise to high-frequency hallucinations. The secondary auditory area of Heschl's gyrus provokes illusions in a majority of patients. Stimulation in the region of planum temporale gives rise to auditory illusions and hallucinations with equal frequency. Patients with unilateral Heschl's gyrus lesions do not have any obvious hearing difficulties.

Negative effects

The following areas have been extensively studied in stimulation studies and have demonstrated a relatively stable and reproducible negative response:

- Language areas: anterior, posterior and basal temporal
- Primary and secondary negative motor area
- Other negative effects

Language areas

The initial localization of speech was based on lesional studies, describing an anterior speech area in the left inferior frontal lobe and a posterior or auditory speech area in the first temporal convolution (Figure 105.5).[5,6,184] Penfield and Roberts were able to map these areas intraoperatively inducing speech arrest, alexia, agraphia, anomia, paraphasia, and occasional positive grunting noises with electrical interference.[37,185,186] They also described a superior language area anterior to the Rolandic motor foot area in the mesial frontal lobe,[186] which is now thought to be related to an overall inhibition of movement.[187] A third speech area has been described in the basal temporal region.[52,188] Reading aloud is a reliable screening task for mapping both language areas. Additional testing is warranted whenever slowing of speech or speech arrest is elicited and includes: object naming, auditory word repetition, auditory and reading comprehension, and spontaneous speech. Although electrical stimulation preferentially affects verbal fluency when stimulating Broca and evokes comprehension deficits when stimulating Wernicke, a significant overlap of symptoms is seen.[189,190] Other mechanisms interfering with speech production have to be excluded: perioral muscle contraction, arrest of motor movement other than speech, or distracting hallucinations.[191]

Broca's area resides within the inferior and middle frontal gyrus (Figure 105.3). The anterior and posterior borders are 4.0–4.5 cm and 1.5–2.0 cm anterior to the rolandic fissure respectively. The superior border is about 3.5 cm above the sylvian fissure.[190] Wernicke's area resides within the posterior aspect of the superior and middle temporal gyrus, angular gyrus and the supramarginal gyrus (Figure 105.3).[192] The anterior border is felt to be approximately 1 cm behind the junction of the rolandic and sylvian fissures. The posterior border is approximately 5.5–6.5 cm behind this junction. The areas most consistently involved with language function in the basal temporal area are the fusiform gyrus, inferior temporal gyrus and the parahippocampal gyrus (Figure 105.4) in decreasing order of frequency.[193] The anterior and posterior borders of the basal language area are about 1.1 cm and 6.1 cm posterior to the anterior temporal tip respectively. The most lateral and mesial borders are felt to be 1.4 cm and 5.9 cm from the lateral edge of the temporal lobe respectively. Similar to the anterior and posterior speech areas, electrical stimulation of the basal temporal area results in speech arrest as well-impaired comprehension.[52,187,193–195] This is particularly noticeable at higher stimulus intensities. In patients who underwent resection of the basal temporal language area, after the area had been identified by preoperative stimulation

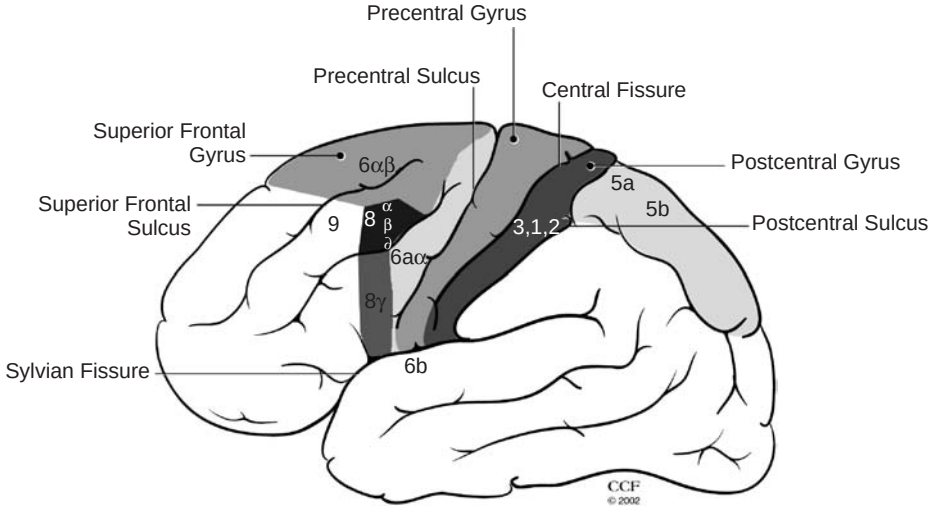

Figure 105.5 Diagram showing lateral view of sensorimotor cortex and neighboring brain areas.

studies and who demonstrated a postoperative language deficit, the language deficit tends to clear by 6 months after surgery.[195]

Negative motor area

Negative phenomena induced by electrical stimulation other than language function are less well described in the literature, partially since they may not lead to readily acknowledged postoperative deficits (Figure 105.4).

Penfield and Jasper noted a negative motor effect in selected cases that underwent cortical stimulation in the inferior frontal gyrus, just anterior to the primary facial motor representation, termed the primary negative motor area (PNMA).[37,53,196] Subsequently, a supplementary NMA (SNMA) was identified in the mesial portion of the superior frontal gyrus immediately in front of the face motor area of the supplementary sensory motor area.[54,170] Stimulation in this region may result in a negative motor response involving the contralateral and, to a lesser extent, even the ipsilateral muscle groups. More recently, a more broader distribution of NMAs for the upper extremities were found throughout the lateral premotor cortex, while NMAs for the tongue were only found in the inferior frontal gyrus of the dominant hemisphere.[197] During selective removal of the PNMA in two patients, transient hand clumsiness was observed in one patient, consistent with its presumed role in motor control.

Other negative effects

The angular gyrus (Brodmann area 39) forms a part of the temporoparietal (heteromodal) association cortex along with the supramarginal gyrus (area 40) and the banks of the superior temporal sulcus, including Wernicke's area and the caudal aspects of area 7 in the superior parietal lobule. Lesions of heteromodal association cortex produce deficits involving higher cortical functions, as opposed to lesions of unimodular association cortex, which lead to deficits specific to a single sensory modality. Lesions of the dominant temporoparietal region sparing Wernicke's area produce a combination of deficits including Gerstmann syndrome, alexia, anomia, and constructional apraxia.

Neurophysiological substrate producing positive and negative symptoms

Brodmann's (1909) cytoarchitectural map distinguishes between a primary motor area (area 4) encompassing the anterior bank of the precentral sulcus and a premotor area (area 6) in the precentral gyrus and the posterior portion of the superior frontal gyrus.[162] These findings, along with converging lines of evidence from clinical observations and cortical ablation experiments performed in monkeys, led Fulton (1935) to propose that the motor cortex could be divided into a primary motor area (area 4) and a premotor area (area 6).[163] In contrast to the hierarchical concept proposed by Fulton in which the higher level motor areas participate in the generation and control of distal movements through projections to the primary motor cortex.[163,198] it is known that only a third of the corticospinal and corticobulbar fibers arise from the primary motor area. Another third arises from the premotor cortex located on the lateral aspect of Brodmann area 6, the supplementary sensory motor area located on the medial aspect of Brodmann area 6, and the cingulate motor area located along the dorsal and ventral banks of the cingulate sulcus.[199] The remaining fibers have their origin in the parietal lobe (arising mainly from the somatosensory cortex of the postcentral gyrus).[200,201] These projections explain the positive motor effects seen with electrical cortical stimulation outside the primary motor area.[199,202] In contrast to the clonic movements elicited with stimulation of the primary motor cortex, responses from the premotor areas tend to be tonic involving more proximal muscle groups bilaterally. The characteristics of the response and the unilateral somatotopic representation seen over the primary motor and somatosensory cortex correlate well with permanent functional deficits after resection suggesting a high degree of functional specialization and limited ability for recovery.

Stimulation-induced negative symptoms interfere with the function of the cortex being stimulated, with the patient unaware of the effect until they are asked to perform a specific function. This can either lead to the inability to perform a language or motor task, but includes other cognitive tasks when tested. In the dominant hemisphere, the anterior language area is thought to be involved in the organization of fine motor movements allowing speech production, whereas the negative motor area in the non-dominant hemisphere participates in the overall organization of fine motor movements. However, a direct inhibition of the primary motor areas resulting in the observed negative motor effect cannot be ruled out. Both potential mechanism may explain why small lesions restricted to the primary negative motor area but also in the anterior language area often recover substantially after a temporary deficit and show a higher degree of cortical plasticity than the primary motor and sensory cortices (see Figure 105.5).

Special considerations in children

Cortical mapping in children poses additional unique challenges.[191] The changes inherent to the developing nervous system and lack of firm guidelines for electrical safety necessitate that the energy and charge requirements be kept to a minimum. The longer chronaxies in children can be often more effectively stimulated by not only increasing the stimulus intensity but also the pulse width from 0.3 ms used in adults up to a maximum of 1.0 ms.[203] The authors were also able to elicit responses as well as afterdischarges, in some young patients (< 5 years), by increasing the stimulus duration after failing to obtain any response at the maximal fixed duration stimulation. Clinical responses in children are often obtained at or above the afterdischarge threshold.[203] Language and motor tasks should be adapted to the patient's age and neurocognitive status. Attention span and cooperation in children are often limited and several sessions may be necessary.

Motor movements are obtained at all age groups with some ontogenic trends. In children younger than 2 years of age, tongue movements are difficult to elicit and in this age group, stimulation may induce bilateral rather than unilateral responses from lower face when the lower rolandic region is activated.[191] Individual finger movements are usually first manifest at or after 3 years of age. Clonic finger movements appear after tonic finger movements. These observations are likely to be a result of the maturing systems in cortical area 4. Children with developmental disorders or disorders with aberrant cortical formation are more likely to show atypical distribution of the motor or language cortex and the results may have to be validated with data obtained from functional imaging studies.

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106 Cortical mapping by electrical stimulation of subdural electrodes: primary somatosensory and motor areas

AS Tanner and HO Lüders

Introduction

One of the most important issues faced during invasive evaluation of patients with intractable epilepsy is the localization of the epileptogenic zone and its surrounding eloquent areas with the goal of planning a resection that renders the patient seizure free with minimal or no neurologic deficits. The task of 'cortical mapping' is to assist in determining the location and extent of the eloquent regions and to establish their relationship to the epileptogenic zone. This information will then be used to define a surgical strategy.

This chapter will review the cortical mapping of the motor and somatosensory areas.

Historical background

In 1870, Gustav Fritsch and Eduard Hitzig published a paper entitled 'On the Electrical Excitability of the Cerebrum.' They found that

> A part of the convexity of the hemisphere of the brain of the dog is motor . . . another part is not motor. The motor part, in general, is more in front, the nonmotor part more behind. By electrical stimulation of the motor part, one obtains combined muscular contractions of the opposite side of the body.[1]

Their experiments, which were conducted mostly in dogs, were groundbreaking not only because up until that time it was believed that the cerebral hemispheres were not excitable by any stimuli, but also because this publication had a major impact on subsequent work in cerebral physiology.[2,3]

A few years later David Ferrier's experiments published in his monograph on *The Functions of the Brain*[4] not only confirmed Fritsch and Hitzig's work, but found in the brain of monkeys several more areas where movement could be elicited by electrical stimulation. His ablation work also contributed to the localization of sensory functions as well. He was able to produce convulsions experimentally and also elicited precise movements of individual muscles and groups of muscles by electrical stimulation of localized cortical centers in dogs, rabbits, cats, and guinea pigs.[5]

Charles Sherrington continued the work of Ferrier, but he added a new emphasis involving the use of the concepts such as integration, evolution, and reflex as guiding principles. His work in the laboratory also promoted a change from the concept of a large, overlapping sensorimotor cortex to the concept of a more narrow and discrete frontal motor cortex separate from the parietal sensory area.[6]

In subsequent years this research was continued by Sir Victor Horsley who conducted brain stimulation experiments in primates, but also went on to perform one of the first surgeries for epilepsy.[7] During these operations he actually used intrasurgical electrical stimulation in humans to localize the motor strip.

The work of Sir Victor Horsley was later expanded by Fedor Krause and Otfrid Foerster in Germany, who made major contributions to this field. Krause introduced faradic stimulation and suggested this was the best method to map the different areas of the human motor cortex which he mapped in exquisite detail. Foerster continued the detailed mapping of the human cortex and in the operating room he used local anesthesia so that the patient could report sensory responses during the operation.[8–12]

Finally, Wilder Penfield, deeply influenced by Charles Sherrington, Sir William Osler and Otfrid Foerster, used the technique of intraoperative cortex stimulation under local anesthesia to confirm the somatotopic distribution of the human motor cortex. He was the first to use the homunculus to graphically visualize the organization of the human cortex.[13,14]

The work of Penfield and his antecessors set the stage for further development of invasive recordings for localization of the epileptogenic zone and detailed mapping of eloquent cortex in the extraoperative setting.

Anatomy of the primary somatosensory, motor and premotor cortex

The primary somatosensory and motor cortices form together what has been termed the central lobe, a concept that has been

considered and in use since these areas were defined by stimulation studies. This central cortex includes the precentral and postcentral gyri. The characteristics of the surface anatomy of these regions are important when studying the area using MRI imaging specially when attempting to define the localization of subdural electrodes.

The primary motor cortex (MI) is contained within the precentral gyrus which extends from the precentral sulcus to the central sulcus. The cortex in this area is unusually thick due to the presence of giant pyramidal cells of Betz that vary in size and density in different areas of MI: they are usually largest in the paracentral lobule, and smallest inferiorly in the opercular region. The central sulcus is usually interrupted before it reaches the sylvian fissure and, therefore, the inferior segment of the precentral gyrus tends to communicates with the postcentral gyrus to form the central operculum. The central sulcus is also interrupted in the mesial surface before it reaches the cingulate sulcus, leading again to a communication of the mesial MI and the primary sensory area (SI) regions in the paracentral lobule. There are no clear boundaries of the anterior extent of MI in the paracentral lobule and inferiorly MI touches the caudal extension of SSMA (supplementary sensorymotor area). The functional representation of MI in humans was first defined by Fedor Krause and later confirmed by Otfried Foerster.[10–12] Wilder Penfield refined their observations and was the first one to represent the organization of the human MI by a homunculus.[14] Their studies showed that there is ample overlap and minor differences among individuals, but that the orderly sequence of motor representation appears relatively constant. Some studies have also suggested that there may be some redundancy for particular motor and somatosensory functions. In general though, the face is represented inferiorly, followed superiorly by the thumb, hand and shoulder; the trunk lies near or in the area of the interhemispheric fissure, and the leg and foot are located within the mesial surface. These four groups perform as functional units rather than individual isolated areas. Electrical stimulation of MI evokes contractions that usually involve functional muscle groups concerned with specific movements; however individual movements can be contracted separately.

The premotor cortex lies between the primary motor cortex and the prefrontal lobe. Histologically, it corresponds to Brodman area 6. It resembles MI and it is composed primarily of large pyramidal cells but there are no giant cells of Betz. The anterior boundary is variable, but is placed approximately on a line linking the eye fields with the anterior border of the supplementary sensorymotor area.

The cortical eye field lies rostral to the premotor area and occupies the caudal part of the middle frontal gyrus. Stimulation usually causes conjugate deviation to the opposite side.[15,16]

The primary somatosensory area is located in the postcentral gyrus in the posterior part of the paracentral lobule. Its configuration is similar to the precentral gyrus with comparable functional units.[16–18]

The secondary somatosensory area (SII) lies in the superior bank of the lateral sulcus and extends posteriorly into the parietal lobe.[19]

A concept that is important to discuss when reviewing functional anatomy is that of the degree of neurologic deficits produced after resection of certain eloquent areas. While it has been thought that the resection of such regions will always produce a major significant deficit, we now know that some of these areas can be resected with minimal consequences. With this in mind, eloquent cortical areas can be further divided into dispensable, partially dispensable and indispensable based on the deficit and recovery expected, as well as the ability of the brain to compensate for certain of these lesions. Therefore resection of indispensable cortex will lead to a chronic deficit without major recovery (i.e., resection of hand motor area), resection of partially dispensable cortex will produce a chronic deficit but some recovery and compensation are expected (resection of SSMA), and resection of dispensable cortex will produce no detectable neurologic deficits (i.e., Basal language area).[20]

Primary motor cortex: an experimental point of view

Perhaps one of the most exiting fields of experimental neuroanatomy is the study of functional anatomy in nonhuman primates. Among them, the macaque brain has been extensively studied.

Various architectonical maps of the motor cortex of the macaque monkey have been published since the early nineteenth century. Traditionally, the agranular frontal cortex of nonhuman primates has been subdivided into two regions: areas 4 and 6 according to Brodman[21] or 'precentral' and 'intermediate precentral' areas according to Campbell.[22] Area 4 (or 'precentral' area) is characterized by giant pyramidal cells, whereas, these cells are missing in area 6 (or 'intermediate precentral'). This somewhat simple map corresponded to a similarly simplistic view of functional organization that included the motor, premotor and supplementary sensorymotor areas. However, over recent years, research has shown that instead of three functional entities, the primate motor cortical system is made up of many structural and functional fields, each processing different aspects of motor behavior.[23] Similar to the motor cortex, a multiplicity of areas have been identified in the posterior parietal cortex, each of them involved in the analysis of distinct visual and somatosensory information.[23]

An interesting observation is that the maps have changes substantially over the years: Brodmann for instance defined two areas [21] while Matelli has defined seven.[24] The above is not only due to obvious advances in research techniques but also to different criteria to define extent and function. A classification that is widely used, and appears to have been validated by other techniques [25–28] is that one of Matelli.[24] He divides the motor cortex in seven areas: area F1 corresponding to the primary motor cortex proper, areas F2 and F7 located on the dorsolateral cortical convexity, areas F3 and F6 on the mesial cortical surface, and areas F4 and F5 on the ventrolateral convexity.

Area F1 is characterized by low cell density and a very prominent giant pyramidal cell in layer V. It receives inputs from several areas of the nucleus ventralis of the thalamus, as well as corticocortical connections from the supplementary motor area (SMA), the premotor cortex and areas 1, 2 and 5.

Somatotopically the face area is represented laterally close to the Sylvian fissure, the leg medially, and the arm and hand in between. Proximal parts of the extremities are represented on the exposed cortical surface whereas distal parts of the extremities and acral parts of the face are represented in the rostral bank of the central sulcus. Fingers, lips and tongue have larger areas of representation. Evidence shows that muscles, joints or movements are represented as overlapping (not as segregated neuronal populations), with individual muscles activated at multiple, spatially separated locations or multiple muscles activated from a single site. In fact, there is evidence indicating that most of a primate's motor cortex is active during movement. Intracortical micro-stimulation (ICMS) triggers movements that are fast, short-acting and restricted (i.e., one joint).[23]

Areas F3 and F6 correspond to what is described as 'SMA' in humans. In the primate, it is divided in SMA proper and pre-SMA. These two are differentiated on histochemical bases: F3 is comparable to F1 (poorly laminated) whereas F6 is clearly laminated. F3 lies mesially immediately anterior to F1, and F6 lies anterior to area F3. It appears that their connections and inputs are different as well: F3 receives more information from the putamen and pallidum, while F6 receives information from the cerebellum and the caudate. Somatotopically, area F3 has representation for the arm, leg, and orofacial areas, while F6 has only arm representation. ICMS of area F3 requires higher thresholds than for F1 and elicits more complex and proximal movements. ICMS of area F6 requires higher thresholds than for F1 and F3 with decreased excitability and more proximal movements. The function of the primate SMA (SMA proper and pre-SMA) has been the subject of extensive research. It appears that it contributes to many aspects of motor behavior including the control of both simple and complex motor tasks, externally triggered as well as self-initiated tasks, and both distal and proximal movements.[29,30] There is evidence to suggest that area F3 (SMA proper) corresponds to the supplementary sensorymotor area (SSMA) and that F6 (preSMA) is equivalent to the supplementary negative motor area in humans.[31]

Areas F2 and F7 constitute the dorsolateral premotor cortex (PMd) and are part of parieto-frontal connections. Their function is believed to be related to planning and controlling arm and leg movements using external cues. They are also involved in controlling saccades in the context of complex motor movement.

Areas F4 and F5 form the ventrolateral premotor cortex (PMV). They are also part of complex circuitries that involve the parietal lobe. It is thought that its function is related to planning movements directed towards specific objects, goal-directed movements and execution of a motor action.

The somatotopic organization of the primary motor cortex of the macaque and the human brain is therefore similar, but for both this should not be oversimplified as overlaps exist. An excellent review by Meyer and Matelli[23] suggest that an organizational principle similar to the macaque also exists in the human brain (i.e., primary motor cortex, SMA and pre-SMA, dorso- and ventrolateral premotor cortex) and that functional gradients likely exist within the human nonprimary motor cortex.

Indications and objectives for mapping of the primary somatosensory and motor cortices

Cortical mapping of the motor, premotor and somatosensory cortex is a valuable pre-surgical technique in those cases in which the pre-surgical noninvasive evaluation suggest that the epileptogenic zone is partially overlapping or in close proximity to these cortical areas.

Responses of motor stimulation

Stimulation of MI, SSMA and the premotor cortex elicits clonic and tonic responses. Stimulation of MI tends to elicit primarily distal, clonic muscle contractions whereas stimulation of the SSMA and of the premotor area produces preferentially proximal, tonic muscle contractions. However, tonic responses may also be elicited by stimulation of MI and clonic responses may occur when stimulating the SSMA. There is also evidence that the stimulus parameters determine the clonic or tonic character of the response.[32,33]

There is evidence that continuous high-frequency (20–100 Hz) stimulation can induce a clonic muscle contraction that is a subharmonic of the actual stimulation frequency (5–10 Hz). However, the response becomes tonic when the intensity of stimulation is increased.

From a more practical point of view, the stimulation of subdural electrodes should be done in an organized and orderly fashion. Ideally all electrodes in a grid should be stimulated. If this can not be done due to time constraints or other causes, a rationally planned group of electrodes should be stimulated. The technical details of stimulation are discussed elsewhere in this textbook, but it is important to note that all electrodes analyzed should be stimulated with the same parameters, starting at the same current and using the same techniques in each of them. To make sure that the results are reliable, it is advisable to reproduce all positive responses.[20,34–37]

Stimulation of the premotor cortex can produce positive or also negative motor responses.[36,38] The negative motor responses are discussed in a separate chapter.

Mapping of the eye fields should be done in the same fashion. Findings include eye version or contralateral conjugated eye movements. In many cases saccades can be observed as well. In one study [39] head version, following the eye movement, was seen in roughly half of the patients studied. In the same study it was noted that most patients had motor cortex contiguous to the eye field and that there was no silent cortex between the strip and the motor cortex.

Stimulation the motor cortex frequently also elicits sensory responses. When stimulating at relatively low stimulus intensity the patient will describe sensations such as numbness, tingling or feelings such as 'tension', pain, or 'spasm' in the same muscles that eventually contract when the stimulus intensity is increased. Sometimes these represent actual sensory responses, but not infrequently they may represent motor responses that the patient perceives but are invisible to observers.

In these cases, the stimulus intensity should be increased in small increments (0.1 to 0.2 mAmps) starting at subthreshold intensities in an attempt to differentiate motor from sensory responses.

Similarly, motor responses can also be obtained when stimulating the sensory cortex, usually at relatively high intensities. In this case, starting with lower intensities and using smaller increments may avoid eliciting motor responses.[20]

Responses of somatosensory stimulation

The responses to electrical stimulation of the primary somatosensory area include strictly contralateral sensation in a defined, relatively limited somatotopic distribution. The most common responses include: numbness, tingling, warm sensations, pulling sensations, throbbing sensations and alien sensations. Stimulation of SII consists of contralateral, ipsilateral or bilateral responses, most frequently tingling or numbness, that tend to have a widespread distribution.[19,20,40,41]

Complications of stimulation of somatosensory and motor cortex

Electrical stimulation of subdural electrodes can produce afterdischarges and seizures.[20]

Afterdischarges are characterized by the appearance of runs of epileptiform discharges triggered by electrical stimulation of a given intensity, repetition rate and duration. They frequently are seen in the exclusively in the stimulating electrodes, but may spread to neighboring electrodes and occasionally even extensive cortical areas without producing signs or symptoms. Symptoms or signs elicited by electrical stimulations that induce afterdischarges can be caused by activation of the stimulated electrodes but also by activation of other electrodes to which the afterdischarge spread. Therefore only the symptomatology obtained by stimuli that do not produce afterdischarges should be used for cortical mapping. EEG recordings of the stimulated and adjacent electrodes is essential to make sure that no afterdischarges occurred when the stimulation elicited signs or symptoms.

Seizures can also occur during electrical stimulation. In these cases, the electrical stimulation tends to elicit first afterdischarges that spread leading to focal seizures or even secondarily generalized motor seizures. Seizures occur when stimulating the epileptogenic zone as also any other nonepileptogenic cortex. The seizures elicited by cortical stimulation may be similar to the patient's habitual seizures (usually when stimulating at the epileptogenic zone or its neighborhood) or semiologically totally different seizures. The localization value of inducing habitual auras or seizures by electrical stimulation of subdural electrodes will be discussed elsewhere.

Correlation with other techniques

Accurate identification of MI, SI, and SSMA is essential to minimize deficits after resective surgery around the central sulcus. Therefore, other techniques should be used routinely to supplement the information provided by cortical stimulation. This includes somatosensory evoked potentials recorded from sunbdural electrodes and noninvasive techniques like functional magnetic resonance (fMRI), positron emission tomography (PET), MEG of somatosensory evoked potentials, and transcranial magnetic stimulation. A detailed description of each of these techniques is beyond the scope of this chapter and some of them are explained elsewhere in this textbook. A brief overview will be presented in this section.

Median nerve SSEPs recorded from subdural grids are characterized by large amplitude N1 and P2 peaks, a restricted distribution in the immediate perirolandic area and a phase reversal across the central sulcus, making them ideal for localization.[42,43] SSEPs to lip stimulation are also used. However, because of this relatively short short latency special attention should be taken to avoid that the early response can be is obscured by stimulus artifact.[43] Lip SSEP usually shows no phase reversal across the central sulcus. Posterior tibial nerve SSEPs can also be used for localization of the leg SI area. However the unusual orientation of the generator makes its interpretation more complicated. Our experience shows that because of variations on the mesial anatomy, a clear phase reversal is not always seen, but when recorded best localizes the central sulcus.[44]

Functional MRI (fMRI) has the advantage over electrical stimulation and subdural recorded SSEP that it is not invasive and entails no exposure to radiation. Several investigators have confirmed and validated fMRI data with intracranial electrical stimulation both in normal brains as well as in patients with distorted anatomy due to lesions such as tumors, vascular malformations or when functional reorganization is suspected.[45,46]

Positron emission scanning has also been used for functional studies and previous work has confirmed the spatial concordance between PET activation and cortical stimulation Furthermore, there is some evidence to suggest that the activation produced by fMRI imaging and PET scanning correlates fairly well.[47]

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107 Cortical mapping by electrical stimulation of subdural electrodes: negative motor areas

P Smyth

Introduction and historical overview

Early observations of the cessation of spontaneous movements after electrical cortical stimulation in nonhuman animals were published in the late 19th century.[1] The concept of 'inhibitory centers' in animal cortex was thus available to guide the intraoperative discovery of similar effects in humans by Penfield and his collaborators during the first part of the 20th century.[2] For Penfield, stimulation-induced motor inhibition was limited to the mesial frontal lobe in a relatively undifferentiated supplementary motor area (SMA).[2,3]

In the later decades of the 20th century, systematic extraoperative study with implanted subdural grids resulted in finer anatomic subdivision, competing descriptive terminologies, and the recognition of a lateral negative motor area.[4–7] Figure 107.1 shows the lateral and mesial negative motor areas in relation to nearby homunculi. The descriptive terms 'lateral' and 'mesial' negative motor areas used in this chapter are synonymous with primary and supplementary negative motor areas (PNMA, SNMA). Inhibitory effects due to stimulation of mesial and lateral negative motor areas must be recognized in context with other forms of cortically-mediated motor inhibition (Figure 107.2), which will be described further below.

Contemporary study of negative motor areas focuses on their strategic location between frontal and motor output cortex. Though the mechanism of the stimulation-induced negative motor effect is unknown, its existence and properties is considered indicative of 'higher level' integrative and organizational function. This idea emerged in the 19th century following stimulation experiments involving animal supplementary motor area and are based on the timing and inferred meaning of associated signals in adjacent cortex, peripheral nerve, and muscle.[3] These ideas continue to shape our view of these areas.

The histologic and anatomic techniques that provided the foundation for earlier work remain useful in defining connectivity. Extraoperative cortical stimulation, a routine clinical tool in epilepsy surgery evaluation, may also provide insights into the mechanism of stimulation-induced negative motor phenomenon; a testable hypothesis is outlined in this chapter. Of particular importance are recent functional imaging approaches used to explore the dynamic connectivity of the pre-SMA[8] as well as possible 'higher level' functions in motor and cognitive processes, including the interface between volition and movement.

Definitions and testing protocol (DVD examples)

The data and concepts summarized in this chapter come mainly from cortical mapping in epilepsy patients with subdural electrode grids. Cortical mapping in this setting involves the systematic stimulation of electrodes using parameters and procedures described elsewhere in this volume. In general, the response at each electrode to high frequency stimulus (50 Hz, varied from 1–15 mA, lasting several seconds) may be one of four kinds: a positive effect, a negative effect, no response, or excessive electrical activity called afterdischarge.

A 'positive effect' from cortical stimulation is a symptom or sign, such as an unusual sensation (inherently subjective) or muscle contraction (which may be objective), elicited by stimulating primary input or output cortex.

A 'negative effect' from cortical stimulation is the cessation or inability to do something, and may (but does not inevitably) result from stimulating associative cortex. Negative effects from cortical stimulation are well known: both receptive and expressive aphasias have been elicited with stimulation of 'language areas', presumably because nonphysiologic stimulation interferes with the function of the stimulated cortex.[9,10] So-called 'negative myoclonus' has also been elicited by cortical stimulation.[11]

Conceptual and semantic confusion has arisen from the failure to consistently distinguish categories and the relationships between them. A suggested structure, used in this chapter, considers 'negative effects' (physiological or due to stimulation) to include 'negative motor effects', which again may be physiological or due to stimulation. These relationships are summarized in Figure 107.2. The focus of this chapter is 'stimulation-induced negative motor effects', in particular those arising from high frequency stimulation of mesial and lateral negative motor areas in the frontal lobe.

A 'stimulation-induced negative motor effect' is defined as the inability to make a voluntary movement or sustain a voluntary motor contraction at a cortical stimulation intensity that does not produce any positive sign or symptom and is not

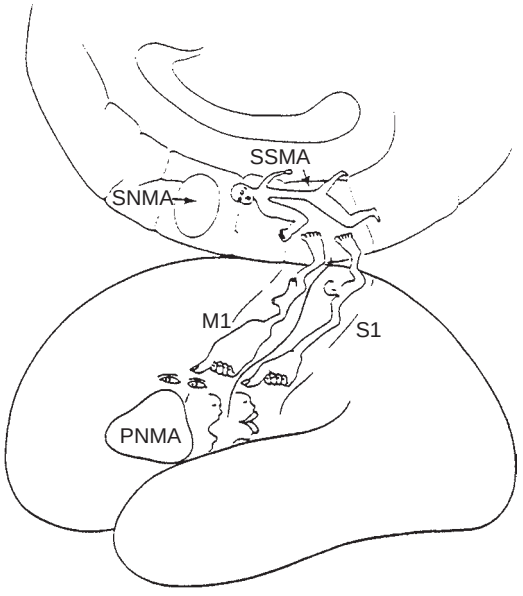

Figure 107.1 Lateral (primary) and mesial (supplementary) NMA, from ref. 6.

associated with an afterdischarge. There must also be no alteration in awareness. By definition, wherever such effects occur is a 'negative motor area'.

The Cleveland Clinic testing protocol for stimulation-induced negative motor effects includes initial screening for language followed by more detailed testing at promising sites.[6] This protocol was developed by initially exploring proximal and distal limb movements as well as trunk and face movements. From these more elaborate investigations, the protocol was devleoped to reliably identify the kinds of movements (mostly distal and mostly contralateral) known to exist and tested during routine cortical stimulation.

Screening for language function is as follows: at a given electrode, if stimulation in 1 mA increments from 1–15 mA results in no positive effect, the patient is asked to read a passage aloud while that electrode is stimulated. The intensity is set at 15 mA (by supposition, there was no obvious effect at this stimulation during earlier testing). If afterdischarges were previously seen at this electrode, an intensity just below the stimulus intensity causing afterdischarge is used.

If reading slows or halts, the read-aloud screening test is positive and further testing is done. The patient is asked to perform a repetitive movement while incremental stimulus is applied, and any inhibition of that motion during stimulation is noted and and rechecked to verify reproducibility. Movements include the tongue (stick out and move back and forth), the eyes (horizontal or vertical oscillation), sustained contraction (fist or feet), and finger and toe wiggling. Typically the patient initiates a given movement for about 5 seconds before the stimulus is applied, and the application of the stimulus is done surrepetitiously to avoid cueing the patient.

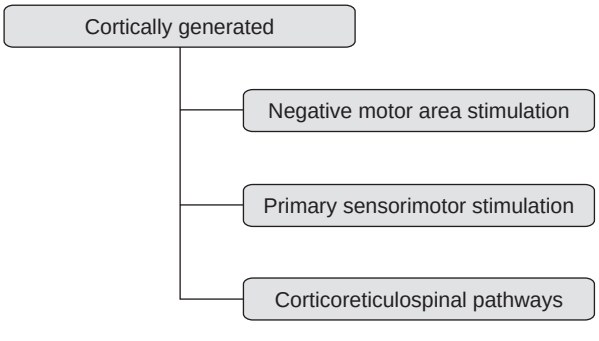

Figure 107.2 Types of cortically mediate negative motor phenomena.

The value of this protocol clinically is roughly defining boundaries of cortical function prior to surgery, as with all cortical stimulation. In terms of the phenomenon of stimulation-induced negative motor effects, the protocol reliably makes the phenomenon available for further study. It is possible that different forms of stimulation-induced negative motor (or sensory or cognitive) effects exist and have not been recognized; this protocol is unlikely to elicit them but remains useful clinically and as a starting point for further investigations.

The DVD accompanying this book includes a mesial and a lateral example of the negative motor effect. Three-dimensional image reconstructions with subdural electrode placement are shown for each case. The abrupt onset and offset of the effect seen in these example is characteristic, but responses may be delayed and partial as well (slowing versus stopping movement).

* **Mesial Negative Motor Video Example: tongue and finger motions stop**
* **Mesial Negative Motor 3D image with electrodes showing stimulation site**
* **Lateral Negative Motor Example: tongue and finger motions stop**
* **Lateral Negative Motor 3D image with electrodes showing stimulation site**

Anatomy and negative motor characteristics

Human anatomy

Two frontal lobe regions are known to produce stimulation-induced inhibition of movement. One area is lateral, the other mesial. In this chapter they are referred to in these unambiguous, anatomic terms for clarity, though 'primary' and 'supplementary' have been used in the past.

The lateral area ('primary' negative motor area) is in the inferior frontal gyrus, anterior to the motor strip representation of the face. In the dominant hemisphere, this area overlaps Broca's area.[5,7]

The mesial area corresponds roughly to the presupplementary-sensorimotor area (pre-SSMA) and is found in the mesial superior frontal gyrus anterior to the face representation of the SMA proper.[4] This area has recently been a focus of connectivity and functional imaging studies in human and non-human animals, discussed further below. Figure 107.3 illustrates a common frame of reference based on imaging[12] and receptor and histologic data showing differences in the regions defined by these imposed markers.[13–15] A line drawn between the anterior commisure and the posterior commisure is called the AC–PC line. Lines extended perpendicularly (dorsally) at the AC and PC are designated VAC and VPC, respectively. Between these lines lies the SSMA, and anterior to the VAC is the pre-SSMA,[16] a region which includes the mesial

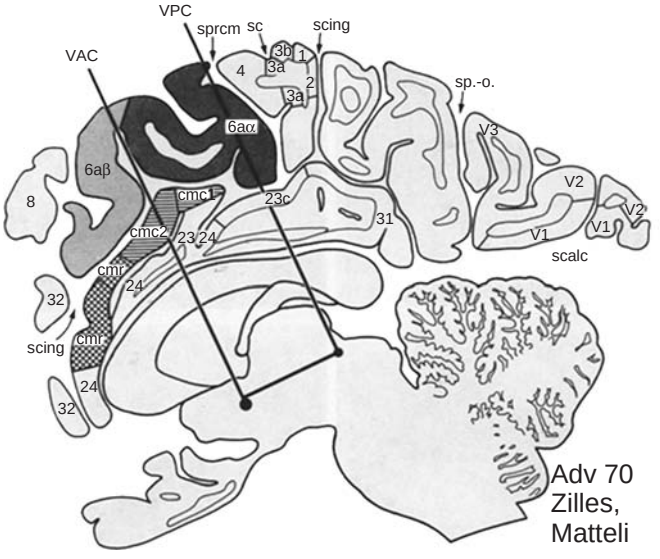

Figure 107.3 Mesial anatomy.

negative motor area. Not every stimulus in this area gives rise to a negative motor effect, though, and stimuli with different parameters may give different results, as described below. Unpublished data from two patients at the Cleveland Clinic with mesial frontal subdural electrode grids shows that the mesial area may extend up out of the fissure onto the continguous lateral surface of the superior frontal lobe. Whether this represents a region of displaced function, extended function, or a variant location for this function is unknown.

Negative motor characteristics

Conclusions based on systematic extraoperative study of negative motor areas were summarized in 1995 by Lüders *et al.*[6] In a series including 42 lateral and 15 mesial negative motor areas, proximal and distal limb movements, as well as movement of the face, tongue, and trunk were studied. 'Subjective effects' were considered in that the patient was kept unaware of which electrode was being stimulated and when it was being stimulated. By definition, stimulation at a negative motor electrode causes no known effect when the patient is at rest during routine stimulation.

Stimulation-induced motor inhibition of the mesial and lateral areas share common features.[6,7] Inhibited movements are primarily distal, involving the fingers, toes, and tongue, as well as eye movements. A given electrode may inhibit one or several of these movements, and subsequent stimulation of that electrode gives the same pattern of distribution. The response at any single site may vary from abrupt cessation of the tested movement(s) at low stimulus intensity to delayed slowing at higher stimulus intensity. Responses are mostly contralateral, but may include a less intense and momentarily delayed ipsilateral component; overall the pattern of responses suggested an abbreviated form of somatotopy in that tongue/eye responses were generally anterior to reponses including other parts of the body. Postural tone is maintained both proximally and distally (for example, if the response is 'finger tapping stops', the arm remains extended in front of the body and the fingers remain in a pincer configuration). The effect can be relatively long lasting and was seen during both brief (1–3 second) and longer (up to 20 second) stimulations. Finally, not all patients with subdural grids covering lateral or mesial areas show a negative motor effect at electrodes in the grid.

In the lateral negative motor area, 18/42 patients[6] with perirolandic subdural grids showed a negative motor effect. Once demonstrated in a given patient at a particular electrode, the effect was repeatable, so the effect is robust, but not invariable. Either the area is there and is not seen, or it is not always there. Reasons for this intriguing finding may include gaps in electrode coverage, variations in individual anatomy, local pathology, or brain states of variable duration that make the effect more or less prominent (eg, learning, compensation, or connectivity). Dominant and nondominant hemisphere responses in the lateral area were observed (12/26 and 6/16, respectively). In the dominant hemisphere, instances of simultaneous negative motor effect (inability to move the tongue) and language interference (both receptive and expressive) were noted with stimulation of the lateral negative motor area. This is consistent with prior reports of interference with both receptive and expressive language when stimulating in Wernicke's area, Broca's area, or the basal temporal lobe.[9,10] Presumably this results from interference with the function served by the underlying cortex.

Mesial negative-motor area stimulation was less well represented in the Cleveland Clinic series due to less frequent clinical indication for mesial frontal electrode coverage. Of 15 patients with such coverage, a negative motor effect was found in ten. Characteristics were similar to those found in the lateral negative motor area, but no interference with language was noted.

Context, functional significance, and mechanisms

Types of cortically mediated negative motor phenomenon

The focus of this chapter is the inhibition of movement due to direct electrical stimulation of the mesial and lateral negative motor areas in the frontal lobe. Though the exact mechanism is unknown, it is presumed to be cortically mediated. Other cortically mediated forms of motor inhibition are also known, and are here organized by their anatomic substrate and clinical correlates. This is summarized in Figure 107.2.

Corticospinal inhibitory pathways and postural tone

An inhibitory pathway connecting cortex through brainstem centers to spinal motor neurons has been characterized in animals and humans.[6] Brainstem centers in the pons and medulla are known to inhibit postural tone based on chemical agonist and electrical stimulation studies.[17,18] These include inhibitory centers in the dorsorostral pons (nucleus reticularis pontis oralis pars medialis and n.r. subceruleus), rostral medulla (n.r. magnocellularis dorsal beta), and caudal medulla (n.r. gigantocellularis).[18]

Cortical influence on these centers from prefrontal cortex, area 4, and premotor area 6 through excitatory connections has also been described,[19–21] and labelling studies have suggested bilateral distribution of corticofugal fibers in the lower pontine and medullary levels,[22] with resulting bilateral influence.

Despite an extra synaptic step in the corticoreticulospinal pathway, larger-diameter fibers may make it faster than the

direct corticospinal pathway.[23,24] This indirect but faster corticoreticulospinal system maintains axial and proximal tone, while the direct yet slower corticospinal pathway controls fine movements of more distal muscles. Profound inhibition of postural tone via the corticoreticulospinal pathway may account for bilateral clinical events including axial atonic seizures and focal seizures manifesting 'drop attacks'.[6]

Given the observed preservation of postural and proximal tone during motor inhibition with stimulation of negative motor areas, the corticoreticulospinal system should be relatively unaffected. This provides an important constraint on the relationship between negative motor area cortex and the cortical areas implicated in postural control through the corticoreticularspinal system, at least during negative motor area stimulation.

Cortico-cortical I: cortical inhibition of tonic excitatory output and negative myoclonus

Although the negative motor effect due to cortical stimulation at mesial and later 'negative motor areas' likely involves cortico-cortico interactions, a distinct inhibitory corticocortical mechanism is known from transcranial magnetic stimulation (TMS) studies. It should be noted that TMS, like electrical stimulation may also be excitatory. For example, a recent study by Matsunaga *et al.* found that 5 Hz repetitive TMS stimulation of the SMA transiently increased the excitability of connected primary motor hand areas and their corticospinal connections.[25] In addition, though motor-evoked potentials (MEP) and silent periods (SP) are discussed below with respect to TMS, they can also be elicited by electrical stimulation using single pulse electrical stimulation.[26]

TMS stimulation of motor cortex may produce a MEP followed by a SP on EMG at the affected muscle,[27,28] the SP being inherently inhibitory. The MEP and SP are not invariably associated, though and can be generated independently in close or even adjacent but nonoverlapping areas of cortex.[29,30] Furthermore, the SP is thought to consist of an early component due to intrinsic spinal cord mechanisms (reviewed in ref. 6) and a later component due to corticocortical interactions.[30]

Whether this form of cortically-mediated motor inhibition, involving interactions between primary motor and sensory cortices, is responsible for 'negative myoclonus' has been debated. When negative myoclonus is preceded by positive myoclonus, it is likely that the first clinical event (positive myoclonus) corresponds to the MEP seen in stimulation studies, while the second clinical event (negative myoclonus) corresponds to the SP.[31] A patient with negative myoclonic status epilepticus was studied and a correlation found between the duration and amplitude of an EEG spike in hand sensory cortex and the subsequent SP duration, suggesting that the discharge in the sensory region inhibited tonic excitatory output of the corresponding motor cortex through corticocortical connections.[6]

On the other hand, negative motor areas have also been proposed to account for negative myoclonus.[32,33] Ikeda *et al.* distinguished three types of responses to single pulse subdural grid responses (MEP followed by SP; SP alone; and MEP alone) when stimulating in primary and nonprimary motor areas, including the NMA in two patients.[26] Their results were generally consonant with prior TMS data suggesting inhibitory corticocortical mechanisms in primary sensorimotor cortices,[27,34] and their finding of a single MEP-SP complex in nonprimary cortex (in one of two negative motor areas tested; the other showed no response) also illustrates an additional level of complexity in that the cortex designated 'negative motor area' may display different functions and properties depending on the stimulus parameters used.

Thus while electrical correlates like those associated clinically with negative myoclonus has been seen during stimulation of the negative motor area (i.e., MEP-SP), negative myoclonus is more consistently associated with distinct, primary sensorimotor cortical inhibitory phenomenon. The relationship between this corticocortical mechanism and the negative motor effect that is the focus of this chapter is, in this light, intriguing and will be discussed further below.

On the whole, it seems reasonable to conclude that there is a cortico-cotrical inhibitory mechanism involving the inhibition of tonic excitatory output of the primary motor cortex by adjacent sensorimotor areas, and that this is the most frequent, if not exclusive, mechanism underlying clinical or epileptic negative myoclonus.

Cortico-cortical II: inability to generate voluntary movements with stimulation of mesial or lateral negative motor areas

With respect to the two additional forms of cortically mediated motor inhibition above, the picture of the inhibitory effect seen with stimulation of the PNMA and SMNA becomes at once sharper and more complex. The dissociation of fine, distal movements from preserved posture with NMA stimulation argues for separate systems, and the corticoreticular-spinal pathway is well established.

While TMS-elicited MEP-SP inhibition in primary sensorimotor cortex and the response to 50 Hz electrical stimulation in the negative motor areas do have significant differences, the relationship between them is less clear. Like the MEP-SP response, activation of the NMA may lead to combined positive and negative responses, as in a case of ictal face twitching with ispilateral paralysis.[6] This combination is not known to occur with stimulation, though. Also, the correlation between induced effect (MEP-SP) and clinical effect (positive myoclonus followed by negative myoclonus) is more compelling for the MEP-SP form of corticocortical inhibition. The existence of even the single MEP-SP complex by stimulation of a negative motor area by Ikeda *et al.*[26] highlights two further issues: the dependence of the negative motor area cortex's response on stimulus type, and the possibility that these two forms of cortical inhibition depend on each other and may use common intermediate circuits.

Additional sources of uncertainty concern the relationships between the physiologic function of these areas in a normal brain, varying pathology in the relatively small number of patients studied, and varying brain states that may affect the gating and input/output characteristics of adjacent and distant cortical areas. Precisely what a given form of stimulation achieves in terms of meaningful neural circuits (combinations of functional ablation, inhibition, or activation) is also unclear.

Overall, though, it seems reasonable to consider that the brief MEP-SP response seen on TMS stimulation of primary sensorimotor cortex depends on reciprocal corticocortal connections that inhibit tonic excitatory motor output, and that this is distinct from the motor inhibition elicited by high

frequency stimulation of negative motor areas, which persists for up to the 20-second duration reported by Lüders *et al.*[6] To gain insight into the circuits on which negative motor area effects depend, we now consider animal correlates and connectivity.

Animal correlates and connectivity

Primate studies: connections, and stimulation data

Extending early 20th century work by the Vogts[35] and Brodmann,[36] more recent studies of primates show three key results. First, primate mesial frontal cortex can be divided on the basis of cytoarchitecture,[13] connections to the thalamus[37,38] and cortical areas,[39–45] and responses to behavioral tasks and stimulation[46–52] into caudal and rostral areas that analogous to the human SMA and pre-SMA. Second, those results are consistent with a 'higher level' motor function for the area analogous to the human pre-SMA. Finally, in primate lateral frontal cortex, there is an area whose cytoarchitecture, pattern of connection, and physiologic response to goal-oriented movement is similar to the more rostral portion of the primate mesial frontal cortex.

The primate mesial frontal region corresponding to the human supplementary sensorimotor area (SSMA) has been designated F3 by Matelli *et al.*[13] It contains giant pyradimal cells in layer Vb and has output to corticospinal tracts.[41,42] The more rostral area, corresponding to human pre-SSMA, has a layer V, but not pyramidal output cells. This area is called F6, and it does not contribute directly to corticospinal output.[40,45] Where thalamic afferents to F3 from the putamen via the nucleus ventralis lateralis, pars oralis (VLo), F6 afferents originate from the caudate via the nucleus ventralis anterior, pars parvocellularis (VApc).[37,38] Corticocortical connections also differ: F3 receives afferents from F1 (corresponding to Brodmann's area 4), F2 and F4 (corresponding to Brodmann's area 6), and the cingulate. F6, in contrast, receives extensive connections from prefrontal areas and F5 (Brodmann's inferior area 6), which is anterior to the primate premotor area.[43,45,48,53] Figure 107.4 schematically shows these cortical afferents. Coupled with behavioral studies showing F6 cell response prior to reaching as a function of whether or not the target is reachable[51,52] and easily elicited somatotopic movements from F3 but more complex, natural appearing movements at higher thresholds from F6,[46,49] these studies support the notion of a 'higher level' planning or organizational function in the rostral portion of primate medial frontal cortex. The more caudal portion, F3, is tightly linked to areas with corticospinal output, and contributes corticospinal output itself, consistent with a role in the execution of movements.

The lateral primate cortex includes F2 superiorly and areas designated F4 and F5, as shown in Figure 107.4. As noted, the rostral mesial frontal area F6 receives afferents from F5, but not from F4. The firing of subpopulations of neurons in area F5 correlate with goal-related ipsilateral and contralateral distal movements involving the hand and mouth, and are also responsive to sensory and visual stimuli.[54] The overlap in humans between the lateral NMA and Broca's area, taken with these results, suggest that area F5 in primates corresponds to the human lateral NMA. It is also tempting to speculate that the evolution of language in humans, including gestures and fine motor aspects of facial and laryngeal muscles in producing speech, is rooted in the functions of this area.

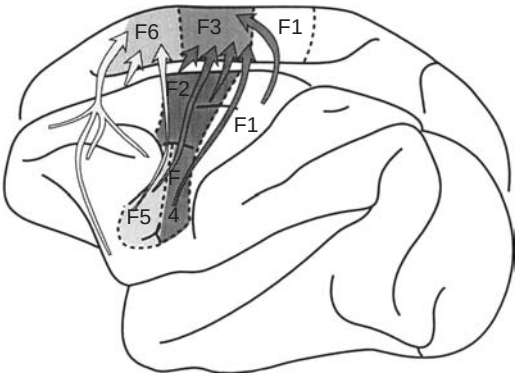

Figure 107.4 Primate cortical connectivity, from ref. 66 (Matelli *et al.*) in ref. 6.

Apraxia versus paralysis: a testable hypothesis

The considerations above suggest a testable hypothesis to distinguish a mechanism for the negative motor area effect at the level of analagous clinical descriptions: apraxia versus paralysis.

If stimulation of negative motor area cortex interferes with higher level organization of fine, distal movements, then the 'downstream' machinery, including corticospinal connections from primary motor cortex, should be intact. Simultaneous stimulation of the negative motor area (interrupts organization) and the positive motor area (intact circuitry) results in a typical brief jerk characteristic of primary motor stimulation in (for example) the finger area, which has been previously mapped with standard mapping technique. This result is consistent with metaphoric 'apraxia,' a concept that properly refers to complex volitional behavior.

If negative motor area inhibition instead operates by disabling that subset of motor outputs for the affected movements, simultaneous stimulation should result in an absence of a typical primary motor response for the affected muscles, consistent with paralysis.

Clinical correlates and effect of resection

Clinical correlates for negative motor areas include data from seizures, strokes, and electrophysiologic study. One report attributed focal akinetic seizures of the contralateral arm to lesions in the medial frontal area,[55] though the conrtibutions of the lesion and its extent, as well as the epileptic activity, are difficult to separate and may occupy altered anatomy.

Negative myoclonus in the contralateral upper limb following anterior mesial stroke has also been reported.[56] It has been postulated that negative myoclonus may result from activation of negative motor areas,[57] though this has been disputed on the basis of the time disparity between brief negative myoclonus and sustained, longer stimulation-induced negative motor effects[58]

and discussed earlier in this chapter. Differences between intrinsic activation by epileptic activity may be quite different than extrinsic activation by cortical stimulation. A recent study with stereo-EEG stimulation suggested that transient negative motor area activation following SSMA stimulation might be responsible for silent periods not preceded by enhanced EMG activity[11] despite the time disparity between stimulation-induced negative motor effects and negative myoclonus.

There appear to be no surgical outcome studies specifically addressing either the mesial or lateral NMA. An 'SMA Syndrome' following SMA resection has been described in tumor and epilepsy patients. Features include reduced spontaneous movements and movement to command with relatively unaffected limb tone and preserved overleaned motor actions; hemineglect and apraxia of contralateral limbs are also seen. Transient speech deficits are seen when the resection involves the dominant hemisphere, and there may be preoperative increased signal on functional MRI in the SMA of the healthy hemisphere.[59] If motor cortex is spared, these tend to be transient with recovery in a few weeks and virtually complete recovery by 24 months.[60] In a recent series of 27 tumor patients with variable resection of the posterior third of the superior frontal gyrus, the incidence of any deficit was 26% and all deficits had resolved at 24 months follow-up.[61] These studies comprise limited numbers of adult resections of diverse pathology that may include, but are not limited to, the pre-SMA. Inferences about pre-SMA function and postoperative deficits are therefore tenuous.[62,63] Relating functional imaging findings from cognitive and motor control studies with pre-SMA and SMA proper differentiation may be a fruitful area for further exploring the negative motor effects as well as surgical outcomes.

In the area of the lateral NMA, a small series of patients with seizures involving the face and head seemed to follow the general rule that, if primary motor cortex is spared, postoperative deficits are transient or mild.[64]

Nomenclature and the term 'negative motor area'

The term 'negative motor' is used in two ways: to specify a location (negative motor area) and to describe an effect seen with cortical stimulation (negative motor effect).

Calling a cortical location a 'negative motor area' implies that some cortically generated negative motor phenomenon (stimulation-induced, epileptic, or physiologic) is subserved by that cortical area. The term may thus be considered vague unless a more specific effect (as in the 'Mechanisms' section of this chapter) is made explicit, or unless all cortically generated negative motor effects are intentionally referred to as a group. Thus, specifying a location as a 'negative motor area' seems valid when the distinction between types of negative motor effects is clearly comprehended and communicated. At a more fundamental level is the question of whether 'negative motor' itself as an adjective is appropriate to describe a category including stimulation-induced, epileptic, or physiologic inhibition of movement.

The distinction between 'negative' and 'positive' is fundamental, and is considered coherent and useful elsewhere in medicine (e.g., the negative and positive symptoms of schizophrenia; 'negative and positive myoclonus'). In the context of inhibiting certain types of movement, a 'negative' response to cortical stimulation is perhaps less intuitive, but as robust as the clonic jerks (M1) or more complex movements (SSMA) elicited by cortical stimulation as described elsewhere in this volume. One might suppose that 'negative motor effect' means an movement that is opposite (opposing muscle group) to a corresponding positive movement. Also, since movement occurs due to muscle contractions ('positive') and there is no corresponding active 'relax' signal generated by the nervous system, the term may again seem counterintiutive or confusing. As with many terms in medicine and elsewhere, some prior knowledge is assumed in order to understand this term and how it is used. Thus, the term 'negative motor' usefully names a category of cortically mediated inhibition, and can be appropriately qualified to refer to specific kinds of inhibition within that category.

Summary

Electrical stimulation of regions in specific regions of the mesial superior and lateral inferior frontal lobe at 50 Hz interrupts distal, mostly contralateral movement of the fingers, toes, hands, tongue, and eyes in variable combinations with no alteration in awareness until the patient notices the inability to enact the movements. This may be mediated through interruption of higher-level 'organizational' aspects of motor output (apraxia) or by disabling a subset of cortical motor output (paralysis). Simultaneous stimulation of positive and negative motor areas affecting the same muscles would be informative in distinguishing these two possibilities. The category of cortically mediated negative motor phenomenon also includes corticoreticulospinal pathways with bilateral influence mediating postural and proximal muscle tone, and cortico-cortical connections that inhibit tonic excitatory output from primary motor cortex as seen with TMS-induced silent periods.

Negative motor areas have a special interest in the era of functional imaging because of their strategic location between 'lower order' motor output cortex and 'higher order' frontal cortex, promising insight into general mechanisms of interaction among cortical areas serving diverse functions at different levels.

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108 Cortical mapping by electrical stimulation of subdural electrodes: supplementary sensorimotor area in humans

DS Dinner and HO Lüders

Introduction

In the second half of the nineteenth century Fritsch and Hitzig pioneered electrical stimulation studies of the brain in a animals.[1] They discovered that electrical stimulation of the cerebral cortex produced contralateral motor activity. In 1888 it was demonstrated in monkeys that electrical stimulation of the precentral gyrus and the mesial aspect of the superior frontal gyrus anterior to the primary motor representation of the lower limb could produce movements.[2] The anatomic and electrical stimulation work of the Vogts demonstrated that the different cytoarchitectonic areas correspond to functionally independent regions.[3] On the mesial surface of the cerebral cortex, they defined three motor areas that they referred to as the primary, secondary, and tertiary areas that corresponded approximately to Brodmann's cytoarchitectonic areas 4, 6aa, and 6aB (Figure 108.1). Stimulation of area 4 produced movements of individual joints. These movements could also be produced by stimulation of area 6 but at higher stimulation intensities. They showed that this was via activation of area 4. Stimulation of area 6aa on the medial surface was also able to produce complex movements. Stimulation of area 6aB required even higher stimulation intensities to produce individual movements that were dependant on area 4, but also could produce postural movements including contralateral version.

Experimental electrical stimulation of the human cerebral cortex was first performed by Bartholow in 1874.[4] Krause (1911) was the first to elicit motor responses to electrical stimulation of human cortex.[5] Foerster reported on the findings from electrical stimulation of the cortex performed in more than 300 patients. He described accurately the human homunculus in area 4 including the somatic distribution of the leg and foot in the mesial precentral region (Figure 108.2).[6] In area 6aa he described movements of isolated joint movements similar to those elicited in area 4 but triggering of isolated joint movements required higher stimulation intensities and the effects were dependant on an intact area 4. On the other hand, following lesions of area 4 stimulation of area 6aa was still able to produce complex movements. These earlier observations were complemented by the work of Penfield and Brodley, who did extensive studies using electrical stimulation intraoperatively to describe the motor and sensory representation of the human cerebral cortex.[7]

Penfield and Welch were the first to define in humans the supplementary motor area (SMA), the region of the mesial superior frontal gyrus (SFG) from where motor responses were elicited by electrical stimulation and distinguished it from the primary motor area (PMA) of the mesial and lateral convexity of the frontal lobe.[8,9] They found that stimulation of the mesial surface of the superior frontal gyrus elicited complex postural movements of all extremities. In addition vocalization, speech arrest, paresthesiae, inhibition of movement, and autonomic changes were elicited. They named this region the supplementary motor area (SMA). They chose the term supplementary not because they thought this region had a supplementary role in terms of motor function but to distinguish it from the primary motor area on the mesial and dorsolateral convexity. The SMA in humans was thus defined not anatomically but electrophysiologically. Motor and sensory representations within this functional region are intimately associated which led Lim *et al*. to refer to this area as the supplementary sensorimotor area (SSMA).[10]

Functional anatomy of the motor cortex

Traditionally the motor cortex was described as consisting of three motor areas: the primary motor cortex (PMA or M1) in the precentral gyrus, which houses a complete somatotopic representation of body movements; the supplementary motor area (SMA) or supplementary sensorimotor area (SSMA) on the mesial surface of the superior frontal gyrus rostral and ventral to the PMA, also containing a complete motor representation and the premotor cortex (PMC) on the lateral cortical convexity anterior to the PMA (Figure 108.2).[7]

However, in the latter part of the twentieth century investigations of non-human primates, particularly macaques has demonstrated a more complex division of the regions involved in the processing of movement. The use of modern anatomical and physiological techniques has enabled

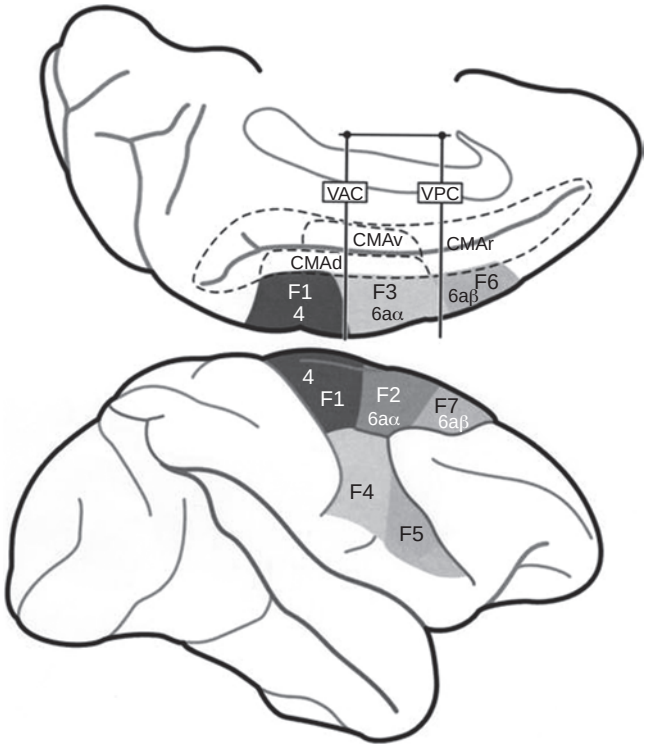

Figure 108.1 Diagram of macaque brain demonstrating motor areas with the cytoarchitectonic regions according to Brodmann and the regions according to the nomenclature of Matelli.

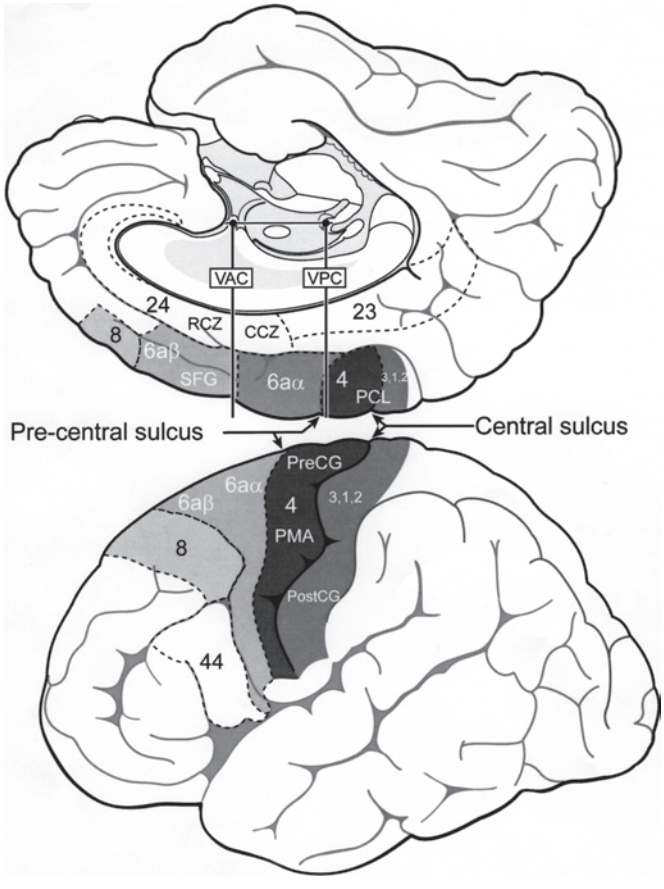

Figure 108.2 Diagram of human bain demonstrating motor areas with cytoarchitectonic regions according to Brodmann. SFG – superior frontal gyrus, PCL – paracentral lobule, PMA – primary motor area, Pre-CG – precentral gyrus, post-CG – postcentral gyrus.
VAC = Vertical anterior commisure line
VPC= Vertical posterior commisure line

researches to explore and define additional subdivisions of motor areas in both humans and primates.[11]

The PMA in macaques is in region F1 (Figure 108.1) which corresponds with area 4 in humans (Figure 108.2).[11,12] Rostral to this region area 6 can be subdivided on the mesial surface into the SSMA proper (F3) and pre-SSMA (F6) (Figure 108.1). On the dorsolateral cortical surface is the premotor cortex (PMC). Dorsolaterally is the dorsal PMC (F2 and F7) and on the dorsoventral cortical surface the ventral PMC (F4 and F5) (Figure 108.1). In addition motor responses have also been found in the cingulate cortex.

Primary motor area

It is agreed upon by most investigators that the primary motor cortex corresponds with Brodmann's area 4 and with F1 according to the nomenclature of Matelli.[11,12]

The PMA is located in the precentral gyrus on the anterior wall of the central sulcus and corresponds to Brodmann's area 4 (Figure 108.2). On the basis of cytoarchitectonic criteria, area 4 is recognized primarily by the presence of Betz cells (giant pyramidal cells) in cortical layer V and the absence of the granular layers II and IV. The central fissure marks the border between the agranular motor cortex and the granular somatosensory cortex in the postcentral gyrus.[13] The border between the two regions lies deep within the central sulcus. The rostral portion of the anterior bank and the superficially exposed part represents the anterior part of the cytoarchitectonic area 4 and is referred to as subarea 4a. The part of the precentral gyrus that is completely buried in the central sulcus and corresponds to the posterior portion of area 4 is referred to as subarea 4p. The lower layer III pyramidal cells are larger and more densely packed in area 4a and are smaller and loosely aggregated in area 4p. The cells are even larger in area 6. There are no differences in the Betz cells in area 4a and 4p. These two areas are also different in terms of their neurotransmitter binding sites, with a higher concentration of neurotransmitter binding in 4p than 4a.[14,15] The somatotopic organization of the primary motor cortex was elucidated by the pioneering work of Krause, Foster, Penfield, Jasper and others.[5,6,16] In Brodmann's area 4 simple movements can be elicited with the lowest intensity of electrical stimulation.[17] Maps of the motor cortex demonstrate an orderly arrangement with the tongue and lips close to the sylvian fissure and thumb, digits, arm, and trunk represented successively along the central sulcus ending with the leg, foot, and toes on the medial surface. The layout of the motor homunculus is topographically similar to that of the somatosensory homunculus, which resides immediately behind the PMA in the postcentral gyrus. The output of the PMA is directed to the corticospinal and corticobulbar tracts as well as to the SSMA and homologous areas in the opposite hemisphere via corpus callosum.[18]

Supplementary sensorimotor area

The supplementary sensorimotor area (SSMA) is a distinct anatomic region located on the mesial surface of the superior

frontal gyrus (SFG) and its adjacent dorsal convexity.[9] The cerebral cortex of the SSMA corresponds to the mesial portion of area 6 of Brodmann's cyto-architectonic map of the brain (Figure 108.2). The SSMA similar to the PMA cortex is referred to as agranular cortex, because the granular layers (layer II and IV) are not prominent. In contrast to area 4, area 6 does not contain Betz cells.[19] An extension of the precentral sulcus on the medial surface defines the border between the PMA for the foot and the posterior limit of the SSMA.[10,20] No clear cytoarchitectonic or anatomical boundary exists to separate the SSMA from the adjacent premotor cortex. [21]

Histological studies found very similar architectonic features in Macaque F3 and F6 and human mesial areas 6aa and 6aB respectively.[21,22] Area F3 and mesial area 6aa both have increased cell density in lower layer III and layer V. Both are well demarcated on the dorsal convexity from area F2 and from lateral area 6aa respectively. Area F6 and mesial area 6aB are clearly laminated and both have a prominent layer V, are well separated from layer III and layer VI. Both are well demarcated on the dorsal convexity from area F7 and lateral 6aB respectively. In humans the border of mesial area 4 (PMA) and mesial area 6aa corresponds with the vertical through the posterior commissure (VPC) line. The border between mesial area 6aa (SSMA proper) and mesial area 6aB (pre-SSMA) corresponds with the vertical line through the anterior commissure (VAC) line (Figure 108.1 and 108.2). These lines are perpendicular to the AC-PC line.[21,23]

Neurochemical binding sites appear to be similar in these areas in macaques and humans.[15,21,22] The receptor densities are highest in the somatosensory areas. Of the motor areas, area 4 has the lowest mean densities of GABA-A, muscarinic M1 and M2, kainite, 5-HT1, a1 and a2 receptors. Pre-SMA has higher densities of M2, kainite, 5-HT1, a1 and 5-HT2 receptors than the lateral premotor cortex. The inverse relationship between the receptor densities in both areas is found for AMPA and 5-HT1 receptors. M2 receptor density is lower in the rostral portion of the cingulate (cmr) than in the pre-SSMA, but is higher in the medially adjoining cingulate periallocortex. The NMDA, AMPA, a1 and 5-HT2 receptors are of higher densities in the cmr than in the pre-SSMA.

Microstimulation studies demonstrated that the F3 region corresponding to SSMA proper could be activated at low intensity stimuli.[24] It was found that there was a somatotopic organization within this region. The hind limb is located caudally and the forelimb rostrally. A small orofacial representation lies anteriorly at the border with area F6. This is similar to the somatotopic organization defined in the SSMA proper of human cortex.[10] The average excitability threshold in F3 was higher than in F1.

The movements elicited from stimulation of area F3 were complex, whereas those from F1 were simple movements. The majority of the movements elicited by stimulation of F3, were proximal movements alone or were combined with movements of other segments. A pure distal movement in response to stimulation of F3 was infrequent.

In contrast, in F6 excitability was less than in F3. However, movements could be produced at about 50% of the tested sites, when stimulating with long train durations or stimulating while the monkey was making spontaneous movements. The movements usually are of the forelimb but neck and upper face movements were also observed. Whereas movements elicited from stimulation of F3 were fast, those from F6 were mostly slow and many mimicked natural movements of the animal.

In terms of single neuron activity, phasic neuronal activity time locked to movement onset was more frequent in F3 than F6.[25,26] Premovement activity was longer and more frequent in F6 than in F3.[15,16]

In F6 there were neurons related to arm movements that discharge greatly in advance of the actual movement and their activity was influenced by the distance of the object from the monkey.[27]

Further studies showed that F3 and F6 differ in regard to their cortico-cortical, cortico-spinal and thalamo-cortical connections.[28]

All these differences in the two areas support that they are two distinct regions with independent functions. F3 corresponding to the SSMA proper plays a role in motor control close to movement execution. F6 corresponding to the pre-SSMA may represent a nodal point in transmitting information from prefrontal and cingulate areas to other premotor areas and thus may play a role in motor control at a higher hierarchal level. The division of these two functional areas led Tanji and his co-workers to propose that the caudal area F3 be termed SMA proper and the rostral area F6 be termed the pre-SMA.[29] Because of the similarity of the two mesial areas in monkeys and humans Zilles and co-workers proposed that the same terms be adopted in regard to human SMA, area 6aa be termed SMA proper and area 6aB be termed pre-SMA.

Premotor cortex

The term premotor cortex (PMC) was coined by Fulton in 1935 to describe the third major component of the motor cortex. This area encompasses the more loosely defined agranular cortex of the lateral frontal convexity rostral to the PMA,[7,30] which corresponds to the lateral portion of Brodmann's area 6 (Figure 108.1). It is very difficult to define the anterior border of the agranular PMC in humans, where a broad zone of progressive transition exists between area 6 and the granular cortex of Brodmann's frontal area 8.[31] In the macaque the premotor cortex is further subdivided into a dorsal portion (PMd) corresponding to F2 and F7 on the dorsolateral convexity and a ventral portion (PMv) corresponding to F4 and F5 on the ventrolateral convexity (Figure 108.1).[12] Despite the lack of direct correlation between microstructure and function in humans, the two subdivisions of the premotor cortex are considered to have homologous counterparts in the human brain.

The motor and premotor cortices as well as the frontal eye fields and the anterior cingulate cortex (area 24) have been shown to have reciprocal connections with the SSMA. Anatomic labeling experiments in the macaque have demonstrated that the more anterior dorsal PMC projects to the spinal cord challenging the notion that the premotor cortex, unlike the PMA and SSMA lacks prominent cortico-spinal connections.[30,32,33]

According to the classic schema, the PMC is responsible for the preparation and organization of movements.[21] Several recent studies have shown that the PMC also plays a

central role in non-motor attentional and receptive domains. Therefore, our current understanding suggests a dual PMC function pertaining to motor and cognitive behavior.[34]

Cingulate cortex

The cingulate motor cortex, which was previously linked to the limbic system, is now viewed as a potential fourth motor area. The cingulate in humans can be divided into an anterior and a posterior portion with the border approximately midway between the VAC line and the VPC line. The anterior part of the cingulate cortex is agranular with layer IV absent. Layer V is prominent. In contrast the posterior portion of the cingulate cortex is granular with the layer IV being present. Strick and colleagues subdivided the cingulate cortex into two zones, separated by the VAC line into the caudal cingulate zone (CCZ) and the rostral cingulate zone (RCZ).[35] The CCZ overlaps with the posterior part of area 24. The RCZ overlaps with the anterior part of area 24 and with area 32 and is subdivided into an anterior part RCZa and a posterior part RCZp.

Prefrontal cortex

The term 'prefrontal cortex' is used to define the extensive part of the frontal lobe that lies anterior to the motor and premotor zones.[14] It includes the mesial frontal cortex anterior to the SSMA, the dorsolateral cortex and the orbitofrontal cortex.

Functional neuroimaging

Activation studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) allude to the complex organization of the motor system. The breadth of cortical and subcortical areas activated with even the simplest movements attest to the wide distribution and extent of interconnected neural networks underlying motor control.[36] Observed movements presuppose a series of parallel or sequential processes involving the selection, planning, preparation, and initiation of action.[36,37]

PET

PET scans have shown an increase in cerebral blood flow in the mesial frontal region in association with finger movement, proximal arm movement, and eye movements. There appears to be a somatotopic organization in that the activation with finger movements is anterior to that with proximal arm movements and that with eye movements is the most anterior.[38] This is similar to the somatotopic organization that has been documented by electrical stimulation.[10] A significantly higher activation has been documented with complex finger movements rather that with simple movements.[39] The Parma group found that with simple movements only a restricted portion of the mesial frontal cortex demonstrated an increase in the regional CBF. This region by co-registration with MRI was located in the region between the VAC and the VPC lines in the region consistent with the SSMA proper. Only when the subjects were required to plan or perform complex sequences of movements was there more extensive activation of the mesial frontal cortex, the rostral region thought to be involving the prefrontal cortex and the more caudal region attributed to involvement of the SSMA. In studying the effect of simple distal movements and proximal movements, both resulted in increase regional CBF in the region of the SSMA proper.[40]

However the PET scan measures blood flow only over relatively long periods of time, 1 – 2 minutes, compared to a baseline or resting condition. This does not provide the temporal resolution necessary to examine the premovement activity associated with movement preparation.

fMRI

The early studies with fMRI studies used blocked designs in which the individual being studied alternated between periods of continuous task performance and baseline or resting conditions. Thus only static activation maps could be produced showing areas of the brain which significantly change in their activity overall while performing the task. Figure 108.3 demonstrates the activation of the SSMA in patient performing finger movements of both hands.

More recently single event related or time resolved fMRI have been employed and are able to provide some temporal resolution and to detect the time course of hemodynamic responses in the different regions with different tasks. The BOLD fMRI responses are much slower than the neuronal activity, reaching peak amplitude about 4–5 seconds after the event and returning to baseline approximately 10–12 seconds after the event.[41] Several studies using event-related and

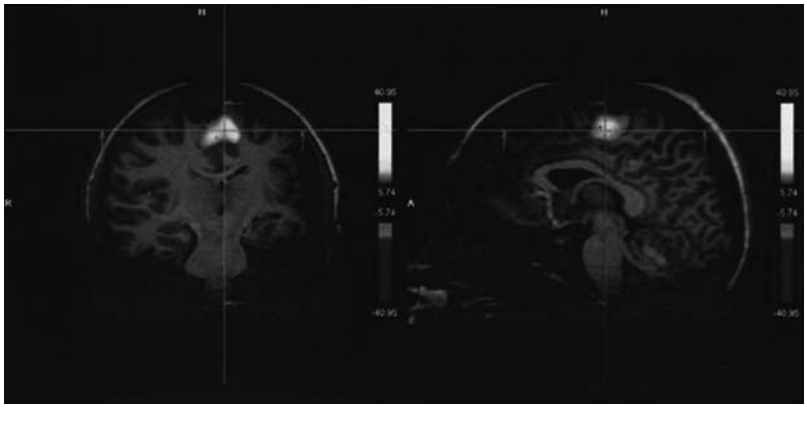

Figure 108.3 Functional MRI demonstrating activation of the SSMA in response to finger-tapping of both hands. (See Color plates.)

time-resolved fMRI have examined the time sequence of activation during self-initiated movement. These studies demonstrated that activation in the pre-SSMA preceded activation of the PMA by 2.0 secs which is similar to the premovement duration of the Bereitschaftspotential.[42–45]

High-field fMRI's obtained with 3 Tesla magnets have been used to investigate the somatotopic organization of the motor representation in the medial aspect of the cerebral hemisphere.[46] They had normal volunteers move either the right forefinger or their toes. They defined separate areas of activation in the SSMA and in the cingulate motor area (CMA). They found within the SSMA that finger movements resulted in activation more rostral than toe movements. This somatotopic organization is similar to the findings on electrical stimulation in humans.[10] The area activated by finger movements extended rostral to the VAC line into the region which usually is defined as the pre-SSMA. However, a recent cytoarchitectonic study provided evidence that the SSMA proper may be subdivided into a rostral and a caudal portion and that the rostral portion may extend as much as 20 mm rostral to the VAC line.[23]

Electrical stimulation

Methodology

The initial electrical stimulation studies of the SSMA in man were performed intraoperatively. Although during intraoperative electrical stimulation, direct visualization of the position of the electrodes in relation to the cortical surface anatomy is possible, there are distinct disadvantages to this technique. The mesial aspect of the SFG is difficult to access due to the presence of bridging veins. It is also very difficult to recognize by direct visualization specific gyral landmarks within the depths of the interhemispheric fissure. There are significant time constraints when electrical stimulation is performed intraoperatively. Extraoperative electrical stimulation via depth or subdural electrodes has definite advantages most importantly the relative absence of time constraints. Responses to electrical stimulation may be repeated to ensure reproducibility and videotaped for subsequent review. However, the disadvantages of the extraoperative technique is that it requires an additional surgical procedure and complications (infections, increased intracranial pressure) from having an intracranial foreign object implanted. Besides the electrodes are in a fixed location, cannot be moved as is the case for intraoperative electrical stimulation studies, and the relatively large size of the electrodes makes fine somatotopic studies impossible.

In regard to placement of depth electrodes, X-rays of the skull, gaseous encephalography, vertriculography, and angiography were performed to define the location of the depth electrodes in the French studies.[47] In Van Buren's study, localization of the electrodes was based on tracings of the lateral pneumoencephalogram superimposed on lateral skull X-ray films with electrodes in place.[48] In our earlier studies, the anatomic location of the electrodes[10,49] was determined by superimposing the lateral skull X-ray with the subdural electrodes in place on the pre-operative magnetic resonance imaging (MRI) scan.

The studies reported here were performed using subdural electrodes that are non-ferromagnetic thin platinum disks, with the exposed surface measuring 2.3 mm in diameter. Platinum-iridium electrodes may have a theoretical advantage in stability as compared to stainless steel electrodes when current is passed. The interelectrode distance was 1 cm. The array of electrodes varied from 8×8 to 1×11 grids or any combination there of and it was tailored to the cortical area of interest.

The position of the electrodes on the cortical surface was verified by identifying them individually on post-operative 3-D MRI. It is important to ensure that there is an adequate coverage of the cortical area whose function we attempt to evaluate by stimulation (Figure 108.4). Safe delivery of focal electrical stimulation with minimal spreading to adjacent cortical areas is necessary to determine that an observed response can be attributed to the stimulated area. Nathan *et al.*, by using finite element modeling found that the current density drops off rapidly with increasing distance from the tissue underlying the stimulating electrodes (FEM).[50] Recessing the edges of the electrodes in the plastic, which embeds them, provides reliable focal stimulation with a rapid and smooth current drop away from the stimulating site.

There is evidence that intermittent cortical stimulation carried out over several days for mapping in humans with the current protocols specified below does not result in any cortical damage and is felt to be safe.[51] The afterdischarge thresholds may vary over a tested region of the brain with recurrent

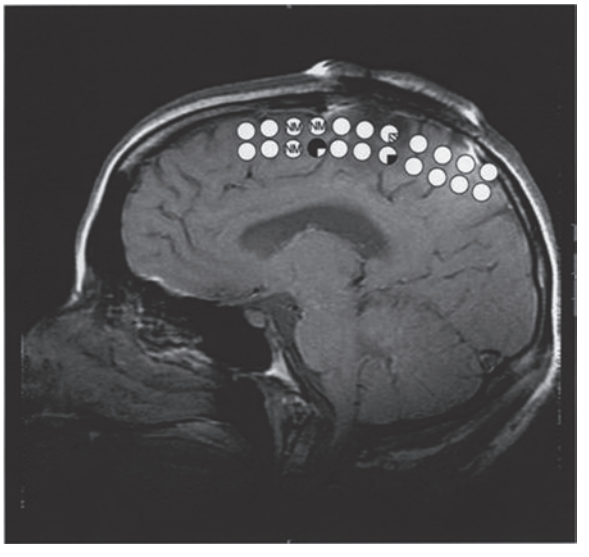

Figure 108.4 Midline sagittal MRI of the right cerebral hemisphere in a patient with electrodes for evaluation of here intractable mesial frontal lobe epilepsy. Electrode positions were defined by postoperative MRI with electrodes implanted. Electrical stimulation of the electrodes resulted in responses demonstrated.
NM = Negative motor response
L= Left
abd= abduction
BUE= Bilateral upper extremity
LLE= Left lower extremity
Sz = seizure

electrical stimulation on different days, but there is no evidence to support any progressive decrease in the afterdischarge threshold which would be expected with a kindling phenomenon.[52,53]

We use stimulus pulses of 0.3 ms duration of alternating polarity at the rate of 50 pulses per second. The testing is routinely begun at a low intensity of 1.0 mA and increased gradually by 0.5–1.0 mA until an afterdischarge, clinical response or maximum stimulus strength of the instrument is reached (15 mA with Grass S88 stimulator, 17.5 mA with Grass S12 stimulator, and 20 mA with an Ojeman stimulator). The duration of a stimulus train is usually 5 sec for the initial screening. When afterdischarges occur, one can usually retest at the same stimulus intensity without recurrence of afterdischarges. Subsequently, it is not unusual to observe that a gradual increase in the stimulus intensity much beyond the initial threshold for afterdischarges can be attained, without eliciting additional afterdischarges. It is important to bear in mind that the afterdischarge threshold can vary even within adjacent electrodes and from one day to the other, and hence one must establish the afterdischarge threshold for each cortical area every time it is tested.[52]

Responses

Positive motor response

In the initial study, the Montreal group found that on the dominant hemisphere, the SSMA was separated from the PMA by a strip of cortex.[8,9] The French group, however, reported no separation between the SSMA and the PMA.[47] We also found no separation between the SSMA and the PMA.[10]

In a preliminary study of contralateral upper extremity movements elicited by electrical stimulation of the PMA and the SSMA, we found that PMA responses were predominantly clonic in nature and distal in distribution, whereas the responses from the stimulation of the SSMA were predominantly tonic and proximal.[10] Based on these observations, we classified isolated movements of the contralateral lower extremity that were predominantly clonic and distal as PMA-type responses, while those that were predominantly tonic and proximal as SSMA-type responses. Besides, bilateral movements of the lower extremities, ipsilateral extremity movements, and combined upper and lower extremity movements, were defined as SSMA-type motor responses. With regard to ipsilateral and bilateral extremity movements, Fried noted that these movements were elicited almost exclusively from the right hemisphere and interpreted this as an indication of a left-right hemispheric specialization.[54] However, we found these movements from both hemispheres, more often from the left (dominant) hemisphere in five patients, than the right (non-dominant) hemisphere in two patients.[10]

SSMA-type positive motor responses can also be elicited from the dorsal convexity of the SFG; we found this in three of our 15 patients. This observation was first made by the Montreal group.[8,9] We found SSMA-type responses were elicited not only from the mesial surface of the SFG but also from the lower half of the paracentral lobule (Figure 108.2). The possibility that such responses in these regions were due to spread of current to the classical SSMA location (mesial SFG) is unlikely since in our study we ensured stimulation was always below the afterdischarge threshold and there were other types of responses or no responses between these regions and the mesial SFG. We cannot exclude the possibility of activation of the mesial SFG by interhemispheric interconnections.[55–57] In fact, there is evidence of reciprocal interconnections between the SSMA and the PMA.[58,59] However, different characteristics of movements in man when stimulating the SSMA and the PMA argue against indirect activation of the PMA.[10] The SSMA does have direct projections to many subcortical structures including the spinal cord.[60–64] It has been reported that stimulation of the anterior cingulate cortex in humans produces various complex behaviors such as touching, rubbing, and sucking.[65] In our study we confirmed that stimulation of the upper half of the middle portion of the cingulate gyrus in humans could elicit bilateral tonic lower and upper extremity movements. However, we could not verify Talairach's findings of eliciting complex automatisms by stimulation of electrodes over the anterior third of the cingulate gyrus.

Supplementary eye field (SEF)

The term supplementary eye field was introduced to refer to a region on the dorso-medial surface of the frontal lobe in monkeys where conjugate contralateral eye deviation was elicited by electrical stimulation.[66] This region was within area 6. Eye movements in response to electrical stimulation were also described with the initial description of the human SSMA.[8,9] The French group described that they elicited eye movements in association with head movement anterior to the region for the SSMA upper extremity representation.[47] Most of the responses were from the mesial surface of the SFG with some responses from the upper half of the anterior cingulate gyrus. In our study, we found also that eye movements were closely associated with head movements. These responses occurred from the mesial SFG and from the paracentral lobule.[10] The responses had similar characteristics to those elicited by stimulation of the frontal eye field over the lateral convexity.[67]

Sensory responses

The Montreal group speculated that a region with sensory representation of the extremities bilaterally should exist within the sagittal fissure posterior to the Rolandic foot area.[8,9] They referred to this region as the supplementary sensory area (SSA). However, they could not confirm its presence by extensive stimulation studies. The French group also could not confirm the presence of a SSA ('caudal to NI foot area').[47] Van Buren subsequently found sensory symptoms from electrical stimulation of the mesial SFG and the cingulate gyrus.[48] The sensory responses from the mesial SFG were contralateral and localized while those from the cingulate gyrus were diffuse with only a questionable contralateral predominance.

In our study, we found sensory symptoms consisting of numbness, tingling, or a pressure sensation which occurred in response to electrical stimulation of the mesial SFG, and cingulate gyrus. These phenomena occurred contralateral or bilaterally.[10]

Autonomic responses

Autonomic phenomena consisting of mydriasis and tachycardia were described in response to stimulation of the SSMA.[17] These findings were also described by the French group.[47] More recent studies have not confirmed these findings.

Somatotopic organization of the human SSMA

In the initial descriptions of the SMA, the Montreal group did not define the presence of a somatotopic organization.[8,9] Woolsey and colleagues were able to confirm the findings of the Montreal group but also did not define any somatotopic organization.[68] One of the great limiting factors was gaining adequate intrasurgical access to the mesial surface of the cerebral hemisphere (frontal lobe) to stimulate the SSMA. Human studies were usually preformed in regions in close proximity to structural lesions or epileptogenic cortex that could have resulted in distortions of the normal anatomy of the SSMA. A somatotopic organization was first described by the French group in their study of the SSMA with depth electrodes.[47] They described the presence of eye movements elicited in response to electrical stimulation anterior to the upper extremity responses. The presence of a somatotopic organization in the SSMA was confirmed more that 20 years later by the Yale group.[54] They demonstrated that representation of face, upper extremity, and lower extremity in the SSMA was organized in a rostral to caudal direction. We confirmed this somatotopic organization with lower extremity, upper extremity, and head representation from posterior to anterior, with the supplementary eye field located within the region for the head representation (Figure 108.5).[9] Figure 108.6 demonstrates the results of electrical stimulation in a patient with electrodes over the mesial SFG with responses from the primary motor representation of the foot and responses from the SSMA

Supplementary negative motor area

Inhibition of movement in response to electrical stimulation in the SSMA was first described by the Montreal group.[8,9] In our study, electrical stimulation of the mesial SFG resulted in inhibition of movement of all four extremities as well as the tongue.[10] This negative motor area is distinct from the primary negative motor area which is located over the lateral convexity of the frontal lobe. This supplementary negative motor area always appears to be located anterior to the SSMA ('pre-SSMA').

Speech function and SSMA

Speech arrest was first described in response to electrical stimulation in the initial description of the SSMA.[8,9] This was interpreted as aphasia, namely as indicative of speech function being represented in this region. Subsequently, Penfield and Roberts (1959) stated that speech interference could be caused

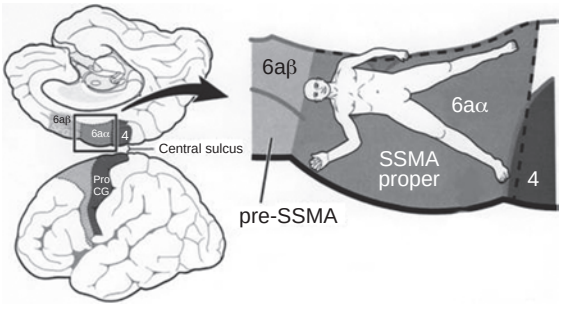

Figure 108.5 Diagram of the somatotopic organization of the representation in the SSMA proper.

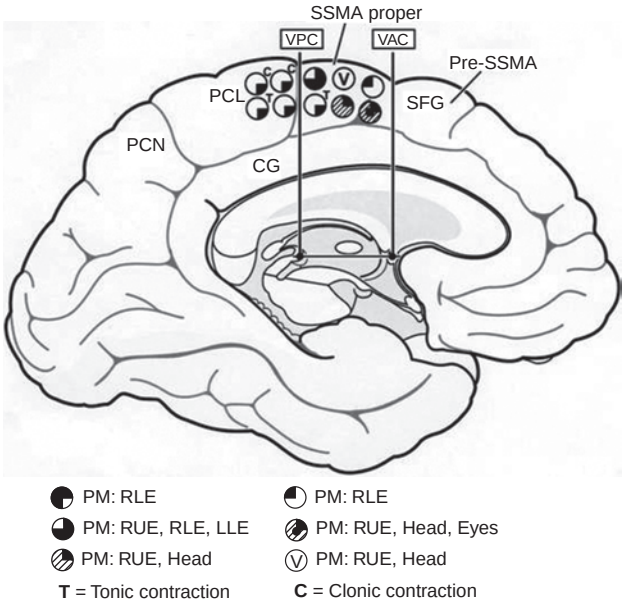

Figure 108.6 Diagram of the motor responses defined by electrical stimulation of the mesial frontal lobe in a patient with intractable left mesial frontal lobe epilepsy. Clonic and tonic contraction of the right lower extremity were observed. Somatotopic representation of motor responses in the SSMA proper is shown with tonic contraction of both lower extremities and the right upper extremity occurring more posterior and right upper extremity, head and eye movement from regions more anterior.
PM Positive Motor Response
RLE Right Lower Extremity
RUE Right Upper Extremity
LLE Left Lower Extremity

either by inhibition of movement resulting in slowing or arrest of speech or aphasia. Van Buren and Fedio interpreted the speech interference in this region as being secondary to inhibition of movement and did not think there was an independent language area in this region.[48] In our series, two-thirds of the patients demonstrated speech arrest or a greater than 50% slowing of speech secondary to inhibition of movement of the tongue. None of these patients had any interference with language comprehension or speech arrest independent of a negative motor response involving tongue movement and frequently also the extremeties.[10] In previous studies which demonstrated speech arrest in the SSMA, there was no systematic evaluation made for the presence of a negative motor response involving the tongue that may have explained this finding. Thus it likely that the speech disturbance observed by Penfield and Roberts was also secondary to a negative motor response.

Repetitive vocalization in man from electrical stimulation of the mesial superior frontal gyrus was described by Penfield's group and subsequently by Erickson and Woolsey (1951).[69] The French group also elicited vocalization in half of the patients from both the left and the right hemisphere.[47] Vocalization was also found in the study by Fried.[54] In our study, vocalization was elicited in four patients.[10] In three patients this was elicited from the left hemisphere and in one patient from the right. The vocalization was usually associated with rhythmic movements involving the mouth and jaw bilaterally and we interpreted this response as an expression of a positive motor response.

Movement related cortical potentials

Movement related cortical potentials (MRCPs) are cortical potentials associated with voluntary movement. ('Shibasaki *et al*.[39] described 3 MRCPs'.). The initial potential is the Bereitschaftpotential (BP), which is a gradual, usually negative polarity slope with onset several hundred msec prior to the movement.[70] This is followed by an increase in the negative slope which is labeled the NS′ potential. The third potential is the motor potential (MP). Early scalp recordings already suggested that the SSMA, in addition to the PMA, was involved in the generation of these MRPs.[39,70–73] This appeared to be the case, particularly with regard to the early components of the MRCP, the BP.[74,75] Our recordings from subdural electrodes also showed that the MRCPs recorded from scalp are most probably a summation of bilateral PMA potentials[76] and bilateral SSMA potentials.[77,78] These studies also demonstrated that the BP and NS′ associated with foot movements were of similar amplitude in the SSMA proper and PMA and that these potentials also occurred simultaneously. MRCPs in the SSMA associated with single and repetitive movements were also studied showing that both types of movements were associated with potentials of similar amplitude.[78]

The study also demonstrated that MRCPs associated with any given movement were strictly localized to electrodes which by electrical stimulation elicited movements in a similar somatotopic distribution. Thus, there was a clear somatotopic organization of MRCPs in the SSMA proper corresponding with the somatotopic organization demonstrated by electrical stimulation.[77] The BPs recorded from scalp are usually of negative polarity. However, with intracranial recordings from subdural or depth electrodes in experimental animals, BPs had a bipolar distribution with a negative pole at the surface and a positive pole in the deeper gray matter.[79–83] Recordings from subdural grids in humans confirmed these observations.[77,78] The onset time of the BP from the foot area of the PMA and of the SSMA proper are similar, but the movement related desynchronization before movement onset starts earlier at the SSMA proper than at the PMA.[84] The foot area of the SSMA proper generates BP with contralateral as well as for the ipsilateral movements. In contrast the foot area of the PMA generates BPs only in association with contralateral movements. The PMA generated BPs in association with movements at both slow and rapid repetition rates.[85] Movements in response to external stimuli resulted only in transient potentials most likely related to a discrimination task (namely, selection of the appropriate movement in response to an external dichotic stimulus). These potentials were recorded at the pre-SSMA with onset and peak latencies of 200 and 600 ms after S1 in the S1-choice of Go/No Go choice and S2-reaction time paradigm.[86,87]

Role of the SSMA

It has been specualted that the function of the SSMA is only providing a supplementary role in motor function as evidenced by the fact that surgical resection of this area tends to produce just minimal permanent neurologic deficits.[10,88,89] However, a significant bilateral motor neglect, worse on the contralateral side, together with mutism may follow resection of the SSMA proper. Although most of the neurologic deficits are transient (improvement in speech occurs in days to weeks), some impairment in bimanual coordination is frequently permanent. In a recent study it was found that if resection of atumor was at a distance of less than 5 mm from the SSMA proper, then the patients were likely to have post-operative neurologic motor or speech deficits, including contralateral hemiparesis and mutism.[90] Besides, all lesional studies only consider unilateral resections of the pre-SSMA or partial unilateral resections of the SSMA proper. We certainly do not know the possible impact of a *complete* unilateral SSMA resection or of a bilateral SSMA lesion. It is very likely that such lesions would have a major effect on voluntary movements. Bloodflow studies also show an increased perfusion in the SSMA during the phase of planning and execution of complex motor movements suggesting a supramotor role.[88,91] It is likely that the pre-SSMA (supplementary negative motor area in humans) plays an important role in the preparation of movement acting as a focal point in transmitting information from prefrontal and cingulate cortex to other motor areas including the SSMA proper and thus may play a role in movement at a higher hierarchal level.

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109 Cortical mapping by electrical stimulation of subdural electrodes: language areas

Nitin Tandon

History of cortical stimulation

The first record of stimulating the exposed human brain with electricity dates back to 1802, when Aldini (Luigi Galvani's nephew) produced right facial contractions by stimulating the left hemisphere of a criminal who had been judicially decapitated.[1] Shortly thereafter, there followed a publication by fellow Italian Luigi Rolando, relating to stimulation of the cerebrum and cerebellum in pigs.[2] In 1829, Rolando published the monumental *Della Struttura degli Emisferi Cerebrali*, detailing the surface morphology of the cerebrum, and describing the central area.[3] The notion of cortical localization proposed by him was contradictory to the prevailing notion of the times, which held that the motor centers of the brain resided in the corpus striatum. Advancement had to await the work of John Hughlings Jackson on patients with seizures, who proposed of this notion, a localizationist's view of cortical organization to explain the semiology of fits experienced by his patients.[4] In 1870, Gustav Theodor Fritsch and Eduard Hitzig provided irrefutable proof regarding the focal organization and excitability of mammalian motor cortex by stimulating canine cortex using Galvanic (direct) currents.[5] This, and the work of Ferrier,[6,7] confirmed the notions of Jackson, regarding the discrete spatial organization of motor functions.[8]

The understanding of cortical organization provided by this work and by postmortem studies on patients with focal neural deficits,[9,10] led to the birth of functionally guided neurosurgical procedures. In 1879, Sir William Macewen became the first to use these maps of motor function to diagnose and to operate on a patient with focal motor seizures. The first record of cortical stimulation in the awake human dates to 1874, when a Cincinnati surgeon, Roberts Bartholomew[11] elicited motor responses using insulated electrical wires passed through the dura in a patient with large bilateral calvarial and cutaneous defects. This patient had previously suffered extensive burns of the scalp, then developed bone loss related to a hair prosthesis, resulting in these large defects. She developed generalized convulsions following the stimulation and died three days later. Despite this sobering experience, the use of intraoperative cortical electrical stimulation to guide neurosurgical procedures continued, and as early as 1888, Charles Mills produced the first map of cortical localization, synthesizing data from multiple patients and using a variety of techniques.[12]

In 1886, Victor Horsley, at the National Hospital for the Paralyzed and Epileptic in Queen Square, performed a craniotomy on a patient with seizures that commenced in the face and found no visible lesion on the cortical surface. He became the first surgeon to perform intraoperative cortical stimulation, and to use localization data to plan a resection.[13,14] Two years later, William Keen became the first American surgeon to stimulate the human cortex as part of a craniotomy. He mapped motor function in a patient who experienced seizures beginning in the hand and resected the hand motor area, which improved the epilepsy.[15]

A German surgeon, Fedor Krause, used intraoperative cortical stimulation to guide the drainage of an 'encephalitic cyst' in a patient wracked by frequent focal motor seizures; the patient was rendered seizure free and led a healthy life for many years thereafter. His work on 400 patients with epilepsy led to the first detailed and accurate map of the human motor cortex.[16–18] Another German, Otfrid Foerster, a neurologist turned surgeon, through extensive work on soldiers with penetrating cerebral trauma suffered in World War I, generated maps of brain regions even outside of motor cortex. He was assisted in this by a visiting American neurosurgeon, Wilder Penfield.[19] Foerster also pioneered the use of intraoperative electrocorticography[20] to detect abnormalities in the EEG in the vicinity of cerebral lesions and was the first to describe vocalization related to cortical stimulation, of a portion of the medial frontal lobe that would later be termed the supplementary motor area.[21] He had a notable impact on many visiting neurosurgeons that included the likes of Paul Bucy, Percival Bailey, and Wilder Penfield, but his work and that of other European neurosurgeons was over shadowed by the outbreak of World War II.

Wilder Penfield's travels in Europe had been supported by a grant from the Rockefeller Foundation. Upon his return to Montreal, he obtained further assistance from them to create the Montreal Neurologic Institute. The MNI, with Penfield as its director soon became the global leader of advancements in epilepsy surgery and cortical localization. Penfield's close collaboration with Herbert Jasper led to the use of the EEG in preoperative and intraoperative evaluation of patients with epilepsy. Chief among Penfield's original contributions to epilepsy surgery were – cortical localization, including that of language,[22,23] the development of temporal lobectomy for epilepsy and the use of chronic invasive recordings.[24] In 1929,

after an initial resection of the central area of one hemisphere, and a subsequent contralateral exploratory craniotomy failed to impact the epilepsy in a patient with very frequent seizures, a partial temporal lobectomy was performed, which led to a marked improvement. During the following decade, using intraoperative EEG recordings, Penfield extended temporal lobar resections to include aspiration of the amygdala and hippocampal formation.

The concurrent development of the first generation of anticonvulsant drugs, led to a gradual decline in surgical cases for several years. It soon became apparent however, that drugs were ineffective in certain cases of medial temporal lobe epilepsy and focal neocortical epilepsy, where surgery might have much greater impact. These changes in the patient population coming to surgical intervention, coupled with advances in EEG technology and neuroimaging led to a gradual shift in the goals of cortical stimulation. While the principal therapeutic motivation in prior years had been to produce focal seizures that mimicked patients' typical events, and to use this information to guide resection of the epileptogenic zone, the principal goal now became the localization of important cortical regions to prevent injury to them during the resection. Given that many of these resections targeted the temporal lobe, awake language mapping became an intrinsic part of epilepsy surgery.

The observation that specific cortical areas were essential for language function had gained some acceptance after the work of Paul Broca and Carl Wernicke.[25] This strict localization related approach to cortical function enabled the creation of testing strategies that would localize language regions precisely and reliably. Penfield[23,26] soon established that stimulation mapping localized discrete cortical areas, much smaller than the larger regions described by Broca and Wernicke – these areas were designated 'eloquent'. Ever since, the localization of functional regions by electrical stimulation mapping has been held as the 'gold standard' for the preservation of functional cortical regions.

The first human case undergoing chronic recordings was reported in 1939. This involved the use of epidural 'peg' electrodes, which are unsuitable for stimulation mapping due to the excitation of nerve endings in the dura, and are limited by the amount of cortex they sample from. For several decades, language mapping was performed exclusively in the context of an awake craniotomy, until advances in materials sciences led to the development of sub-dural electrode arrays that allowed for chronic recordings and extraoperative cortical stimulation. In 1954 – Penfield described chronic invasive recordings using subdural strips and wires.[24] The method was not widely used initially, with epidural peg electrodes and depth electrodes being used in many centers. Further reports of the efficacy and safety of subdural recordings[27] led to wider use of subdural recordings, and ultimately, the use of craniotomies and implantation of stainless steel electrode arrays – called 'grids' or 'plates' – impregnated in Silastic and Teflon.

Further advances in miniaturizable biocompatible materials engineering aided the wider use of chronically implanted subdural electrodes. Implanted sub-dural electrodes need to possess a few salient characteristics – they need to be biologically inert for extended periods of time, produce minimal resistance to current flow, be compact enough to produce minimal mass effect on neural tissues, and preferably, be MRI compatible. Options that provide these properties are electrodes made with platinum black or an alloy of platinum-iridium. These have excellent charge deposition characteristics, are hypoallergenic by nature, and biologically inert. The non-ferromagnetic nature of these materials renders them relatively compatible with magnetic resonance imaging (MRI), allowing for the use of selected postoperative imaging sequences to corroborate the exact placement of the electrodes, and to rule out any complications.[28,29] However, these electrodes are relatively expensive and stainless steel electrodes are still widely used, especially in developing countries. The caveat here is that postoperative MRI scans cannot be obtained in these cases.

Stimulation mapping of language function

Mapping of the cortex using focal electrical currents – or cortical stimulation mapping (CSM) is carried out in one of two clinical settings. The first, (and historically older) method involves the use of a bipolar probe to stimulate a small volume of cortex. This procedure, carried out in an operating room setting, with the cortex exposed by a craniotomy, is characterized by us as 'intraoperative cortical stimulation mapping' (iCSM), and is discussed in detail in Chapter 115.

The other clinical setting involves passing controlled currents into electrodes implanted into the cranium. This type of mapping is typically carried out in an epilepsy monitoring unit, with ongoing video-EEG monitoring and is referred to as 'extraoperative cortical stimulation mapping' (eCSM).[30] While maps created using eCSM and iCSM are generally similar, there are some relative advantages and disadvantages of each method. The amount of cortical surface covered by iCSM is generally smaller than for eCSM, as regions outside the craniotomy are not stimulated. Also, there is a limited amount of time available for sophisticated cognitive or sensori-motor testing in the operating room, imposing limits on data acquisition using iCSM.

On the other hand, disadvantages of eCSM include that two surgical procedures are needed – one to implant electrodes and one to remove them. The second operation generally includes the resection of an epileptogenic zone or lesion. The placement of SDEs elevates the morbidity of the procedure, and the risks of two procedures are likely greater than a one-step awake craniotomy.[31,32] These risks appear to be greater in adults than in the pediatric population,[31,33,34] perhaps as a consequence of the atrophy produced by a combination of aging and a lifetime of seizures and the generally longer recording sessions in adults compared with children, who tend to have more frequent seizures. The benefits of delineating the ictal onset zone and obtaining a more thorough language map using SDEs should, therefore, be weighed against the relatively small but real risks.

The neural elements depolarized and rendered transiently dysfunctional track with the rate, intensity and the duration of stimulation.[35] Estimates of the charge distribution around subdural electrodes have been theoretically computed.[36] but no direct measurements have been carried out to confirm these estimates. Measurements of the effects of CSM using optical imaging of intrinsic brain signals,[37,38] a technique discussed in detail in Chapter 113B, show that the local effect of this stimulation is fairly focal. However, given that even a single

supra-threshold electrical pulse lasting less than 0.3 mSec[39,40] can result in alterations of electrical activity in remote connected cortical regions, the volume of 'eloquent' cortical regions determined by CSM appears to be affected by the currents used for the stimulation. Also, as of now, a mathematical description of the relationship between current density and the population/volume of neurons rendered transiently lesioned by subdural electrode stimulation is lacking.

Methodological considerations

The precursor to language mapping is the appropriate implantation of SDE electrodes overlying the cortical regions of interest. This of course varies depending on the brain region being studies; the archetypal implant includes a grid placed on the exposed lateral temporal cortex (usually an array four electrodes high and six to eight electrodes long, assuming 1 cm inter-electrode distance, placed along the length of the temporal lobe), a series of strips placed in the sub-temporal location and one or more grids of varying size over the lateral and orbital surfaces of the frontal lobe. While it is obvious that electrodes should be placed over brain regions that are likely targets of resection, electrodes may not be placed over classic language sites that are adjacent to proposed resection sites. It is useful to place additional electrodes over these regions so they may serve as positive controls during the eCSM process. For this reason, a large craniotomy that exposes most of the lateral temporal surface, the perirolandic region and the inferior frontal gyrus, is used. Intraoperative photographs, taken before and after placement of the electrodes (Figures 109.1 and 109.2) are very useful in relating the CSM maps to the Sylvian and Rolandic fissures and to superficial vasculature.

Patients who have undergone placements of subdural electrodes need to be observed closely in the immediate postoperative period, for the development of extra-axial fluid collections, venous infarctions, and cerebral edema.[32] The judicious administration of intravenous mannitol and dexamethasone,[31] is useful in managing elevations in intracranial pressure that may occur after the addition of the SDEs to the intracranial volume. We routinely obtain both CT and MRI scans of the brain on the first postoperative day after electrode implantation, to rule out any complications, and to assist in localizing individual electrodes. Once these scans are reviewed, the patient is transferred to the epilepsy monitoring unit (EMU) for the phase 2 evaluation. These scans can be used to generate a 3D representation of the electrodes on the cortical surface that aids in the planning of the mapping session and the subsequent resection (Figure 109.3).

Mapping is carried out in the EMU usually after localization of the ictal onset zone is complete, with the patient on therapeutic doses of anticonvulsants, although it may be done anytime during the phase 2 evaluation. It is advantageous to carry out the mapping procedure as remote from the grid implantation as feasible, so that the patient needs minimal if

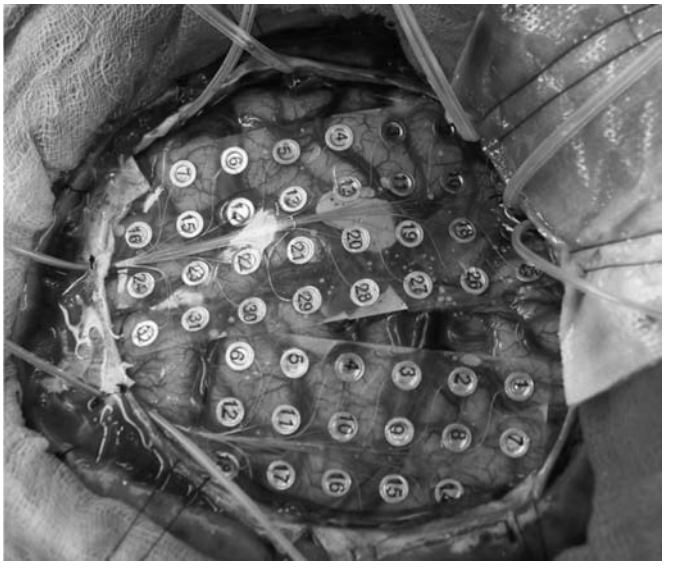

Fig 109.2 Same case as Figure 109.1 after placement of subdural electrode grids and strips. A lateral temporal grid (4 × 8 contact) and a lateral frontal grid (4 × 6 contact) are seen.

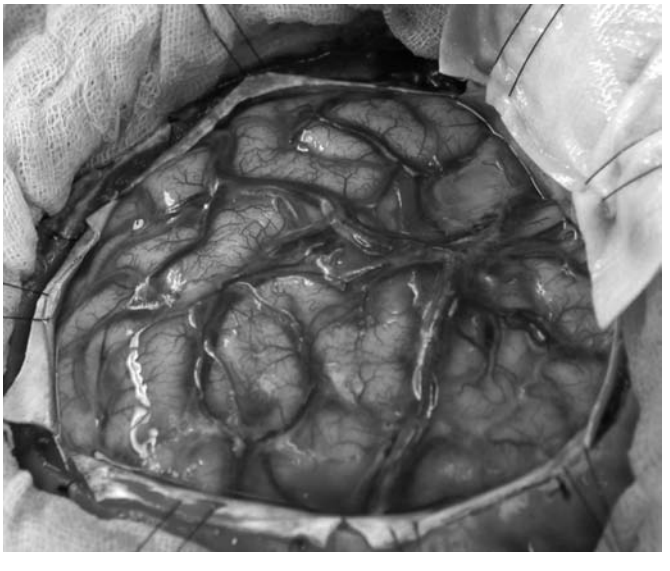

Figure 109.1 Intraoperative photograph after a left fronto-temporo-parietal craniotomy, with the dura opened. The sylvian fissure is situated in the middle of the photograph.

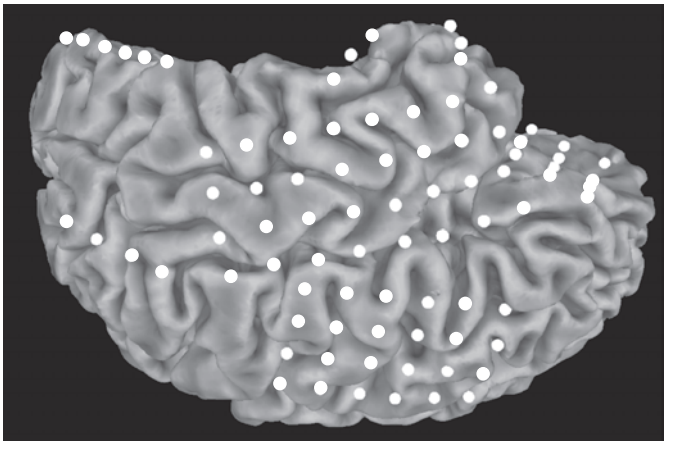

Figure 109.3 Three-dimensional reconstruction of the patient's preimplantation MRI scan, which is coregistered with the postimplantation CT scan, allows for the creation of a spatially accurate depiction of the location of the implanted electrodes.

any narcotic pain medications, which may impair the very cognitive processes being assessed by the mapping process. Patients are familiarized with the process and introduced to the stimuli that will be presented, in advance of the actual testing, to assure comprehension of the task and reliability in task performance. To minimize confounds, stimuli that the patient has difficulty with are removed from testing during eCSM.

Stimulation parameters

Stimulation is carried out using a balanced faradic current, to avoid charge deposition in the brain. The pulse generators commonly used for this purpose are the Ojemann stimulator OCS-1 (Integra Lifesciences Corp, Plainsboro, New Jersey), a portable, constant current, battery-powered unit that generates biphasic rectangular waveforms (5–100 Hz, 0.1–2 mSec duration, 0–20 mA) and is powered by four 9-volt alkaline batteries, and the S88 Grass stimulator and variants thereof (Grass Technologies, West Warwick, Rhode Island) which can generate one or two trains of biphasic rectangular waves with greater variations of range (.01–1000 Hz, .01–10000 mSec duration, 0–1000 mA).

The usual current type used is comprised of 'balanced' positive and negative square waves, delivered at 50 Hz (or 25 Hz depending on whether the components of each wave are viewed together or separately). The total duration of each set of waves is between 200 and 500 μS. A train of theses waves is delivered for 3–5 seconds during task performance, via two contacts (bipolar stimulation) located on the cortical surface (Figure 109.4). Stimulation currents range from 1–15 mA (rarely up to 20 mA), and mapping is performed at 15 mA or at 1 mA below the potential that results in persistent after discharges (ADs), overt phenomenology or discomfort, whichever is lower. It is preferable to maximize currents at each cortical site regardless of adjacent AD threshold rather than to map the entire cortex at a single current level.[41,42] Concurrent electrocorticography is essential to monitor for after-discharges and seizures. It also provides visible evidence of completeness of the electrical circuit, by the presence of artifacts in the recording. The passage of currents meeting these parameters has been shown to be generally safe and does not appear to cause any neuronal injury.[43]

Testing procedure

The patient, having been placed back on anticonvulsants, and familiarized with the testing process, is positioned comfortably in bed (which is adequately padded), either sitting or propped up with pillows. The video camera is adjusted to view the entire body. Oxygen and a nasal cannula should be available if needed. Stimulation is started at 1 mA and increased in increments of 1–2 mA to 15 mA if no overt phenomenology (muscular contractions, eye deviation, involuntary vocalization, phosphenes, version, paresthesias, headache, ipsilateral face pain) or ADs seen. The highest integral value of current density where these phenomena are not *consistently* noted is used for CSM. The tasks used for CSM of language vary across institutions, but the ones commonly used are:[44]

- *Reading sentences* in an overt manner
- *Object naming* in an overt manner, using pictoral stimuli from the Boston naming test[45] or other similar sources[46–48]
- *Auditory comprehension* using the token test or one/two step commands[49]
- *Spontaneous speech* – counting, reciting the alphabet, nursery rhymes etc – useful in mapping anterior language sites and in mapping patients with prominent verbal deficits.

In addition, more sophisticated language paradigms can be used to provide a more holistic language map.[44,50,51]

- *Reading words* (real and non words) aloud
- *Verb generation/Action naming* from pictures of objects or actions
- *Verb generation* from written nouns
- *Repetition* of spoken words or phrases
- *Auditory naming* – naming driven by a phrase or a sentence (e.g., question – what a king wears on his head – answer – crown)

Electrodes where the screening task results in a delay/paraphrasias/anomia/dysnomia, are noted, as are those locations where stimulation produces overt phenomenology.

Functional imaging of language function shows a clear impact of overlearning in the extent and loci of neural substrates involved in language tasks.[52] Such effects have also been demonstrated to occur during CSM.[53] In other words, with repetitive stimulation of specific regions, using the same task, they may no longer seem essential to the task being performed. It is not clear whether this implies that the region is essential or not, as it is non-essential only for the overlearned task. To minimize such confounds, it is useful to have a large battery of stimuli per task that is used, to minimize repetition of individual stimuli.

Cortical stimulation mapping carries a small risk of producing seizures. While the patient population in which it is carried out are patients with poorly controlled epilepsy and generally have frequent seizures, a seizure during stimulation,

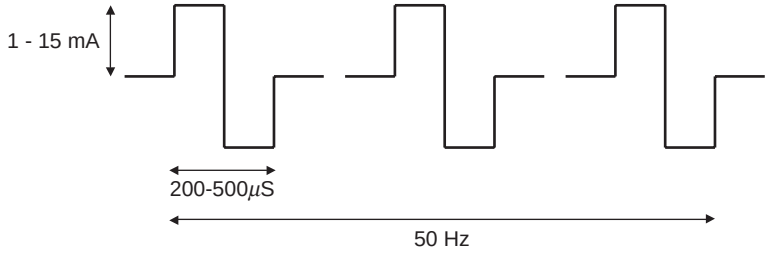

Figure 109.4 Characteristics of the electrical current typically used for stimulation with implanted electrodes.

and /or its treatment with short acting benzodiazepines, may severely curtail the mapping process or lead to a postponement of the planned return to the OR. To minimize the possibility of this occurring, patients should be on therapeutic doses of anticonvulsants prior to mapping. If it is not possible to accomplish this simply by restarting oral dosages of medication, it is useful to administer an intravenous loading dose of phenytoin or fos-phenytoin before starting the session. Intravenous levetiracetam may be considered in patients with allergies to phenytoin or in cases where ADs persist after phenytoin loading. Hyponatremia, if present, should be corrected prior to beginning CSM. Despite this, the stimulation of perilesional electrodes can result in the onset of focal seizures. In the setting of intraoperative mapping, this problem can be handled easily by the irrigation of the brain surface with ice-cold saline,[54] but in the context of eCSM, the only other option available, is to abort the seizure with a second pulse of stimulation.[55,56] A short duration (0.3–2 sec) stimulus applied at the same electrode/s that incited the ADs, within 4–5 seconds of the onset of the ADs and at the peak of the negativity of the after-discharge, may interrupt the ADs.

Given that different language processes engage spatially discrete neuronal substrates, there is likely no single task, whose disruption would provide a 'complete' map of language related areas. The picture naming task with a variable carrier phrase,[57] followed by an auditory comprehension/naming task[50] test language networks in both the visual and auditory domains and may come close to providing a holistic map of essential language areas.

Once the mapping is complete and the patient returns to the operating room for the resection, the mapping data may be overlaid onto the 3D model created earlier (Figure 113.3). In addition, it is useful to label the functional regions and seizure onset sites on the cortical surface at the time of removal of the electrodes to guide the resection (Figures 113.5 and 6).

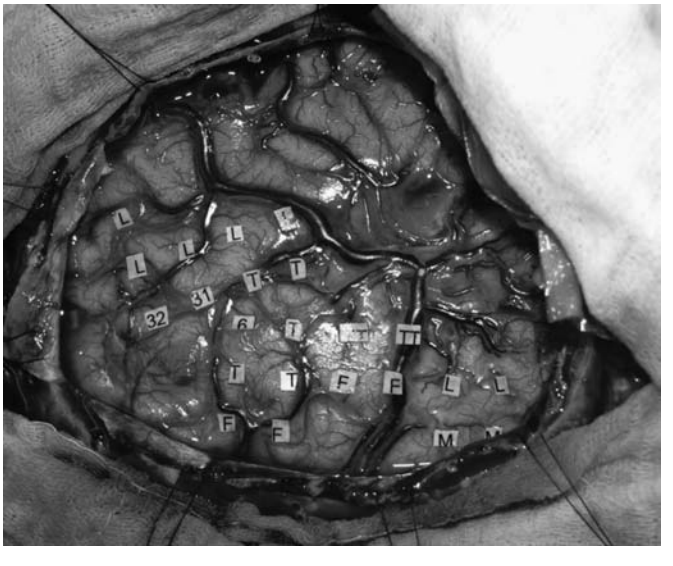

Figure 109.5 Same case as Figure 113.1. The electrodes have been removed and locations of electrodes overlying functional regions are labeled with sterile paper markers. L = language; T = tongue movement; F = face movement; TT = Throat sensation; M = Sites of verbal working memory. Ictal onset was at 31 and 32, with very rapid medial temporal seizure propagation and amplification.

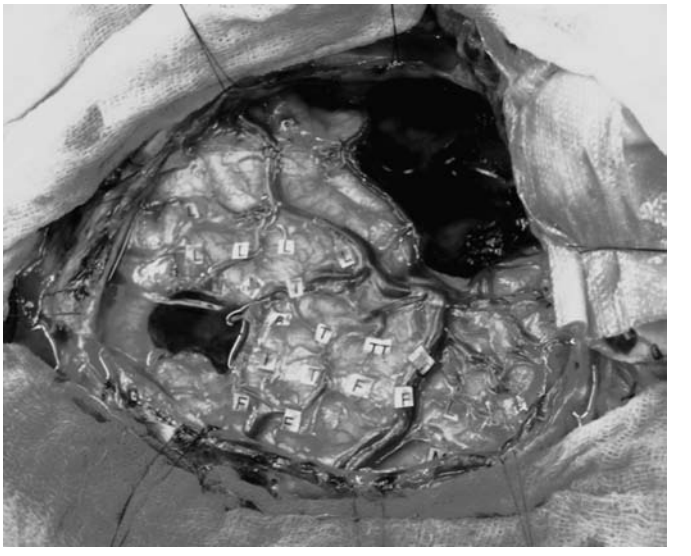

Figure 109.6 Intraoperative view after resection of portion of the inferior parietal operculum, anterior temporal lobectomy and amygdalo-hippocapectomy. Patient had a mild dysnomia post-op that resolved markedly within 6 weeks post-operatively.

Special considerations during mapping in children

In addition to functional mapping in the context of a phase 2 evaluation, electrodes may be implanted purely for functional mapping in children, as some of them are unable to participate in iCSM.[58] However, it is generally difficult to disrupt cortical processing in children using electrical stimuli. Stimulation parameters that work well in adults often do not work well in children, possibly because partly myelinated or unmyelinated nerve fibers need longer pulse durations to be activated.[35] This difficulty may be overcome by lengthening the pulse durations beyond the usual 300 μs (up to 3500 μs in an incremental fashion), along with stepwise progression in the intensity, to arrive at the appropriate chronaxy[59] for each child. If these measures are not taken, it is possible to obtain one or more false-negative sites of stimulation in children.

Variations in CSM for language localization

Several aspects of stimulation mapping vary widely across institutions. Some of these variations are simply a matter of preference and have predictable impacts on the maps generated. They include variations in hardware (types of electrodes and types of current generators), the thoroughness of functional mapping and whether the mapping is performed intraoperatively or extraoperatively.

Most centers in the US use arrays with the electrodes made of platinum-iridium alloy; some still use stainless steel electrodes. The arrays used also vary in their geometry, in inter-electrode distance and in the size and shape of each electrode. Generally electrodes placed along a grid 1 cm apart from each other are used. The electrodes are either convex (disc) shaped, have recessed edges (top-hat design) or are flat discs. Nathan et al.[36,60] suggest that the 'edge effect', an increased current density at the perimeter of electrodes, may be minimized by using recessed or hemispherical rather than disk electrodes and by using arrays with an inter-electrode distance of 0.5 cm

rather than the 1.0 cm separation commonly used in clinical practice.

Another source of variability relates to the choice of the electrode pair used for stimulation. Either two adjacent electrodes (so called 'bipolar' stimulation) or an electrode coupled with a more remote reference (so called 'unipolar' stimulation) may be used. The advantage of adjacent electrodes in 'bipolar' stimulation is the relatively low charge spread, with a rapid fall-off of charge density 0.5 cm away, but it may become unclear which of the two electrodes is indeed over the eloquent region and various combinations of electrode pairs need to be used to determine this.[36] Finite element modeling suggests that 'unipolar' stimulation results in activation of a wider region, than with 'bipolar' stimulation, but this has yet to be conclusively demonstrated in vivo.

Significant variability also exists across institutions in regards to the tasks used for language mapping. In addition to the ones listed above, others that are used include the naming of pictures of famous people (proper naming), naming of places, or of tools and a word stem completion task triggered by a letter or the beginning of a word (orthographic lexical retrieval).

Language maps produced by grouped analysis of CSM data

The availability of language mapping data from more than a few individuals, allowed Penfield and Foerster to create population maps of functional localization. Such work resulted in the maps of the sensori-motor homunculus and also in several maps of the organization of human language. Additionally, Penfield's work established that stimulation of the inferior frontal gyrus led to interference with language output – including speech arrest, alexia, agraphia, paraphrasia, anomia.[23,24] These maps were expressed as two-dimensional representations of language loci overlaid on (often hand-drawn) renderings of the cortical surface[61] and not either as Brodmann Areas (Brodmann 1909), or in stereotaxic space (Talairach'88) and therefore, while quite useful in directing clinical care are untenable for accurate, unbiased comparisons between patients, or with functional imaging data (MEG, PET or fMRI). Despite these limitations, these maps have provided valuable information and advanced our understanding of human language.

The largest grouped analysis of human language organization comes from George Ojemann's seminal publication[57] based on intra-op awake mapping of 117 left hemispheric dominant patients (Figure 113.7). He determined that language sites are diffusely organized all around the left perisylvian region and that these sites are part of a multiple modular cortical system, each module being specific to a particular aspect of language function, and activated in parallel during language processing.[62] Significantly, no language sites were found in Wernicke's area in 36% of subjects and none were found in Broca's area in 21%;[57] this work was extended further to show that no posterior language area could be identified in 10% and no anterior language site could be identified in 9%.[63] These findings were taken together to imply significant language variability across patients with left hemispheric epilepsy. For many years these observations have guided the application of stimulation mapping techniques for the resection of epileptic and neoplastic lesions in and around the classic language sites.

Other work by Ojemann and colleagues has suggested that the total area of exposed cortex 'essential' for naming is rather small $\leq 6\,cm^2$ in 85% of individuals, especially in individuals with high verbal fluency; that focal sites involved in language function can be mapped using CSM in patients as young as 4 and as old as 80 years of age;[63] that there is limited variability in the location of anterior language areas and much greater variability in the locations of posterior temporal and temporo-parietal language sites;[64] and that a remarkable subspecialization of cortical regions in handling differing aspects of language such as naming, reading, phoneme identification etc. exists, with more than half of all sites localized by stimulation mapping being involved in only one aspect of language.[65]

While results from other groups have generally been in agreement with Ojemann's observations in regards to specific regions involved in categorically defined language functions, there is some disagreement regarding the extent of interpatient variability in language sites. For instance, a study of 45 patients with implanted subdural electrodes,[66] with exhaustive extraoperative language testing and a specific evaluation of 'negative' motor areas, revealed language sites in and around classical Broca's and Wernicke's locations and in the basal temporal lobe only (Figure 113.8).

This apparent disparity may be attributable either to the statistical probability method used by Ojemann, the limited time available for language testing in the intra-op environment or to the inherent limitations of making population language maps based solely on cortical surface anatomy (Schaffler and colleagues used post-op roentgenographs to co-localize electrodes). The published works by Ojemann make an incomplete distinction between areas where CSM results in consistent anomia versus those where errors or dysnomia are produced above a statistically significant threshold. Since the behavioral aspect being quantified is the 'essential' nature of the region to language, the fact that normal language (at least based on the function being tested) can be produced during stimulation of a region, at all, argues against it being 'essential'. Importantly, however, Ojemann and colleagues did show a decline in long-term language outcome if the resection margin was carried to within 1 cm of an essential language site.

The discordance of these studies have led to a wide variation in practice patterns between epilepsy groups regarding language localization prior to a dominant temporal lobectomy. A comparison of a large series of standard right versus left temporal lobectomies, in whom typical language lateralization had been shown by Wada testing revealed that in the absence of language mapping, about 7% of patients had a significant deterioration in naming ability at 6 months postoperatively. Some centers choose to map language in all cases, some choose to never map language and some focus on selective resection of medial structures trying to spare as much neocortex as possible.[67] Incredibly, there are no good data to suggest a better neuropsychological outcome with any of these strategies. It has been suggested that damage to the cholinergic outflow from the nucleus basalis of Meynert occurs in patients who undergo a trans-sylvian selective amygdalo-hippocampectomy, and is the mechanism of the verbal decline seen in them. Very recent work suggests that a sub-temporal approach that spares most

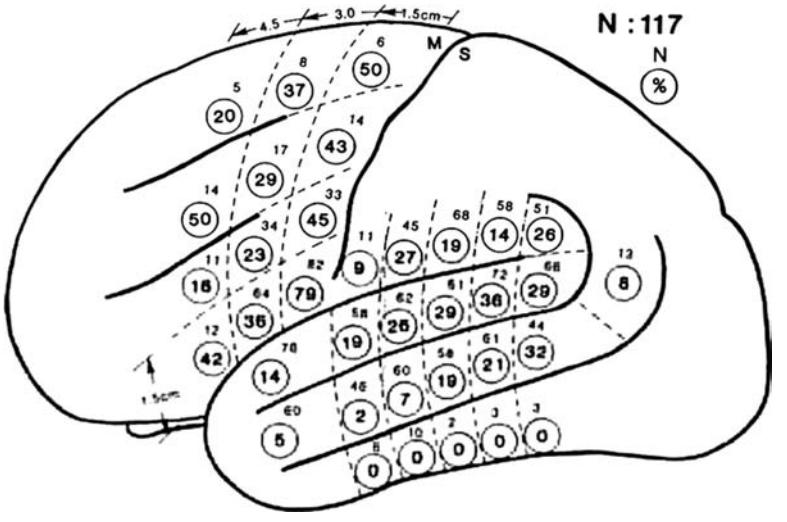

Figure 109.7 Schematic representation of language mapping results from 117 patients who performed an intraoperative naming task. Data were aligned using the central sulcus and the end of the sylvian fissure. Numbers in circles denote the percentage chance that stimulation in that grid resulted in dysnomia; numbers above the circles denote the number of times that zone was tested in the population. (From Ojemann G, Ojemann J, Lettich E, et al. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 1989;71:316–326).

of the temporal neocortex may minimize the decline in verbal memory;[68] but this needs to be substantiated in languages that use syllabograms rather than morphograms, and its long term impact on temporal lobe epilepsy needs to be qualified.

The results of other grouped analyses have pointed to the specific role of Broca's area in verbal[49] as opposed to non-verbal processing[44,69] and also that comprehension deficits occur with either Broca's or Wernicke's area stimulation. In some patients, stimulation of anterior language areas has been shown to result in language deficits extending well beyond language output – to include deficits in auditory verbal comprehension, such as the token test and two step commands.[49] It is unclear if some of these diverse effects stem from the long stimulation – 5–20-second trains of 25 Hz pulses, or reflect the distributed nature of language processing, or the role of Broca's region in verbal working memory,[70] as has also been suggested by the functional imaging literature.

What matters ultimately, is the specificity and sensitivity of mapping results as related to language outcome following focal resections. In this regard, Ojemann and others have pointed out that carrying the resection to within 1 cm of a site that leads to consistent anomia or speech arrest, is likely to result in a permanent long term verbal deficit.[64,71] Obviously, there are limited data in regards to actual resection of 'essential' language sites, so the exact specificity of CSM for language sites is difficult to establish. It is becoming clear though, from work on patients with brain tumors located in eloquent cortex.[72,73] that substantial plasticity in language organization is possible even in adults (more on this in a later section).

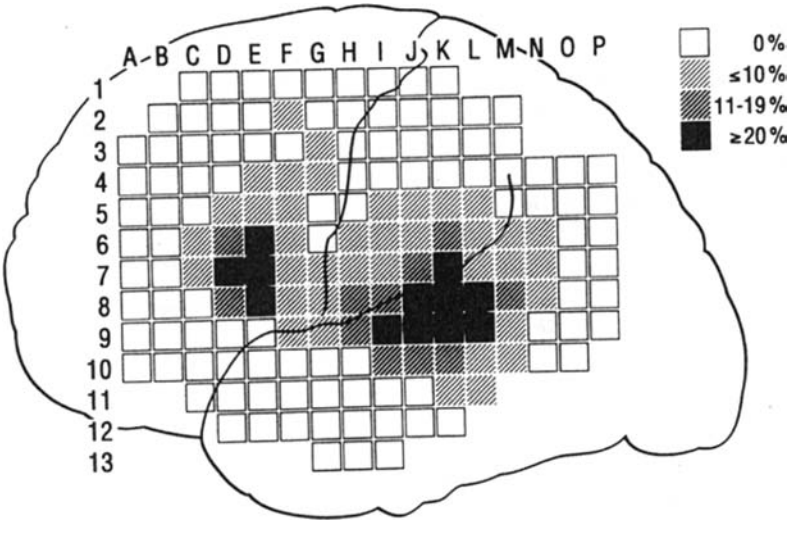

Figure 109.8 Population map showing frequency of language sites mapped using implanted subdural electrodes and extraoperative mapping in 45 patients. Coregistration was accompliahed using skull X-rays after grid implantation. (From Schaffler L, Lüders HO, Beck GJ. Quantitative comparison of language deficits produced by extraoperative electrical stimulation of Broca's, Wernicke's, and basal temporal language areas. Epilepsia 1996;37:463–475).

Insights into the neurobiology of language provided by invasive electrophysiology

Stimulation mapping has provided unique insights into the biology of human language and its organization in various disease states. This knowledge has informed other modalities of evaluating language function, such as functional imaging and has served to validate and refute various theories of language organization.[74] Ojemann's work, revealed the parallel activation of multiple, function specific modules during language processing,[62] a model that stood in distinction to traditional models of hierarchical serial processes starting with decoding in the posterior temporal lobe and eventual phonation by the inferior frontal lobe,[75] and one that is generally accepted today. Dissociation between naming and comprehension[76] demonstrated by CSM has pointed to the existence of a direct non-semantic pathway for picture naming. CSM of the dominant premotor cortex has revealed its distinct roles in articulation (ventral PMC) and naming (dorsal PMC).[77]

Language organization in multilingual patients

Lesion studies in polyglot aphasia have limited ability to tell us about the organization of multiple languages in the cortex. Plasticity after brain insults, the relatively large size of the lesions and difficulty in accurately determining the premorbid linguistic competence of an individual patient in each language, prevent exhaustive comparisons of the impact of the lesion of each language. Additionally, the spatial resolution of functional neuroimaging techniques prevents precise delineation of adjoining cortical regions that perform similar functions in different languages,[78] so electrical mapping possesses unique characteristics suited for the study of multilingualism. Varying locations of naming sites for different languages in the same individual were first described in 1978 by Ojemann and Whitaker.[79]

CSM maps reveal that naming areas in languages acquired later in life (L2) tend to cover a larger cortical area than for the primary language that is acquired earlier in life (L1). As proficiency in a language develops, the areas essential for it may become more compactly organized.[63] CSM of bilingual patients, reveals, in many, though not all patients, that sites responsible for naming and reading in two different languages are distinct from each other,[80,81] that L2 specific sites are located exclusively in the posterior temporal and parietal regions, and that these sites are more confined spatially than the L1 sites.[82] This corresponds well to data obtained by functional imaging of individuals who learnt L2 late in life.[78] Based on the spatial disparity of language sites in polyglots, mapping in each language that the individual is proficient in should be carried out, whenever practicable, to minimize the possibility of a monolingual decline in verbal fluency.[81]

Acquisition of a second language does not seem to impact upon the organization of the primary language. Interestingly, the L2 sites correspond closely to maps of language in monolingual children, suggesting that L2 acquisition is dependant on the same processes and substrates that children use to first acquire language, but outgrow, as their language skills mature.

Basal temporal language

Much like the discovery of the role of the SMA in vocalization, the role of basal temporal language areas in language is also an original contribution of CSM. Based on clinico-pathologic data, Mills and Martin postulated[83] the existence of a 'naming center' in the basal temporal lobe. The region has since been studied extensively using invasive electrophysiological techniques[84] and by functional neuroimaging techniques and has been shown to contain subdivisions, which preferentially process particular visual stimuli, such as written words (visual word form area),[85] faces (fusiform face area)[86] and places such as buildings (parahippocampal place area). Perhaps the process of learning to read, results in the development of the infero-temporal visual word form region. This region is more responsive to written words than to other stimuli when studied by functional imaging. In contrast, the representation of particular classes of objects/faces appears to not be sharply delimited to a specific region but is distributed rather widely across the ventral temporal region.[87,88]

The exact extent of the BTLA for the purposes of CSM is imprecisely defined. Strictly speaking, the term should perhaps apply just to the fusiform gyrus, including structures about 1 cm lateral to the hippocampal sulcus and 1 cm medial to the lateral edge of the inferior temporal gyrus. However, it is sometimes loosely used to describe language regions in the entire ventral surface of the temporal lobe, from the temporal tip to the temporo-occipital junction, and including the inferior temporal gyrus. Comprehensive characterization of the region by Lüders and colleagues,[89] and others,[90–92] have found language areas over a wide region, involving the parahippocampal and fusiform gyrii, extending from 11–75 mm caudal to the temporal tip. Usually, however, the BTLA is restricted to a zone that has a 4 cm or smaller extent in the rostro-caudal axis.[93] By varying the onset of electrical interference relative to a behavioral task, so called time slicing technique, it appears that processing of verbal object meaning in the occipito-temporal gyrus occurs 450–750 mSec after stimulus presentation.[94]

The most consistent deficit seen during stimulation of the BTLA is a disturbance in confrontation naming. Other deficits noted in early studies include impairments in auditory and visual comprehension (affecting reading, responsive naming, performance on a token test, and repetition).[89–91,93]

Deficits seen after dominant temporal lobectomy, comparing patients who undergo a resection of the BTLA with those where it is not, involve only confrontation naming. To explain this discrepancy, it has been suggested that stimulation of the BTLA may indirectly affect functions of remote regions such as the lateral temporal neocortex.[93] Deficits in non-visual language processing have not been found in more closely controlled recent experiments, and the mapping data may reflect the effects of larger currents that spread beyond the BTLA.[95,96] An alternative explanation is that the BTLA is 'involved' in the recognition of visually presented language materials, but is not 'crucial' to this function.[93] This implies that much like in the motor system (SMA stimulation), CSM of language may lack perfect specificity in regards to functional outcomes following resection of language sites.

Recent studies in Japanese subjects who speak using Kanji and Kana characters have shown that the BTLA may play an important role in connecting visual semantic decoders (Kanji characters, like Cantonese, uses morphograms; Kana characters,

like English, are syllabograms) with phonological processors.[96] To this end, there is a special interest in designing surgical strategies that would spare as much of the fusiform gyrus as possible by using a subtemporal-transventricular-transchoroidal approach for hippocampectomy,[97] for speakers of languages that use morphograms. Whether this actually results in improved verbal fluency without compromising seizure-free outcomes is unproven so far.

Effects of age of epilepsy onset on language organization

A comparison of distribution of language sites in pediatric patients with patients older than 16 years, reveals a relative paucity of perisylvian language sites in children[58] and also a relative deficit in the number of frontal lobe sites. These differences suggest that the language maturational process leads to the development of new cortical foci essential for language.[98] While developmental lesions and early-onset seizures do not necessarily impact on the hemispheric organization of language cortex, lesions (especially those affecting the frontal or parietal lobe language loci) acquired before the age of 5 years results in a significant local reorganization, and sometimes its displacement to the contralateral hemisphere.[58,99] Seizure onset early in life appears to displace language away from its usual location in the basal temporal locations.[93]

Markers of early left hemisphere damage, such as seizure onset in childhood, poor verbal IQ and memory dominance in the right hemisphere increase the possibility of finding essential language areas for naming and reading in the anterior temporal lobe (1.5–3.5 cm from the temporal tip) (Figure 113.9).[100] These findings are somewhat contradicted by observations suggesting that there are no significant differences in the proportion of naming errors in different parts of the brain in patients categorized into early and late onset epilepsy groups and that while male patients with low pre-op verbal IQ (VIQ) are more likely to have language sites in the superior temporal gyrus and inferior parietal lobule, patients with high VIQ tend to have essential sites for naming in the middle temporal gyrus.[57,63]

In summary, it may be safe to state that normal brain development creates a small volume of highly specialized language cortex, while pathological processes that occur early in life can induce various types of variability in the organization of language and more spatially diffuse language organization.[58,100] Yet, this specialized node is part of a more diffuse network, and individuals with higher pre-op verbal function, and the onset of the epilepsy at a later age generally have more to lose and appear to be more likely to do so,[101] following a dominant temporal resection.

Electrophysiology of language production

Recordings from an awake human brain provide an unparalleled window for the study of cortical regions involved in language. George Ojemann and Itzhak Fried pioneered this endeavor, which has led to an enhanced understanding of the

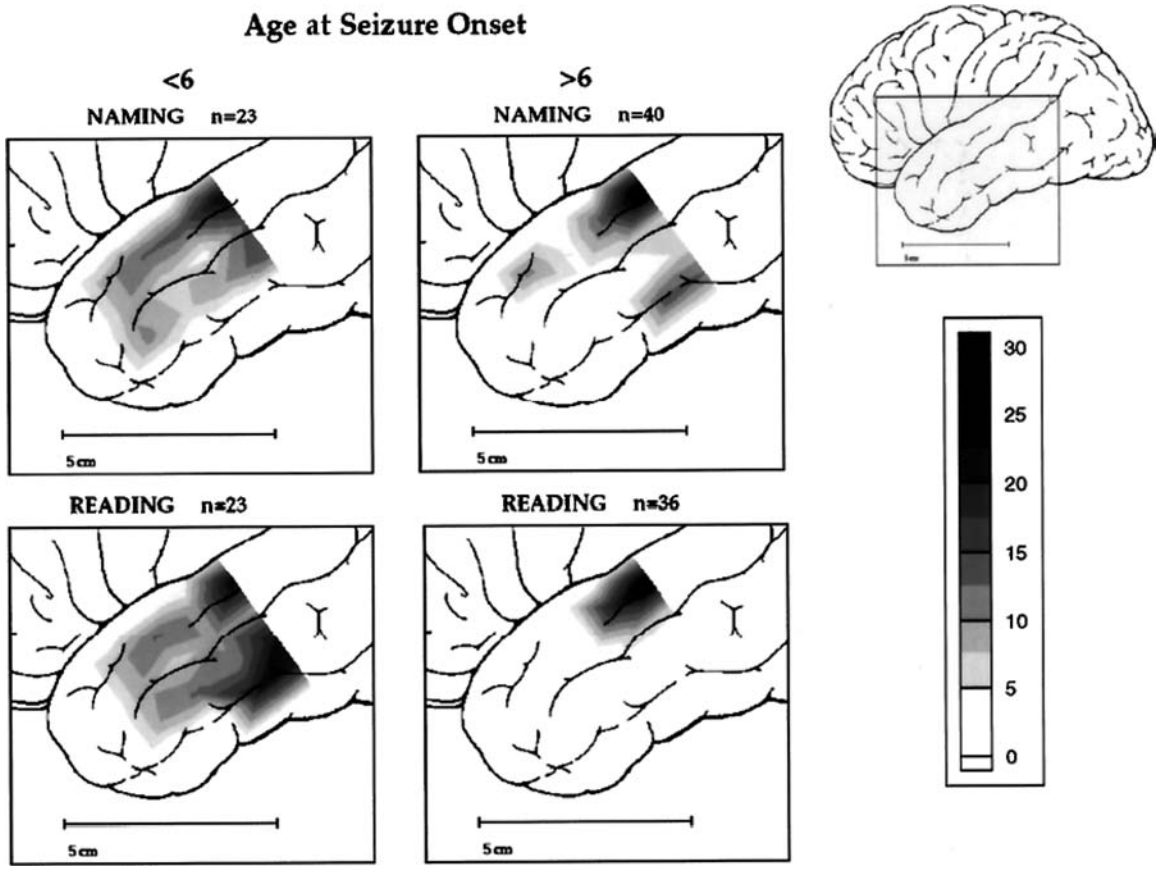

Figure 109.9 Diagrammatic representation of the distribution and frequency of naming and reading errors in the anterior temporal lobe depending age at seizure onset, in a population of 67 patients mapped extraoperatively with subdural electrodes. The gray scale represents the percentage of patients in whom stimulation interrupted a given function in a 1 cm^2 area. (From: Schwartz TH, Devinsky O, Doyle W, et al. Preoperative predictors of anterior temporal language areas. J Neurosurg 1998;89:962–970.)

behavior of neuronal ensembles (evaluated by local field potentials – LFPs) and single units (evaluated by tungsten microelectrodes) during language perception and production.

Recording cortical activity using the macro-electrodes used for seizure localization/CSM during language processes is variously characterized as local field potential (LFP) or evoked potential (EP) or electrocorticographic (ECoG) recording. A localized desynchronization in the alpha (7–12 Hz) range,[102] maximal at between 700 and 1200 mSec after presentation of a naming stimulus, with persisting low-voltage higher frequencies, occurs at most temporo-parietal, though not frontal naming sites.[103] Slow potential shifts occur at the onset of naming in frontal naming sites as well in motor cortex[103] and changes in electrical activity in the frontal and temporo-parietal language sites occur in parallel and not sequentially.[63] Evoked ECoG-potentials to words heard or spoken differ; with a wider response seen with overt speech.[104]

More recent work has focused on studying correlated activity between language regions at higher frequency ranges.[105] Activity in the high gamma range (70–150 Hz) has been shown to be spatially correlated with CSM derived language maps.[106–109] Measurements of the average dynamical changes in amplitude of the entire width of the recorded EEG spectrum – event related spectral perturbation – provide an unbiased estimate of changes in cerebral activity by an experimental event.[109] However, comparisons of the BOLD fMRI signal change with LFPs recorded from calcarine, fusiform and lateral temporo-occipital regions show inconsistent relationships,[84] with the maximal effects of duration of stimulation occurring in different frequency bands across different brain regions. This suggests the need for a clearer understanding of the relationships between these types of mapping data.

Micro-electrode recordings of neurons from regions of cortex not categorized as 'essential' to language processing show changes in activity that are specific to distinct language tasks – such as naming, listening, speaking.[63] Neurons in the (anterior) superior, but not middle or inferior temporal gyrii respond to phonetic but not semantic aspects of spoken language.[110] Responses to heard music tend not to differ as much across gyrii or across hemispheres.[111] Additionally, these techniques reveal the existence of widely distributed neural networks for modality specific identification and recall[112]

In multilingual patients, these changes are sometimes limited to naming in a single language. This suggests a lack of 'general purpose' neuronal assembliess. Also, akin to the maps produced by stimulation mapping, the electrophysiology of cortical regions, measured using micro-electrodes, identifies neurons whose functions change with the performance of only one of several language tasks.[113]

Limitations of CSM in evaluating language function

Mapping the cerebral cortex with electricity is a technology that is more than a century old at this point, but remains the existing 'gold standard' for perioperative functional localization. However, several disparate groups of evidence suggest that the technique has notable limitations.

Limitations in sensitivity

This is the ability of the technique to accurately detect an existing essential language site, i.e., minimization of false negatives. This is impacted by at least three factors. The first is that only the crowns of gyrii (i.e., only a third of all cortex) are evaluated. Although it has been suggested that 'buried' language sites are not associated with adjacent sites on the cortical surface,[57] this matter merits further evaluation. 'Acute' functional reorganization has been noted following a tumor resection.[114] A second obvious limitation is the sampling restriction imposed by where the electrodes are placed or which portion of the cortex is accessible for iCSM. Thirdly, the induction of seizures, during mapping can seriously impact mapping especially immediately around the epileptogenic zone, which is of course where the planned resection is likely to have the greatest impact. Lastly, the limited time and the obvious physical restrictions in both the iCSM and eCSM environments impose restraints on the nature and extent of the cognitive testing that can be carried out.

Whether related to these factors or not, two things are clear. First, CSM does not consistently reveal language areas. In Ojemann's 1989 series – no language sites were found in Wernicke's area in 36% of subjects and none were found in Broca's area in 21%. In another large series, known to have left-sided language function, no posterior language area could be identified in 10% and no anterior language site could be identified in 9%.[63] While it remains unclear if this is an indicator of language variability across patients with left hemispheric epilepsy, it is also possible that CSM is not sensitive enough in detecting all of the cortical substrates of language comprehension/generation. Secondly, language deficits can develop despite exhaustive language mapping and preservation of these language sites during resection. One strategy, incompletely proven at this point, to minimize this possibility may be the application of CSM to localize sites responsible for verbal memory in the temporal neocortex.[115]

Limitations in specificity

A bigger concern is the propensity of CSM to categorize regions as essential that may not indeed be so, confining the extent of resection.[106,116] Testing language by CSM creates a brief unphysiologic stimulus that is capable of influencing other brain regions. This is especially true with regions in the ventral temporal region, when despite the interruption of multiple functions during stimulation, minimal or no effect on language are seen after resection of these 'statistically significant' language sites.[44,91] Results of CSM may need to be weighed cautiously in cases where language is bilaterally organized or if the resection involves a developmental epileptogenic lesion (e.g., cortical dysplasia) in a perisylvian location.[116]

While the local effects of cortical stimulation may be well contained, there clearly are some distant effects of electrical stimulation. The recording of cortico-cortical evoked potentials from a brain region[39,40] following single pulses of current delivered to a pair of electrodes overlying eloquent cortex, suggests that the behavioral effects measured during CSM may not all relate to disruption of just the region being

stimulated, but also to its effects on the distributed components of the network to which the region belongs.

Relationship between CSM and functional imaging of language areas

Some of the concerns regarding the spatial specificity and sensitivity of CSM listed above, and the need for additional procedures (SDE placement for eCSM) or operative time (for iCSM), led to interest in supplanting CSM for localizing language function, using noninvasive mapping strategies (NIMS) to measure neural activity (MEG) or regional cerebral blood flow increases concomitant with such activity (fMRI, PET, iOIS) during language processing.

While efforts to supplant CSM for localizing regions involved in motor function with NIMS have been generally successful,[117] imaging techniques have limited applicability for localizing language sites.[118] This is especially true for temporal and temporo-parietal language regions,[119–121] but also for frontal language sites.[122] This is likely on account of a variety of reasons. The first is that these techniques provide a map of the network involved in, but not of the nodes of that network essential to, language generation. This problem worsens with increasing sensitivity of the mapping technique used – as more functional areas are detected by lowering the statistical threshold used to create the language map – the specificity of the map becomes lower. The second reason is that the cognitive 'load' of 'simple' language tasks such as object naming that are typically used for CSM is relatively low, so that the neuronal activation or its hemodynamic correlate are not easily discernible from background activity. A third limitation is secondary to multiple technical issues: spatial resolution of the imaging technique; mismatches in coregistration of functional data sets with high resolution MRI scan data used for intraoperative stereotactic guidance; and problems with patients' abilities to comprehend the task or cooperate with scanning.[123] Lastly, speech production in both MEG[124] and clinical fMRI environments is generally covert, as movement associated with articulation produces artifacts and signal dropout. Covert speech does not activate some of the frontal opercular regions that are indeed essential for articulation.[122]

A battery of language tasks is better at the functional localization of 'critical' language areas, such areas then being defined as regions consistently activated across a variety of tasks. Combining 'simple' language tasks (e.g., picture naming) with more cognitively demanding tasks, such as comprehension of visually or acoustically rendered phrases, provides a more complete map of language areas, and one where 'critical' language areas may be more easily assigned.[118,125–127]

So far, these efforts have been unsuccessful in demonstrating absolute and reliable concordance between CSM and functional imaging derived maps.[123] Hence, stimulation based mapping remains the prevailing standard for functional localization of language regions at the current time.[128] Maps derived using multimodal language activation strategies are, however, of value in guiding the CSM effort and in providing a better understanding of language localization in patients with atypical results following an intracarotid amytal procedure.

'Eloquent cortex' and degenerate neural systems

The four functions that are most frequently mapped in the neurosurgical setting are language, motor control, vision, and memory. The cortical regions without which these functions would no longer be considered to be normal are designated as 'eloquent'. This designation does not imply that other neural functions are not essential or that there are necessarily non-eloquent brain regions that can be resected with impunity.[129] Instead, it is a categorization of cortical regions based on the lasting effects of lesions and the impacts of these lesions upon the activities of daily living. The term 'eloquent' has been used in this chapter to allude to cortical regions without which language function could not be discerned as normal.[9,10] Yet, it is unclear that eloquence is absolutely determined by CSM.

It is clear from multiple lesional studies that a reorganization of language function can occur even in the adult brain.[130] Recently, it has been shown that sites localized by CSM demonstrate spatial plasticity both acutely[114] and as slow growing lesions encroach upon them.[131] While resection of language sites generally does result in an acute language impediment, significant and sometimes complete recovery of function can occur, over a period of 3 to 6 months.[72,73] Lasting deficits are more likely when the subcortical substrates of function are damaged in some way.[25] The best level of recovery is generally observed, when compensatory recruitments take place in the perilesional area, along the rim of the injured tissue, rather than in the homologous region of the non-dominant, contralateral hemisphere.[132–134]

These findings, along with the fact that large amounts of dominant temporal neocortex can be resected with relatively few deficits, support the concept of an implicit degeneracy in language systems. The term 'degenerate' is used to describe structurally discrete neural elements that perform the same function.[135] Functionally degenerate systems, capable of a particular cognitive computation, may deliver their output to a separate 'essential' or to a 'degenerate' region. Some of the lack of specificity of CSM may stem from the fact that non-physiologic stimulation of one degenerate region may interfere with the output from a second non-stimulated region that may be sufficient to carry out the cognitive function being tested.

A holistic approach that integrates the results of functional imaging, lesional analysis, CSM with the potential for plasticity (based on age, site of planned resection) would probably provide a more precise way of determining which cortical regions are truly eloquent.

Recent advances in the localization of language regions

Functional localization based on individual anatomy

High-resolution MR imaging combined with 3D reconstruction of cortical surfaces allows for representation of brain anatomy in more exquisite detail than previously possible. This may allow for the accurate delineation of the hand motor area[136] and of Broca's area[137] without functional mapping, if these regions are not involved by or adjacent to overt lesions. Scans done at high field strength MR systems (e.g., 7 Tesla systems) may allow for further development of this approach.

Functional localization based on population maps

The ability to co-register imaging data sets to each other, with adjustments made for individual anatomic differences, allows for the generation of population maps of cerebral anatomy and functional activation. The generation of high resolution 3D cyto-architectonic maps[138] or spatial probability maps from meta-analyses of functional imaging data[139] that can be co-registered onto a patient's 3D structural MRI provide novel ways for functional localization.

Focal cortical cooling

Focal cortical cooling has been promoted as an alternative to the passage of cortical stimulation for language mapping. A cooling device irrigated by cold saline[140] and a Peltier chip[141] have been used. Neurons cooled to about 30°Centigrade seem incapable of normal processes and are rendered transiently dysfunctional. At the current time this technology is experimental, and its use in the clinical environment is not proven or approved. However, there are clear theoretical advantages to a methodology that produces a transient lesion without seizure induction or spread of the stimulation effect to remote locations, especially for intraoperative mapping. It remains unclear if and how this method could be successfully applied in the extraoperative (i.e., SDE) context.

Localization of sub-cortical pathways

Essential cortical regions can function only in the context of appropriate afferent and efferent information flow. Stimulation of both the arcuate fasciculus[142,143] as well of the inferior longitudinal fasciculus[144] has been shown to interfere with language production. The ability to image these pathways non-invasively[145] with diffusion tensor imaging (DTI) provides additional information that may be useful in preventing postoperative dysphasia. The further development of DTI to generate connectivity based parcellation techniques, that imply functional segregation by variations in cortico-cortical connectivity, provides yet another method for non-invasive functional localization.[146]

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110 Cortical mapping by electrical stimulation: other eloquent areas

M Hoppe

In order to avoid new neurological deficits for patients undergoing resective epilepsy surgery, the eloquent cortex in the region where resection of the epileptogenic zone is considered has to be identified and its extension has to be defined as precisely as possible.[1] This can be done on an electrophysiological basis by direct electrical stimulation of the cortex under question using subdural or intracerebral depth-electrodes. This chapter will cover the visual and auditory cortex, insular cortex, as well as those cortical structures which are functionally and anatomically connected via the Papez circuit: olfactory cortex, amygdala, and cingulum. In conclusion, the alien limb syndrom and laughter evoked by stimulation with subdural electrodes will be presented as case studies.

Visual cortex

Introduction

Already 50% or more of patients with occipital lobe epilepsies evaluated for epilepsy surgery show visual field impairments preoperatively.[2–6] Nevertheless, because resections within the occipital lobe can increase preexisting visual defects or cause new ones in unaffected patients, identification of cortex-bearing visual functions is desirable when performing resective epilepsy surgery in patients with occipital lobe epilepsies. This can be done on an electrophysiological basis by direct electrical stimulation of the cortex under question, if subdural or intracerebral electrodes are used in the diagnostic work-up.

Functional anatomy of the visual cortex

About one-third of the human brain is estimated to be involved in visual processing.[7] Brodman distinguished on the basis of cytoarchitectonic studies of areas 17–19 within the occipital cortex (cited from ref. 8). Area 17 corresponds to the striate cortex, named after the stria of Gennari. An average of 67% of it is buried in the calcarine fissure, its branches or accessory sulci.[9] It receives input from the corpus geniculatum laterale, and therefore has a retinotopic organization and is considered to be the primary visual cortex (cited from refs 7 and 8). The representation of the horizontal meridian lies roughly on the base of the calcarine fissure. The fovea is represented at the occipital pole and extending onto the lateral convexity for about 1 cm, whereas the peripheral retina is represented more anteriorly and extends to the junction of the calcarine and parieto-occipital fissures.[10] More than 50% of the striate cortex is occupied by the representation of the central 10° of vision, which causes the high magnification of central vision. The lower half of the retina (upper half of the visual field) projects below, the upper half of the retina (lower half of the visual field) above the calcarine fissure, with the meridians lying at the boundaries between striate (V1) and extrastriate (V2) cortex.[10]

Referring to microelectrode studies in primates, and supported by case studies with various lesions and anatomical and functional imaging studies, different cortical areas with different functional capabilities can be described. Besides the primary visual cortex (V1 = area 17), there are secondary visual processing areas V2 to V5 which serve for different aspects of vision, e.g., motion (V5), color (V4), and form (cited from refs 7 and 8).

Clinical ictal characteristics

Visual auras of different types – elementary or complex, unformed or formed, hallucinations or visual loss – are generated from the posterior cortex (occipital, temporo-occipital, parieto-occipital, temporo-parietal-occipital).[2,3,5,11]

Electrical cortical stimulation studies

Besides direct intraoperative stimulation these studies were done using either subdural grid electrodes, stereotactically implanted depth electrodes or a combination of both. The first to describe visual phenomena due to cortical stimulation were Krause and Foerster (cited from ref. 8). The seminal studies of Penfield and co-workers[12,13] yielded two different types of visual perceptions depending on the site of stimulation. Simple or elementary versus elaborate or complex or hallucinations. The first were the result of stimulating the mesial and lateral occipital cortex, the latter resulted from stimulation of the posterior temporo-parieto-occipital junction. Succeeding studies of other investigators[8,14–16] confirmed these findings. The elementary sensations consist of white or coloured spots with various forms, most of them stationary, but sometimes moving phosphenes occur. Studies covering

the mesial part of the occipital lobe with up to 80 subdural electrodes[8,15,16] showed that the phosphenes occur in the visual half field contralateral to the stimulated lobe, in the lower quadrant when stimulating the upper part of the striate cortex (above the calcarine fissure) and vice versa. However, Brindley *et al.*,[16] who implanted very densely distributed electrodes to serve as a visual prosthesis, noticed exceptions to this retinotopy and furthermore detected many discontinuities of the map of the visual field on the cortex. Neighbouring points on the cortex were sometimes far apart in the field, and neighbouring points in the field sometimes far apart on the cortex. This may be explained by the fact that the striate part of the mesial occipital cortex lies deep in the calcarine fissure. Thus, it is not easily made accessible to electrodes and the topograhical relationship between the stimulating electrodes and the calcarine fissure may remain uncertain. Visual responses near the fixation point were smaller than those farther away from the fixation point,[8] thus reflecting the magnification of central vision (see above).

Interestingly, in two studies[8,14] phosphenes could also be elicited outside the striate cortex on the lateral aspect of the occipital lobe. Kaido *et al.*[14] could prove that comparable to the striate cortex the phosphenes represented retinotopy, with coordinates consistent with the axis of the polar angel and the eccentricity from the center of the visual field. As a possible explanation the authors propose that there is a direct projection from the lateral geniculate nucleus not only to the striate cortex but to the extrastriate cortex as well. This is supported by transcranial magnetic stimulation studies which were able to produce phosphenes by stimulating the lateral extrastriate cortex.

Stimulation of mesial and lateral extrastriate cortex via depth electrodes implanted in posterior brain regions revealed visual phenomena different to the elementary perceptions mentioned above. Static phenomena like visual object distortion were provoked by lateral stimulation of the middle occipital gyrus, as white or colored flashes by mesial stimulation of the cuneus around the calcarine fissure, as blurred vision when mesially stimulating the posterior cingulate region and inferior precuneus.[17] Visual motion perceptions like a transparent moving circle occurred during stimulation of the medial portion of the parieto-occipital fissure and of the posterior cingulate gyrus. Stimulation at sites 1–2 cm apart did not evoke these phenomena. The authors concluded that within the extrastriate cortex the medial parieto-occipital region is the only region of specific sensitivity to motion processing effects. Due to limitations of their study they could not rule out, that additional areas might be involved, and that the medial parieto-occipital region is likely to be part of a multiarea system processing visual motion analysis.

Studying color processing with subdural electrodes, Allison *et al.*[18] found sensations like 'shimmering' or 'flashing' when stimulating the medial lingual or cuneate gyri. Changes in color perception could be seen on stimulation of the lateral and fusiform gyri. These findings support studies based on clinical, anatomical and PET imaging data, which indicate that there is a region of the human inferior occipital cortex which is involved in color perception and which may be homologous with area V4 described in monkeys.

Visual experiential responses, for example consisting of seeing a scene, a group of people or a recognizable object could be produced by Penfield *et al.*[13] by stimulating the temporal lobes. This occurred more often when the nondominant hemisphere was involved. In the right hemisphere the stimulation points were scattered throughout the temporal lobe. On the left side the responses were either on the lateral side comprising the first and second temporal gyri, or more frequently on the superior aspect of the first temporal gyrus. Summarizing, Penfield *et al.* concluded that stimulation sites associated with experiences that are largely visual tend to be located in the posterior temporal cortex near the visual sensory area of the occipital lobe on the right, nondominant side. Obviously, this area is devoted to the purposes of the interpretive cortex and apt to produce recall of visual experiences. On the contrary, stimulation of this site in the left, dominant side which corresponds to the large speech area of this lobe, never produced visual experiential responses.

VEP

VEP are generated from the primary visual cortex. Because the evoked potentials exhibit characteristics of near field potentials,[19] subdural or depth electrodes outside this cortex do not record VEP. The sequence of peaks recorded from the cortex resembles those recorded from the scalp, but the amplitudes are much higher. However, depending on the location of the electrodes, polarity may be different to scalp recordings (which can be explained by the solid angle concept theory),[20] and the latencies of the peaks also depend on the electrode location and therefore differ at least slightly from those obtained with scalp recordings.

From the perspective of planning resection of the presumed epileptogenic region within the occipital lobe and trying to define functional eloquent cortex, it can be stated that electrodes lying on the primary visual cortex will show evoked potentials on visual stimulation of the patient, whereas electrodes outside will not. VEP are applicable as pattern reversal VEP in patients with chronically implanted electrodes. Stimulation with pattern reversal using appropriate check sizes will predominantly stimulate the macular region and produce responses of the visual cortex responsible for central vision[21–23] which is the decisive part of the eloquent cortex to be preserved. Obviously, the use of VEP in presurgical diagnostics of occipital lobe epilepsies is not established very well, as reports based on larger numbers of patients do not mention their application.[2–5,11,24]

VEP might be considered in uncooperative or mentally retarded patients who can not reliably cooperate during subdural stimulation, provided they are able to fix their gaze on the screen of the monitor. In addition, in one recent study[25] a flashing strobe light was employed to study the driving response of the visual cortex intraoperatively. The occipital driving response to photic stimulation could be used as a means of monitoring the integrity of the visual cortex and offering the advantage that averaging is not necessary, and therefore, a more immediate feedback to the neurosurgeon is possible.

Conclusion

Stimulation of the posterior cortex may evoke two major groups of visual perceptions: elementary or simple ones,

consisting of white or colored different spots of variable shape (phosphenes), and more complex ones. The origin of the first is the primary visual cortex (area 17, striate cortex, V1) and can in addition encompass the extrastriate cortex on the lateral surface of the occipital lobe. Their retinotopic organization may assist in defining the borders of resection in order to prevent new or deterioration of already existing visual field defects. The more complex visual phenomena, including hallucinations, are generated in the occipital lobe outside the afore mentioned area. The site of these generators may extend into adjacent parietal and temporal cortex. It is still unclear what the clinically relevant sequelae of a resection of these cortical areas are.

Auditory cortex

Introduction

Compared to stimulation studies dealing with language functions, the number of stimulation studies confined to pure auditory functions is much smaller. This reflects both the high impact of preserving language ability and the less prominent awareness of neuropsychological deficits in the auditory domain in epilepsy surgery patients.

Anatomy of the auditory cortex

The superior temporal gyrus (STG) contains the auditory cortical areas in man.[12,13,26–28] Its superior aspect is buried in the Sylvian fissure and can be seen only after removal of parts of the frontal and parietal opercula. On its middle part lies the Heschl's gyrus (HG), demarcated posteriorly by the transverse temporal sulcus. Posterior to this sulcus begins the planum temporale (PT). The anterior border is less clearly demarcated by the acoustic sulcus, an extension of the superior temporal gyrus. There may be one or two gyri on each side. A MRI study of the normal signal intensity pattern in HG and the surrounding areas in the STG and middle temporal gyrus on T2-weighted images demonstrated lower signal intensity of the cortex in the HG and surrounding STG compared with that of the middle temporal gyrus.[29] Combining cytoarchitectonic studies and these morphologic data, Brodmann's area 41 and 42 match with HG. Areas 52 and 22 correspond to the posterior part of STG, PT and extend into the long gyrus of the insula and the parietal operculum.

Clinical ictal characteristics

Auditory auras may consist of hearing different sounds and noise or altered perception of normal sounds of the environment.[12,13,26,30] Their occurrence as an early ictal sign in temporal lobe epilepsy is indicative of an lateral, neocortical seizure origin.[31]

Electrical cortical stimulation studies

Penfield *et al.*[12] found auditory sensations when stimulating a narrow region of the STG that bordered the posterior third of the Sylvian fissure. Only infrequently Heschl's transverse gyrus on the superior temporal surface was uncovered and in these cases the same auditory sensations could be evoked. They were elementary, consisting of a wide variety of sounds. The frequency of the sounds was not found to be dependent on the localization of the stimulus sites. Most often the sounds were projected to the contralateral ear, less frequently to both ears. More complex auditory perceptions, referred to as auditory experiential responses by Penfield *et al.*,[13] could be elicited by stimulation of the lateral and superior face of STG, but not of the Heschl's gyrus. A more comprehensive access to those parts of STG hidden in the lateral fissure were achieved in further studies which applied stereotactically inserted depth electrodes.[32] Recording auditory evoked potentials with depth electrodes, Liegeois-Chauvel[28,33] were able to define the primary auditory area more precisely and limit it to the posteromedial part of Heschl's gyrus. This is supported by an elaborate stimulation study[26] with 65 patients, 71% of the depth electrodes being placed in HG (38% of leads in the right area 41, 62% in left and right area 42), 10% in PT, 17% in the middle part of STG (area 22) and 12% in the anterior part of STG (area 38). Regarding Heschl's gyrus, stimulation of area 41, the primary auditory area, provoked more high frequency sensations than that of area 42, the secondary auditory area. The nature of the sensations was mostly simple hallucinations, meaning sounds and noise which were heard binaurally or monaurally (usually contralateral), when area 41 was stimulated. Activation in area 42 provoked more illusions, i.e., perception of altered voices and sounds, rather than hallucinations. In PT and the remaining regions, illusions were more frequent than hallucinations, their type being not different from those elicited by stimulation of HG. Hallucinations were mainly binaural, illusions could be also binaural or just contralateral. Although there are some discrepancies to the aforementioned studies of Penfield and co-workers, which amongst others are probably related to the different stimulation method (monopolar versus bipolar), one consistent finding is that area 41 of HG has some unique features that distinguishes it from the rest of the auditory cortex. In two recent studies[34,35] HG was explored with depth electrodes implanted roughly parallel to its long axis. In addition, subdural grids electrodes were placed over the middle and posterior aspects of the lateral STG. Averaged auditory potentials were recorded from both sites. Thus, a posterior lateral superior temporal area (PLST) could be identified which was activated by a variety of simple and complex sounds. Bipolar electrical stimulation of HG activated a circumscribed area of the lateral STG that overlapped the acoustically defined PLST. These results provide evidence for a functional projection from primary auditory cortex on HG to an associational auditory cortex on the lateral surface of STG. This cortical area may play an important role in auditory motion processing, since Ducommun *et al.*[36] report on a patient who developed a selective deficit for the perception and discrimination of auditory motion after right temporal lobe resection. In addition to the anterior temporal lobe the resection included also the posterior STG, lateral PT, and lateral HG, because intracranial ictal recordings had shown that seizure activity had spread to these structures. Preoperatively, electrical stimulation of the posterior STG was experienced by the patient as incoming moving sounds and intracranial auditory evoked potentials revealed motion-specific responses selectively over this area. Postoperatively, analysis of auditory stimulus identity and location within the auditory scene remained intact. In two patients with focal

epilepsy caused by tumors of Heschl's gyrus intraoperative stimulation failed to produce auditory hallucinations, illusions or other acoustic phenomena.[27] In one patient, his auditory aura continua (ringing sound) ceased after resection of the tumor and stimulation after this event still failed to evoke any auditory perceptions. To our knowledge this is the only report in which electrical stimulation of the primary auditory cortex failed to provoke any auditory sensations. A possible explanation for these surprising findings could be that both tumors (astrocytoma grade III, oligodendroglioma grade II) led to alteration of the primary auditory area sufficiently enough to cause severe cortical dysfunction.

AEP

As shown in the paragraph above, the intracranial recording of auditory evoked potentials (AEP) complements direct electrical cortical stimulation. It provides valuable support in defining auditory cortex in patients presenting with auditory auras and in patients with lateral temporal or occipital-temporal epilepsies, in whom the posterior, superior or anterior borders of resection need to be determined.[33]

Conclusion

Resection/destruction of structures within the auditory cortex can impair various functions or abilities, ranging from spatial localization[37] to altered music processing.[38] This is a reflection of the complex organization of the auditory cortex which encompasses the primary auditory area and several additional, secondary auditory areas, analogue to the visual cortex.

Although modern functional imaging methods can provide a reliable measure of the activity of human cortical neurons[39] direct electrical cortical stimulation is still an indispensable tool when attempting to define auditory cortex and preserve it from unnecessary resection.

Insula

Introduction/anatomy

The insular cortex is covered by the frontal, temporal and parietal opercular cortices. Thus, it is not easily accessible to direct electrical stimulation and therefore has been explored less frequently than other areas.[40,41]

Clinical ictal characteristics

Frequent propagation of seizure activity often makes a precise differentiation between ictal symptoms of temporal lobe epilepsy and insular lobe epilepsy difficult. Isnard *et al.* were able to demonstrate a variety of symptoms which tend to occur in a particular sequence:[42,43] sensation of laryngeal discomfort, unpleasant paraesthesia affecting large cutaneous areas, dysarthric speech, elementary auditory hallucinations, often focal dystonic postures at the end of the seizures.

Electrical cortical stimulation studies

Early intraoperatively performed stimulation studies yielded varied results[44] consisting predominantly of various types of abdominal sensations: nausea, umbilical sensation or pain, borborygmi, belching, and desire to defecate (pages 107 and 424 in ref. 12).

Recent studies using intracerebral depth electrodes were able to overcome many of the limitations of earlier intraoperative stimulation studies. Applying an elaborate approach of stimulating the insular cortex by using transopercularly implanted depth electrodes[41,45,46] the responses could be subdivided into the following categories:

- Somatosensory responses were the most frequent and were elicited when stimulating the posterior insula. They comprised neutral or unpleasant and painful sensations, the majority of them being confined to the contralateral face, neck, hand and upper limb.
- Viscerosensitive responses were evoked in the anterior part of the explored area and consisted of feelings of constriction of the pharyngolaryngeal region or various types of sensations within the abdomen or thorax which resembled the initial ictal symptoms in mesial temporal lobe epilepsy.
- Less frequent – in about 10% of cases – simple acoustic hallucinations, experiential phenomena, olfactogustatory or vegetative responses were evoked.

The involvement of the insula in cardiac regulation has been demonstrated in patients with left-insular cortex lesions[47] and has been suggested to play an important part in the pathogenesis of sudden unexplained death in epilepsy via cardiac asystole.[48] Monitoring ECG and intra-arterial blood pressure, Oppenheimer *et al.* found bradycardia and depressor responses more frequently produced than tachycardia and pressor effects when stimulating the left insular cortex. The converse applied for the right insular cortex.[49]

Conclusion

Stimulation studies reveal a broad spectrum of somatosensory and viscerosensory phenomena. However, when considering a resection in an patient with medically refractory insular epilepsy, the planning of the surgical procedure is guided by the extent of the lesion and the assessment of the ictal onset zone. In suitable cases postoperative seizure freedom can be achieved without causing permanent neurological deficits.[50]

Olfactory cortex

The cortical regions subserving olfactory functions have not been definitively defined.[51,52] The primary olfactory cortex consists of the anterior olfactory nuclei, olfactory tubercle, piriform and lateral entorhinal cortex. The piriform cortex receives direct input from the ipsilateral olfactory bulb via the lateral olfactory tract and projects to the insular and orbitofrontal cortices, the latter assigned to the secondary olfactory region. These structures together with the thalamus form a loop with the thalamus receiving input from piriform cortex and olfactory tubercle and projecting to orbitofrontal and insular cortices. The lateral part of the entorhinal cortex has connections with the hippocampus.[53]

According to Greenberg[54] there is an overall paucity of olfactory hallucinations in the stimulation literature. The data

from three large epilepsy centers in Germany prove olfactory sensations to be a very rare phenomenon.[52] Halgren *et al.* studying the temporal lobes of 36 epileptic patients with depth electrodes and and performing 3495 stimulations of the medial temporal lobe found 267 mental phenomena of different modalities but no olfactory sensations.[55] Stefan *et al.*[56] as well as Weingarten *et al.*[57] failed to stimulate olfactory hallucinations when exploring the patients temporal lobes with depth electrodes. Penfield *et al.*[12] were able to elicit unpleasant smells regularly when stimulating the olfactory bulb but only occasionally when stimulating the uncus or the amygdaloid nucleus. Van Buren[58] obtained reproducible olfactory sensations when stimulating with depth electrodes 'from within or very close to the amygdala'. Andy[59] stimulated intraoperatively the right amygdala and hippocampus of a patient suffering from posttraumatic epilepsy with olfactory as well as experiential auras and complex partial seizures. Stimulation of the amygdala led to habitual olfactory sensations (in combination with afterdischarges and spread to the hippocampus), whereas stimulation of the hippocampus, although accompanied by afterdischarges but with minimal spread to the amygdala, failed to do so. Repeat stimulation of both structures after having them surgically separated yielded the same results, thus proving that the amygdala was crucial for the occurrence of the olfactory phenomena. In another case[60] electrical stimulation of the amygdala of the dominant side also produced olfactory (and gustatory) perceptions. Interestingly, their unpleasant character could be altered to a more pleasing one by interacting with the patient. There is only one study[61] in which stimulation outside the corpus amygdaloideum elicited olfactory sensations, which may be due to limited accuracy of defining the precise location of the stimulating depth electrodes. Contrary to these electrical stimulation studies, investigating the contemplable olfactory cortical regions with PET by exposing normal subjects to a set of eight different odorants, revealed a strong bilateral activation of the piriform cortex and right sided activation of the orbitofrontal cortex.[51] Both areas are difficult to access with electrodes and this represents a major disadvantage of the electrophysiological approach. Thus, we concur with the conclusion of Greenberg[54] that

> while the gross localization of epileptic olfactory hallucinations to activation of deep limbic nuclei in a proportion of patients seems secure, the exact region(s) necessary and sufficient for subserving the generation of false perceptions of smell, the precise mechanism by which this is achieved, and the factors that determine individual susceptibility all remain obscure.

Amygdala

Besides the above-mentioned olfactory hallucinations electrical stimulation of the amygdaloid corpus elicits a set of other responses which likewise consist of altered mental functions and are referred to as experiential phenomena.[62] This designation bears on their character which resembles real life experiences. Although Penfield *et al.*[12,13] ascribed them to stimulation of the lateral temporal cortex, in further studies[55,63,64] experiential responses were predominantly obtained by stimulation of the limbic structures, i.e., the medial part of the temporal lobe. This portion of the temporal lobe had been only infrequently stimulated by Penfield and co-workers. In the study of Gloor *et al.*[63] the responses elicited were most often not associated with an afterdischarge or the afterdischarge remained confined to the area of stimulation. They included perceptual hallucinations or illusions, emotions, experiential responses in the form of flashbacks as well as *déjà vu* illusions and forced thinking. The likelihood with which responses could be elicited had an anteroposterior gradient, the amygdala showing the highest incidence of responses. The likelihood further decreased from the hippocampus to the parahippocampal gyrus. This anatomical relation was also found in the studies of Halgren *et al.*[55] and Fish *et al.*[64] Among emotions, fear or anxiety are the most frequently encountered. Halgren and Chauvel [65] hypothesize as an explanation that electrical activation is a very crude means of activation and induces limbic hyperactivation and disorganization. Such limbic disorganization could also arise when the organism is confronted with an event that it can not emotionally integrate, either because it is completely novel or because it contains elements with conflicting emotional implications. Electrical stimulation would then often induce anxiety because as an external unnatural stimulus it cannot be integrated by preexisting limbic circuits. The pivotal role of the amygdaloid corpus has been demonstrated also by measuring intracranial event-related potentials when presenting frightening facial expressions to epileptic patients implanted with depth electrodes during a presurgical evaluation. Specific potentials to fear beginning 200 ms poststimulus were observed in the amygdala, occurring 100 ms earlier than potentials to disgust recorded in insula. Potentials to fear were initially confined to the amygdala and later spread to occipital-temporal, anterior temporal and orbitofrontal cortex.[66] Fear as an ictal sign, however, did not occur in four patients with fear as the main feature of their seizures until additional structures of the frontal lobe become involved.[67] These patients were studied with depth electrodes implanted in the temporal and frontal lobes including anterior cingulate and orbitofrontal regions. Ictal involvement of the amygdala alone was not accompanied with a feeling of fear. Fear behavior occurred not until orbitofrontal and anterior cingulate cortex became involved. Electrical stimulation of the amygdala evoked fear and the sensation of a shadow behind her in one patient but without the habitual ictal fear behavior. In the other reported patient with stimulation, ictal discharges did not involve the amygdala and stimulation of the amygdala did not lead to any symptoms. Another recent stimulation study with special emphasis on the adjacent perirhinal and entorhinal cortices[68] demonstrated evoking of fear or anxiety, experiential (*déjà vu*, *déjà vecu*) phenomena and viscero-sensitive perceptions when stimulating the amygdala, and also the hippocampus and both rhinal cortices. However the experiential phenomena were more frequently induced by rhinal than by hippocampal-amygdala stimulations. The involvement of medial temporal structures in generating ictal fear has also been evidenced in an study applying magnetic resonance spectroscopy to the hippocampus and demonstrating metabolic changes along its axis.[69] Summarizing, we would like to cite Gloor's hypothesis[62] that the stimulation of the amygdala and further medial temporal lobe structures:

> can induce the elaboration of patterns of excitation and inhibition in widely distributed neuronal networks, some

of which are capable of forming a specific matrix representing the substrate of a given experience. Neuronal networks engaged in parallel distributed processing have the capacity to recreate the totalness of a given experience when only a fragment of the network is activated... [Thus] ...experiential phenomena are positive expressions of temporal lobe and limbic functions.....

Cingulum

In 1949, Pool and Ransohoff[70] published data on autonomic effects provoked by bilateral stimulation of the anterior part of the cingulate gyrus in psychotic patients treated with bilateral frontal gyrectomy or fractional corticectomy of Brodmann's areas 9 and 10. Their study was designed to look only for autonomic effects. Changes of blood pressure, pulse rate and respiratory rate could be produced and consisted of either elevation or decrease of the values. Most of these effects were confined to the duration of the stimuli, but occasionally could outlast the stimuli. Control stimuli applied to medial and lateral aspects of Brodmann's areas 9 and 10 did not lead to autonomic effects. Similarly, Penfield *et al.*[12] observed that stimulation of the anterior and inferior portion of the cingulate gyrus caused patients to stop breathing, but that the patients were able to breathe voluntarily when asked to do so during stimulation. In two epileptic patients whose cingulate gyri were partially covered with subdural electrode grids[71] sensory responses occurred during electrical stimulation. Stimulation of the posterior region of the right cingulum caused in one patient a 'feeling as in a dream, like a TV scene' or 'buzzing' in the ears or a 'shock' all over the body. The second patient who was stimulated in the right midcentral region experienced bilateral 'numbness' with left preponderance in varying parts of the whole body including trunk, extremities and face. A comprehensive study[72] of epileptic patients who were investigated with depth electrodes implanted in the anterior and middle cingulate gyrus as well as orbito-frontal, lateral superior and middle frontal gyri and supplementary motor area yielded the following symptoms in the stimulated patients: 25% hallucinations, 8% signs of emotions (fear, crying, moaning), 17% visceromotor, 74% viscerosensitive, 35% sensory, 18% contralateral deviation of head, 17% grimacing and pouting, 8% clonic, 17% oroalimentary automatisms, 33% arrest of speech. Compared to the other areas, visceromotor and viscerosensory symptoms were most frequently and oroalimentary automatisms exclusively observed when stimulating the cingulate gyrus. Talairach *et al.*[73] and Bancaud *et al.*[74] reported in several studies with depth electrodes on a unique type of motor automatisms elicited by electrical stimulation of the anterior part of the cingulum. These automatisms involved primarily fingers, hands, lips and tongue, only rarely the eyes. They were based on a few simple movements, such as touching, stretching or sucking which often developed into more complex movements that seemed to be directed by the situation. They lasted for the stimulation and were involuntarily, experienced by the patients as forced onto them. Automatisms of hand and fingers occurred contralaterally to the stimulated side. Sometimes in addition, changes in mood, level of consciousness or autonomic phenomena could be observed. The pattern of stimulation points showed no somatotopic organization. This type of motor automatisms, which is different from those provoked by stimulation of the motor areas, was considered to result from the integration of motor, sensory and mnestic functions and to represent elementary basic motor functions, i.e., 'to consist of the smallest parts of movement formed by the integration of gnostic and mnestic praxial motor functions'.[73] As shown above, these motor automatisms – in contrast to the additional phenomena – have not been encountered in stimulation studies of other investigators. They were differentiated from paroxysmal, i.e., ictal behavior, on a clinical base and electrographically not accompanied by paroxysmal, that means ictal patterns. However, the authors described a 3–8 Hz regular rhythm appearing at neighboring electrodes and sometimes recordable from the scalp with maximum at the midline (vertex). This activity spread to homologous areas of the contralateral cingulate gyrus as well as to the frontal medial cortex and posterior cingulate gyrus, but not to the hippocampus. Even though these changes might lack some features to be unequivocally considered an ictal pattern they might indicate a spread of electrical activity beyond the cingulate gyrus and an involvement of additional medial frontal cortical areas. Summarizing, electrical stimulation of the cingulate gyrus produces a wide variety of motor, sensory, visceral/autonomic and psychic phenomena, the autonomic, viscerosensitive and visceromotor being the most frequent and distinguishing ones. However, its physiological function is by far more complex[75] and has been described as an 'interface between emotion and cognition'.[76]

Case presentation: alien limb syndrome evoked by stimulation with subdural electrodes

Alien limb phenomena (ALP) consist of a variety of abnormal motor and sensory symptoms of the extremities leading to seemingly purposeful but often erratic limb movements. They are perceived as foreign and forced onto, as if they were alien induced.[77] Furthermore, the ownership of the affected limb (verbal asomatognosia) is denied in some but not all patients.[78,79]

We present a 14-year-old patient who had parietal lobe epilepsy due to a malformation of cortical development in the left postcentral cortex. Neurological examination and neuropsychological testing were normal apart from a postictally occurring paresis of his right leg. The electrical stimulation of two electrodes above the border between the precentral and the postcentral gyrus and one electrode above the frontal operculum (see Figure 110.1) induced episodes of involuntary grabbing maneuvers of the right arm accompanied by the perception of alienness ('someone else is playing with that arm'). These involuntary movements persisted under visual fixation of the right arm and terrified the patient.

Focal epileptic seizures as a possible etiology of transient ALPs have already been discussed in previous reports.[80,81]

The motor activity may be interpreted as limb automatisms – otherwise neglected in complex partial seizures – but now realized under preserved consciousness. It may be speculated that the simultaneous appearance of motor automatisms

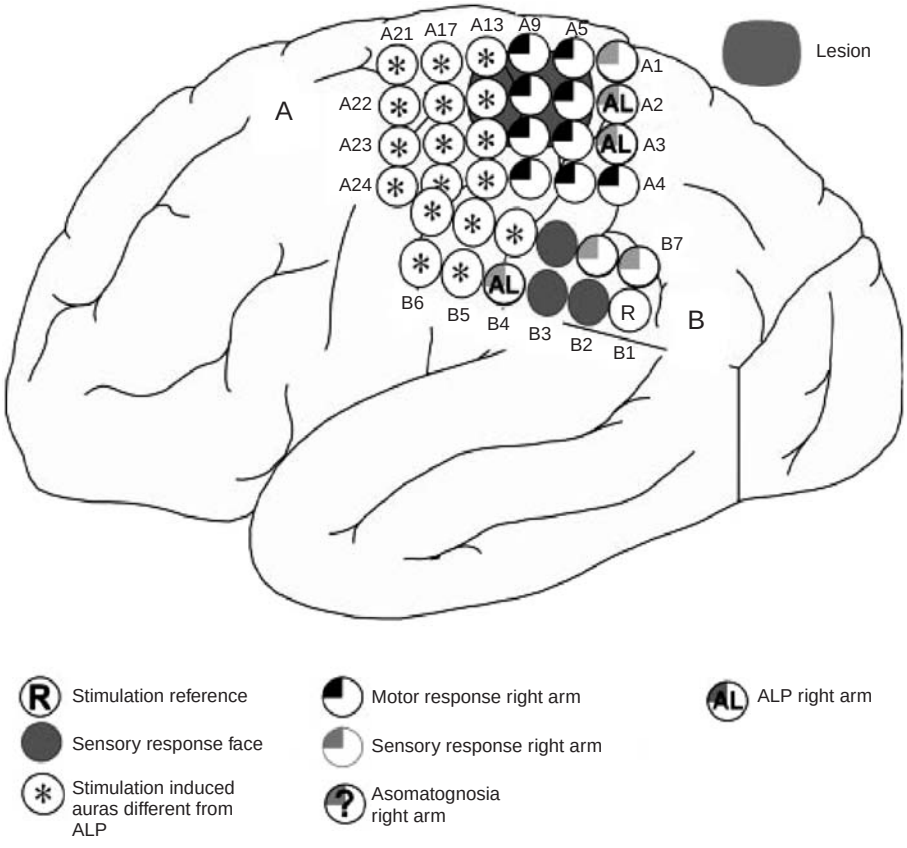

Figure 110.1 Alien limb phenomena (ALPs) were induced by electrical stimulation of the electrodes A2 against A3, A3 against A4, and A2 against reference electrode B1. The latter electrode pair induced symptoms lasting for a further 10 seconds after the end of stimulation, which was accompanied by an EEG seizure pattern over the electrodes adjacent to A2. The electrodes A2 and A3 were shown to be located above the border between the precentral and the postcentral gyrus by stimulating the adjacent electrodes. Furthermore, the stimulation of electrode B4 against B5 and against the reference B1 also induced ALP. In a widespread cortical area located anterior to the lesion (*), the stimulation induced either somatosensory (tingling) or unclassified auras (indescribable wholebody perception), indicating the irritative zone. (From Boesebeck F, Ebner A. Paroxysmal alien limb phenomena due to epileptic seizures and electrical cortical stimulation. *Neurology* 2004;63:1725–27, with permission from Lippincott, Williams & Wilkins.)

and ictal asomatognosia[82] in the same limb reflects a time-locked activation/inhibition of two or more distinct cortical areas. This could explain the relative rarity of ictal ALP because semiologies in partial epileptic seizures normally follow a topic and temporal propagation and, in the case of complex motor automatisms, are regularly accompanied by an impaired awareness of the ictal symptoms. The eliciting of ALP by previous ipsilateral movements may be attributed to the rare condition of simple partial reflex seizures induced by voluntary movements of the affected limb[83] but has also been noticed in nonepileptic posterior ALP.[84,85]

The stimulation of two distant cortical areas in the left hemisphere elicited ALPs in our patient. One cortical area is located in the crossing between the primary sensory cortex (S1) and the primary motor cortex (M1)–both representing the affected limb. The second area is located in the supplementary sensory area (S2) of the planum infraparietale.

It may be speculated that stimulation of electrodes above the rolandic fissure may have led to a bidirectional propagation of electrical current in our patients, which may have led to a simultaneous inhibition of primary sensory areas (asomatognosia) and activation of primary motor areas (involuntary movements) that were subjectively experienced as alien movements. Another possible mechanism may be a functional disconnection of association fibers between the primary (S1) and supplementary sensory areas (S2).

This case report is based largely on the report of F. Boesebeck and A. Ebner.[86]

Case presentation: laughter evoked by stimulation with subdural electrodes

Laughter is the principle symptom of gelastic seizures. Recently it has been reported also as a postictally occurring symptom.[87] This seizure type is predominantly encountered in patients with hypothalamic hamartomas (HH)[88–90] but has been observed also in symptomatic epilepsies of the frontal lobe,[91–93] temporal lobe,[92,94] parietal lobe,[95] or in cryptogenic epilepsies.[89] The character of laughter is involuntary, forced, but can seldomly be accompanied by feelings of mirth. In patients undergoing invasive presurgical evaluation, laughter as an ictal symptom of their habitual gelastic seizures could be induced by electrically stimulating with SEEG electrodes,[88,93] but only in very few patients could laughter be electrically evoked without inducing seizures.[92,96] Moreover, in these patients laughter

was not part of their habitual seizures. We present a 35-year-old woman suffering from focal epilepsy since early childhood due to a cortical dysplasia located in the middle and posterior part of the right superior frontal gyrus. Her seizures consisted of somatosensory auras of left arm and hand evolving into asymmetric tonic seizures. No gelastic seizures. She was evaluated with subdural electrodes covering laterally the primary sensorimotor area and as a 10-electrode strip mesially the supplementary sensorimotor area (SSMA). It could be shown by electrical stimulation and fMRI that the lesion lay sufficiently anteriorly to eloquent cortex to be resected completely. This rendered the patient seizure free. When stimulating the two superior electrodes of the anterior row of the mesial strip which lay on the cranial anterior part of the SSMA, the patient immediately started to laugh and stopped reading the text which she had been asked to read. This could be demonstrated repeatedly and without afterdischarges. The nature of the laughter was involuntary, forced and without a concomitant feeling of mirth. Stimulation of adjacent electrodes yielded either the habitual tonic seizures or negative motor responses (electrode beneath). To our knowledge, there is only one other case of laughter elicited by stimulation of mesial frontal cortex in or adjacent to SSMA. Unlike the other case published by Fried,[96] our patient did not experience mirth or merriment. Other sites where laughter could be evoked were anterior cingulate gyrus and orbitofrontal cortex (Sem-Jacobsen cited in ref. 92) and fusiform and parahippocampal gyrus.[92] Based on their two stimulated patients that had an accompanying feeling of mirth and one patient with proven ictal onset of gelastic seizures without mirth in the cingulate gyrus, Arroyo *et al.*[92] hypothesized that the cingulate gyrus plays a primary role in the motor execution of laughter, and that the basal temporal cortex processes the emotional aspects of laughter. Biraben *et al.*[67] who were able to demonstrate SPECT ictal hyper- and interictal hypoperfusion in the orbitolateral region continuing into the temporal region in one patient with cryptogenic epilepsy with gelastic seizures, stress the involvement of the cingulate gyrus and orbitofrontal cortex in the generation of ictal laughter. However, our and Fried's data demonstrate that stimulation of the frontal cortex in the anterior part of the SSMA also elicits the motor execution of laughter, both with or without concomitant feelings. Obviously, due to the small number of studies and the complexity of the subject, there is not yet enough knowledge to identify the essential structures (or their interplay) required to enable the motor execution of laughter, let alone the emotional perception of mirth. The data of our patient has meanwhile been published by Schmitt and Ebner.[97]

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111 The role of electroencephalogram and magnetoencephalography synchrony in defining eloquent cortex

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Introduction

Attempts to correlate the human electroencephalogram (EEG) with cognitive and behavioral states go back to Hans Berger's observations on the alpha rhythm. Such relationships are implicit in routine clinical interpretations of EEG (e.g., the reactivity of the mu rhythm to motor activity), but for today's epileptologist, the EEG remains overwhelmingly a diagnostic tool for evaluation of seizures and encephalopathy. However, the vast nonclinical literature in the EEG-magnetoencephalography (MEG)/cognition/behavior area, from fields as diverse as basic neuroscience, linguistics, psychology and the emerging discipline of complex systems, provides neurologists interested in higher cognitive function with valuable signposts to investigating their own clinical datasets. Some of this literature is alluded to in this chapter; for overviews on selected aspects, see.[1–3]

Normal, 'free-running' EEG has a number of well-defined characteristics and waveforms. It is also clear that external stimuli will sometimes passively 'drive' it (e.g., the photic following response from flicker). Studies of EEG in relation to cognition are interested, by contrast, in waveforms (or other attributes) that can be clearly distinguished from normal background, not directly driven by the stimulus, but somehow 'caused' by the task. The term 'induced rhythm'[4] (distinguished from the term 'evoked response' used in its usual sense) is sometimes used for this purpose. These may be novel rhythms (waveform epochs or single potentials) or modification of pre-existing rhythms (e.g., event-related desynchronizations). Induced rhythms are conventionally interpreted, at some risk of oversimplification, into two schools. One may wish to identify discrete cerebral foci corresponding to ever more complex tasks (School I: an approach that recalls the popularly-dubbed 'grandmother cell'[5] hypothesis). Else (School II), one follows the hypothesis that the brain works by recruiting large number of simple units (neurons) into complex networks ('functional neural assemblies',)[6] and looks for interareal cooperation between distributed cortical regions (the doctrine of 'Neurons that Fire Together, Wire Together': a thesis originally attributed to Hebb.)[7,8] This chapter emphasizes the latter approach, though it should be borne in mind that everyday clinical neurology, based on lesion-deficit analysis, is School I thinking. This is also true for cortical stimulation mapping, a commonly used technique in surgical epileptology for identifying eloquent areas. Clearly, a fuller understanding of the neural basis of cognition will reasonably incorporate ideas from both schools.

Neurophysiology of cognition

The macroscopic scalp EEG represents the summated extracellular potentials (the local field potential, or LFP) of neurons in the vicinity of the recording electrode.[9] An oft-quoted figure is that simultaneous activity of about six square centimeters of cortex is necessary for a waveform to be discernible on the scalp.[10] Scalp-EEG is thus the aggregate of many millions of excitatory and inhibitory postsynaptic potentials; it does not directly represent action potentials, except under circumstances of pathological synchrony (e.g., a seizure, when the recorded LFP reflects the spatiotemporal summation of repetitive action potentials). Nevertheless, a correlative relationship between the LFPs and neuronal information processing is often assumed:[11] one interpretation of EEG is thus as a surrogate of neuronal activity. Distinct from this, the nature of EEG enables unique use as a brain mapping tool (i.e., different from metabolic methods such as fMRI or PET). First, the fine temporal resolution of EEG (limited only by the bandwidth of the recording technology) allows tracking of rapid changes inaccessible by fMRI or PET. Second, because the amplitude of EEG depends largely on neuronal synchrony, it can be independent of individual neuronal firing rates.[12] Thus EEG 'activation' can occur irrespective of overall neuronal metabolic change, a feature again invisible to metabolic imaging.

The MEG signal represents the same neurophysiological phenomena as EEG.[13] On a practical level, the biophysical aspects of signal generation and detection however give rise to information that is somewhat different, and possibly complementary to EEG.[13,14] Clearly, it is ideal for every neurophysiological study of cognition to be performed with both EEG and MEG. In the absence of such information, it is reasonable to assume that results from either method contribute towards a common neurobiological interpretation.

Which waveform?

Induced rhythms may be of various sorts, and the experimenter will usually decide beforehand what the neurophysiological 'end-point' of the study is. This may be based on an

a priori biological hypothesis or be guided by technical feasibility. In turn, determination of the waveform of interest guides, to an extent, what questions the experiment may reasonably ask.

Event related desynchronization (ERD) has a long history, arising naturally from early observations on the reactivity of the alpha rhythm. This approach identifies changes in spectral power in specific frequency bands over extended brain regions.[15] Influential theories on the neural basis of integrated cognitive function emphasize large-scale synchrony between multiple cortical areas,[16,17] a viewpoint that ERD has provided some evidence for in recent years.[18] Cognition-related event-related potentials (ERPs) are another candidate neurophysiological waveform: the literature on this is large and continues to grow. ERPs are essentially a long-latency evoked response, but thought to be independent of the physical characteristics of the stimulus, and related to the higher processing of elementary sensory information.[15] Though the advantages of ERPs in terms of their high temporal resolution and reproducibility have been stressed, their identification involves signal averaging of many trials. This limits the types of neuropsychological paradigms that may be investigated. In addition, the location of the generators of ERPs is usually controversial, and interpretation of results at a neural or structural level difficult. DC shifts are probably the electrical counterpart of functional imaging: 'slow' potentials (of the order of 1 s) due to continuous afferent input or multiple depolarizations of cortical neurons are induced by long-lasting tasks.[15] Lastly, an entire spatiotemporal 'block' of EEG (or MEG) may be of interest. Waveforms, believed to be induced by the task, are characterized by their duration, frequency content and spatial distribution. Analysis of crosschannel congruence or dissonance is the intuitive basis of EEG coherence[19] (and similar methods such as phase synchrony).

Though it appears that comparison of all the above neurophysiological measures within any particular experimental paradigm is straighforward, such published data is rare. This makes the choice of induced rhythm rather arbitrary for any particular experiment, which may, in part, explain the diversity of results reported in the literature.

Methodological issues

Experimental paradigms are naturally designed to fit the modality under study. For assessing the neurophysiological response to elementary sensation, for example, this is hardly controversial. Cognitive experiments present pitfalls such as controlling for intrinsic patient ability and attention. Nevertheless, neuropsychological paradigms described in the literature appears to be fairly homogeneous. 'Oddball' paradigms are particularly suited to the ERP literature, given the need for averaging over multiple trials to detect the waveform of interest and the requirement to precisely time stimulus presentation. Studies of language use a variety of paradigms: synonym search[20] and silent reading and naming[21,22] represent the more intensive and long-duration stimuli, recalling the paradigms of functional neuroimaging; distinguishing words from nonwords,[23,24] or vowels from nonvowel sounds[25,26] represent more passive experimental paradigms. It should be noted that there is a large literature that explores the neurophysiological correlates of different linguistic tasks. These represent an effort to understand the more complex aspects of language processing; by contrast, the former studies (more relevant to the epileptologist), merely aim to distinguish language from nonlanguage. Memory studies usually use variants on the standard Sternberg task, presented visually or aurally.[27,28]

Data gathering is more of an issue with EEG than MEG. MEG is customarily recorded with whole-head magnetometers with dense sensor arrays. The MEG signal does not need a reference, sensors do not contact the scalp, and the signal is not distorted by the effects of intervening tissues; all these are caveats with EEG.[14] However, most scalp-EEG studies work with less than 20 electrodes, and data display is rarely more sophisticated than bipolar or referential formats. Increasing the number of electrodes to beyond 100, and the use of spatial deblurring algorithms may enhance the data value of raw EEG.[29,30] The latter also usefully contributes to the debate on reference contamination, a particular issue in the computation of coherence.[31–39]

Post processing methods employed for cognitive neurophysiological data range from the simple averaging methods well-known in evoked potential work, through the spectral methods of classical signal processing, to newer methods derived from the analysis of nonlinear time series.[15,40] For a review of the promise of the latter methods in EEG, see ref 41. Measuring EEG synchrony between brain regions is based on the Hebbian idea that regions of the brain that work together must temporally bind. For an equivalent EEG signature one simplistically imagines two EEG time series being synchronous if there is a high degree of 'overlap' when they are superimposed. Formally, the cross-correlation R of two signals s_1 and s_2 (EEG or MEG time series) with Fourier transforms S_1 and S_2 is

$$R(\tau) = \int_{-\infty}^{+\infty} s_1(t)\, s_2(t+\tau)\, dt;$$

its Fourier transform $\Im(R) \equiv S_{12}(f) = S_1(f) S_2^*(f)$ is the cross-spectrum (the asterisk denotes the complex conjugate). If S_{11} and S_{22} represent the autospectra (i.e., individual power spectral densities), coherence is defined by

$$C(f) = \frac{|S_{12}(f)|^2}{S_{11}(f) S_{22}(f)}.$$

In practice, ideal spectra do not exist, and the above values are best estimates from the data.[40] The coherence at any frequency is thus a number between zero and unity, independent of the mean amplitude of the original signal. A nonzero value of coherence at a particular frequency of two EEG epochs implies that both epochs possess that frequency, with larger values implying greater sharing of power at that frequency. The phase of the cross-spectrum is a measure of the temporal relationship between the signals at that frequency; this may be used, for instance, in the detection of small time differences between EEG events that appear synchronous between channels.[42] However, cross-spectral phase is a meaningful quantity only if the coherence is itself significant;[42] this limits the use of the former as a 'pure' measure of synchrony. Other drawbacks in using coherence to assess synchrony are that large-amplitude signal overlaps may swamp low-amplitude,

possibly physiologically more meaningful frequencies, and that the analysis is unable to follow modest frequency trends in the data[43] (i.e., the method, like most classical signal-processing paradigms, assumes stationary data). The method of phase synchrony overcomes these limitations by explicitly 'decoupling' amplitude fluctuations from the signal epochs of interest, so that comparison is made purely of phase overlaps.[43] That is, the question is *whether* the signals are synchronous, not *how much*. Formally, the method defines the analytic function Z associated with a narrow-band signal *s* as

$$Z(t) \equiv s(t) - iH\{s(t)\},$$

where the operator H is the Hilbert transform

$$H : s(t) \rightarrow \frac{1}{\pi} \int_{-\infty}^{+\infty} \frac{s(\tau)}{t-\tau}\, d\tau$$

The analytic function uses the antisymmetry properties of the Hilbert transform in the Fourier domain, so that the original real-valued function $s(t)$ is recast as $Z(t)$ on the complex plane, which allows disambiguation of amplitude and phase.[44] Instantaneous phase ϕ is then uniquely 'tracked' (independent of amplitude) by

$$\phi(t) = \arctan \frac{H\{s(t)\}}{s(t)}.$$

Thus defined, analytic phase is restricted to the interval $[-\pi, +\pi]$ and its time series are repeats of a cycle increasing from $-\pi$ to $+\pi$, with 2π-phase-slips occurring at $-\pi$ and $+\pi$. The function can be made continuous ('unwrapped') by adding 2π at these points. Phase difference between two signals is calculated by simple subtraction

$$\psi(t) = \phi_1(t) - \phi_2(t),$$

with synchrony being defined as ψ = constant (or zero) over an agreed time period. Intuitively, this corresponds to two waveforms bearing a fixed relation to each other (either a constant distance apart, or exactly in step). Over a total length of time T, the degree of phase synchrony may be summarized by the phase-locking factor (PLF), the time average of phase differences between candidate signals. For discrete data with N data points $T = N\Delta t$, where $1/\Delta t$ is the sampling rate of the continuous data and

$$\mathrm{PLF} = \left| \frac{1}{N} \sum_{j=0}^{N-1} e^{i\psi(j\Delta t)} \right|.$$

Perfect synchrony between two EEGs implies a PLF of unity; complete asynchrony, a PLF of zero.

See refs. 3, 43 and 45 for a fuller discussion of the method; Figures 111.1(a–e) illustrate the central concepts.

Language and memory

How have neurophysiological studies contributed to brain mapping? The literature points to great variability of results; nevertheless, we suggest a synthesis along three main lines. First, there is little doubt that activity-related EEG and MEG changes are a robust and readily identified phenomenon. Second, widespread and bilateral activation is seen with many paradigms. Neurophysiological correlates of perception, attention and awareness have been explored by both EEG[46,47] and MEG[48–50] in normal subjects; typically, these studies describe event-related band power, coherence, or phase synchrony changes over widespread areas during the target task. Diffuse induced rhythms are also described in more focused cognitive activation paradigms. The review of Weiss and Mueller[2] (this paper provides a large bibliography of similar work) describe a study of EEG activation with respect to word categories. Activations were classified into six frequency bands between 1–31 Hz, related to concrete nouns, abstract nouns and verbs; coherence calculations suggested low-frequency increases related to nonspecific and attentional mechanisms, with higher frequency increases more associated with word type. A verbal memory study carried out by the same group[51] demonstrated that the likelihood of a presented word being recalled was related to widespread coherence networks involving both hemispheres, anteriorly and posteriorly. Klimesch and colleagues[27] carried out an ERP study of memory, measuring also event related band power in the theta range. Remembered stimuli in their Sternberg-type task could be distinguished from nonremembered ones by a different ERP profile as well as theta-frequency spectral power measured over the centroparietal region. Gruber and co-workers[52] measured phase synchrony in a paired association learning task. When the second stimulus of a previously memorized stimulus pair was presented, widespread synchrony in the gamma range was observed between multiple electrode sites across both hemispheres. Sarnthein and colleagues[53] described high theta coherence between prefrontal and posterior electrode sites during a working memory task. The third strand of synthesis is that, in several EEG studies certain subparadigms produce reliable *regional* activation. Dobel and colleagues[54] studied responses to semantic, versus syntactic, tasks to line drawings of concrete objects. In their healthy, right-handed cohort, a significant left-lateralized anterior activation was seen in the slow wave component of the ERP between 300–600 s, for the syntactic, but not semantic task. In a similar study,[55] two visually-presented stimuli (either letter strings or nonverbal graphics) were compared by healthy, right-handed subjects according to various verbal and graphic criteria. A remarkable observation was that just the presentation words and word-like strings elicited an N470 in the left, but not right, temporal region. Among processing tasks, there was an asymmetry (left enhanced) of the P620 for phonological matching as opposed to semantic matching. In another study described by Weiss and Mueller,[2] healthy, right-handed subjects were presented a succession of spoken sentences containing either a subject-subject (SS), or a subject-object (SO) relative clause. The latter are acknowledged to be more demanding of verbal processing ability; this was reflected in a significant asymmetry of coherence between frontal sites, left greater than right. The MEG literature, on the other hand, is conclusive in obtaining language-related activations over the dominant hemisphere in both normals[56] and neurological[24,25] patients. Activations in these studies are ERPs modelled as equivalent current dipoles with standard algorithms. Similar results have been obtained with alternative MEG signal-processing techniques.[21,23]

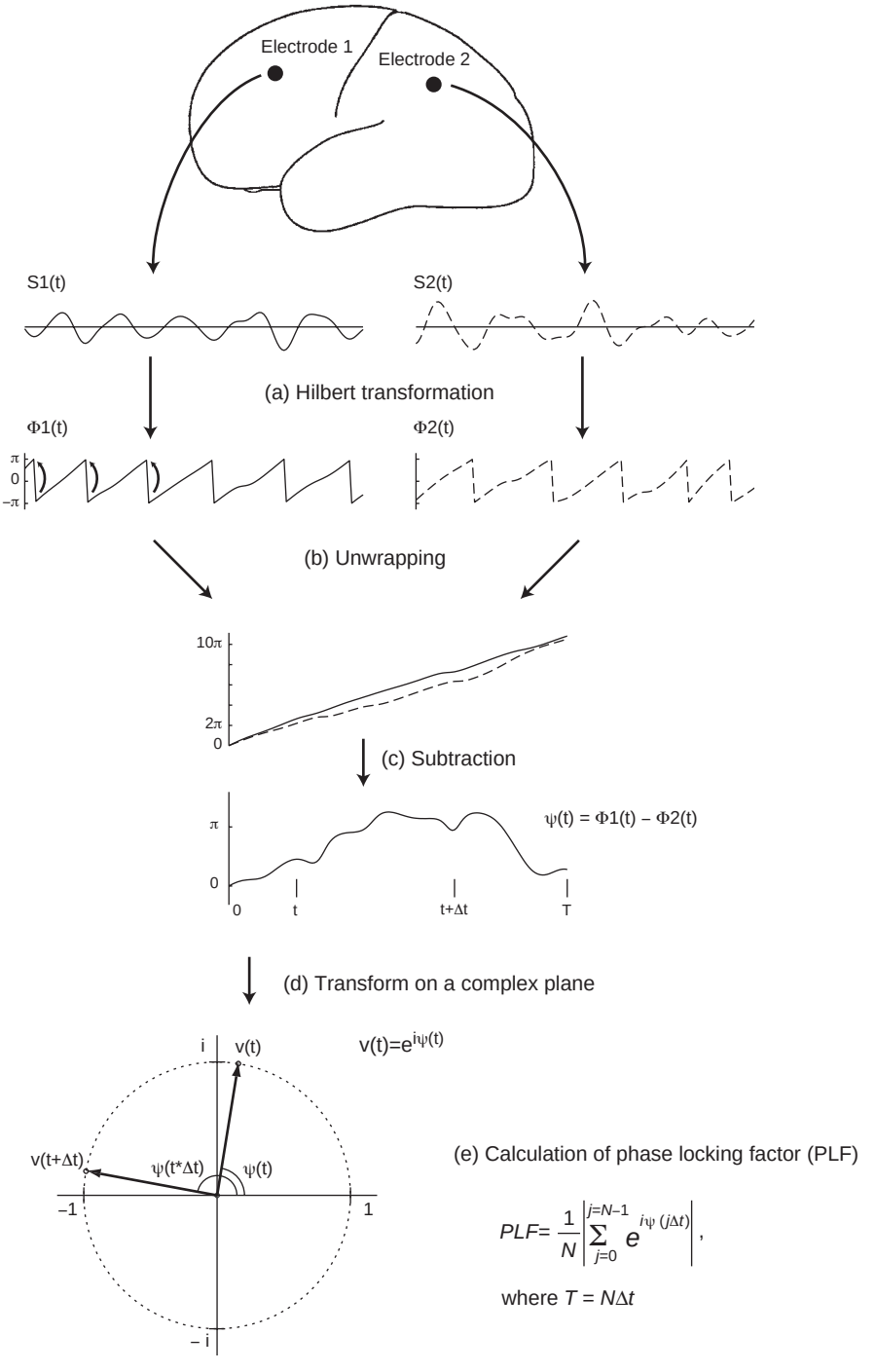

Figure 111.1 Schematic illustration of phase synchrony analysis. See text for details. (a) Two segments S_1 and S_2 of length T of bandpass-filtered EEG are picked up by different electrodes and subjected to the Hilbert transform to extract analytic phase ϕ_1 and ϕ_2. (b) Analytic phases are 'unwrapped' and overlaid for comparison. (c) Pointwise subtraction of the two waveforms yields ψ, the instantaneous phase difference. (d) Successive values of $v = \exp i\psi$ are plotted on the complex plane. (e) Their averaged vector sum provides the phase locking factor (PLF), the length of which grows to unity if the phase difference is constant over T, or shrinks to zero if the phase difference is random.

Intracranial studies

A comprehensive review of the neurophysiology of cognition with invasive recording has recently been provided by Lachaux and colleagues.[57] As these authors point out, the majority of studies record LFPs or spike trains (the latter with intracellular electrodes). A smaller number of studies record oscillatory activity (usually in the high-frequency gamma range) in a few contiguous electrodes. The activity recorded by a single intracranial electrode is essentially that of a small volume (approximately 1 cm^3) of neighboring brain tissue,[57] so that cognitive paradigms explored through such means are restricted to testing School I hypotheses. Aspects of attention,[58] emotion[59] and mental imagery[60,61] have been explored through such studies, in addition to studies of language[62,63] and memory.[64] Though there is evidence for high specificity of single sites for complex stimuli (see refs 65 and 66, for instance) it is also clear that responses to highly-defined stimuli may arise from widepread, disjoint parts of the brain.[67]

The latter naturally lead to the question of spatially distributed networks for cognition (School II). The intracranial EEG literature on this is rather more limited. There is no published study on cortico-cortical interactions during language processing; the study of Sinai and colleagues[63] identified local changes of gamma-frequency activity over sites that were subsequently identified as language-eloquent by electrical stimulation. Short-term visual memory was explored in a study of two patients,[68] who were asked to identify whether a presented shape had been shown previously or not. Synchronies in the beta range were found between the inferior temporal and occipital regions in both patients during the retentive portion of the task. Verbal memory was explored in patients with depth electrodes in the limbic structures and adjacent temporal lobe.[69] Gamma band synchrony was higher between the entorhinal cortex and hippocampus for words that were successfully recalled.

Summarizing, scalp EEG studies suggest that certain aspects of language and memory have a large cortical distribution; other aspects, relating to some paradigms and choice of particular induced rhythm, point to a more focal distribution over the classical areas of the dominant hemisphere. By contrast, MEG studies with source localization methods reliably achieve asymmetric activations. For memory, the current EEG literature perhaps indicates nonspecific aspects of processing, pending further studies that arrive at the appropriate paradigms and signal-processing methods to identify more focal activation. Neurophysiological results obtained with invasive data are thus anticipated: there is evidence of *both* extreme focality as well as distributedness to the representation of cognitive function.

Language-associated phase synchrony in intracranial EEG

We studied auditory language perception in five pre-surgical epilepsy patients undergoing invasive EEG (iEEG) evaluation with subdural grids.[70] The clinical indication for iEEG in these patients was to precisely identify the ictal onset zone (which was unclear on standard noninvasive investigations), as well as demarcate this area from (traditionally-defined) eloquent cortex. The research study sought to further identify 'language-eloquent' areas by the method of phase synchrony in contrast to those identified by conventional means.

Methods

Study participants were recruited from consecutive patients who were older than 15 years, right-handed, native English speaking, having normal or near-normal baseline cognitive function, and electrode coverage over the left (language dominant) hemisphere including at least the posterior part of the lateral temporal lobe. Three of the five patients had normal high-resolution MRI brain scans. Clinical characteristics of the patients are summarized in Table 111.1. Recordings were performed extraoperatively, at least 48 hours after the operative procedure for grid implantation, and before any EEG or clinical seizures were observed. For technical reasons, not all implanted electrodes could be recorded from in every patient.

Full details will be provided elsewhere; essential methodology and central results are described here. Stimuli were presented on a computer screen (Superlab; Cedrus Corp, San Pedro, CA, USA) and marked simultaneously on running digital EEG. Data processing was done offline (Matlab; The Mathworks, Inc., Natick, MA, USA) and adapted from recently published sources on phase synchrony analysis.[3,43,45] Two types of auditory stimuli were presented: either a short segment (~20 s) of normally-spoken English, or an equivalent length of 'pseudospeech' (defined below). The subject was asked to pay attention to the stimulus and try to understand it, while looking at a visual target (a black dot) on a computer screen placed a convenient distance away. Subjects were informed prior to the experiment that they would hear a random assortment of speech segments in English or an unknown language. The 'unknown language' (unintelligible to all patients) was in reality pseudospeech – reversed play of the same English segment presented either immediately before, or after. Six different sets of speech and pseudospeech segments were presented; the experimental data thus comprised 6 sets of 20-second EEG, each set corresponding to one speech and one pseudospeech segment. Raw EEG was filtered into two passbands (10–30 Hz; 30–50 Hz), after which each epoch was further divided into four 5-second blocks. PLFs (as above) were calculated for each data block for every possible combination of electrodes. Thus, 24 PLFs (4 blocks of 6 sets) were calculated for each electrode pair, corresponding to each speech and pseudospeech perception task.

Results

Significant differences of mean PLF (mPLF) between the target and distractor tasks were assessed with a Student's

Table 111.1 Clinical characteristics of subjects

Case	Age, sex	Epilepsy	MRI	No of electrodes implanted
I	18, M	Left TLE	Normal	116
II	40, M	Left TLE	Normal	140
III	18, F	Left FLE	Cortical dysplasia left orbitofrontal region	122
IV	21, M	Left PLE	Previous resection left parietal PNET	147
V	17, F	Left TLE	Normal	90

TLE: temporal lobe epilepsy; FLE: frontal lobe epilepsy; PLE: parietal lobe epilepsy. PNET: primitive neuroectodermal tumor.

t-test ($p = 0.01$). Both increases and decreases of mPLF were observed, corresponding to the physical conditions of 'synchrony' or 'desynchrony'. We sought to obtain a 'map' of significant, language-related dynamic connections, between different pairs of electrodes. This is diagrammatically illustrated in Figure 111.2, which shows real data from an experimental subject (Case I). We identified 93 significant dynamic connections in this patient during auditory language processing, roughly half corresponding to a significant increase of synchrony, the remainder corresponding to a significant decrease of synchrony (i.e., increase of desynchrony). We interpreted these as foci of language-participating cortex.

At a later stage in their pre-surgical evaluation, all patients also underwent mapping of language-eloquent areas with electrical stimulation. We used the usual method of delivering 50 Hz electrical pulses of various amplitudes to the cortical surface through the electrodes for several seconds, while the patient was tested with tasks such as reading, naming objects, or following spoken commands. The patient's inability to follow the task during the stimulation was attributed to the presence of elementary language function in the cortex directly beneath the stimulating electrode.

Summarizing the results, statistically significant changes of phase synchrony were observed in a small (1–2%) proportion of electrode pairs, in Cases I, II and III. For brevity, only Case I's results are amplified below; Cases II and III were qualitatively similar. Significant changes were either an increase (synchrony) or decrease (desynchrony) of mPLF during the target speech perception task, in comparison to the control task, and were independent of frequency band (10–30 Hz or 30–50 Hz). Significant nodes (electrodes) were scattered over the hemisphere, bearing no clear spatial relation to the classical language areas identified by cortical stimulation. Figures 111.3a–c show the location of significant nodes in this patient, along with their transcortical projections. The position of the classical language areas identified by cortical stimulation is also shown. Figure 111.3(a) gives an impression of the overall subdural grid positioning; a total of seven significant nodes (electrodes) of synchrony or desynchrony are marked (with a number, as well as small letter 's' or 'd'). This denotes the number of significant connections made by that electrode, and whether they were of synchrony or desynchrony. Figure 111.3(a) thus shows there were 2 nodes of desynchrony (10–30 Hz) in the posterolateral temporal region, one node of desynchrony (30–50 Hz) and one of synchrony (30–50 Hz) in the orbitofrontal region, two nodes of synchrony (10–30 Hz; 30–50 Hz) in the anterolateral temporal region, and one node of synchrony in the lateral frontal region (10–30 Hz). It can be seen that none of these overlapped the receptive or expressive language areas identified (in their usual locations) by cortical stimulation. Transcortical connections of the seven significant electrodes were mainly projections to the anterolateral temporal lobe (Figure 111.3(b, c)).

Comments

Our language paradigm was designed to be easily reproducible and non-demanding of patient effort. Nevertheless, the literature[23–26] suggests that it may have been sufficiently discriminatory to separate language from nonlanguage and attentional confounds. For data processing, we chose to use phase synchrony for reasons outlined above. Our finding, in three of five patients during language processing, was of distant projections of a small number of significant nodes to other areas in the hemisphere, mostly to the convexity of the adjacent temporal neocortex. Significant nodes had no particular relation to eloquent areas identified by stimulation mapping. Long-distance interaction occurred between electrodes without involvement of intermediate sites, excluding volume conduction or reference contamination as an explanation for inter-electrode synchrony.

EEG/MEG-defined eloquent cortex

This chapter has discussed EEG and MEG synchrony in the more general context of the neurophysiological correlates of cognition. We have presented the view that the majority of EEG

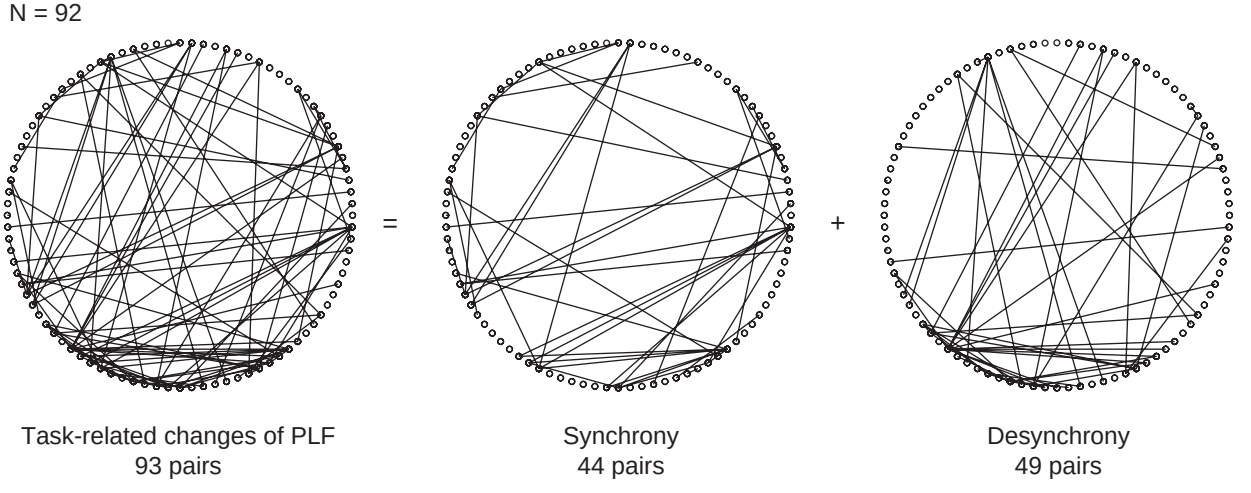

Figure 111.2 Connectivity map (10–30 Hz passband) of Case 1. Each circle represents an electrode. Each line represents statistically significant changes of PLF during the language task between the two corresponding electrodes. There were a total of 92 electrodes in this patient; 93 electrode pairs (out of a possible 4186) showed significant language-related phase changes (left figure). These were either increases (synchrony; middle figure) or decreases (desynchrony; right figure) during the task.

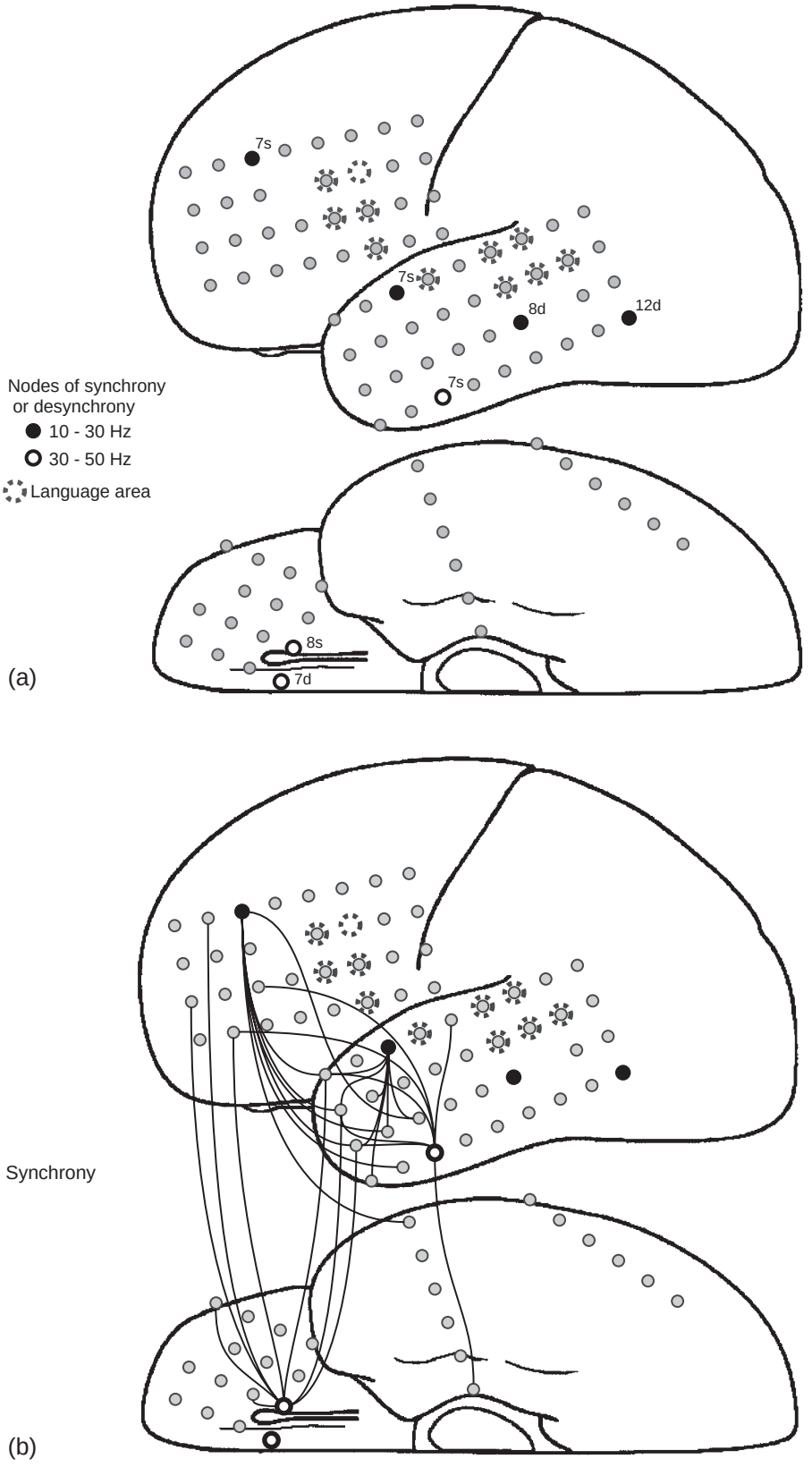

Figure 111.3 (a) The overall positioning of subdural electrodes in Case I, covering the left frontotemporal convexity, orbitofrontal region and basal temporal and temporo-occipital regions. Each circle (of any type) denotes an electrode contact. Electrodes with a sunburst halo denote language-eloquent sites as determined by stimulation mapping. Solid (10–30 Hz passband) and empty (30–50 Hz passband) circles indicate nodes of significant synchrony or desynchrony, along with the number of such connections. For example, the solid circle marked '12d' over the lateral posterior temporal cortex indicates a node of significant desynchrony connecting to 12 other nodes in the 10–30 Hz passband. (b) Transcortical connections of the synchronous nodes (lines emanating from solid and empty circles).

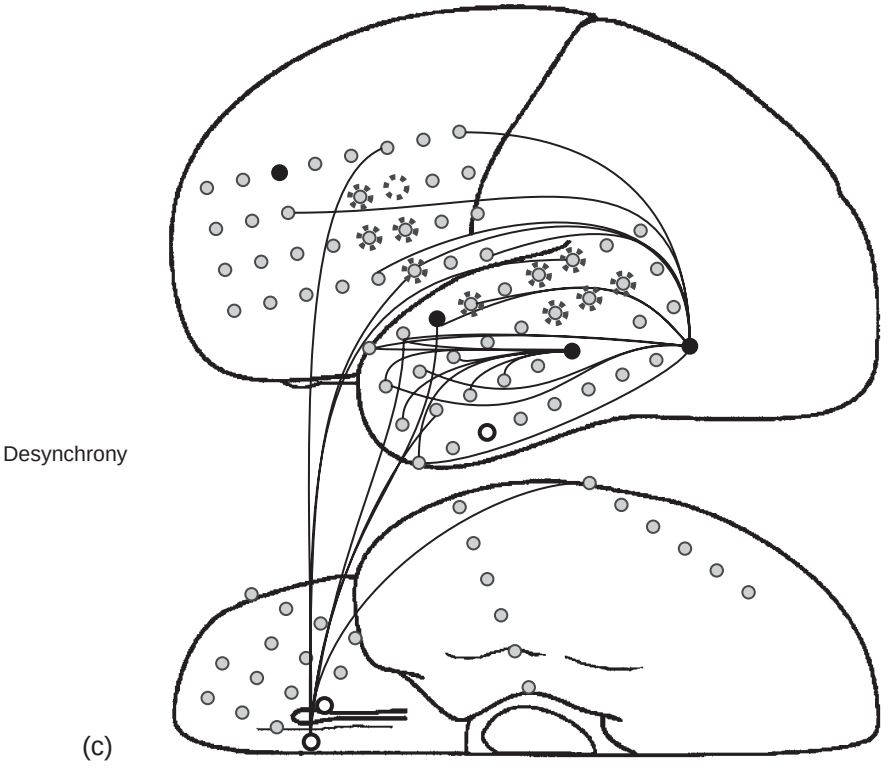

Figure 111.3, cont'd (c) Transcortical connections of desynchronous nodes (lines emanating from the solid and empty circles).

(both nonivasive and invasive) and MEG work may be grouped into an interpretation that argues for both the 'grandmother cell' and 'functional neural assembly' models of cognition. Indeed, experimental design and data gathering/processing methods are influenced by whether the experimenter's biases are 'localizationist' or 'globalist'.[71] We have described phase synchrony analysis as a tool for investigating hypotheses driven by the latter view.

The clinical coalface demands that resective surgery in patients spare eloquent cortex, however that may be identified. It is clear that resection of primary speech, motor, sensory and visual areas (as unequivocally identified by stimulation mapping) results in significant long-term neurological deficit. Beyond this bare fact, the interpretation of research studies is just one of several practical difficulties in defining 'eloquent' cortex. First is the familiar situation of the patient who wakes up postoperatively with a neurological deficit, even after 'safe' resections.These deficits usually resolve in a few weeks, and are put down to local tissue changes from trauma. Yet, the argument that such deficits result from resection of truly eloquent cortex whose function is rapidly subsumed by neighboring areas, cannot be dismissed. Second, all epileptologists recognize that certain areas of the cortex (e.g., the basal temporal language area; the supplementary motor area) are 'eloquent' to electrical stimulation, yet perfectly dispensible. Third, some patients experience minor longer-term deficits from even carefully-tailored resections. Finally, eloquence as defined by electrical stimulation is not identical to that obtained by focal cooling or transcranial magnetic stimulation, and is substantially different from techniques that map activity-related blood flow (functional imaging).

These caveats notwithstanding, what role may be envisaged for phase-synchrony identified eloquent cortex? The current state of the art only admits speculative interpretation, pending further work that reveals common patterns to synchronous nodes across patients. The outstanding observation of our language study was that significant nodes did not overlap Wernicke/Broca. While this indicates the corresponding regions of cortex were not indispensable to language, the question of their functional significance remains. Ojemann and colleagues document the wide perisylvian representation of language, essentially over a region distributed between, and surrounding, the classical speech areas.[22] Our results, particularly those of the projections of significant synchronous nodes, appear visually similar. A more formal comparison must await further work. Clearly, this is just one of a number of open issues: what is the reproducibility of synchronous node patterns? is there a dependence on type of language task? what paradigms *do* in fact activate Wernicke/Broca?

The most persuasive evidence for phase synchrony analysis relating to 'orthodox' eloquent cortex, to our knowledge, is the MEG study of Simoes and co-workers.[72] The right median nerve was stimulated in normal volunteers. The normal MEG response over the contralateral primary sensory area (S1) phase-locked with activity from the ipsilateral second sensory area (SII) at frequencies ≈20 Hz and at a latency of 80–90 ms after stimuli. The authors excluded the possibilities of synchrony arising from a common response to the stimulus, and volume conduction from a common source. Again, though these results identify areas of cortex known to be eloquent, the interpretation of phase synchrony itself is less clear. Ipsilateral sensory deficits with lesions of SII are not described to our knowledge, though sensory symptoms during seizures or stimulation involving SII commonly include the ipsilateral side of the body.[73]

Neurobiological issues

The scientific underpinnings and implications of electroencephalography and magnetoencephalography have traditionally stayed ahead, and aside, of clinical application. Some argue that recent advances in data gathering, signal processing and multimodality imaging may change this relationship in the future.[74] However, there is little doubt that the neurophysiology of phase synchrony and coherence requires further systematic study in patient groups before it can be put to practical clinical use. The gathering of such data, though, may be valuable to wider scientific enterprise.

The profound 'perceptual binding problem' is one such: how does the sense of a unified percept arise, despite the distributed processing architecture of the brain? The observation of Gray and colleagues[75] of intercolumnar synchrony in the cat visual cortex relating to global stimulus attributes provided the first experimental evidence for the Hebbian idea of perceptual binding occurring via neural 'temporal correlation'.[76] This idea now pervades integrative neuroscience (for reviews, see refs 16 and 17) and has been the foundation for recent theories of brain function.[77] While detection of interareal synchrony inform the binding problem, identification of participating areas constitute brain mapping. Apart from identifying eloquent cortex, this is relevant to understanding neural information processing (e.g., language) and the functional anatomy of integrated action (e.g., motor tasks).[78] Clinical relevant applications include identification of epileptogenic neural networks and tracing of seizure propagation pathways.[79,80] Finally, results of neurophysiological investigation may retrospectively inform experimental hypotheses and help develop brain theories.[3,81]

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112 Cortical mapping using evoked potentials and Bereitschaftspotentials

A Ikeda and H Shibasaki

Introduction

Surgical treatment for medically intractable partial epilepsy is currently regarded clinically useful, and the ways of presurgical evaluation especially in mesial temporal lobe epilepsy have been well formulated among institutes.[1] On the other hand, the success of epilepsy surgery in patients with neocortical epilepsy, i.e., the maximum seizure control and the minimum functional deficits, strongly depends on presurgical evaluations.[2]

It is essential to delineate an epileptogenic zone and to define the functional area at or close to the epileptogenic zone for demarcating the boundary between resectable and unresectable areas, that varies significantly among patients. Detecting structural abnormalities is very important in epilepsy surgery, because it often plays a key role in generating seizures or in amplifying the seizure activity arising from or very close to the lesion. A great advance in imaging studies, especially fine anatominal analysis by MRI, enabled us to delineate even subtle, but very important, anatomical abnormalities such as cortical dysplasia or minute bleeding with cavernous angioma, that have not been detected by MRI in the old era. However, (1) we still have many patients who have cortical malfomation as intractable epileptogenic zone which is not detected by even current MRI investigation, and thus it is still very difficult to delineate the boundary between the epileptogenic and functional zones. (2) There are no established methods other than electrophysiological approach (i.e., cortical stimulation or evoked potentials, etc.) to define the functional area in a specific way. Functional MRI or magnetoencephalography could localize the eloquent area but its specificity and the reliability are not sufficient for presurgical decision. Based on these two reasons, presurgical examination by means of chronically implanted subdural electrodes is still a very specific, gold standard to complete the above two purposes (delineate an epileptogenic zone and functionally important zone), as compared with other invasive methods (depth electrode, foramen oval electrodes, epidural electrodes).[3] Furthermore, not only the primary sensori-motor areas but also ones employing higher cortical functions such as language, higher motor control or memory are very important, and so far only electric cortical stimulation can assess all of them. Evoked potential studies could delineate most of the primary cortices and several, nonprimary higher cortical areas as well.

In this chapter, we will describe the functional mapping of the primary and non-primary cortices by means pf evoked potentials, including Bereitschaftspotentials (BP)[4,5] for motor mapping from the viewpoint of epilepsy surgery.

Recording of sensory evoked potentials

Currently both cortical electric stimulation (employing high-frequency electric pulses) and sensory evoked potentials are clinically established methods for functional cortical mapping. Cortical electric stimulation will be extensively discussed in another chapter, and it would be worthwhile mentioning that this method activates or depolarizes the cortical neurons by intensive electric current (exogenous excitation), and elicits the behavioral response of the patients. The obtained cortical mapping would not be necessarily identical to one by evoked potentials because the latter reflects the intrinsic, cortical neuronal activation by means of positive afferent input or by endogenous neuronal activation before voluntary movements. Therefore, the final interpretation for cortical mapping should be made by taking all the considerato n into account.

Subdural recording of somatosensory-, auditory- and visually-evoked potentials can localize the primary sensory cortices.[6] For somatosensory evoked potentials (SEPs), the primary somatosensory cortex (SI),[7–10] the second sensory area (SII)[11–13] and supplementary motor area (SMA) proper[14–16] can generate them (Table 112.1).

Recording equipment and methods

Clinical applications of those short-latency, evoked potentials in epilepsy surgery has started in the 1980s,[6] and the recording principle is essentially the same as that in noninvasive recording. The only difference is decreased sensitivity setting by 1/7 – 1/10 because of direct epicortical recording. Since the purpose of the recording is to delineate cortical function by detecting near field potentials, it is important to select the proper reference electrode at Grid 2 which would not pick up either far-field or near-field potentials. One of the implanted subdural electrodes is chosen which records neither spikes or slow waves, and thus is presumably located on the

Table 112.1 Sensory evoked potentials for cortical mapping in epilepsy surgery

	Main generators depending on the latencies		
Sensory evoked potentials	***Short***	***Middle***	***Long***
Somatosensory			
electric	SI (area 3b,1)	SII, SMA	TPJ
pain			SII,SMA SI (area 1) TPJ
passive movements	SI (area 3a,2)	SMA	TPJ
Visual			
pattern reversal		V1	
motion		V5	
flash		V1 and others	
Auditory			
tone burst	PAC	PAC and others	

Essential criteria of short, middle, and long latencies (<30 msec, 30–75 msec and >75 msec, respectively) were adopted from Chiappa.[61]
SI = primary somatosensory cortex, SII = second sensory area, SMA = supplementary motor area, TPL = temporo-papietal junction, PAC = primary auditory cortex.

nonfunctional area. With regard to the occurrence of far-field potentials, it is usually negligible because the sensitivity is too low to pick up the far-field potentials arising from the reference electrode. Currently available equipment for evoked-potential recording could record and average signals in multiple channels of more than 20 or 40 simultaneously, or digital EEG machines could record ECoG signals of more than 100 electrodes with a high sampling rate applicable for even short-latency evoked potentials, and thus the data are transferred to the other software to make averages and analysis.[17]

Somatosensory evoked potentials (SEPs)

Short-latency SEPs

Short-latency SEPs to peripheral nerve stimulation by electric current are clinically useful to define the central sulcus. In electric stimulation, median, tibial and lip (or trigeminal) nerve stimulation are clinically applied in subdural recording. Low-frequency filters (LFF) and high-frequency filters (HFF) are set to 15–30 Hz and 1500–3000 Hz, respectively, and the HFF depends on the limitation of the sampling rate, which is set to 3–5 per sec, as is done in the scalp recording.

For median nerve stimulation, N20–P20 complex, P25, P30–N30 complex, and N35 are identified in the contralateral hemisphere[7–10] as shown in Figure 112.1 and Table 112.2. Tangential and radial dipoles are located in the posterior bank of the central sulcus and in the crown of the postcentral gyrus, respectively. It would be noteworthy that: (1) since the central sulcus is not always oriented perpendicular to the lateral convexity surface even in normal brain, the tangential dipole is not well detected as a pair of positive and negative fields across the central sulcus in a rostra-caudal direction, and thus, if so, only one polarity would be picked up; (2) a tangential dipole not infrequently shows 0.5–2.0 msec time difference of the peak latency between a pair of negative and positive field potentials since the whole layers of cerebral cortex are not activated simultaneously by an afferent volley but sequentially from layers III–IV to more superficial layers;[14] and (3) in patients with partial epilepsy having seizure focus close to the central sulcus, normal functional distribution could be distorted very much. Thus, the final interpretation of the data should take all the other aspects including anatomical information and location of the epileptogenicity into account.

For tibial nerve stimulation, the initial peak latency potential is identified as P35 and is located in both pre- and post-central gyri in the paracentral lobule in the interhemispheric fissure.[18] There is no apparent phase reversal activities in subdural recording, as opposed to median nerve stimulation. It is because, in the paracentral lobule, the central sulcus becomes shallow and is ill-defined in the upper half of the paracentral

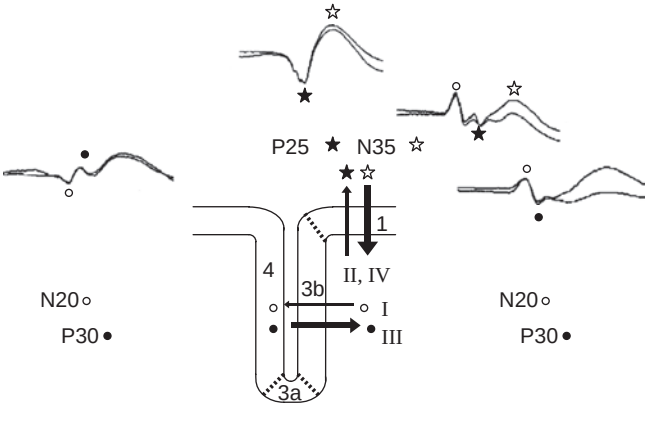

Figure 112.1 Schematic representation of origin of short-latency SEPs in humans. Nomenclature of potentials and dipole locations are adopted from the publications of Allison's group.[7–10] N20-P20 arises from the posterior bank of the central sulcus (area 3b), represented by a tangential dipole (I) generating parietal N20 and frontal P20 (as shown by open circles). It is followed by P25 arising from the crown part of the postcentral gyrus (area 1), represented by a radial dipole (II) which generates central P25 (as shown by a filled asterisk). Later, similar sequential activations occur in N30-P30 by a tangential dipole (III) in area 3b (as shown by filled circles), and then N35 by a radial dipole (IV) in area 1 (as shown by an open asterisk).

Table 112.2 Cortical generators of short latency SEPs to median nerve stimulation

Dipole	*Direction*	*Polarity*	*Origin*
N20–P20	Tangential	Frontal positive, parietal negative	Area 3b
P25	Radial	Central positive	Area 1
P30–N30	Tangential	Frontal negative, parietal positive	Area 3b
N35	Radial	Central positive	Area 1

lobule, and disappears in the lower half, that results in all the short-latency SEPs defined as the radial dipoles on the paracentral lobule. There is no apparent time difference of peak latencies between pre- and postcentral gyri.[18,19]

For lip stimulation, a pair of skin electrodes are placed in the edge of the unilateral lip and stimulated at 3–5 Hz, as done previously.[6] From the technical points of view, as opposed to the median or tibial nerve stimulation, lip stimulation on the skin easily causes large stimulus artifacts through Grid 1 or Grid 2, as the reference if placed in the contralateral mastoid process, and waveforms sometimes become obscured. Therefore, stimulation with alternate polarity between the stimulus skin electrodes or an ensemble with each half-set of stimulation by opposite polarity in one session is useful to eliminate the stimulus artifacts.[6] The initial evoked potential is labeled as P15 just located in the central sulcus.[6,20] The largest response to lip stimulation was located 1.5 cm ventrolateral to a response to median nerve stimulation.[21] Since the central sulcus in the face area is much deeper, a tangential dipole can be clearly present, but as mentioned above, when the central sulcus happened to be buried from the lateral convexity with an oblique angle, it would produce essentially one polarity activity across the central sulcus (Figure 112.2).[20]

Short-latency SEPs are also recorded from the SMA proper and pre-SMA. Initially all the responses from the SMA proper and pre-SMA were reported with latencies later than 40 msec irrespective of the stimulus sites in the body.[14,15,22] Recently, both pre-SMA and SMA proper showed the early potentials by means of depth electrodes, but the generators were judged to be remote, deep-seated structures,[16,23] and thus the potentials with peak latencies longer than 40 msec is clinically useful for functional mapping. From the practical point of view for functional mapping, primary foot motor area and foot area in the SMA proper are located very closely and the latter is, at times, defined in the lower half of the paracentral lobule extending the precentral sulcus posteriorly.[24] Electric cortical stimulation is not sufficient to differentiate between the two, and short-latency SEPs to tibial nerve stimulation is sometimes useful to define the boundary.[19]

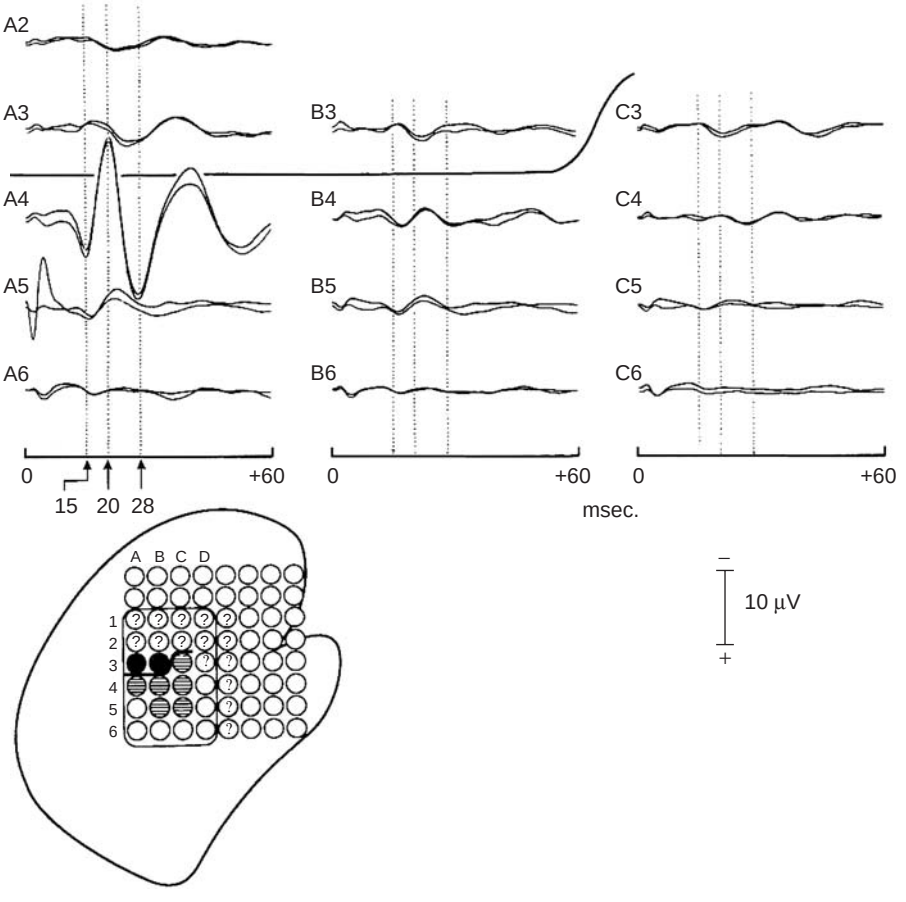

Figure 112.2 Subdural recording of SEPs to lip stimulation in a patient with electrode grid on the right pericentral cortex. A positive response (15 msec), a negative response (at 20 msec) and a positive response (28 msec) are shown by vertical dotted lines, respectively, which are maximum at the tongue sensory area delineated by cortical electric stimulation (cited from ref. 19 with permission).

In addition to electric stimulation for short-latency SEPs, passive movement SEPs are applied in scalp recording, and application to the subdural recording provides physiological information by showing the cortical generators of P22–25 most likely in the area 3a, 2 or 4.[25]

Middle to long latency SEPs

One of the most robust responses are from SII located along the sylvian fissure.[11–13] SII is located in on the superior bank of the sylvian fissure in the region of the planum infraparietale of the operuculum.[26] As opposed to the short-latency SEPs, it usually needs long interstimulus interval of more than 3 sec, and opened LFF is more preferable. Most of the response to median nerve stimulation showed the peak latencies of 140 msec, although delayed P25 by 2.4 msec was also recorded to the median nerve stimulation (Figure 112.3).[11]

In addition to electric stimulation, pain SEPs (Figure 112.4), and passive movement SEPs (Figure 112.5) employing proprioception are applied in scalp recording, and application of those modalities to the subdural recording provides physiological information. Pain SEPs in subdural electrodes or depth electrodes showed the sources in the SII and parietal operculum, and recently in SI with the peak latency of 220 msec.[27–29] Passive movement SEPs with short-latency showed broad positive potentials of 23.8–27.4 msec of latency along the central sulcus, suggesting the activation at areas 2, 3a, and 4 (Figure 112.5). Passive-movement SEPs with long latency will be described below in the section on temporo-parietal junction. As compared with short-latency SEPs, midde-latency SEPs may provide rather limited information for functional mapping in epilepsy surgery, mostly because those sources often showed no positive symptoms by cortical electric stimulation, or resection resulted in little functional deficits. However, in order to clarify the functional significance, it will be very important to accumulate the combined information on evoked potentials, cortical stimulation, functional MRI, and surgical outcome of function.

Auditory evoked potentials (AEPs)

The primary auditory cortex (PAC) (Area 41) is located on the transverse gyrus (Heschl's gyrus; HG) which lies on the dorsomedial surface of the superior temporal convolution, and is buried in the floor of the sylvian fissure. Therefore, a subdural electrode grid placed on the lateral convexity can record the potentials distant from PAC or from the surrounding cortices.[30] Only depth electrodes can approach PAC and the related structures which generate AEPs.

Currently, at least six auditory cortices are described within the superior temporal gyrus (STG), i.e., PAC located in the medial and intermediate part of the HG, secondary auditory cortex (SAC) located in the lateral part of HG, planum temporale (PT), caudal portion of the STG, anterior part of the STG and the long insular gyrus. In response to the tone burst stimuli of 1 kHz about every 1 sec with intensity of 70 dB, a series of near-field potentials are recorded. Only PAC can generate N13/P17/N30 complex as the earliest potentials, and other areas generate middle latencies of around 70 msec and then 140 msec in latency.[31–33]

Those auditory cortices other than PAC can contain the several specialized functions. The PT was for language processing, different types of spectrotemoral pattern processing such as spatial analysis pitch sequences, environmental sounds and music; the caudal portion of the STG for hierarchical auditory processing such as complex sound perception; and the insular cortex for auditory motion perception and vestibular functions. In general, resection of these auditory cortices may lead to a difficulty in sound localization, musical, or complex sound perception. From the practical point of view, differentiation of these several auditory cortices provides little clinical significance until each function will be established, and further accumulated studies is essential.[34]

Visual evoked potentials (VEPs)

In scalp recorded VEPs, N75, P100, and N145 are well observed in the occipital area with paradoxical lateralization, and thus the main generators are most likely the primary visual cortex burid in the calcarine fissure.[35,36] Setting of LFF and HFF is the same as one for scalp recording (1–100 Hz).

More than 50% of the striate cortex is occupied by the representation of the central 10° of vision. Therefore, with full-field stimulation, the net vector almost entirely reflects activity in the macular and paramacular areas of the visual area, the former being more representative than the latter. Nevertheless, central and peripheral vision may be checked by employing different stimulus conditions. Small checks (12–16 minutes) and small fields (2–4°) are for central vision, and the large checks (40–50 minutes) and large fields (16–32°) for peripheral vision.[37] Namely, in scalp-recorded VEP studies, peripheral hemifield stimulation can enhance contralateral negativity (N105) while the ipsilateral P100 markedly diminish (Figure 112.6).[38]

Nonprimary visual cortices such as V4 (inferior occipitotemporal region) and V5 (the lateral aspect of the posterior temporal lobe) are responsible for color and motion, respectively. Motion VEPs are not widely used in clinical medicine, but it would be useful to deliniate the V4 in patients with partial epilepsy as one of cortical mapping, but currently it is of limited use from the practical point of view (Figure 112.7).[39]

Flash-evoked VEPs are also applied but in the limited situation of scalp-evoked potential studies, because they are much more widespread, complex and variable than that of pattern reversal VEPs, their clinical significance would be very limited.

It was reported that frontal eye fields also generated VEPs with a latency of about 100 msec,[40] but it is not well supported by other institutes. In a CNV paradigm employing paired visual stimuli for both S1 and S2, the lateral dorsal premotor area can generate signal-related potentials (with a peak latency of 176–194 msec always after visual LED signals).[41]

Multisensory convergence of middle latency, evoked potentials

Temporo-parietal junction (TPJ) lesion is related to visual, auditory, and tactile extinction, and the posterior part of the STG lesion causes hemispatial neglect. In the subdural evoked-potential studies, SEPs, VEPs and AEPs were employed to obtain

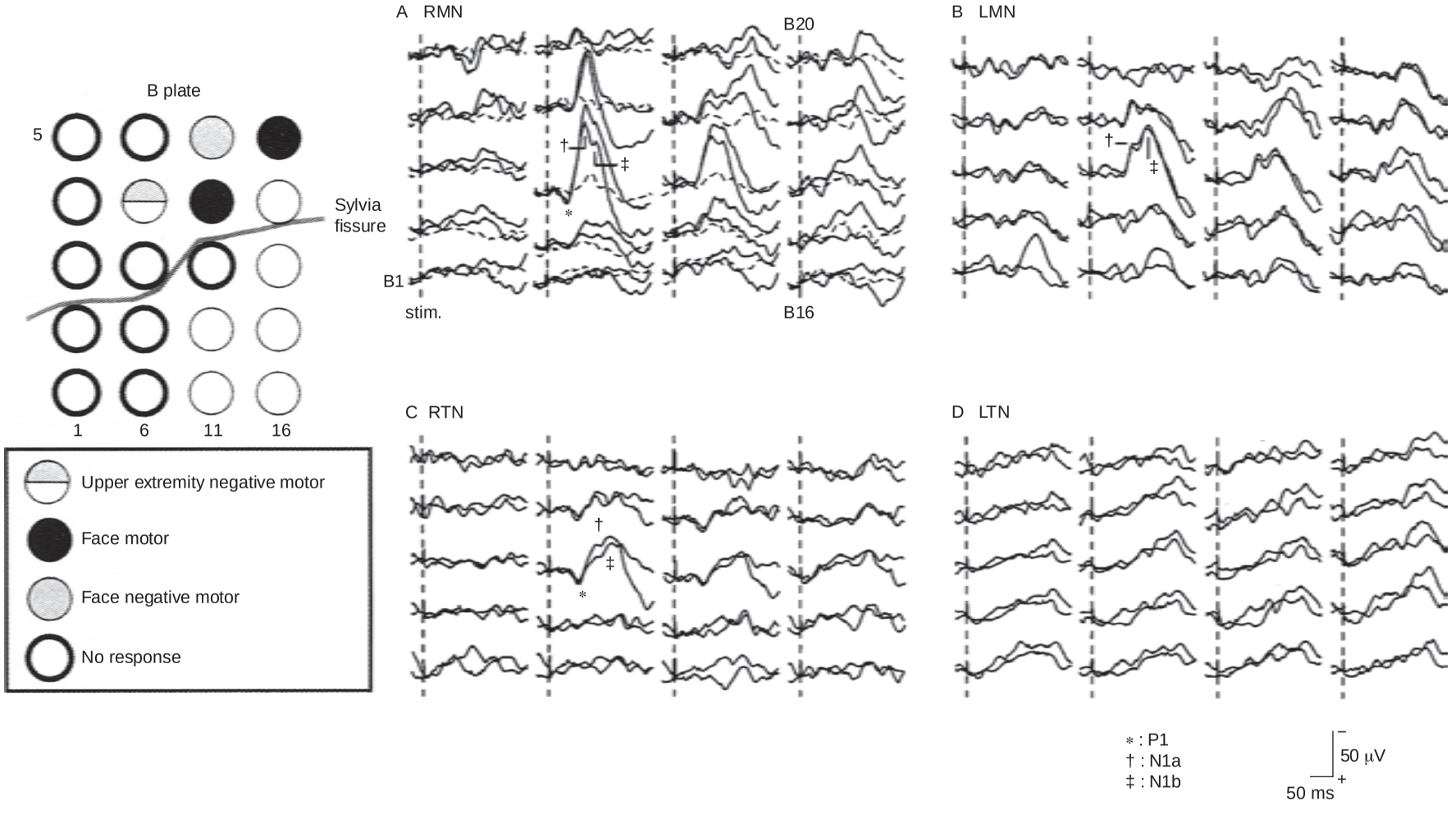

Figure 112.3 SEPs recorded subdurally from the electrode grid on the left frontal cortex (left half), in response to electric stimulation of the right (A) and the left (B) median nerve at the wrist, and the right (C) and the left (D) tibial nerve at the ankle (right half). Two sets of SEPs with ISI of 2.9 s are superimposed. SEPs with the shorter ISI (0.9 s) are also shown by interrupted lines in (A). Vertical interrupted lines show the stimulus onset. Each recognisable peak is indicated in the figure by the same symbols (cited from ref. 12 with permission). RMN = right median nerve, LMN = left median nerve, RTN = right tibial nerve, LTN = left tibial nerve.

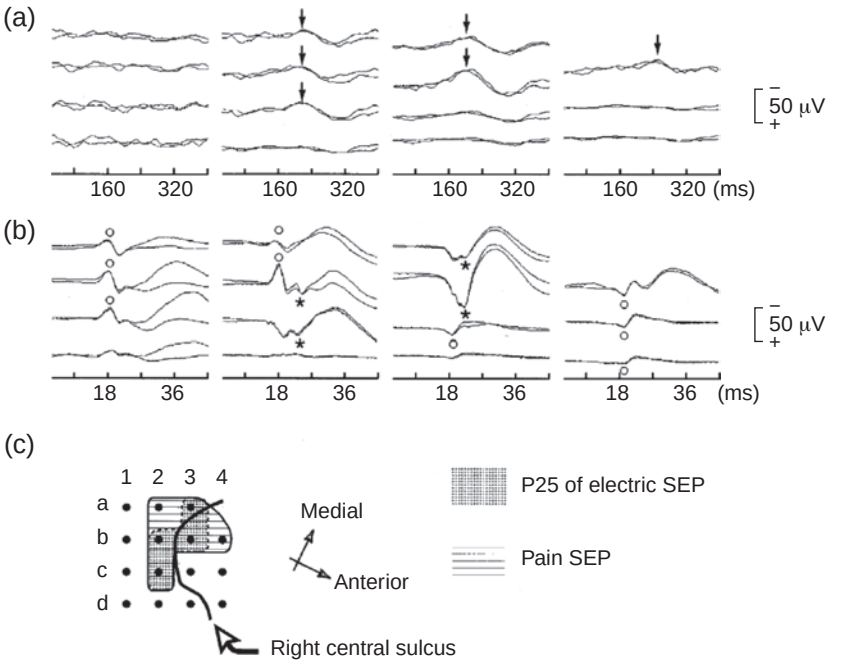

Figure 112.4 SEPs recorded subdurally from the right perirolandic cortex to painful CO_2 laser stimulation of the dorsum of the left hand (a) and to electric stimulation of the left median nerve at wrist (b) in an epileptic patient. Each electrode position is shown in c. a: Arrows indicate the first negative deflection to painful CO_2 laser stimulation with a peak latency of 220 ms. b: Open circles indicate N20 and P20 of electric SEPs along the postcentral gyrus, and asterisks show P25 located slightly medial-anterior to N20. Note that the cortical area involved by the negative potential of pain SEP is larger than that for P25 of electric SEPs (cited from ref. 29 with permission).

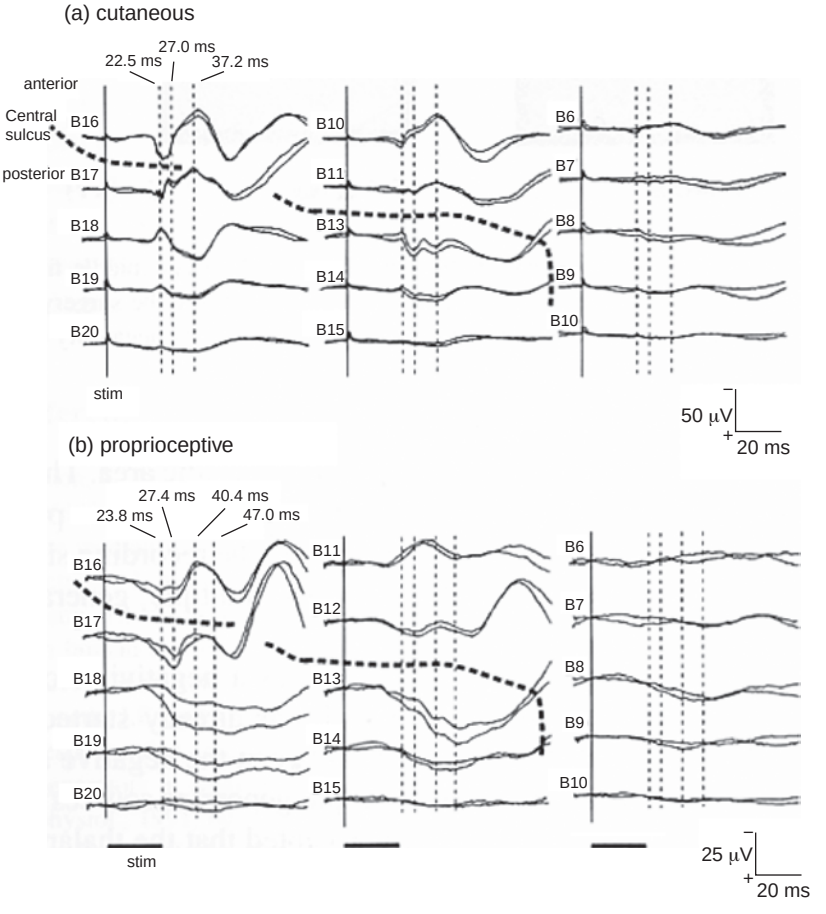

Figure 112.5 SEPs recorded subdurally from the right perirolandic cortex to electric stimulation of the right middle finger (a), and to the proprioceptive stimulation of the same finger by passive finger motion. Thick, dotted lines indicate the location of the central sulcus. For proprioceptive stimulation, the duration of the passive movement is demonstrated as a horizontal black bar at the bottom (4° in 25 ms) (cited from ref. 25 with permission).

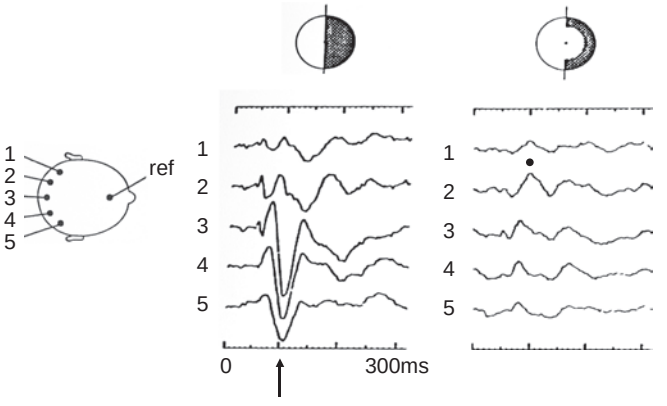

Figure 112.6 The effects of increasing of radii experimental scotomata on the right half-field stimuli in a normal subject. Results of intact half-field (left) and 10° of scotoma (left) are shown. P100s (as shown by an arrow) are elicited more on the right occipital area in response to the right half-field stimuli (left), while contralateral N105 (as shown by a dot) is enhanced and P100s are attenuated for right half-field stimuli with 10° of scotoma (right). (modified from ref. 38 with permission).

the common response area.[42] As compared with ordinary short-latency, evoked potential studies, LFF was set to shorter, and the interstimulus interval was set to longer; every 3–4 sec in SEPs, every 3.33 sec in AEPs, every 294 msec in pattern-reversal VEPs. In motion VEPs, the gating pattern moved to a horizontal direction at an angular velocity of 22° per sec for 500 msec.

In the results, the most prominent responses were either positive or negative in polarity among subjects, and the polarity was consistent regardless of the stimulus modality within each individual subject. The peak latencies of SEPs were 50–115 msec to median nerve stimulation, 75–160 msec to tibial nerve stimulation, 60–120 msec to passive finger movement and 310–340 msec to hand pain stimulation. The peak latencies of AEPs ranged from 50–220 msec, pattern-reversal VEPs of 105–130 msec, and motion VEPs of 125–300 msec. Among five patients investigated in a previous studies, essentially one electrode within the large electrode grid showed a common respose in the posterior end of the superior temporal sulcus (Figures 112.8 and 9). It may correspond to the superior temporal polysensory area (STPA) in monkeys.

The response from the SII is described in above. TPJ is clearly different from SII as follows: (1) SII is located more anterior along the sylvian fissure close to the rolandic fissure; (2) SII generates potentials to the somatosensory stimulation of either hand or foot but not to the other modalities; and (3) a somatotopy in response to upper and lower nerve stimulation is present within SII whereas TPJ show a small, common response area.

Bereitschaftspotential (BP) for mapping of motor cortices

For mapping the SI, recording of SEPs and high frequency-cortical stimulations are equally useful. Central sulcus could be delineated by SEPs, but it does not directly represent the location of the primary motor cortex (MI) but merely either radial or tangential dipoles arising from the postcentral gyrus, as shown in Figure 112.1. Therefore, only cortical stimulation was reliable for direct mapping of MI, and no evoked potentials arising from MI were clinically available. As with SEPs for the postcentral gyrus, we have proposed the clinical usefulness of BP for localization of the motor cortices in epilepsy surgery.[43–47]

BP is defined as the slow cortical potentials arising from the motor cortices occurring about 1.5 sec before the onset of self-paced voluntary movements, and it is only recorded with the long time constant of the amplifier. BP reflects excitatory postsynaptic potentials (EPSPs) in the superficial layer of the motor cortex occurring in the apical dendrites of the pyramidal neurons.[48]

It is well accepted that premovement potentials consist of three components regardless of movement sites of the body; BP in a narrow meaning or readiness potential,[4] negative slope (NS')[5] and motor potential (MP) (Table 112.3).[4] It is followed by postmovement potentials called reafferente Potentiale (RAP).[4] All the four components are called together as movement-related cortical potentials (MRCPs).[5]

Motor mapping by BP accompanies the following four positive characteristics: (1) it reflects the endogenous activity of the motor cortices which are actually involved in preparation for and execution of voluntary movements, (2) BP is examined for voluntary movements of any parts of the body,[49,50] (3) cortical activity at the bank in the sulcus (like the anterior bank in the central sulcus) can be recorded as a tangential dipole, and (4) it is not associated with the risk of seizure induction in contrast to high frequency cortical electric stimulation. On the other hand, BP has the following two negative characteristics as compared with cortical electric stimulation: (1) voluntary movements of one kind should be repeated at least 50 times to obtain averaged wave forms, and (2) thus it needs the patient's cooperation to conduct the task of voluntary movements and to obtain the satisfactory results.

We routinely perform direct recording of BPs by using chronically implanted subdural electrodes in the presurgical evaluation of the motor cortices.

Recording condition and methods

As conventional chronic subdural EEG monitoring, HFF is set to the same condition as that of scalp-EEG recording, but

Table 112.3 Movement-related potentials (MRCPs) for cortical mapping in epilepsy surgery

	*Onset time**	*Origin*	*Laterality*
BP	–2–1.5 sec	Pre-SMA, SMA proper, MI-SI, premotor	Bilateral
NS'	–0.3 sec	Pre-SMA, SMA proper, MI-SI	Bilateral Contralateral dominance
MP	–50 msec	SMA proper, MI-SI	Contralateral
RAP	after movement	SI	Contralateral

* Onset time is measured from EMG onset of movements.
BP = Bereitschaftspotential (readiness potential), NS' = negative slope, MP = motor potential, RAP = reafferent potential, MI-SI = primary sensorimotor cortices.

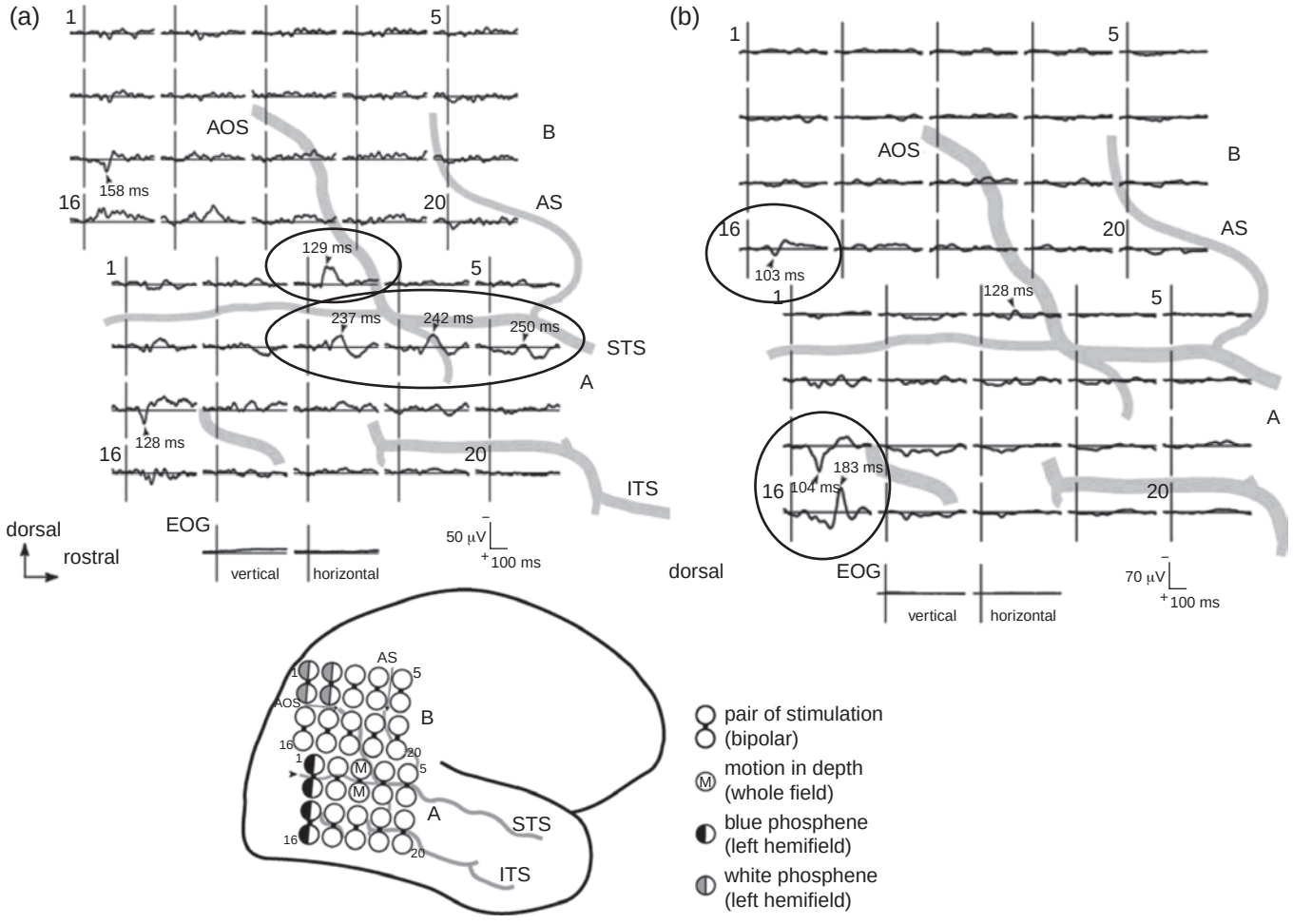

Figure 112.7 Subdural recording of motion-related visual-evoked potentials (motion VEPs) (left) and visual-evoked potentials to pattern reversal stimuli(pattern VEPs) (right). Group average waveforms are shown in relation to sulci. In motion VEPs, prominent responses were recorded in the dorso-rostral quadrant of Plate A (A3, A8–10), whereas in pattern VEPs large primary potentials at the caudal end of plates (A11, A16, B16) in the lateral occipital area. Results of cortical electric stimulation are shown in the lower figure. Motion-in-depth perception involving the whole visual field was elicited by stimulating a pair of A3 and A8, while stationary phosphenes in the left visual hemifield were elicited by stimulating the caudal part of grids (pairs of A1-6, 11-16, B1-6, 2-7). STS: superior temporal sulcus, ITS: inferior temporal sulcus, AS: angular sulcus, AOS: anterior occipital sulcus. STS had double ending to AS and AOS. An arrowhead shows a sulcus extending to the occipital area from the end of STS (cited from ref. 39 with permission).

opening of LFF down to 0.03 or even 0.01 Hz is important to record slow subdural EEG satisfactorily. As opposed to scalp-recorded BP, subdural EEG of slow shift is well recorded without significant slow artifacts, even though the patients do not necessarily remain motionless on the bed. EEG signals are continuously recorded with the sampling rate of at least 200 Hz, preferentially 500 Hz. When fast activity is aimed for analysis, a larger sampling rate such as 1000 Hz is recommended. Sensitivity is usually set to 70 μV/mm, one seventh of that of scalp EEG.

Recording can be started soon after patients recover from the first craniotomy to place the subdural electrode grids. Surface EMG and EOG are recorded simultaneously as done in the scalp-EEG studies. In scalp EEG studies, EOG is monitored in order to exclude the EOG artifacts on the scalp-EEG. Subdural EEG is almost free from artifacts of extracranial origin such as EMG or EOG. Therefore, EOG is not necessarily monitored in this respect.[51]

For obtaining BP, voluntary movements of any parts of the body can be examined as long as fiducial points can be accurately timed with the movement onset, and this depends on the purpose of the recording. The movement should be identical and self-paced at intervals of 5–10 sec. Subdural EEGs are finally averaged backward and forward time-locked to the trigger pulse, for which the onset of surface EMG discharge is usually used. Subdural EEG has a better S/N ratio than scalp EEG, but at least 50 trials should be averaged for one session. Rapid-rate of movement task (1–2 Hz) is also applicable to delineate the cortical generator of MI.[52]

Multiple cortical generators of BPs

Based on the distribution of each component over the scalp, the BP was thought to represent the activity of the bilateral supplementary motor areas (SMAs), while the NS' and MP mainly reflect the activities of the contralateral primary motor and sensory cortices (MI-SI). So far, subdural EEG studies revealed that MI-SI, SMA proper and pre-SMA are main cortical generators of those premovement potentials (BP, NS′, and MP) (Figure 112.10) (Table 112.4),[53] and a part of the premotor area also generates BP of positive polarity.[54]

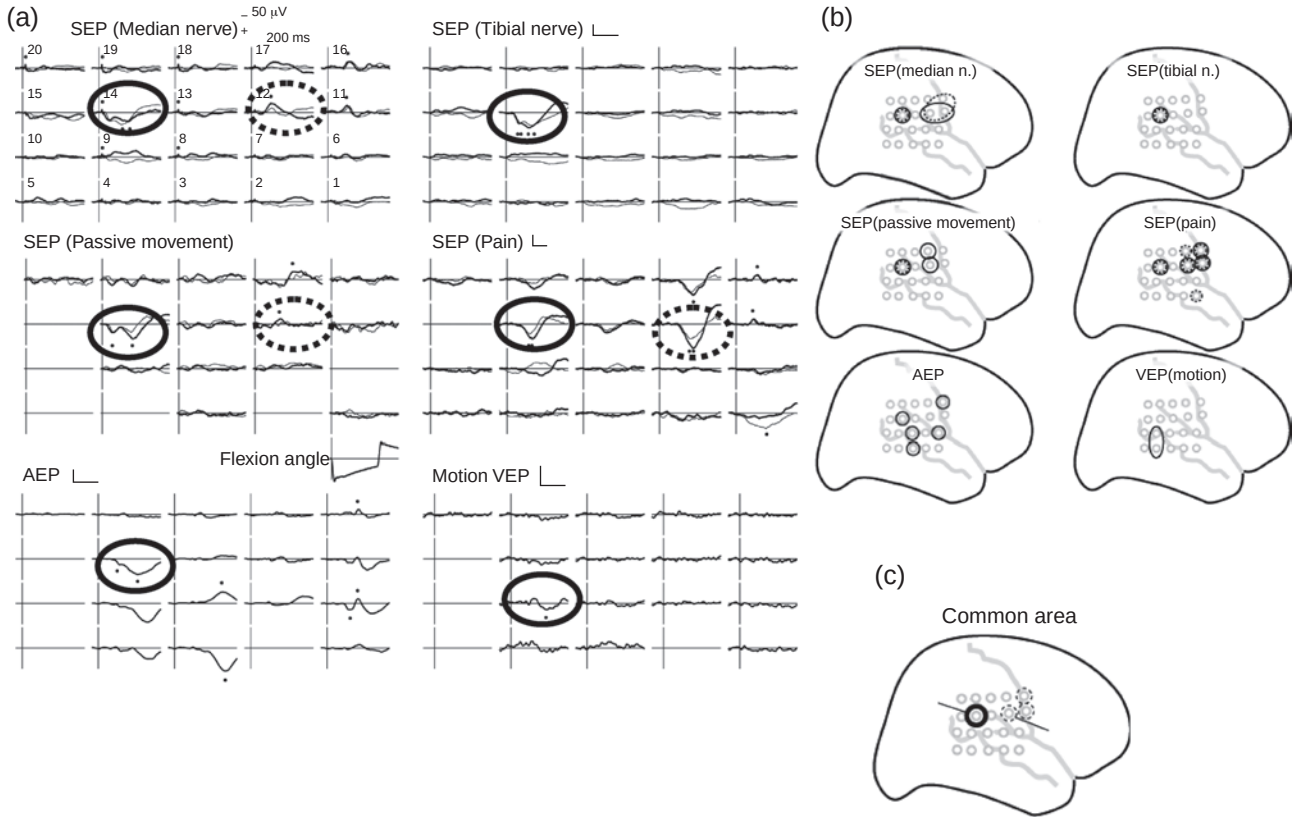

Figure 112.8 Subduraly recorded waveforms, distribution and common response area in the right temporo-parietal junction from a patient. (a) Waveforms of evoked potentials to each form of sensory stimulation. Thick lines: responses to the contralateral (left) stimulation, thin lines: those to the ipsilateral (right) stimulation. Dots indicate response peaks. Calibration shown on top of each plate: 200 msec, 50 μV, negative polarity shown upward. (b) Distribution of evoked response peaks to each sensory stimulation. Electrodes showing peak amplitude of 75% or larger of the local maximum are circumscribed for each stimulus modality. Electrodes showing independent peaks are highlighted by separate circles. For SEPs, electrodes showing response peaks to the contralateral stimuli are marked with solid lines while those to the ipsilateral stimuli with broken lines. (c) Distribution of the response area common to stimuli of multiple modalities. Electrodes which showed responses to two or more modalities are marked. Circle by thick line (14): common response areas to five forms of stimulation. Circle by broken line (12): common response areas to two different forms of stimulation. (cited from ref. 42 with permission).

Precentral gyrus (positive motor area) and postcentral gyrus

In early studies, Neshige *et al.*[55] recorded BP associated with self-paced finger movements from subdural electrodes placed over the lateral frontal convexity in epilepsy patients. All of three components; BP, NS′, and MP, were highly localized at a part of MI and SI each somatotopically corresponding to the moving finger, particularly at the part of MI where high frequency (50 Hz) cortical electric stimulation elicited positive motor response such as finger twitching. With unilateral finger movements, the BP was recorded from bilateral MI-SI hand areas, and the NS′ was predominantly from the contralateral MI-SI hand area, while the MP was recorded only from the contralateral MI-SI hand area. Those potentials were surface negative in polarity at all recorded sites, and no phase reversal was observed across the central sulcus (Figure 112.11).

In the self-paced tongue protrusion task, clear premovement slow potentials were recorded from the ventral perirolandic area where high-frequency cortical electric stimulation produced positive motor responses in the tongue.[20]

It was expected that the MP might represent the activity of pyramidal neurons that directly project to the corticospinal tracts as the final motor output to the spinal cord whereas BP and NS' could represent preparatory activity of the neurons in MI and the adjacent areas. In the epicortical recording of premovement potentials, BP, NS′, and MP are not necessarily generated from common electrodes, but rather from different electrodes within MI. Our recent observation showed that the

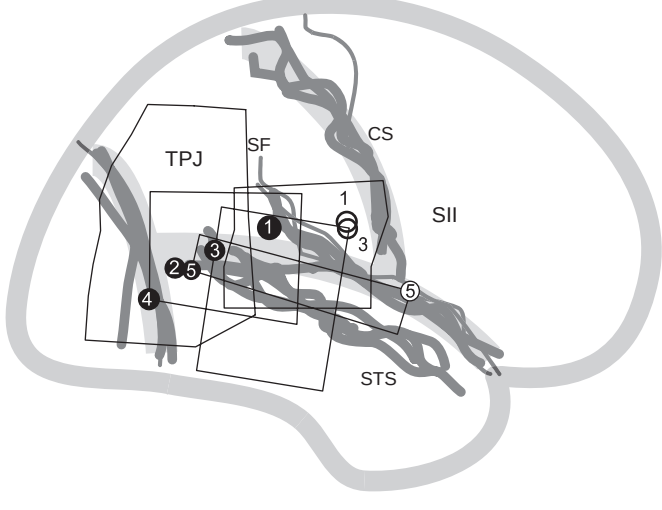

Figure 112.9 Multisensory response area vs. second sensory area (SII). White numbers in filled black circles indicate multisensory response area in each patient. Open circles indicate SII. CS = central sulcus, SF = sylvian fissure, SFS = superior temporal sulcus. (cited from ref. 42 with permission).

Table 112.4 Characteristics of Beietschaftspotentials (BP) recorded from subdivisions of motor cortices

	Pre-SMA	*SMA proper*	*Lateral rostral frontal area*	*MI-SI*
Surface polarity	Negative	Negative	Positive	Negative
Somatotopy	(–)	(+)	(–)	(+)
Effect of movement rate		(++)	(+)	(–)

SMA = supplementary motor area, MI-SI = primary sensorimotor cortices, (–) = absent, (+) = present, (++) = strongly present.

electrode on the crown part of the precentral gyrus selectively generating MP for hand movements elicited MEPs in the hand muscle when electrically stimulated. When recording premovement potentials (BP/NS′/MP) in association with self-paced movements of various parts of the body, the distribution of the potentials along the central sulcus was consistent with the somatotopic representation in the precentral gyrus. Therefore, BP or rather MP analysis by subdural electrodes is clinically useful for functional mapping of the so-called 'primary motor area' (MI) (which is defined by positive motor responses to high-frequency electric cortical stimulation) in epilepsy surgery.

In summary, a somatotopic representation of MI disclosed by BP/NS′/MP recording is consistent with that of the positive motor area in the precentral gyrus as revealed by electric cortical stimulation (Figure 112.10),[19,55] but BPs for each task often appear to be distributed wider than the motor map made by cortical stimulation. It may be partly because BP is generated not only by the anterior bank of the central sulcus but also by the crown part of the precentral gyrus,[20] from both of which the corticospinal pathways essentially originate.

Lateral rostral frontal area

Recently we observed that, whichever part of the body was voluntarily moved, the lateral frontal area at or adjacent to the lateral negative motor area (LNMA),[56] located just rostral to the MI face area, generated surface-positive premovement slow potentials (Omni-BP).[54] It still remains to be solved whether this potential is generated from areas 44 and 45 anterior to the precentral sulcus, or from the ventral premotor area (area 6aα) posterior to that sulcus.

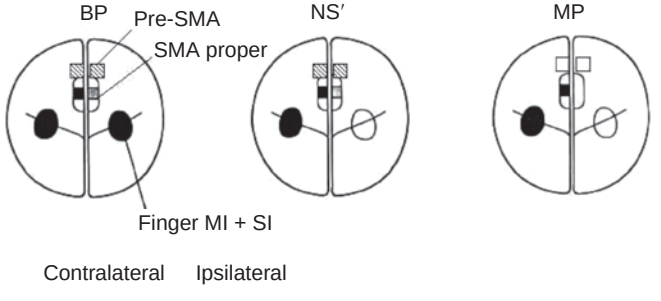

Figure 112.10 Schematic representation of the cortical generators of BP, NS′, and MP for hand movements viewed from the top. The degree of darkness of the shading in the pre-SMA, SMA proper and MI-SI is approximately proportional to the amplitude of the corresponding potentials. MI = primary motor area, SI = primary sensory area (cited from ref. 55 with permission).

Supplementary motor area (SMA)

SMA is currently subdivided into caudal- (SMA proper) and rostral (pre-SMA) parts by VAC line in humans as well as in monkeys, and both SMA proper and pre-SMA generate premovement potentials. SMA proper, like the precentral gyrus, has a somatotopic organization based on electric cortical stimulation as well as BP/NS′/MP (Figure 112.12).[19,57,58] Pre-SMA generates BP invariably regardless of the sites of body movements (Figure 112.13).[59]

Furthermore, the following findings aid us in differentiating the motor cortices located in the mesial frontal area.

1. Onset time of BP in the foot MI area and the foot area at the SMA proper has no significant difference, but movement-related desynchronization before the movement onset starts earlier at the SMA proper than at MI.[58] Foot area at the SMA proper generates BP not only for the contralateral but also for the ipsilateral movements whereas the foot MI generates BP exclusively for the contralateral foot movements. The latter generates clear

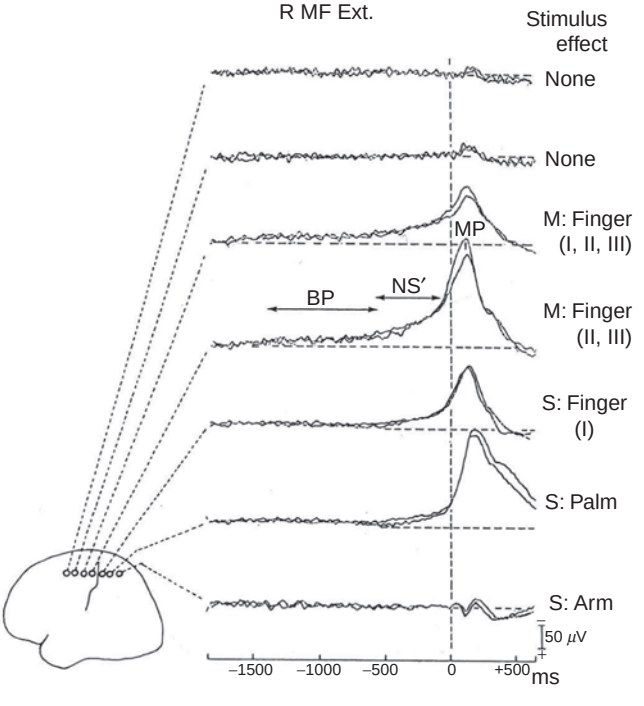

Figure 112.11 Movement-related cortical potentials in association with self-paced extension of the right middle finger recorded from the subdural electrodes placed across the left central sulcus in an epilepsy patient. BP, NS′, and MP are well localized to the finger motor area, and to a lesser degree, to the sensory area. M = motor, S = sensory (cited from ref. 51 with permission).

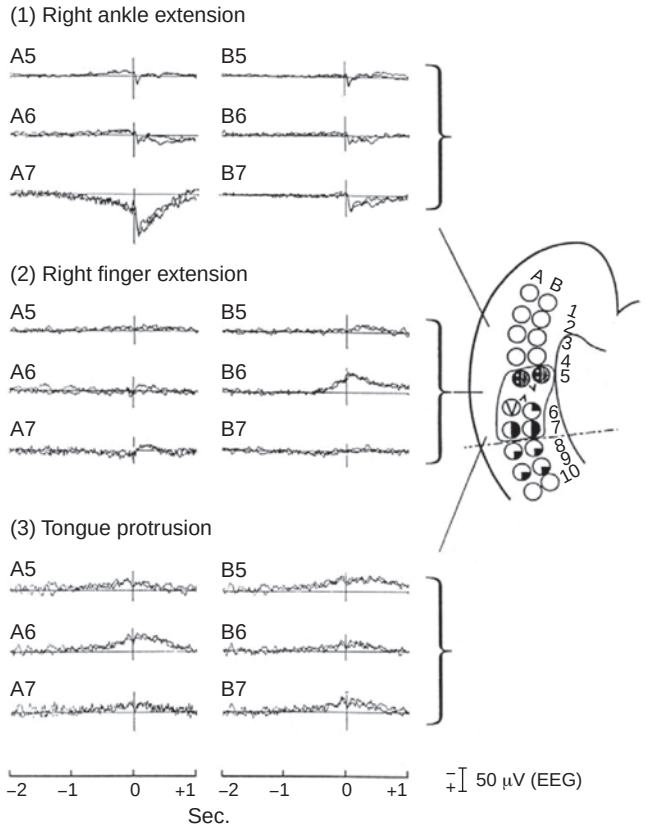

Figure 112.12 Movement-related cortical potentials in association with self-paced movements of the right foot (1), right finger (2), and tongue (3) recorded from the left SMA in an epilepsy patient. The figure illustrates the somatotopic distribution of the BP within the SMA proper, consistent with the results of cortical stimulation. The broken line shows the boundary between the foot MI posteriorly (lower part in the right figure) and the SMA proper anteriorly (middle part in the right figure). Symbols in the figure show the results of electric cortical stimulation (A5 and B5 = positive motor response in the face and negative motor response of the bilateral hands; A6 = rhythmic vocalization; B6 = tonic motor response of the right hand; A7 and B7 = positive motor response of the right hand and foot; A8, B8, A9, and B9 = clonic motor response of the right foot). (cited from ref. 19 with permission).

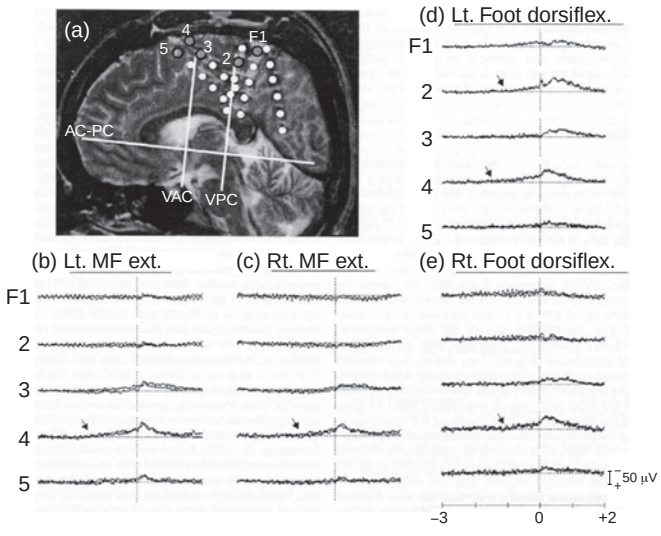

Figure 112.13 Movement-related cortical potentials in association with self-paced extension of the left middle finger (B) and the right middle finger (C), and dorsiflexion of the left foot (D) and the right foot (E), recorded from the right mesial frontal cortex in an epileptic patient. In all tasks, negative BP is observed at F4, located anterior to the VAC line, being most likely pre-SMA. F2 just on the paracentral lobule (most likely foot MI area) generates BP only in association with the left foot movements. VAC = a line on the anterior commissure perpendicular to AC-PC line, VPC = a line on the posterior commissure perpendicular to AC-PC line. (cited from ref. 59 with permission).

RAP immediately after the movement onset whereas the former does not.[19] Since SMA proper is often defined in the lower half of the paracentral lobule,[24] the boundary between the foot MI and the foot SMA proper could not be delineated only by anatomical finding.

2. Pre-SMA and SMA proper generate clear BP in the slow-rate repetition of voluntary movements but little BP in the rapid-rate repetition of movements, whereas MI generates clear BP equally for slow- and rapid-rate repetition of movements.[52] In the rapid-rate repetition of movements, voluntary movements may be conducted as a kind of so-called 'automatic' movements, while in the slow-rate repetition of movements each movement is regarded as discrete, individual execution, each of which may involve different motor control mechanisms. Characteristics of BP recorded from subdivisions of motor cortices are summarized in Table 112.4.

Currently, in epilepsy surgery, the functional delineation between the primary foot area and the foot area at the SMA proper, or between the SMA proper and the pre-SMA is made exclusively by high frequency cortical stimulation or just by anatomical approach. BP can be clinically useful at least for complementing the result of cortical stimulation.

Conclusion

Multiple cortical generators of sensory evoked potentials and BPs are revealed for cortical mapping before epilepsy surgery from the clinical point of view. The results of short- and middle-latency evoked potentials are relatively clear, whereas the generators of long-latency evoked potentials and event-related potentials are usually multiple and the degree of significance of each generator remains to be solved. At this moment, three points are stressed as below.

1. Similar to short-latency, sensory-evoked potentials, BPs are useful to delineate the motor cortices responsible for voluntary movements since their cortical generators are already well investigated in subdural recording.
2. Cortical mapping of primary (sensory or motor) cortices are relatively clear because it is judged by the direct response of motor or sensory phenomena, by means of cortical electric stimulation or evoked-potential techniques.
3. When nonprimary cortices are targeted for mapping, intercortical connection plays a significant role in manifesting higher cortical function or the compensation mechanism of function, and thus just one modality for cortical mapping may mislead the final decision. Since cortical mapping in epilepsy surgery especially

needs reliable, specific findings to decide the resectable and unresectable areas, it should be very important to take into account the results of several modalities such as electric cortical stimulation, evoked potential, magnetoencephalography, and functional neuroimaging. Analysis of event-related potentials and long-latency sensory-evoked potentials would be useful for functional mapping of nonprimary or association cortices in epilepsy surgery or functional surgery in the near future as well.

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113a Cortico-cortical evoked potentials to define eloquent cortex

R Matsumoto and DR Nair

Introduction

Cortical electrical stimulation was first performed by Bartholow in 1874 and was extensively developed by the Montreal group in the early to middle 1900s. It has become a gold standard methodolgy to explore various cortical functions and greatly enhanced the field of functional neurosurgery by defining regions of eloquent cortices. Standard cortical stimulation is performed using a train of biphasic square-wave pulses with a stimulus duration of 0.1–0.5 ms at a rate of 10–50 Hz. Each train of electrical stimuli is delivered to the cortex for a duration lasting from 2–5 seconds. Together with direct cortical electrical stimulation, various advancements in the last decade in functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), has brought additional insight into the functional organization of the cortex. In order to better understand the workings of the brain systems, a detailed knowledge of neuronal connectivity between these functional cortical regions is essential. There is in fact very little that is known regarding human interareal or cortico-cortical neuronal connectivity. This is mostly due to the fact that there is a limited repertoire of suitable anatomic techniques that can be used in the living human brain.[1] At present, knowledge of human white matter connectivity such as cortico-cortical and cortico-subcortical connections has mainly come from extrapolation from invasive tract-tracing studies performed in nonhuman primates. Retrograde and anterograde tracer techniques were introduced in the early 1970s with horseradish peroxidase (HRP) as the tracer and have revolutionized the understanding of connections in the nonhuman primate brain.[2,3] Besides anatomical tracer studies, neuronal connectivity has been investigated physiologically using electrical stimulation in nonhuman primates. Intracortical microstimulation technique in combination with single- or multi-unit recording has successfully evaluated orthodromic or antidromic responses in the remote cortical regions via cortico-cortical connections.[4,5] It is also noteworthy to state in this epilepsy textbook that a technique based on tracing the spread of experimentally-induced seizures, namely strychnine neuronography, was used to study these pathways before the advent of these modern tract-tracing techniques.[6–8]

As it relates to higher brain functions proper to humans, such as language and cognitive functions, studies performed in nonhuman primates are largely not relevant. In this sense, it is essential to explore interareal or cortico-cortical connectivity directly in humans. Moreover, functional brain systems, such as the motor and language systems, need to be evaluated in the *in vivo* setting for each individual patient in functional neurosurgery. Nevertheless, the corresponding information has almost exclusively come from 'admittedly impoverished' data obtained from postmortem studies such as gross anatomic dissections[9] or clinical pathological correlation of postmortem brains using a modified reduced silver method.[10] Obviously the latter has limitations due to the inability to control lesion size and location.

In vivo connectivity studies in humans have only recently begun using noninvasive methods, such as diffusion tensor imaging (DTI) and combined use of transcranial magnetic stimulation and positron emission tomography/functional magnetic resonance imaging (TMS-PET/fMRI).[11,12] DTI promises to shed new light on the understanding of white matter pathways by its ability to image fiber trajectories.[13,14] This technique enabled to visualize '*in vivo* dissections' of association and commissural fibers, and confirmed the presence of major white matter fasciculi in the living human brain.[15,16] DTI, however, cannot provide details of functional aspects of the brain, i.e., cortical functions and functional connectivity among cortical regions. It would be optimal if both functional cortical regions and their white matter connections could be mapped within the same patient, to be able to tract exact neuronal connections. We have recently developed an *in vivo* tracking method using direct cortical stimulation, which we termed 'cortico-cortical evoked potential (CCEP)'.[17,18] By means of subdural electrodes chronically implanted for the presurgical evaluation of intractable partial epilepsy, a single electrical pulse is applied over the cortex to look at the cortical evoked potentials that emanate from a distant region of the cortex via cortico-cortical connections. This technique provides a unique opportunity to track functional connectivity among the various cortical regions that are physiologically and anatomically defined within the same subject by means of standard cortical electrical stimulation and MRI-electrode co-registration, respectively. We will review the methodology, recent studies[18–20] and the future perspective of CCEP in this chapter.

CCEP methodology

We hypothesized that the external or surface electrical stimulation of the cortex could similarly generate orthodromic discharges in cortico-cortical projection neurons, thus activating the cortico-cortical short- or long-association fibers to convey the impulses to the cortical area where they project. The efficacy of surface cortical stimulation upon activating projection neurons is supported by the fact that surface electrical stimulation of the motor cortex successfully produces motor-evoked potentials through activation of pyramidal tract neurons in humans[21] and that the surface electrical stimulation produces stereotypical postsynaptic responses, called 'the direct cortical response (DCR)' in the very adjacent cortex in humans and other species.[22,23] It is further supported by the TMS-PET/fMRI studies in which TMS of the cortex gave rise to increased cortical activity, as measured with an indirect hemodynamic response, in the remote cortex.[11,12]

The recording procedure is as follows. After the standard presurgical functional cortical mapping with 50 Hz electrical stimulation,[24] single-pulse electrical stimulation is applied in a bipolar fashion to a pair of adjacently placed subdural electrodes (1 cm apart) by a Grass S88 stimulator (Astro-Med, Inc., RI) or an equivalent constant-current electric stimulator. The electrical stimulus used for this purpose consists of a constant-current square-wave pulse of 0.3 ms duration, which is given at a fixed frequency of 1 Hz. Polarity of stimulus current is alternated to; (1) reduce the stimulus artifacts, (2) avoid electrical charges building up at the cortex (a safety consideration), and (3) avoid polarization of platinum electrodes which can decrease the current density over time. The current is given at 80–100% of the intensity that produces either clinical signs or afterdischarges (ADs) during the standard 50 Hz stimulation. The intensity is set at 10–12 mA if no clinical sign or ADs are present at 15 mA. In cases in which excessive artifact obscures the recordings, the intensity is lowered stepwise by 1 mA until artifacts become small enough to visualize the evoked responses. The artifact usually consisted of a baseline drift that typically persisted for several milliseconds from the stimulus, and appeared to originate from either relatively poor electrode impedance or possibly the existence of the cerebrospinal fluid beneath the stimulating electrode. Electrocorticograms (ECoGs) are recorded with a bandpass filter of 1–1000 Hz (or 0.5–1500 Hz) and a sampling rate of 2500–5000 Hz (Axon Epoch 2000 Neurological Workstation, Axon Systems Inc., NY or Biotop; NEC–Sanei, Tokyo, Japan). All the subdural electrodes are referenced to a scalp electrode placed on the skin over the mastoid process contralateral to the side of electrode implantation. CCEPs are obtained by averaging ECoGs with a time window of 200–500 ms, time-locked to the stimulus. In each session, at least two trials of 20–100 responses are averaged separately to confirm the reproducibility of the responses. During the recording of CCEPs, the subjects are not requested to perform any specific task, just lying or sitting on a bed. Anatomical location of each electrode is evaluated with a three-dimensional MRI co-registration technique reported elsewhere.[18]

Figure 113a.1 shows examples of CCEPs. CCEPs are elicited in the adjacent cortex and/or in the remote cortical regions. CCEPs usually consist of a small positive deflection followed by a large negative potential (N1). Some CCEPs are followed by the second negative potential (N2). In Figure 113a.1(a), stimulation of the basal temporal area (symptomatogenic zone of the habitual aura revealed by 50 Hz stimulation) elicited CCEPs from the adjacent electrodes with its maximum at electrode D5 peaking at 12 ms. Figure 113a.1(b) shows CCEPs recorded from the right fronto-parietal area by stimulating the prefrontal area at the inferior frontal gyrus. In addition to large short-latency CCEPs (peak latency 12–15 ms) observed in the electrodes adjacent to the electrode pair of stimulation, CCEPs were recorded remotely in the posterior part of the inferior parietal area with N1 and N2 potentials peaking at 25–37 ms and 106–138 ms, respectively. The responses were site-specific: stimulation of Pair 3 (most caudal pair), and, to a lesser degree, Pair 2 (middle pair) elicited CCEPs while Pair 1 (most rostral pair) did not.

The generator mechanism of CCEP, however, is not precisely known. Because of the alternating polarity of the stimulus current employed to counterbalance the stimulus artifact and electric charges, the stimulated neurons are indeed the mixture of different neuronal populations depolarized by anodal and cathodal stimulation.[25,26] Thus the excitation of projection neurons occurs likely through synaptic action by activation of afferent input as well as direct depolarization of the initial segment. The relatively long peak latency (≤10 ms) observed in the locally evoked DCR[27,28] supports that direct cortical stimulation produces oligo- or multi-synaptic responses in the local cortical circuits. This local jitter of synaptic activity at the site of stimulation and at the target cortex could account for the relatively long-latency, blunt negative peak of the N1 potential (e.g., up to15 ms at the very adjacent electrodes). The first positive deflection (usually several milliseconds in the absence of stimulus artifact) at the target cortex might reflect the very first monosynaptic impulse projecting into the middle or deep cortical layer via large cortico-cortical projection fibers, giving rise to a surface positive potential. It is also possible that antidromic activation of the presynaptic axonal terminals of the association fibers could play a role in generation of CCEP. Compared with highly structured pyramidal neurons or interneurons, poorly organized arrangements of these small axon terminals are less favorable for effective direct activation.[29] Nevertheless, extensive arborization of the presynaptic terminals might increase the chance to be excited by cortical surface stimulation. In this case, the antidromic activation of the pyramidal neurons in the deep cortical layer at the target cortex would be recognized as a small surface positive potential reflecting the very first volley of impulse. The following large blunted negative potential could then be produced at the target cortex upon the first impulse arrival or generated as a result of mixture of both orthodromic and antidromic excitation of the neurons in the target cortex. In addition to the direct cortico-cortical pathway, the cortico-subcortico-cortical pathway may be an alternative mechanism. Nonreciprocal cortico-thalamo-cortical circuits[30] or cortico-basal ganglia-thalamo-cortical circuits[31] could be a candidate. The N2 potential usually has a larger distribution than the N1 potential. After the excitation of the cortex via mechanims mentioned above giving rise to the N1, the N2 potential could then be generated in and immediately surrounding the cortex via either a local cortico-cortical or a cortico-subcortico-cortical reverberating cirtuit.

Although the CCEP technique is applicable only during the invasive presurgical evaluation of intractable epilepsy patients,

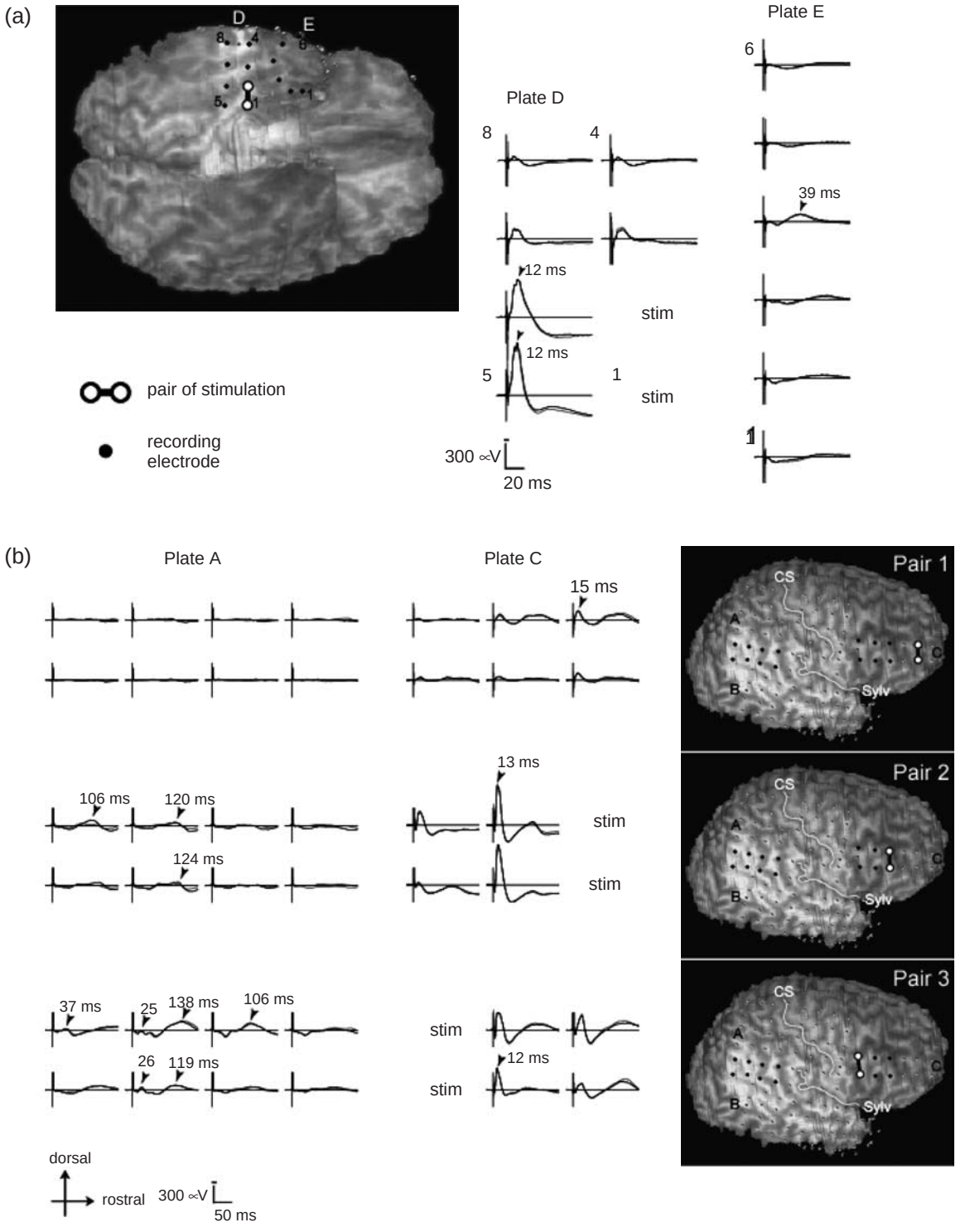

Figure 113a.1 Short and long latency CCEPs recorded from a patient with mesial temporal lobe epilepsy. (a) CCEPs recorded from the basal temporal area (Plates D and E) by stimulating electrodes D1 and D2 (symptomatogenic zone of the habitual aura revealed by standard 50 Hz stimulation). Stimulation elicited short-latency CCEPs from the adjacent electrodes in Plate D (maximum at D5) as well as from Plate E (maximum at E4). The vertical bar corresponds to the time of stimulation. Two trials (black and gray lines) were superimposed. Black circles denote the recording subdural electrodes co-registered with 3D MRI. (b) CCEPs recorded from the right frontoparietal area by stimulating the prefrontal area at the right inferior frontal gyrus. In addition to large short-latency CCEPs (peak latency 12–15 ms) observed in the electrodes adjacent to the electrode pair of stimulation, CCEPs were recorded remotely in the posterior part of the inferior parietal area with the early and late negative potentials peaking at 25–37 ms and 106–138 ms, respectively. The responses were site-specific: stimulation of Pair 3 and, to a lesser degree, Pair 2 elicited CCEPs while Pair 1 did not. CS, central sulcus; Sylv, sylvian fissure. Other conventions are the same for Figure 113a.1(b). From ref. 17 with permission.

it provides a unique opportunity to track *in vivo* cortico-cortical networks and has advantages over other methods. Compared with TMS-PET/fMRI studies, the CCEP study provides: (1) direct neuronal responses to the stimulation; and (2) more localized cortical stimulation with better temporal and spatial resolution. Moreover, in contrast to the DTI study, this technique is capable of providing the direction of connectivity, at least electrophysiologically, by stimulating both ends of connection. The CCEP study, however, cannot identify the actual anatomical pathway of the circuit, and in this regard it may well be regarded as 'functional tractography' as compared with 'anatomical fiber tractography' by DTI. Combination of the functional and anatomical fiber tractography will complement each other and become one of the powerful tools to explore human *in vivo* connectivity.

In terms of clinical practicality, the CCEP method is highly practical because it can be done: (1) easily with online averaging technique in a short time (less than a minute or two for each stimulus site); (2) without any cooperation of patients; and (3) with least chance of provoking seizures (no seizures reported in references).[17,18,20]

Studies using CCEP methodology

Exploring the functional systems of the brain

Combined with functional cortical mapping of the eloquent cortex, the CCEP technique allows us to understand specific functional brain systems. Our initial focus in studying particular functional systems was on language.[18]

Eight patients who underwent chronic subdural electrode placement for the presurgical evaluation of medically intractable partial epilepsy were studied (age 13–42, two FLE and six TLE patients). Six patients had subdural electrodes placed in the hemisphere dominant for language and two had bilateral language representation as judged from the intracarotid amobarbital test. Stimulation of the anterior language area elicited CCEPs in the lateral temporo-parietal area (7/8 patients) in the middle and posterior part of the superior temporal gyrus, the adjacent part of the middle temporal gyrus and the supramarginal gyrus (Figure 113a.2). CCEPs generally consisted of early N1 and late N2 potentials. The peak latency of N1 ranged from 22–36 ms (mean 27.9 ms) and that of N2 from 113–164 ms (mean 144.6 ms). The distribution of N2 (3–21 electrodes) was larger than that of N1 (1–20 electrodes) ($P < 0.01$, two-tailed paired T-test). In relation to the electrodes which produced language impairment at 50 Hz stimulation, CCEPs occurred at or around these electrodes. The connection between the anterior and posterior perisylvian language areas was electrophysiologically bi-directional. Stimulation of the posterior language area elicited CCEPs (3/4 patients), though less well defined, in Broca's area and the surrounding silent prefrontal or face motor area. In addition to these interlobar connections, two adjacent interareal circuits with shorter-latency CCEPs were observed within the perisylvian area (Figure 113a.3). First, stimulation of the anterior language area elicited CCEPs in the frontal operculum (N1 peak; 11–19 ms, 2/2 patients), which is the presumed region for the articulatory planning.[32,33] Second, stimulation of the face motor area produced CCEPs (N1 peak; 13–24 ms) in the ventral postcentral gyrus (the face somatosensory area) and the adjacent portion of the anterior inferior parietal area (2/2 patients).

Upon stimulation of the anterior language area, similar CCEPs were obtained in the anterior to middle portions of the inferior temporal and fusiform gyri (the basal temporal language area)[34] in all three patients studied (N1 peak at 19–47 ms, N2 peak at 120–187 ms) (Figure 113a.4).

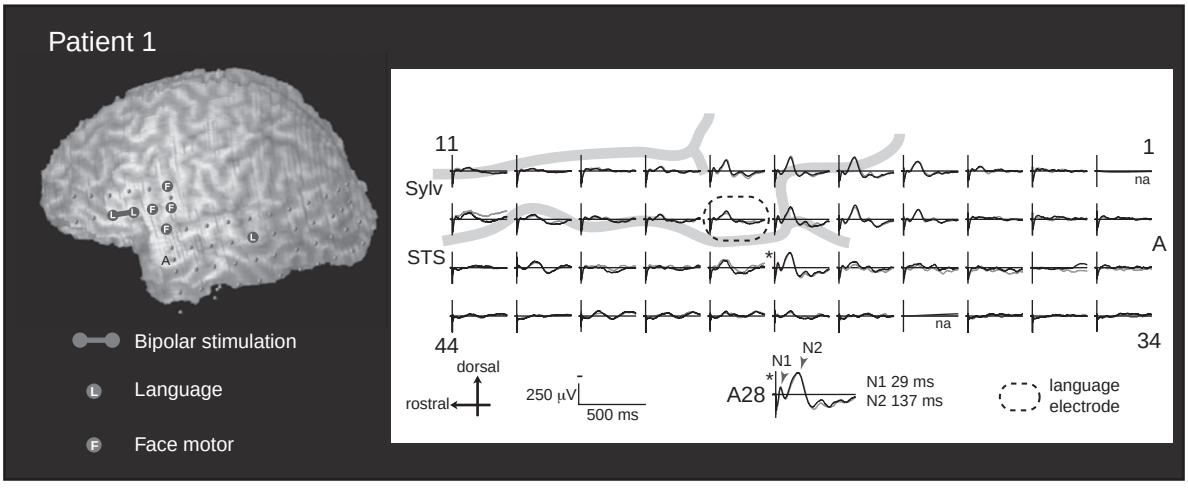

Figure 113a.2 CCEPs recorded from the posterior language area (plate A) time locked to single-pulse stimulation delivered at the anterior language area. Two trials are plotted in superimposition for each electrode. The vertical bar corresponds to the time of stimulation. Evoked responses were mainly recorded from the posterior part of the superior temporal gyrus and the adjacent portion of the middle temporal gyrus in and surrounding the language electrode defined by standard cortical stimulation (A18: highlighted with a dotted circle). Maximal activity was seen at electrode A28 with a clear early N1 and a late N2 potential, peaking at 29 and 137 ms, respectively. STS – superior temporal sulcus, Sylv – sylvian fissure, na – CCEP not available due to high impedance in the recording electrode. Other conventions are the same as for Figure 113a.1 From ref. 18 with permission.

In contrast, stimulation of the adjacent face motor area did not elicit CCEPs in the basal temporal area. Stimulation of the posterior language area did not evoke clear CCEP responses, while stimulation of more caudally situated electrode pairs at the temporo-occipital junction elicited small N1 and N2 potentials in the inferior temporal gyrus.

The present study revealed cortico-cortical connections within the perisylvian language area as well as between the perisylvian and extrasylvian language areas, via long and short association fibers and/or through the cortico-subcortico-cortical pathway. Different from the classical Wernicke-Geschwind model, our study revealed, at least electrophysiologically, a bi-directional connection between Broca's and Wernicke's areas likely through the arcuate fasciculus. Larger distribution of CCEPs than that of the posterior language area identified by electrical stimulation suggests the existence of a rather broad neural network surrounding the previously recognized core region of this area. This broad distribution is consistent with the recent DTI study that demonstrated the connection of the anterior language area (Broca's territory) to the lateral temporal (Wernike's territory) as well as the inferior parietal (Geshwind's territory) area.[35] Since the evidence in the nonhuman primate brain points to a much more extensive parietal than temporal projections to the ventral premotor area – a presumed homologue of Broca's area,[36,37] one may speculate that increased connectivity demonstrated between Broca's and Wernicke's territories in humans is the results of the evolution and acquisition of language function.

Functional connectivity demonstrated here supports the contemporary concepts of language organization, namely that neuronal groups participate as components of a network by means of feed-forward and feed-back projections.[38] In contrast with classical aphasiology descriptions, the conventional electrical stimulation of either Broca's, Wernicke's or the basal temporal language area can interfere with both language production and comprehension.[39,40] It is likely that the language network itself is functionally disturbed by high frequency stimulation, because even a single-pulse stimulus in one language area reaches the other language areas via different cortico-cortical connections.

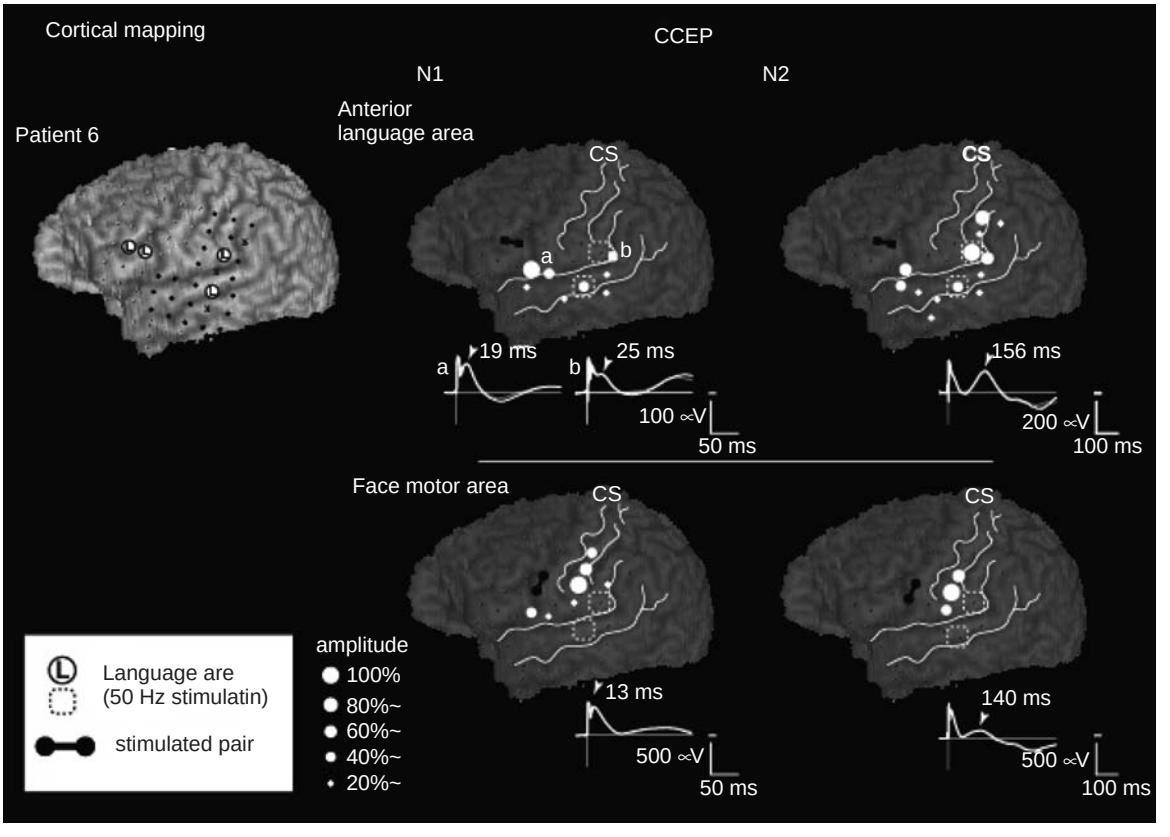

Figure 113a.3 Long and short cortico-cortical connections within the perisylvian language area. The distribution of CCEPs is presented in a circle map which shows amplitude percentage distribution in relation to the maximal response displayed below each map. Middle and right columns show the distribution of N1 and N2 activities, respectively. The result of cortical mapping and the distribution of recording electrodes (colored black) are shown in the left column. Electrodes highlighted with a dotted square in the middle and right columns correspond to those which stimulation produced language impairment on standard 50 Hz stimulation. Stimulation of the anterior language area (upper column) elicited CCEPs in the lateral parieto-temporal area (maximum at Circle b). In addition to this inter-lobar connection between the anterior and posterior language areas, another CCEP field with shorter peak latency (19 ms vs. 25 ms) was recorded in the frontal operculum region (Circle a). On the other hand, stimulation of the face motor area (lower column) showed entirely different CCEP distribution in the ventral postcentral and adjacent anterior parietal areas with shorter N1 peak latency (13 vs. 25 ms). Modified from ref. 18 with permission.

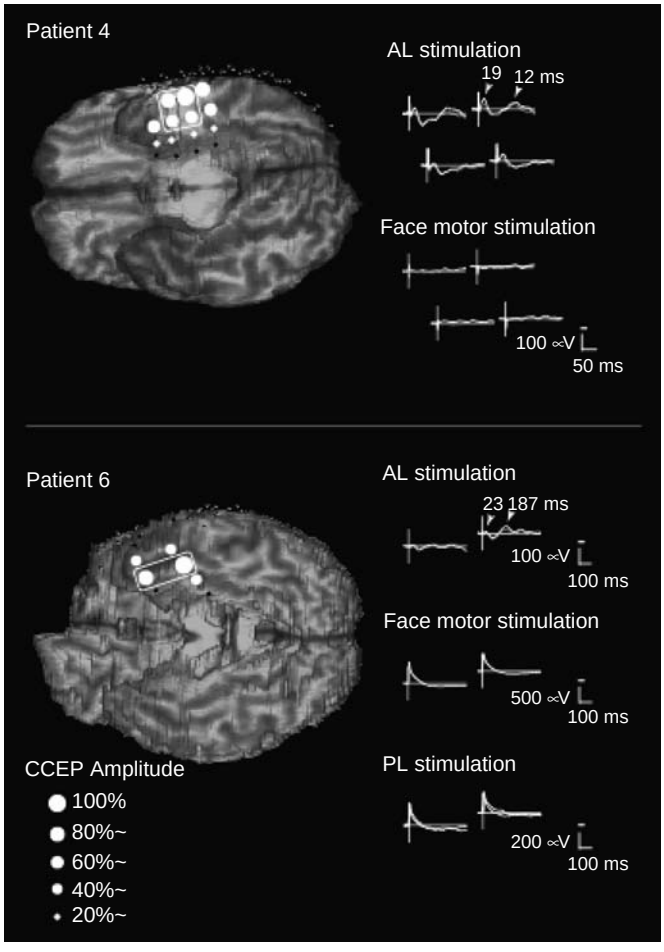

Figure 113a.4 CCEPs recorded from the basal temporal area. Stimulation of the anterior language area (AL) elicited clear N1 and N2 potentials in the inferior temporal and fusiform gyri in all three subjects studied for this connection. In contrast, no CCEPs were observed when stimulating the adjacent face motor area (2/2 patients). Waveforms of evoked responses are shown for electrodes encompassed by a rectangle. Circle maps are shown for the N1 potential of the AL stimulation. PL: the posterior language area. Other conventions are the same as for Figure 113a.3. Modified from ref. 18 with permission.

The connections revealed within the perisylvian area most likely reflect normal brain function since the epileptogenic focus or EEG seizure onset zone was outside the perisylvian area. It is interesting, however, to note that CCEPs could also be recorded from pathological brain tissue (microcalcification and cortical dysplasia in the lateral temporal area) in two patients as well as from the epileptogenic focus (the basal temporal area) in two (Figure 113a.5). The CCEP study may help identifying normal cortico-cortical connections in the brain region where normal brain function co-exists with pathology.

Our next attempts to study brain systems using CCEPs involved investigations in the motor system. In order to understand the rapid spread of epileptic discharges through the cortico-cortical networks involved in ictal motor manifestation, cortico-cortical connections between the lateral and medial motor cortex were studied by means of CCEP. The study demonstrated a human cortico-cortical network connecting: (1) anatomical homologous areas of the lateral and medial motor cortex along the rostro-caudal cognitive-motor gradient (e.g., supplementary motor area (SMA) to the caudal lateral premotor/primary motor (MI) area, pre-SMA to the rostral lateral premotor area); and (2) the somatotopically homologous regions in the lateral and medial motor cortex (e.g., the hand SMA to the precentral hand motor area, see Figure 113a.6) in a reciprocal manner.[20] These circuits could account for the propagation of epileptic discharge from/into SMA[41,42] and the atypical motor responses infrequently seen in standard cortical stimulation: tonic and clonic responses in MI and SMA stimulation, respectively.[43]

Detailed knowledge of the parieto-frontal network is important for understanding the spike propagation from the parietal to the frontal lobe in parieto-occipital lobe epilepsy. From the neuroscientific point of view, this network is essential in sensori-motor integration for various complex behaviors, and is associated with pathophysiology of apraxia. CCEP investigation of this network revealed that the human rostral and caudal parietal areas connect to the caudal and rostral frontal areas, respectively, (e.g., the primary somatosensory to the primary motor area, the superior/inferior parietal lobule to the dorsal/ventral premotor area) in a one-to-one or in a divergent fashion (unpublished data, reported preliminarily as an abstract form).[44]

Exploring pathophysiology of epilepsy

In addition to explore organization of the brain systems, the CCEP methodology could be applicable to *in vivo* exploration of the pathophysiology of epilepsy – to investigate the epileptogenicity and to locate the circuit involved in the spread of epileptic discharges.

Little is known about *in vivo* epileptogenicity, especially transition from the interictal to ictal state in humans. Although extensive researches have been performed in this field by means of animal models and surgical specimens, alternation of intracortical excitatory and inhibitory system has not been well elucidated *in vivo* in humans. This is because of the paucity of the techniques that allow the investigation of excitatory and inhibitory mechanisms of the cortex *in vivo* in humans. Paired-pulse stimulation paradigm, either noninvasively by TMS or invasively by direct electrical cortical stimulation, offers a unique opportunity to assess intracortical excitatory and inhibitory mechanisms.[45,46] This paradigm, however, has been confined to MI where the final common pathway can be assessed by the motor evoked potential (MEP) in the target muscle. Reported here is based upon the notion that, by analogy to the motor system, the intracortical inhibitory and excitatory mechanisms could be evaluated at the site of cortical stimulation by applying subthreshold conditioning and suprathreshold test electrical pulses to analyze the size change of CCEPs. In this way, instead of the corticopyramidal neurons giving rise to MEP, the cortico-cortical projection neurons whose excitation elicits CCEP were evaluated. Indeed, though with much longer interstimulus intervals (ISIs), similar paired-pulse stimulation has been infrequently employed to study the *in vivo* epileptogenicity in patients with mesial temporal lobe epilepsy by means of depth electrodes placed in the hippocampus.[47] By applying paired-pulse stimulation directly to the focus, we documented *in vivo* alternation of intracortical inhibitory and excitatory mechanisms in epileptogenesis or ictogenesis of focal cortical dysplasia (FCD).[19]

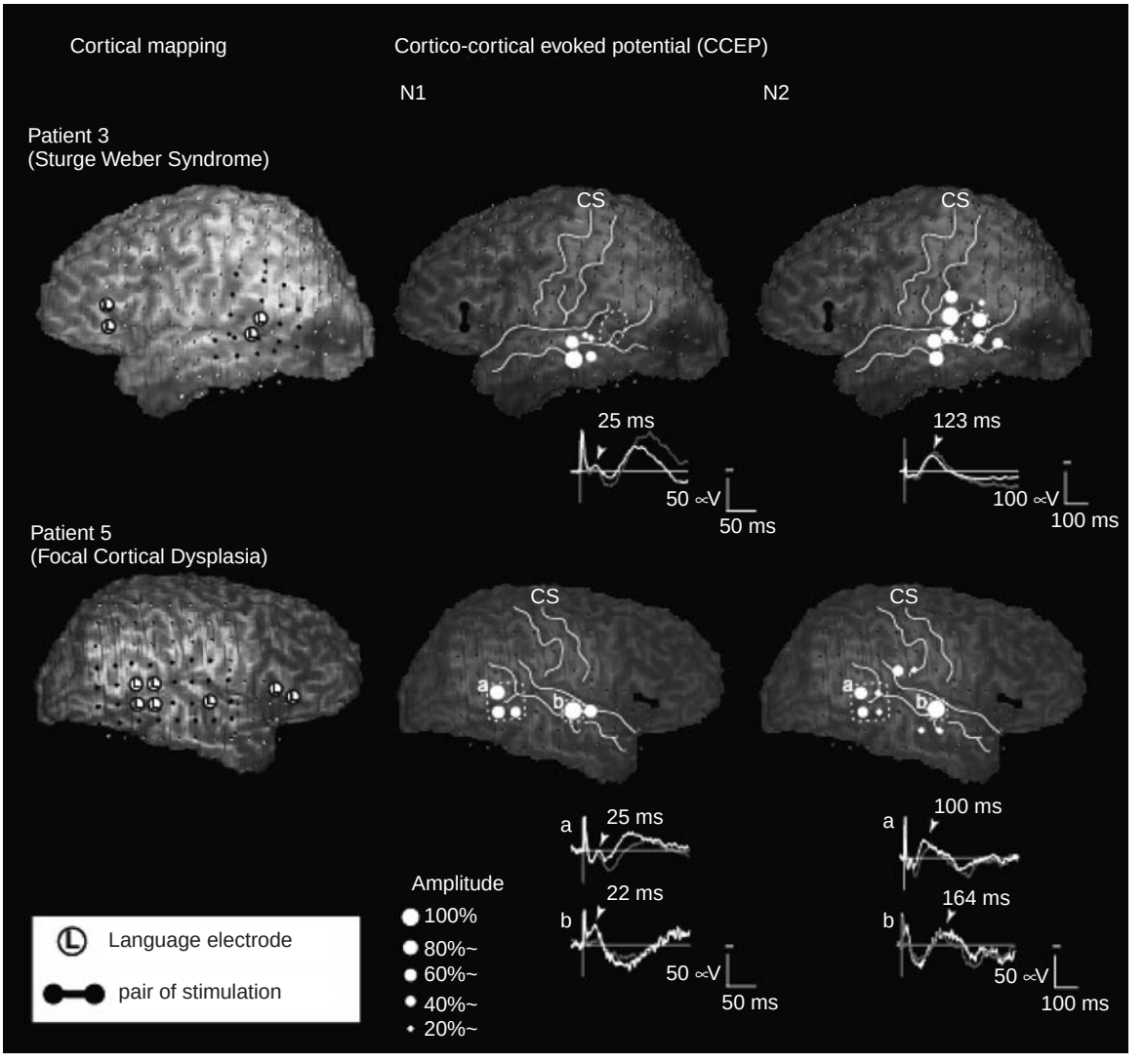

Figure 113a.5 Cortico-cortical connections within the pathology. Upon stimulation of the anterior language area, CCEPs were obtained at and around the posterior language area defined by standard cortical stimulation within the MRI abnormality consistent with Sturge-Weber syndrome (Patient 3) and cortical dysplasia (Patient 5). In Patient 5, CCEPs were *seen split* in the two distinct language areas possibly separated by abnormal nonfunctioning dysplasic cortex. Conventions are the same as for Figure 117a.3. Modified from ref. 18 with permission.

A 31-year-old man with intractable partial epilepsy who underwent invasive monitoring with subdural electrodes was investigated. The seizures started with somatosensory auras of the left foot, which evolved into either left foot clonic seizures or bilateral asymmetric tonic seizures. Invasive evaluation revealed a seizure onset zone in the primary sensorimotor area of the left foot. The patient underwent resection of the focus and the pathology was FCD (Type IIB of Palmini *et al.*).[48] First, single-pulse stimulation was performed in order to determine the threshold intensity to elicit CCEPs (TH_{CCEP}). Stimulation of the focus was performed at the primary foot somatosensory area (foot SI), while that of the control cortex at the hand SI, a functionally homologous area away from the focus. Current intensity was gradually increased by 0.5 mA, and TH_{CCEP} was determined when two trials of 20 averaged responses first showed reproducible CCEPs. Then, the paired-pulse stimulation was performed by conditioning (TH × 50%) and testing (TH+1 mA) stimuli with interstimulus interval (ISI) of 1–100 ms. Intracortical inhibition (ICI) at the stimulated site was investigated by analyzing amplitude change of CCEP at the electrode showing the maximum CCEP in comparison with the CCEP amplitude of single-pulse stimulation.

Single-pulse stimulation at the foot and hand SI elicited CCEPs from the surrounding areas with the maximum CCEP at the foot and hand MI, respectively, most likely via projection from SI to MI. Paired-pulse stimulation of the focus revealed abnormally enhanced intracortical inhibition at ISI of 1–10 ms (max 22%) compared with control stimulation of the hand SI (ISI of 1–2 ms; max 18%) in the interictal state ($P < 0.01$) (Figures 113a.7 and 113a.8). Owing to the incidental seizure, we had an opportunity to demonstrate dynamic alternation of the cortical excitability during transition from interictal to ictal state. In another series of paired-pulse stimulation, subjective paraesthesia of the left foot occurred spontaneously between stimulus sessions. Confirming the absence of ictal discharges on ECoG, the study was continued in the

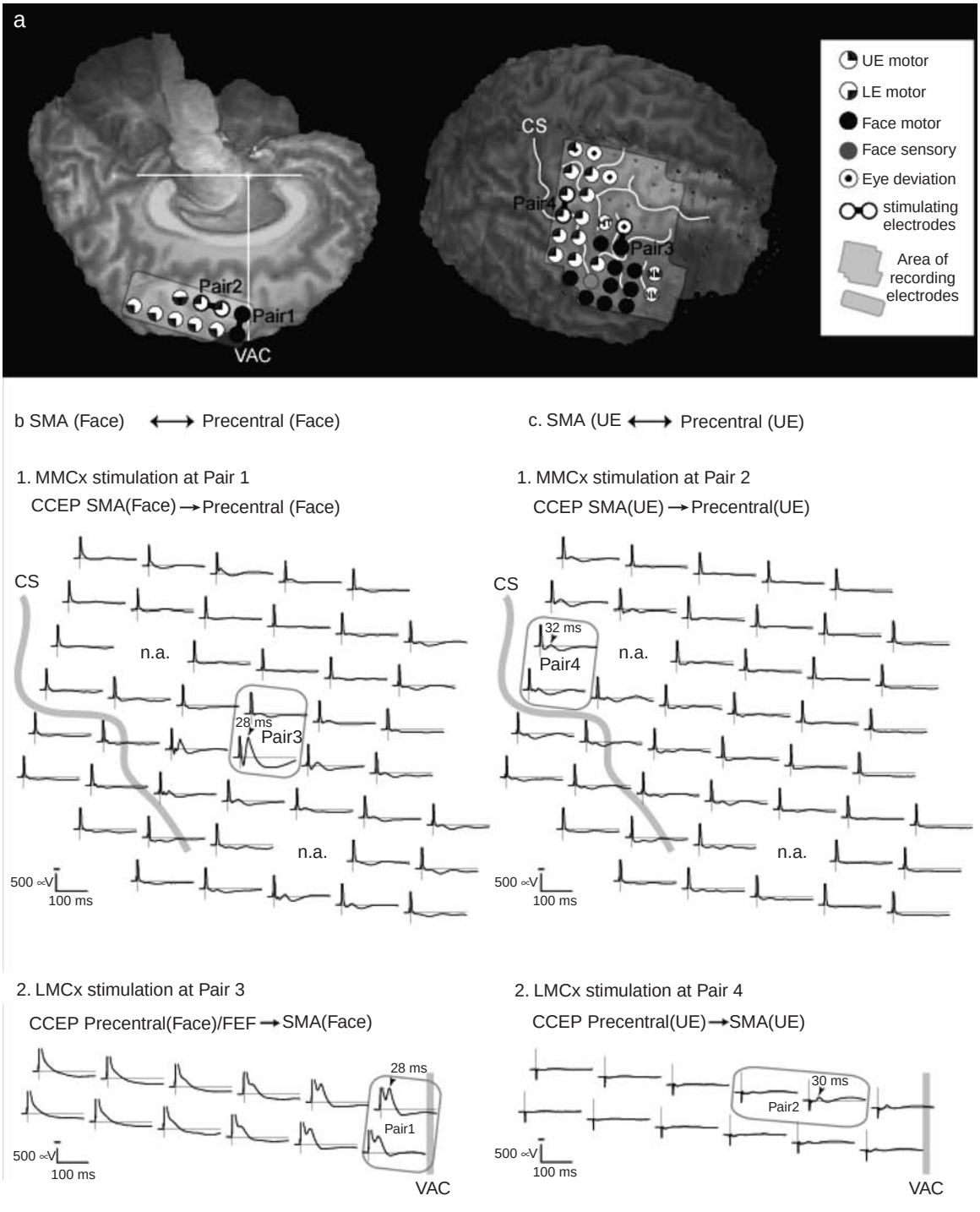

Figure 113a.6 Reciprocal connections between the somatotopically homologous regions in the medial (MMCx) and lateral (LMCx) motor cortex. (a) Results of functional cortical mapping and placement of recording electrodes shown on 3D MRI. Stimulating pairs (Pair 1-4) are plotted as well. UE: upper extremity, LE: lower extremity, HT: head turning, NM: negative motor area. (b) Reciprocal connections between face SMA and the precentral face motor area. Stimulation of face SMA (Pair 1) elicited CCEPs in LMCx with the maximum CCEP at the precentral face motor area (a lower electrode of Pair 3) (b-1). Stimulation of Pair 3 (precentral face motor area/frontal eye field (FEF)), in return, gave rise to CCEPs in the rostral part of SMA, being maximum at the initial stimulation pair (Pair 1: face SMA) in MMCx (b-2). CS: central sulcus, VAC: vertical anterior-commissural line. Other conventions are the same as for Figure 113a.2. (c) Reciprocal connections were also observed between the upper extremity portion of SMA (Pair 2) and that of the precentral motor area (Pair 4) (c-1,2). The procedures and conventions are the same as for Figure 113a.7b. Modified from ref. 20 with permission.

presence of this sensation under the notion that this protocol did not at least provoke the somatosensory aura. The patient, however, presented with the left foot/leg clonic seizure in eight minutes after the sensation started, and it was concluded at that time that the somatosensory sensation frequently observed during the standard 50 Hz cortical mapping was actually the somatosensory aura. This series of stimulation was cancelled with limited investigation. While the patient was having the somatosensory aura, cortical excitability was increased as judged from the enlarged CCEP (140%) in response to single-pulse stimulation (Figure 113a.7). This was accompanied by a decrease of the interictally enhanced

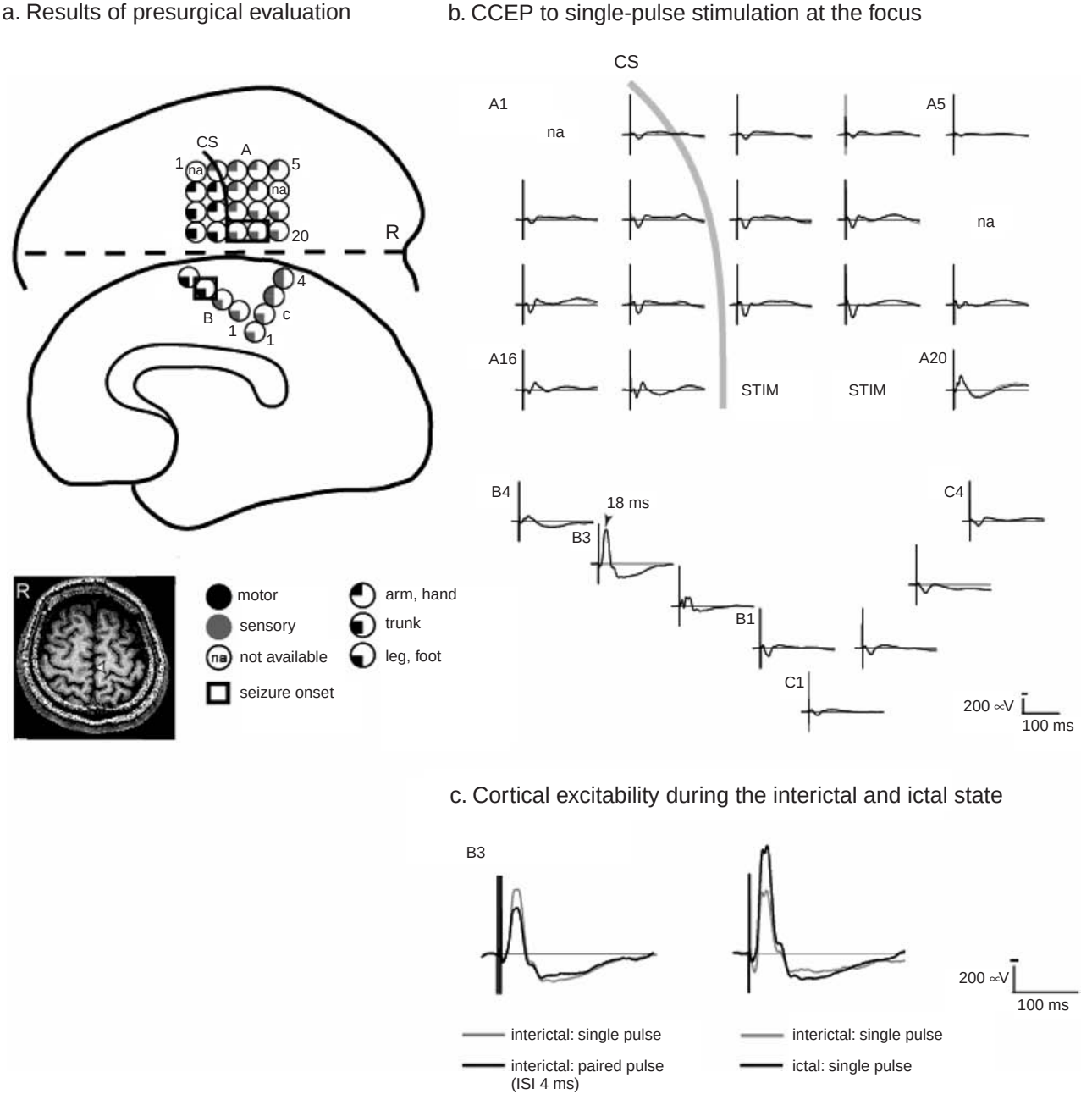

Figure 113a.7 Interictal and ictal CCEPs elicited by stimulation of the epileptic focus in a patient with focal cortical dysplasia at the left foot primary sensorimotor area. (a) Arrangement of subdural electrodes and results of the invasive presurgical evaluation. Ictal onset zone was situated in the foot primary sensorimotor area at and around the right central sulcus (arrowhead) where T1-weighted MRI (3 tesla) showed blurring of the gray/white matter junction. CS: central sulcus, na: no data of cortical function available due to high impedance of the electrode. (b) CCEPs elicited by single-pulse stimulation of the focus in the interictal state. Subaverage waveforms are plotted in black and gray lines. CCEPs were recorded in the adjacent cortices with the maximum response at the foot MI (electrode B3), most likely via projection from the foot SI to MI. STIM: site of stimulation. Other conventions are the same as for Figure 113a.1. (c) Cortical excitability during the interictal and ictal state. Magnified waveforms are shown at electrode B3 where maximum CCEPs were recorded. During the interictal state (left column), paired-pulse stimulation of the focus showed decrease of CCEP size (intracortical inhibition, maximum 22%). During the left foot somatosensory aura (right column), single-pulse stimulation showed the enlarged CCEPs (140% at electrode B3) compared with those in the interictal state, suggesting increased cortical excitability during seizure generation. ISI: interstimulus interval. Modified from ref. 19 with permission.

intracortical inhibition albeit studied at limited ISIs (4, 8 ms) (Figure 113a.8). In summary, during the aura, interictally enhanced intracortical inhibition at the focus was replaced by increased cortical excitability and decreased intracortical inhibition, suggesting increased net intrinsic epileptogenicity during seizure generation (ictogenesis) in this particular patient with FCD.

This 'paired-pulse CCEP method' could be of help in delineating alternation of the intracortical inhibitory and excitatory mechanisms *in vivo* at and around the epileptic focus. In particular, detailed comparison between the *in vivo* excitability at the focus electrodes and immunocytochemical findings in the corresponding surgical specimen will be useful.

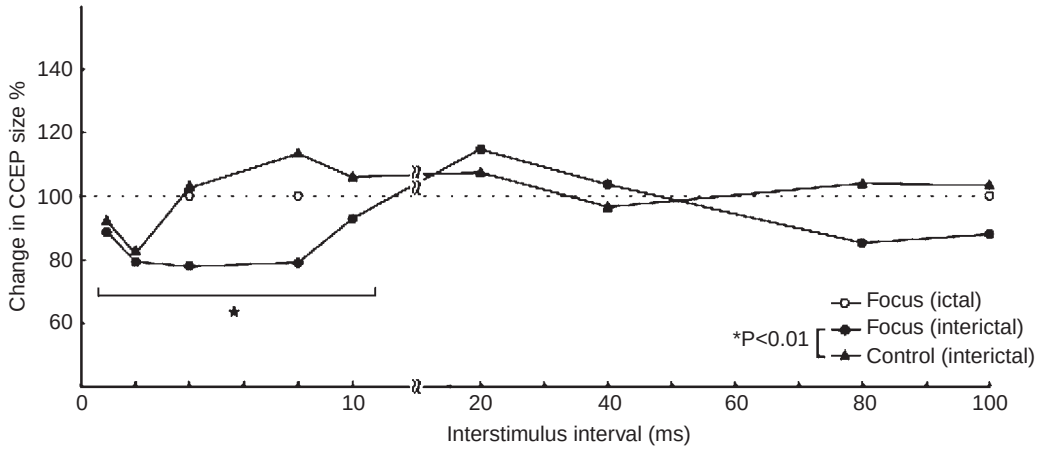

Figure 113a.8 Cortical excitability studied by paired-pulse stimulation of the epileptic focus (foot SI) and control (hand SI) cortex. At each interstimulus interval (ISI), the mean size of the conditioned responses is shown as a percentage of that of the unconditioned CCEP. Interictally, focus stimulation showed intracortical inhibition throughout the 1–10 ms range of ISIs (maximum of 22 % at ISI 4 ms) whereas intracortical inhibition was seen only at ISI of 1–2 ms in the control stimulation (maximum of 18 % at ISI 2 ms) ($P<0.01$ at ISIs of 1–10 ms; Mann-Whitney U-test). When the patient was having the left foot somatosensory aura, intracortical inhibition was not observed, though tested for limited ISIs (4, 8, 100 ms). Solid circle, open circle and solid triangle denote results of interictal focus stimulation, ictal focus stimulation and interictal control stimulation, respectively. From ref. 19 with permission.

Another potential clinical use of CCEP for understanding epilepsy is to track the pathways involved in the spread of epileptic discharges. Knowledge of the underlying physiological cortico-cortical connections is essential for a better understanding of pathological connections involved in the spread or propagation of epileptic discharges. When combined with detailed analysis of interictal and ictal discharges, the CCEP technique seems useful in this regard because it could track the pathway for each individual patient based on stimulation in the epileptogenic or irritative zone. This approach would be of importance in the presurgical evaluation of extra-temporal lobe epilepsy in which the complex functional and anatomical organization with multiple reciprocal connections facilitates rapid spread of epileptic discharges and thus produces a variety of seizure semiology.[49,50] Whether the excitability of these connections is enhanced abnormally (normal vs. pathological connection) at the epileptic focus will be an important issue to be solved.

Conclusion

CCEP provides us a new way to explore interareal connectivity *in vivo* in humans. In addition to its impact on the basic systems neuroscience, this method, in combination with conventional cortical mapping, could contribute clinically to map the functional brain systems by tracking the cortico-cortical connections among the functional cortical regions in each individual patient. This approach may help identifying the normal cortico-cortical network within the pathology or the plasticity of brain systems in conjunction with pathology. In relation to epileptogenicity, CCEP helps us to study the cortical excitability as well as to locate the circuit involved in the spread of epileptic discharges. Further verification is warranted to establish the clinical utility by recruiting more patients, combing the findings of other modalities such as DTI and the feedback from surgical results.

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113b Cortical mapping by intra-operative optical imaging

MM Haglund and DW Hochman

Introduction

Increases in neuronal activity trigger a number of physiological and metabolic changes, including increases in blood perfusion and the redistribution of ions in brain tissue. When neurons fire action potentials, the microscopic pial arterioles near the firing neurons dilate,[1] leading to localized changes in blood volume and oxygenation.[2] Glial cells swell and shrink as they shuttle ions between the extracellular and intracellular spaces to maintain homeostasis following neuronal activity.[3] Each of these activity-evoked physiological changes lead to localized alterations in the way brain tissue absorbs and scatters light, and hence the optical properties of brain tissue can serve as a surrogate for neuronal activity.[4] Intraoperative optical imaging (IOI) is the method of mapping the small optical changes in exposed cortical tissue that result from neurons firing action potentials. The IOI method involves illuminating the exposed cortical surface with visible or near-infrared light, and using sensitive cameras and computer imaging techniques to measure the ongoing dynamic changes in the light scattering properties of tissue.

A typical IOI setup consists of a digital CCD camera mounted on an operating microscope (Figure 113b.1). As illustrated in Figure 113b.1, the cortex is illuminated with light from a stabilized intense source, filtered at specific wavelengths of interest. Digital images are then acquired during a rest, or 'control' state, and throughout some stimulation paradigm that might involve sensory activation or electrical stimulation of the cortex. The stream of digital images provides a movie of the dynamic optical changes that occur as a result of the stimulus, and can be analyzed in a number of ways. Figure 113b.1 shows data acquired from an awake patient who was instructed to move their tongue against their soft palette for 10 seconds. Images acquire during the peak of the activation were subtracted from control-images to yield a 'difference-image' that was pseudocolored to emphasize small optical changes. All optical imaging systems are designed around this basic theme, though with variations on the detectors, illumination wavelengths and systems, and the analysis of data. An important feature of optical imaging is that the spatial resolution is determined by the optics of the microscope and the pixel-size on the CCD chip. In this way, IOI is a very flexible imaging modality in that it can monitor macroscopic changes occurring over centimeters of cortex, and quickly zoom in to map changes occurring at the cellular level with micron-scale resolution.

IOI is still an experimental technique, but has the potential to be a valuable neurosurgical tool for at least three reasons. First, since it relies on changes in the intrinsic optical properties of tissue, it does not require the administration of contrast-enhancing agents or the placement of electrodes on the cortical surface. Second, experimental data suggests that it can localize normal and epileptic activity more quickly and with significantly greater spatial resolution than is currently possible with EEG, PET, or fMRI. Finally, it is relatively inexpensive by comparison to other imaging techniques, costing on the order of tens of thousands of dollars in contrast to PET and fMRI devices which cost millions of dollars. A major limitation of IOI is that it is not capable of mapping activity in deeper structures below the cortical surface, and hence the primary application of this technology is in localizing functional and epileptic activity in the cortex.

Importance of IOI for epilepsy surgery

Approximately 1% of the population suffers from epilepsy, and 30% of epilepsy patients are not able to adequately control their seizures with existing therapeutics.[5,6] Epilepsy patients with focal onset who are intractable to antiepileptic medications may become candidates for the surgical treatment, where the primary goal is to remove the epileptogenic tissue while sparing brain regions dedicated to critical functions.[7] Ideally, a technique is desired which would allow one to accurately map areas of cortex committed to critical functions such as speech and sensory processing, as well as the boundaries of epileptogenic tissue. Surgical treatment of epilepsy is a lengthy and expensive procedure; it has been estimated that the total accumulated costs per patient in the United States from diagnosis to completion of surgical treatment is over $100 000.00.[8] A significant portion of this time and cost is consumed by the procedures presently used to localize the seizure focus and to determine the functional significance of the epileptogenic tissue and surrounding cortical regions.[9] In the United States, there are approximately three million patients who are refractory to medical therapy, with 5 000 – 10 000 added annually; yet only 2 000 surgical procedures are performed each year.[5,10] It has been suggested that this underutilization of the surgical treatment of epilepsy is slowly being reversed as a direct result of technological improvements in neuroimaging and EEG methods for the localization of functional areas and seizure foci.[11] IOI is a relatively inexpensive technology that is capable of providing

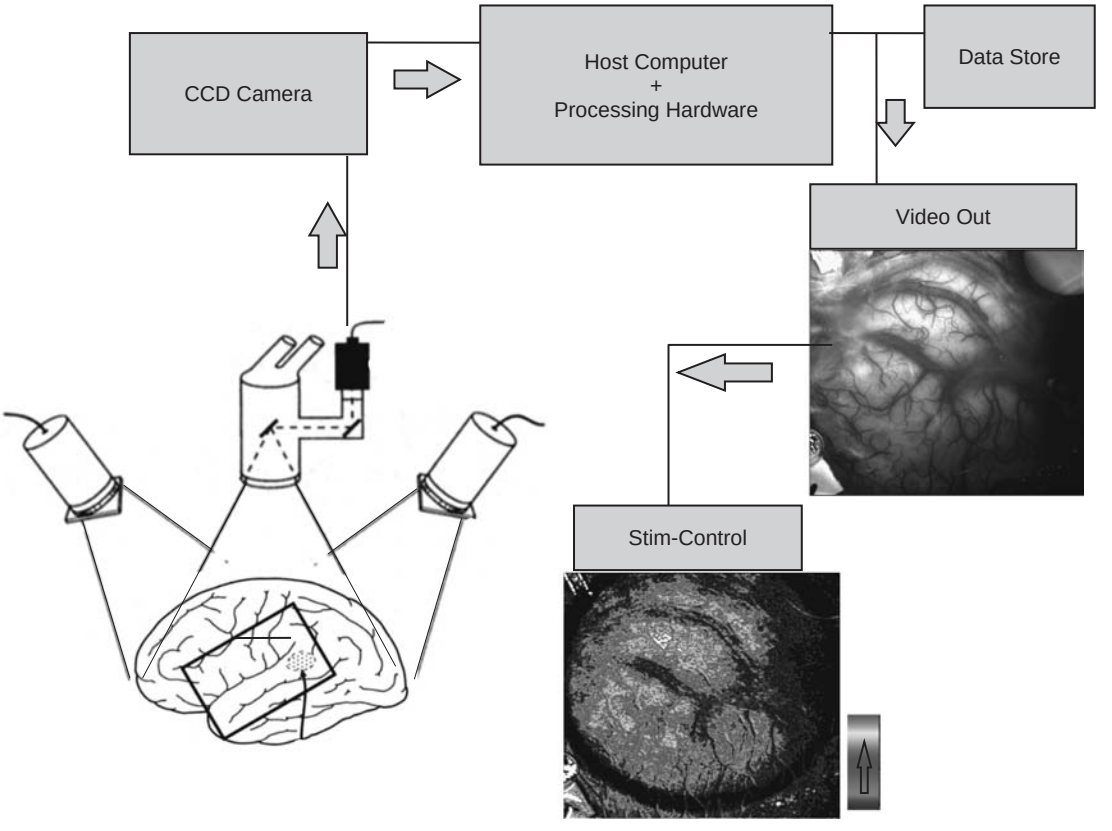

Figure 113b.1 Schematic of an intraoperative optical imaging (IOI) device: the amount of light absorbed and reflected from cortical tissue varies as a function of neuronal activity. These small changes in the optical properties of tissue can be used as a means to map dynamic patterns of neuronal activity. Shown in this figure is a schematic of a typical IOI setup, which includes a sensitive optical detector, such as high-quality cooled digital CCD camera, mounted to the operating microscope. The surface of the cortex is illuminated with a highly stable light source, such as a regulated xenon lamp. The light is usually filtered to allow illumination with specific wavelengths of light. A small glass plate can be place on the cortical surface to reduce small movements caused by respiration and heartbeat. A series of digitized images of ongoing activity are stored in computer memory, and can be replayed as a movie showing patterns of neuronal activation. The gray image shown here is a view of tongue motor and sensory cortex when illuminated with 535 nm (i.e., green) light. In this experiment, the patient was instructed to move their tongue against their palate for 10 seconds, which elicited a significant increase in neuronal activity and associated optical changes. A spatial map of the activity-evoked optical changes was generated by subtracted an image acquired during tongue-stimulation from a 'control' image acquired when the patient was at rest. This difference-image was then pseudo-colored to render small differences in the optical properties between the two images readily apparent. The maximal changes were colored red and white, representing in increase of approximately 5% in light absorption by the tissue during tongue movement. Black and blue pixels represent baseline noise. (See Color plates.)

'online' intraoperative mapping of functional cortex and seizure activity with significantly greater resolution than other imaging modalities.[4] Consequently, IOI has the potential to make a dramatic impact on the surgical treatment of epilepsy by reducing costs, improving patient outcomes, and allowing surgical treatment to be accessible to a larger number of patients. The greatest impact of IOI in the near future may be as a tool for the localization of epileptic foci on those patients with neocortical epilepsy showing no evidence of a lesion with MRI or metabolic imaging, especially since these patients consume the greatest proportion of the resources.[12]

A brief history

Detection of activity-evoked optical changes in neuronal tissue has a long history, although it has only been recently applied to mapping the human cortex. More than 50 years ago, Hill and Keynes first reported that optical changes occurred in nerves from an invertebrate when electrically stimulated.[13] They noted that upon electrical stimulation, the opacity of a nerve increases and light-transmission through the tissue is reduced; this optical change could be quantitatively measured with the simple photocells that were available in that era. These observations demonstrated that the light scattering properties and the electrical activity of axons were correlated, and served to motivate a series of further studies on invertebrate preparations over the subsequent decades, ending in the early 1970s with Larry Cohen's extensive set of studies on the birefringence changes that single neurons undergo when firing action potentials.[14] The rebirth of interest in optical brain mapping techniques occurred following a pair of publications in *Nature* in 1986 where researchers applied the newly available video and computer imaging technologies to studying primate visual cortex.[15,16] Those studies demonstrated the power of optical imaging by providing high resolution maps of the functional organization of visual cortex. Researchers showed that it was possible to generate striking images of ocular dominance and orientation selectivity columns from data acquired during a single experiment (Figure 113b.2).

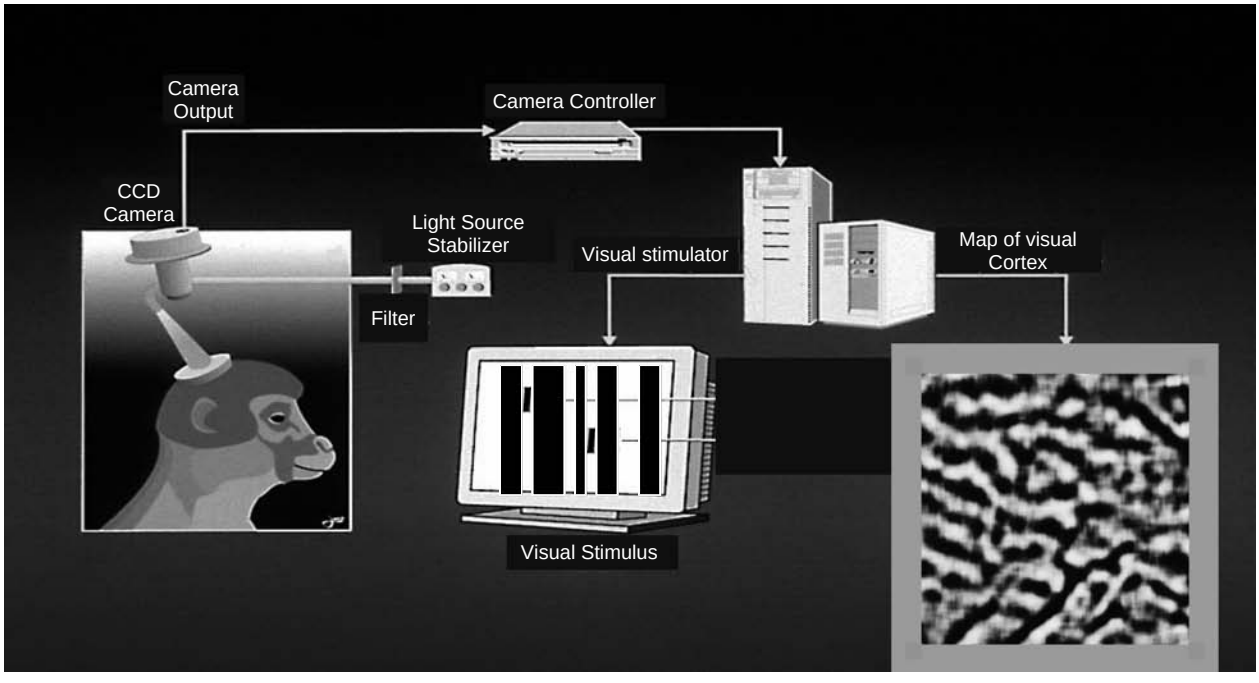

Figure 113b.2 Optical imaging of the functional organization of monkey visual cortex. The power of optical imaging was made apparent through studies on primate visual cortex published in the 1980s by two independent groups of researchers.[15,16] Those studies demonstrate that maps generated in single experiments with optical imaging could reveal patterns of cortical organization that were previously only made apparent through years of electrophysiological recordings from single neurons. Optical imaging is now a commonly used tool by visual cortex researchers. Illustrated here is a typical experiment, similar to the early pioneering studies. A cranial window is created over primary visual cortex and a CCD camera mounted to a microscope. A computer display is used as a 'visual stimulator' to display moving patterns to the monkey. Optical images of the visual cortex are acquired while each eye is stimulated independently while the other eye is closed. If left-eye images are subtracted from right-eye images, the ocular dominance columns become visible as zebra-striped patterns. Cortical neurons in each cortical column respond only to either left-eye or right-eye visual stimuli.

Previously, mapping of this cortical organization required data provided by hundreds of delicate electrophysiological experiments that involved recording the activity of single neurons one at a time, for which Hubel and Weisel were awarded a Nobel Prize.[17]

Motivated by the success in these primate studies, optical imaging techniques were finally adapted for use in the operating room in 1992.[18] These first human studies demonstrated that functional and epileptic activity could be mapped in patients undergoing surgical treatment for epilepsy.

Physiological mechanisms underlying generation of optical signal

It is known that there are at least three distinct physiological components that generate activity-evoked optical changes in cortex: (1) blood volume changes; (2) blood oxygenation changes; and (3) blood-independent changes likely involving activity-evoked swelling of glial cells.[4] It is hypothesized that it is possible to dissociate and map each of these types of changes independently by illuminating the cortex with light at the appropriate wavelength.[19]

Optical changes related to cortical hemodynamics: activity-evoked blood volume and blood oxygenation

Much of what is known about the responses of the cortical vascular network to increases in neuronal activity was elucidated by George Mchidlishvili and his co-workers through-out the 1970s and 1980s.[20,21] This work demonstrated that the microscopic pial arterioles lying on the surface of the cortex are entirely responsible for the redistribution of blood in the cortex during increases neuronal activity. The critical fact is that when neurons fire action potentials, the smallest pial arterioles near the firing neurons dilate. Work from the laboratory of H. R. Winn has shown that a pial arteriole typically dilates by approximately 30% from its resting diameter, and this vascular response is highly localized to within microns of firing neurons.[22] Such small dilations result in a tremendous amplification in blood flow, since flow is proportional to the fourth power of vessel diameter.[23] It is believed that only the terminal ramifications of the surface arterioles, prior to their penetration into the depth of the cortex, dilate. That is, the veins, larger arteries, and branches of vessels that penetrate into the cortex are thought not to respond to neuronal activation.

Two important consequences follow from the activity-evoked hemodynamic changes just described. First, since blood flow is dramatically increased by the dilating arterioles, the transit time of blood in active cortical tissue is sharply reduced, leading to an *increase* in blood oxygenation in the draining venous network. Indeed, this activity-related increase in blood oxygenation is the source of the signal measured by Bold fMRI.[24] Second, the localized increases in the diameter of the pial arterioles near firing neurons represent a localized *increase* in the blood volume of the cortical tissue. Since oxygenated (HbO_2) and deoxygenated (Hb) hemoglobin differ in the way the absorb light of various wavelengths, optical

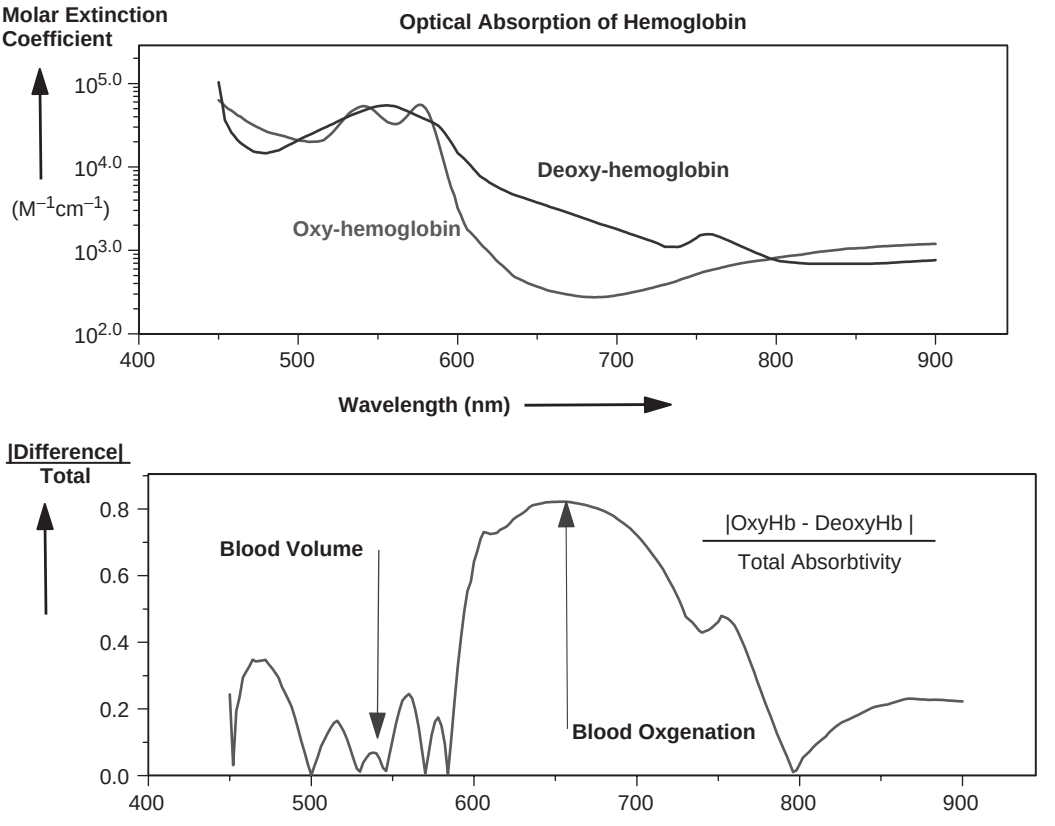

Figure 113b.3 Absorption spectra of oxy- and deoxyhemoglobin. These graphs show how much light is absorbed by hemoglobin at various wavelengths throughout the optical spectrum. The upper graph shows the spectra plotted logarithmically. The points where oxy- and deoxyhemoglobin intersect are called 'isobestic points', and represent wavelengths that are optimal for measuring changes in blood volume. Points on the graph that are maximally different are suited for mapping changes in the oxygenation state of hemoglobin. The bottom graph shows the normalized differences between oxy- and deoxyhemoglobin plotted on a linear scale.

imaging techniques can be applied to take advantage of these changes. Figure 113b.3 shows graphs of the optical properties of blood, where the upper plot shows the optical absorption spectra of Hb and HbO_2 (i.e., graphs of how much light Hb and HbO_2 absorb at each different pure wavelength); since they are plotted logarithmically, subtle features are difficult to distinguish. Hence the data has been re-plotted on the bottom as a single graph of the absolute differences between Hb and HbO_2 optical absorbances. Several features of these spectra are important to note. First, there are several 'isobestic points' – wavelengths at which the absorbances of both Hb and HbO_2 are indistinguishable (e.g., 530–535 nm and 800 nm). Since the absorption spectrum of hemoglobin at these wavelengths is independent of its oxygen state, and hence is only dependent upon the total number of hemoglobin molecules as consequence of Beer-Lambert law;[25] thus isobestic points represent ideal wavelengths to measure blood volume changes independently of blood oxygenation changes. Since Hb and HbO_2 have identical values at isobestic points, wavelengths representing isobestic points are located where their differences in light absorption vanish (i.e., where bottom graph touches the *x*-axis). Second, there are wavelengths at which Hb and HbO_2 are maximally distinguishable (660 nm and >900 nm). Consequently, these 'oxygen sensitive' wavelengths are ideal for optically monitoring changes in the oxygen state of blood, and are represented as maximal values in the bottom plot.

Imaging at blood volume wavelengths (530–535 nm) has been shown to reveal different patterns than imaging at blood oxygenation wavelengths (660 nm). For example, optical imaging of the human cortex during electrical stimulation shows that blood volume-selective wavelength are distributed diffusely throughout the tissue where the neurons are firing. However at the blood oxygenation-selective wavelength, the largest changes are restricted to the draining veins.[19] The significance of this is that optical imaging of blood volume (rather than blood oxygenation) provides the most accurate localization of neuronal activity.

Intraoperative localization of epileptic cortical activity

Ictal-like afterdischarge activity, as elicited by direct electrical stimulation of the cortex has been the most commonly mapped type of epileptiform activity mapped with optical imaging (Figure 113b.4). A more recent study suggests that IIOI may be useful for localizing tissue regions involved in the generation of spontaneous interictal activity.[19] Shown in Figure 113b.4 is data from an experiment in which the cortex of an awake patient was stimulated with a current set slightly above the afterdischarge threshold for triggering ictal seizure activity; recordings with EEG electrodes place on the cortical surface were acquired simultaneously for comparison to the optical maps (recording electrode marked as 'r' in the upper-left greyscale image). The image represents a 4 cm 4 cm area of cortex, where the distance between the bipolar stimulating

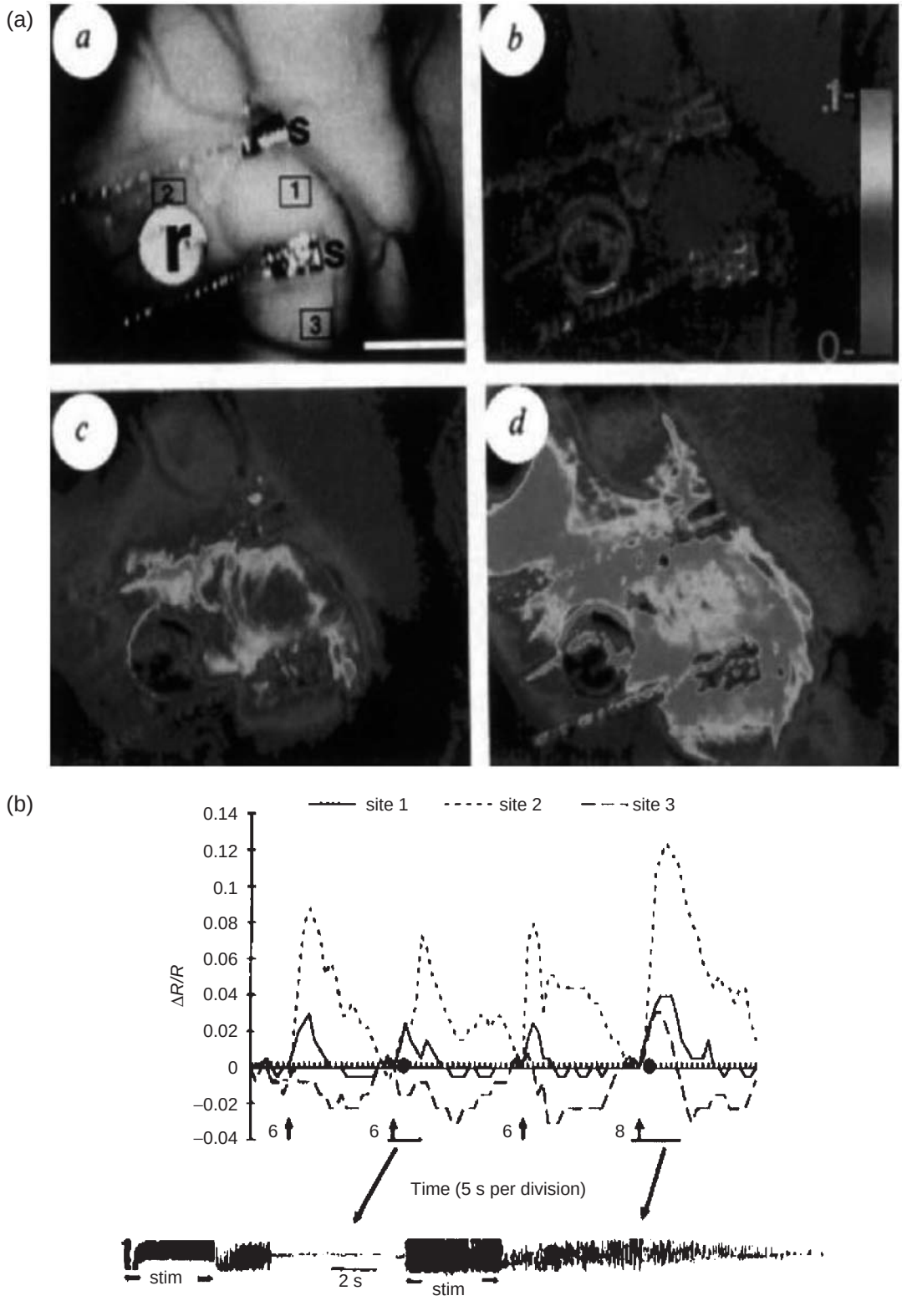

Figure 113b.4 Optical imaging of electrical stimulation-evoked ictal activity. Four consecutive afterdischarge episodes were elicited by direct electrical stimulation of the cortex with a bipolar stimulating electrode (marked 's' in the upper left a(a). a shows data acquired during two of the four episodes. Peak optical changes are represented as red. The first afterdischarge episode was less intense and of shorter duration than the second shown episode, as evidenced by the electrographic traces recorded by a surface electrode (marked 'r' in the upper gray-scale figure), shown as black traces on the bottom. Figure a(b) shows the optical image of baseline noise, and a(c) and a(d) show the peak optical changes evoked by each of the two afterdischarge episodes. Normalized optical changes from the three boxes labeled in a(a) are shown in b. The arrows represent stimulus application for four seconds and the number beside the arrow is the constant current stimulation intensity in mA. At the bottom of b are EEG traces from each of the four consecutive afterdischarge episodes. (Image adapted from previously published source).[18]

electrodes (marked 's') is approximately 1 cm. In this subject, different stimulation trials evoked afterdischarge episodes of varying durations and intensities, as the black and white electrographic recordings on the bottom of the figure demonstrate. In addition to representing data as pseudocolored difference-images, it is also possible to plot the absolute percentage change in the optical signal over time from various regions of interest. Optical changes from three different sites from the boxes labeled '1', '2', and '3', were plotted this way in the black and white plots immediately below the colored images. This quantitative analysis demonstrates that not only was a larger area of interest evoked involved in the spread of activity generated by longer-lasting afterdischarge episodes, but also the magnitude of the optical changes were large for more intense ictal activity.

Intraoperative mapping of sensory and evoked optical change

Other application of IIOS with significant practical potential is in the intraoperative localization mapping of sensory and language cortex. As an illustrative example applied to sensory localization, Figure 113b.5A shows an experiment where tongue and palate sensory cortex were first identified with electrical stimulation of the cortical surface of an awake

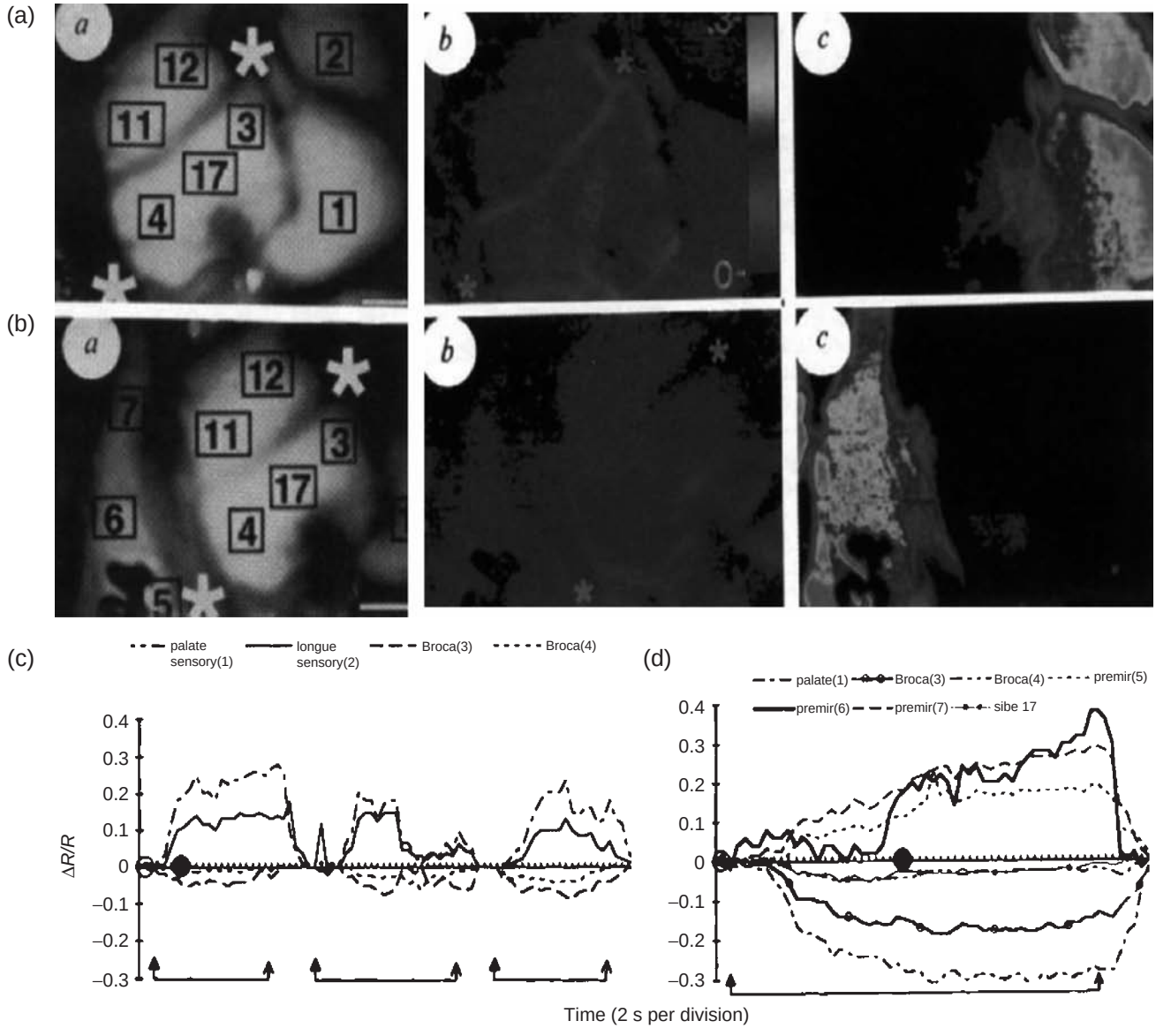

Figure 113b.5 Optical imaging of language and tongue motor sensory cortex. Anterior is to the left, posterior to the right, superior top and sylvian fissure bottom. Asterisks on the cortical surface are reference points a and b, where the field of view was slightly shifted forward. The numbered boxes in 4a(a) represent sites where electrical stimulation evoked palate tingling (1), tongue tingling (2), speech arrest-Broca's areas (3,4) and no response (5, 11,12,17). First the patient was instructed to move their tongue against their palate for 40 seconds and then allowed rest for several minutes; this tongue movement exercise was repeated three times. The solid circle in C indicates when tongue movement began. Next the field of view was shifted slightly forward to incorporate more of premotor cortex. After viewing several blank slides (control), the patient was then required to name pictures appearing every 2 seconds. b(c) shows optical changes acquired near the end of this naming exercise, showing that the maximal changes were located in the premotor region. The solid circle in the time axis in d shows when the naming began. Normalized optical changes acquired during tongue movement and naming are plotted in c and d. (Image adapted from previously published source).[18] (See Color plates.)

patient (i.e., stimulation at cortical sites marked '1' and '2' in the upper left grayscale image elicited a tingling sensation). Optical images were acquired while the patient moved their tongue from side to side against the roof of their palate. This is similar to the data shown in Figure 113b.1 though from a different patient.

Intraoperative mapping of different aspects of language function is currently a time consuming procedure. IIOS has yielded data suggesting it may be a valuable technique for localizing multiple language sites and functions in cortex. Data has been acquired from the language dominant hemispheres of awake patients in which imaging of the posterior inferior frontal and posterior temporal cortex was performed during that naming of common objects presented to the patients on a portable slide projector. Initially, essential naming sites were identified by electrical stimulation mapping. Optical maps were acquired during both overt and silent naming and compared to the maps of tongue motor and sensory cortex on the same patient (Figure 113b.5(b)). In posterior frontal cortex, optical changes occurred immediately in front of face motor cortex during overt naming, where no optical changes were observed during tongue sensory stimulation. The maximal optical changes occurred more frontally to sites at which electrical stimulation caused speech arrest. Graphical quantitative analysis of the optical changes revealed that the optical changes were initiated in the inferior frontal gyrus, and over time spread out form the site marked '6' towards the sites marked '5' and '7' (Figure 113b.5(c)). This demonstrates that optical imaging yields both spatial and temporal information of cortical language processing. Further investigation is required to determine which aspects of the optical maps provide the most reliable information for preservation of the patient's speech.

Optical imaging experiments over posterior temporal cortex also were correlated to sites of speech arrest during electrical stimulation, however in a more complex manner. Specifically, optical changes were observed in a wider area than had been identified by electrical stimulation, though no optical changes were observed in sites which naming was not interrupted by electrical stimulation (Figure 113b.6). These observations suggest that cortical areas critical for naming may extend to areas immediately surround those sites identified by electrical stimulation alone. During one experiment, the temporal resection was performed close to an electrical stimulation-identified posterior temporal language site. Naming exercises were performed by the patient during the procedure to help guide the resection, the resection being stopped when naming errors appeared, as identified by the solid line in Figure 113b.6. Experience has showed that resections stopped at that point do not lead to permanent language

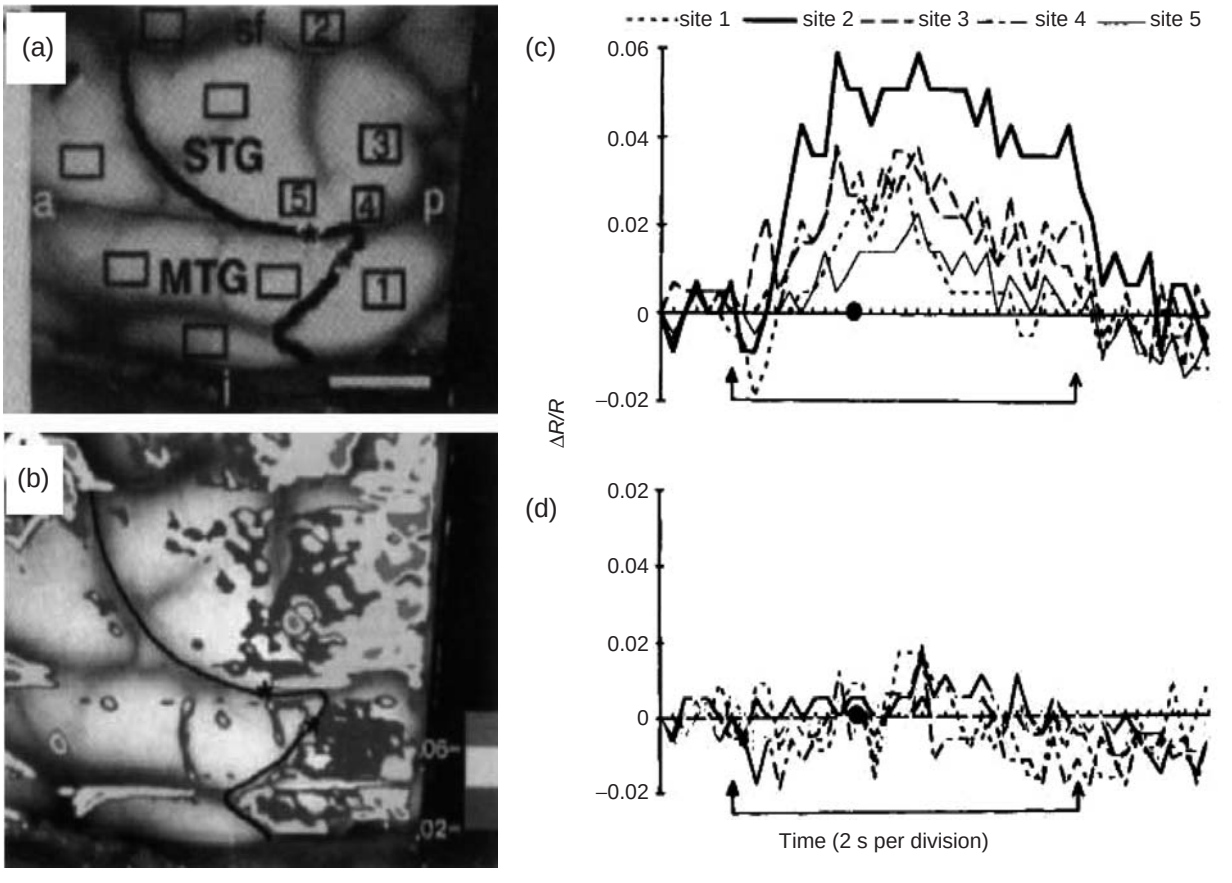

Figure 113b.6 Optical imaging of changes in Wernicke's area. a Shows dominant temporal lobe with sites 1, 2, 3, 4, and 5 representing sites where speech was identified with either electrical stimulation (sites 1, 2, and 3) or when the resection (thick black line) came from the anterior (a) to the posterior (p) in the temporal lobe (sites 4 and 5). Open boxes represent where electrical stimulation had no effect on naming objects. b shows the peak optical changes with the greatest changes localized in areas that were important for naming. c Shows optical changes during naming (arrows below axis show the start and end of the naming) at sites important for language. d shows optical changes at sites not found to be critical for naming. (Image adapted from previously published source).[18]

deficits, and this patient experienced no permanent problems. Optical imaging maps coincided exactly where the surgical resection was stopped. This provides strong evidence suggesting that IIOS can provide sufficient information for the mapping of language sites in a way that can used to guide cortical resections for the preservation of function.

Future prospects: optical imaging as a practical intraoperative tool

Although IIOS is still a research technique, it has considerable potential to be a practical intraoperative tool for the localization of epileptic and functional areas. In the authors' opinion, optical technologies and techniques have been developed to the point where it will soon be possible to take the next step of performing clinical trials aimed at validation and approval of IIOS for clinical applications. There are still several aspects of research and development which would help to further improve the IIOS technique. First, further research elucidating the relationships between the optical changes and neuronal activity will help establish the ultimate resolution of IIOS. Second, continuous improvements in computer and optoelectronic technologies are continuing to be more powerful and less expensive, and currently IIOS is the least expensive brain-mapping modality.

As described in this chapter, it has already been demonstrated that imaging of optical changes in the human cortex can provide dynamic, accurate maps of language, motor and sensory areas in human cortex. Further, the dynamic spread of epileptic activity throughout the cortex can be mapped. A further future development will be the use of noninvasive optical mapping techniques for preoperative evaluations, to support the intraoperative techniques. Such noninvasive methods are currently used in a number of academic laboratories.[26] These noninvasive techniques use longer wavelength near-infrared light which can monitor activity through the intact cranium. Although the noninvasive techniques have significantly reduced resolution by comparison to intraoperative techniques (i.e., centimeter resolution as opposed to micron resolution), these methods may supplant the need for current methods that are used for preoperative language localization and the mapping of seizure onset sites in patients suffering from neocortical epilepsy.

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114 Functional localization of the cortex with depth electrodes

J-P Vignal and P Chauvel

The two objectives of intracranial recordings, electrocorticography (ECoG, subdural electrodes) and stereoelectroencelography (SEEG, depth electrodes) are to define the cortical region whose removal will result in complete cessation of seizures and to estimate the functionality of the cortical areas to be resected as well as related cortices. The cortical functions can be localized on the basis of the analysis of clinical signs and symptoms of the seizures themselves but more specifically from the results of electrical stimulations. If there are many publications on the mapping of the cortex on the basis of subdural electrodes, the publications based on the use of depth electrodes are rare. ECoG realizes a systematic but superficial exploration of the cortex. SEEG proceeds as a more targeted exploration of the cortical volume and its analysis is based above all on the spatio-temporal dynamics of spontaneous or evoked discharges. All the cortices can be explored, particularly in medial structures, but also the infolded cortex buried in the depth of intermediate sulci. The electrical stimulation is delivered in the cortex, or in the white matter, or in both. The obtained response can be the consequence of a local activation, or of a local activation triggering propagation through a neuronal network thus involving regions situated at some distance from the stimulated point. This underlies the way to interpret the stimulation effects according to the fact that it has provoked an afterdischarge or not. However, outside the primary sensory cortices and the motor cortices local afterdischarges often represent the condition to obtain cognitive or behavioural effects.

The functional localization of the cortex is constrained by the position of the electrodes. The position of the electrodes during SEEG is pre-established according to the hypothesis based on surface localization of the interictal paroxysms, of the recorded seizures and of the imaging data. The number and the position of the electrodes are optimized in order to achieve three goals: to localize the origin of seizures, to describe the ways of propagation, to identify the functions of the areas involved in the 'epileptogenic zone' and of the related areas. Bipolar stimulations were carried out between two adjacent electrode contacts. The stimulation frequency may vary from 1–50 Hz. Stimulation of the low threshold cortices (mainly the sensori-motor cortex) is performed through shock of short stimuli (~1 ms) at low frequency (1–5 Hz). In these cortices, 50 Hz stimulation provokes supra-threshold tonic responses, with a high risk of artificial tonico-clonic seizures. The associative and premotor regions have to be stimulated with a 50 Hz frequency. The stimulation intensity varies from 0.25–6 mA. The stimulus is a biphasic rectangular wave pulse, with each pulse lasting 1 ms.

The consequences of an electrical stimulation performed with depth electrodes differentiate themselves from a stimulation with subdural electrodes mainly on two points. With depth electrodes, the stimulation produces a more intense and focal perturbation. While with subdural electrodes, the motor cortex is stimulated with a 50-Hz frequency and with the intensity that can go up to 15 mA, it could be hazardous to stimulate the motor cortex with depth electrodes at 50 Hz, a single bipolar shock of 1 millisecond being enough to obtain a motor response. The sensitivity of this method is probably higher. We do not have any example where the motor cortex could not be identified, contrary to subdural stimulations.[1] The disadvantage of this very focal character of the stimulation is observed when it is necessary to synchronize a more extended cortical set to obtain a behavioural response like in language areas investigation. The second difference is the capacity to disturb neuronal networks by the stimulation of fibers underneath the cortex. The alterations imposed to cortical physiology can then be more complex and the interpretation in terms of deficit versus activation remains poorly understood.[2]

Localisation of somato-sensory and motor cortex

The localization of the somato-sensory and motor cortices has been established on the basis of subdural stimulations. Numerous maps which show the somatotopic organization of these areas along the central sulcus have been published.[3] This method, easy to implement, is the most widely used. It allows making a picture of the motor cortex from the surface. However, taking into consideration the complex convolutions of pre- and postcentral gyri, only a superficial part of the motor cortex can be stimulated, and the stimulation of the paracentral lobule is difficult. The functional maps obtained by stimulation of depth electrodes during SEEG represented, for their authors, localisations of fibers efferent from or afferent to the cortex.[4] Exploration of right parietal epilepsy. Electrodes P and L are placed to investigate the role of the sensori-motor cortex.

The stimulation of P by a 1 Hz shock at increasing intensities from 0.5–1 mA.

- P1–2: responses of left vastus lateralis
- P2–3: responses of left iliopsoas and vastus lateralis
- P3–4: no response
- P4–5: responses of left pectoralis major and deltoid
- P5–6: responses of left deltoid
- P6–7: responses of left deltoid
- P7–8: responses of left deltoid and triceps brachi
- P8–9: no response
- P9–10: tingling at the external side of the left wrist
- P10–11: tingling at the back side of the hand
- P11–12: idem
- P12–13: no effect

The stimulation of L is negative.

Interpretation: Taking into consideration the shape of the central sulcus, the electrode P explored along its trajectory the primary motor cortex of the leg and of the arm in their proximal parts and the primary sensory cortex of the hand. It crossed the central sulcus between leads 8 and 9, the latter in the upper limb distal representation in SI and the former in the proximal representation in MI, the two representations being not exactly facing each other. There is no need in this case to imply a relay of white matter stimulation to interpret this sequence.

Case 2. Exploration of epilepsy of the left operculo-temporal region. A cyst was evident in the left frontal opercular region. The etiology of this epilepsy was unknown. But seizures had been observed starting from the neonatal period. The perisylvian region showed a morphological change the consequences of which have to be cleared. He was a right-handed man but the Wada test showed the absence of speech arrest during injection into the left carotid. The objective of the electrodes P′ and S′ was to explore the motor cortex. The electrodes T′, H′ and J′ explored the superior temporal gyrus up to the junction with the parietal lobe. O′ was situated in the region of the Broca's area.

Stimulation of P′ at 1 hertz and 1 mA intensity:

- P′1–2: responses of the right deltoid
- P′2–3: responses of the right deltoid
- P′3–4: responses of the right deltoid
- P′4–5: responses of the wrist flexors
- P′5–6: responses of the wrist extensors
- P′6–7: numbness of the back side of the right hand, rhythmed by stimulation
- P′7–8: no response
- P′8–9: no response

Interpretation: Electrode P crosses the central sulcus as in the preceding case, thus the sensori-motor cortex; the stimulations activate the cortex, but possibly also the corticospinal fibres (after reconstruction of the electrode trajectory in Talairach's atlas).

Stimulations of S' at a frequency of 1 hertz and the intensity of 1 mA:

- S′1–2 and S′2–3: responses of the flexors muscles of the right wrist
- S′3–4: responses of the flexors muscles of the elbow
- S′4–5: responses of the thumb flexor
- S′4–5 to S′ 9–10: no response

Interpretation: The responses are the consequence of the stimulation of the corticospinal fibres.

The stimulations at 50 Hz for 5 seconds also provide data on the functional capacity of the explored cortex. No stimulation has provoked either phasic troubles or speech arrest. The stimulation of K′11–12 at 2.5 mA provoked an afterdischarge for 3 seconds on the external leads of K′ accompanied by a contraction of the right hemiface. The stimulation of K′10–11 provoked a sensation of swarming in the right cheek and a afterdischarge for 7 seconds on the external leads of K′ and on the external B′. The stimulation of J′8–9 at 2.5 mA provoked an afterdischarge for 3 seconds on external S′, external K′, external P′, external B′ and external J′ and a contraction of the right labial commissure followed by a clonic fall of the right arm. The interpretation of these responses is complex because of a local afterdischarge and, in one case, extended afterdischarge, and because the stimulations at 1 Hz of these electrodes had not evoked any response. However, it shows a reorganization of the sensori-motor opercular cortex.

The stimulation of H′2–3 at 1.5 mA evoked a sensation of painful heat in the right ear. During the stimulation of H′4–5 at 1.5 mA, the patient described an impression of turning with her bed in the room.

The excision of the cortex implied the region where electrodes S′, J′ and K′ were implanted. During the postoperative period no motor, sensitive or language deficit was observed.

The localization of the somato-sensory and motor cortex is based on the position of the electrodes correlated to the anatomic location reconstructed in three dimensions using angiography and stereotaxic MRI.

Localization of the supplementary motor area (SMA)

The stimulation of SMA with intracerebral electrodes allows provoking motor manifestations close to those observed during stimulations in corticography. To localize the SMA, stimulations at 50 Hz frequency and at 1–3 mA intensity have to be used. The stimulations by shock of 1 ms duration are inefficient. Talairach and Bancaud[4,5] localized the SMA at the medial aspect of supetior frontal gyrus using this method. The occurrence of diverse motor signs has been reported by Chauvel *et al.*[6] Speech arrest either accompanied or not by motor arrest was reported in 73% of positive stimulations. The tonic motor raising and abduction of the contralateral upper limb in 42% of the stimulations, deviation of head or eyes occurred in 31% of the stimulations of the medial cortex. The motor modifications of the arm were predominant over the proximal musculature realizing a movement of abduction and of rising of the shoulder. Deviation of head and eyes was tonic and contralateral to the side of the stimulation. Vocalizations were frequent (27% of the stimulations). A motor modification of the inferior limbs was rare and consisted of an extension associated with an abduction of the leg. Chauvel *et al.* insisted on the association of these signs. He remarked that speech arrest frequently occurred alone (50% of the total of positive stimulations) and with the weakest intensity values. A movement of the inferior limb or an adversion of the head rarely occurred in isolation (10.6% and 2.2% of the stimulations). These observations, an analysis of the

intensity values and of the plots on which these signs were obtained allowed Chauvel *et al.* to discuss the respective roles of the SMA and of the lateral cortex of areas 6 and 8. Only the coactivation of these two regions could explain the emergence of some signs such as the adversion and the postural tonic modifications of the superior limb.

Negative motor areas have been localized in the lateral and medial frontal cortex including SMA using high frequency cortical stimulations with subdural electrodes.[7] The stimulations by shock (1 Hz) at intensities from 0.4–3 mA provoke negative myoclonia. These negative myoclonias (more precisely a brief silent period at EMG) could be evoked in an extended cortical zone including the premotor cortex (including the SMA), the motor cortex and the somatosensory area.[8] Only the stimulations of the SMA provoke the periods of silence which do not depend on the intensity of stimulation suggesting a particular role of this structure in the organization of negative myoclonias.

Localization of Broca's area

The high frequency stimulation of Broca's area provokes speech arrest sometimes preceded by paraphasia.

Case 3. Exploration of epilepsy of left prefrontal regions in a right-handed patient aged 18. The Wada test confirmed dominance of the left hemisphere for language. MRI showed a dysplasia in the frontal interior gyrus. The purpose of the exploration is to study the relation between the lesion and the epileptogenic zone and to define the posterior limit of cortical excision in localizing Broca's area.

We sum up the main results of the stimulations. The stimulations of O′ at 50 Hz for 5 seconds at 2.5 mA and 3 mA had no effect.

Stimulation of P′ at 1 Hz at 3–6 mA:

- from P′2–3 to P′8–9 successively: periodical twitch of the right labial commissure, then of the right hemitongue, then of the superior lip or muscles of the chin.

Stimulation of R′ at 50 Hz for 5 seconds at 1.5 mA:

- from R′ 1–2 to 7–8: no effect
- from R′8–9 to R′11–12: speech arrest after some paraphasia

Stimulation of I′ at 50 Hz for 5 seconds at 1.5 mA:

- from I′1–2 to I′8–9: no effect

Stimulation of I′ at 50 Hz for 5 seconds at 2.5 or 2.8 mA:

- from I′ 1–2 to I′ 4–5: no response
- of I′5–6, I′ 6–7, I′ 7–8, I′8–9: each one of these stimulations provoked a seizure. These seizures started by speech arrest or by paraphasia with sometimes a start of jargonophasia. Then we observed a smile, face flushing, and gestural activity repeated twice: the patient crossed and uncrossed his legs, scratched his thorax with his left hand, hit his stomach with the right hand and then with his left hand. The discharge onset involved the lateral leads of O′, of R′, of A′ and the medial leads of F′. Then, the discharge spread to T′, H′. During the postictal period a language deficit was noted

These results allowed to conclude that P′ was situated in the face motor cortex, R' in Broca's area, while I′ was in the epileptogenic zone, but outside Broca's area. Excision of the lesion (DNET) and cortex around I′ and O′ did not provoke any language deficit. There is no study evaluating the reliability and the sensitivity of this method to localize Broca's area.

Localization of the sensory areas

The stimulations of the superior temporal gyrus provoke hallucinations and auditory illusions which allow localizing the auditory cortices.[9] De Graaf *et al.* showed that 76.7% of the electrodes in the temporal superior gyrus provoked auditory responses. The stimulations were delivered at 50 Hz for 5 seconds with intensity varying between 0.5 and 2.5 mA. There was no relation between the existence of a afterdischarge and obtention of an auditory response. The study of 180 stimulations of the superior temporal gyrus reported 32% of elementary hallucinations and 30% of illusions. The hallucinations were described as whistling, buzzing, and sizzling usually situated in the contralateral ear by the patient. Illusions were reported as modifications of intensity or tonality of the observer's voice or of the patient's own voice. The illusion of reverberation or echoing was also frequent. These illusions could be unilateral as well as bilateral. Complex auditory hallucinations were exceptional, contrary to the data obtained in electrocorticography by Penfield and Perot.[10] For de Graaf *et al.* this difference could be explained by the fact that Penfield and Perot stimulated with monopolar electrodes the surface of the cortex in patients who often presented seizures including auditory hallucinations. So, the hyperexcitability of the stimulated region, added to the technique of stimulation, allied to engage a larger cortical network as a result of stimulation. De Graaf *et al.* showed that it is possible with the stimulations to discriminate with precision between the primary and secondary auditory cortex and associative auditory areas in the superior temporal gyrus and temporal plane.

No auditory responses were provoked outside the superior temporal gyrus.

The localization of the gustatory cortex presents less interest for surgical planning, but is important for localizing seizure onset. The gustatory cortex is localized in the insula and in the frontal operculum. A secondary gustatory area is described in the orbito-frontal latero-caudal cortex. Hausser-Haw and Bancaud[11] described nine sites where the stimulation provoked a brief and isolated gustatory hallucination without an afterdischarge or with a local afterdischarge. They identified six different regions. In four cases the hallucination was provoked by the stimulation of the rolandic operculum and of the parietal operculum in one case. Two of these patients did not present any gustatory hallucination during their seizures. The other sites were amygdala in one case, the hippocampus in another one, the medial aspect of T1 in one patient and the anterior part of T2 in one patient. It must be observed that all the stimulations were right sided. All the stimulations had been delivered at 50 Hz with the exception of one case done at 2.5 Hz. These hallucinations were usually unpleasant. The opercular rolandic region plays a major role in the

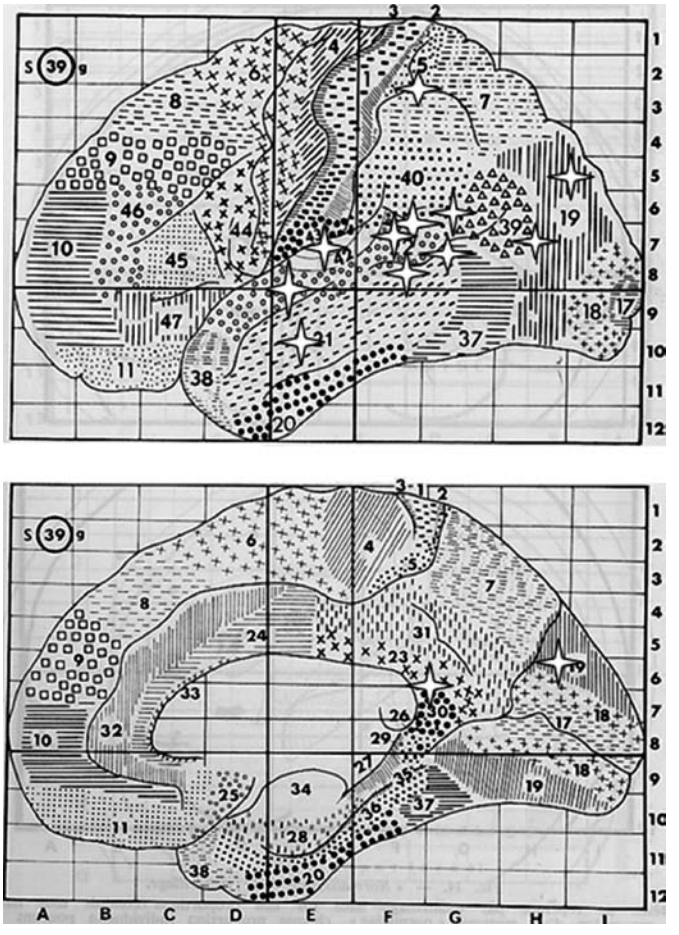

Figure 114.1 Location (✧) of 31 stimulations which evoked vertigos (19 patients).

emergence of gustatory hallucinations, either directly because of the location of the gustatory cortex or indirectly because of its connections with the temporal lobe, especially amygdala facilitated by the presence of an epileptogenic zone. Obtaining a gustatory hallucination by stimulation with subdural electrodes seems rare and has not been reported.

Vestibular projections are situated near the somatosensory face representation and the limit between the somesthaetic cortex and the motor cortex. Kahane *et al.*[12] defined vestibular manifestations as an illusion of rotation or of moving which concerns the patient himself or the environment. These authors showed that the sites the stimulation which induced a vestibular illusion were widely distributed in the lateral temporal and parietal cortex, with predominance in Brodmann areas 40, 21, and 22 of. The stimulations were delivered either at 50 or 1 Hz with intensities between 1 and 3 mA. A personal unpublished study (Figure 114.1–2) performed from 160 SEEG found this dispersion in the parietal and temporal lobes. This dispersion was even more extended, especially by existence of numerous responses in the posterior cingulate gyrus (areas 23, 31). Using these responses, Kahane *et al.* postulated the existence of a vestibular temporo-perisylvian cortex which would be the homologue of the vestibular parieto-insular cortex of the monkey. However, the clinical interest of these vestibular responses for surgery is limited but they have proven to be useful for understanding seizure organization, even though the anatomical significance is still lacking.

Localization of the insula

Insula is involved in visceral and autonomic functions, particularly control of digestive motility, taste and cardiovascular regulation, and pain. A change in heart rate and in blood pressure is provoked by the stimulation of the insula in man.[13] These stimulations have been realized during surgery and after the ablation of the superior temporal gyrus. Apart from surgery, only SEEG allows exploring the insula. The publications on the stimulations of insula using depth electrodes have not studied their effects on the cardiovascular system.

The stimulation of insular cortex provokes visceromotor and viscerosensitive responses and somesthetic manifestations.[14] The responses have been obtained by stimulating at high frequency (50 Hz for 5 seconds at intensities between 1 and 5 mA), and exceptionally by stimulating at low frequency. Viscerosensitive manifestations were nausea and a sense of abdominal and thoracic fullness. Visceromotor responses were movements of mastication and lip smacking. Somesthetic responses were usually contralateral to the side of stimulation, sometimes bilateral and painful or not. Viscerosensitive and visceromotor responses were provoked by stimulation of the anterior insula, while somesthetic manifestations were provoked by stimulation of the posterior insula. Ostrowsky *et al.* showed a somatotopic organization of somesthetic responses, painful in the superior part of the posterior insula and not painful in the posterior insula of both hemispheres. These authors have not studied changes in blood pressure and in heart rate.

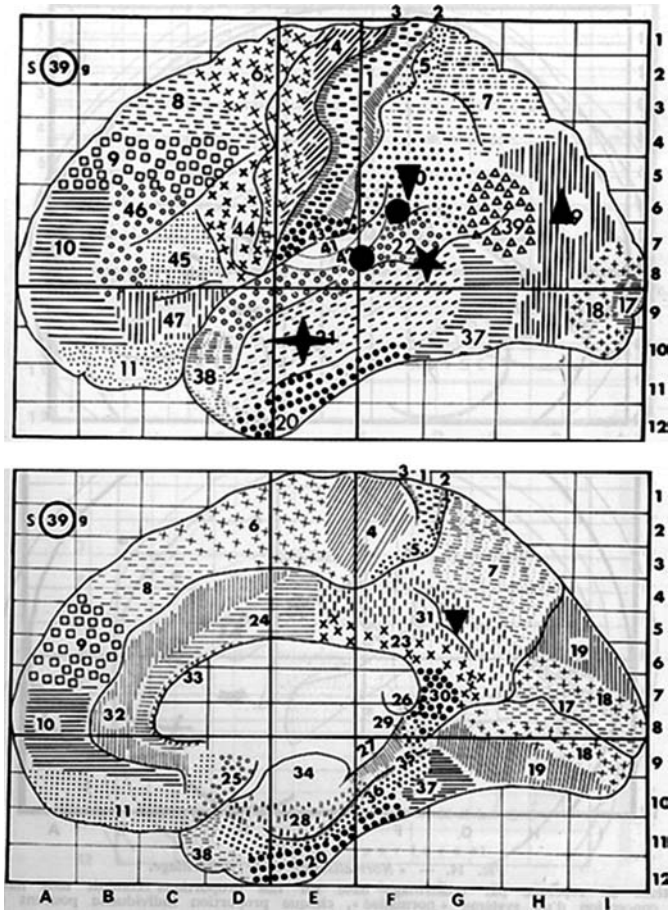

Figure 114.2 Responses to stimulation: 'gliding' (cross), 'falling' (star), 'environment turning from right to left' (triangle up), 'moving back' (triangle down), 'rolling sensation' (circle).

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115 Intraoperative cortical mapping and intraoperative electrocorticography

DR Nair and I Najm

Introduction

It was Hans Berger who first pioneered the technique of electrocorticography (ECoG) in humans by studying a patient with a recent trephined skull.[1,2] The early investigations using ECoG were concentrated on proving the cortical origin to the electrical activity being recorded. The use of ECoG during surgical exposure was performed on patients with brain tumors and finding that the distortion of ECoG seen from brain tumors resulted from damage to adjacent cortex and did not emanate from the tumor itself.[3] The focus of ECoG shifting to the field of epilepsy occurred in Montreal in the late thirties with Wilder Penfield and Herbert Jasper at the Montreal Neurologic Institute. Electrocorticography was an established and integral part of epilepsy surgery for several years. It was through the use of ECoG that Penfield established the concept of epileptogenic anatomic lesion and the epileptogenic physiologic lesion.[4] It became recognized that convergence of these two regions was often necessary for a good post-surgical outcome. There are further subdivisions that one can use to differentiate regions associated with epileptogenicity. For example the epileptogenic lesion may be mesial temporal sclerosis; this area is surrounded by a fairly large area of interictal epileptiform activity described as the irritative zone. The area which represents the detected ictal onset is referred to as the ictal-onset zone. The area which when removed by surgery and results in rendering the patient seizure-free is referred to as the epileptogenic zone (Figure 115.1). The epileptogenic zone can only be inferred retrospectively after surgery. For epilepsy surgery to be a success, it is usually required that these various defined areas converge to one particular region.[5] Intraoperative ECoG has played an important role in the management of medically refractory focal epilepsy. It has been used to map epileptic tissue, monitor after-discharges during cortical stimulation, and for prognostication of surgical treatment of epilepsy. Despite these clinical usage there has been relatively few studies that have evaluated the efficacy of its use.[6]

With the onset of new technology, namely high-resolution MRI scan, positron emission tomography (PET), single photon emission computed tomography (SPECT), in addition to video-EEG monitoring data, convergence of data can be used to plan epilepsy surgery at times without the need for ECoG. There are, however, times during the evaluation of a patient for epilepsy surgery when ECoG can still be of benefit. This chapter will underscore some of the utility, methodology, limitations, and future directions for intraoperative ECoG.

Indications

Around the late 1940s and early 1950s, temporal lobe epilepsy became a well-recognized syndrome in patients with focal epilepsy. This introduced the therapy of temporal lobectomy as a surgical therapy in these patients. Many of the centers doing this surgery initially used ECoG to guide their surgical resections. It was through the use of ECoG that it became clear that mesial resection in including amgdala, hippocampus, and uncal regions were required to gain full benefit from this surgery for the patient. Once the surgery became standardized, the role of ECoG became progressively less used in a number of centers. For those centers that continue the use of ECoG in these surgeries, the use of this modality is aimed at either evaluating a possible extratemporal lobe involvement that was previously undetected by the extraoperative evaluation, for monitoring after-discharges during cortical stimulation for localizing language function, or for the detection of persistent epileptiform activity around the margins of the initial resection to determine if further extension of the margins of resection is needed.[7] The use of intraoperative ECoG in patients with extratemporal lobe epilepsy is more frequently used. These patients often represent a challenge to the neurosurgeon when either the anatomic abnormality may be subtle or a clear localization of the extraoperative physiology may not be available.

Various issues which remain unclear with regards to intraoperative ECoG include:[8]

- Is it important to include the irritative zone in all cases of epilepsy surgery, or is the epileptogenic zone encompassed by the irritative zone?
- Is there prognostic value in cases of residual interictal epileptiform activity in the postresection ECoG?
- Does activation of epileptiform pharmacologically provide useful data?
- Are there morphological or topographical criteria that can be used to predict prognosis or perhaps pathology?

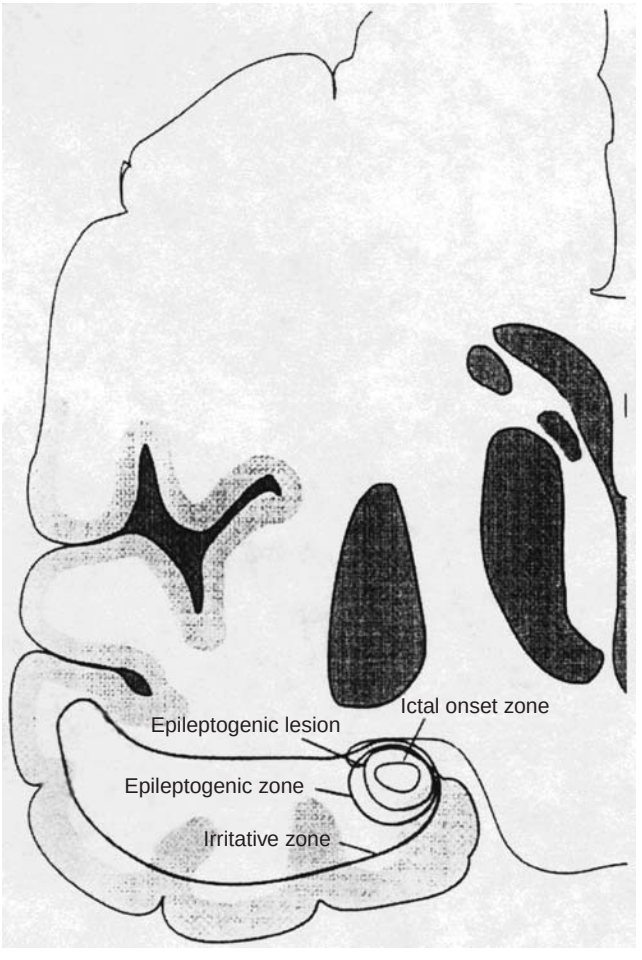


Figure 115.1 Outlining various regions converging to one particular cortical region. Taken from Dinner *et al.,* 1998.

Intraoperative ECoG is most often used as a guide in the operative management of patients with epilepsy to determine margins of resection. Intraoperative ECoG is also being used to address issues relating to prognosis for the patient as well as a research tool in the study of epilepsy.

Classification of abnormalities

There have been a variety of attempts proposed in order to create a systematic classification of ECoG abnormalities.

Interictal nonepileptic abnormalities

Spikes on the scalp-EEG are defined as a paroxysmal discharge lasting less than 80 msec with a mono- bi-, or polyphasic morphology followed by an aftergoing slow wave. Spikes recorded in the setting of use of subdural or depth recordings pose some unique challenges. For instance, it is not possible to differentiate various normal variants, such as small sharp spikes, in intracranial recordings.[9] This is due to the obvious lack of ability for recording ECoG in normal patients. Therefore, sharply contoured waveforms seen on ECoG have an unclear clinical significance. The requirements of amplitude, duration, morphology for intracranial recordings do not yet exist. In spite of this major limitation, most of the classifications have taken the aim of classifying spikes based on a quantification measure. Spikes were analyzed in one study by describing a *spike discharge rate*. This was defined as the percentage of spiking per unit time (seconds). The spike discharge rate was considered high frequency if greater than 50% and low frequency if lower than 50%.[10]

$$\text{Spike discharge rate} = \frac{\text{No. of seconds with any spikes}}{\text{Total seconds of recording}} \times 100$$

A number of continuous epileptiform discharges can be seen in ECoG. In a study of patients with cortical dysplasia, the frequency of spiking patterns appeared to be closely related to the outcomes of the patients, which will be described later in the chapter. In this study, three different patterns were discussed, one of which was essentially an ictal epileptiform pattern. The two other patterns may also represent an ictal pattern or a transition between ictal and interictal states due their very repetitive and rhythmic characteristics in three noted spiking patterns. *Continuous or quasicontinuous rhythmic spiking* consists of prolonged trains of spikes that occur rhythmic at 2–8 Hz and at times may be continuous or periodic (Figure 115.2). *Repetitive bursting patterns* refer to a high-frequency rhythmic polyspikes that appear suddenly and last from 5–10 seconds and then abruptly disappear. The frequency of these discharges varies from 10 to 20 Hz.[11]

Other classifications of interictal epileptiform activity differentiated spikes based on their frequency characteristics as well as their persistence. *Frequent spiking* was described as five or more spikes in 10 seconds. *Continuous frequent spiking* was described as *frequent spiking* defined above occurring every 30 seconds or more. *Very frequent spiking* was described as 20 or more spikes every 10 seconds. *Continuous very frequent spiking* was described as *very frequent spiking* as described above occurring in two bursts every 30 seconds or more. *Bursts of fast activity* was described as fast activity occurring at 10 Hz or higher in bursts lasting 2 seconds or more.[12]

Ictal epileptiform abnormalities

The presence of ictal recordings during intraoperative ECoG is a rare occurrence due to the time limitations of the recordings and perhaps due to anesthetic suppressive effects. In the study of Palmini *et al*., one of the three frequent spiking patterns were characterized as clear ictal events. *Repetitive electrographic seizures* refers to isolated spikes that progressively increase in their frequency and rhythmicity for several seconds and attain a frequency of 12–16 Hz that later may slow (Figure 115.3). This was followed by a focal slowing and attenuation of the recording.[11]

The use of intraoperative ECoG may be limited in the temporal and spatial resolution when compared with extraoperative ECoG, especially when it comes to the analysis of ictal epileptiform activity. This is particularly problematic when the ictal onset occurs at the edges of the plate. In this case, actual onset outside the margins of the plate cannot be ruled out.

Methodologic considerations

The technique of recording ECoG has remained essentially the same since its introduction. The machinery used to record ECoG does not differ substantially from that which is used to

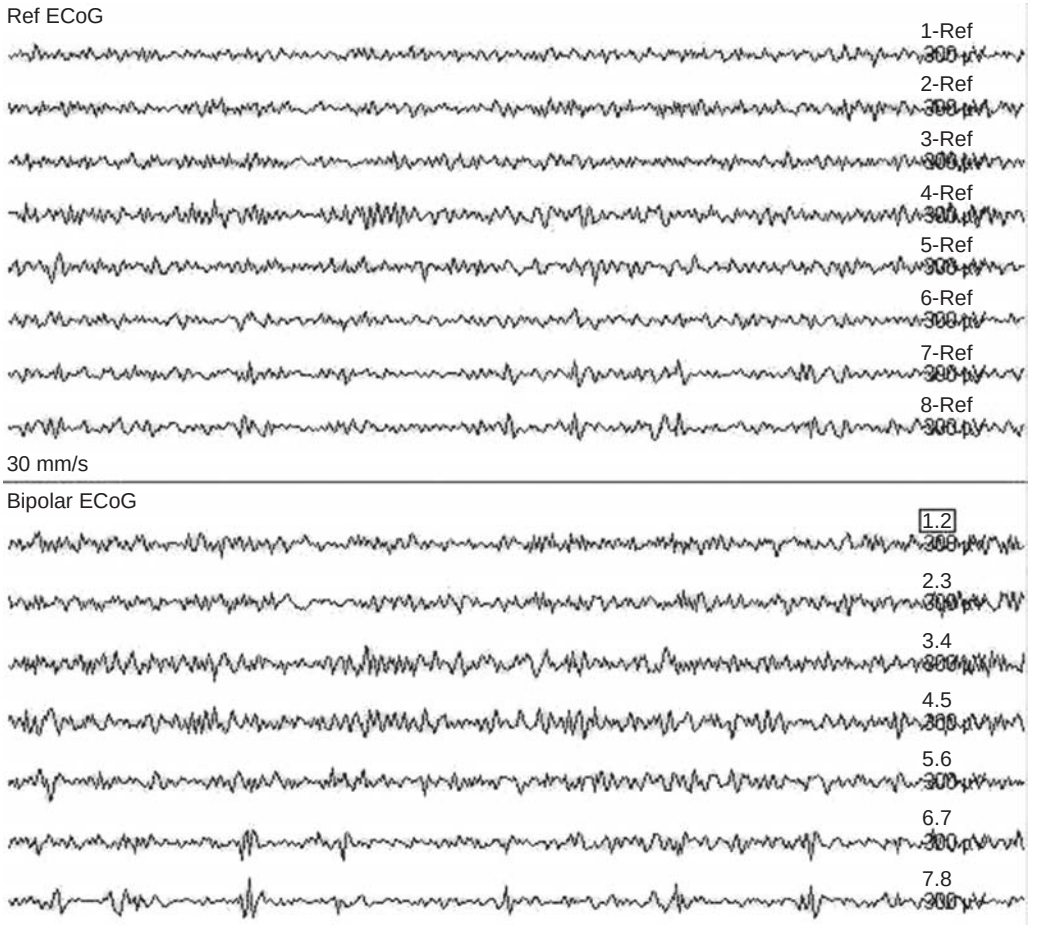


Figure 115.2 Continuous epileptiform discharges seen during intraoperative ECoG involving electrodes 7 and 8.

record standard EEG. There are a few considerations to note. The reference and ground can consist of needle electrodes placed into the surgical wound. The recording band pass filters can be 0.3 to 1.0 Hz to 70 Hz. Gain should be adjusted to prevent saturation of activity. A typical sensitivity range is 50–75 μvolts/mm.[13] The low-cut filter can be increased to 5 Hz if there are excessive slow waves obscuring the recognition of epileptiform activity. This filter setting will not allow for interpretation of focal slowing which is usually of little consequence when evaluating for epileptiform activity. Recordings can be made from 10 to 20 minutes in each position.

The recording is performed using a subdurally placed electrode array (Figure 115.4). The electrode sizes on these arrays can vary from 3 to 4 mm in diameter, embedded in medical-grade silicone plates, flexible Silatastic, or Teflon strips. The electrodes are made up of stainless steel or platinum (so that the electrodes are MRI compatible). The interelectrode distances is 1 mm and a variety of strips and grids can be made ranging from a 1 × 4, 1 × 8, 4 × 4, 8 × 8, etc.[5,14] These grids cannot be resterilized for use in another patient due to lack of adequate sterilization techniques. We tend to use larger arrays of electrode grids such as 4 × 4 intraoperatively, which allows for more spatial resolution and decreases time required for a more extensive coverage. For ease of recordings intraoperatively either 4 × 4 array over the lateral neocortical surface or strip electrodes for subtemporal regions are used. Several different positions/placements of the arrays are studied and regions of interest are marked on the cortex using sterile paper with numbers or letters or sterile marking pen. Previously electrode sets were used for recording. These sets were mounted in a holder attached to the patient's skull and were designed so that they were quickly moveable and were reusable. During the recordings immediate interpretation and communication of findings to the surgeon are required. Also, adjustments in sensitivities, filters, and time constants may be required. Total recording time is about 30–60 minutes, but can vary dependent on spike frequency and spatial distribution. Factors that may influence interictal spike frequency include inhalational anesthetic agents, opioids, antiepileptic medications, postictal state, and sleep.

Anesthetic requirements

Inhalational agents can have varying effects on epileptiform activity. There are some agents that have been known to activate epileptiform activity, such as enflurane. Other agents such as halothan, high-dose isoflurane or nitrous oxide can suppress epileptiform activity.[15] The effects of isoflurane on spike frequency may be dose-related and, based on varying reports in the literature, there appears to be a tendency to suppress spike frequency at concentrations of 0.5–1.5% but potentially increase spike frequency at a dose of 1.5%.[16,17] However, the study evaluating the higher dose of isoflurane was near the burst-suppression doses and brings up the question if these spikes have similar spatial relations and other characteristics to the patient's 'native epileptiform spikes.'

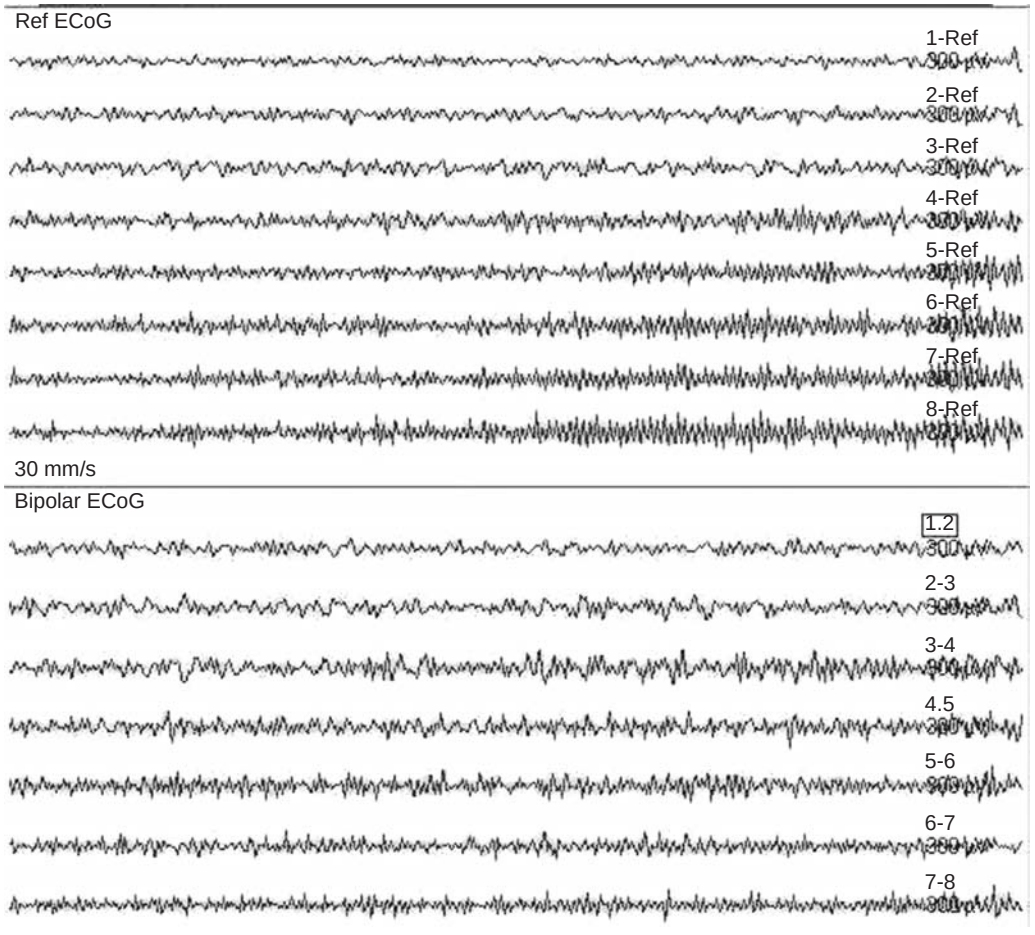
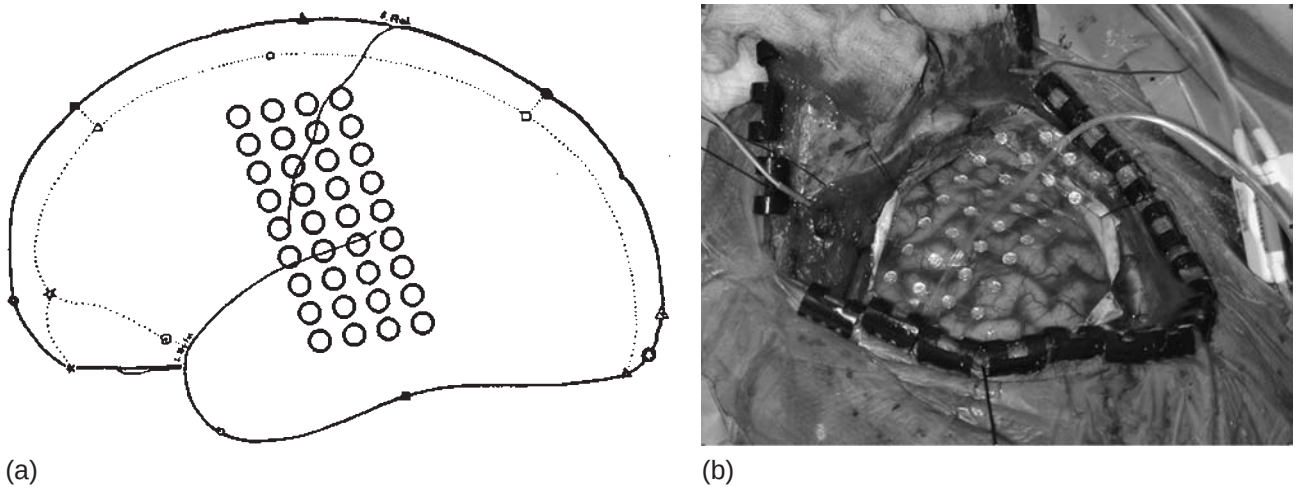


Figure 115.3 Electrographic seizure demonstrated during intraoperative ECoG beginning at electrode 8 and spreading to adjacent electrodes.

The role of nitrous oxide is also somewhat unclear in that a study evaluating spike frequency during intraoperative ECoG showed that there was no noticeable effect from nitrous oxide on epileptiform activity.[18] The use of light anesthesia such as using isoflurane with a narcotic drip is often selected for intraoperative ECoG. However, there is a higher risk for intraoperative awareness and recall for the patient. This method still has the potential for suppression of epileptiform activity as a result from anesthesia.

Opioids have the potential for proconvulsant properties. There is evidence to suggest that alfentanyl induces epileptiform activity. This is demonstrated by an increase in interictal epileptiform activity from the mesial temporal lobe as well as mesial temporal seizures associated with alfentanyl administration in one case.[19] There are various barbiturates, such as methohexital that are used to induce epileptiform discharges.[20–22] Again, the activation by methohexital may be inaccurate and demonstrate spikes not representative of the



(a) (b)

Figure 115.4 (a) Intraoperative map of subdural electrode 8 × 9 array placement. Diagram of photo shown. (b) Intraoperative photo showing subdural electrodes covering the left fronto-parieto-temporal cortex.

patient's native interictal epileptiform population.[23] Some authors suggest that it may be reasonable to consider the use of pharmacologic activation only in circumstances if the preexcision ECoG shows no interictal epileptiform activity.[23,24]

The use of three-dimensional MRI images with intraoperative stereotaxic guidance allows for the surgeon to locate the electrodes in relation to the patient's MRI anatomy as well as lesion (Figure 115.5). This modality offers additional reference to the surgeon beyond just visual inspection of the cortical structures.

Preexcision electrocorticography

The goal of localization of the epileptogenic zone is of primary importance in guiding epilepsy surgery. In cases where there is concordant data from noninvasive video EEG-monitoring, MRI data, other neuroimaging studies, the likelihood for further benefit from intraoperative ECoG becomes less likely. However, there are conflicting findings regarding the diagnostic yield and prognostic value of ECoG.[25–28]

Temporal lobe epilepsy

In a survey of several institutions, 68% of epilepsy centers showed that ECoG was being used during anterior temporal lobectomies, with 56% saying that the cortical resections were altered by the intraoperative ECoG data.[29] Some studies have shown that intraoperative epileptiform activity may have prognostic importance.[25–28] It is noted however that successful anterior temporal lobectomy has been preformed for epilepsy surgery without the use of intraoperative ECoG.[29,30] A study evaluating the predictive value of intraoperative ECoG in patients with unilateral hippocampal sclerosis undergoing selective amygdalohippocampectomy, showed that a greater percentage of patient with spikes recorded only in the mesiobasal temporal lobe remained seizure free more frequently than other patients studied.[31] A clear statement on prognostic significance for this finding requires the study of this issue with a large number of patients to verify these findings.

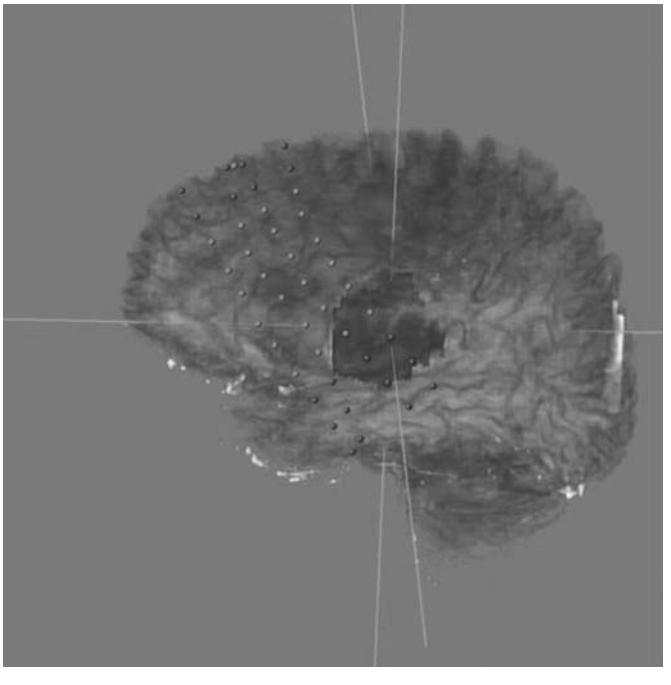


Figure 115.5 Intraoperative co-registered image of three-dimensional MRI scan of the brain with subdural grid shown in relation to the brain tumor.

Extratemporal lobe epilepsy

In one study, of patients with frontal lobe epilepsy, the distribution of the interictal epileptiform activity was focal in 15% of patients, lobar in 32%, and multilobar in 25%.[32] In this study patients who were seizure-free following surgery mostly demonstrated a regional distribution of interictal epileptiform activity. The multilobar distribution of interictal epileptiform activity was seen mostly in children.

A study of nontumoral intractable frontal lobe epilepsy, showed that interictal epileptiform activity from two or less gyri and absence of postexcision of was associated with a favorable outcome. This was in contrast to those with interictal epileptiform activity seen in three or with more gyri and the presence of postexcision, especially at a distance from the resection margin, where it was associated with a poor outcome.[33]

Postexcision electrocorticography

There is no general agreement in the ability of the postoperative ECoG findings to predict outcome. Some reports suggest that interictal epileptiform activity seen in the postexcision ECoG portends a poor prognosis as discussed in extratemporal lobe epilepsy. The use of intraoperative ECoG for standard temporal lobectomy is controversial. There are some who feel that it may be helpful in cases of temporal lobe epilepsy due to hippocampal sclerosis. In a case series that included 17 patients who underwent corticoamygdalohippocampectomy and underwent pre- and postresection ECoG found that in those cases with only isolated spikes as compared to those with high frequency or continuous discharges statistically tended toward good seizure control.[34] However there are many centers that perform standard temporal lobectomy without the use of intraoperative ECoG with excellent seizure-free outcomes.

Disadvantages

ECoG adds substantially to cost, personnel, and equipment. It also requires training of a specialized neurophysiologic team. It also increases the length of the surgical procedure by 30–60 minutes. The use of invasive extraoperative monitoring also made the use of intraoperative ECoG redundant in some circumstances. Due to the relatively short time available in the intraoperative setting, ictal ECoG findings are relatively infrequent occurrence. Therefore the clinical decisions are made by evaluating the interictal ECoG findings. The localizing significance of the irritative zone in the need to resect the epileptogenic zone is unclear.[5]

Special considerations

Isoflurane has been also shown to decrease spike frequency in children with neocortical epilepsy. It has been noted that the spatial pattern of spiking was similar in a study that looked at differences in the same children in the extraoperative to intraoperative settings. It was also found when comparing intraoperative spiking to ictal onset zones seen in during the extraoperative setting that spike frequency of <1 spike/minute was a poor indicator of the epileptogenic zone, whereas regions of cortex that should show a maximal spike frequency of more than one spike per minute were concordant with regions of ictal onset.[9] In the study of patients with cortical dysplasia, there appeared to be particular patterns of spiking that have prognostic value.[11] The three patterns described in this paper (see above for description) showed a high degree of spatial correlation with the anatomic extent of the dysplasia. This was in contrast to those patients in whom there was extensive lesion either visible or not on imaging studies, who tended to have a wider region of epileptogenicity. The focal-appearing lesions with focal or lobar electrocorticographic patterns correlated with a positive surgical outcome. Continuous spiking may be seen with other pathologies, such as with glioneuronal tumors, although these findings may be seen more commonly with focal cortical dysplasia.[35]

Future directions

Many of the studies of intraoperative ECoG in the literature are retrospective with small numbers of patients. There is a lack of large scale prospective studies looking at the efficacy of this modality.[6] Further studies that evaluate interictal epileptiform discharges seen in the postresection period are also need. Determining what types of postresective spikes suggest either a poor prognosis and potentially guiding in the extension resection margins would be a significant contribution to the literature. The determination of prognostic markers for intraoperative ECoG would likely influence the indication and make clearer the utility of this modality in various epilepsy syndromes. Currently the results from different centers of extending resection or ignoring postresection data is conflicting and often difficult to compare.[36,37] In patients with rare interictal abnormalities, the evaluation with ECoG may not help in prognostication as the absence of interictal abnormalities may be due to a number of different reasons and not a total elimination of the epileptogenic zone.[7] The use of ECoG in temporal lobectomy may become beneficial in cases undergoing selective removal of hippocampus and tailored temporal lobectomy in attempts to minimize memory outcomes. Various procedures such as multiple subplial transections maybe aided by the use of ECoG.[38]

The use of intraoperative ECoG is still a useful modality in circumstances where the exact localization of the epileptogenic zone is yet unclear despite a full pre-surgical evaluation and appears to be useful in guiding the surgeon in tailoring the resection, especially in some cases of extratemporal lobe epilepsy.

The use of combining modalities such as MEG, three-dimensional MRI, PET scan, and other neuroimaging data with intraoperative ECoG data may provide added understanding of the relationship with interictal epileptiform activity as it relates to lesions and also provide potential strategies for surgery when attempting to localize the epileptogenic zone. The relationship between spike frequency and prolonged seizure-free outcome has not been assessed across different epilepsy syndromes in large number of patients.

Cortical SSEP mapping

Somatosensory evoked potentials (SSEP) are electrical potentials generated in various parts of the somatosensory pathway in response to stimulation given to a peripheral nerve. The initial cortically generated potential appears in the primary somatosensory area contralateral to the stimulated side. These responses are closely related to the functional sensorimotor representation of the stimulated body part from the patient. So that, for example, the location of the SSEP after median nerve stimulation corresponds well to the 'hand area' in the primary somatosensory cortex. For the purpose of the definition of eloquent cortex, SSEP can be used as a localization tool of the primary sensory cortex. In this chapter, we will review the current understanding of SSEP, mainly those obtained from direct cortical recording.

Methodology

Standard settings for the scalp-recorded SSEP are well described. Generally, electrical stimulation is applied transcutaneously over the course of a peripheral nerve. Short monophasic electrical pulses (100–300 usec) are commonly used. The site of the stimulation can be any part of the body. Median nerve and stimulation at the wrist and posterior tibial nerve and stimulation at the ankle are the most popular sites, representing 'hand' and 'foot' areas, respectively. For trigeminal area SSEP, stimulation can be applied directly on the lip (mandibular branch of the trigeminal nerve), cheek, or chin, etc. The polarity of the stimuli can be alternated to minimize stimulus artifact, most typically done with the trigeminal SSEP, as the stimulus artifact is much larger using this technique due to the proximity of stimulation to the recording site. The intensity of electrical stimuli is usually set at the motor threshold, motor plus sensory threshold, or three to four times the sensory threshold. Stimulus rates of 1 to 10 per second are commonly used. To obtain the larger middle- to long-latency cortical responses or the secondary sensory responses, lower stimulus rates are recommended (<1 Hz). Averaging of 500 sweeps is usually enough to obtain sufficient signal-to-noise ratio in scalp-SSEP. A low number of sweeps is necessary in cortical-recorded SSEP, since the signal-to-noise ratio of the response is 5–8 times higher than in the scalp-EEG. A low-pass filter should be set at higher than 2000 Hz to avoid phase distortion. A high-pass filter is set at lower than 3 Hz to offset baseline. These settings are generally common to both scalp- and cortical-recorded SSEP.

Cortical SSEP with stimulation of the median nerve has been used to identify the central sulcus at the level of the hand sensorimotor area. Several studies have been reported about waveform characteristics of extraoperative cortical SSEP.

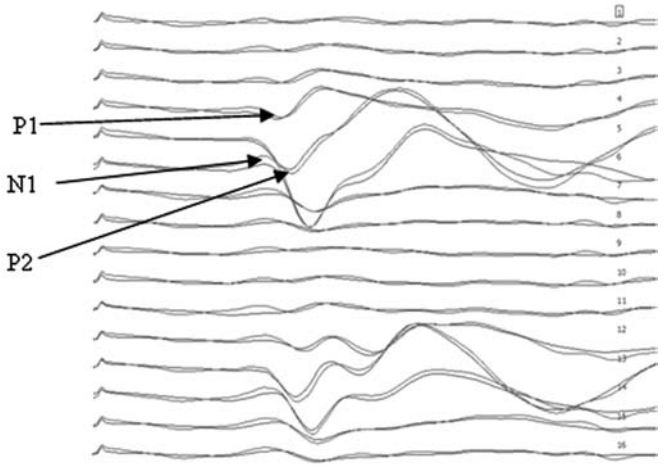


Figure 115.6 Phase reversal between the pre-central and post-central regions on a referential derivation, caused by two opposite polarities.

There are different terminologies that have been used to describe the various components seen in the median nerve cortical SSEP. One terminology uses the naming system of N1, P2, and N2, indicating their order of appearance among peaks of the same polarity. Another system uses the latency which is characteristic in between patients so that terms of N20, P20, and P25 are used. Though different terminology may confuse interpreters, some correspondence can be found in the early responses. Peak latencies of the responses later than P25 and P2 are highly variable between individuals. We will use both nomenclatures according to original investigators.

The initial cortical response is seen at a peak around a latency of 20 ms in adults. This component consists of negative polarity in the postcentral area the N1 response (also called N20) and smaller positive polarity in the precentral area (P20). The peak latency is same between these two maxima, or either peak, precedes the other by 2 ms. The two opposite polarities make a phase reversal between the pre-central and post-central regions on a referential derivation (Figure 115.6), which is one of the most reliable indicators for the central sulcus location.

Cortical stimulation

Cortical stimulation is typically performed in the useful patient, although some cortical function can still be evaluated in the setting of sedation, such as motor response. Cortical stimulation is used to evaluate the regions of brain termed eloquent cortex. The term eloquent cortex refers to those regions of brain which, when resected, would lead to significant neurologic disability. The method for analysis of these regions with cortical stimulation is performed by directly applying a series of electrical stimuli to the cortex to see what effect they have on functions such as sensation, motion, vision, language, etc. The electrical current consists of a series of repetitive square-wave electric currents of alternating polarity with a pulse width of 0.3 ms and a frequency of 50 Hz which were delivered for 2–5 seconds (Grass S-88 and SUI-7, Asro-Med Inc., R.I., USA). This stimulator is not FDA approved for human use, yet many institutions have fathered its use in patients due to its long history of use if the field of epilepsy and brain tumor patients requiring eloquent function mapping. The stimulus is typically delivered to the cortex via implanted subdural electrodes in the case of a patient undergoing long-term monitoring for epilepsy surgery. In the operative setting the stimulus can also be applied using a hand-held bipolar stimulator. During the delivery of cortical stimulation, simultaneous electrocorticography is typically being recorded in order to look for the presence of after-discharges that have been induced by the stimulation. After-discharges are epileptiform activity that has been generated following a cortical stimulus. If the after-discharges evolve either spontaneously or after repeated trials of cortical stimulation, it could result in a clinical seizure.

The subdural electrodes covering areas of functional interest were studied using cortical stimulation. Details of the methodology for cortical stimulation and the subsequent cortical mapping have been described elsewhere. Cortical areas were defined as language areas where stimulation produced an interruption of the ability to read aloud a sentence in the absence of the following: (1) positive tongue motor response

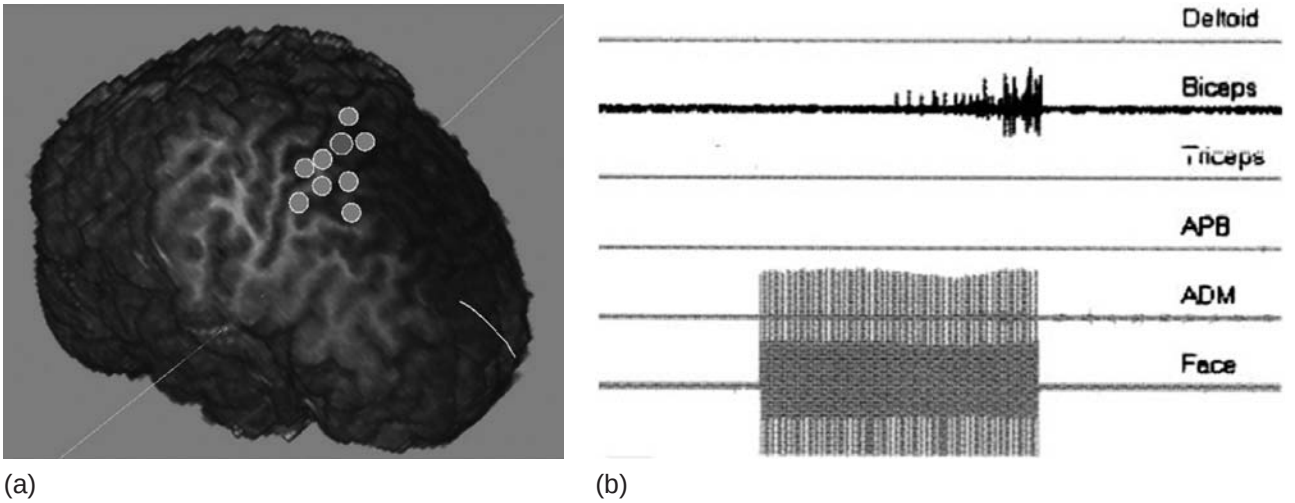


Figure 115.7 Cortical stimulation using hand held bipolar stimulation in the shaded position resulted in biceps contraction location one region of arm representation on the cortex.

(e.g., tonic tongue contraction), (2) negative tongue motor response (e.g., impairment of rapid alternating movements) and (3) after-discharges (ADs). Cortical stimulation of the location of motor representation can be done with direct observation of tonic, clonic, activity of limb or face, or by use of EMG electrodes (Figure 115.7). While testing of language function must be done under a wakeful setting, motor function can at times be tested with the patient lightly sedated or with low levels of general anesthesia. The motor thresholds will vary using this technique and may require higher levels of stimulus intensity or stimulus duration that used in the extraoperative setting. Stimulation testing for motor function under the influence of anesthesia is difficult in younger patients particularly in ages less than 10 years of age.

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SECTION 15

Resective surgical procedures for epilepsy

116 Resective surgical techniques: mesial temporal lobe epilepsy

DK Binder and J Schramm

Introduction

In case after case, we found the cortex to be tough in the anterior and deep portion of the first temporal convolution. This abnormality extended into, and grew more marked in, the uncus and hippocampal gyrus. The tissue was tough, rubbery, and slightly yellow ... We have gradually realized the importance of this discovery, as the epileptogenic focus was often shown by electrocorticography to be situated here, and furthermore patients returned with continuing seizure when we had made anterior temporal removals without excision of this area.

Penfield and Jasper, Epilepsy and the Functional Anatomy of the Human Brain, p. 333 (1954).

Historical background

The earliest resections for epilepsy, from Macewen[1] and Horsley[2] to Krause[3] and Foerster,[4] were largely designed to remove cortical areas reflected in patients' ictal semiology. Following Hans Berger's discovery of the human electroencephalogram (EEG) in 1929,[5] EEG was adapted to identify and better localize epileptiform abnormalities, particularly in the temporal lobe. In the late 1930s, Wilder Penfield and Herbert Jasper at the Montreal Neurological Institute developed the use of EEG in combination with electrocorticography and functional mapping of 'eloquent' brain areas to tailor epilepsy resections.[6,7] The developing concept of 'psychomotor' or temporal lobe epilepsy and its surgical treatment[8–10] led to the advent of anatomically standardized *en bloc* temporal lobe resection.[11–13] Soon after, it became clear that pure lateral temporal cortical removal was associated with unsatisfactory seizure outcome, and removal of the deep structures including hippocampus and amygdala was required[6,14–18] (see quote above). Bilateral resections were abandoned early since they resulted in dense anterograde amnesia.[19]

Over the last half-century, many modifications to either 'tailored' or 'anatomic' temporal lobe resections have been adopted. Anatomically standardized resections rely on the concepts that resection of pathology seen on imaging studies will include the epileptogenic zone, and that resection of eloquent areas will be avoided by conforming to certain anatomic boundaries. In contrast, tailored resections emphasize altering degree of resection based on individual pathophysiology, functional mapping of eloquent cortex, and intraoperative electrocorticography. Of course, the goal of all epilepsy surgery remains extirpation of the epileptogenic zone without producing neurological or cognitive deficits.

This chapter reviews the various anatomic techniques of temporal lobe resection currently in use. There are three main differences among the techniques. The first is the relative extent of mesial temporal versus neocortical resection, from neocortical resection without mesial resection[20,21] to mesial resection without neocortical resection (selective amygdalohippocampectomy).[22–24] The second is the exact extent of mesial resection, with variations in amygdalar resection[25,26] and hippocampal and PHG resection.[25,27–31] The third difference is surgical approach (e.g., transsylvian[23,24] vs. transcortical[22] selective amygdalohippocampectomy). In this chapter, a step-by-step description of the most commonly-used surgical techniques will be presented. A detailed discussion of the tailored approach, including the use of intraoperative functional mapping and pre- and postresection electrocorticography, is beyond the scope of this chapter, and excellent reviews are available.[32–35] Patient selection, preoperative work-up, anesthesia,[36] outcome and complications will not be considered here. In addition, the reader is referred to other references that present detailed anatomic discussions of the intricate surgical and vascular anatomy of the temporal lobe.[37–51]

Classic anterior two-thirds lobectomy

Overview

There are many variations in the technique of anterior temporal lobectomy. Neocortical removal alone without removal of the mesial structures[20] has been largely abandoned in that it poorly controls seizures;[6,30] it is primarily used now in specific cases of neocortical lesionectomies (see below). Review of epilepsy programs participating in the second Palm Desert conference revealed that the median length of resection from the temporal tip was 5.5 cm in the nondominant temporal lobe, 4.5 cm in the dominant temporal lobe, and 3 cm of hippocampus.[52]

En bloc anterior temporal lobectomy was described by Falconer and colleagues[11] and subsequently used or adapted by others.[18,29] In this procedure, the neocortical and mesial temporal structures are removed together in one specimen. Alternatively, the temporal neocortex can be removed first followed by resection of the deep structures.[39] Most current temporal lobectomy procedures conform to the latter two-step procedure, and what follows is a step-by-step description of one method of performing such a two-step anterior temporal

lobectomy with staged resection of the neocortical block and deep structures.

Surgical procedure

The head is positioned so that the lateral surface of the temporal lobe is approximately horizontal. To prevent stress on the neck and minimize venous congestion, the patient is positioned supine with the shoulder elevated and the head turned, or in some cases the patient may be positioned in the full lateral position. The standard scalp incision is a 'question mark' shape extending from the superior border of the zygomatic arch just in front of the tragus above the auricle then superiorly and anteriorly to the hairline. This spares the frontalis branch of the facial nerve and can also be performed so as to preserve the superficial temporal artery. Following skin incision, the temporalis muscle is incised and reflected inferiorly leaving an appropriate cuff, or may be elevated together with the skin as a musculocutaneous flap. Next, a standard temporal craniotomy is fashioned with the superior margin just above the sylvian fissure (more frontal lobe is exposed if intraoperative electrocorticography will be performed). The inferior and anterior margins of the craniotomy are rongeured to reach closer to the floor of the middle fossa and temporal pole. The dura is opened and reflected anteriorly. A Cushing needle is used to measure the length of resection from the temporal pole (~4.5 cm on the dominant side, ~5.5 cm on the nondominant side) (Figure 116.1). The pia of the STG parallel to the sylvian fissure is coagulated, and also perpendicularly at the posterior resection margin down to the floor of the middle fossa. The plane between the STG and the sylvian fissure is dissected subpially with a Penfield dissector, protecting the MCA and its candelabra (Figure 116.2). This subpial dissection is carried down to the uncus inferomesially. A small amount of leptomeningeal hemorrhage is often seen following subpial dissection, which will cease with cottonoid packing or oxidized cellulose (Surgicel).

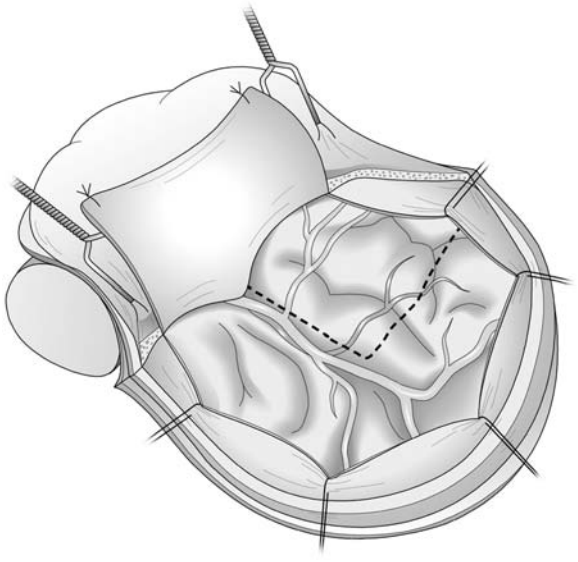
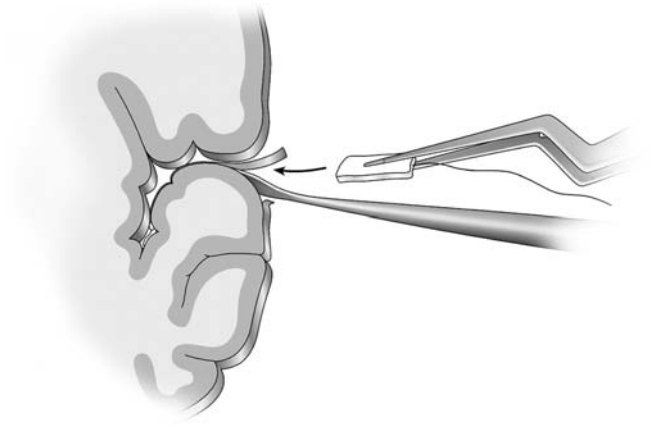


Figure 116.1 Exposure of the lateral temporal lobe (right side shown). The position of the cortical incision is indicated by the dashed line, extending from the STG parallel to the sylvian fissure perpendicularly at the posterior resection margin to the floor of the middle fossa. © 2006 Isabel Christensen and Johannes Schramm.

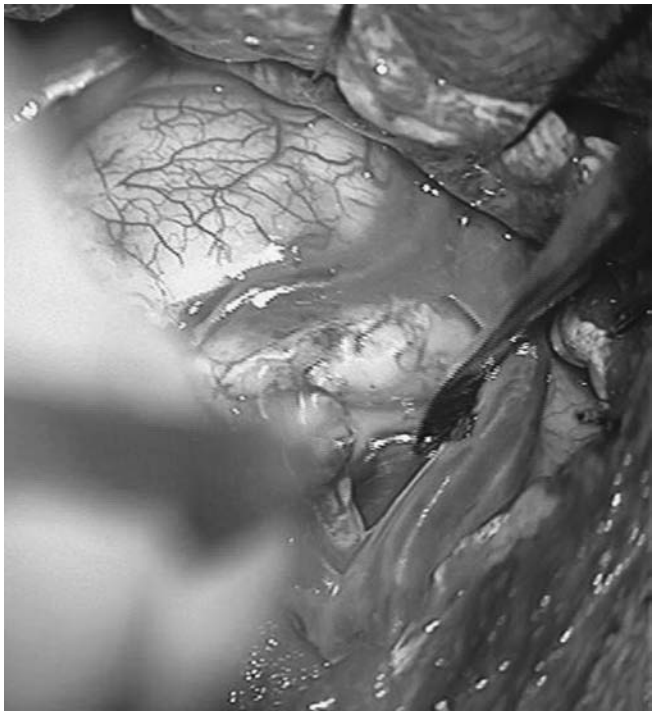
The next step is identification of the ventricle. This is done by incising the temporal stem at the inferior circular sulcus in the proper trajectory (Figure 116.3). An incision too medial may result in injury to the optic tract (producing a hemianopsia); an incision too lateral will result in missing the ventricle and arriving at the cortex over the floor of the middle fossa (Figure 116.3). Care must be taken at this step as the ventricular surface of the hippocampus may lie in close apposition to the white matter of the temporal stem, especially at the anterior margin of the temporal horn. Entry into the ventricle is confirmed by the appearance of bluish ependyma, choroid plexus, CSF, and/or view of the ventricular surface of the hippocampus. An alternative method of identifying the ventricle is to progressively deepen the posterior resection line through the white matter of the temporal stem in a coronal plane.[53]

Following identification of the level of the ventricle, disconnection of the neocortical block can be completed (Figure 116.4). First, a disconnection line is fashioned slightly oblique from the inferior circular sulcus and extended baso-laterally. This disconnection may further open the ventricle but not injure the hippocampus, and leaves the uncus in place. Second, the neocortical block can only be removed if the arachnoid at the base and alongside the pole is cut whereas it is left on the lateral neocortical gyri on the outer surface. Dissection down to the arachnoid deep to the lateral neocortical gyri is accomplished with the ultrasonic aspirator to approximately the level of the collateral sulcus. The posterior margin of the neocortical incision can then be extended to join with the prior disconnection to the ventricle. Vessels running obliquely and supplying cortex posterior to the resection line should be preserved. These steps can be performed in a number of different sequences.[18,53] The remaining arachnoid attachments of the neocortical block are cut, and it can be removed.

Next, attention is turned toward resection of the mesial structures (amygdala, uncus, hippocampus, PHG, entorhinal cortex). It is critical to recognize that the uncus and mesial aspect of the hippocampal formation lie over the tentorial hiatus, and therefore great care must be taken to use the ultrasonic aspirator on low settings to preserve the arachnoid protecting the important underlying structures (PCA, cranial nerve III, basal vein of Rosenthal, midbrain peduncle). First, the uncus can be emptied with the ultrasonic aspirator extending mesio-basally at the level of the limen insulae (working parallel to the ascending M1 segment), which includes removal of the most anterior portion of the amygdala. The next step is further opening of the temporal horn extending to the anterior tip. In view within the ventricle will be the choroid plexus, choroidal fissure, head and anterior body of the hippocampus, and amygdala. The hippocampus lies within the floor of the temporal horn (Figure 116.5) while the amygdala forms the roof of the anterior portion of the temporal horn and extends superomesially. Now comes the classic step of connecting the choroidal point with the limen insulae along the CP-LI line (Figure 116.6). Identified intraoperatively, the choroidal point is the anterior limit of the choroid plexus in the choroidal fissure (at the joining of the fimbria with the stria terminalis). The portion of the amygdala inferolateral to the CP-LI line can now be removed with ultrasonic aspiration. Care must be taken not to extend the



(a)



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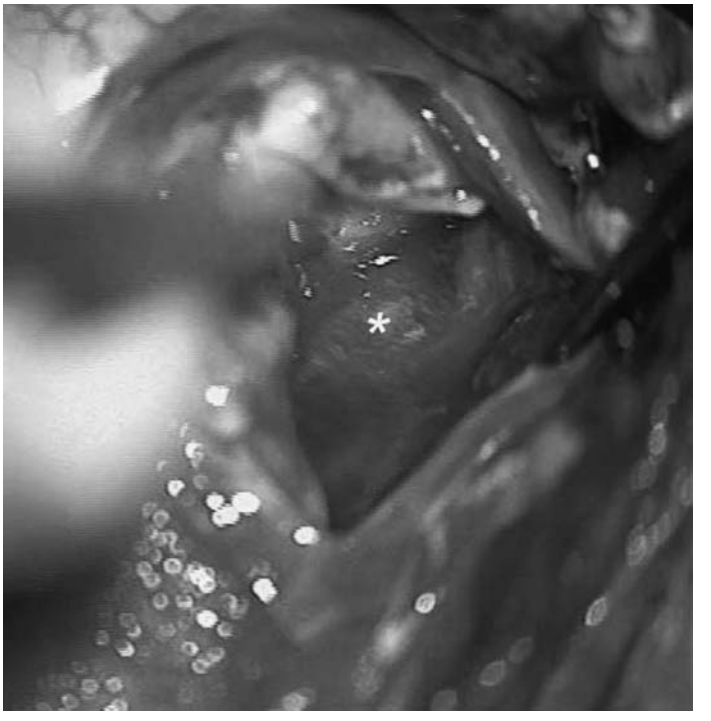

(c)

Figure 116.2 Subpial dissection technique. (a**)** Coronal view of subpial dissection in plane between the STG and the sylvian fissure using Penfield dissector and cottonoid. (b) Early stage of subpial dissection between left STG and sylvian fissure. (c) Later stage of subpial dissection. Note that sylvian vessels (asterisk) are protected at all times by not violating the arachnoid layer. © 2006 Isabel Christensen and Johannes Schramm.

amygdala resection superomedially into the globus pallidus. During this step, the entorhinal cortex (anterior portion of PHG) will be transected and removed.

Next, the fimbria hippocampi, which forms the medial border of the hippocampus and the lateral boundary of the choroidal fissure, can be loosened from its attachments (taenia fimbriae) mediolaterally. This reveals the hippocampal sulcus (hippocampal fissure), a duplicate layer of arachnoid containing the arterial branches (Ammon's horn arteries) from the P2 segment of the PCA and anterior choroidal artery (Figure 116.7). Next, the arachnoid of the PHG is identified and sectioned, allowing the subpial elevation of the PHG out of its arachnoid bed in parallel to the choroidal fissure and the hippocampal sulcus. At this stage, the small perforating vessels entering the hippocampal sulcus are identified and divided close to the substance of the hippocampus (i.e., working preferably within the hippocampal sulcus) (Figure 116.8), allowing the mobilization of the combined block of PHG and hippocampus. Thus, the four steps of hippocampal removal are as follows. The first step was lateral disconnection, already done by removal of the neocortical block. The anterior disconnection was done when the uncus and temporal pole were removed by suction. The mesial disconnection was done by opening the choroidal fissure and dissecting along the CP-LI line which leaves only the posterior disconnection, which is done with the ultrasonic aspirator. In this way, the hippocampus-PHG block can be removed (*en bloc* if desired) by

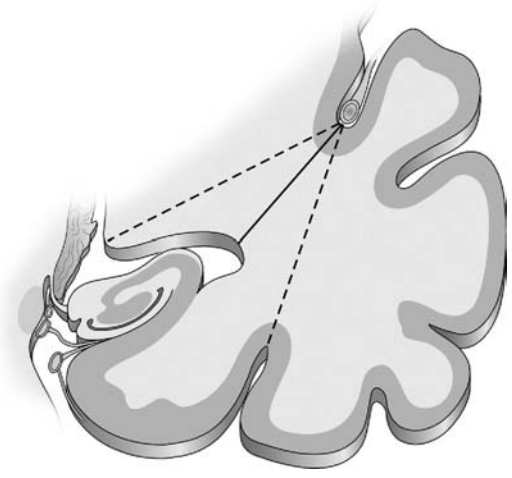

Figure 116.3 Identification of the ventricle. The ventricle is reached by making an incision through the temporal stem. The ideal trajectory is illustrated by the solid line (center). An incision too medial (medial dashed line) may miss the ventricle and result in injury to the optic tract; an incision too lateral (lateral dashed line) may miss the ventricle and arrive at the cortex over the floor of the middle fossa (pictured, over the collateral sulcus between PHG and fusiform gyri). Aiming a bit too lateral and then turning medially is a good technique. © 2006 Isabel Christensen and Johannes Schramm.

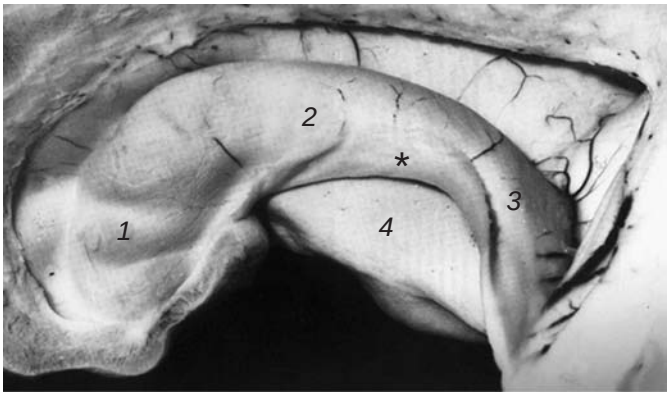

Figure 116.5 View of the hippocampus within the floor of the temporal horn of the lateral ventricle. 1, head of hippocampus; 2, body of hippocampus; 3, tail of hippocampus; 4, subiculum. Choroid plexus has been removed and fimbria (asterisk) has been elevated. Modified from Duvernoy HM. The Human Hippocampus (3rd edn.), Figure 3, p. 15, © Springer-Verlag, 2005 (with permission).

careful subpial dissection, taking care to protect the structures in the tentorial hiatus. Variations of these steps have been described.[53]

At the conclusion of the resection, the arachnoid has ideally been left intact and through it the tentorial hiatus, cranial nerve III, basal vein of Rosenthal, PCA, and anterior choroidal artery, and smaller branches and the midbrain peduncle can usually be appreciated. Use of bipolar cautery in the arachnoidal bed is mostly unnecessary and can be dangerous; oxidized cellulose (Surgicel) is sufficient for hemostasis in the majority of cases. Following adequate hemostasis, the craniotomy is closed in standard fashion.

Anterior one-third lobectomy combined with amygdalohippocampectomy

Overview

Based on the observation that some patients explored with depth electrodes had seizure onset that was quite posterior in the hippocampus, Spencer developed a technique in which limited cortical removal was followed by extended hippocampal resection.[54] This has also been termed *anteromedial temporal lobectomy* or *radical hippocampectomy*.[31,41] The rationale is to preserve functional lateral temporal neocortex while providing access for removal of mesial structures that reaches far more posterior than the neocortical resection.

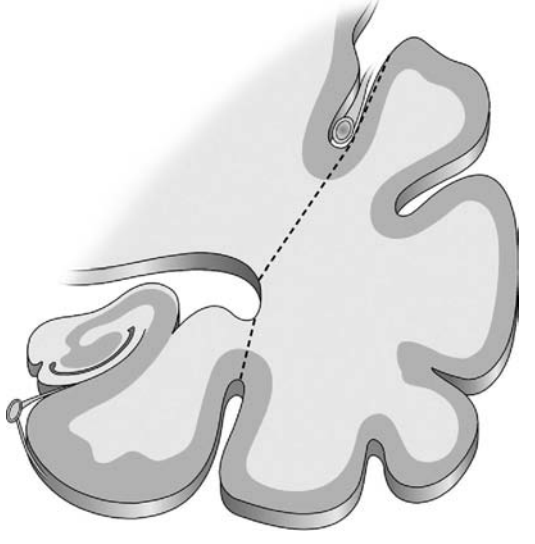

Figure 116.4 Disconnection of the neocortical block. Coronal view demonstrating lines of resection for *en bloc* neocortical removal. Upper line: STG to ventricle; lower line: ventricle to collateral sulcus between PHG and fusiform gyri. © 2006 Isabel Christensen and Johannes Schramm.

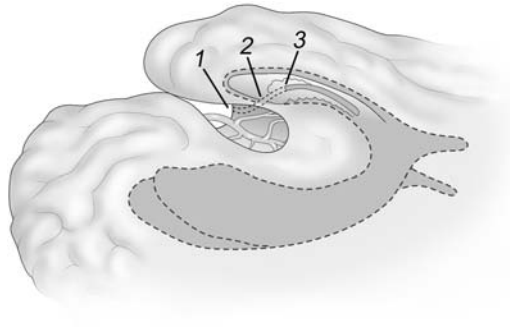

Figure 116.6 Surgical view of temporomesial structures demonstrating the choroid plexus-limen insulae (CP-LI) line. 1, limen insulae; 2, CP-LI line; 3, choroidal point. © 2006 Isabel Christensen and Johannes Schramm.

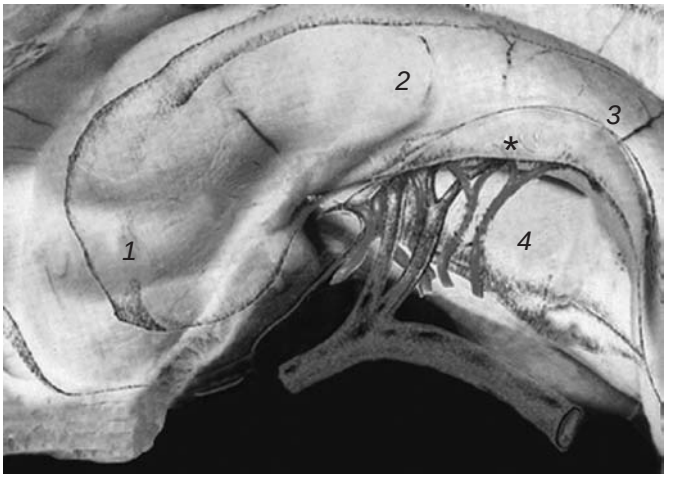

Figure 116.7 View of the hippocampus demonstrating vessels in hippocampal fissure. 1, head of hippocampus; 2, body of hippocampus; 3, tail of hippocampus; 4, subiculum. Choroid plexus has been removed and fimbria (asterisk) has been elevated to reveal hippocampal fissure with vessels. Modified from Duvernoy HM. The Human Hippocampus (3rd edn.), Figure 3, p. 15. © Springer-Verlag, 2005 and Yaşargil MG, Microsurgery of CNS Tumors, Figure 17–7b, p. 259, Thieme, 1996 (with permission).

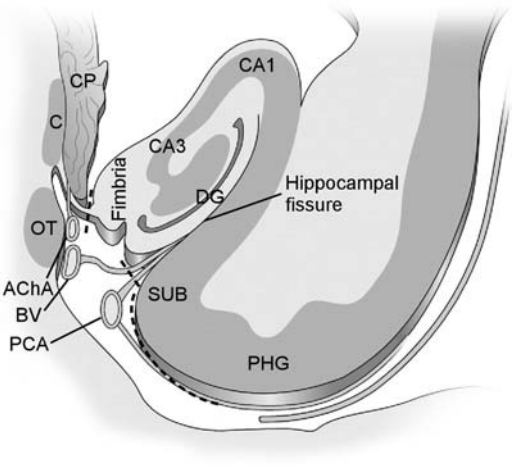

Figure 116.8 Coronal view of right mesial temporal lobe demonstrating steps of hippocampal disconnection. AChA, anterior choroidal artery; BV, basal vein of Rosenthal; C, tail of the caudate; CA1 and CA3, areas of Ammon's horn (*cornu ammonis*) of the hippocampus; CP, choroid plexus; DG, dentate gyrus; OT, optic tract; PCA, posterior cerebral artery (P2 segment); PHG, parahippocampal gyrus; SUB, subiculum. Three disconnection lines (dashed) demonstrate disconnection of fimbria hippocampi from attachment to choroidal fissure; transection of vessels within hippocampal fissure; and subpial elevation of the PHG out of its arachnoid bed. (c) 2006 Isabel Christensen and Johannes Schramm.

Operative procedure

The patient is positioned supine with the head placed in pin fixation and turned laterally so that the zygoma is at an angle of ~10° to the floor, enabling a line of sight along the temporal horn and hippocampus. A temporal craniotomy is performed, exposing ~5–6 cm of temporal lobe and the sylvian fissure and orbitofrontal region (or up to 9 cm in another description).[31] A cortical incision is made in the superior margin of the MTG 3–3.5 cm from the temporal tip which then curves inferiorly across the MTG and ITG. The superior margin is the arachnoid of the STG, which is spared. A lateral neocortical block is removed extending to a depth of ~3 cm, approaching but not entering the temporal horn.

The second step is dissection of the medial structures. Self-retaining retractors are placed on the STG and the posterior aspect of the resection bed, and the ultrasonic aspirator is used to enter into the temporal horn. An incision is made anteromedially to the amygdala and then inferiorly to the tentorial incisura, at which time the uncus is gently removed with ultrasonic aspiration. Next, an incision is made through the temporal horn and the occipitotemporal (inferior longitudinal) fasciculus to the floor of the middle fossa, and extended posteriorly to the arachnoid margin over the fusiform gyrus, at the point where the hippocampus curves medially posterior to the brainstem. The lateral temporal cortex is continuously retracted and slightly elevated with a retractor. The removal of the mesial structures is then accomplished. Proceeding in an anterior to posterior direction, the incision is carried from uncus and amygdala along the choroidal fissure. Attention is now turned toward resection of the hippocampus. The small vessels lying in the hippocampal fissure are identified, coagulated, and divided, allowing mobilization of the hippocampus, and the fimbria hippocampi is freed from its arachnoid attachment. Lastly, the incision from the middle fossa floor is joined to the incision of the posterior body of the hippocampus, and the hippocampus and PHG are removed *en bloc*. Structures identifiable in the resection cavity include choroid plexus, arachnoid overlying optic tract and midbrain, medial edge of the tentorium, cranial nerve III, and occasionally cranial nerve IV.[31] Following meticulous hemostasis, the wound is closed in standard fashion.

Transsylvian selective amygdalohippocampectomy

Overview

The term *selective amygdalohippocampectomy* refers to that group of procedures aimed at resection of mesial structures only without neocortical resection. Strictly speaking, it is not 'selective' as the PHG is usually included in the removal, as are the uncus and part of the amygdala. This would amount to an unco-amygdalo-hippocampo-parahippocampectomy but the initial terminology is more practical and accepted. Indications include patients with clear evidence of mesial temporal lobe seizure foci or lesions and lack of involvement of lateral temporal neocortex (i.e., typical cases of mesial temporal sclerosis). The *transsylvian* approach was pioneered by Yaşargil and Wieser.[23,24,37] Among the original proposed advantages are the lack of a neocortical incision as required by the transcortical approach, and the lack of temporal lobe retraction necessitated by the subtemporal approach (see below).

Operative procedure

The patient is positioned either in a lateral decubitus position or supine with the shoulder elevated. Unlike the position for standard temporal lobectomy or transcortical selective amygdalohippocampectomy, the head is turned so that the malar eminence is the highest point, making the sylvian fissure approximately vertical. The head is placed in pin fixation. A semilunar incision is used, and a craniotomy is fashioned that extends superior to the sylvian fissure by ~1.5 cm. The craniotomy can be smaller than that used for a standard temporal lobectomy. Next, the sphenoid ridge is flattened with the drill down to the anterior clinoid process to allow optimal dural

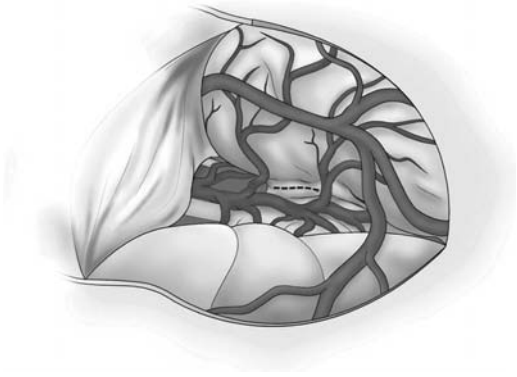

Figure 116.9 View following opening of the right sylvian fissure demonstrating temporal and frontal opercula, anterior insular cortex, limen insulae, and associated vascular anatomy. Dashed line demonstrates site for 10–15 mm incision into the anterior temporal stem for access into the temporal horn. Modified from Yasargil MG. Microsurgery of CNS Tumors, Figure 17–7b, p. 259. © Thieme, 1996 (with permission). Final version © 2006 Isabel Christensen and Johannes Schramm.

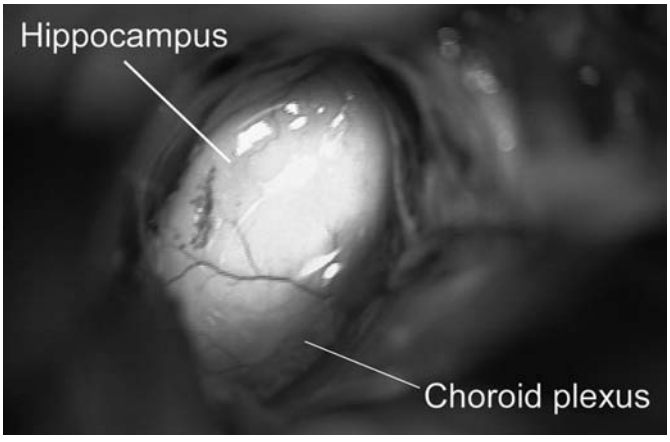

Figure 116.11 Intraoperative view of the hippocampus (left transsylvian approach). The temporal stem has been incised, the temporal horn has been opened, and the shiny ventricular surface of the hippocampus (alveus) can be seen along with the choroid plexus in the choroidal fissure mesially.

retraction. The dura is opened in semicircular fashion and reflected toward the sphenoid ridge and orbit. The sylvian fissure is opened from the carotid bifurcation through the MCA bifurcation and ~2 cm more distally, exposing the ascending M1 branch, the limen insulae, the anterior third of the insular cortex and associated M2 branches, and the mesial surface of the uncus and temporal pole (Figure 116.9). The positions of the lateral M2 branches – including temporopolar and anterior temporal arteries – are noted. The inferior circular sulcus is identified which separates the temporal operculum from the insular cortex.

Next, a ~10–15-mm incision into the anterior temporal stem is made at the level of the limen insulae (Figure 116.9). Opening of the temporal horn is accomplished by carrying this incision down to the uncus parallel to the M1 segment.

Uncoamygdalohippocampectomy is then performed as follows (Figure 116.10). The uncus is emptied with the ultrasonic aspirator, taking care to set low values for suction and amplitude to leave the arachnoid intact. The bulging portion of the amygdala (identified grossly by its speckled brown color) along the CP-LI line can then be resected with the ultrasonic aspirator or dissector. Together with this the entorhinal cortex (anterior extent of PHG) is resected. Next, the temporal horn is opened further to better visualize the choroid plexus and choroidal fissure marking the mesial boundary of the hippocampal dissection (Figure 116.11). A disconnection is then made lateral to the hippocampus along the ventricular border lateral to the collateral eminence, using a dissector or the aspirator in the anterior-posterior direction, aiming approximately to the level of the collateral sulcus. The fimbria hippocampi is disconnected mesially by gentle dissection of the taenia fimbriae attaching to the choroidal fissure, and the medial aspect of the parahippocampal gyrus (subiculum) can then be subpially elevated with a dissector. Identification, coagulation, and transection of the hippocampal vessels (Ammon's horn arteries) in the hippocampal fissure is performed, with great care taken to preserve the larger trunks of the anterior choroidal artery and

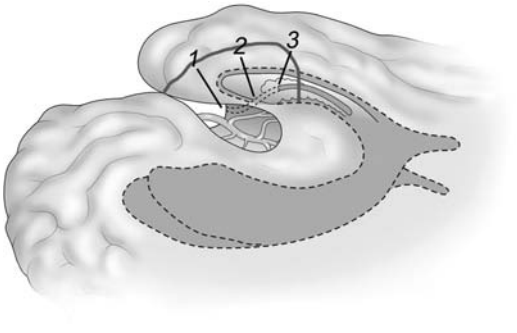

Figure 116.10 Extent of resection in selective amygdalohippocampectomy. 1, limen insulae; 2, CP-LI line; 3, choroidal point. Red Line demonstrates extent of temporomesial resection in transsylvian selective amygdalohippocampectomy (includes portions of hippocampus and amygdala, entorhinal cortex, uncus, parahippocampal gyrus). © 2006 Isabel Christensen and Johannes Schramm. (See Color plates.)

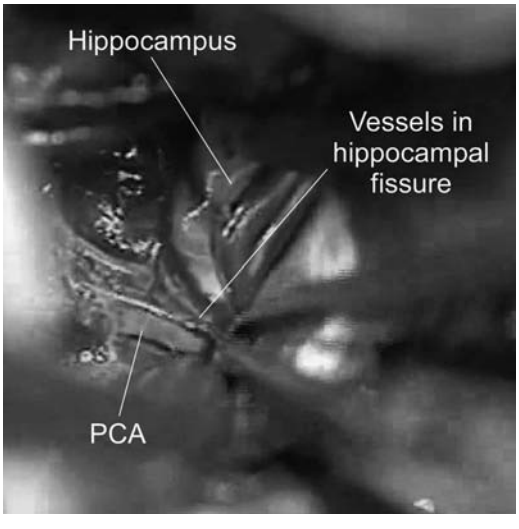

Figure 116.12 The hippocampal-parahippocampal tissue block is elevated out of its arachnoid bed by the Penfield dissector to the right, demonstrating the basal vessels in the hippocampal fissure. Careful microsurgical identification, coagulation, and transection of vessels in the hippocampal fissure arising from the P2 segment of the PCA (shown) and the anterior choroidal artery is the key to successful hippocampal resection.

P2 segment of the PCA (Figure 116.12). This is safely achieved by transecting the hippocampal vessels within the hippocampal fissure. Finally, the combined hippocampus/PHG can be disconnected posteriorly by mediolateral transverse section with the ultrasonic aspirator, and can be freed from its arachnoidal cover either by rolling it from mesial to lateral or vice versa (Figure 116.13). The specimen can be removed *en bloc* if desired (Figure 116.14). Hemostasis is accomplished with oxidized cellulose (Surgicel) and the wound is closed in standard fashion.

Transcortical selective amygdalohippocampectomy

Overview

In 1958, Niemeyer introduced the *transventricular amygdalohippocampectomy*,[22] which has been subsequently termed transcortical selective amygdalohippocampectomy. He used this in patients thought to have mesial pathology but normal lateral temporal neocortex. Niemeyer described an approach through an incision in the MTG, providing access to the temporal horn of the lateral ventricle. The hippocampus (~3 cm), amygdala and PHG were then removed with subpial dissection. In 1969, Niemeyer and Bello reported on a microsurgical route to these structures.[55]

Olivier subsequently described a modification of this technique through an incision in the STG.[27,56] In this variation, the anterior 2 cm of the STG are resected to allow access to the amygdala, which is resected, the temporal horn is opened, and the anterior 1–2 cm of hippocampus are removed. Olivier and others have also used the superior temporal sulcus[57] although it should be noted that Olivier has since reverted to the original Niemeyer approach through the MTG, terming the STG approach 'more tedious and less satisfactory'.[39]

Operative procedure

The position of the head is similar to that used for a standard temporal lobectomy approach. A linear or slightly curved incision in front of the tragus may be used. Neuronavigation is extremely helpful in planning both the craniotomy (which can either correspond to the standard pterional approach or be much smaller 'keyhole' craniotomy centered over the MTG).[56] Furthermore, neuronavigation can be subsequently used to plan the trajectory to the ventricle, hippocampus and amygdala.

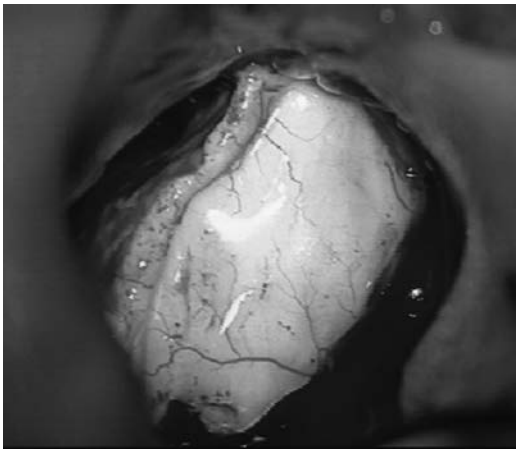

Figure 116.13 Intraoperative view of the hippocampus (left transsylvian approach) following lateral, medial, and posterior disconnection.

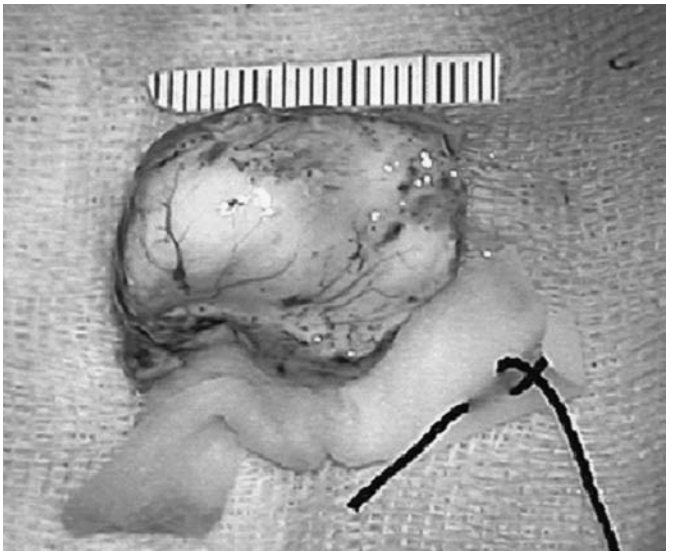

Figure 116.14 Resected *en bloc* hippocampal specimen (~3.5 cm).

At the Montreal Neurological Institute, all of these procedures since 1992 have been performed using MRI-based frameless stereotaxy.[56] The pial surface of the MTG just inferior to the superior temporal sulcus is coagulated, and a 2–3 cm anteroposterior incision is made. On the nondominant side, Olivier places the incision anterior to the central sulcus; on the dominant side, it lies anterior to the precentral sulcus.[56] Dissection down to the temporal horn is performed via slit-like transection of the white matter in the anterior-posterior direction. Retractors are then inserted to provide an unobstructed view of the hippocampus within the temporal horn. The ependyma must be opened sufficiently to see the bulge of the amygdala and the tip of the temporal horn anteriorly. Resection of the hippocampus is initiated by entering the PHG by transecting laterally at the ventricular sulcus between the hippocampus proper and the collateral eminence. Thus an endopial intragyral removal of the PHG is performed along its longitudinal extent. Care is taken not to injure the P2 segment of the PCA which runs under the pia near the medial border of the PHG. Dissection is carried forward into the PHG and the anterior portion of the uncus is entered. The hippocampus proper can then be mobilized laterally and the fimbria hippocampi resected longitudinally revealing the hippocampal sulcus. Posteriorly, the hippocampus proper can be transected at the junction of the body and tail, enabling it to be lifted gradually off the hippocampal sulcus. Careful dissection, coagulation, and division of hippocampal vessels in the hippocampal sulcus is performed, and the hippocampal specimen may be progressively mobilized and ultimately removed. It should be noted that large *en bloc* removal of the hippocampus is difficult with this approach. Subpial resection is then carried forward to the apex of the uncus (intralimbic gyrus), and then the anterior uncus is also emptied with careful aspiration. Next comes the resection of the amygdala. The amygdala is resected as far and as high anteriorly as the horizontal (M1) segment of the MCA. In this approach, in contrast to the transsylvian approach, the amygdala is visualized and resected following the main hippocampal resection. Finally, if more posterior resection of the hippocampus and PHG is desired, this can be accomplished

with endopial aspiration back to the level of the superior colliculus.[39,56,58] After careful hemostasis, the wound is closed in standard fashion.

In our center, we prefer the transsylvian to the transcortical approach to selective amygdalohippocampectomy. One of the supposed advantages of the transcortical approach is the sparing of fiber tracts running through the temporal stem; however, our results suggest a greater chance of inducing a homonymous hemianopia compared with the transsylvian approach (Clusmann et al., unpublished data), a result which is supported by anatomic studies.[47] When we perform the transcortical approach, we make an incision in the MTG. Furthermore, we typically work underneath the PHG and reach the fimbria hippocampi transventricularly. In this way, the hippocampus-PHG may be removed *en bloc* together, albeit in shorter segments than using the transsylvian approach.

Furthermore, the transcortical approach gives a more mesially pointed direction of view, making it more difficult to gauge the extent of resection of the amygdala toward its mesial border.

Subtemporal and other approaches

In addition to the above-mentioned transcortical and transsylvian approaches to selective amygdalohippocampectomy, several authors have reported subtemporal approaches and variants. Hori et al. initially described the subtemporal approach to amygdalohippocampectomy in 4 patients.[59] The approach involved cutting the tentorium to reduce temporal lobe retraction and *en bloc* excision of the fusiform gyrus to provide access to the temporal horn. A subsequent variation by the same authors is the retrolabyrinthine presigmoid transpetrosal approach to subtemporal amygdalohippocampectomy.[60] In 1989, Shimizu et al. described access to mesial temporal structures via a subtemporal 'zygomatic' approach in five patients, involving removal of the zygomatic arch and access to the mesial structures via limited resection of the ITG.[61] Later, Shimizu et al. reported on a lateral temporal polar approach to mesial temporal lesions in 25 patients.[62] Park and colleagues describe a subtemporal transparahippocampal approach to amygdalohippocampectomy in eight patients, allowing preservation of the fusiform gyrus and the lateral temporal lobe.[63,64] Recently, Miyamoto et al. have described a combination of the subtemporal and transventricular/transchoroidal approaches.[65]

The primary rationale for subtemporal approaches is that they spare temporal neocortex and do not involve incision of the temporal stem. However, drawbacks include temporal lobe retraction, venous anatomy, surgical orientation and access, and the potential importance of basal temporal language areas in some patients.[66,67] Temporal lobe retraction places the vein of Labbé at risk. Exactly where to enter the temporal lobe on its inferior surface, either through the PHG, collateral sulcus, fusiform gyrus, or ITG may be unclear or may require intraoperative neuronavigation. Thus, orientation may be difficult, beginning with patient positioning; and variations in venous anatomy may make retraction of the basal surface of the temporal lobe difficult or impossible. Furthermore, while exposure of the hippocampus may be adequate, exposure and removal of the uncus and amygdala are difficult from this operative trajectory. It is probably best limited to lesionectomies of the posterior hippocampal/mesial temporal region.

Several other approaches to exposure or ablation of the mesial temporal structures have also been described. Vajkoczy et al. describe a modification of the transsylvian approach, termed the transsylvian-transcisternal approach,[68] which involves opening the arachnoid of the basal cisterns and *en bloc* resection of the mesial structures. Stereotactic removal or ablation of the amygdala and hippocampus has been reported,[69–74] although no large modern series are available for outcome comparisons. Gamma knife radiosurgery for mesial temporal lobe epilepsy is under investigation[75–77] and is the topic of an ongoing multicenter US trial.

Combined amygdalohippocampectomy and lesionectomy

The majority of cases of temporal lobe epilepsy are associated with hippocampal pathology, most often 'mesial temporal sclerosis' characterized by neuronal loss and gliosis and specific imaging findings.[78–82] In such cases, resection of the mesial structures appears critical for seizure-free outcome.

Another group of patients, however, present with lesional temporal lobe epilepsy.[83–85] Smaller temporal lobe lesions are being increasingly diagnosed with the advent of modern MRI imaging.[86,87] These may include glial or glioneuronal tumors, cortical dysplasias, or vascular malformations. It is clear that lesionectomy is necessary for adequate seizure control.[85] However, experience has shown that lesionectomy alone may not be sufficient for seizure control.[88,89] Depending on preoperative workup, lesion size and location, and electrophysiology, the recommendation may be for lesionectomy with or without concurrent mesial resection. For example, small tumors or cavernous malformations in the temporal pole, amygdala, and head of the hippocampus may be seen. With these the presurgical evaluation frequently leads to the recommendation to remove only the adjoining part of the hippocampus as opposed to a classic hippocampectomy. The combination of lesionectomy and amygdalohippocampectomy may also be performed from a posterolateral or subtemporal approach, usually for small tumors or cavernous malformations in the dorsal parahippocampal or fusiform gyri.

A final group of patients presents with dual pathology, i.e., the coexistence of two lesions such as MTS and an extrahippocampal lesion such as a neuronal migration disorder.[90,91] The presence of dual pathology or extrahippocampal pathology may be a poor prognostic factor for seizure outcome, unless both pathologies can be excised completely.[92–94]

Summary

The diversity of surgical approaches developed for temporal lobe resection has reflected the history of concepts of temporal lobe epilepsy, the diversity of lesions found within the temporal lobe, and also the progressive innovations in neurosurgical techniques and approaches. All of the approaches share the philosophy of minimal but efficacious removal of pathologic tissue with preservation of cognitive and neurologic function to the greatest degree

possible. Selective amygdalohippocampectomy without lateral cortical resection has shown excellent results in cases of solitary mesial temporal lobe pathology (e.g., MTS). Over the last 15 years, there has been a trend toward reducing the extent of neocortical resection and increasing the extent of resection of mesial structures. Nevertheless, presence of lateral pathology or dual pathology clearly requires either standard temporal lobectomy or tailored approaches. Mass lesions should be treated with lesionectomy possibly including resection of adjacent or involved mesial structures. Further clinical studies are required to determine the relative role of anatomic *vs*. tailored resections, better delineate epileptogenic *vs*. normal tissue,[95] and assess long-term seizure, neuropsychological, cognitive, and functional outcomes.

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117 Resective neocortical techniques in adults

EO Richter and SN Roper

Introduction

In contrast to medial temporal lobe epilepsy, which is a fairly consistent epilepsy syndrome associated with a specific pathologic substrate, neocortical epilepsy is a heterogeneous group of disorders which arises from a variety of pathologies and whose clinical manifestation and treatment options are determined more by the precise location of the focus than by the pathology. In addition, the eloquence of various neocortical areas may limit surgical options. The various methods of localizing the focus, including history and physical examination, seizure semiology, EEG, long-term video monitoring, neuropsychological testing, MEG, advanced imaging, and invasive and intraoperative electrophysiology recordings have been discussed extensively in other chapters. In this chapter we will discuss briefly the overall decision-making process before proceeding to operative techniques of neocortical resections and the eloquence of various neocortical regions, or what deficits may be expected from resections of these areas.

A major consideration in planning for extratemporal seizure surgery is the presence of a lesion on neuroimaging (Table 117.1). As discussed more fully elsewhere in this text, the success rates in lesional epilepsy surgery are considerably better than those in which no lesion can be identified where electrophysiological evidence is the only means of guiding the resection. This decision algorithm is depicted in Figure 117.1 for nontemporal neocortical epilepsy. In patients with complex partial seizures and electrophysiological evidence of lateral (neocortical) temporal onset, dual pathology (additional involvement of mesial temporal structures) is not uncommon, and requires consideration. Our suggestion for a rational approach to these cases is depicted in Figure 117.2.

Surgical technique

General techniques for neocortical resections

The fundamental principles of topectomy are a careful subpial resection of the gray matter in the defined region of epileptogenisis with careful preservation of the vasculature and avoidance of injury to adjacent cortex, as such injury may in itself be epileptogenic.

The pia overlying the top of the gyrus to be resected is carefully coagulated with bipolar electrocautery and incised (Figure 117.3). The pial flap is then gently elevated and the underlying gray matter gently suctioned off. Intermittent bipolar coagulation may be necessary at a low setting. Some centers use an ultrasonic aspirator at a low suction and vibration setting for this process. The sulci are not disturbed, and any significant vessels passing over the gyrus may be skeletonized and left in situ (Figure 117.4). The subpial resection is carried to the base of the sulcus. The dissection should not be taken deeper, because removal of underlying white matter will not improve seizure control and risks injury to underlying projection fibers.

Particular attention must be given to preservation of the ascending veins to the superior sagittal sinus. This is important during resections of the dominant midline and parietal lobes, or when preoperative vascular studies have indicated a paucity of drainage to the superficial sylvian system. Venous compromise may lead to increased postoperative edema or even venous infarction.

Dural reflection, while not usually considered a major step in brain surgery, can be a time consuming and important phase in these procedures. Extratemporal seizure foci are often associated with areas of prior injury or surgery and may have extensive dural scar and adhesion formation. In some cases, safely separating the dura without risk of vascular injury may require microsurgical techniques.

Frontal resection

Deficits after frontal resections, provided they are unilateral, generally fall into the broad categories of cognitive dysfunction

Table 117.1 A list of some potentially epileptogenic lesions that may be demonstrated with MRI scanning

Some potentially epileptogenic lesions	
Developmental:	Cortical dysplasia Hamartoma Hetrotopia
Tumors:	Low-grade glioma Ganglioglioma DNET
Vascular:	AVM Cavernous malformation
Injury:	Gliosis (trauma, CVA)
Infectious:	Granuloma Parasitic cyst

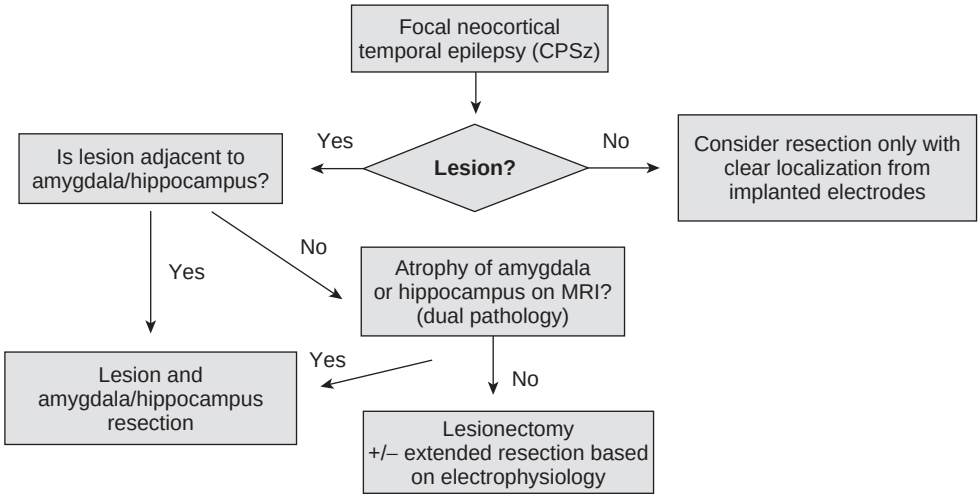

Figure 117.1 Treatment algorithm for patients with neocortical temporal origin. CPSz = complex partial seizures.

(which is usually so mild as to be clinically inconsequential, though demonstrable on sophisticated testing),[1] motor, and language deficits.

The frontal area most associated with language is Broca's area, situated in the pars opercularis of the inferior frontal gyrus. When performed under general anesthesia, it has generally been regarded as safe to spare the posterior 2.5 cm of the gyrus.[2] However, variable localization of language function has been demonstrated in the frontal lobe,[3–5] and awake mapping, either intraoperative or extraoperative, is preferable. Cortical stimulation has demonstrated reproducible effects on language in the superior and middle gyrus, as well as the parasagittal cortex. Resection of accessory motor language areas (superolateral or parasagittal frontal cortex) can produce a dramatic postoperative mutism that clears gradually over weeks.[6]

Conversely, if the area that anatomically would be expected to be Broca's area shows no speech deficit with stimulation testing, it can be safely resected, provided such function has been localized elsewhere in the frontal lobe. Transient motor dysphasia is common whenever the resection is carried within a centimeter or two of areas in which stimulation has caused consistent errors. This usually clears completely within a few weeks.[7]

To avoid motor deficit, it is crucial to carefully preserve the vascular supply to the precentral gyrus, skeletonizing vessels as necessary. Given meticulous vascular preservation, it is safe to resect up to the precentral sulcus if stimulation testing has been negative.[7]

Temporal resection

Neocortical temporal resections, as alluded to above, have been associated with considerable controversy. Some consider these poor surgical candidates, while others recommend resections tailored completely by intraoperative corticography. The presence of a lesion and the possibility of dual pathology are primary considerations in surgical planning. In addition, the location of eloquent areas in the temporal lobe is extremely variable.[8] The primary concern is language, and it seems clear that the more posteriorly the caudal cortical incision is made during a standardized resection, the more likely a postoperation language deficit. In general, 3 cm from the temporal tip in dominant cortex (4 cm in nondominant cortex) avoids postoperative aphasia.

Mapping studies have demonstrated that language localization is extremely variable, and no landmark provides reliable

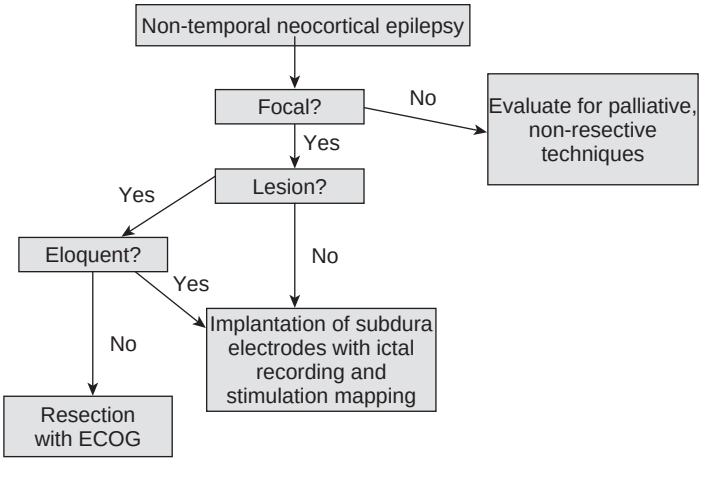

Figure 117.2 Treatment algorithm for patients with nontemporal epilepsy.

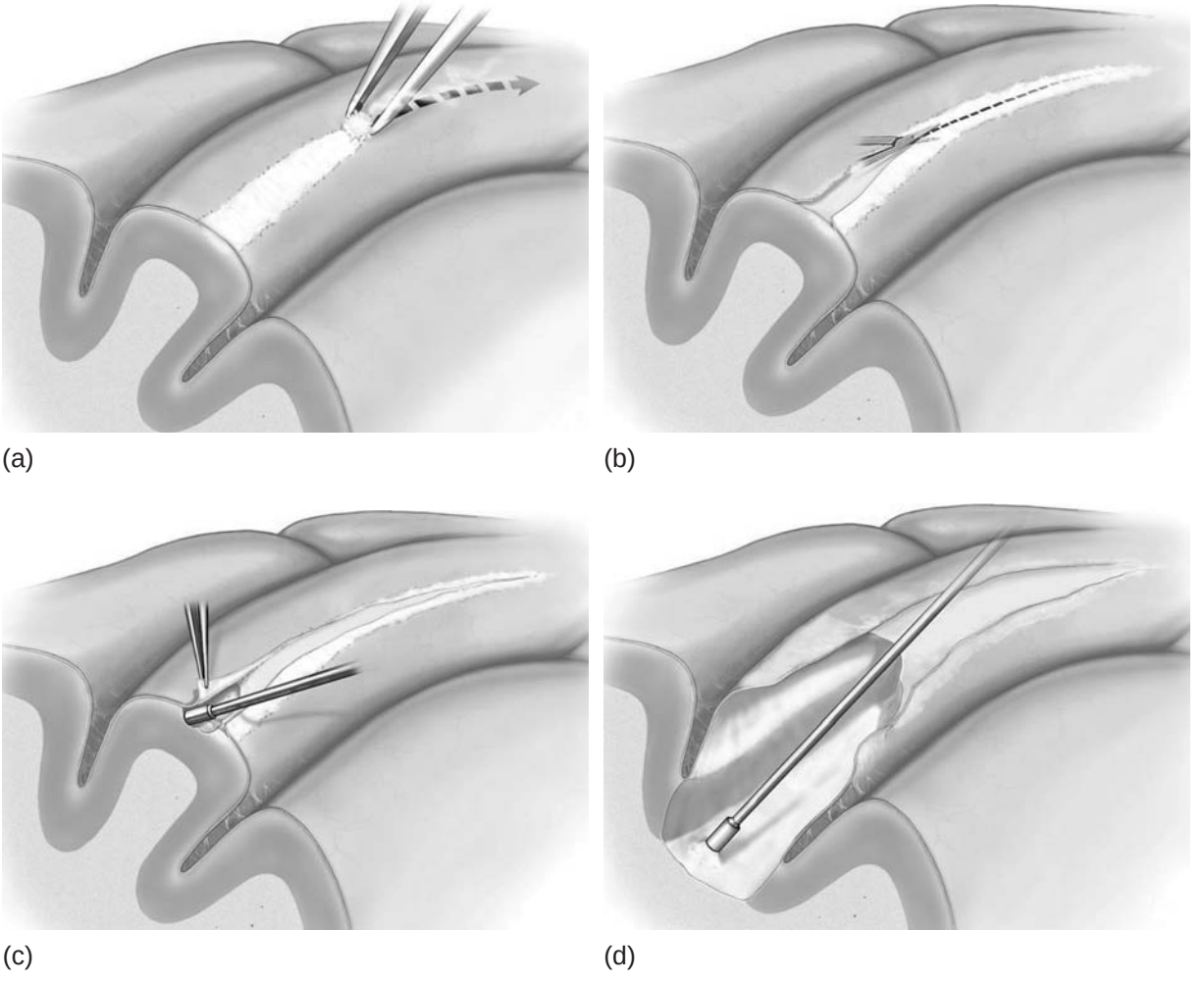

Figure 117.3 Technique for topectomy. (a) The pia over the center line of the gyrus is coagulated with bipolar electrocautery a nd (b) divided with microscissors. (c) The pial flap is then elevated and the gray matter evacuated with gentle suction. Bipolar electrocautery is used for small vessel hemostasis, and occasionally to disrupt tissue that is not easily suctioned. (d) The resection is carried down to the bottom of the gray matter of the sulcus. White matter in the gyrus may be resected to this level, but not further.

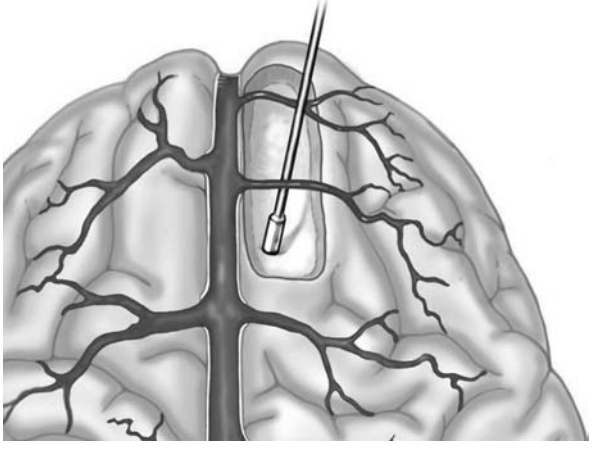

Figure 117.4 Preservation of vessels in topectomy. Respect for the vasculature is of the utmost importance, as sacrifice of en-passage arteries or bridging veins may result in infarction of adjacent, functional cortex, leading to loss of function or a new epileptogenic focus. In this representation, a parasagittal gyrus is resected, skeletonizing the bridging veins.

guidance for anatomic resection.[8] Speech areas are not necessarily confined to the superior temporal gyrus, and in some, no temporoparietal language site can be identified at all.[9] It is thought that unusually located essential language areas may be responsible for aphasia after standardized resection.[10] When such sites are identified, no deficit is likely if the resection spares a 2-cm margin along the gyrus.[8] Despite these concerns, large series of standard ATLs have not reported an increased incidence of aphasia.

Most commonly, language is tested using a naming task, and areas that repeatedly cause anomia with stimulation testing are considered essential language cortex. It is clear that other language functions can be delineated with specific testing and are discretely localized, such as naming in a second language[10,11] or reading.[12,13] In patients for whom these are vital functions, it may be best to map them independently. Other studies have demonstrated that some areas that produce aphasia with stimulation mapping may be safely resected with only occasional and mild lasting language deficit.[14–16]

The localization of memory function within the temporal lobe is also controversial. Most data suggests that postoperative

memory decline is based on resection of a functional hippocampus especially in the language dominant temporal lobe. Memory function is generally assessed preoperatively with the sodium amytal (Wada) test. When the patient suffers profound transient memory deficits with this test, it is expected they would have a high morbidity in terms of short term memory with a standard ATL. Various approaches to this situation have included surgical exclusion or minimizing the extent of mesial resection.[17,18]

Ojemann espouses a different conception of the role of the temporal lobe in memory function, and emphasizes the role of a tailored neocortical resection guided by stimulation testing.[18] He points out that significant work demonstrates that certain sites in the temporal neocortex cause acute disturbances in recent verbal memory during stimulation testing,[13,19,20] and that these are independent of language effects. The technique is time consuming because normal individuals will make memory errors without stimulation, and memory testing involves three phases (input, storage, and output) compared to the simple task of naming in language mapping. The baseline error rate in memory testing means that more testing cycles per stimulation site are required for a statistically significant difference between essential memory cortex and nonessential cortex. Thus he suggests that when the sodium amytal test indicates a major role of the epileptogemic temporal lobe in memory function, rather than denying the patient surgery or limiting the mesial resection, it may be best to tailor the lateral resection with stimulation memory mapping. They have presented two patients[17,18] in whom Wada testing suggested complete dependence of memory on the side of the resection, but had no postoperative decline in verbal memory after such resections. He also points out that dominant temporal resection patients with postoperative verbal memory deficits had large lateral rather than medial resections, and suggests that this is due to resection of lateral cortex essential for the input or storage phases of verbal memory.

Finally, in the posterior temporal lobe, care must be taken to avoid resection below the sulci, as the visual field fibers may be interrupted. The deficit from resection of the temporal pole is very mild and well tolerated, but that obtained by too deep a resection in a posterior temporal corticectomy can be much more profound and disabling.

Central cortex

The deficits associated with resection of face cortex vary both with the extent of resection and with the side. Generally, partial resection of nondominant face cortex will leave no permanent deficit, only a transient facial asymmetry. Complete nondominant resection leaves permanent perioral weakness in half,[21] but generally is not severe if the resection stays at least 2 mm below the lowest site of thumb activation with stimulation.[22] Of course, the stimulation of face, throat or tongue motor cortex on either side may interfere with the movements required for speech and so interfere with language function. Usually, these motor manifestations are clear and be easily distinguished from true language effects. On the dominant side, resection of face cortex can lead to a dysarthria or dysphasia, particularly if there has been any manipulation of surrounding cortex.[7] Rasmussen[21] has successfully resected dominant face cortex without these problems. Care must also be taken in resections in this area not to go too deep, as the underlying white matter includes the projection fibers of the adjacent hand area en route to the internal capsule.

Resection in the hand primary motor cortex will always leave a permanent fine motor deficit and should be reserved for patients without useful hand function. Removal of primary leg cortex results in a postoperative flaccid paralysis that partially[21] recovers if the remainder of the primary cortex is intact. In general, white matter can be removed in the gyri, but it is important not to undercut adjacent cortex. When necessary, white matter stimulation mapping can warn of important subcortical white matter motor tracts and avoid damage.[23]

Removal of the leg portion of the post-central gyrus results in long-term deficits of proprioception and joint sense. Resection of the face portion leads to long-term loss of two-point discrimination. Both of these deficits are well tolerated.[24] Removal of the hand cortex, however, is much more poorly tolerated, with 70% having severe multimodality sensory complaints and 40% having ipsilateral complaints.[24]

Parietal resection

Similar to frontal resection, the side of resection is important in parietal resections. The entire nondominant parietal lobe posterior to the post central sulcus may be relatively safely removed with a 0.5% risk of hemiparesis. Visual field defects may be encountered after parietal resections, usually contralateral lower quadrant defects, the counterpart of the superior quadrantanopsia of temporal resections. They are generally more poorly tolerated than their temporal counterparts[25,26] and are usually associated with too aggressive a resection of underlying white matter.

The major additional consideration in the dominant parietal lobe is the language cortex. The location of Wernicke's area cannot be reliably predicted by anatomic criteria.[3,4,25] Therefore, mapping is essential. Reading and other more complex language functions may be more broadly localized than simple naming.[3,4]

Occipital resection

Occipital foci are relatively uncommon, and often become symptomatic only after spread to the temporal lobe. Given the high risk of visual deficit, it is important to have an accurate assessment of the patient's preoperative visual status (normally including formal visual fields) and usually to obtain very precise intracranial localization of the seizure onset. In cases of documented occipital onset seizures that do not become symptomatic until temporal spread, some recommend a temporal resection for symptom control, rather than risk primary visual cortex.[27] However, as this has been demonstrated to yield poor long-term seizure control, most recommend either resection of the epileptogenic tissue, or nonsurgical therapy. If such a resection is attempted, the anterior limits of resection are into the parietal and parietotemporal areas, with the most important emphasis on preservation of calcarine cortex and optic radiations.

Summary

A variety of methods exist for determining the precise location of neocortical epileptogenic foci. The most crucial of these are imaging and electrophysiologic methods. Once localized, these foci can be resected with a careful subpial technique, taking care to preserve the vasculature and underlying white matter. Careful attention to the location of eloquent cortex in each lobe, using both anatomic criteria and awake mapping, can minimize the risk of a postoperative neurological deficit.

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118 Epilepsy and vascular malformations: spectrum of lesions and strategies for management

P Jabbour and I Awad

Spectrum of cerebral vascular malformations

Cerebral vascular malformations are known to affect 2–4 % of the population, predisposing their host to a lifetime risk of hemorrhagic stroke and epilepsy. These are a hetregeneous group of lesions, with distinct angioarchitecture, and also biologic mechanisms of lesion genesis and progression. Risk and mechanisms of epilepsy are also variable among different lesion types, and treatment decisions often consider not only their epileptogenicity, but also the prospective risk and potential sequelae of hemorrhage.

Arteriovenous malformations

The arteriovenous malformations (AVMs) exhibit mature vessel wall elements with direct communications between arteries and veins, and a high flow profile predisposing to vascular recruitment, arterialization of venous structures and gliosis of intervening and adjacent brain tissue (Figure 118.1). They have three major components: arterial feeders, nidus, and venous outflow. The AVMs are associated with significant gliosis in the nidus and in adjacent brain, thought to result from ischemia caused by arteriovenous shunting and venous hypertension.[1–5] AVMs are prone to apoplectic hemorrhage by rupture of nidal vessels or associated aneurysms, or by venous outflow obstruction.[6–8]

The AVMs have a distinct phenotypic profile, recognizeable on magnetic resonance (MR) imaging and angiography, and these can reveal nidus size and major arterial feeders and draining veins. The MRI also reveals parenchymal ischemia and gliosis in adjacent brain, and areas of encephalomalacia related to previous hemorrhage.

The AVMs typically present as solitary lesions, except in the rare setting of Hereditary Hemorrhagic Telangiectasia (HHT), or disease of Osler-Weber-Rendu, which includes multifocal AVMs, including tiny lesions in skin and mucosa, and multiple organs in addition to brain. The lesions all represent direct arteriovenous shunts, with lack of capillary bed in the nidus, and secondary changes of arterial recruitment and venous engorgement. HHT disease has recently mapped to the endoglin gene (a TGFβ binding protein expressed on endothelial cells) on 9q, or the activin receptor-like kinase gene on chromosome 12q, also expressed on endothelial cells and related to the TGFβ receptor system. The genetic heterogeneity in HHT is associated with apparent differences in disease manifestations, with more frequent cerebral and pulmonary AVMs in association with endoglin mutations. A third gene locus Smad4 on Chromosome 5 has recently been associated with familial colon polyposis in addition to manifestations of HHT.[9]

Cerebral cavernous malformations

Cerebral cavernous malformations (CCMs) represent clusters of dilated sinusoids filled with blood and lined with endothelium without intervening parenchyma (Figure 118.2). They appear to grow by a process of vascular cavern proliferation in the setting of repetitive lesional hemorrhages. The CCMs exhibit brittle vascular morphology devoid of mature vessel wall elements.[10,11] They do not exhibit the high-flow features of AVMs and are less commonly associated with apoplectic hemorrhage.[12–15]

The CCM lesion are commonly missed or misdiagnosed on computed tomographic scans of the brain, because of small size and often isodense appearance related ot subacute hemorrhage or microcalcifications. They are angiographically occult. However, the CCM lesions are easily detected on MR imaging, and manifests a specific appearance of mixed signal in the lesion itself on T1 and T2 sequences, surrounded by a ring of T2 hypointensity from leakage of hemosiderin. Smaller CCM lesions may only be seen on gradient echo MR images because of tell tale hemorrhagic signals.

Solitary CCM lesions occur in 40–60% of cases, with remaining cases manifesting multiple lesions and familial inheritance in autosomal dominant pattern. Familial CCMs have been linked to one of three gene foci on chromosomes 7q, 7p, or 3q.[16] The identified proteins encoded by CCM genes appear to interact with endothelial cytoskleton during angiogenesis,[16,17] and are expressed in neural tissue, hence potentially explaining propensity of lesion genesis in the central nervous system.[16,17] A hallmark of familial disease is the presence of multiple lesions, some of which may only be appreciated on gradient echo MR imaging (Figure 118.3). Solitary sporadic (nonfamilial) CCMs are frequently associated with venous anomalies as noted below, and

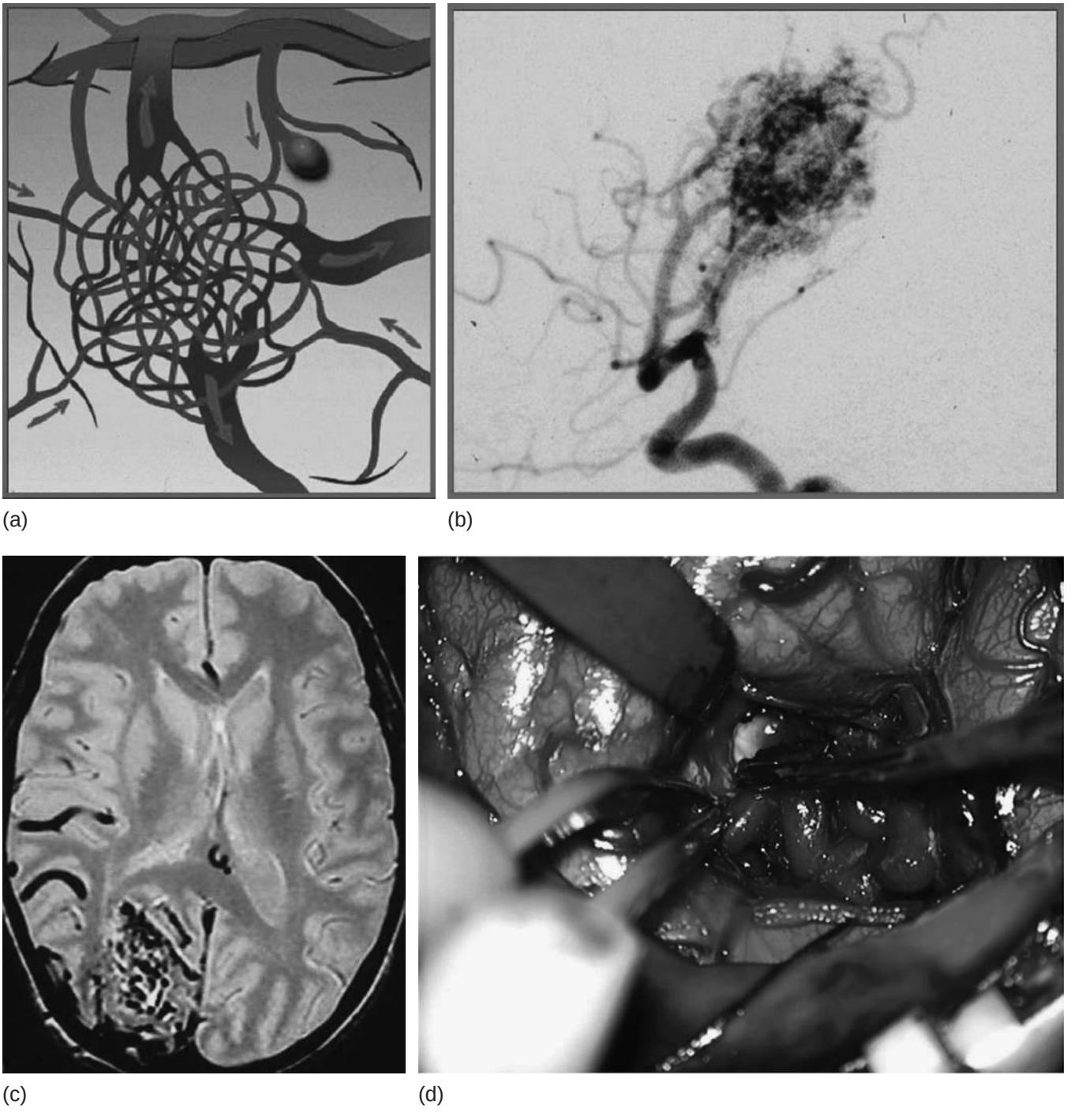
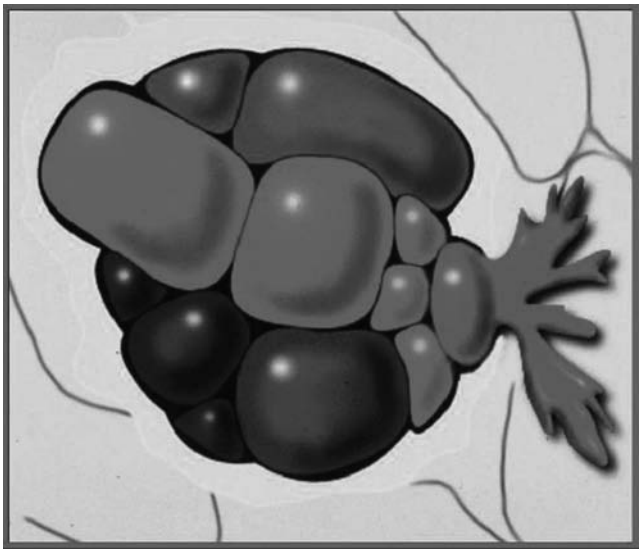


Figure 118.1 (a) Drawing showing the AVM with the arterial feeders, draining veins and the nidus. (b) Cerebral angiogram showing an AVM. (c) Brain MRI showing the flow voids of the AVM. (d) Intraoperative photograph showing brain AVM with arterialized engorged veins within the frontal lobe of the brain.

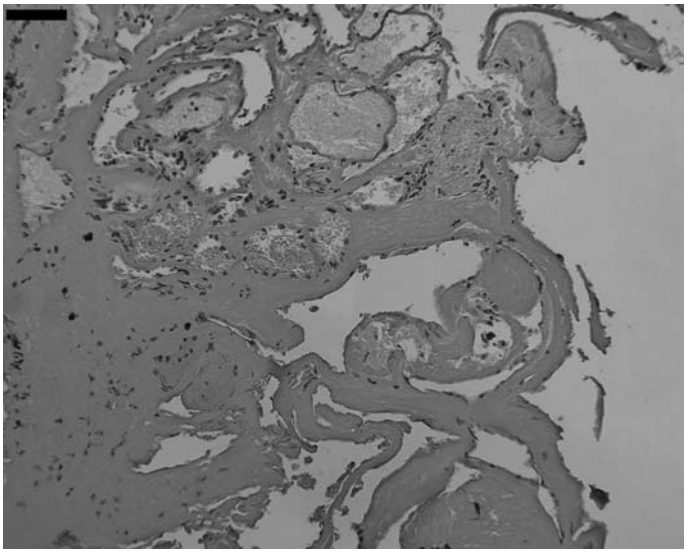
these can easily be recognized on contrast enhanced T1 MR sequences.

Capillary malformations

Capillary vascular malformations, also known as capillary telangiectasiae are vascular malformations that consist of a collection of dilated capillaries with normal intervening brain parenchyma.[18–21] They are most commonly located in the pons. They are typically and incidental finding at autopsy, but some cases of symptomatic capillary malformations have been visualized on MRI as vague patches of punctate contrast enhancement[19,22–24] (Figure 118.4). They may also be found in association with more clinically overt lesions, such as CCMs or venous malformations. Microscopically, the vessel walls appear similar to normal capillaries, lined with a single layer



(a)



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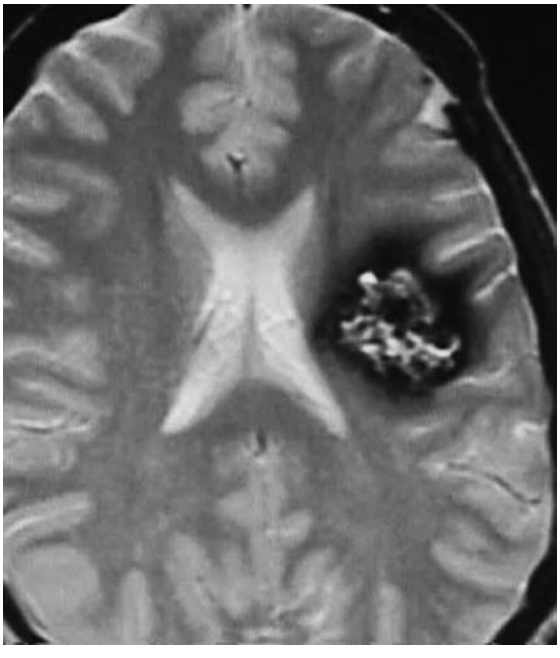


(c)

Figure 118.2 (a) Drawing showing the mulberry like cavernous malformation. (b) Photomicrograph showing the blood filled caverns forming the CCM, with positive immunostaining of endothelial cell lining. (c) MRI scan showing left Rolandic CCM with mixed signal features characteristic of the lesion, and the perilesional ring of decreased T2 signal characteristic of hemosiderin.

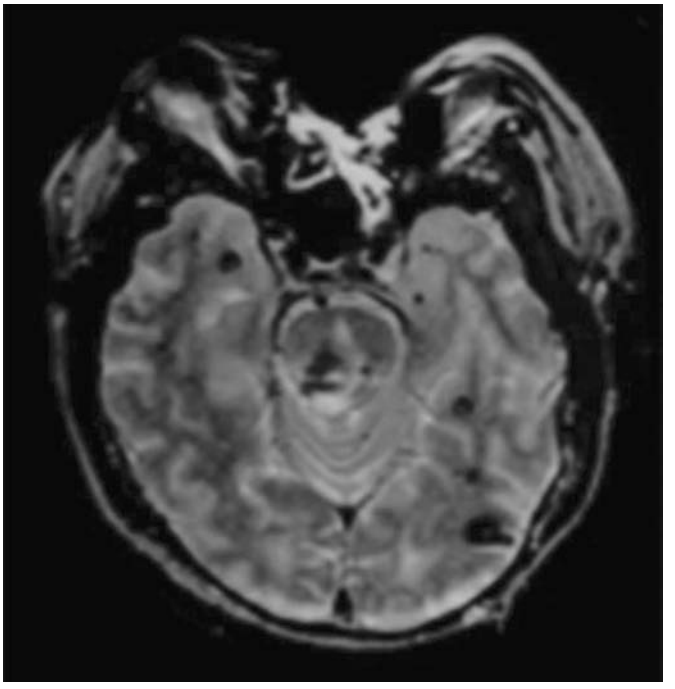
of vascular endothelium. While both capillary telangiectasiae and CCMs represent dilated capillaries, the presence of hemorrhage (on MR imaging or histopathology) is a cardinal difference that clearly distinguishes CCMs from capillary malformations.

Venous malformations

A fourth and the most common form of cerebral vascular malformation is the venous malformation (VM), also known as venous angioma or venous developmental anomaly (Figure 118.5). The VM rarely bleeds except when associated with a CCM lesion [25,26] (Figure 118.6). It is composed of abnormally enlarged venous channels separated by normal neural parenchyma.[27, 28] These vessels are arranged in a radial pattern extending from a dilated central venous trunk, which itself drains into either a deep or superficial venous sinus.[19,27,29,30]

Mixed and dural vascular malformations

Despite the apparently distinct clinical-radiologic-pathologic profiles of the various cerebral vascular malformations, some lesions exhibit mixed or transitional features implying related pathobiologic mechanisms.[23,31–34] Portions of CCMs may exhibit partial or complete mature vessel wall elements akin to AVMs (Figure 118.6), and many CCMs appear to arise in close proximity to venous malformations (Figure 118.7).[1,4]



Firgure 118.3 Gradient echo MRI showing the hemosiderin of multiple CCMs.

It is not known if mixed vascular malformations with CCM component occur in the setting of genetic predisposition to CCM. Both CCMs and AVMs may rarely be associated with skin lesions (even in the absence of HHT) although such skin pathology has not been carefully characterized in association with various lesion types. Rare metameric vascular malformations have also been associated with complex abnormalities and AVM extension into adjacent skull, face and skin.[35–37]

Dural AVMs are another category of vascular malformations with arteriovenous shunting involving the pachymeninges, but may manifest retrograde letpomeningeal venous drainage into the cerebral circulation. This feature may result in venous hypertension in brain parenchyma, and has been associated with seizures and focal neurologic deficits [38–41] (Figure 118.8).

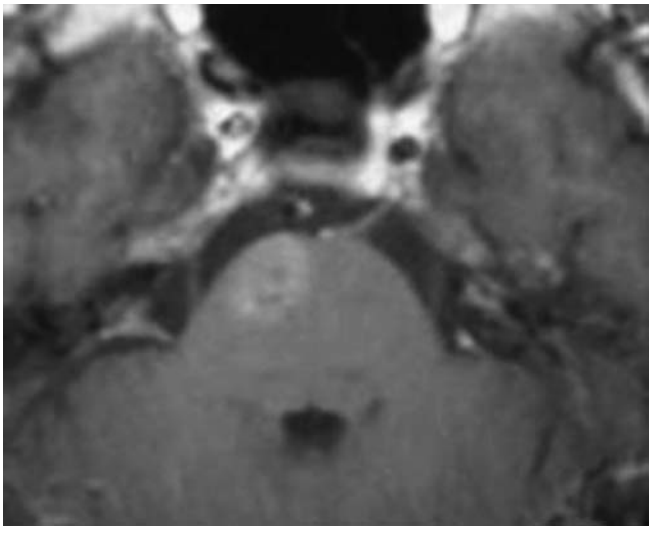


Figure 118.4 T1-weighted MRI image with gadolinium showing pontine capillary telangiectasiae.

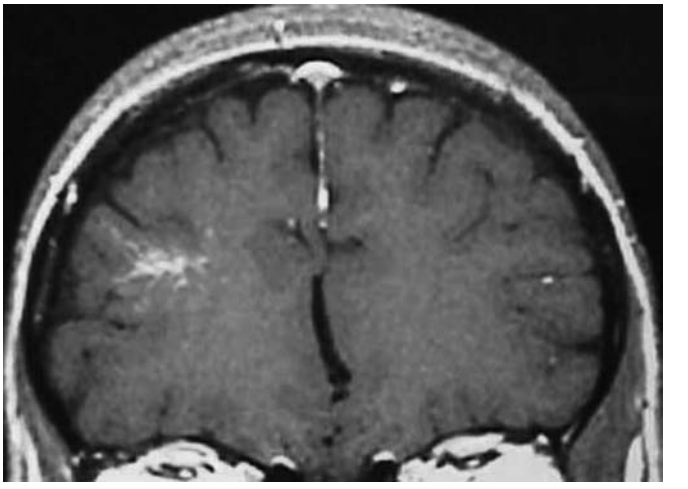


Figure 118.5 T1-weighted MRI with contrast, showing venous developmental anomaly or VM, characterized by large transmeduallry vein with caput medusae morphology, and no other abnormality in adjacent brain. T2-weighed and gradient echo images would not typically reveal any evidence of bleeding.

Mechanisms of epilepsy

Both diagnosis and treatment of localization-related epilepsy have been greatly improved by modern neuroimaging methods. This has led to the reclassification of many 'cryptogenic seizures' into lesional epilepsies, many of these epilepsies are amenable to surgical treatment with the potential for cure or significant reduction in seizure frequency with lesion resection. Lesional epilepsy is thought to be a direct consequence of a focal brain lesion that could be neoplastic, vascular, dysgenetic, traumatic or ischemic.

Localization-related epilepsy is also likely affected by host predisposition, as identical lesions (type, size and location) may cause varying manifestations in different patients, including a spectrum of severity of seizure disorder. Host predisposition may also affect seizure intractability, propensity for pharmacologic seizure control, and the cure or recurrence of epilepsy after lesion excision.

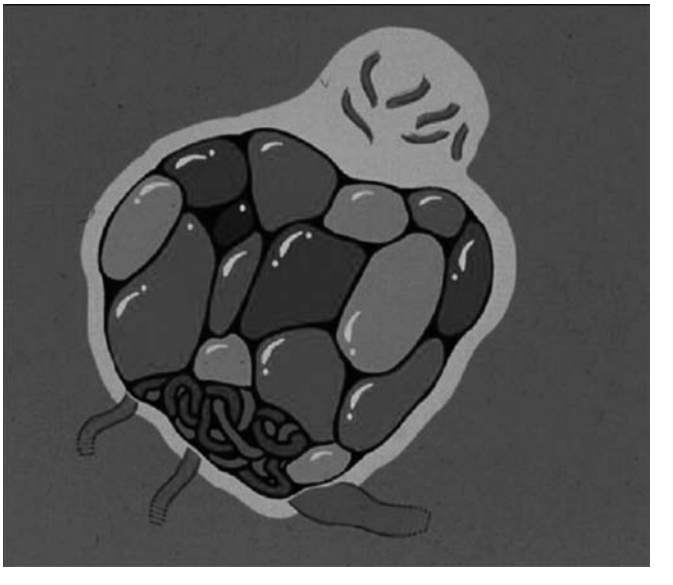


Figure 118.6 Drawing showing a mixed lesion, CCM-AVM and CCM-capillary telangiectasia.

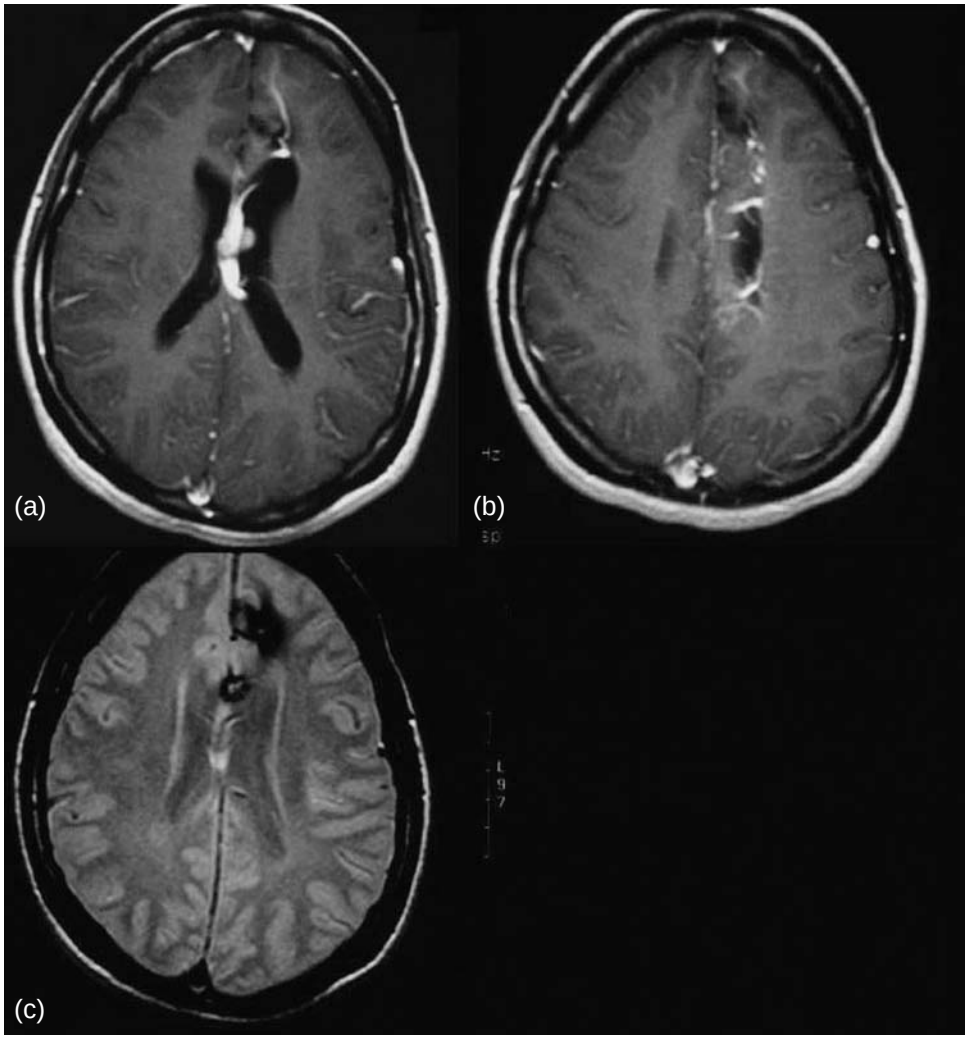
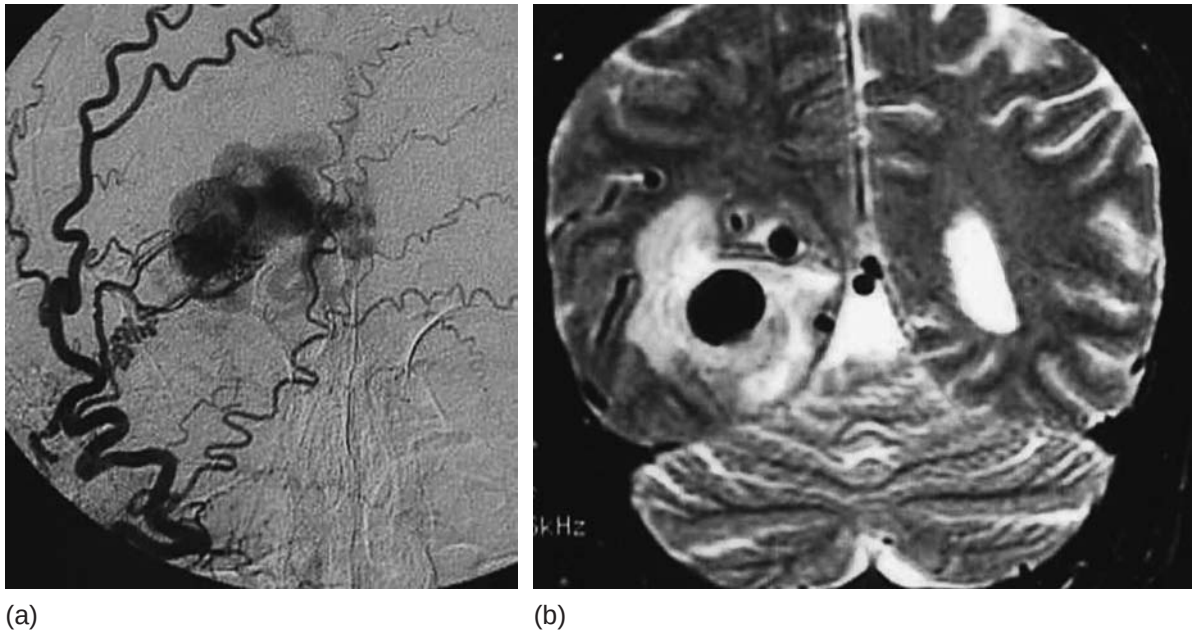


Figure 118.7 (a and b) T1-weighted MR with contrast showing prominent venous anomaly, with associated mixed-signal abnormality in mesial frontal lobe. (c) T2FLAIR image clearnly illustrating CCM lesions in association with the venous anomaly.



(a) (b)

Figure 118.8 (a) Common carotid angiogram showing dural AVM with large associated cortical varix. (b) MRI from the same case revealing varix and associated edema. Patient presented with new onset seizures and homonymous hemianopia.

Epileptogenesis in adjacent brain

The vascular malformations are malformed blood vessels and do not typically include funtioning neural tissue. Hence they are not intrinsically epileptogenic, but induce seizures by their effect on the surrounding brain tissue. These may include ischemia, venous hypertension, gliosis, deposits of blood breakdown products, and/or cellular and humoral inflammatory response. Epilepsy in association with vascular malformations has been shown to induce different firing patterns in adjacent hippocampal slices than epilepsy associated with neoplasia.[42]

These alterations may induce epileptic activity that is dependant on the presence of the vascular malformation, and may not support ongoing epileptogenic activity in the absence of that primary lesion. Other changes in adjacent brain may represent permanent (independent) epilep-togenic foci. In these cases selective resection of the MRI-visible lesion may not be sufficient to abolish all the seizures.[42] There is thought to be a spectrum of such maturation of independent epileptogenicity, and time course is thought to be important in the establishment of independent seizure foci. Hence, lesion-related epilepsy is postulated to be more likely permanent or independent of the instigating pathology, after longer duration of epileptogenicity.

Overt hemorrhage from AVMs and CCMs may create encephalomalacia and cortical scars that may be independently epileptogenic. These are often noted on MR imaging and may be associated with correlative focal neurologic deficits. Chronic deposition of blood breakdown products is characteristic of CCMs, where gliotic hemosiderin-stained brain adjacent to the lesion is thought to be the source of epileptogenic activity. In contrast, AVMs may induce gliosis from ischemia in adjacent brain or vasogenic edema form venous hypertension, both related to arteriovenous shunting. Venous angiomas, may rarely cause venous hypertension in adjacent brain, or may reflect regional gyral dysmorphism, itself responsible for seizure activity.

Epileptogenesis in remote brain regions

Lesions may induce changes in the brain tissue located at a significant distance from the primary epileptogenic lesion, and this may contribute to epilepsy syndrome, and even to independent distant foci of epileptogenicity. The limbic structures, and to a lesser extent neocortex, may 'learn' to generate seizures independently and, may become secondarily epileptogenic, after constant exposure to the repetitive seizures caused by an epileptogenic lesion. Over time this may alter network relationships in such a way as to lead to secondary epileptogenesis in these remote regions.[44] This has been most frequently demonstrated in mesial temporal structures adjacent to structural lesions, and much less likely in human neocortex.

Another form of remote epileptogenicity is commonly seen in association with venous hypertension from AVMs, or more commonly dural AVMs, where arteriovenous shunting in the vascular lesion causes alterations of circulation and neurologic manifestations in remote brain. This can often be gleaned from careful analysis of lesion angiodynamics and 'vasogenic edema' signals on MRI.

The demonstration of dual epileptogenic activity in association with a single vascular malformation does not necessarily imply that the second focus, more remote from the lesion, will remain active after lesion excision. In fact, this seems to be uncommon in the setting of single vascular malformation-associated seizure disorder. Often, this dictates a staged approach, with excision of lesion and surrounding epileptogenic brain, at first stage, and more extensive investigations of remaining epileptogenicity only in those uncommon cases where seizures persist after lesion excision. The more frequent the seizures, the more likely a secondary focus to become permanent. This raise the question of early surgical intervention when medical therapy fails.[45]

Multiple lesions

Dual and multifocal pathologies are important for the understanding of the pathogenesis of epilepsy and also for surgical planning. Patients who preoperatively demonstrate multiple structural lesions require more extensive preoperative investigations and tailoring of interventions for control of epilepsy.[46–48]

The CCMs are frequently, and AVMs more rarely, associated with multifocal vascular lesions, any one of which may contributing to epileptogenesis. While the larger lesion, or one with most recent bleeding or other clinical manifestations, is more likely the source of seizures, this cannot be taken for granted. Resection of the wrong lesion will not only fail at controlling seizures, but may result in catastrophic functional sequelae when the remaining epileptogenic lesion resides in contralateral temporal or frontal lobes.

The most sensitive imaging studies must be evaluated in the setting of cerebral vascular malformations to demonstrate or exclude multifocal structural pathology, that may be contributing to epileptogenicity. In cases of CCMs or venous malformations, gradient echo MR images must be performed to demonstrate or exclude multiple foci of occult hemorrhage. In cases of HHT, formal cerebral angiography may demonstrate exceptional multiplicity of cerebral AVMs not evident on MRI,[49] while MR imaging may reveal areas of previous ischemia from paradoxical embolism caused by pulmonary AVMs.

Treatment options

Medical therapies

The first line treatment of seizures associated with a vascular malformation is always medical. Different anticonvulsant agents are associated with varying effectiveness in different seizure types. And several newer drugs are associated with fewer side effects, or may be safer in potential pregnancy. These drugs will be reviewed in detail in different sections in this book.

After a first seizure, the decision to start anticonvulsant medication is based on the risk of seizure recurrence and on the potential risks associated with chronic antiepileptic therapy. Whenever a structural lesion is identified on imaging studies, decision must be made about its likely relation of the lesion to the seizure disorder. In the setting of cortical CCM, AVM, and certainly where seizure semiology is clearly related

to the lesion locale, this relationship is easy to establish. In other instances, such as with infratentorial or subcortical vascular anomalies, or seizure precipitated by alcohol, drugs or trauma, the possibility of incidental lesion may be considered. Venous malformations are extremely common in the general populations and are often incidental to various neurologic symptoms, including seizures, especially when seizure semiology does not suggest appropriate localization. Electrophysiologic studies may be helpful in this regard, especially when positive and with appropriate lateralization or focality, but a normal electroencephalogram does not rule out epileptogenicity.

If a vascular malformation is thought to be the cause of seizure, long-term anticonvulsants are indicated, as seizures likely will recur and may progress toward intractability. A drug is chosen based on the type of seizure, and on potential side-effects in the particular patient. When the drug of first choice has been selected this drug almost always is used in monotherapy. Only when seizures recur despite verified compliance and therapeutic doses of monotherapy is a second agent added.

Patients with vascular anomalies in cortical locations are subject to a prospective lifetime risk of new seizures. This is greatest with CCMs located in temporal, frontal, and perilimbic locations, and may affect occupational clearance for pilots and other professions. Clinical history is important in such patients, to elicit possible auras or other stereotyped symptoms that may represent seizure activity. However, prophylactic treatment is rarely indicated in these instances unless epileptic activity has been established.

Lesionectomy

Surgical resection of vascular malformation may be undertaken to prevent future hemorrhage, and/or to assist in seizure control. This can involve resection of the lesion alone known as lesionectomy, which is associated with an excellent postoperative control of seizure activity in many patients.[12] The likelihood of postoperative seizure control following simple lesion excision is greater in patients with less intractable preoperative epilepsy, and also in patients with extratemporal lesions. Unlike temporal lobectomy there are no anatomically standard operations for performing a simple lesionectomy. These procedures are divided in temporal lesionectomy and extratemporal lesionectomy. In patients with temporal lesions and intractable epilepsy, studies of lesionectomy alone without resection of mesial structures showed a low seizure control rate ranging from 20 to 45%.[50–52] In extratemporal lesional epilepsy, lesional resection alone has provided favorable results with seizure control rate varying from 65 to 95%.[50–53]

Most patients achieving postoperative seizure control will still require long term anticonvulsants, often with fewer agents and at lower doses. The decision to taper or discontinue anticonvulsant therapy is often performed very cautiously to avoid precipitating new or recurrent seizures. In the setting of new onset localization-related seizures and single cerebrovascular anomaly, especially CCM, up to half of cases that are seizure free after lesion excision may successfully taper off all anticonvulsant medications.[54–57] This promising outcome, and its associated positive impact on quality of life, may play a role in decision to excise a solitary accessible cerbrovascular anomaly, especially a cortical CCM, even when seizures are not truly intractable to medical therapy.

Lesionectomy and cortisectomy

Surgical resection of structural lesions can involve resection of the lesion alone or resection of the lesion and epileptogenic cortex. A tailored resection may be performed to avoid the eloquent cortex. Many studies have compared lesionectomy and lesionectomy with cortisectomy,[51,53,58,59] with controversial results. A meta-analysis evaluating seizure outcome following lesionectomy or lesionectomy and cortisectomy concluded that at 2-year follow-up, the percentage of patients with persistent seizures following lesionectomy ranged from 1.4 to 4 times that following lesionectomy and cortisectomy. Low grade gliomas, gangliogliomas, and vascular malformations were most successfully treated with lesionectomy and cortisectomy.[60] On the other hand patients with fewer seizures before presentation, shorter preoperative seizure history, or seizures that responded to antiepileptic medications are more likely to be seizure free following lesionectomy alone.[61–67]

Several studies have shown that complete lesion excision is necessary for seizure control in the majority of patients where the lesion is shown to be responsible for the seizure disorder.[53] It also is well documented that lesion excision alone may not always sufficient for seizure control, especially in patients with truly intractable epilepsy. Many patients with persistent intractable seizures following lesion excision have involved lesions in the temporal lobe.[50] Some of these patients were rendered seizure free by additional resection of epileptogenic brain in the same region.

Resection at first operation of epileptogenic brain in addition to the lesion may accomplish seizure control, sparing the patient a second surgical intervention. But the functional impact of resection of additional brain must be considered in this decision. This is especially important when considering resection of mesial structures in the presence of high or normal material specific neuropsychologic function, or in other eloquent areas (such as dominant temporal neocortex). Intraoperative electrocortigoraphy is sometimes performed to further delineate the extent of the cortical epileptogenic zone. This technique may provide prognostic information by indicating the areas of residual discharges after the resection of the vascular malformation or what was thought to be the seizure focus.[68–72] However, residual spikes in adjacent brain areas do not reliably predict residual epileptogenicity, nor does their absence guarantee postoperative seizure control.

Disconnection surgery

Multiple subpial transections are mainly used to treat partial epilepsies that reside within eloquent cortical regions.[73] The technique involves disconnecting the gray matter columns that lie in eloquent cortex. This can inhibit synchronization and spread of seizure activity with less drastic effect on eloquent function.[74–77] Most patients who have multiple subpial transections in eloquent brain have subtle transient deficits corresponding to the area transected most pronounced in the first week after surgery.[78–82]

Corpus callosotomy is another potential palliative treatment in patients with multiple or poorly lateralized epileptogenic foci, secondarily generalized tonic-clonic seizures, and injurious drop attacks due to tonic or atonic seizures with resultant falls and injury[83–86] In 70% of patients, elimination or more than 80% reduction of seizures has

been reported.[84,85,87] Complications specific to this procedure consist of acute disconnection syndromes more common with total callosotomy.[88,89]

Neuroaugmentative surgery

Vagus nerve stimulation is a palliative treatment for intractable seizures, with data in the literature showing a seizure reduction rate varying from 35%–75% in the setting of various seizure types, with most patients remaining on anticonvulsants. Specific results in seizure disorder associated with cerebrovacular malformations have not been reported to our knowledge. The side-effects can include voice alteration, hoarseness, throat or neck pain, headache, cough, dyspnea, vocal cord paralysis, and aspiration.[90–93] It is a relatively simple procedure technically, but discussion with the patients about their expectations after such procedure is very important.

Deep brain stimulation has been attempted for the modulation of seizure activity, with electrode stimulation targets in the cerebellum; in anterior, centromedian, and ventralis intermedius thalamic nuclei; and in the caudate nucleus has.[94,95] Stimulation of the hippocampus in an attempt to block temporal lobe seizures has recently been used.[96] The stimulation of the subthalamic nucleus reduced daytime seizures by 80%.[94]

Management strategies

First seizure

The surgical option is rarely considered for the goal of seizure control in patients with a first seizure in association with known or newly diagnosed vascular malformation. Lesion excision may be performed for the purpose of preventing hemorrhage, and in rare cases, especially with solitary and accessible CCM, to allow a chance at discontinuing anticonvulsant medications. Medical treatment is typically initiated to try to classify the patient in the well controlled or uncontrolled seizure group.

Arteriovenous malformations

The cause of epileptogenesis from cerebral AVMs is not always evident. A number of different hypotheses have been proposed,[57, 97–102] including focal cerebral ischemia attributable to a 'steal' phenomenon resulting from neighboring arteriovenous shunting. Gliosis, neuronal degradation, demyelination, and hemosiderin deposits lining the AVM bed have been suggested. And there have been noted secondary epileptogenesis at a distant site attributable to a 'kindling' phenomenon, in which epileptic discharges are enhanced by excitatory synaptic connections from the AVM.

Cerebral cavernous malformations

The CCMs are known to be more epileptogenic than other cerebrovascular anomalies, as they are more frequently associated with seizures and with intractability of epilepsy. The exact mechanisms by which CCMs cause seizures are unknown although a number of electrophysiologic and pathophysiologic theories have been proposed. These include changes in altered neurotransmitter levels (GABA and somatostatin), free radical formation and altered second messenger physiology.[103] Morphological changes have also been identified such as alterations in vascular supply, neuronal cell loss, glial proliferation and subtle subcortical disconnections.[57] Most investigators suspect that the breakdown products caused by repeated small microhemorrhages deposit ferric ions into the surrounding cortex which are known to be highly epileptogenic. In animals, the injection of ferric ions into the cortex and subcortical regions creates a potent and reproducible model of recurrent and intractable seizures.[104] These different pathophysiologic mechanisms my present unique opportunities for developing specific anticonvulsant strategies better suited to such mechanisms.

CCMs in the Rolandic or peri-Rolandic cortex, as well as near limbic areas (temporal lobe and cingulate gyrus lesions) tend to be the most epileptogenic. Lesion size may represent an additional factor in epileptogenicity. A final issue that must be considered is the possibility that the CCM identified on imaging may represent an incidental finding and not playing any role in seizure onset. This may be the situation in up to 6% of cases of patients with cavernous angiomas and epilepsy.[105] It is also possible that the CCM represents a structural lesion coexistent with mesial temporal sclerosis.

Capillary and venous malformations

The risk of hemorrhage of capillary telangiectasia is extremely minimal, there are some reports in the literature decribing the association of capillary malformations with seizures and hemorrhage.[106,107] Seizures can occur as a direct result of the hemorrhage caused by the capillary malformation, a transformation likely converting the lesion into a CCM.

Venous angiomas are rarely associated with seizures. Moreover these lesions are often difficult to relate causally and topographically to the epileptogenic zone.[108–110] More often they are occasionally observed during the diagnosic evaluation of different incidental clinical scenarioss. These lesions are often associated with cavernous malformations or AVMs and in this setting the seizures are probably due to the associated malformation rather than the venous angioma itself.[108–111] Rarely, brain dysmorphism (gyral or lobar developmental anomalies) are associated with regional venous dysmorphism. In those instances, the venous anomaly is an index or associated dysmorphic brain that may be epileptogenic. Careful electrophysiologic studies and interictal and ictal functional imaging are indicated in these cases to clearly associate the lesion with epileptogenic zone.

Controlled seizures

Regardless of the type of vascular malformation, the risk of surgical intervention for any vascular malformation is not typically warranted in the setting of well-controlled epilepsy unless there exists another indication for lesion excision. Often, lesion excision is considered to prevent future hemorrhage, but not necessarily to assist with seizure control.

Some patients not compliant with their antiseizure medications but otherwise with medically-controlled seizures would be candidate for resection of the vascular malformation for seizure control purposes, or patients that do not want to be on antiseizure medications because of adverse effects or other reasons, may also benefit from a surgical resection. In these cases it is very important to take into account the location of the malformation and the feasibility of the procedure, weighting

the risks and benefits, and enhanced seizure control or discontinuation of medicatiosn cannot be guaranteed.

Patients with controlled seizures harboring an AVM may need their lesion treated for reasons different than seizures, mainly for the purpose of avoiding a risk of hemorrhage from the AVM which varies between 2–4% per year.[112] Different treatment modalities are available depending on the grade of the AVM: surgery, endovascular embolisation, or stereotactic radiosurgery. These considerations are beyond the scope of this chapter.

Cavernous malformations have a lower risk of apoplectic hemorrhage compared to AVMs, but lesions with prior overt hemorrhage or demonstrated lesion growth are often considered for lesion excision to prevent further neurologic sequelae.

Intractable seizures: prognosis and outcome

The presence of a vascular malformation in association with intractable seizures is a challenging situation. Surgical intervention for resection of the malformation is usually performed in an attempt to control the seizures.

Arteriovenous malformations

In the majority of AVM patients with seizures, the emphasis of surgical intervention is the elimination of the risk of intracerebral hemorrhage rather than seizure control.[97] Most seizure disorders associated with AVMs can be well controlled with anticonvulsant medication. Seizures might improve, remain unchanged, or worsen after any therapeutic intervention for an AVM.[66, 97,113–117] De novo seizures have also been described after AVM resection. Intractable seizures often become much easier to control after AVM excision, and in a few cases anticonvulsants may be discontinued altogether after a seizure-free period. There is no evidence that extensive monitoring, mapping, and excision of epileptogenic brain is necessary, cost effective, or achieves a better overall outcome relative to seizure control than the primary treatment of AVMs. In cases of persistent intratctable seizures after AVMs excision, formal mapping and excision of epileptogenic zones can achieve seizure control.[118]

Some factors are implicated in the likelihood of postoperative seizures: age at seizure onset <30, duration of preoperative seizures >12 months, AVM size >3 cm, location of the AVM in the vicinity of mesial temporal or peri-Rolandic cortex, prior hemorrhage and gliosis surrounding an AVM.[57,66,97,98,114,119]

Cerebral cavernous malformations

Patients with solitary CCMs and uncontrolled epilepsy with semiology related to lesion location are candidates for surgical excision of the CCM to improve seizure control. Overall analysis of the data demonstrates improvement of symptoms in the majority of patients.[12–14, 120,121] Of patients treated with surgical resection of the offending lesion, 50%–90% were postoperatively seizure free with or without anticonvulsant therapy.[13,14,120] Persistent seizures have been reported in conjunction with incomplete lesion resection. In order to maximize the likelihood of seizure control, excision of the CCM should be accompanied, whenever possible (i.e., in noneloquent brain regions), by resection of the gliotic hemosiderin-stained brain surrounding the lesion.[12,13,55,110]

As with AVMs, there is no evidence that extensive preoperative mapping or additional brain excision at initial surgery will improve seizure outcome beyond that of lesionectomy and perilesional gliotic brain in cases with solitary CCMs and intractable epilepsy. The rare cases with residual or recurrent seizures after lesionectomy may be considered for resection of residual lesion, adjacent or remote epileptogenic brain at the second operation. Such reoperations require comprehensive preoperative and intraoperative mapping and functional studies as in other localization-related epilepsies.

In patients where there is any question whatsoever about relationship of a CCM to the intractable seizure disorder, the patient should not undergo empiric lesion resection with the remote hope that intractable epilepsy might resolve, instead, detailed preoperative mapping and recording should be performed. This is particularly true in cases with mutiple CCMs, where the single offending lesion is not always easy ot define. In these cases, careful preoperative mapping and other diagnostic studies must be undertyaken before preoposing the resection of one of the lesions for seizure control.

Conclusion

The direct relationship between structural vascular malformations and seizures, is not always clear cut. Prolonged preoperative mapping and careful recording are mandatory in clarifying cases in which the lesion may not be the primary epileptogenic drive, may simply be incidental or unrelated to the seizure disorder, or in cases with multifocal pathologies. Complete resection of a solitary AVM or CCM is the best approach to optimize seizure control if the lesion is indeed believed to be epileptogenic. Thresholds for considering lesion excision are dictated by the projected natural history of the lesion, and its surgical accessibility. In the different senarios families and patients should be aware of all expectations from different procedures.

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119 Resective neocortical techniques in children

F Villarejo

Definition

Resective surgery can be used to treat any epilepsy that originates in the neocortex outside the medial structures of the temporal lobe.

Introduction

Cortical resection to treat refractory epilepsy was first described by Victor Hosley in 1886.[1] His classic paper on the subject described a young adolescent with numerous daily crises who was completely cured after the surgery. Despite the efforts of this pioneer neurosurgeon, surgery for refractory epilepsy was only accepted after the work of Penfield and Jasper[2] from the Montreal Neurological Institute. They described the role of electroencephalography, or EEG, and confirmed that a good prognosis depended on multidisciplinary teamwork among epileptologists, radiologists, neuropsychologists, neurosurgeons and anesthetists. The series published by these authors and other institutions in the second half of the twentieth century included mostly adults and only a few young people.

Papers by Rasmussen[3] and Goldring[4] demonstrated that this surgery was safe in a developing brain. Various factors have lead to more widespread greater acceptance of surgical treatment for refractory epilepsy in children in recent years. The most important is the awareness of the natural history of some pediatric syndromes that only have surgical treatment. Although the intensity and frequency of the crises should decrease with time, the patient's intelligence decreases progressively if the seizures persist. What is more, spontaneous remission of the crises is very rare. And, some anticonvulsants are known to have a negative effect on intellectual development.

Second, the advances in neuroradiology, metabolic studies, and functional MRI have improved our identification of the structural lesions that are responsible for the epilepsy as well as the relations between the lesions and important functional areas.

Third, we would note that the development of techniques to map brain function has enormously improved the surgical prognosis in pediatric patients. The safety of these procedures has also been helped by the new neuroanesthetic techniques.

Differences between adults and children's refractory epilepsy

The epilepsy of adults and children presents many similarities but there are also differences. First, a developing brain has a low crisis threshold and this means that catastrophic epilepsy is frequent. It is characterized by a type of malign epilepsy that associates multiple crises with a severe psychomotor developmental retardation.

The pathological substrate is also similar in adults and children. Lesional epilepsy, particularly, and anomalies in cortical development are much more common among the pediatric population while medial temporal epilepsy or temporal medial sclerosis is quite common in adults and very rare in children. The symptoms and EEG of the pediatric syndromes that are curable with surgery are also different. The auras and temporal manifestations of a seizure are frequently overlooked in children while in adults these auras are a common clue or factor that can help locate the origin of the focus of the crisis. These symptoms are frequently interpreted as a generalized epilepsy in children.

These differences motivate important differences in the pre-surgical study of refractory epilepsy in children.

Pre-surgical evaluation

The most important part of a pre-surgical evaluation is to identify the epileptogenic zone or the area of abnormal cerebral tissue that is responsible for the seizures and to determine its relation with the eloquent cortex. Before now, this identification was only based on the ictal and interictal EEGs. High-definition MRI has been an important advance, especially the 1.5 and 3 Tesla functions that have made it possible to identify very small lesions during pre-surgical evaluation. After identification of the pathological substrate, the patient's response to anticonvulsants, the frequency of the seizures, and also the prognosis for psychomotor development are primordial. The family history and the family members' description of the seizures help to identify the type of seizure while frequency must be documented through careful neurological examination. Often the neurological examination is what allows us to focalize the seizures.

Neuroradiological study

The brain anatomy and lesions that may be located are fundamental for pre-surgical evaluation and for guiding the electrophysiologist in determining whether there is any correlation between the MRI image and the alterations that may be found on the EEG study. The MRI study is performed following the existing protocols for neocortical study.

Use of the high definition MRI allows the identification of a pathological substrate in 80 % of pediatric patients.

Metabolic imaging

The introduction of positron emission tomography or PET into the treatment of childhood refractory epilepsy has been very important. It is an extremely helpful study in patients with demonstrated lesions on the MRI because it measures the relation between the hypermetabolic area identified by the PET and the epileptogenic area, if this has been determined with the EEG. If the focus has not been identified, PET can help determine the lateralization, and this is fundamental when the MRI is normal. However, SPECT, or single photon emission computed tomography, is problematic in children because their seizures are usually short and this test has low anatomical resolution. Generally it is performed after a seizure and more than locate the lesion itself, it helps to lateralize the lesion.

Video-EEG

A recording or registry of one or more seizures is very important in confirming the epilepsy diagnosis in a child as well as to help lateralize and localize the epileptogenic area. The most important factor of the video-EEG is identifying the irritative zone and the interictal spikes, as well as the ictal area or area that is triggering the seizures. Generally, several seizures are registered and their symptoms are analyzed together with the ictal EEG registry. The ideal is to be able to locate both the interictal zone and the ictal zone during the video-EEG.

However, this ideal is very difficult to realize in children with refractory epilepsy, even in tumoral pathologies, since their interictal activity can be quite widespread or it may not be possible to lateralize the seizure onset. These are the most significant differences in epilepsy between adults and children.

Invasive registries

When it has not been possible to define the ictal zone adequately by noninvasive studies, invasive techniques employing electrodes must be used. There are three main types of electrodes: foramen oval electrodes; deep electrodes, and lastly, subdural electrodes.

Subdural electrodes are the most widely used electrodes in children. Employing strips or grids of electrodes makes it possible to cover wide areas of the cerebral cortex when performing an EEG registry or a cortical map. The drawback is that placing a strip or grid requires a very large craniotomy, and this implies a significant blood loss and increased risk of infection for the child. Placed as strips, subdural electrodes can be placed through a burr hole, but the difficulty is that children's brain tissue is very soft, more so in very small children, and they do not have a well-developed subarachnoid space, so that it is possible to produce cortical lesions while placing this type of electrode.

At this time, subdural electrodes are not commonly placed under stereotaxic guidance.

Another important point in pre-surgical localization of the dominant hemisphere and memory evaluation is the Wada test, although it is not commonly applied in small patients. Generally, most epilepsy services are more commonly employing functional MR and the Wada test is only used in our own service in patients over 12 years of age.

Neuropsychology

The epileptogenic zone is characterized by an area of persistent dysfunction. The neuropsychological evaluation will attempt to identify specific deficits associated with the area where the cortical dysfunction is occurring. Unfortunately, the information supplied by the children, despite our use of specific tests, very rarely allows us to lateralize the lesion.

Functional mapping

When the lesion or epileptogenic zone affects or is adjacent to eloquent cortex, it is necessary to perform functional mapping in order to achieve maximum safety during resection. Mapping is mostly done when the resections will be close to the central area, in the dominant hemisphere in the frontal lobe, inferior in the dominant hemisphere or in the posterior part of the temporal lobe, as well as in the precentral surcus and in the dominant parietal lobe or the occipital lobe. Different methods exist to map these functional areas including modern technologies like functional MRI and magnetoencephalography.

Craneotomy in the conscious patient

This technique has advanced with the introduction of propofol in anesthesia. The patient must be an older child who can cooperate with an anesthesiologist familiar with this technique. The technique keeps the patient awake while areas adjacent to the language area are being resected. It should only be done in patients over 13 years of age and requires the placement of an electrode grid for pre-surgical mapping of the language area.

Incidence

The Neurological Institute of Montreal study reported that, of the 2,167 epilepsy surgeries they performed, between 1929 and 1980, 56% were temporal lobe surgeries.[5] In March 1987, Olivier presented his own series of 525 patients, and temporal lobe was affected in 74% of the patients in this series, the frontal lobe in 11%, the central area in 1%, the parietal area in 9% and the occipital lobe in 8%. Multilobal and/or total or partial hemispherectomies were performed in 2.5% of the patients and callosotomies in 9.5%.[6]

However, the proportions are completely the reverse in the pediatric population[7] and 60% of epilepsy surgeries affect extratemporal areas in children. Of 86 children operated in the Hospital Garrahan in Buenos Aires, Argentina, between

1988 and 1997, 63 were children and 23 were adults. The temporal lobe was affected in 73.9% of the surgeries in adults and in 42.8% of the children.

Differences between temporal and extratemporal lobe surgery

Professor Rasmussen published his famous triad for rationalizing procedures for epilepsy surgery in 1987.[8] The triad consists of three queries:

(a) Where does the seizure begin?
(b) How much of the cerebral volume is involved for the seizure to be triggered?
(c) How much tissue must be extirpated to stop this seizure?

These three basic questions are quite difficult to answer in the context of extra temporal epilepsy.

In his work, Rasmussen suggests that epileptogenic lesions in the extra temporal areas are much more variable in extension and configuration than in the temporal lobe.[9,10] In addition, differences in the triggering threshold between the cerebral cortex and other cerebral areas are notable. For example, the triggering threshold in the postcentral area is lower than in the precentral area so that stimulation of the latter has a smaller risk of producing a seizure during intraoperative cerebral mapping than stimulation of the post central area.[11]

This is particularly important if surgery is being done on a conscious patient, given the high risk associated with a seizure occurring during surgery. If the patient is unconscious, it is quite difficult to provoke a symptom of the patient's epilepsy through cortical stimulation when the patient is asleep, since, for example, stimulating the motor area that corresponds to the hand will not easily obtain hand movement. This is particularly true in children, in whom the process of cerebral maturation or myelinization is incomplete.

Classification of extratemporal resections

There are three patient groups:

1. Patients with organic lesions.
2. Patient who show no correlation between their existing lesion and their epilepsy.
3. Patients without an identifiable organic lesion.

Patients with organic lesions

The first step is obtaining a clinical and neurological diagnosis of the type of crises that the patient has. First, one attempts to correlate the MRI lesion with the clinical expression of the seizures. The next step is to correlate the clinical symptoms of the seizure with the EEG. This is done by performing a normal EEG placing electrodes on the scalp surface and then recording a seizure. Obviously, this is difficult, so generally, one performs a video-EEG. The patient is admitted to the Epilepsy Unit and the symptoms of the seizure are recorded simultaneously with the alterations in the EEG. Depending on the site of the lesion, if it is in an eloquent area, and, depending on the patient's age, it would be very helpful to perform an ictal and interictal registry placing an electrode grid to perfectly delimit the eloquent areas. If it is not an eloquent area, and the MRI and video-EEG findings correlate with one another, one can go directly to surgery during which an intra operative electrocorticography can be performed to confirm the relation between the lesion, its periphery and the EEG alterations.

Patients who show no relation between their lesion and their epilepsy

If there is no clinical correlation between the lesion and the patient's epilepsy, despite the MRI clearly showing a lesion, it is important to demonstrate the relation with the epileptogenic focus that is producing the convulsive seizures before surgery. In these cases it is absolutely necessary to place a subdural grid of as many as 24 or 32 electrodes and correlate the ictal alterations with the lesions that are visible on the MRI. The time in which the subdural electrodes are in place and the video-EEG is being performed is used not only to locate the original focus of the seizures, which would be the primary epileptogenic area and its propagation route, but also to make a cerebral map of the areas on which the electrodes are placed; this process should provide a significant safety margin for the actual surgery. Once the focus has been mapped, the second surgical time can be planned in which the epileptogenic area or zone will be resected. An electrocorticography is done during surgery to corroborate the site of the epileptogenic focus and to be sure that surgery does not leave potentially epileptogenic areas. An adequate surgical technique would employ microsurgical techniques, bipolar coagulation and an ultrasonic sucker.

Persistence of points that are distant from the site of the resection is an indication that the resection should be enlarged to completely extirpate any residual focus. The value of the points close to the border of the corticectomy is under discussion in the literature with no clear criteria at this time as to how to treat them.[12,13]

In our own series of resections in children we always finished with a normal electrocorticography, although this did not always coincide with a cure or normalization in the postsurgical EEG.

Patients with no organic lesion

We apply the above method, but with extreme caution. Since the CT and MRI are normal and thus there is no anatomical orientation, it is absolutely necessary to have a symptomatic diagnosis of the patient's epilepsy that can locate the focus from a clinical and electroencephalographic angle. Without this minimum information it is impossible to plan surgery in this group of patients.

Normally the lesions in this third group without a visible lesion on their MRI and with refractory epilepsy are extratemporal and the epileptogenic area is also extra temporal.[14] These patients make up about 20–30% of all patients who are evaluated for surgery in the centers dedicated to epilepsy surgery.[15–17] The percentage that can become seizure free after resection in between 30–50%,[18] reflecting the difficulty in identifying the epileptogenic area without a visible lesion on the MRI.

Histopathologically, most authors think that there is an undetected organic focus that provokes this partial epilepsy in children. Histological study of many of these patients with a normal MR has found small areas of cortical dysplasia, small vascular malformations and even small tumors. Even the tissues that appear to be normal or do not present any of these alterations, do often show a proliferation of astrocytes, and neuronal or myelin loss.[19]

In 1984 Meencke and Janz [20] defined the term microdysgenesis to describe minor histological alterations with a congenital origin during cerebral development but that do not reach a size large enough for them to be included among the parameters of a cortical dysplasia. These changes consist in aberrant neurons in the pia mater and white matter, alterations in cortical neurons and Purkinje cells as well as in the granular and molecular layer and the white matter. One must also note that these changes are found in patients who have no history of epilepsy. The neurophysiological study of the video-EEG of patients without an MRI lesion can reveal ictal and interictal anomalies that, although they do not identify the epileptogenic area, do lateralize it. In these pre-identified patients, a PET and SPECT can locate the hypermetabolic area or area of increased blood flow in specific cortical areas, which if it coincides with the EEG alterations, will also allow us to lateralize the location of the epileptogenic area. The proportion of patients without MRI alterations but with PET hypermetabolism, whose alterations coincide with the EEG is one-third of the cases in which it is possible to locate the epileptogenic area, and this proportion is similar for the ictal SPECT sequences.

Returning to group 1, patients with a focal lesion on the MRI, the lesions should be subdivided among:

(a) Tumoral lesions (gangliogliomas, DNTS and gliomas)
(b) Developmental disorders (cortical dysplasia, hamartomas and phacomatosis)
(c) Vascular lesions (cavernomas and arteriovenous malformations)
(d) Infectious lesions (tuberculomas, neurocysticercosis)
(e) Ischemic or hypoxic lesions
(f) Traumatic lesions.

Tumoral lesions

The incidence of seizures among patients with cerebral tumors is related with the pathology and location of the tumor.[21] It is important to note that 50% of patients with a cerebral tumor have epileptic seizures.[22] Within tumoral pathology, the only symptoms produced by gangliogliomas and dysembrioplastic neuroepithelial tumors in most cases are the epileptic crises, while gliomas can produce a syndrome of intracranial hypertension, anf focal deficits as well as seizures, although, differently from DNTS, gangliogliomas can also sometimes produce a syndrome of neurological deficit, basically of cerebral edema.

Depending on their location, tumors located in the central parietal region and in the temporal lobe are the ones that most frequently produce seizures.

The diagnosis of these tumors is basically done with MRI. (Figures 119.1 and 119.2) The problem is how to manage a patient with refractory crises and a cerebral tumor. To the author, the answer is clear: any and all cerebral tumors must be surgically removed, even in eloquent areas since with modern surgical methods (stereotaxis, ultrasound, surgical microscope, ultrasound sucker, cortical stimulation of the conscious patient, etc.) the resulting cerebral damage is minimal. Also, with surgery it is possible to identify the histology and thereby avoid growth or hemorrhage, and what is more, in most cases we can solve the problem of the seizures. Once we identify the histology, it is possible to administer coadjuvant therapy (radio or chemotherapy), if necessary.

If the epilepsy is chronic and the image on the MRI seems to show a benign tumor like a ganglioglioma, DNT or benign astrocytoma, we would advise surgical resection.

Vascular lesions

The two types of vascular lesion that most frequently cause epilepsy are cavernomas and arteriovenous malformations. The difficulty is that the surgical indication is completely different in both types.

Cavernomas make up 5–6% of all intracranial vascular malformations;[23] a third present with seizures, another third with intracranial hemorrhages and the last third produce a compression syndrome because of their size. We would firmly

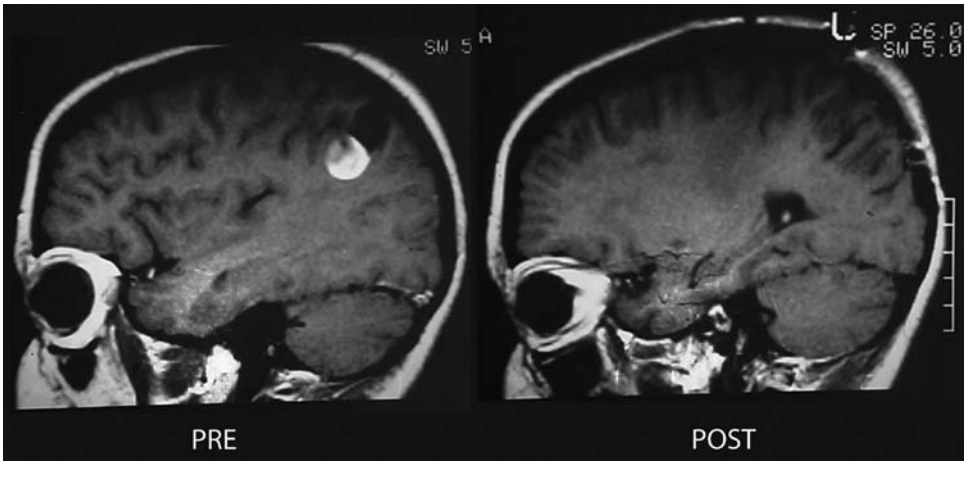


Figure 119.1 Sagital MRI shows parietal DNT before and after surgery.

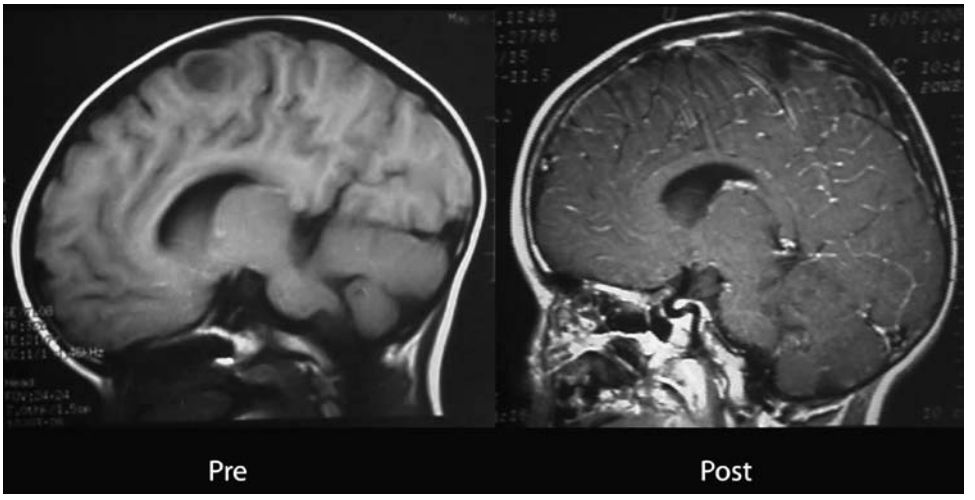


Figure 119.2 Sagital MRI shows central ganglioglioma before and after surgery.

advise surgery for any supratentorial or infratentorial cavernoma, except for those located in the brain stem if they do not cause symptoms.

On the other hand, arteriovenous malformations may present with hemorrhages or seizures (20%).[24] When these malformations are diagnosed, the surgical indication is largely influenced by the size of the malformation. The treatment of very large malformations located in eloquent areas and that only produce seizures is still controversial. We believe that the first step is to control the seizures with medical treatment. If the malformations are small, less than 3 cm, and in eloquent areas, radiosurgery should be attempted. When they are not located in eloquent areas the treatment *of choice* is surgery.

Developmental lesions

Cortical dysplasia is produced by an anomalous development in the formation of the intracranial sulcus and gyrus with disorders in cerebral cortex cell organization; the most severe forms are schizencephalia, polymicrogiria, pachygyria and lysencephalia. These dsysplasias may be limited to certain surci and therefore produce clinical seizures, or there may be some migratory disorder that produces isolated cortical heterotopias in the white matter that may be isolated or quite wide. These seizure-producing smaller cortical dysplasias and isolated heterotopias can be treated by extirpating the malformed area. (Figures 119.3, 119.4, 119.5, 119.6)

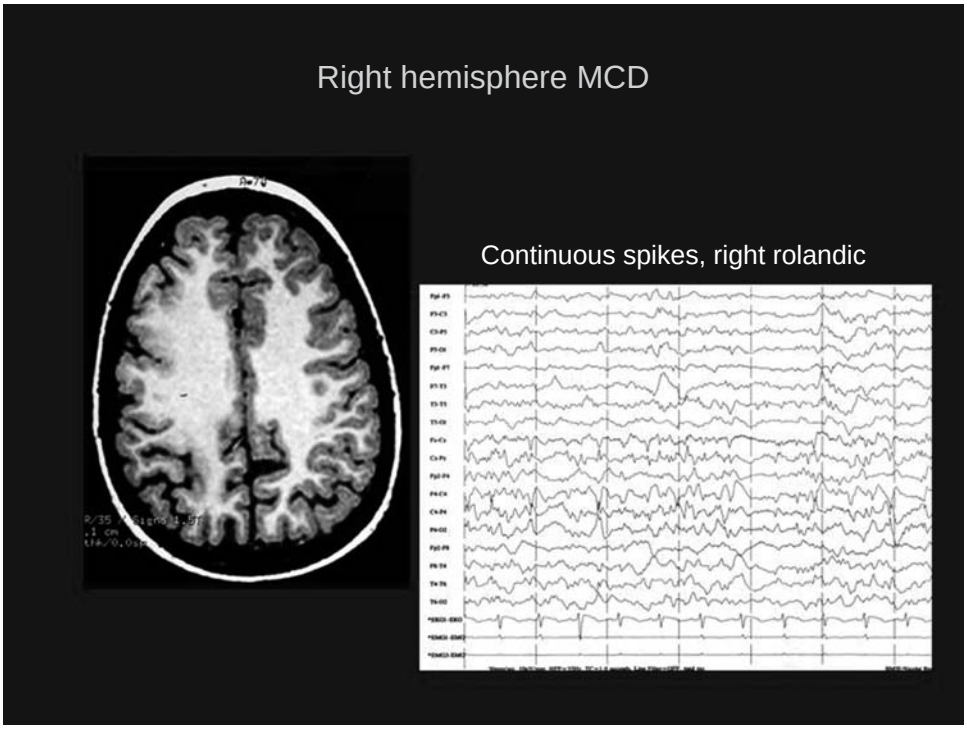


Figure 119.3 MRI and EEG right hemisphere malformation cortical development.

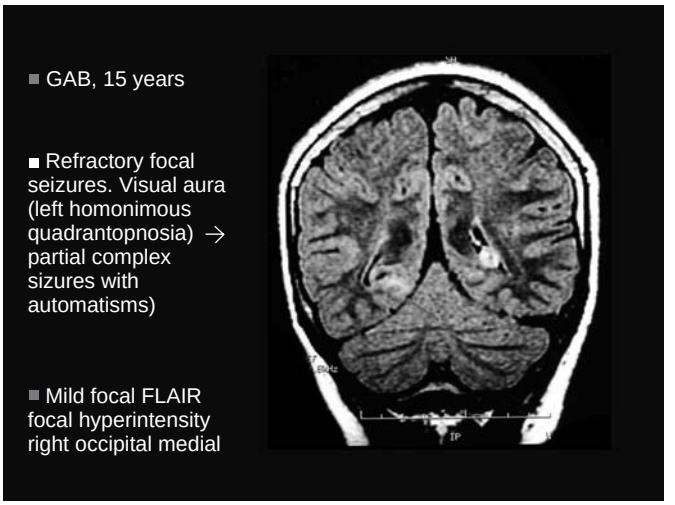


Figure 119.4 MRI coronal view shows occipital displasia.

A larger disorder would be a hemimegalencephalia, (Figure 119.7) with a dysmorphic hemisphere with pachygyria, heteroptopia, polymicrogyria and the loss of the union between white and gray matter. Other cases may present lysencephalia or agyria. These patients usually present multifocal crises and the best treatment is a functional hemispherectomy.

Hamartomas can be considered tumors, but in reality they are a developmental anomaly which results in the formation of small masses of diverse cell types, usually in the temporal lobe. They are treated by surgery.

A phacomatosis is made up of neurofibromatosis, tuberous sclerosis and Stuger-Weber syndrome. In the first two types, epilepsy is related with the cortical tumors that are characteristic of these processes, so that in some cases extirpating the processes would treat the epilepsy. However, in Sturge-Weber syndrome the malformation occupies almost the entire hemispheric cortex and the treatment would be a hemispherectomy.

Infectious lesions

Nowadays it is very difficult to encounter a seizure-producing tuberculoma. Medical treatment can dissolve the mass, but if the process continues to grow and clinically produce seizures or there is an expansive process, the appropriate treatment is surgical extirpation.

Intracranial cysticercosis is more frequent, and between 50 – 70% debut with epilepsy. When the epilepsy is not medically controllable, the indicated treatment is surgery. Rasmussen encephalitis is an encephalopathy of possible viral origin that was first described in 1958 by Rasmussen. (Figure 119.8)

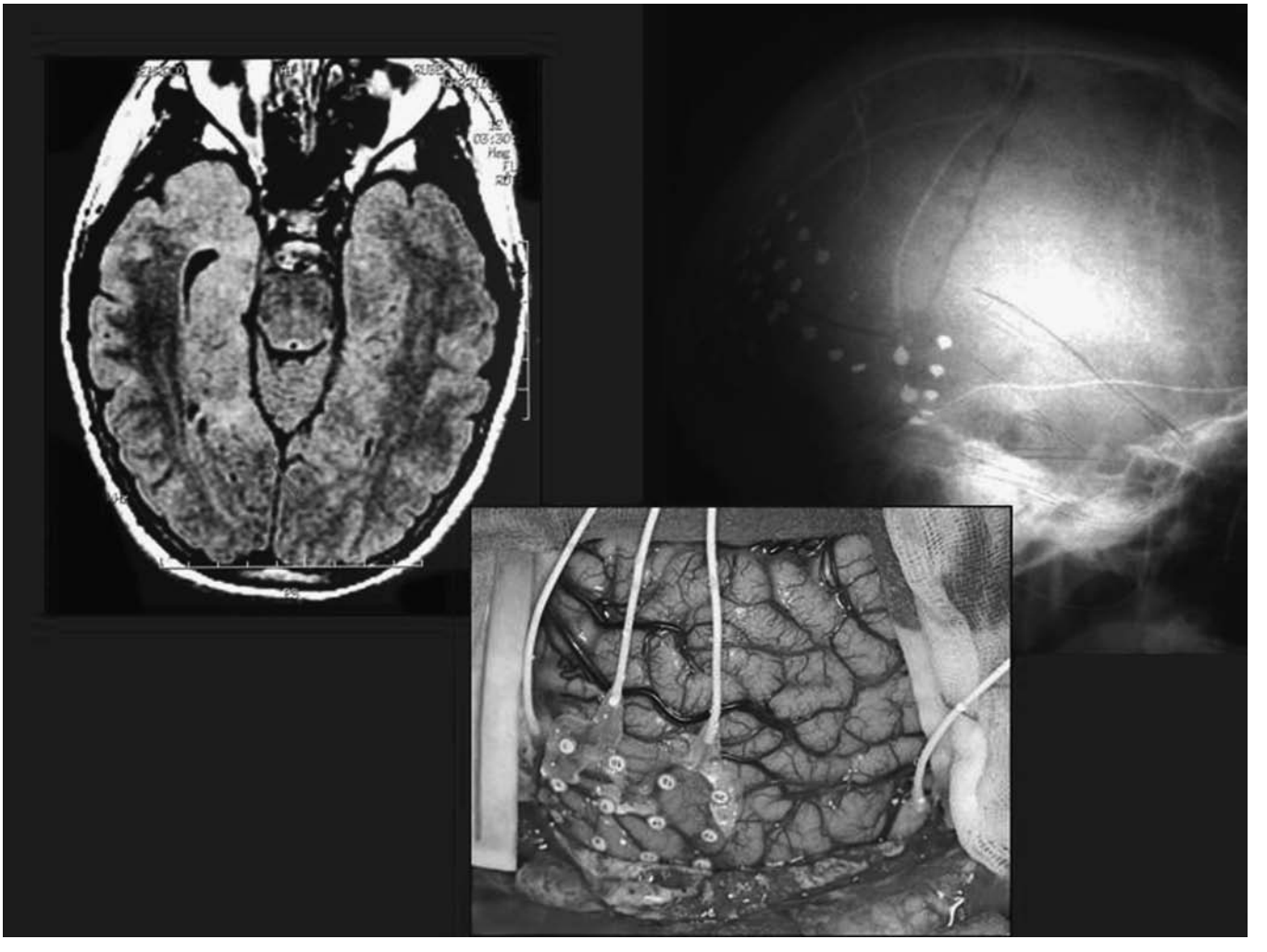


Figure 119.5 MRI sagital view, same case, craniotomy and subdural electrodes placement skull X-ray to see location of electrodes.

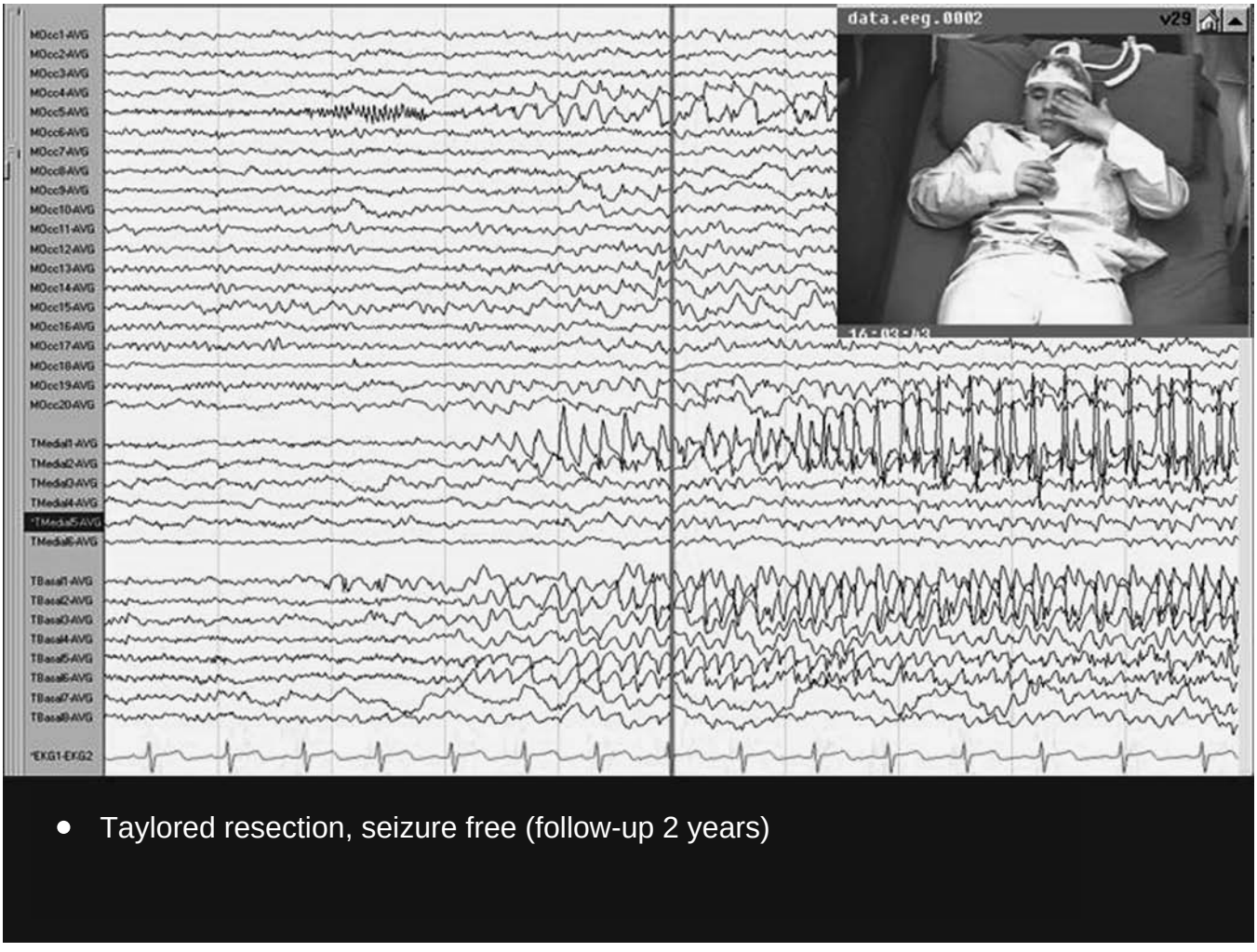


Figure 119.6 EEG after tailored resection.

It produces a syndrome of progressive unilateral motor deficit accompanied by focal seizures that can become generalized as well as progressive mental deterioration. Treatment consists in hemispherectomy.

Herpes simplex can also produce an encephalitis that usually mostly affects the temporal lobe and the indicated treatment is surgery if produce refractory epilepsy.

Hypoxic or ischemic lesions

Hypoxia or ischemia during pregnancy or birth can produce small or larger infarcts with later atrophias, gliosis and cyst formation. These can occasionally produce seizures and their treatment is the same as for a focal cortical dysplasia. (Figure 119.9)

Traumatic and post-traumatic lesions

Head injuries can induce seizures in the acute period, that is, shortly after the trauma, or in a more chronic manner, several months after the trauma. In the first early period the only surgical indication would be to treat any hematoma, if it existed. Later, if the patient had seizures it becomes necessary to investigate their origin. There may be small scars in the cortex at the level of the cerebral contusion or the site of the hematoma. Surgery is indicated in only a very few cases since most are pharmacologically controllable; the incidence is very low (4–7%).[25]

Surgical techniques in neocortical epilepsy in children

Frontal resection (Figure 119.10)

This can be divided into:

Total frontal lobectomy

The frontal lobe is resected in two steps during the same surgical approach from its pole until the precentral gyrus. We generally locate these structures under general anesthesia using evoked potential cerebral mapping. Once the postcentral area (primary of the brain) is located, we know that the central surcus is immediately in front of it and in front of that the motor area. The latter is the posterior limit of the resection. The first stage of the surgery is to do an en bloc resection of the three frontal gyrus (in the nondominant hemisphere), which would correspond to the convexity of the frontal lobe, and the second step is to resect the cingulum. Neither the posterior orbitofrontal cortex nor the subcallosum gyrus are resected.

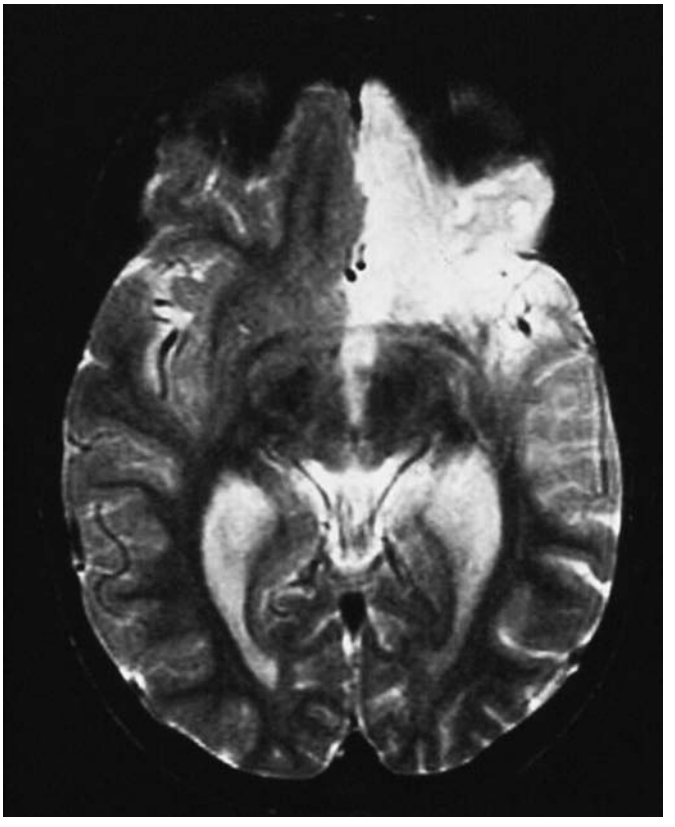


Figure 119.7 MRG axial view shows hemimegalencephaly.

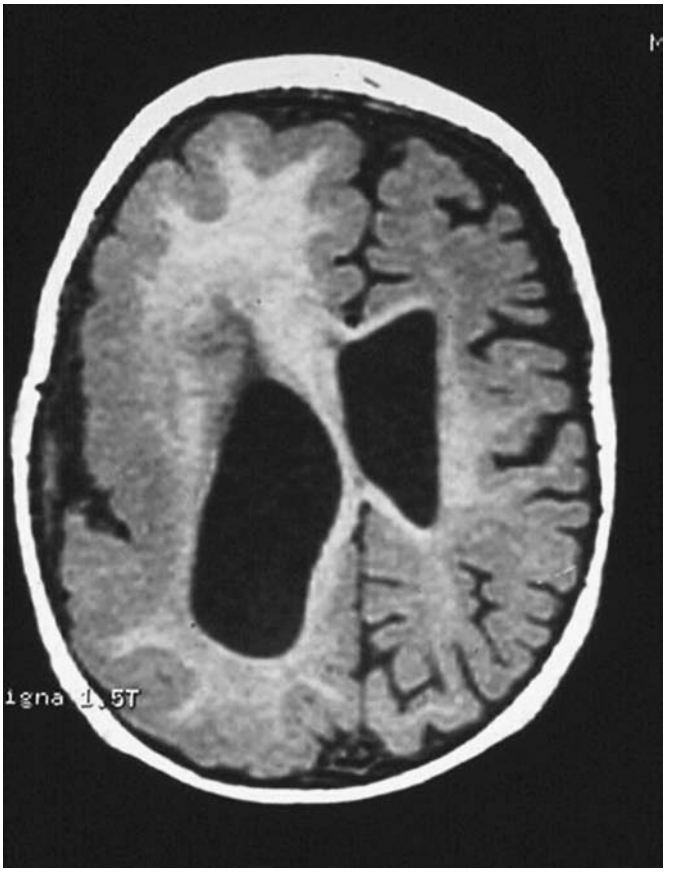


Figure 119.8 MRI axial view of Rasmussen's encephalitis.

In the dominant hemisphere, one does a resection from the second frontal gyrus until the midline respecting the third gyrus. Olivier[26] believes that a resection of the dominant hemisphere has more of an anatomical than neurophysiological base. That is to say, the surgeon preferentially refers to the area limits determined in the angiography or MRI rather than to neurophysiological findings or cerebral mapping of eloquent areas. It is extremely important to respect the venous circulation in order to avoid aphasic sequelae. The avascular area between the cerebral media and the cerebral anterior corresponds to the second frontal circumvolution, the posterior limit to the resection in the dominant hemisphere. Veins that flow toward the superior longitudinal sinus must not be sacrificed unless you are certain that they can be replaced by veins that drain into the sylvian system.

Paramedian resections

One begins at the crista galli apophysis and continues towards the precentral gyrus and laterally toward the middle of the second circumvolution. The gyrus cinguly should preferentially be resected employing an ultrasound sucker and respecting the norms of subpial resection so as not to lesion the arteries and veins, which would lead to sequelae of edema and ischemia. It must be remembered that the vessels run in the depth of the pericallosum and marginal callosum sulcus. Vein coagulation will be done at the end of the procedure to avoid congestion and edema in the brain that would make ending the surgery difficult.

Frontopolar resection

This resection should go from the crista galli apophysis to the middle part of the frontal lobe. This the most frequent type of posttraumatic epilepsy.

Central area resections

Resections of the pre- and post central area can reach as far as 3 cm from the sylvian fissure. The seizures that can originate in them can be motor or sensitive and they can be surgically treated, even in the dominant hemisphere.[27] It must be remembered that the limit of the resection is obtained in an unconscious patient, placing stimulation electrodes on the tongue, thumb and lips and then registering the arrival of the stimulus at the cerebral cortex; that is to say the areas that, if damaged will produce dysarthrias, which, given their location would be equivalent to forms of aphasia, are mapped. In the central area it is more important than in any other area to respect the basic norms of surgery epilepsy: bipolar coagulation and low intensity ultrasound sucking to respect the arteries and veins in the area affected by subpial dissections.

Lateral convexity resection

This resection can include a small part of the frontal lobe in the convexity, depending on the location of the structural lesion.

Parietal resections

As in temporal lobe surgery, surgery of the frontal lobe undoubtedly requires the anatomic and neurophysiologic identification of the central area and basic to this is identifying the precentral gyrus. The inferior portion of the post central gyrus can be resected as far as 3 cm from the sylvian fissure.

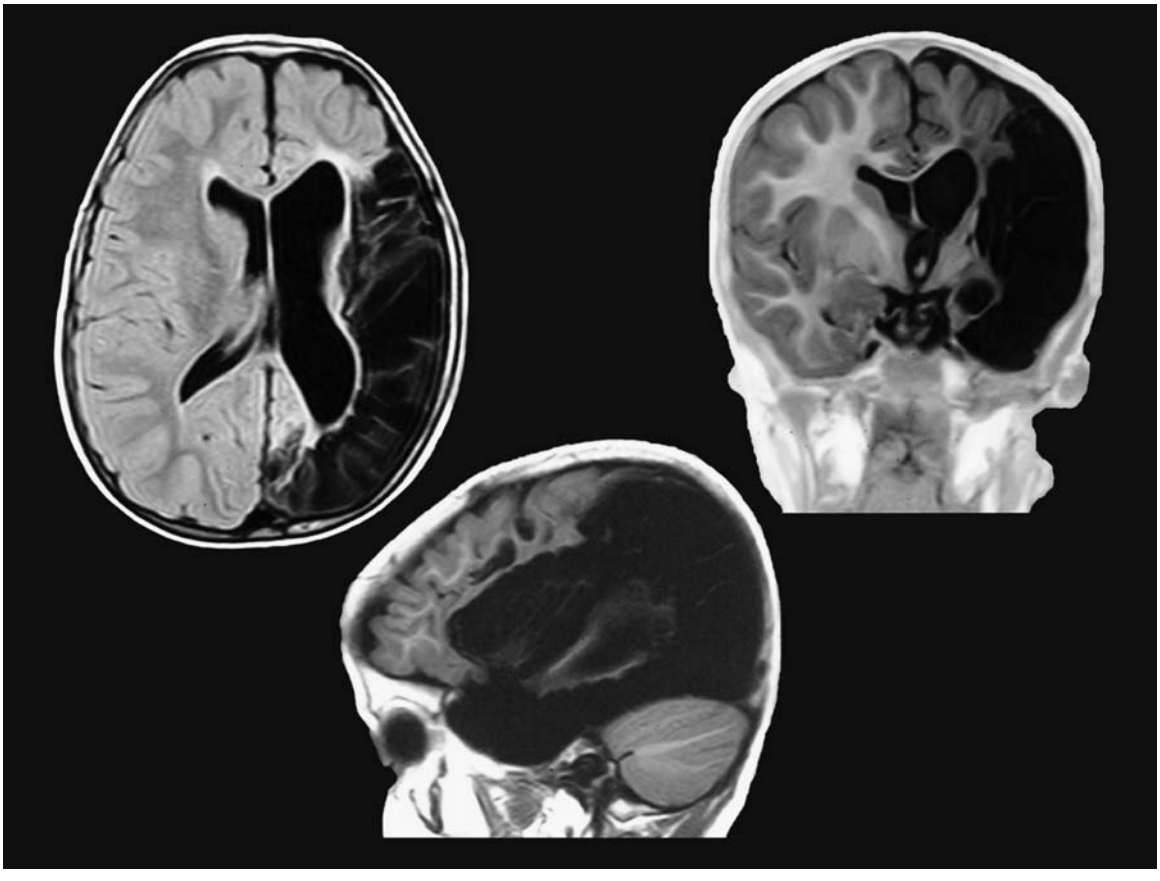


Figure 119.9 MRI axial view shows a large hemisphere infarct.

A larger resection could leave sequelae of a severe sensi-tive deficit. Campimetric alterations may also result. The superior limit of resection in the dominant hemisphere is the superior parietal lobe. The deep and inferior limits are the interparietal surcus and the anterior limit is the postcentral surcus.

Occipital resections

The symptoms produced by visual seizures–hallucinations, transitory loss, flash, shines, colors or unorganized geometric shapes–may evolve into a contralateral sensitivomotor seizure with head and eye turning. Obviously, with such vague symptoms, surgery can only be planned if there is a focus that is demonstrated by subdural electrodes and an electrocorticography. Occipital lobe seizures can spread to the temporal lobe or the central area.[28] Epilepsies that are generated by occipital foci can be treated with a deconnection or lobectomy of the temporal lobe, which will avoid the campimetric deficit that is produced by a complete resection of the occipital lobe.

Multilobar resections

These resections are performed when there are very wide and large destructive lesions that affect more than one lobe in the affected hemisphere and they consist in resecting small regions of several lobes in one hemisphere.

Lesionectomies

In 1993 Fried and Cascino[29] proposed four possible surgical strategies. The first was the lesionectomy or an extirpation of the lesion (Figures 119.11 and 119.12); the second, extirpation of the lesion with its margins; the third, extirpating the lesion and the secondary epileptogenic lesion that is usually elsewhere; and the fourth consisted in resecting the second-ary epileptogenic lesion without extirpating the primary lesion.

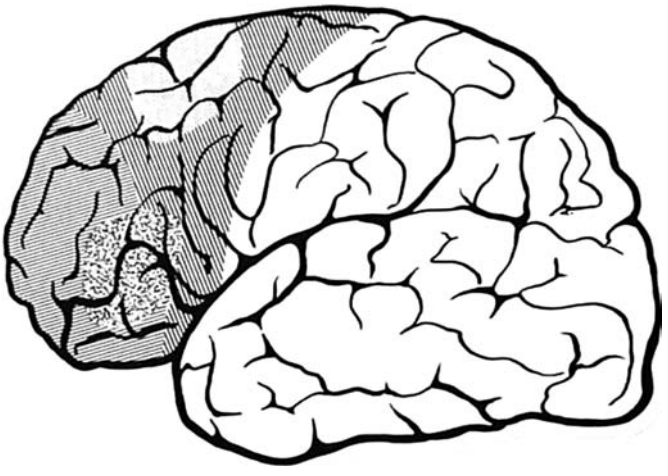
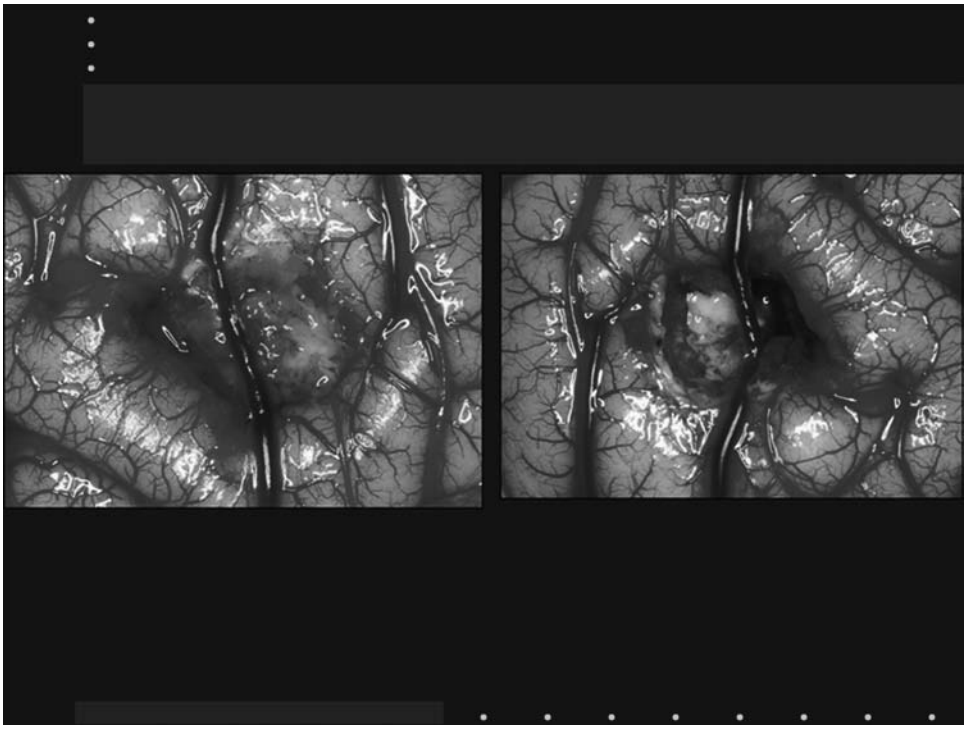


Figure 119.10 Types of frontal resections.



Figures 119.11 and 119.12 Lesionectimy of a parietal DNT.

The first strategy is quite clear and most authors agree, ourselves included. With the second strategy, when the images of the lesion produce clear alterations in the elecrocorticography, one can resect as much as 2 cm beyond the borders, but only in non eloquent areas. Awad[30] did not find a notable difference in the prognosis for the seizures if one included the lesion borders in the resection. With regard to the third strategy, the technique is quite controversial and the prognosis and indications have not been clearly defined.[31,32] Last, series employing the fourth strategy are too short to allow conclusions.

Conclusions

Epilepsy surgery began with extratemporal resections; however, it only became an accepted therapeutic possibility with the success obtained in temporal lobe epilepsy. Large series of prestigious centers report a percentage of cure or significant improvement of not less than 75%. Seven out of ten patients with temporal epilepsy, whether it is medial or neocortical, may be cured with surgery. Nevertheless, surgery for extratemporal epilepsy offers more uncertain results. The large extension of the brain, the existence of eloquent areas that increase the risk of neurological sequelae, the difficulty of precisely determining the primary epileptogenic area, even with invasive techniques like subdural or even intraparenchymatous electrodes, explain why the results for cures or improvement are no better than 50% in patients with extratemporal lobe epilepsy. More patients are improved than cured, differently from what can be achieved in temporal lobe epilepsy surgery.

In this context one must emphasize the great advantage for surgical treatment of extratemporal epilepsy brought about by the so-called 'imaging revolution', particularly the development in the middle of the 1980s of the MRI and also the PET and SPECT.

Today there is no doubt that detecting the origin, which is the orienting substrate of extratemporal epilepsies, has substantially improved the prognosis of their surgical treatment.

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120 Hemispherectomy techniques

SJ Nagel, SK Elbabaa, EJ Hadar, and WE Bingaman

Introduction

Hemispherectomy offers selected patients with unilateral hemispheric epilepsy a surgical cure. Common etiologies include congenital neurodevelopmental disorders, ischemic/anoxic brain injury, Sturge-Weber disease, and Rasmussen's encephalitis. Clinical manifestations include intractable seizures and contralateral motor and visual field deficits, often with developmental delay. Early control of catastrophic epilepsy is desirable as seizures arising from the diseased hemisphere suppress and limit the neurodevelopmental potential of the undamaged brain.[1,2]

During the last 75 years, surgical approaches to hemispheric epilepsy have evolved to address concerns reported in some patients after anatomic hemispherectomy.[3,4] Perhaps as valuable in contributing to the care of these patients was the evolution of neuroimaging during the last two decades, coupled with improved microneurosurgical techniques. Prior to this, the physician relied on limited imaging data to recommend patients for operation. Currently, the spectrum of disease to which these techniques are applicable has expanded, and, conversely, the age of the patient at operation has decreased.[5–7]

History of hemispherectomy

The hemispherectomy operation has evolved over several decades. The surgical technique was first described by Walter Dandy in 1928. He reported on the use of hemispherectomy for the treatment of glioma in five patients involving the right hemisphere.[8] Hemishperectomy was first utilized for epilepsy surgery in Toronto by McKenzie in 1938 when he performed hemispherectomies on patients with infantile hemiplegia.[9] Krynauw popularized the procedure in 1951 after reporting hemispherectomy on 12 children with infantile hemiplegia resulting in good seizure control.[10] After Krynauw's report, the procedure became recognized as valuable and effective in controlling not only seizures, but also improving cognitive outcome. Robert White published multiple experimental animal studies on hemispherectomy between 1957 and 1962 detailing surgical techniques, physiologic consequences, and clinical implications of hemispherectomy on the monkey.[11–13]

Between 1952 and 1960, multiple minor modifications of the classic anatomic resection were introduced.[14–21] By 1961, HH White had collected 267 operated cases in many neurosurgical centers, with a mean postoperative follow-up of only 16 months. He concluded that hemispherectomy was safe and effective.[22]

The procedure continued to gain popularity until early signs of trouble were reported by Laine, *et al* in 1964 including three catastrophic late complications of unknown etiology in a series of 20 hemispherectomies.[17] Oppenheimer and Griffith in 1966 reported their observations made in three autopsies of patients who died many years after hemispherectomy for control of seizures associated with infantile hemiplegia.[23] All of the patients enjoyed a trouble-free period lasting many years after surgery before they died from gradual neurological decline. Their major autopsy findings included hemorrhagic subdural membranes extending into the ventricular system, hydrocephalus, obstructive granular ependymitis, and superficial cerebral hemosiderosis (SCH). Brett in 1969, Falconer and Wilson in 1970, and Rasmussen in 1973 reported a high incidence of SCH in anatomical hemispherectomy series ranging from 22 to 34% in patients followed longer than five years with a mortality reaching 33%.[24] After these reports, the popularity of the procedure declined and the procedure was effectively abandoned for several years until new hemispherectomy techniques emerged aiming at eliminating these late complications.

In 1970, Wilson performed the first modified anatomical hemispherectomy.[24] Functional hemispherectomy was first described by Rasmussen in 1974 as a subtotal anatomical resection with complete physiological hemispherectomy.[4] Rasmussen reported excellent results after functional hemispherectomy in the Montreal Neurological Hospital's series from 1937–1971. Other modifications included the Oxford modification by Adams in 1983 aimed at reduction of the subdural space by a dural plication technique after anatomic hemispherectomy and the shunted hemispherectomy modification by the UCLA group.[1,25]

Hemicorticectomy (or hemidecortication) was first described by Ignelzi and Bucy in 1968.[25] Hoffman at Toronto (1979) reported a good seizure outcome in infants with Sturge-Weber syndrome treated by hemicorticectomy but with preservation of basal ganglia.[26] Carson, at Johns Hopkins, reported a 96% seizure-free outcome after hemidecortication in 52 patients and emphasized the importance of anesthetic management and blood replacement during surgery.[27] In order to further improve on perioperative safety, functional hemispherectomy has been further modified to a less invasive method termed hemispherotomy. Delalande, in 1992, described hemispherotomy as a safe disconnective procedure aimed at disconnecting the epileptogenic hemisphere from the

subcortical centers via parasagittal hemispherotomy.[28] Villemure, in 1995, reported a seizure control rate reaching 80% via peri-insular hemispherotomy. He described the peri-insular approach as a radical hemispheric tractotomy, resulting in a completely disconnected hemisphere with advantages that include shorter operative times, a less stormy postoperative course, and better anatomic preservation of the operated hemisphere, thus presumably reducing long-term complications.[29–31]

Hemispheric deafferentation, another form of functional hemispherectomy, was first described by Schramm in 1995 as a less-invasive microsurgical procedure, followed by a 2001 report describing a transsylvian keyhole approach to further reduce the operative time and need for blood replacement.[32,33]

As described above, the hemispherectomy procedure has followed an interesting evolution over several decades. The early reports of SCH lead to the loss of confidence in the anatomic procedure. Hemispherectomy regained its popularity after technique modifications lead to similar seizure control rates, but with decreased complication rates. The most recent modifications concentrated on making the procedure less-invasive but with equally good seizure control and low complication rates.

Patient selection and evaluation

Selecting a patient for hemispherectomy requires multidisciplinary evaluation. The onset of seizures should localize to one hemisphere on electroencephalography (EEG). Seizure semiology should be concordant with the EEG findings. Magnetic resonance imaging (MRI) and positron emission tomography (PET) should confirm structural and functional abnormalities in the diseased hemisphere and the relative integrity of the other hemisphere. Ideally, the patient should have a preexisting hemiparesis and hemianopsia opposite the diseased hemisphere.

Infantile hemiplegia with seizures secondary to perinatal stroke was the first epilepsy associated disease to be treated with hemispherectomy.[10] This diagnosis was the most common cause of seizures in patients treated by hemispherectomy for several decades. A contemporary series of 115 patients operated on between 1986 and 2002 at UCLA reflects the current etiology of seizures in patients treated with hemispherectomy (Table 120.1).[5,6] In a comparable study of 111 patients who underwent hemispherectomy between 1975 and 2002, Rasmussen's syndrome was the most common etiology reflecting institutional referral patterns. (Table 120.2).[7] Cortical dysplasia when hemimegalencephaly is included is likely the most common etiology however. Refractory status epilepticus has also been successfully controlled with hemispherectomy.[34]

History and physical exam

A detailed medical history which includes the perinatal period and family history and a thorough physical exam is an essential component of the preoperative evaluation. Specifically, the patient and/or family should be queried on seizure onset, any inciting event, and changes in type, frequency or location of seizures. A medication history should reflect seizures refractory to dosage adjustments and prescription changes.

Table 120.1 Etiology of seizures in a 115 patients treated with hemispherectomy at UCLA between 1986–2001[5,6]

Hemispheric disease	Number of patients
Cortical dysplasia	39
Infarct/ischemia	27
Rasmussen's encephalitis	21
Hemimegalencephaly	16
Sturge-Weber	2
Other*	10

*Tumor, trauma, encepahalitis.

Assessing motor and sensory deficit in infants and young children can be difficult.[35] Most patients will be hemiparetic or hemiplegic; contralateral muscle atrophy is often present. In the first year of life, motor findings can be subtle. Children with only a mild hemiparesis often have diminished motor function following surgery and are usually left with a 'helper hand'.[36] Hemianopsia is always present post-operatively. A formal ophthalmology exam can sometimes verify a visual field defect preoperatively depending on the age of the patient. Absent or partial hemianopsia preoperatively should not deter the patient and/or surgeon from proceeding. After surgery, the hemianopsia may preclude driving if the patient is seizure free. It is important to ascertain parental and patient expectations and offer realistic goals prior to surgery.

Neuroimaging: functional and structural

Magnetic resonance imaging (MRI) is the structural imaging technique of choice for all candidates and should include T1- and T2-weighted, proton density, and fluid attenuated inversion recovery (FLAIR) sequences. High-resolution volumetric acquisition with very thin (1.5 mm) contiguous slices and 3-dimensional reconstructions detect more subtle abnormalities than conventional spin-echo imaging.[37,38] Contrasted studies are valuable in select cases such as Sturge-Weber.[39] The role of MRI is to establish a diagnosis, evaluate the normal

Table 120.2 Etiology for seizures in 111 patients treated with hemispherectomy at Johns Hopkins between 1975–2002[7]

Hemispheric disease	Number of patients
Rasmussen's syndrome	47
Developmental dysplasia/ migrational defects	24
Congenital vascular injuries	17
Hemimegalencephaly	11
Sturge-Weber syndrome	5
Other*	7

*Nonspecific inflammation, malignancy, tuberous sclerosis.

hemisphere, and aid in surgical technique selection. When evaluating the MRI, the surgeon should identify areas of deep dysplasia and pay careful attention to ventricular size, which may influence surgical technique. An atrophied or hypertrophied cortical mantle may influence the decision to proceed with an anatomic or functional hemispherectomy. Abnormalities within the contralateral hemisphere should be investigated as an active or potential source for epileptic activity.

Functional imaging using single photon emission computed tomography (SPECT) or [18F]fluoro-2-deoxyglucose([18F]FDG) PET can be used to verify hemispheric pathology and confirm lateralization of seizures. Patients with hemispheric epilepsy typically show widespread decreased glucose consumption with [18F]FDG PET in the epileptogenic hemisphere and normal glucose metabolism on the opposite side.[35,40]

Electroencephalography and adjunctive tests

All candidates for hemispherectomy should undergo inpatient continuous video EEG monitoring of ictal and interictal activity to document epilepsy and identify the region of ictal onset. Lateralization of diffuse hemispheric discharges confirms the site of pathology and is of prognostic value.[39] This is especially true when imaging, clinical findings, and EEG are concordant.

Wada test (intracarotid sodium amytal) is indicated to assess language and memory localization in older patients when the transfer of these processes to the contralateral hemisphere remains uncertain. All age appropriate patients should be tested on verbal and nonverbal communication and undergo neuropsychological testing pre and postoperatively.

Surgical techniques

In theory and in practice there are only three ways to surgically eradicate a diffuse unilateral hemispheric seizure focus, inhibit impulse transmission to the contralateral hemisphere, and impede its materialization in the body through the brainstem:

1. Resect the hemisphere in its entirety
2. Disrupt the fiber tracts projecting from the cortex

or *anatomic hemispherectomy*, *functional hemispherectomy* and *hemidecortication respectively* (Table 120.3).

Table 120.3 Operative techniques used in the treatment of unilateral hemispheric seizures

I. Anatomic hemispherectomy Oxford modification
II. Functional hemispherectomy Perinsular hemispherotomy Hemispheric deafferentation Keyhole hemispherectomy Trans-opercular hemispherotomy Vertical hemispherotomy
III. Hemicorticectomy (hemidecortication) Ultrasound-tailored functional hemispherectomy

General concepts

The surgeon's recognition of the anatomic relationships within the hemisphere is of paramount importance and cannot be overestimated. This ensures not only the success of the operation but also the patient's safety. Very often, the disease process has distorted the hemisphere challenging even the experienced surgeon. It is instructive to begin the dissection of the cerebral hemisphere with a survey of the surface landmarks which delimit the operation and project over the deeper structures. Retraction or resection of the fronto-parietal operculum exposes the insular cortex and the C-shaped cortical association fibers of the superior and inferior longitudinal fasciculus. (SLF/ILF) The SLF is divided until reaching the projections of the internal capsule which form the corona radiata. This white matter is opened to expose the lateral ventricle. The pericallosal artery travels in the pericallosal cistern superior to the ventricle. The course of the pericallosal artery is useful to direct the surgeon with callosotomy from genu to splenium (Figure 120.1).

To disconnect the mesial temporo-parietal structures, the fornix is divided just anterior to the splenium and the mesial gyri enveloped by the temporal lobe are resected through the temporal horn. The frontal horizontal fibers, which include the uncinate and occipitofrontal fasciculus are cut anterior to the frontal horn, following the course of the anterior cerebral artery in the mesial frontal pia back to its junction with the internal cerebral artery (Table 120.4).

Preoperative care

Dexamethasone and antibiotics are administered before induction. Antiepileptic medications are taken the morning of surgery and continued postoperatively in conjunction with an epileptologist. An anesthesiologist dedicated to pediatric neuroanesthesia should be routinely used in such patients. The surgical site is confirmed, an arterial line and bladder catheter placed, and central venous access is obtained.

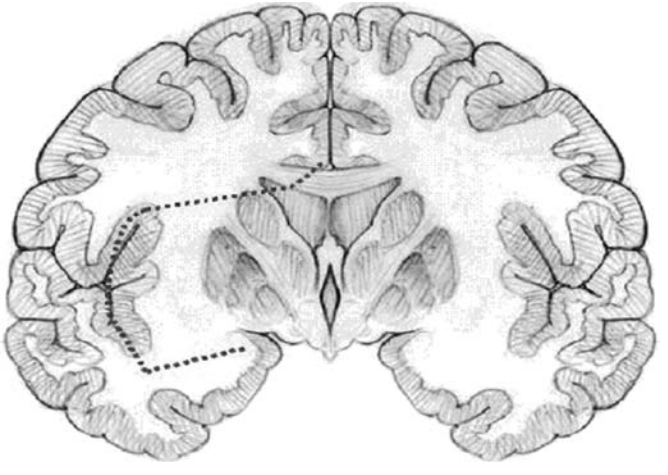

Figure 120.1 Schematic representation of an anatomic hemispherectomy including callosotomy, resection of the mesial temporal structures and sparing of insula and basal ganglia.

Table 120.4 Intra and inter hemispheric connections sacrificed during functional hemispherectomy and hemispherotomy[56]

Callosal fibers	
Rostrum and genu	Frontal lobes
Truncus (rostral)	Premotor and supplementary
Truncus (middle)	Prencentral
Fasciculi	
Superior longitudinal fasciculus	Connects the frontal, parietal, occipital and temporal lobes
Anterior limb	Connects speech areas (Wernicke, Broca) with Area 8 (frontal eye fields)
Posterior limb	Connects Areas 18 (secondary visual area) and 19 (tertiary visual area) and middle temporal Area with Area 8 (frontal eye fields)
Uncinate fasciculus	Connects temporal pole and amygdale with orbitofrontal cortex
Occipito-frontal fasciculus:	Projections from Area 22 (rostral auditory association cortex), Area 20,21 (visual fields below the superior temporal sulcus) and sulcal cortex of the prefrontal cortex.

All patients are typed and crossed for expected blood and plasma transfusions.

Anatomic hemispherectomy

In recent years, there has been renewed interest in this operation; seizure control is excellent and the safety profile has improved. It is the surgery of choice at our institution for hemimegalencephaly, select cortical malformations, and reoperation after failed functional hemispherectomy.[35]

The patient is positioned supine on the operative table with an ipsilateral shoulder role. The head is turned 30∞ to the side and positioned with the vertex slightly down to allow adequate visualization of the mesial temporal structures. A 'T' incision is marked to allow access to the entire hemisphere (sagittal sinus to floor of middle fossa). The operative field is prepped and draped widely. Local anesthetic is injected along the planned incision which is opened with the scalpel. Every effort should be made to optimize hemostasis. The scalp flaps are mobilized to expose the temporalis muscle. This is reflected to expose the zygomatic root and the anatomic keyhole for placement of burr holes. The craniotomy is performed to allow exposure from the floor of the middle fossa to the parasagittal cortex just off the midline. The length of the sylvian fissure is exposed. The bone flap is carefully elevated and dura tacked up to the skull. The dura is opened in H-fashion and reflected back on the sagittal sinus (Figure 120.2).

The sylvian fissure is opened using microdissection and the middle cerebral artery exposed. It is subsequently ligated distal to the lenticulostriates but proximal to its bifurcation. The insula and surrounding superior and inferior circular sulci are identified. Once the sylvian fissure is widely opened and the MCA ligated, the infrasylvian portion proceeds with removal of the temporal lobe in stepwise fashion. First the lateral temporal lobe is removed by a posterior line of resection at the level of the posterior sylvian fissure. This line of dissection involves coagulation and division over the lateral and basal temporal lobe mesially to the collateral sulcus. From here the collateral sulcus is followed up to the temporal white matter and the temporal horn is entered. From the inferior circular sulcus, the white matter of the temporal horn is aspirated to open the temporal horn along its entire length. The lateral ventricular sulcus is identified and opened, following it down through the fusiform gyrus to the pia along the tentorium. This is coagulated and divided and the lateral temporal lobe including the temporal pole is removed, leaving behind the amygdala, hippocampus, and parahippocampal gyrus.

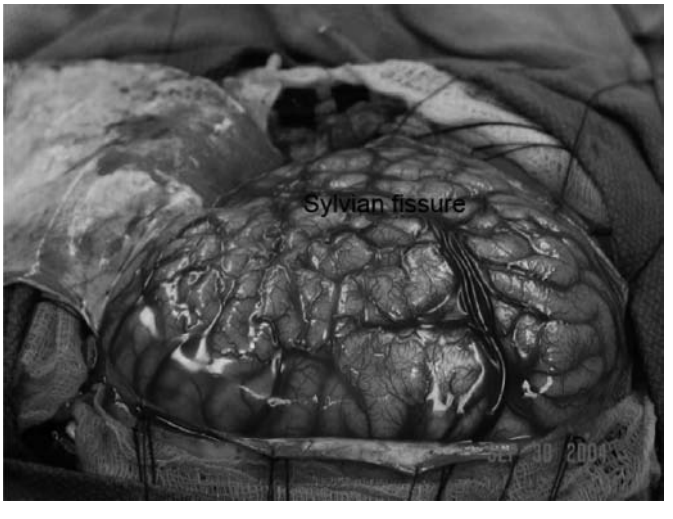

Figure 120.2 Intraoperative photograph illustrating the cerebral hemisphere in a patient with hemimegalencephaly prior to anatomic resection.

The suprasylvian stage begins with exposure of the superior circular sulcus and division of the MCA branches supplying the fronto-parietal cortex. The superior circular sulcus is used as a template to divide the corona radiata and facilitate the opening of the length of the lateral ventricle. The foramen of Monroe is exposed and plugged with a cotton ball to limit blood and cellular debris from accumulating in the contralateral ventricle. From within the lateral ventricle, a complete callosotomy is performed. The ventricular roof is incised at its junction with the septum pellucidum. This exposes the pericallosal cistern and traversing arteries. A parasagittal sectioning of the callosum ensues from the rostrum to the splenium disrupting the mesial fronto-parietal commissural fibers and ipsilateral cingulate gyrus. The dissection is carried posteriorly along the falx with removal of the ipsilateral cingulate gyrus until the previously exposed tentorium is brought into view below the sylvian fissure. The fornix is subsequently divided at the hippocampal tail adjacent to the atrium and just anterior to the splenium. Care should be taken to insure that the splenium is completely disrupted. The posterior branches of the MCA irrigating the parietal and occipital cortex are divided so that the entire lateral ventricle is opened.

Finally the pia along the edge of the falx is coagulated and divided following the falx and tentorium mesially and inferiorly towards the mesial temporal lobe. The cingulate gyrus transitions to the parahippocampal gyrus and these structures are removed as the pia is dissected along the edge of the tentorium. During this phase, the posterior cerebral artery will be encountered and divided as it crosses the tentorium on its way to the occipital lobe.

Anteriorly, at the level of the genu, the mesial frontal lobe is slowly aspirated and branches of the ACA ligated as they are encountered. The pia along the edge of the falx is coagulated and divided down to the anterior aspect of the anterior cranial fossa. Here, the olfactory nerve is encountered. Care should be taken to skeletonize it as the ipsilateral gyrus rectus is aspirated and the contralateral mesial frontal lobe is visualized. Both pericallosal arteries and anterior cerebral arteries should be identified and protected to avoid inadvertent injury to the arterial supply to the other hemisphere. Dissection along the mesiobasal frontal lobe should continue back to the level of the internal carotid artery and optic nerve. Ultrasonic dissection is useful for the subpial dissection required at this stage.

Prior to removing the hemisphere, the large draining veins to the sagittal sinus and transverse sinus must be coagulated and divided. Once this is accomplished, the hemisphere is removed en bloc and sent to pathology. The remaining tissue to be removed includes the amygdala, hippocampus, insular cortex, and perhaps some residual parahippocampal tissue. This is done by identification of several anatomic landmarks including the choriodal point, M1 trunk of the MCA, choroid plexus, lateral geniculate body, and edge of the tentorium. The bulk of the amygdala is resected below a line connecting the M1 trunk and the choroidal point. Care is taken to stop below this line to avoid injury to the basal ganglia. The hippocampus is resected by cutting the tail at the trigone and aspirating the fornix just below the choroid plexus to expose the hippocampal sulcus. The hippocampal sulcus is coagulated, divided and the hippocampus is removed by subpial aspiration being careful to avoid injuring the mesial pia overlying the brainstem and the perimesencephalic structures (posterior cerebral artery, basal vein of Rosenthal, oculomotor nerve, posterior communicating artery, and anterior choroidal artery). Finally, any residual parahippocampal gyrus is subpially aspirated including the uncus back to the level of the trigone where the dissection from above will be encountered. The insular cortex may be aspirated when indicated (Figure 120.3) by careful aspiration of the long and short gyri underneath the pia of the sylvian fissure.

The cavity is irrigated and bleeding controlled (Figure 120.4). A ventricular catheter is placed in the cavity and tunneled out through the skin. The dura is sutured closed and the bone flap secured with a microplating system or sutures depending on the patients age. The muscle fascia is closed and the incision sewn in two layers after insertion of a subgaleal drain.

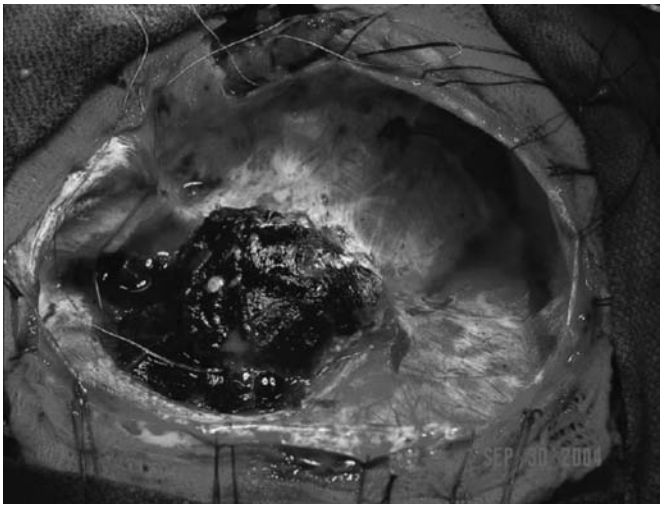

Figure 120.3 Intraoperative photograph demonstrates the resection cavity.

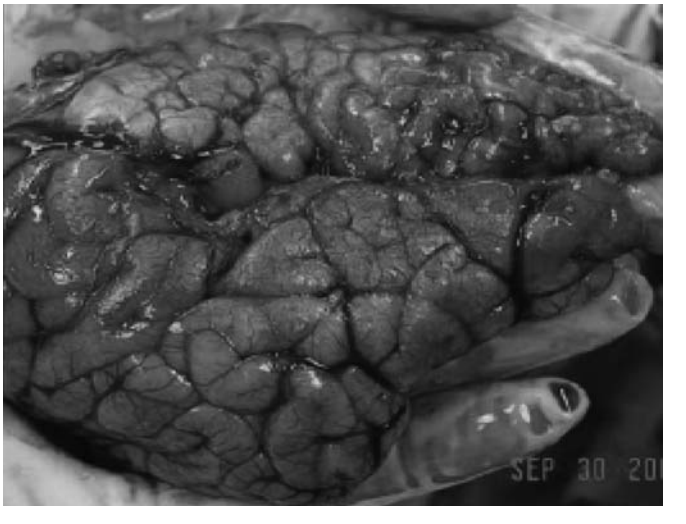

Figure 120.4 En bloc specimen of the left cerebral hemisphere after anatomic hemispherectomy.

Oxford modification

Adams devised a modification of the standard anatomic hemispherectomy to prevent SCH. This method was first attempted by Gibbs and Wilson in 1968.[24] By plicating the excess dura to the exposed falx, tent, and floor of the empty hemispheric cavity, he shrunk the subdural space and expanded the extradural cavity isolating it from the ventricles. Adams also occluded the ipsilateral foramen of Monroe with a muscle plug to prevent the contents of the subdural space from spilling over into the third ventricle.[3] Other attempts to curb the late complications of anatomic hemispherectomy included duraplasty and implantation of space-occupying material such as omentum, silicone prosthesis and Zenoderm graft on-lay.[31,41–43] Although of historic note, this modification is no longer in use today.

Functional hemispherectomy

Although Oppenheimer and Griffith proposed disconnecting the abnormal hemisphere, it was not until Rasmussen that the concept and practice of functional hemispherectomy ushered in the modern era of surgical treatment for hemispheric epilepsy.[23] This operation consists of a temporal lobectomy, central resection, corpus callosotomy and disconnection of the mesial parietal-occipital and frontal lobes, which are left in situ.

After satisfactory general endotracheal anesthesia, the patient is positioned supine with the head turned to the appropriate side and rigidly fixed with the vertex angled slightly down. The hemicalvarium is shaved and a pterional reverse question-mark incision 1 cm anterior to the tragus reaching medial to the superior temporal line is marked out. The temporalis muscle is elevated to gain wide exposure to the cranial floor. A fronto-parietal-temporal bone flap is turned to expose the sylvian fissure (Figure 120.5). The infrasylvian phase is then performed as in the anatomic operation. This includes a large temporo-parietal resection to the posterior exstent of the sylvian fissure with resection of the mesial structures.

The suprasylvian phase is designed to preserve the anterior frontal lobe and the posterior parietal and occipital lobes. Care must be taken to preserve the arterial and venous supply to these areas (anterior frontal and parieto-occipital MCA branches, PCA, and ACA supply).

A central segment of the hemisphere (fronto-parietal operculum) is resected beginning at the superior margin of the sylvian fissure through the frontal operculum and extending anteriorly to the rostrum of the corpus callosum and posteriorly to the splenium. This window typically includes the inferior and middle frontal gyri as well as a portion of the inferior parietal lobe. The dissection is directed medially and superiorly to the superior circular sulcus of the insula and then continues through the corona radiata toward the ventricle. Branches of the MCA supplying the resected tissue are ligated and divided however care must be taken to spare the large posterior parietal branches and some of the anterior frontal branches to avoid postoperative infarction of the cortex left disconnected but in situ. The lateral ventricle is accessed and this block of tissue removed. The entire ventricular system is opened by aspirating the corona radiata to connect the frontal, temporal and occipital horns.

The corpus callosum is disconnected via the ultrasonic aspirator from the genu to the splenium, as is the adjacent ipsilateral cingulate gyrus. Again, it must be emphasized to carefully look for residual splenium or genu that could lead to postoperative seizure recurrence. The white matter projections to and from the anterior frontal lobe are then disrupted to the pia medially through the frontal horn and caudate nucleus. Posteriorly, the mesial parietal-occipital fiber tracts are sectioned in a similar fashion. The remaining brain is irrigated and hemostasis achieved (Figure 120.6). A ventricular catheter is placed in the cavity. The dura closed and the bone

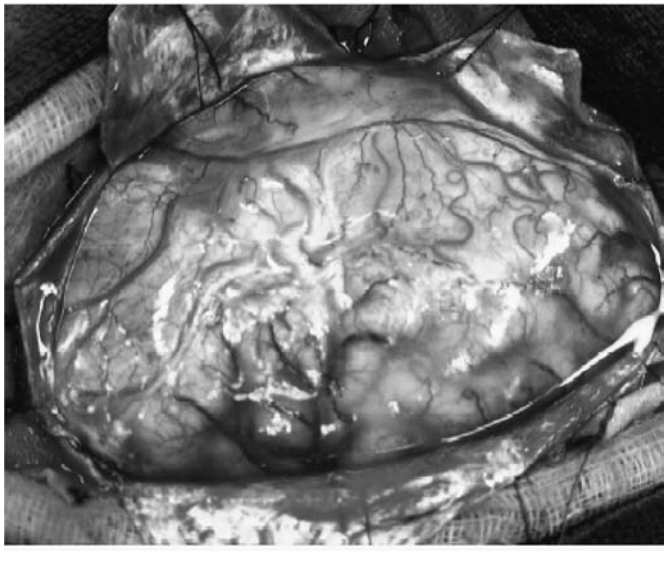

Figure 120.5 Intraoperative photograph taken after removal of bone flap and opening of the dura in a patient with a history of perinatal stroke and epilepsy.

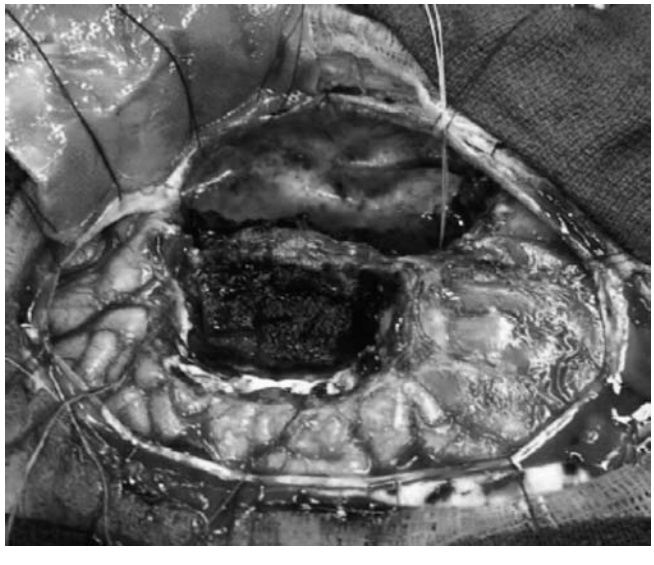

Figure 120.6 Intrapoperative photograph illustrating the preservation of the anterior frontal lobe and posterior parietal-occipitial lobes following resection of the frontal-parietal operculum.

flap secured with a microplating system. A second drain is inserted in the subgaleal space. The muscle fascia is reapproximated and the skin sutured in 2 layers. These steps constitute the functionally complete but anatomically subtotal hemispherectomy. (In his original lecture, Rasmussen stressed preservation of the posterior third of the hemisphere in patients without a homonymous hemianopsia.[4]

Peri-insular hemispherotomy

Hemispherotomy as defined by Villemure is the 'surgical procedure that requires the smallest brain volume removal to accomplish a complete hemispheric disconnection.'[29] Based on this definition, the following surgical goals were advanced: division of the internal capsule, transventricular callosotomy through a suprasylvian window, transection of the frontal horizontal fibers, and resection of mesial temporal lobe structures through an infrasylvian window. This technique, described in 1995, takes maximum advantage of the orientation of the cortical projections on the approach to the corpus callosum.[29] Perinsular hemispherotomy has the theoretical benefits of reduced operative time, minimal blood loss, and fewer postoperative complications with equivalent seizure control when performed correctly. The landmarks are better appreciated in patients with enlarged lateral ventricles, although peri-insular hemispherotomy has been successfully performed in patients without ventriculomegaly.[44]

Hemispheric deafferentation

In the same year that Villemure and Mascott published their description of the peri-insular hemispherotomy, Schramm *et al* published the technique 'hemispheric deafferentation'.[32] These techniques are almost identical in principal but vary in sequence of disconnection. In the hemispheric deafferentation, a standard temporal lobectomy is performed first to gain access to the temporal horn. From within the temporal horn, the ventricle is followed to guide entrance into the lateral ventricle. There were three modifications included in the original report. Modification 1 included selective temporal lobe resection of the first 4 cm of superior temporal gyrus along with amygdalohippocampectomy. Modification 2 describes what is essentially the creation of a perisylvian window as used by Villemure. In modification 3, the keyhole hemispherectomy, outlined below, is discussed.

Keyhole hemispherectomy

Schramm *et al*. refined the hemispherotomy technique with the advent of the transylvian keyhole, functional hemispherectomy or transylvian, transulcal technique.[33] This method goes further to limit the craniotomy to an area directly over the sylvian fissure. Favorable anatomy for this approach include; hemispheric atrophy, enlarged ventricles, porencephalic cysts and an atrophic basal ganglia and insula.[45]

Transopercular hemispherotomy

In 2000, Schimizu and Maehara published their modification of the original hemispherotomy technique, the 'transopercular hemispherotomy'. In this technique, the mesial temporal structures are approached from the medial aspect of the insula. This maneuver facilitates insular fiber resection during access to the hippocampus and amygdala and obviates the need for insular cortex aspiration. The balance of the operation proceeds similarly to the standard hemispherotomy.[46]

Vertical hemispherotomy

The vertical hemispherectomy originally described by Delalande in 1992 is a unique disconnective operation.[28] Nearly the entire operation is carried out in the white matter and dissection is subpial. In 2000, Danielpour *et al*. further described this alternative, minimally invasive, disconnective operation. In comparison to the small hemicorticectomy used to access the ventricular roof by Delalande, their method involves no cortical resection. The surgery is summarized below.[47]

A midline bone flap is turned to encompass the length of the corpus callosum. The dura is incised and the hemisphere retracted laterally. The ventricle is unroofed by dividing the callosum to reveal the entire lateral ventricle. Dissection is carried down to the temporal horn in an inferior-lateral fashion. This serves two purposes: 1) disconnection of afferent and efferent fibers from the internal capsule; 2) establishes a corridor for the resection of the amygdala and anterior hippocampus. Finally, 3) to finish the hippocampectomy, the posterior pillar of the fornix is sectioned.

Hemidecortication (hemicorticectomy)

Hemidecortication, first brought to attention by Ignelzi and Bucy in the treatment of infantile cerebral hemiatrophy in 1968, has maintained a foothold in the therapeutic strategies for diffuse hemispheric epilepsies since its inception. It was popularized in the 1970s when it was instituted by Winston and Hoffman independently.[48] The Johns Hopkins experience includes the largest modern, published series of hemidecortications (n = 111).[7] The operation is best understood as a 'degloving' of the cortex from the supporting white matter. Its theoretical advantage is to minimize entry into the ventricle. However, the operation cannot be accomplished without entering the temporal horn which still exposes the ventricular system to blood and cellular debris. Other drawbacks of this technique include the obliteration of ipsilateral arachnoid granulations which would normally resorb CSF as well as the challenges associated with detecting dysplastic foci buried in the white matter. Blood loss, hydrocephalus, and incomplete disconnection may be more common.[45] The use of ultrasound guidance to characterize the shape of the ventricles and relative location beneath the cortex has been described by Kanev *et al*.[49]

Postoperative care

After functional or anatomic hemispherectomy, patients are usually extubated in the operating room. They are transferred to the intensive care unit with frequent lab assessment, serial neurological exams, and monitoring of fluid status. Careful transfer of the patient and orientation of the patient with remaining hemisphere down may be of value in preventing brainstem hemorrhage.[36] Coagulopathy during the first 48 hours is common and prompt correction with blood products is essential. The external ventricular catheter removes CSF contaminated with blood and surgical debris for 48 to 72 hours. The subgaleal drain is discontinued in 1–3 days.

Antibiotics are continued until the ventricular catheter is pulled. A 1-week course of steroids is usually prescribed. Fevers, often secondary to aseptic meningitis occur frequently and are tolerated for up to one week following surgery before consideration of an infectious cause. A baseline MRI is obtained the morning after surgery. Diet is advanced, fluids weaned, and physical and occupational therapy resumed expectantly.

Technique selection

Recent modifications have focused on minimizing the amount of tissue removed in favor of cortical disconnection. The proposed benefits of the newer approaches are a smaller craniotomy, reduced operative time and blood loss, decreased risk of infection, and prevention of hydrocephalus. In a recent retrospective review comparing hemidecortication to peri-insular hemispherotomy, a reduction in blood loss, transfusion, fever, intraoperative hypotension, recovery time, and hydrocephalus necessitating shunting was observed in patients treated with peri-insular hemispherectomy.[44] However, many of these adverse events depend on the surgical skill, and comfort level of the surgeon with a given operation. Furthermore, functional hemispherectomy and hemispherotomy have a steep learning curve and may be suboptimal surgical approaches for selected hemispheric pathologies. This contributes to the higher reoperation rate observed with functional hemispherectomies.[6]

Cook *et al*. retrospectively reviewed the UCLA case series of 115 patients treated with either anatomic hemispherectomy, functional hemispherectomy, or a modified lateral hemispherotomy.[6] None of the patients required reoperation for seizure control in the anatomic hemispherectomy cohort. A total of 12 patients underwent reoperation for seizure control when using the other techniques (functional hemispherectomy = 8; modified lateral hemispherotomy = 4).[6] The improved rates of seizure control in some recent reports using newer techniques may reflect improved patient selection.

Reoperation

Seizures may persist or recur even with thorough preoperative planning and perfect execution. Postoperative ictal and interictal epileptic discharges arising from both hemispheres are not uncommon and should be carefully analyzed. For example, of 51 patients available for follow-up after vertical hemispherectomy, 80% were seizure free. Nine of the remaining 10 had a 90% reduction in seizure frequency. In each of these cases, epileptic discharges where recorded in the nonoperated hemisphere.[30]

When seizure control is unsatisfactory, surgical failure may also be the culprit. Reoperation may be indicated to complete the disconnection of white matter tracts which have only been partially divided as demonstrated on postoperative imaging. Unfortunately, postoperative MRI and EEG can be difficult to interpret and re-operation with anatomic removal of the hemisphere is sometimes carried out as a compassionate treatment to reduce seizure burden. In other cases, residual tissue will be identified on postoperative imaging and re-operation is indicated. In our experience, problematic areas to be carefully analyzed on MRI include the corpus callosal disconnection, the insula, and the posterior mesiobasal frontal lobe. These are all potential sources of residual epileptic tissue, especially in cases of hemimegalencephaly.

Following the Shimizu perinsular hemispherotomy, reoperation was warranted in 3 out of 34 patients. In each patient, the corpus callosum was incompletely sectioned.[46] Residual epileptic cortex has also been identified after hemidecortication and should be resected when appropriate.[44]

Technique selection: Rasmussen's encephalitis

The symptoms of Rasmussen's encephalitis often consist of epilepsia partialis continua, progressive hemiparesis, and eventual mental deterioration. Increased signal on MRI often heralds the onset of hemispheric atrophy later. When to proceed with surgery is controversial. Peacock has advocated delaying surgery until digital dexterity in the hemiparetic arm is restricted, however, early intervention may limit the cognitive impairment of the disease despite worsening the hemiparesis.[1] This may facilitate the early transfer of function and reduce the overall burden of this disease.[36] Complete disconnection of the affected hemisphere including insular removal is the surgical goal and can generally be accomplished by the functional techniques.

Technique selection: hemimegalencephaly

Hemimegalencephaly is a functionally incapacitating neuronal migrational disorder of unknown etiology. Infants with this malformation demonstrate psychomotor delay, encephalopathy, and refractory seizures. There is overt hemispheric asymmetry and the cortex is diffusely hypertrophic often with enlargement of the ipsilateral ventricle. Gross specimens may show hyperplastic frontal and occipital lobes surrounding a hypoplastic temporal lobe with lissencephalic cortex.[50] Subcortical heterotopia and calcification are usually seen. The microscopic findings reveal the complete absence of normal cortical cytoarchitecture.[39] Hemispherectomy is routinely offered to patients with this condition based on the devastating epilepsy and improved outcomes achieved with surgery in the past.[51,52] Contralateral, independent seizure spikes should not be a contraindication to surgery although this may portend poorer seizure control postoperatively.[52] In these situations, Wada testing may help extract information regarding expected seizure suppression with surgery.[52]

Applying the disconnective techniques to hemimegalencephaly is hampered by the enlargement of the hemisphere and the presence of subcortical dysplastic tissue. The midline often is displaced by the anomalous gyri further obscuring the anatomic landmarks. Thus, anatomic hemispherectomy is the preferred operation for hemimegalencephaly at our institution.[2,35] Sparing parasagittal cortical tissue with anomalous draining veins adjacent to the sagittal sinus may reduce bleeding during resection. [27,51] If a disconnective operation is chosen, resection of the temporal lobe and the frontal operculum is recommended. This is a necessary step to allow for adequate visualization of the hemisphere and reduce the chances of postoperative brain swelling.[33,53] (Figure 120.7).

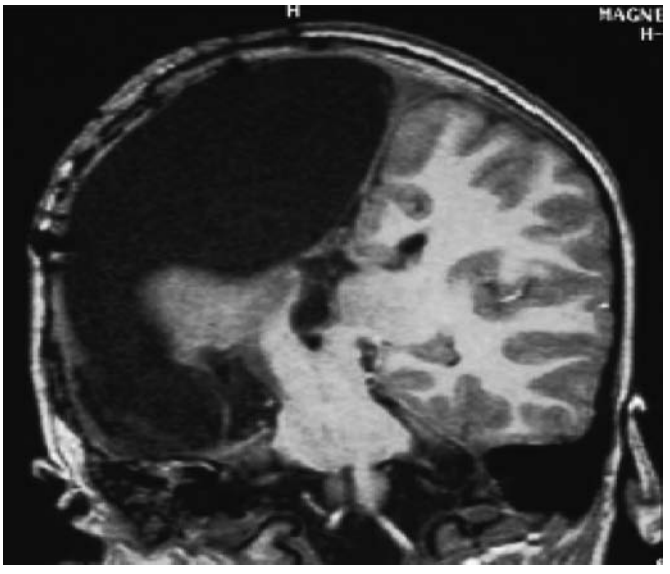

Figure 120.7 Postoperative coronal magnetic resonance imaging following anatomic hemispherectomy for hemimegalencephaly.

Technique selection: Sturge-Weber disease

Sturge-Weber disease or encephalofacial angiomatosis is characterized by the presence of a port wine nevus in the distribution of one or more trigeminal divisions and ipsilateral leptomeningeal venous malformation. Patients are often plagued by seizures with onset in infancy and debilitating hemiplegia. Functional imaging with PET or SPECT may better delineate the extent of the pial angiomatosis than MRI.[39] The description of hemispherectomy as a promising therapeutic option in reducing seizures in patients with Sturge-Weber disease was first published in 1952.[26,54] Falconer later elaborated on his experience in his report of five patients, all of whom had relief from seizures.[26,55] They supported early intervention in patients with diffuse hemispheric disease as the majority had a normal IQ and minimal hemiparesis when operated on in infancy.[26]

Special precautions should be taken in patients with Sturge-Weber who have holohemispheric leptomeningial angiomas throughout the operation. In infants, a staged operation may prevent the complications associated with potential blood loss.[44] Uncontrollable bleeding was encountered after drilling burr holes in one patient because of enlarged diploic veins resulting in the patients death.[27] Hoffman *et al.* published their case series of seven patients in 1979 and recommended en bloc rather than piecemeal removal because this technique limited blood loss from the pial vascular malformation.

Summary

The principle behind hemispherectomy has not changed in 75 years; isolation of the diseased hemisphere from normal brain. The versatile surgeon should opt for a technique tailored to the patient taking into account age, pathology, and anatomy. These surgical approaches are remarkably successful in the treatment of hemispheric epilepsy and hemispherectomy remains one of our most successful operations.

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SECTION 16

Nonresective surgical procedures and electrical or magnetic stimulation for epilepsy treatment

121 Experimental multiple subpial transection: is it still indicated?

T Tanaka, A Hodozuka, K Hashizume, M Kunimoto, and S Takebayashi

Introduction

Multiple subpial transection (MST) is an effective procedure for suppressing focal epileptic seizures and is associated with minimal neurological deficits.[1,2] The rationale of their findings is based upon basic researches.[3–7] It is the method of choice for patients with uncontrollable epileptic lesions situated in unresectable eloquent cortex regions. However, adverse effects of MST following surgery have recently been reported.[8]

In the present study, the postoperative effects of MST were studied in an experimental model of focal cortical seizures induced by an intracortical microinjection of kainic acid (KA) in cats and in rats developed in our institution.[10–11] Electroencephalographic and autoradiographic analyses were carried out in surgically treated animals with and without MST, and the effectiveness and the after-effects of MST were assessed.

Methods and materials

Kainic acid injection into the sensorimotor cortex of cats (8–80 μg) or rats (2–20 μg) under mild pentobarbital anesthesia resulted in a transient focal motor seizure status for a period of 5–10 hours. On EEG, focal seizures lasting for about 30 seconds were repeated every 5–8 minutes at the injected site of the sensorimotor cortex with occasional secondary generalized seizures. An autoradiogram taken during the partial seizures demonstrated three major propagation pathways from the epileptogenic cortical focus: ipsilateral cortico-cortical propagation, contralateral cortical propagation via corpus callosum, and propagations to subcortical structures such as basal ganglia and thalamus. Using this focal cortical seizure model, the following studies were carried out.

1. *Experiment I*: Neurophysiological approach to MST in an experimental cat model. Under mild pentobarbital anesthesia, animals were placed on a stereotaxic frame and a fronto-parietal craniectomy was performed using a surgical microdrill. A cannula was inserted into the unilateral sensorimotor cortex, and EEG electrodes were placed on the dura. An injection needle was inserted into the cannula and KA solution was injected. One hour after focal seizures induction, unilateral craniectomy was performed at the frontal region. In control cats (without MST), the wound was closed with nylon stitches. In the MST group, two parasagittal MSTs were performed to either side of the KA focus. After MST, 5 hours of EEG recording was carried out. The wounds were closed with nylon stitches and the animals were intensively cared for with warm blankets, intraperitoneal water, and electrolyte administration. After recovery from the surgery, the animals resumed their normal condition without any seizure activity in both control and MST groups. Animals were deeply anesthetized with intraperitoneal pentobarbital and processed for pathological analysis 1 week or 1 month after surgery.
2. *^{14}C-deoxyglucose autoradiography in rats with or without MST.* In control rats, unilateral craniectomy was done and only MST was performed. The rats were processed for autoradiographic imaging with ^{14}C-deoxyglucose, as described previously.[11] In KA-group rats, after induction of focal cortical seizures, two parasagittal MSTs were performed at the focus area, and the animals processed for autoradiography. The local cerebral glucose utilization (LCGU) was measured using an image analyzer.

Results

Kainic acid injection into the unilateral sensorimotor cortex resulted in focal cortical seizure status in all cats. In control cats, induced seizure status persisted about 10 hours after KA injection. In the MST group, two parasagittal MSTs immediately arrested the seizure at the KA focus on EEG. Seizures did not propagate to the contralateral frontal cortex. However, high-amplitude beta activities remained in the cortex caudal to the MSTs (Figure 121.1, arrow).

The postoperative course after MST was uneventful without neurological deficit. Seizures did not recur in cats injected with a low dose of KA solution. However, in cats injected with a high dose of KA, transient myoclonic jerk contralateral to the KA injection was observed. In both cases, motor deficits were not induced following MST.

Pathological studies in cats with MST revealed intracortical and subpial hemorrhages at one week after the MST (Figure 121.2). Mild subarachnoid hemorrhage was noted adjacent to the MST area. At 1 month after surgery, gliosis with hemosiderin doposits and microvacuolations were noted along the MST track.

Autoradiography with ^{14}C-deoxyglucose was performed in rats after MST with or without KA-induced focal seizure

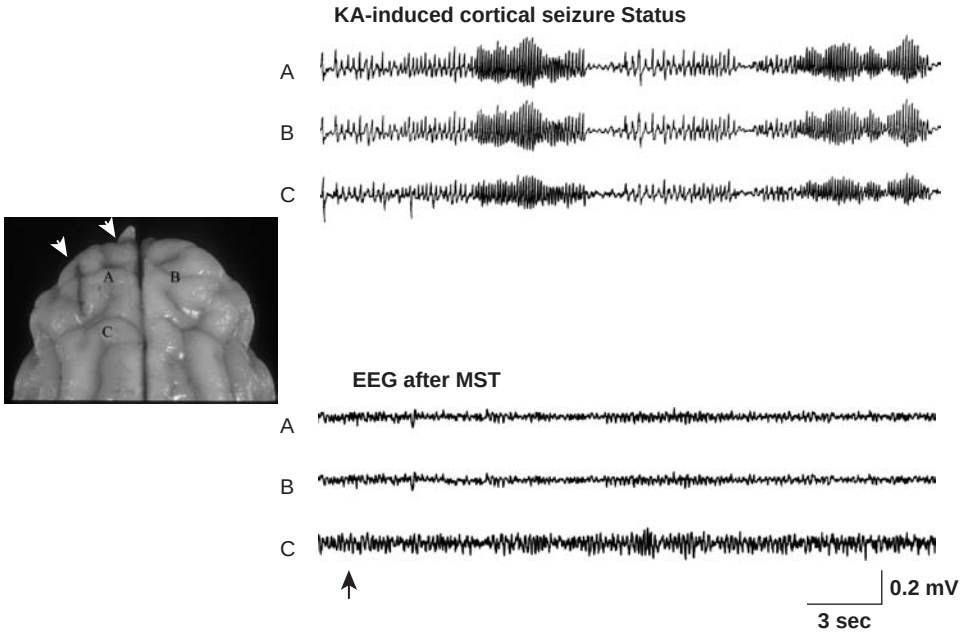

Figure 121.1 Intracortical KA injection resulted in focal cortical seizure status (top). EEG after MST demonstrated seizure suppression in electrodes A and B (bottom). However, high-amplitude beta activities remained in the ipsilateral parietal cortex (arrow).

status. In rats without KA, normal local cerebral glucose utilization (LCGU) was observed even after two MSTs had been performed (Figure 121.3). In rats with KA and MST, suppression of LCGU was noted at the epileptogenic focus in the transected cortex, especially between the two MST sites. However, LCGU of the ipsilateral cortex posterior to the MST, and in the superior part of the caudate nucleus, thalamus, hippocampus and contralateral cortex remained hypermetabolic even after the MST.

Discussion

In refractory extratemporal cortical epilepsy, when the epileptic focus is situated in unresectable cortex such as the speech centers of Broca or Wernicke, visual cortex, or sensori-motor cortex, radical resection therapy is not indicated, since serious functional deficits may result. MST is a relatively new surgical technique for treating intractable epilepsy arising from the eloquent cortex. The aim of the procedure is to transect

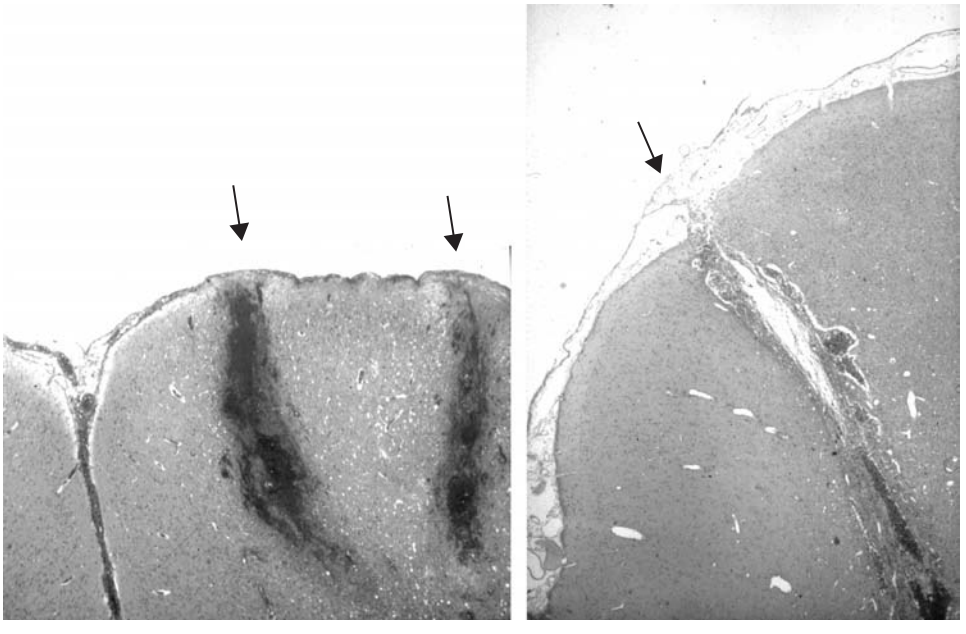

Figure 121.2 Photomicrograph demonstrating hemorrhage at the MST track one week after surgery (a, arrows). Subpial and subarachnoid hemorrhaging were also observed (a). One month after the MST, gliosis and hyalinization were observed along the MST track (b, arrow). Hemosidelin deposits were also observed.

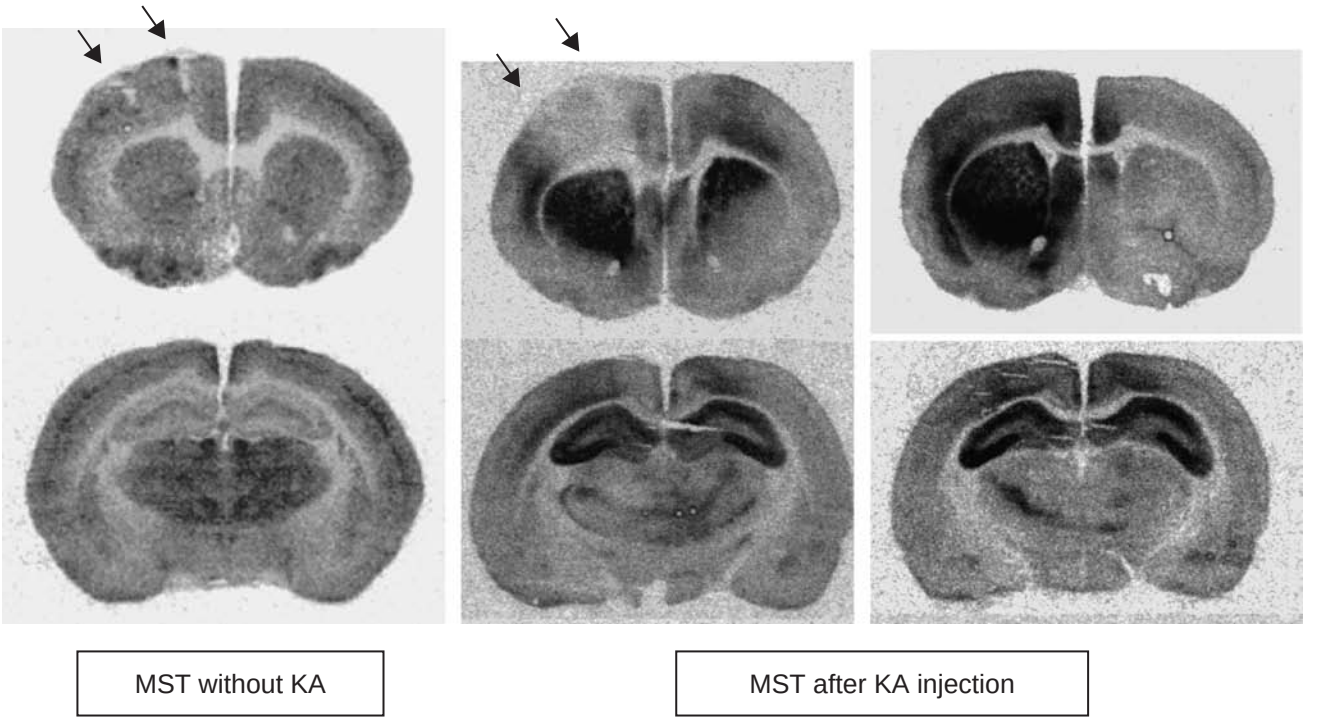

Figure 121.3 Autoradiograms with ^{14}C-deoxyglucose demonstrating normal local cerebral glucose utilization (LCGU) in rats without KA even after two MSTs had been performed (left, arrows). In rats with KA and MST, suppression of LCGU was noted at the epileptogenic focus in the transected cortex, especially at the cortex between two MSTs (middle, top). However, LCGU of the ipsilateral cortex posterior to the MST (left, top), superior part of the caudate nucleus, thalamus, hippocampus and contralateral cortex remained hypermetabolic even after the MST (middle and left, bottom).

horizontally coursing intracortical fibers, which play an important role in seizure spread, while preserving the vertically-oriented cortical columns that are related to normal cortical function.[2] In this study, unilateral KA injection into the sensorimotor cortex in cats resulted in a transient focal motor seizure status with occasional secondary generalizations for a period of 5–10 hours. This KA-induced seizure model is extremely useful for the experimental study of MST as the primary epileptogenic focus is localized within the site of the KA-injected cortical layer. MSTs performed in this study actually suppressed the seizure activities of the sandwiched area of the cortex between the MST sites. Cortical seizure propagations in the horizontal plane on EEG were clearly inhibited by the MST because the cortical seizure did not propagate beyond that focal area of MST.[12–16] In a limbic seizure status model, Imamura *et al.* studied effects of orthogonal transection between the dorsal and ventral hippocampus upon kainic acid-induced amygdalar seizures.[17] Seizures subsided within 24 h, showing no ictal manifestations except for aggressiveness. Overall, seizures were weak and transient compared with those in controls. Histologically, hippocampal neuronal damage was slight. These results indicated that connections between the dorsal and ventral hippocampus are important for full development of KA-induced amygdalar seizures. However, this method is palliative and not curative.

Autoradiographic studies with ^{14}C-deoxyglucose were analyzed precisely in rats with or without KA focus and revealed that the LCGU between the two MSTs was normal. This indicated that the MSTs did not interfere with cortex metabolism even in the surgically sandwiched cortex.

In rats with KA and MST, suppression of LCGU was noted at the epileptogenic cortex between the two MSTs. However, LCGU of the parietal cortex posterior to the parasagittal MSTs, deep cortical layer, superior part of the caudate nucleus, thalamus and contralateral cortex remained hypermetabolic even after the MSTs. This result shows that MST is a good surgical alternative only when the MSTs can sandwich the small epileptic focus in the cerebral cortex, but seizure propagation via vertically oriented cortical columns to the basal ganglia and thalamus remained after MST.

Subacute and chronic pathological analysis revealed a scar formation in the cortex after MST indicating that MST may be an alternative for controlling electrophysiological focal cortical seizures in the eloquent cortex. However, chronic pathological changes should be monitored over long-term follow-up of the procedure.

In clinical cases, bleeding can occur at the site of the transection, but the procedure has been generally well tolerated, with no major complications.[18–28] Spencer *et al.*[29] studied 211 patients from six large epilepsy centers who had undergone either surgical lesionectomy with MST (158/211) or MST only (53/211). In the MST and resection patients, a >95% seizure reduction was obtained in 68% of cases for simple partial seizures. For the patients undergoing MST only, the results were not as good, with a >95% seizure reduction obtained for simple partial seizures in 63% of cases. Surgery-related neurological

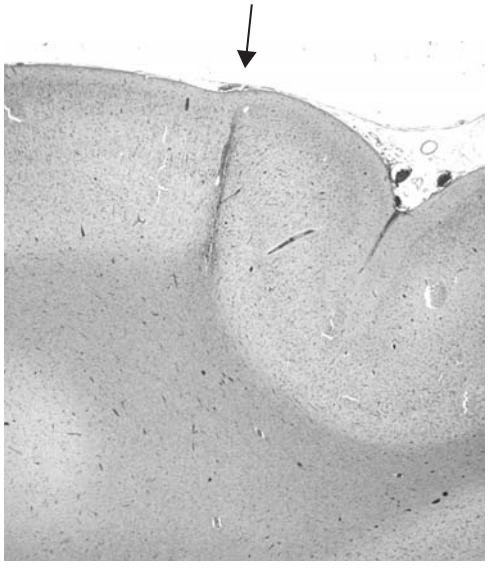

Figure 121.4 Photomicrograph of 9 year-old boy demonstrating a cortical scar by MST 6 months after the surgery (arrow). Along the track of the cortical MST, thin gliotic tissues were observed. Moreover, degenerative process such as micro-vacuolation and hyalinization with hemosiderin deposits were observed.

deficits were present in 47 out of the 211 patients, in 23% of the lesionectomy and MST group, and in 19% of those who had MST only (19%). This study highlighted that the possible neurological deficits from these procedures must be considered.

In our institution, 11 patients underwent MST from 1995 to 2003. In ten patients, lesionectomy with MST was performed. Only one patient who had focal cortical dysplasia over Broca's area underwent MST only. Six patients became seizure-free and three patients achieved 90% seizure reduction after surgery. One patient in the lesionectomy with MST group and one patient with MST only did not show improvement (Engel's Class III). Neurological deficits were not observed in this series of MST patients. In our institution, MST is performed only in areas where remarkable residual spikes are observed on postresection ECG. Damage to arteries and veins over the surface of the cortex are avoided if possible during the MST procedure. Consequently, the distance between the MSTs is variable and not always within 5 mm. This method is not the MST procedure originally described, but the modifications introduced appear to reduce the postoperative adverse effects.

We encountered a 9-year-old boy suffering from intractable complex partial seizure due to focal cortical dysplasia in the caudal part of the left inferior temporal gyrus. Based on the presurgical evaluation, lesionectomy with MST of the temporal cortex was preformed. Postoperatively, seizure recurred 3 months after the surgery. Further evaluation was made and mesial temporal focus was diagnosed. Six months after the first surgery, an antero-medial temporal resection was performed, after which the patient was seizure free. The final diagnosis indicated a dual pathology. Photomicrography of the resected temporal lobe contained a previous MST in the temporal cortex. Along the trace of the cortical MST, thin gliotic tissue was observed. In addition, degenerative processes such as microvacuolation and hyalinization were apparent, as were numerous hemosiderin deposits.

MST has been generally well tolerated, with no major complications reported. Our experimental study in cats clearly demonstrated the possibility of intracerebral hemorrhage along the track of the MST, subarachnoid hemorrhage one week after the MST, and scar formation one month after the MST. Our case with re-operation 6 months after the MST also demonstrated scar formation in the cortex. Late seizure recurrence after MST was recently reported.[8] The recurrence late was ten out of 54 patients (18.5%). Long-term follow-up is necessary after MST due to the potential for scaring of the most vulnerable cortex for epilptogenesis. Additional studies are needed to better define the risks and benefits of this procedure.

Summary

MST was evaluated in animals with KA-induced experimental partial epilepsy.

MST around the epileptic cortical focus suppressed the seizure activities of the cortex on EEG. However, seizure propagations in the subcortical structures remained even after the MST. The postoperative clinical course was uneventful, and subsequent motor deficit was not observed. However, pathological analysis indicated acute hemorrhage and chronic scar formation around the MST track. These results suggested that MST may provide a palliative method to suppress epileptic activity. Long-term studies are needed to fully define the risk-effectiveness of this surgical technique.

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122a Multiple subpial transections

W Harkness

To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin at 'the bench' with basic research — in which scientists study disease at a molecular or cellular level — then progress to the clinical level, or the patient's 'bedside'.

Office of Portfolio Analysis and Strategic Initiatives
National Institutes of Health 2007

Although the phrase 'translational research' may be perceived as relatively recent concept, there are examples in the history of medicine where the inspirational step from the laboratory to the bedside has led to a dramatic change in the management of disease to the benefit of patients. Such an example is the introduction of multiple subpial transections (MST) into the surgical management of epilepsy by Prof. Frank Morrell, a scientist physician with the almost unique distinction of having a surgical procedure and instruments eponymously named after him. Morrell was a most distinguished basic scientist and was one of the 26 founder members of the Society for Neuroscience whose first mission statement is to 'advance the understanding of the brain and nervous system by bringing together scientists of diverse backgrounds, by facilitating the integration of research directed at all levels of biological organization, and by encouraging translational research and the application of new scientific knowledge to develop improved disease treatments and cures'.

The scientific basis to MST

The initial studies to demonstrate the efficacy of multiple subpial transections were carried out by Professor Frank Morrell using an animal model.[1] The scientific premise upon which the hypothesis was based was developed from previous anatomical observations upon the vertical orientation of the cerebral cortex function,[2,3] combined with his own observations on the epileptic spike and it's anatomical orientation,[1] the need for horizontal propagation and the area of cortex required for seizure propagation and spread.[4]

Prior to his work, other authors had described procedures used in animals to demonstrate how tangential connectivity could be disrupted without loss of function.[5,6] These experiments carried out in the visual cortex of the cat demonstrated no change in visual perception and in addition that horizontal cortical cuts did not damage the blood supply to the cortex, thus ensuring preservation of vertically orientated cortical function. Morrells' laboratory work demonstrated that the minimum contiguous cortex necessary to sustain synchronous spiking was 12.5 mm^2 whilst cortical islands greater than 5 mm in width can support paroxysmal discharge with tangential spread occurring at a rate of 0.05 mm/s. In 1989, Morrell and Whistler described their initial experience of the procedure in human subjects,[7] and this has subsequently led to papers exploring the effects of the technique, both clinically and pathologically as well as its use in specific clinical scenarios. Despite the fact that the initial description of the clinical studies was now almost 20 years ago, remarkably few papers have been published describing clinical outcome and those studies that are reported are confounded by the fact that MST is frequently combined with resective or disconnective procedures. A recent multivariant analysis of outcome from a number of major epilepsy centers[8] was able to give some insight into the results but as yet little explanation appears to have been given to the relatively poor uptake of the procedure. This chapter will explore the original surgical technique and subsequent modifications, the histological features following MST as well as postoperative radiological features and finally clinical outcome in terms of morbidity, seizure status, and where possible quality of life improvement.

The surgical technique and its evolution

In the original animal experiments carried out by Morrell, he described a technique whereby intragriseal incisions spaced at 5 mm intervals were placed over the crown of the cortical gyri. This same surgical technique was applied by Morrell and Whisler in their human clinical studies.[7] Whisler has described and demonstrated the surgical technique involving a small pial incision at the edge of the gyral crown and then insertion of specially designed knives to divide the gray matter in a vertical orientation. The knives are modifications of those used in the animal experiments and consist of a single piece of stainless steel with a flexible shaft ending in a flattened tip at 105° to the shaft (modified from the original 90° to reduce the risk of snagging the arachnoid and vessels). The tip is 4 mm in height and 0.3 mm wide and rounded so that when it is drawn horizontally across the gyral crown beneath the pia, the tip of the knife does not breach the pia.

The initial description of the surgical technique involved placing an incision in the pia with a fine blade or needle as far down into the sulcus as the vessels allow. Should bleeding occur, hemostasis is achieved by gentle pressure with or without the application of a hemostatic agent. The end of the knife is then introduced into the breach in the arachnoid and passed

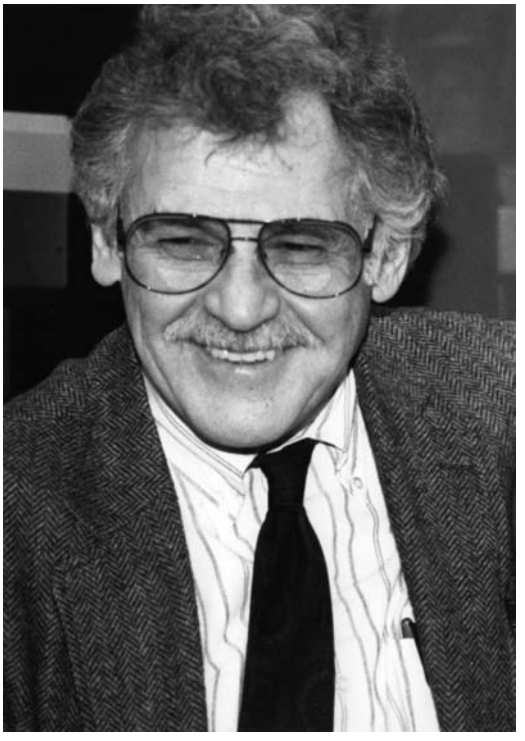


Figure 122a.1 Prof Frank Morrell 1926–1996

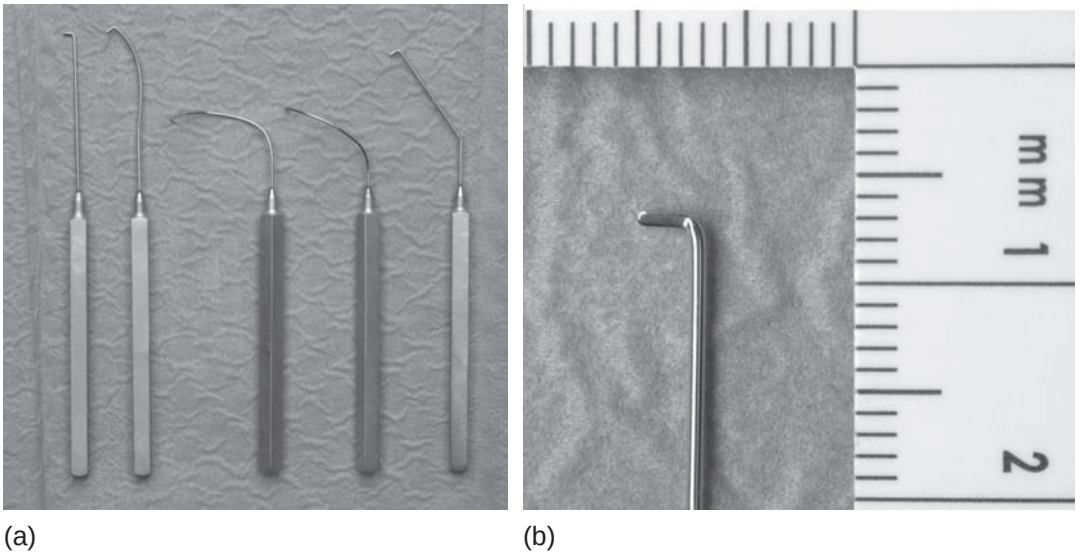
across to the other side of the gyrus, keeping the tip in view at all times. Gentle upwards pressure on the arachnoid will ensure that an incision of the correct depth is placed in the gray matter of the crown of the gyrus. Once the knife is removed and hemostasis achieved, a further breach in the arachnoid is made at 5 mm distance and the process repeated parallel to the first transection and thereby the gyrus becomes marked by a series of thin red lines perpendicular to the long axis of the gyrus.[9] As the gyrus turns the transections should be fashioned in such a way as to ensure that the 5 mm spacing is not exceeded and so a 'fan-like' pattern to the transections may be produced.

In order to determine the area that is to undergo MST, intraoperative electrocorticography is required. Areas showing evidence of epileptiform discharges are then transected prior to the corticography being repeated to ensure that the discharges are ablated. Should discharges persist, it should be considered as to whether the cortical sulci should be opened to allow transection of deeper areas of cortex. In order that an adequate exploration of the cortical surface can be carried out, a wide surgical exposure is necessary. In addition, in the anesthetized patient, it may be necessary to perform SEEPs in order to demonstrate eloquent cortex or alternatively direct cortical stimulation may be carried out in the absence of neuromuscular blockade. Whislers' original cases were performed with the patient awake with direct observation of the effects of cortical stimulation.[7]

One of the theoretical disadvantages of this technique is that a wide area of the anatomical and physiological target does not in fact become transected. Cortex in the vertical plane adjacent to sulci, microgyri, and gyri buried beneath the surface do not undergo transection. For this reason, a number of authors[10–12] have described a modification of the technique in which the knives are passed in a vertical orientation to transect some of this cortex and more than one pial incision made to ensure both sulci can be safely reached.[11] Great care needs to be taken when passing the knife tip downwards to prevent snagging of the arachnoid or vessels deep in the sulcus, as it is not in view unless the sulcus is opened. This is where the 'feel' of the knives becomes so important, that is the tactile feedback afforded by the flexible shafts of the knives. A number of instruments with different angulation and orientation of the knife point facilitates this aspect of the surgery. This modification of Morrell and Whisler's initial technique appears to have adopted more widespread use. A further practical adaptation is in the use of a micropoint diathermy at very low setting to make the pial incision and thus reduce bleeding from the surface vessels.

Pathological changes

Limited attention seems to have been paid to the pathological changes and the microscopical appearances of MST and this is probably due to the paucity of pathological material. One study



(a) (b)

Figure 122a.2 Morrell knives with close-up of tip.

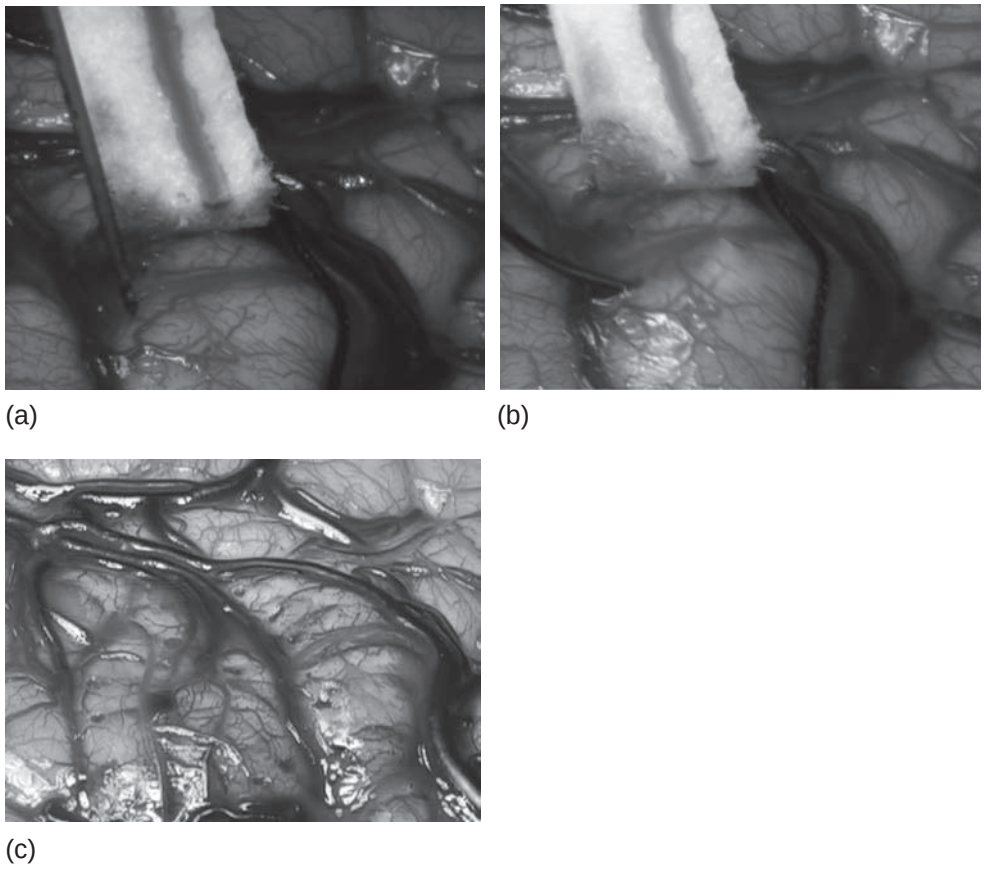


Figure 122a.3 Intra-operative photographs of surgical technique. Micropoint diathermy being used to breach the arachnoid. Tip of Morrell knife seen beneath the arachnoid as it is drawn across the gyrus. Final view of an area of transected cortex.

looked at the acute changes brought on by MST in patients who were in fact undergoing temporal lobe cortical resection.[13] MSTs were carried out immediately prior to the cortex being removed and the results analyzed histologically. The orientation of the transections was appraised, as well as the histological appearances. The authors concluded that in many cases, the orientation of the gyri meant that the transections themselves very often did not comply with the intended vertical orientation, whilst the histological appearances were of an acute hemorrhagic reaction. An abstract from the AES proceedings of 1993[14] described two patients in whom more chronic specimens were obtained, at 8 and 12 months following transection. Personal experience of the morphological consequences of Morrell procedure is confined to one functional hemispherectomy specimen from a 13-year old girl whose management for Rasmussen's encephalitis had included multiple subpial resections carried out on the right motor-sensory strip 4 months earlier. A number of narrow gliotic scars were noted over the crowns of the gyri running perpendicularly to the surface pia; these reach mid-cortical level but in some cases cut right through the cortical ribbon to reach the white matter. Hemosiderin-laden macrophages were noted in such scars. The anatomy of these lesions closely resembles the acute lesions described by Kaufmann *et al* (1996). While the surrounding neural parenchyma appeared unaffected, some scars were adjacent to long strips of cystic cortical destruction running from the gyral crest into the depth of sulci. These changes could correspond to incisions made vertically in the orientation of the sulci as described above but since such cortical destruction could not be distinguished from the burnt-out lesions of Rasmussen's disease, its relationship to the surgical lesions cannot presently be determined. These changes appear to differ from those described by the team from Rush Presbyterian in terms of their orientation but again may be explained by the slight difference in surgical technique (Figure 122a.4).

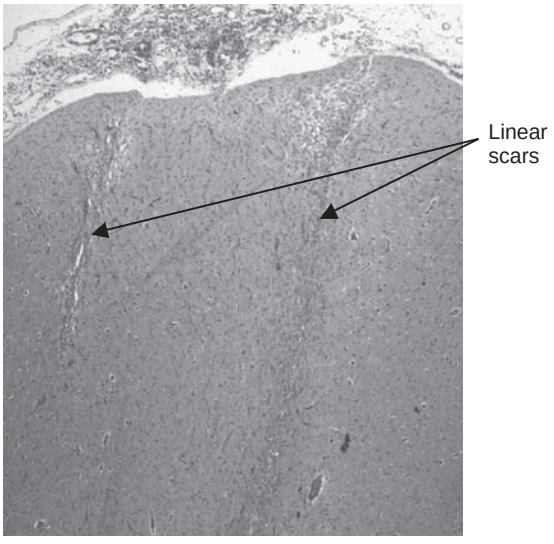


Figure 122a.4 Linear scars.

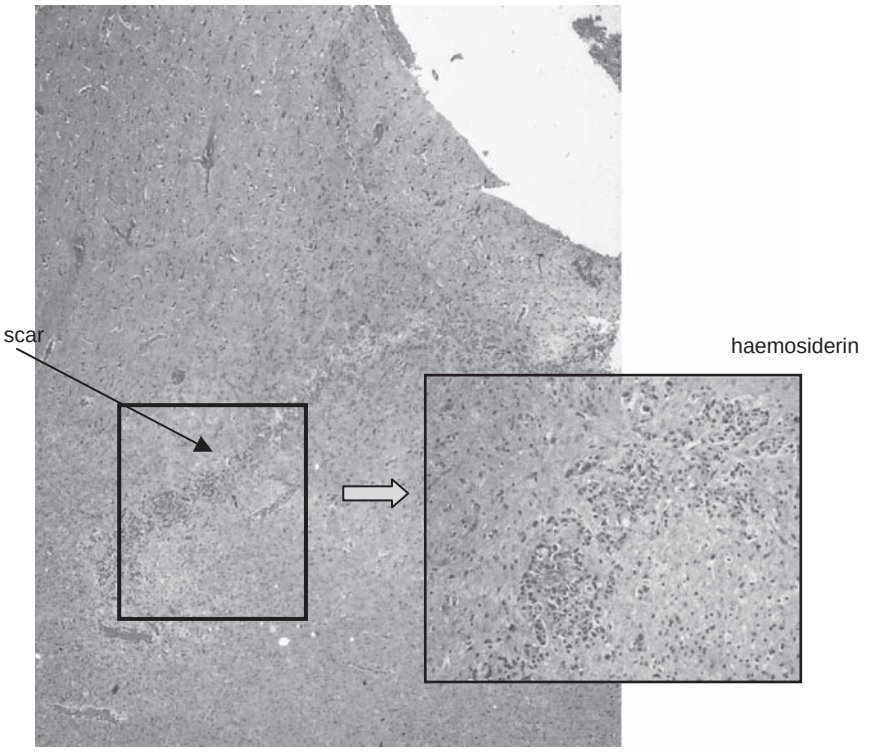


Figure 122a.5

These histological appearances would be consistent with the changes seen on MRI scanning. In the acute phase, there may be evidence of edema and hemorrhage in the superficial cortex and in the longer term, there maybe gliosis and evidence of ischemic change. The long term MRI appearances may also be limited to some mild atrophy, with the transections clearly seen on the T1 imaging. The imaging appearances may be confounded by any progressive changes that may be attributable to the underlying pathological process such as Rasmussen's disease.

Clinical indications and outcomes

The aim of MST is to impair the capacity of cortical tissue to develop sufficient neuronal synchrony to produce epileptiform discharges, without interfering with it's capability to mediate normal physiologic transactions.

Morrell Advances in Neurology 1990;81 259–69

The aim of MST as described by Morrell shows that the primary indication for the procedure is in functionally critical

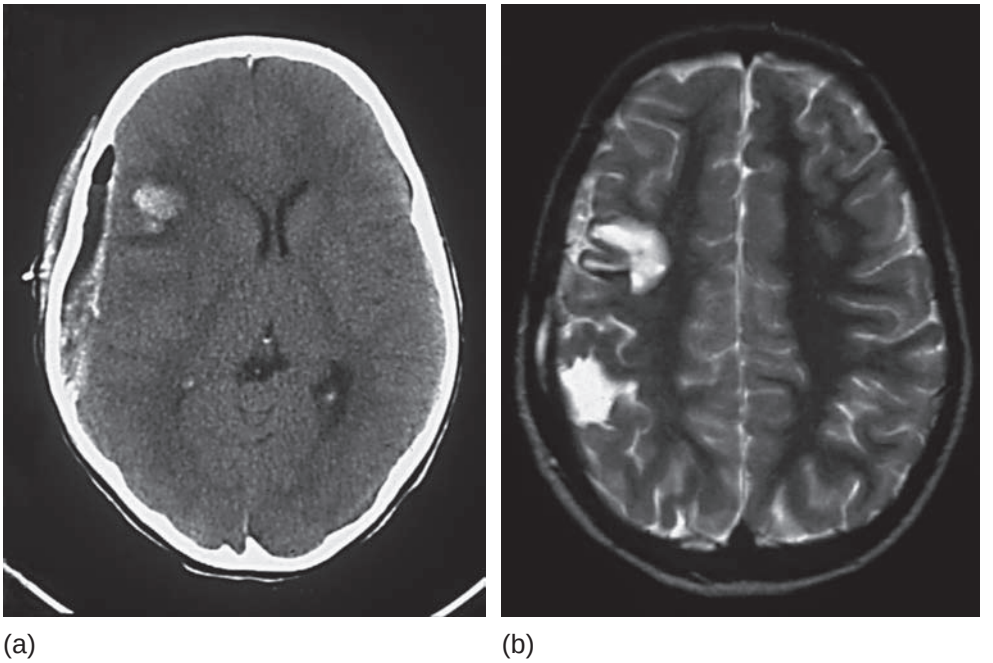
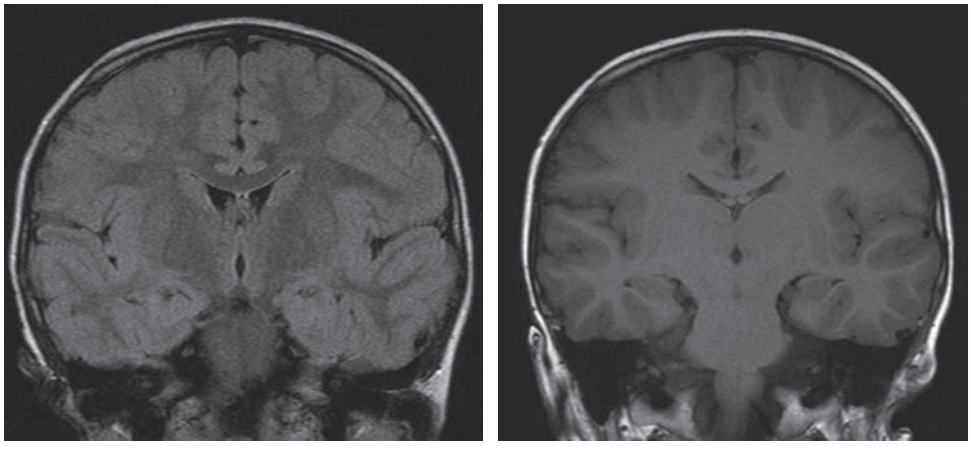


Figure 122a.6 Acute complications of MST. Hematoma deep in sulcus at gray/white Interface and MRI showing superficial edema.



(a) (b)

Figure 122a.7 Interval T1 and FLAIR coronal images following MST in the right suprasylvian region in a child with Landau–Kleffner syndrome showing minimal long term evidence of anatomical disruption.

cortex, with or without evidence of pathology. Four anatomical groupings of patients were treated:

a) pre-central gyrus
b) post-central gyrus
c) Broca's area
d) Wernicke's area involving angular and supramarginal gyri.

In all these patients the procedures were performed awake and with cortical stimulation to confirm functionality. In a chapter published in 1996 Morrell and Whisler reported their accumulated experience of 172 areas of transection in 97 patients up until June 1994.[15] The results of these procedures were described by Morrell with respect to function as well as seizure outcome.

There were 52 transections in the precentral gyrus and in seven of these who had transections in the leg area; two experienced a foot drop, attributed to subcortical venous haemorrhage. In none of the 44 cases in whom the procedure was carried out in the face or hand area was there an ensuing weakness. Two patients subsequently underwent resection of the previously transected areas, due to persistent seizures or progressive pathology and in both cases a profound weakness developed, supporting the underlying thesis of the procedure.

There were 57 cases of transection in the post central gyrus and in none of these was there any discernible postoperative sensory deficit. In 29 out of 57 (51%) there was an unexpected and unexplained deterioration in rapid fine finger movement.

In 23 cases transections were performed in Broca's area with only three showing evidence of decreased verbal fluency. In 45 cases transections were performed in Wernicke's area and the supramarginal and angular gyri and, apart from four cases, all are reported to have retained ability to 'understand, speak, read, write and copy'. In the earlier initial report from Morrell[7] of five patients all had some demonstrable difficulties in naming and word substitution but we do not have similar detail for the later, larger series. One patient who had undergone two previous procedures in the same anatomical location sustained an irreversible deterioration of her speech deficit following a deep subcortical hemorrhage.

Morrell and Whisler report seizure outcome for these patients undergoing purely MST according to the Engel Classification[16] with 53% Engel Class I; 11% Engel Class II; 20% Engel Class III; and 16% Class IV. Bearing in mind the refractory nature of the seizures and the location of the Epileptogenic Zone in eloquent cortex these results are impressive. There was no reported mortality but morbidity that was either procedure specific (e.g., subcortical hemorrhage) or procedure non-specific (e.g., osteomyelitis of bone flap) occurred in 18% of cases.

Subsequently Morrell and other authors went on to describe applications in other areas and in the presence of specific pathologies or clinical seizure syndromes, although the majority of cases reported in the literature are concentrated anatomically in frontal and temporal cortex.

The multi-centric meta-analysis carried out by Spencer *et al.* in 2002 reported standardized data of a total of 211 cases of MST from six centers.[8] The length of follow up and when the cases were accrued is not included in the chapter, implying that this was the total experience over an approximately 20 year period for these major centers. In 53 cases MST was carried out alone; whilst in the remainder MST was performed in conjunction with either resection or disconnection. Of the pure MST 10 cases (19%) developed new neurological deficits which is a figure very similar to the Morrell and Whisler series. Four patients had memory decline, whilst four experienced hemiparesis and one a visual field loss. Interestingly none had a deficit of sensation or speech as a consequence of MST alone, again supporting Morrell's findings. With regards seizure outcome this study did not use Engel's classification but rather a scale wherein an 'excellent outcome' was >95% reduction of monthly seizure frequency. 62% of patients undergoing pure MST fell into this 'excellent' category for simple and partial seizures and 71% had an excellent response as regards generalized seizures. Simple partial seizures were seen to increase in 15–20% of the total group of patients and outcome was better in the presence of focal lesions and worse in progressive or diffuse pathologies.

This analysis is a worthy attempt to bring together the sporadic and sometimes anecdotal reports of MST in the surgical

treatment of epilepsy but sadly can draw no significant conclusions other than MST 'can be considered a viable and effective approach to uncontrolled seizures arising in functionally critical cortical areas'.

Because of the interest in patients with Landau–Kleffner syndrome, which is discussed below, there has been much interest in the application of MST to the pediatric population. Blount *et al*. have reported the results in 30 cases accrued over a four year period, in whom 26 had MST combined with resection and four had MST alone.[17] The surgical strategy applied was to resect the epileptogenic zone and therefore invasive recordings were performed in 23. Outcome was 42% of patients who had resection and MST were Engel Class I and a further 42% Engel II and III. In all there was evidence of motor impairment when primary motor cortex was transected but there was no evidence of any permanent deficits. This outcome is very similar to a comparable adult series although the functional recovery appears superior in the pediatric group.[18,19]

Specific seizure types

Epilepsia partialis continua

When epilepsia partialis continua (EPC) affects the sensori-motor cortex the effects can be disabling and painful and severely affect quality of life. When distinct structural lesions are present it may be possible to carry out a successful resection using a combination of pre- and intra-operative functional information. This is not, however, possible in all cases and therefore when the pathology is diffuse or progressive with as yet little or no neurological deficit then MST may be the only realistic option. There have been five descriptions in the literature of MST being used for EPC in a total of five clinical cases. In one case MST was used in conjunction with resection;[20] another with disconnection[21] while in another[22] it was used as a prelude to invasive recording and focal resection. Molyneux *et al*.[23] have reported a patient with life-threatening complications due to medical treatment of EPC was significantly improved with MST. Despite a negative 0.5 T MRI the underlying pathology from a biopsy taken at the time of surgery was found to be cortical dysplasia. Follow up at eleven years following MST finds the patient had three seizures in the previous year and is working, whilst there have been several years completely free from seizures. A further unreported case from the same institution involves a patient with Rasmussen's encephalitis who had painful sensori-motor EPC with no neurological deficit in whom MST in primary sensori-motor cortex produced a dramatic clinical improvement and at 11 years follow up is having approximately four seizures per year.

Infantile spasms

There has been increasing recognition that infantile spasms may be associated with underlying focal pathology which may be surgical remediable, with associated improvement in developmental progress.[24–26] Chuang *et al*. have described two children (22 months and three years) in whom MST was carried out over an area localized by intraoperative electrocorticography.[27] There was an appreciable reduction in spasms in both cases but neither became seizure free. In one case cortical dysplasia was seen on biopsy and in the other the picture was strongly suggestive of dysplasia due to the asymmetric spasms and localized epileptogenic zone. It could be therefore argued that these cases would have been suitable for a potentially curative resective or disconnective procedure. Patil in describing his series of MST performed on both hemispheres included two patients with infantile spasms, one of whom was seizure free whilst the other was not improved.[28]

Specific syndromes and clinical settings

Landau–Kleffner syndrome with or without autistic features

Landau–Kleffner syndrome is an acquired epileptic aphasia with female predominance following previously normal development and the clinical picture is one of a progressive deterioration of speech, which may be associated with clinical seizures but more typically clinical seizures are less prevalent but EEG abnormalities exist most commonly in the temporal lobe. The neurophysiological findings may include electrical status epilepticus in sleep (ESES).

The severity of the clinical syndrome and the natural history of the disorder can vary considerably and the classical picture may be complicated by other features such as autism.[29] Although the condition may remit spontaneously within 2–3 years, there is evidence that continuing ESES lasting longer than 36 months and a younger age at onset are associated with poorer long term outcome. In addition, even when speech does return there is frequent evidence of impairment both of speech and memory.

Morrell[30] described his experience with 14 children with LKS who underwent MST in Wernicke's area, lateralization being achieved by EEG, methohexitone suppression test, sodium amytal test, and dipole mapping. All surgically treated subjects were developmentally normal prior to the acquisition of LKS and had the condition for a minimum of 2 years. Unilateral MST was carried out under electrocorticographic control with the Sylvian fissure being opened where deemed necessary and in two cases an additional anterior temporal resection was performed.

In seven cases 'normal' speech returned, in five there was a marked improvement in speech whilst in the remaining three there was no change. Changes in speech were usually seen progressively over the first six months following surgery and other gains seen with longer follow up. The presence of persistent EEG abnormality following MST was associated with a poorer outcome.

Grote *et al*.[31]subsequently reported the outcome of a further series of surgically treated patients from a total of 80 patients with LKS. Eighteen patients were operated upon of whom 14 were available for follow up. This study included 10 of the patients from Morrell's original group, four having been excluded on the basis of progressive or bilateral problem. A much more detailed analysis of outcome was available with two patients suffering significant peri-operative morbidity, one child showing a significant decline expressive and receptive language function and only 4 of 14 patients were recorded as returning to normal school. Nonetheless 50% showed a significant improvement in one or other domain tested following surgery.

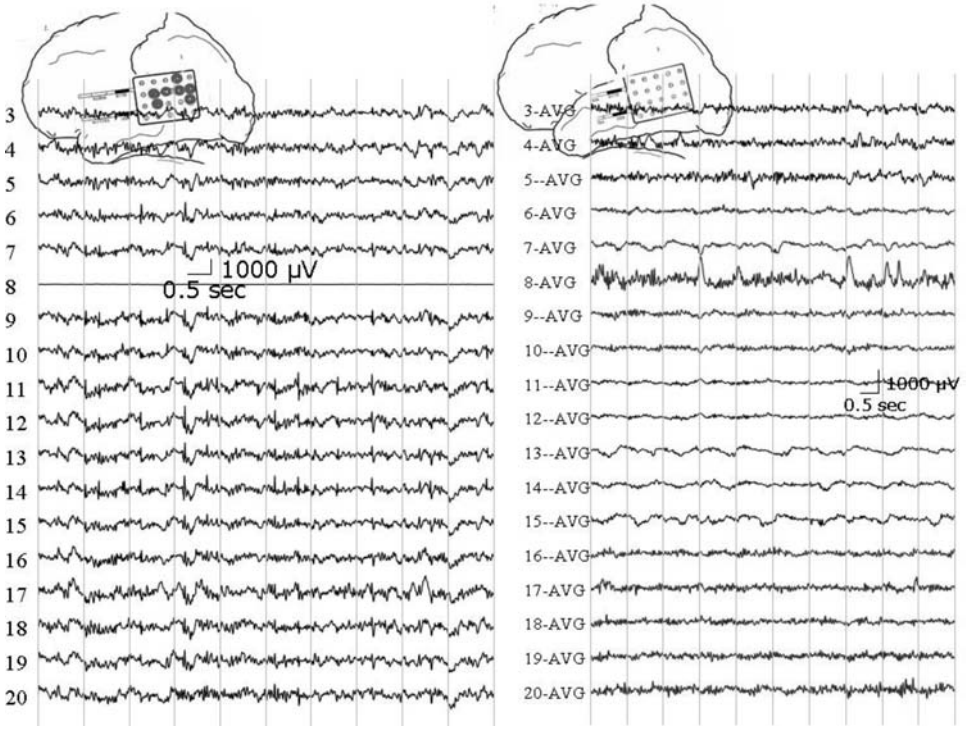


Figure 122a.8 Intra-operative electrocorticography recordings in patient with Landau–Kleffner syndrome before and after MST.

Irwin *et al.*[32] have described five patients with LKS treated with MST over an eight year period. Despite what appears to be an identical surgical procedure the outcome with respect to language was poor with no patient recovering age appropriate language. There was however, a significant reduction in clinical seizures and also an improvement in behavior, with loss of defiant aggressive behavior, improvement in attention span and reduction in hyperactivity. No child had a return of fluent speech but in two patients there was a significant improvement in behavior. This experience is shared in the series from Toronto[17] and in our own series of 10 patients undergoing MST for LKS in whom three showed an improvement of receptive language function and two an improvement of expressive language function.

It is not clear why the results described by Morrell and Grote have not been replicated in these two further studies. In Morrell's original paper children with autistic regression in association with LKS were not included. Certainly other authors have recognized a great deal of variability of the clinical picture with many patients either showing signs of delayed language before regression or failure to acquire language.[33–35] There are also clear links with features of autistic regression as one third of autistic patients undergo language regression under the age of three years and surgical series show evidence of lesions particularly in the right temporal lobe in patients with seizures and autism.[36] Nass *et al.*[37] have described seven cases in whom there were improvements in receptive language and also behavior although these were not always sustained. Neville *et al*[38] have described the response following surgical treatment in two patients with autistic regression one treated with temporal lobectomy and the other with MST, both of whom showed improvements in communication. Patil has reported five cases who showed apparent post operative improvement but this outcome was not quantified objectively.[39] Szabo *et al.*[40] have described five cases of epilepsy surgery in autistic regression with improvement but not relief of the autistic features. Finally, early onset of seizures has been linked with autistic regression and this might support the argument for early referral to surgical centers and the as yet unproven hypothesis that early surgery might minimize the development of autistic regression.[41]

Whilst clearly MST remains a surgical option in the management of LKS,[42] the families of patients need to be carefully counselled as to the expected outcome on the basis of the clinical information available. The outstanding questions of the timing of the procedure in the clinical course of the syndrome and its true clinical efficacy remain unanswered and will require a prospective audit of cases with careful pre- and post- operative evaluation both electroclinically and from the language and behavioral standpoint. The relationship between LKS, autistic regression, and epileptiform activity is a complex one[35] and thus the effect of MST on autistic regression also requires further evidence and remains the subject of discussion.[39]

Rasmussen's encephalitis

Due to the preservation of cortical function afforded by MST it is a surgical option when there is little or no neurological deficit, particularly for the dominant hemisphere.[43] Despite the likely palliative nature of the procedure in the presence of progressive pathology, it may have a role in the management of Rasmussen's encephalitis and has been described as such by a number of authors. Reviewing the major published series it appears that a approximately 19 patients with Rasmussen's encephalitis have undergone MST,[11,15,19,43–45] although two reports from the same center may duplicate cases. Whilst the long-term results are inevitably poor the temporary palliation

afforded may improve quality of life significantly and obviate the need for a hemispherectomy both in the short and long term.

Bilateral independent seizure foci

Patil *et al*. have described their experience of 61 patients in whom they have performed MST to multiple areas in both hemispheres.[28] Seventeen of these patients had an additional resection carried out, although these tended to be small and indicated only when there were persistent discharges detected on intraoperative electrocorticography after extensive MST had been performed. Each procedure lasted for between 10 and 12 hours and there was an interval of between 5 and 7 days between the surgeries to each hemisphere. The clinical seizure types consisted most of complex partial seizures (50 cases) but included Lennox–Gastaut (3 cases) infantile spasms (2 cases), and myoclonic seizures (2 cases). The number of lobes of the brain operated upon ranged from two to eight. Although transient hemiparesis and dysphasia were observed in one patient and there were two peri-operative complications and one patient died from a massive post operative GI bleed, no lasting neurological deficits were seen. Seizure outcome was Engel Grade I in 52% and Grade II in a further 8%. There was no further clinical detail of functional or neuropsychological outcome. This is obviously an apparently impressive response to MST but further outcome data is required before such a procedure could be widely adopted although the authors have demonstrated the safety of this procedure in a potentially difficult to treat patient group.

Focal pathologies

One of the confounding factors in being able to gauge the efficacy of MST has been its frequent use in combination with cortical resection. The rationale has usually been that either the structural abnormality or neurophysiological abnormality extends into eloquent cortex rendering complete excision of either focus impossible. Even when eloquent cortex is not encroached upon it has been argued that MST to the neurophysiological abnormality beyond the structural abnormality may improve seizure outcome. Certainly there is scientific evidence that the tissue surrounding structural lesions such as dysembryoplastic neuroepithelial tumours and gangliogliomas may be abnormal and epileptogenic.[46] In addition as we learn more about the patterns of abnormality of cortical migration and the abnormal circuitry that lies within and around these lesions, it is increasingly apparent that the epileptogenic zone may extend beyond the structural abnormality, supporting the hypothesis for additional MST.[47]

There is reported evidence that resecting the epileptogenic zone in addition to the anatomically evident pathology improves seizure outcome[48] but similarly in the current era of MRI and intraoperative guidance excellent results can be achieved without careful intraoperative neurophysiological guidance.[49] A series from the Toronto group appears to show no additional benefit in 16 cases where MST was applied in conjunction with focal resection in cases of focal cortical dysplasia.[50] In order to prove the additional benefit of MST a large prospective study would be required with considerable funding to support it.

Current questions concerning MST

Because of the fragmented and sometimes repetitive data presented for MST it is difficult to draw firm conclusions as to its role and efficacy. There is no doubt that it remains an immensely innovative procedure and there is evidence that seizures are reduced following surgery in many patients who would otherwise not be considered to be surgical candidates. However, like other palliative procedures such as callosotomy and vagal nerve stimulation it is not possible to accurately predict preoperatively who is likely to benefit from surgery. There are currently a number of questions that need to be asked of MST.

Does MST achieve its anatomical goal?

If the gyral folding of the cerebral cortex were to be smoothed out, then the incisions made over the crowns of the gyri would provide a very incomplete isolation of the cortex into discrete islands of the desired volume; a fundamental thesis of the procedure cannot therefore be achievable. Even with the addition of transections down into the sulci and opening of the major gyri a significant portion of the cortex will remain anatomically and neurophysiologically connected. In addition the thickness of the cortex varies according to anatomical location, varying from 2 mm in the calcarine cortex to 4 mm in the precentral region and also tending to be thinned towards the depths of a sulcus.[51] Furthermore a number of pathological conditions may result in either thickening[52] or thinning of the cortical mantle and therefore the intragriseal transections may either incompletely cut through thickened cortex or extend into the white matter when the cortex is atrophic, resulting in either incomplete disconnection or damage to white matter tracts. Whilst the former may be rectified by further transections if the intraoperative electrocorticography shows persistent electrical abnormality, the latter will be irreversible and may explain some unexpected post operative functional deficits.

Does MST achieve its physiological goal?

When transections are carried out in eloquent cortex the functional results strongly support the hypothesis of preservation of function. Whilst the results are not free of morbidity such morbidity as does occur is frequently linked to a clear explanation such as the presence of subcortical hemorrhage and others may be explained by the variation in cortical thickness as explained above.[51] A single post operative functional PET study has demonstrated functional activity in an area in which MST had previously been carried out.[53] There was also suggestion of recruitment of other areas and this would be supported by the prospective study of functional motor recovery following MST.[54]

Similarly the results with respect seizure outcome are also supportive of the hypothesis of the critical area required for seizure propagation and support the animal data. Nonetheless the increasing understanding of the aberrant physiological circuits present in certain pathologies such as focal dysplasias[55,56] and the very rapid spread of seizures, suggest that the physiology of this pathology is significantly different from normal cortex and therefore the underlying thesis may not apply.[57]

Is there a place for MST in addition to resection?

In certain pathologies the outcomes for anatomical resection are excellent and therefore determining the added efficacy of MST is extremely difficult. Morrell himself suggested that in dominant temporal lobe resections improved outcome could be achieved by combining MST with resection.[15] This approach may be justified when there is a structural lesion rather than mesial temporal sclerosis due to the possibility of incomplete lesional resection or more widespread pathology. Examination of the pathological specimens from 'en bloc' temporal resections from the Maudsley group revealed concomitant 'dual pathology' in the form of mesial temporal sclerosis in 33% and evidence of dysplasia in 25%; although outcome did not appear to be dependent upon extent of resection.[58]

MST as a procedure was conceived in the era prior to the consistent MRI detection of mesial temporal pathology and in view of the excellent results of a Spencer type procedure this approach does not seem to be justified, unless its addition might result in broadening the numbers of patients suitable for surgery.

Why has MST not been more widely applied?

MST was conceived in an era of epilepsy surgery when many structural lesions causing epilepsy could not be identified. In addition much weight was placed on pre- and intra-operative electrophysiological studies, with a great deal of experience of the latter being available. In the MRI era, targeted resections of pathology causing epilepsy is now both feasible and followed with excellent results. In addition, whilst the major epilepsy centers continue to have experience of intraoperative electrocorticography, the field of epilepsy surgery and the numbers of centers performing it have increased dramatically. The emphasis on neurophysiology in many centers has reduced and the availability of intraoperative electrocorticography is not widespread. The debate over the 'structural' or 'functional' approach to the investigation and management of epilepsy has, at times, been a heated one[59] but there is little doubt that the increasing impact of structural imaging has broadened the scope and availability of epilepsy surgery considerably. It is likely that MST will remain a procedure for complex epilepsy centers and indeed experience should be concentrated in major centers so that the appropriate studies can be performed.

Can a multi-center study of the efficacy of MST be carried out?

On review of the data on MST there is a lamentable lack of consistent data that can be compared in an objective way. This is because of the combination of MST with resections and disconnections, the varied pathologies treated, an inconsistent approach to reporting outcome and the lack of any quality of life data. The only way in which a multi-centre trial will be effective is if a distinct entity, such as pure Landau–Kleffner syndrome, is looked at and if MST is assessed on its own merits in the absence of resection or disconnection. The ILAE subcommission for pediatric epilepsy surgery in its Appendix 1 has indicated that MST is the surgical treatment of choice for Landau–Kleffner but the evidence to support this appears confused.[42] The commissions' main document stresses the importance of a careful pre- and post- operative assessment of all pediatric cases so that outcome data can be standardized. However, even in major centers such cases as are suitable for MST are rare and the accumulation of cases may simply be an impossible task.

Does MST have a future?

The introduction of any new surgical procedure is usually followed by a period of increased usage and then a decline, when the indications, outcome and complications become clearer. Due to its very limited clinical application the period of accrual for MST has taken longer than most and the surge of interest in surgery for epilepsy based on anatomical imaging has done nothing to help its cause. The excellent results of focal resection without additional MST make its role in focal pathology very limited. In true MRI negative cases when the epileptogenic focus appears well localized to eloquent cortex and the deficit offered by resection is unacceptable, then MST clearly does still have a role.

A recent paper from Japan has put forward a new innovative role for MST in the management of seizures of hippocampal origin.[60] Twenty-one patients underwent a minimally invasive procedure in which access was obtained into the temporal horn through the temporal stem and then transections carried out in the hippocampal formation, using a modified ring-type transector. The objective of this approach was to reduce neuropsychological deficits in patients who were highly functioning. Seizure outcome was reported in 17 cases with 82% seizure free at one year, comparable with resective techniques. Neuropsychological data

Figure 122a.9

was only available in eight patients and only in one of these was there evidence of deficit in post-operative testing which resolved at six month follow up. It is not clear whether all of these cases were in the dominant hemisphere (12 of the total series had dominant temporal resections) but in any event the neuropsychological outcome is encouraging and further results in term of seizure outcome and neuropsychology are now needed to see if this technique has a role in the surgical armamentarium.

The description of this final innovative surgical application for MST brings us full circle to Prof. Morrell once more. Much of his laboratory and clinical research was directed to the concepts of secondary epileptogenesis in man and the possibility of mirror foci.[61] The intriguing possibility now arises for bilateral temporal surgery to be possible, for if bilateral mesial temporal foci can be targeted without neuropsychological deficit, then a whole group of patients will potentially become suitable surgical candidates.

Summary

Multiple subpial transection is a technique whose role has yet to be clarified. The surgical series reported present a confused picture due to the widely disparate subjects, pathologies and methods of reporting outcome. There is evidence that it does cure seizures in some cases and give good palliation in others. Without careful multi-center trials it will be difficult in the future to establish clearly its clinical indications. It remains an inspired piece of translational science and is likely to remain in the armamentarium of the epilepsy surgeon for the foreseeable future.

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122b Nonresective surgical procedures and electrical or magnetic stimulation for epilepsy treatment mutiple hippocampal transection

H Shmizu

Introduction

Temporal lobe epilepsy is known to be one of the most drug resistant epilepsy in adulthood. However, surgical treatment of temporal lobectomy is very effective in seizure control with around 70% success rate.[1] Temporal lobectomy was established in the 1950s[2–4] and has been widely applied to intractable temporal lobe epilepsy. In spite of good seizure outcome, postoperative memory impairment has been a long-standing unresolved problem.[5–7] If the epileptic focus exists in the left medial temporal area and the preoperative MRI demonstrates no atrophy of the hippocampus, resection of the hippocampus brings about worsening of verbal memory in most cases.[8] This ominous complication cannot be avoided even if the most selective resection of the medial structures, selective amygdalohippocampectomy, is employed.[9]

To cope with this complication, we applied the principle of multiple subpial transection (MST)[10] to the hippocampus. The neuronal structure of the hippocampus is significantly different from that of the cerebral cortex.[11] However, the rationale of MST, disrupting the horizontal interneuronal connections and preserving vertical connection fibers, can be also applicable to the pyramidal layer of the hippocampus.

We applied this new method, multiple hippocampal transection, to patients with intractable temporal lobe epilepsy without hippocampal atrophy on preoperative MRI. We have so far obtained excellent surgical results with regard to preservation of verbal memory and control of seizures.[12]

Rationale for this method

Multiple subpial transection is an established surgical method to surgically treat eloquent areas, particularly as the motor or speech area, with preservation of cortical functions. The basic concept of MST is to interrupt interneuronal connections, most important for genesis of epileptic discharges, and to preserve vertical projecting fibers, critical connections for cortical functions. We hypothesized that if the pyramidal layer of the hippocampus can be treated in the same way as in MST, epileptogenic discharges from the hippocampus might be eliminated.

For this purpose, an adequate access route to the hippocampus without disrupting the memory circuit must be found. There are two neuronal pathways important for the hippocampus: the polysynaptic intrahippocampal pathway and the direct intrahippocampal pathway. The latter is the most important connection for verbal memory in humans.[11] The input fibers of the direct hippocampal pathway mainly originate from the inferior temporal association cortex (area 37) and reach the entorhinal cortex through the perirhinal cortex. Therefore, access routes to the hippocampus through the temporal basal area will disrupt this pathway.

Experimental data from monkeys, using a behavioral test known to most relevantly represent human amnesia, indicated that bilateral section of the temporal stem does not impair the memory function.[13] Based on this experimental data, we developed the following surgical route to the hippocampus, which can preserve the neuronal connections to memory function. A small corticotomy is placed on the superior temporal gyrus within 4.5 cm from the temporal tip and the gray matter is aspirated along the sylvian fissure to reach the temporal stem. As the temporal stem constitutes the roof of the inferior ventricle, the hippocampus can be easily accessed by sectioning the temporal stem (Figure 122b.1).

Although the temporal stem can be also accessed by directly dissecting the sylvian fissure and aspirating the lower part of the superior temporal gyrus as employed in selective amygdalohippocampectomy, the visual field thus obtained is too narrow and too deep to perform very subtle manipulation of hippocampus transection.

As the pyramidal cell layer of the hippocampus is within 2 mm from the surface, we devised a ring transector 2 mm in diameter. To transect the CA4 and the dentate gyrus, deeper transection is necessary. As the pyramidal cell layer descends into the subiculum at the lateral corner of the hippocampus, deep transection is also necessary to transect this CA1 area (Figure 122b.2). Based on these anatomical relations, a ring

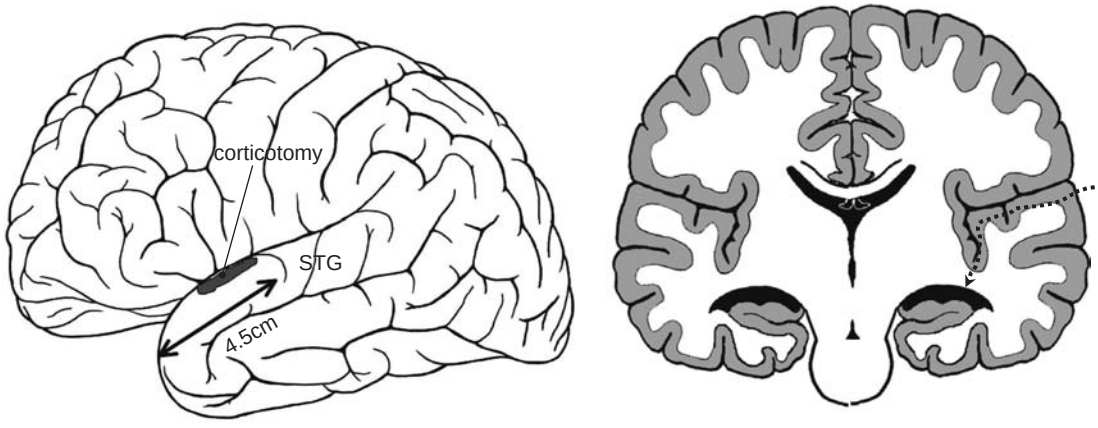

Figure 122b.1

transector 4mm in diameter is designed for transection of the bilateral corners of the hippocampus. At the posterior part of the hippocampus, the transverse diameter becomes smaller, so an oval-shaped transector with 4×2mm diameter is applied to transect the lateral corners without intruding the mid portion of the hippocampus (Figure 122b.3).

Surgical procedure

Under general anesthesia, the patient is placed supine on the operating table with the head tilted almost horizontal to the opposite side. Skin incision and the extent of craniotomy are the same as for ordinary anterior temporal lobectomy. The bone window is widened as much as possible to expose the temporal pole and basal areas. After dural incision, around 2 cm corticotomy is placed on the superior temporal gyrus along the superior sylvian veins. The posterior end of the corticotomy is confined within 4.5 cm from the temporal tip to prevent postoperative speech disturbance. If moderate size arteries cross the corticotomy line, the arachnoid membrane around the arteries and their small branches are dissected or severed and the main arteries are translocated out of the corticotomy area to keep normal cerebral circulation of the left temporal pole.

It is very important to precisely open the inferior ventricle without injuring the hippocampal surface. The optimal point of the ventricular opening is the medial posterior portion of the ventricle, just above the choroid plexus around the hippocampal body. For this purpose, the operating table is adjusted as the patient's head is up and rotated to the opposite side. The ideal trajectory of the temporal stem suction is directed at 45° inward from the center of middle fossa (Figure 122b.4).

Three types of electrodes (Figure 122b.5) are applied to the amygdala, the hippocampal head and the posterior part of the hippocampus to record electrocorticography (ECoG) over these areas and determine the extent of surgical procedure. If the amygdala does not show any independent epileptic discharges, only its surface is pared off to obtain am ample space for manipulating the hippocampal head. If ECoG otherwise documented active independent epileptic discharges from the amygdala, it is resected in the same way as in anterior temporal lobectomy. Generally, the hippocampus shows very active spike discharges. They are sometimes confined to the head or observed throughout over the entire hippocampus (Figure 122b.6).

Based on ECoG data, the extent of hippocampal transection is determined. The alveus, white fiber bundle covering the hippocampal surface, is extremely tough and should be incised with microscissors for inserting a ring transector. The incisions lines are designed 5mm apart as in MST and parallel to the hippocampal digitation marks at the hippocampal head (Figure 122b.7). If vessels (usually small veins) cross the incision lines, they are electrically coagulated with bipolar forceps.

To transect the pyramidal cell layer, which is within 2mm from the surface, a ring transector 2mm in diameter is inserted through the incision lines of the alveus. At both lateral ends of the hippocampus, a larger ring transector 4mm in diameter is employed to completely transect the end folium at the medial portion and the CA1 pyramidal cell layer descending to the subiculum at the lateral border. In the posterior part of the hippocampus, the transverse diameter is smaller and a 4 × 2 mm oval-shaped ring transector is used for transection of the bilateral corners.

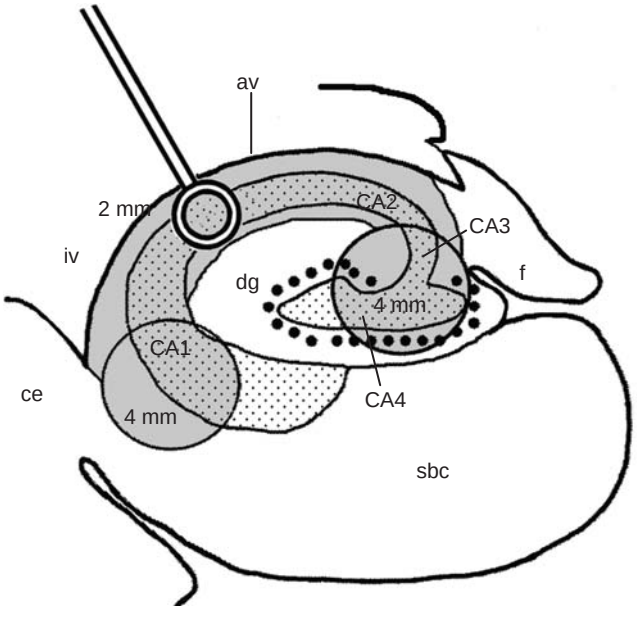

Figure 122b.2

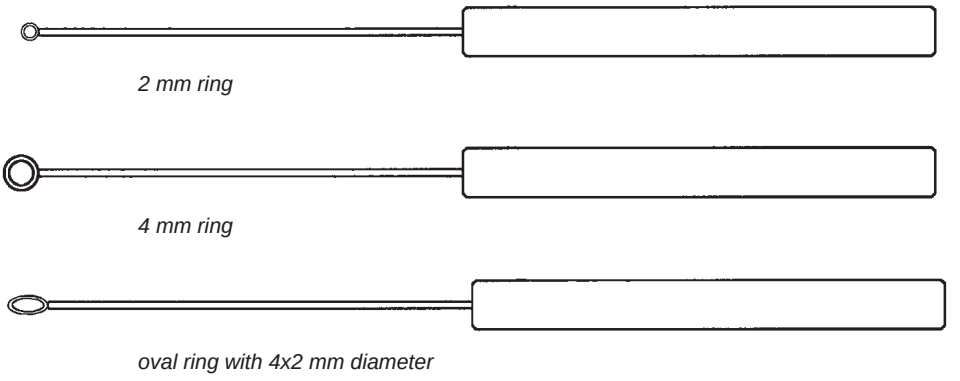

Figure 122b.3

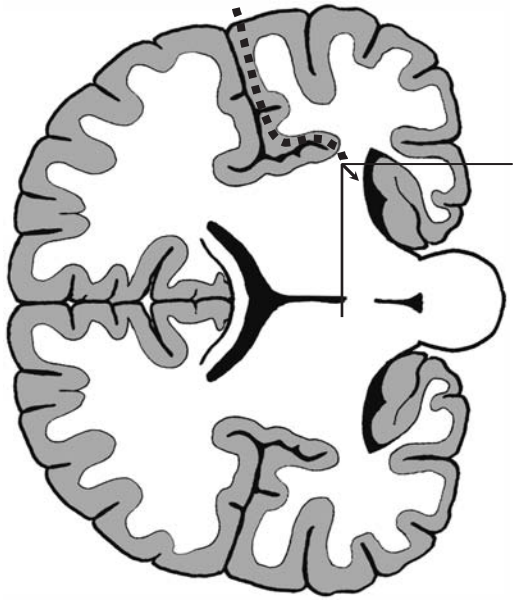

Figure 122b.4

Once hippocampal transection is accomplished, ECoG is repeated over the entire hippocampus. This time, an amygdala electrode is also placed over the hippocampal head and residual spikes are carefully examined. Generally, active epileptic discharges from the hippocampus beautifully disappear as far as transection covers entire epileptic areas (Figure 122b.8). If residual spikes are detected in an untreated posterior part, transection is extended posteriorly. When spikes do not disappear over transected areas, each transection line is carefully examined to check whether they cover the full length of the hippocampal surface. If all of the transection lines are complete and yet synchronized small spikes or sharp waves are still observed over a wide area of the hippocampus, spread of epileptic discharges from the basal temporal area or the temporal cortical surface should be suspected.

After completion of the hippocampal transection, ECoG is further recorded over the basal and superficial temporal surface. When epileptic discharges are detected in the anterior basal area, this area can be approached through the anterior end of the opened inferior ventricle and resected without damaging the surface temporal area. The epileptic discharges in the posterior basal area and the superficial temporal surface area are generally treated by MST without compromising brain functions. With combining hippocampal transection and MST, all epileptic discharges in the temporal lobe are surgically treatable with preservation of brain functions.

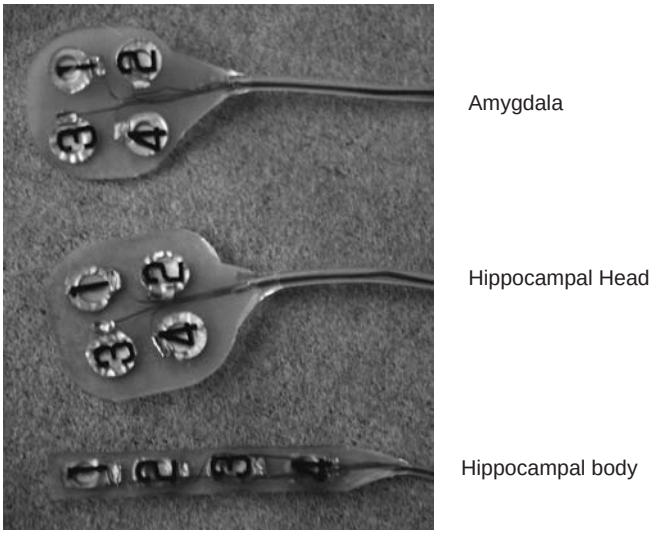

Figure 122b.5

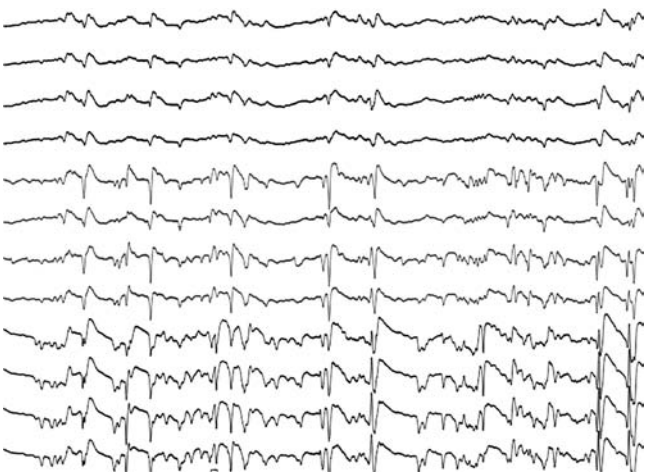

Figure 122b.6

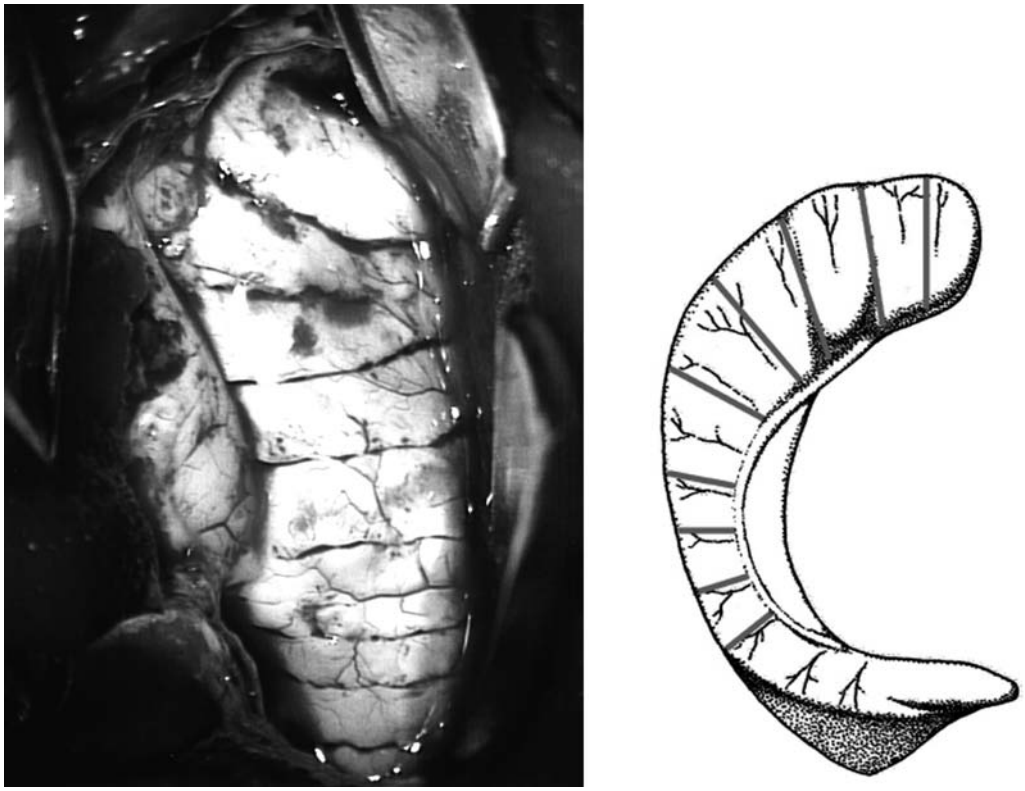

Figure 122b.7

Surgical outcome

Between January 2001 and March 2006, 35 cases of intractable temporal lobe epilepsy without hippocampal atrophy on preoperative MRI and unilaterally diagnosed focus were operated on by hippocampal transection. They consisted of 20 males and 15 females, ranging in age from 2.9 to 48 years with a mean age of 27 years. Left side hippocampal transection was performed in 22 cases and right side in 23 cases.

Postoperative MRI demonstrated the access route from the superior temporal gyrus to the inferior ventricle. However, transected hippocampus did not show any deformity or transected lines when studied six months after surgery (Figure 122b.9).

As evaluation of pre- and postoperative verbal memory, auditory verbal learning test (AVLT)[14] was performed immediately (3–4 weeks) and 6 months after surgery. Seizure outcome was evaluated only in cases with more than one year follow-up.

Verbal memory

In 13 eligible cases undergoing left hippocampal transection, AVLT was performed for evaluation of verbal memory function. If immediate postoperative test demonstrated decline of AVLT score, the test was repeated 6 months after surgery. In all of the cases except one, the scores of AVLT did not become worse at the point of 6 months after surgery

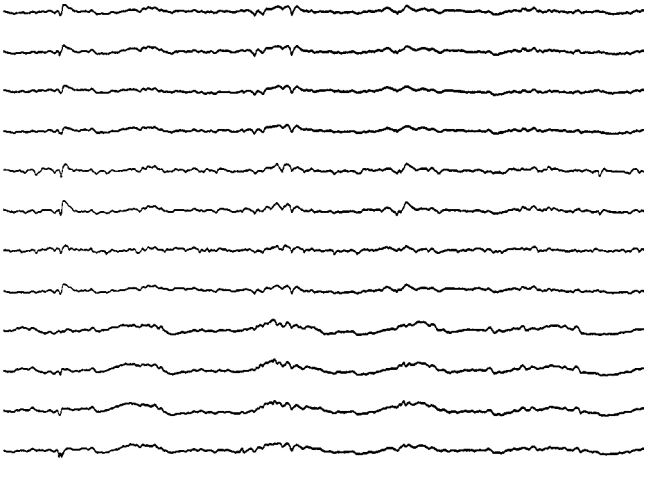

Figure 122b.8

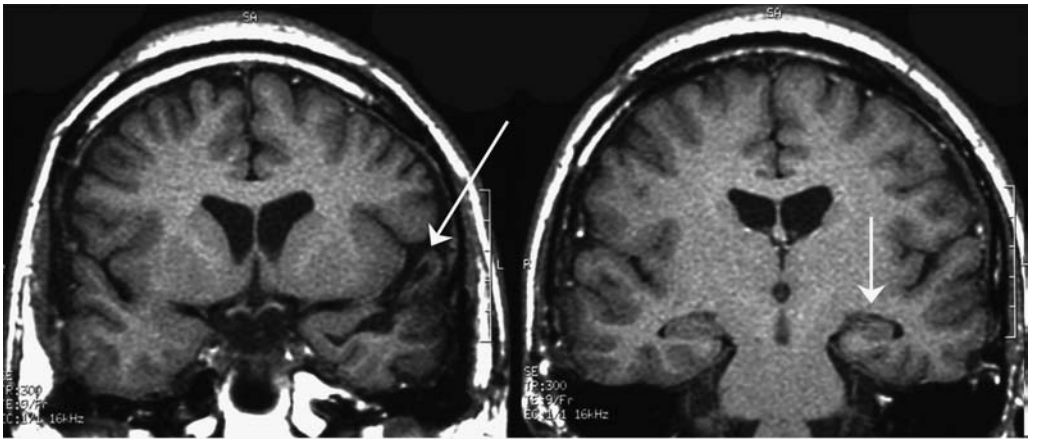

Figure 122b.9

(Figure 122b.10). In one case, the AVLT score worsened after surgery and did not improve even after 6 months follow-up. However, this 33-year-old male did not complain of amnestic symptoms and returned to the preoperative workplace.

Seizure outcome

Seizure outcome was extremely good. In 23 cases with more than 1-year follow-up, 28 cases are seizure free (Engle class IA) and four have rare seizures (Figure 122b.11). In one cases, preoperative seizures have dramatically reduced in frequency and severity, but still has several seizures per month.

Bilateral temporal lobe epilepsy

If the left hippocampus can be surgically treated without postoperative neurological complications, the possibility of surgical treatment of bilateral temporal lobe epilepsy will arise. This possibility is a sea change when we remember the tragic result of H.M., who underwent resection of bilateral mesial temporal structures and suffered an almost compete loss of anterograde memory functions.[15,16]

However, bilateral cases have proved not as simple in distribution of epileptic foci as unilateral ones. Even when transection of bilateral hippocampi was successfully performed in two stages, hidden epileptic foci appeared and caused new types of seizures. These complex patterns of focus distribution were particularly prominent in epilepsy caused by late-onset encephalitis.

We have so far performed bilateral hippocampal transection in ten cases and followed them up for more than 1 year. Good surgical outcome was obtained only in four cases (one: free, three: rare), and the remaining six patients showed poor results. In one case with bilateral hippocampal atrophy, postoperative memory deficit was very severe (after left hippocampal transection) and has not recovered even 3 years after surgery.

Based on the above experience, we now restrict application of hippocampal transection only to unilateral temporal lobe epilepsy. However, taking account of many disabled patients with bilateral temporal lobe foci, future effort is strongly demanded to solve this long-standing problem.

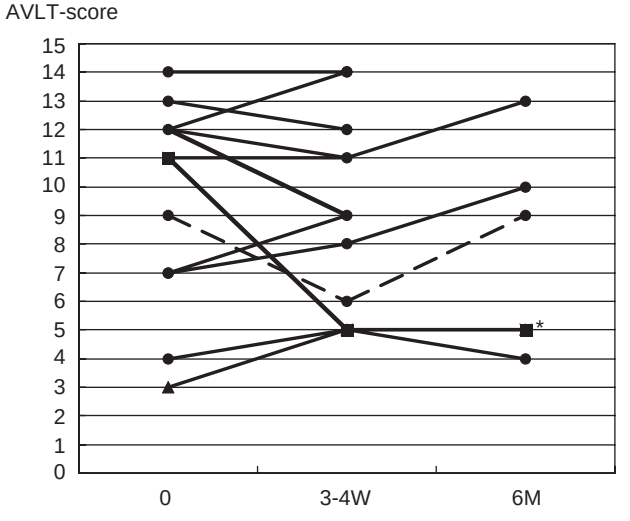

Figure 122b.10

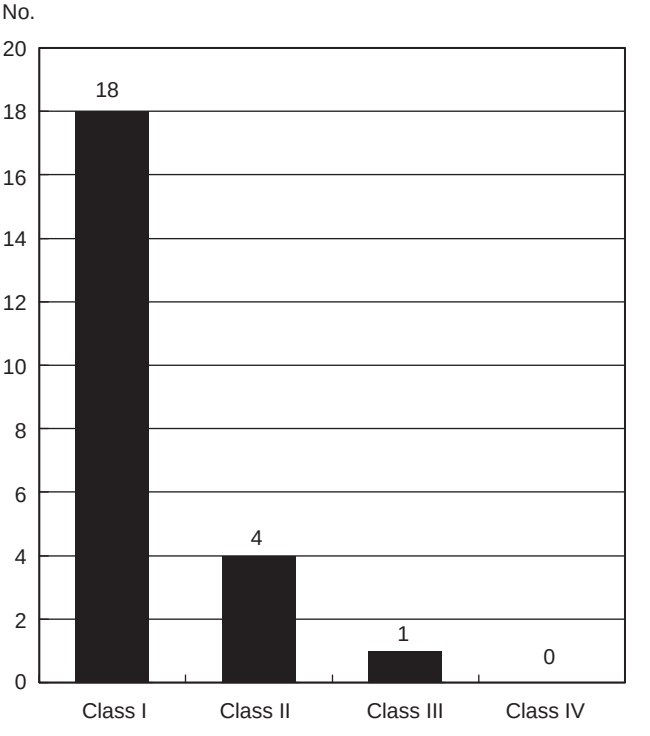

Figure 122b.11

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122c Surgical disconnections of the epileptic zone as an alternative to lobectomy in pharmacoresistent epilepsy

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Abstract:

Temporal lobe epilepsy (TLE) is the most common form of medically intractable partial epilepsy in adults, and surgery (temporal lobectomy or amygdalo-hippocampectomy) is effective in the majority of patients. In extratemporal lobe epilepsy (mainly frontal and multi lobar epilepsy) these results are less favourable but are highly depending on the presurgical evaluation and the possibility to delineate the epileptogenic zone (EZ). However, in the majority of cases, the surgical option usually applied is the removal of the epileptic tissue We report here the method, preliminary results and safety of a new procedure for non lesional TLE and extratemporal lobe epilepsy which consists in disconnecting the EZ without removing it.

Between 1998 and 2004, 62 patients suffering from temporal or extratemporal lobe epilepsy have been treated by surgical disconnection of the epileptogenic zone. 45 TLE patients (35±10 years mean, duration 24±10 years, 16 males and 29 females, handedness 12 left and 33 right) have undergone temporal disconnection (20 left, 25 right) and 17 patients underwent extratemporal disconnection (one frontal, one occipital, seven temporal lobectomy + extratemporal disconnection, and eight multilobar disconnection). Among the patients suffering from TLE, 16 patients (35%) underwent additional presurgical evaluation with depth electrodes (SEEG). while this number reached up to 100% of cases in extratemporal lobe epilepsy cases After the surgical disconnection, all patients underwent a postoperative MRI, neuropsychological testing, and repeated scalp EEG and visual field examination. Postoperative outcome was assessed using Engel's classification. Temporal disconnection was performed under neuronavigation and consisted in disconnecting the lateral temporal neocortex, the whole hippocampus, parahippocampus and the amygdala from the rest of the brain in cases of TLE. Veins and arteries were spared in order to avoid postoperative temporal lobe ischemia and subsequent temporal lobe swelling.

Results in temporal disconnections, 38 patients out of 45 (84.4%) were seizure free (Engel's I) at 2-years follow-up, among which 26 were class Ia (58%). Four patients were class II and three class IV. Postoperative clinical morbidity was as follows: persistent mild hemiparesia (n=1), persistent mild facial paresia ($n=1$), definitive quadranopia (n=23), hemianopia ($n=1$). When the dominant temporal lobe was disconnected, verbal memory was worsened in about 69%.

In extratemporal lobe epilepsy, 75% of patients who received a multilobar disconnection and 85% of of patients who received a temporal lobectomy associated with an extratemporal disconnection were Engel's class 1. One patient who was operated for a frontal epilepsy was Engel's class 2.

Radiological postoperative morbidity was as follows: two patients exhibited asymptomatic thalamic or pallidal limited ischemia, two patients exhibited temporal horn cystic dilatation among which one requested surgical reoperation without clinical consequences. General morbidity was represented by a single case of postoperative phlebitis.

For TLE, scalp EEG performed at 6 months post-op showed temporal spikes in 27% of patients with postoperative seizures compared to 8.5% of patients seizure free. At 1-year follow-up, scalp-EEG showed temporal spikes respectively in 19 and 6% of patients.

In the multilobar disconnected group, 75 % of patients were Engel's class 1.

In conclusion, this technique, in experienced hands, appears to be as effective and safe as cortectomy or lobectomy. The main advantage is that disconnection prevents brain shift and subsequent subdural collections, shortens the duration of the surgery and allows a smaller craniotomy. On the other hand, disconnections do not allow complete histological examination of the epileptogenic tissue but provide only samples. Studies in the future will have to assess the prognosis value of interictal spikes seen on postoperative EEG in order to help predicting seizure outcome during the following period.

Introduction

Resective surgery such as lobectomy, or amygdalo-hippocampectomy, is the major surgical option for intractable pharmacoresistent epilepsy. The global outcome reaches nearly 90% of Engel Class I in temporal lobectomy, 1–3 except when foci are multiple, located remotely from the temporal lobe and bilateral. They however have complications, as they create a large empty volume, which can induce bleeding, brain shifts, and subdural collections (Figure 122c.1). The purpose of this work is to provide an alternative approach by disconnecting the epileptic zone, without removing the brain tissue. Advantages are simpler surgery, reduced operating time, and reduced complications (brain shift and subdural collections).

The rationale of this approach was based on the following considerations:

- Disconnection procedures are effective in children treated by hemispherotomy 4–7 and in cases of hypothalamic hamartomas 7–9.
- Removal of the cortex is not mandatory in nonlesional TLE, when there is no potentially evolutive mass lesion, or no diffuse dysplastic cortex.
- Disconnection might minimize the risk of brain shift, especially in large temporal lobectomy, where the large parenchymal defect favors displacement of the surrounding lobes.
- Disconnection can be performed with a standardized minimally invasive craniotomy, making large craniotomy not mandatory.

Material and methods

Surgical procedure

- Under neuronavigation (Surgiscope, ISIS, Grenoble, France), in dorso-lateral decubitus, a circular craniotomy is performed using a trephine (50 mm in diameter) the center of the craniotomy being positioned at the level of the superior temporal sulcus.

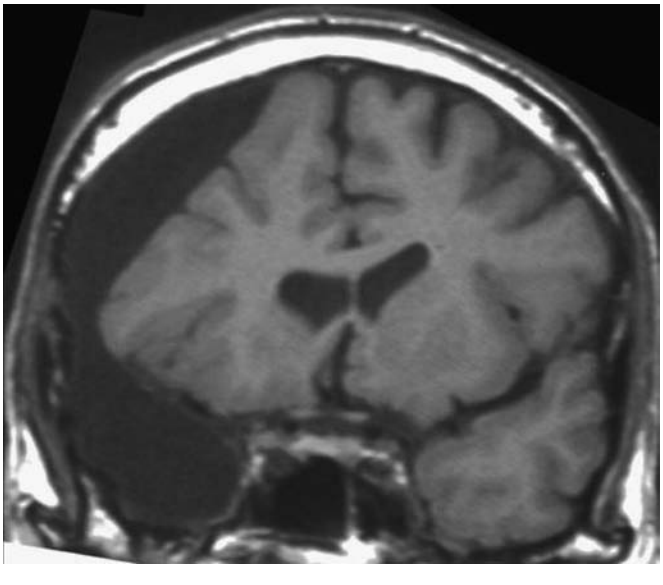


Figure 122c.1 Brain shift and extra cerebral fluid collection following large parenchymal resection.

Presurgical definition of the epileptic zone (Figure 122c.3).

It is basically similar to what is done for lobectomies, as only the technical aspects vary, the indications, basic principles, area to be removed or disconnected being the same.

Video-EEG alone without depth recordings is applied to patients in whom the clinical examination, the natural history of the patients' epilepsy as well as the specific clinical, ictal and interictal electrical features of the seizures have been extensively investigated, are all concordant and point to the same epileptogenic zone (EZ). This leads to a predefinition of the area involved, from the irritative zone where the epileptic discharge is generated to the full field of its propagations, defining the epileptic zone (EZ). Following the currently admitted principles, originating from Talairach's approach to the concepts developed by Lüders, Engel, etc, the video-EEG, associating continuous EEG recording and behavioral videotaping, provides informations on which will depend the necessity or not to be resected.

Stereoelectroencephalography (SEEG), (or subdural grids in other institutions), is performed if additional informations are needed about the precise involvement of deep structures (which is more easily provided by SEEG rather than by subdural grids), or when the presurgical evaluation based on noninvasive tools are not concordant. Similarly to what has been done during video-EEG, and according to the SEEG methodology developed by Talairach and Bancaud,[10] the correlation between the temporo-spatial organization of the discharge and the symptoms, allow to delineate the ictal onset zone and the epileptic zone according to the definition recently released by Nair and Luders[11].

In addition to the electrical and clinical analysis of the seizures, high resolution MRI is performed in all cases to detect any mass lesion, hippocampal sclerosis or dysplasia.

Neuronavigation planning of the disconnection (Figure 122c.3).

It is basically based on a volumetric 3D MRI performed with markers screwed to the skull and the images fed into the Neuronavigation software of the robotized microscope ISS Surgicope®

Using the features of the Neuronavigation software, the first step consists in reporting on MRI the synthetic scheme of the epileptic zone, taking into account the specific anatomy of the patients, following the sulci and avoiding the vessels. One may therefore draw on each adjacent slice from the surface to the depth, the contours of the disconnection.

Delineation of the limits of disconnection

One may take the decision of additional resection of the first temporal gyrus, depending on the morphology of the insula: when the angle between the sylvian valley and the insular plane is close to 90°, it is quite often difficult to dissect the superior temporal gyrus and recline it without damaging it to access to the bottom limit of the insula. Therefore, it happens to be easier to resect by suction, or using a dissectron, the upper lip of the superior temporal gyrus. On the contrary,

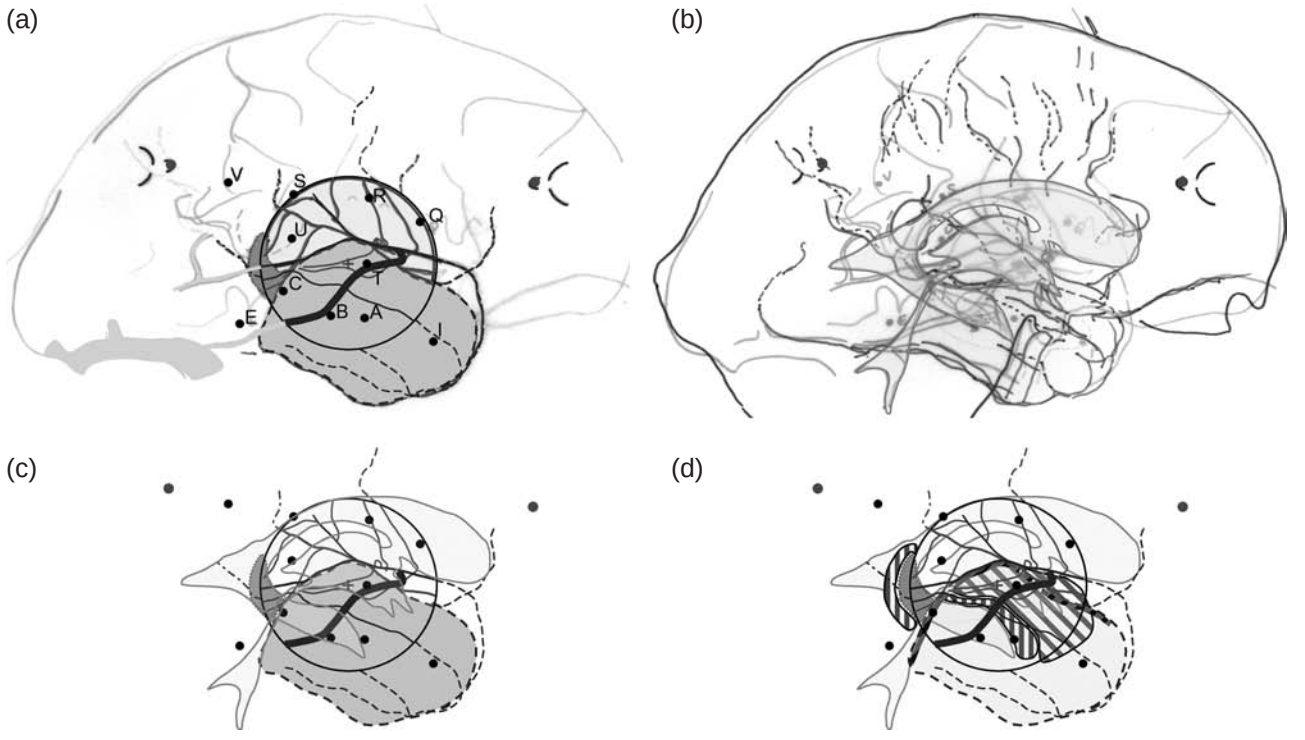


Figure 122c.2 Programming a disconnection of the right temporal lobe. a: synthetic drawing of vessels (arteries and veins), contours of the hemisphere, position of the deep recording electrodes, circular craniotomy (centre marked by the red cross), b: superimposition of the drawing of the sulci and of the ventricular system visualized by ventriculography, (yellow) c: superimposition of the ventricular system (yellow) and of the epileptogenic zone (right temporal lobe in green, tail of the hippocampus in pink), d: steps of the disconnection. Striped grey: windows of disconnection of the cortical convexity of the temporal lobe, sparing the vessels. Oblique stripes in green: subarachnoidal dissection from the sylvian valley of the mesial side of the first temporal gyrus. Vertical stripes in red: section of the white matter from the inferior boarder of the insula to the ceiling of the temporal horn, and posterior inferior disconnection by section of the white matter and cortex surrounding the tail of the hippocampus. (See Color plates.)

when this angle is around 120° or more, the sylvian valley provides a convenient approach to the ceiling of the lateral ventricle. At this stage, it is also important to recognize the particular morphology of the superior temporal gyrus, which is sometimes hidden by the middle temporal gyrus which might be overlapping the superior temporal gyrus. This is misleading, particularly when one has to start a disconnection between the gyrus T1 and T2.

The placement of the center of the trephine is crucial, in order to provide a direct view in the anterior-posterior plane of disconnection, parallel to the sylvian valley as well as in the cranio-caudal plane of the posterior temporal lobe section: most often, the trephine should be centered on the superior temporal sulcus, and not more than one centimeter ahead of the plane of the posterior section of the temporal lobe (Figure 126c.2A):

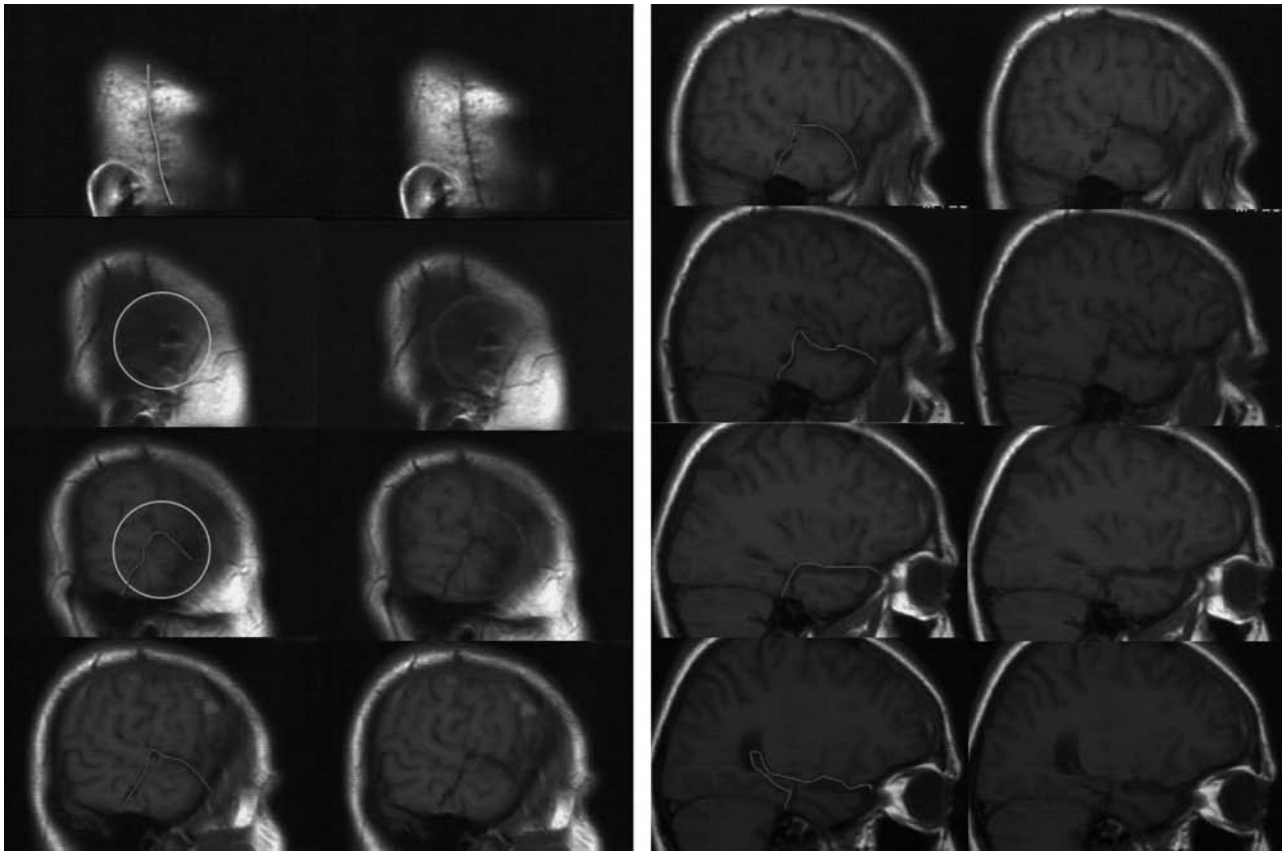
Surgical disconnection

Typical right temporal disconnection

Under general anesthesia, semi-sitting position, the head is fixed on a Mayfield clamp in lateral position. Correspondence between Neuronavigation, Surgiscope, and patient's head (fiducials) is performed, using a pointer which is observed by the camera of the tracking system. Skin incision and trephine are centred on the basis of the Neuronavigation program.

Cruciform opening of dura is performed, its diameter aligned along the superior temporal sulcus, allowing recognition in the visible area of the elements of the brain (arteries, veins, sulci) displayed on the MRI images of the planning (Figure 122c.3A).

1. After tracing on the cortex the posterior limit of the disconnection, which often corresponds to the plane of the acqueduct of Sylvius (Figures 122c.2b and 122c.2c), the temporal lobe is sectioned along this line, using spatula, coagulation and section, down to the base, then to the tentorium and up, where one opens the lateral temporal horn. The arachnoid is cut only on the convexity, while it is not necessary to cut it on the base and on the mesial side, as this provides a security layer against the vessels of the midline and the brainstem
2. Incision of the arachnoid along the sylvian valley is performed carefully, sparing all vessels (veins and arteries), to preserve the vascularization of the temporal lobe which will be left in place and also the vascularization of the basal temporo-occipital cortex which receives branches of the mid-cerebral artery, most often the medial temporal artery (Figure 122c.2D).



(a) (b)

Figure 122c.3 MRI control of a temporal lobe disconnection. The different planes of imaging from the skin to the depth are presented with the MRI images on the left-hand side of each column and on the right-hand side the drawing in green of the craniotomy and in red outline the parenchymal section. Column a: from the skin incision to the convexity cortical section. Column b: parenchymal section from the subcortical planes to the disconnection of the hippocampal formation into the ventricle. (See Color plates.)

3. Using a spatula and a small smooth curette, the superior gyrus is peeled subarachnoidally, and reflected downward, almost perpendicularly, until the plane of the insula. This provides the visibility, through the arachnoid which protects them, of the insular elements, (arterial branches of the mid cerebral artery and veins, and the insula itself, until the reflection of the cortex at the bottom line of the insula), from the posterior section to the anterior part of the insula (Figure 122c.3b). One sees there that the inner surface of the superior temporal gyrus turns, along with the middle cerebral artery, around the fronto-temporal stem, which has to be carefully identified and separated from the frontal lobe (to which it is often adherent) until the pericarotid cistern, where a cotton might be inserted to mark the place, is reached.
4. Back to the posterior section of the temporal lobe, in the lateral ventricle, a cotton is inserted along the sphenoidal horn in the anterior direction, to protect the choroid plexus which is reclined upward, therefore protecting the anterior choroidal artery and its upper anatomical neighbour, the optical tract. The white matter of the insulo-temporal stem, along the inferior limit of the insula, is severed from back to anterior (one must take care to see permanently the ventricular cavity in order not to go medially and above the ventricular horn, where one could end up in the base of the putamen), until the anterior recess of the horn, where the choroid plexus emerges, along with the anterior choroid artery from the arachnoidal veil which separates the ventricle from the Bichat fissure, where the choroidal vein goes.
5. Dissociation of this arachnoidal veil gives access to the pericarotid cistern, where the cotton previously inserted into the cistern from the sylvian dissection is seen. This makes it easy to section the fronto-temporal white matter stem which has been fully circumscribed, and which is, at this moment, the only remaining anterior connection of the temporal lobe. The amygdalo-hippocampic formation has been therefore disconnected from its anterior connections. As this formation has no mesial connections with the extratemporal brain, (the Bichat fissure is obliterated only by an arachnoidal veil which does not need to be severed), its only remaining connection is posterior at the level of the tail of the hippocampus.
6. Going back to the posterior section of the temporal lobe and into the ventricular cavity, using the spatula, the white matter of the temporo-occipital junction is severed along the hippocampal formation, until the spatula touches the arachnoid and, through it, the dura of the tentorium. This section is prolonged backward, following the volume of the hippocampus tail, which turns around the posterior

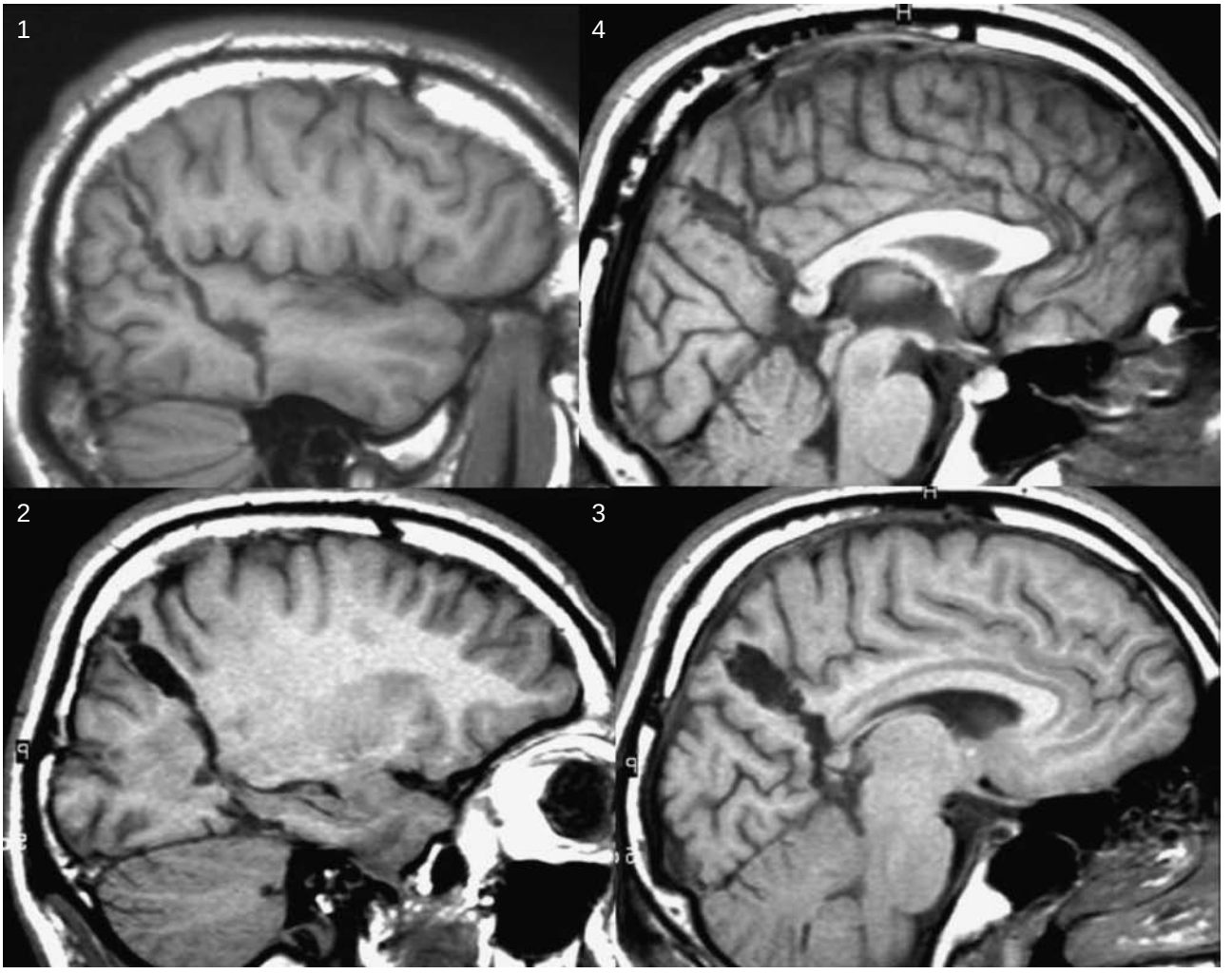


Figure 122c.4 MRI control of an occipito-temporal disconnection. The plane of disconnection is visible from the cortical surface to the mesial face of the hemisphere. In the MRI slices 2 and 3, suction associated to spatula section has created a larger gap in the separation between the disconnected temporo-occipital part from the rest of the brain. The ablation of the disconnected part would have created a large cavity, and possibly a brain shift.

pole of the thalamus, by direct viewing into the ventricular cavity. The posterior part of the Bichat fissure is dissected by sectioning the arachnoidal veil up to the level of the white matter disconnection. At this level, the tail of the hippocampus is sectioned, carefully preserving the vascular lamina which runs in the thin intrahippocampal sulcus. Sometimes, removal of the posterior part of the hippocampus can be also performed as it can be easier and offers the possibility for histological examination to confirm hippocampal sclerosis, which is known to be of good prognosis. (Figure 122c.2D).

Care must be taken not to confound the volume of the hippocampus with the volume of the anterior part of the calcarine formation, which would lead to an hemianopic deficit, less tolerated than the upper lateral homonymous quadranopia which is almost always created by the interruption of the Meyer geniculo-calcarine fibers at the level of the posterior section of the temporal lobe.

When this is achieved, the temporal lobe has no more neural connections with the rest of the hemisphere: the amygdalo-hippocampic formation has been separated from its frontobasal connections at the level of the fronto-temporal stem, and from its posterior limbic connections at the level of its tail, behind the thalamus. The temporal neocortex has been severed from the insula all along the roof of the temporal horn, form the anterior fronto temporal stem, to join the vertical posterior section which disconnects the temporal lobe from all its projections to the parieto-occipital area.

Specific variations

Sparing of the superior temporal gyrus can be indicated when the recording has not proven any electrical involvement of the structure. Therefore, instead of making the incision of the arachnoid along the sylvian valley, one makes it along the superior temporal gyrus, on the upper border of the second temporal gyrus. This makes easier the undercutting of the white matter at the depth of the T1-T2 sulcus (as it is practically in front of the temporal horn), which can be made without significant tissue resection.

On the left side, however, usually the dominant side for language, the superior temporal gyrus has to be spared in its

two posterior thirds. The anterior limit is marked usually by crossing of the anterior temporal artery, which is also at the level of the junction with the sylvian valley of the precentral gyrus on the MRI.

Besides this temporal disconnection and its variations, disconnection can be used also, in different various areas such as the frontal lobe or the occipital lobe, where the duration of the surgery is strongly reduced, as the transhemispherical section, once the midline has been reached, is sufficient and one does not need to ablate the tissue represented by those disconnected lobes.

Different examples are given in Figures 122c.3 (temporal disconnections) and 122c.4 (extratemporal disconnections).

Patients' population

Patient's selection

Indications are the same as for lobectomies: limited epileptic zone, no involvement of functional (motor, sensitive, or visual) cortical areas, absence of potentially evolutive lesion (cavernomas, gangliogliomas, dysplasia? and DNEs), pharmaco resistance, no surgical contraindications.

Fourty-five patients were operated for TLE (16 males, 29 females, mean age 35 ± 10 years, 4 children aged 3–10 years). The mean duration of epilepsy was 24 ± 10 years, 12 patients were left-handed. The TLE involved 20 left and 25 temporal lobes

Pre-op MRI confirmed that the TLE was nonlesional (no mass lesion), hippocampal sclerosis was observed in 83% of the cases, and anterior temporal abnormalities in 37% of the cases

Presurgical evaluation involved in all cases video-EEG, neuropsychological testing, and high-resolution MRI. PET scan was performed in 13 patients, SPECT in 17 patients, and depth recording (SEEG) in 16 cases.

Postoperative follow up (mean follow up is 3 years) comprised in all cases postoperative MRI at 3 and 12 months, postoperative EEG at 3, 6, 12, and 24 months. The postoperative outcome was rated according to Engel's classification.

Seventeen patients were operated for extratemporal epilepsies (six females, 11 males, mean age 27 ± 10, two children, aged 8–16 years old). Two patients out of 17 were left-handed, and one had bilateral representation of language. One patient suffered from frontal lobe epilepsy, one from occipital epilepsy and 15 from multilobar epilepsy (either fronto-temporal or temporo-occipital).

Among these patients, one had a frontal disconnection, one had occipital disconnection, eight had multilobar disconnection and seven had a temporal lobectomy associated with a frontal or parietal disconnection.

Results

Seizure suppression

In the 45 TLE

Thirty-eight patients out of 45 (84.4%) were seizure free (Engel's I), among which 26 were Ia (58%). Four patients were class II and 3 class IV.

Among the seven non-cured patients, one case was related to an incomplete hippocampal disconnection, as seen in the post-op MRI scan, one patient suffered from insular seizure documented by a second SEEG, three patients had late recurrences of seizure (3 years after) for unknown reasons, and two patients had a running up phenomenon related to withdrawal of AED

In the 17 extratemporal epilepsies

In the multilobar disconnected group, 75% of patients were Engel's class 1. The patients operated on the occipital lobe were Engel's class 1 and the one operated on frontal lobe was Engel's class 2. Among the patients which were treated by a disconnection + lobectomy, 86% of them were Engel's class 1.

MRI evolution

In the 45 TLE

There were two temporal horn cysts (one required reintervention), two asymptomatic thalamic or pallidal small ischemia, one incomplete disconnection (posterior hippocampal disconnection), no temporal swelling, and no brain shift.

In the 17 extra temporal lobe epilepsy

In the unique frontal disconnection case, the cortex was atrophic at the 1-year post-op MRI and among the patients operated with multilobar disconnection, the post-op MRI showed an asymptomatic frontal ischemia located in the frontal disconnected tissue in one case and in another case, a severe controlateral ischemia of the perisylvian cortex due to a carotide dissection.

EEG evolution

In the 45 TLE

Of post operative EEG, 70% were available at 2-years post-op. At 3 months post-op, about 75% of patients presented with interictal EEG abnormalities. In the group of patients seizure free after surgery, only one-third of patients did not have any electrical interictal abnormalities. Interestingly, 60% of patients who are not seizure free after surgery had diffuse interictal abnormalities, located outside the temporal region compared to 20% of patients who were seizure free and in whom interictal spikes could be recorded outside the temporal region. The presence of interictal electrical abnormalities outside the temporal region seems to be of bad prognosis when recorded 1 or 2 years after surgery. A patient, seizure free at 2-years follow-up after a left temporal disconnection, exhibited anterior fronto-temporal focal spikes, and electrical, asymptomatic seizures within the disconnected temporal cortex.

Postoperative interictal activity was observed 2 years after surgery in a non-cured patient with left temporal epilepsy, with interictal and independent diffused spikes overlapping in the posterior temporal region (T5 –O1).

In the 17 extratemporal epilepsies: all the patients exhibited interictal electrical abnormalities (mainly spikes and slow waves) usually recorded on scalp-EEG electrodes located in front of the disconnected tissue and this was seen in cured or

non-cured patients. But usually, interictal EEG abnormality were more diffusely distributed in non-cured patients.

Complications

In the 45 TLE

Clinical morbidity affected 3 patients (6%): one persistant mild controlateral hemiparesia (2%), one persistant mild controlateral facial paresia (2%), one persistant hemianopia (2%), and one phlebitis (2%).

Memory deficit in the dominant lobe was observed in 7/20 patients (35%) who had a left temporal disconnection: 6/20 (30%) had a verbal memory worsening, 4/20 (20%) had a visual memory worsening, 4/20 (20%) had a working memory worsening. Lateral superior quadrantanopia was observed in 23 patients (51.1%).

In the 17 extra-temporal epilepsies

One patient had a severe contralateral sylvian ischemia due to a spontaneous dissection of the contralateral carotid at the cervical level, which may be related to the operative position. Postoperative MRI as well as Doppler angiography did not show any parenchymal lesion and the outcome at 2 years after surgery did not present any sequelae.

The other postoperative complications were as following: one transient facial paresia (frontal lobe epilepsy), two transient mild hemiparesia, one permanent quadranopia, one permanent hemianopia (temporo occipital epilepsy) and one double vision. One patient had a postoperative distal sciatic palsy due to a misposition during surgery.

Discussion

Disconnections are used for perisylvian hemispherectomies, and hamartomas of the third ventricle, as surgical procedures meant to minimize the duration of the surgery, and to avoid the ablation of the deafferented parenchyma, as the absence of remnant connections between the epileptogenic area with the rest of the brain is theoretically necessary and sufficient to prevent the occurrence of seizures. In these cases, as well as in the present study, this theoretical concept is verified and validates this approach. For example, our results are similar to those obtained in our group in a series of consecutive temporal lobectomy[2]. Moreover, this approach is justified by the low morbidity, and the reduced morphological disturbance of the brain, particularly concerning the brain shifts and subdural collections.

What happens to the epileptic zone? One could have expected that the deafferented lobe could become deprived from inhibitory influences coming from the rest of the brain, therefore leading to aggravated epileptic states, or even to status epilepticus. This has not been observed, and there are no deleterious effects to be feared, related to an exacerbation of the epileptic focus and associated release of metabolic by-products.

On the contrary, total disappearance of epileptic activity in the deafferented parenchyma has not been observed, discarding the hypothesis of an excitatory influence coming from the rest of the brain, which could be responsible for the sustained epileptic activity before surgery.

What is surprisingly not observed is the existence of infraclinical spikes in the deafferented lobe, supporting again the concept of seizure suppression secondary to the isolation of the epileptogenic zone.

Completeness of disconnection and absence of remnant connective pathways are logical conditions to achieve in order to obtain seizure suppression. However, a better knowledge of the precise pathways responsible for the seizure spreading could open the possibilities of partial resection (superior temporal gyrus, for instance) to facilitate disconnection, dependent on individual anatomical variations, particularly about the insula. Indeed, it might be possible, if not certain, that in lobectomies,[2] as well as in total disconnections, interruption of certain pathways might not be always necessary. Functional imaging, particularly MEG, could provide data allowing such an approach.

What is the benefit of disconnection versus lobectomy?

Postoperative MRI show that there is less bleeding in the cavity, partly because this cavity does not exist, or is much smaller. Similarly, during surgery, it is clear that the section of the parenchyma with a spatula induces little bleeding, because after the section, the application of the two walls of the section reapply on each other and provide a haemostatic effect.

Disconnection needs a shorter operating time: there is no dissection of the hippocampus from the brain stem and the vascular contents of the Bichat fissure, as there is no neural connection all along it. The intrahippocampal vascular lamina does not need to be dissected as well.

What are the drawbacks?

The narrowness of the approach requires the usage of only a thin aspirator holding a cotton as a retractor, and a smooth spatula severing the cortex and white matter, sparing the vessels and not even cutting the arachnoid on the skull base, therefore sparing also all the vasculature contained at this level.

Conclusion

Disconnection has the same efficacy compared with resective surgery. The morbidity is similar or reduced as compared with lobectomy, but a larger number of patients is required before stating a definite conclusion. Disconnecting the EZ is sufficient to cure the patient, removal of the EZ is not mandatory, as long as the cause of the epilepsy is not evolutive. This is evident for tumors, but is not demonstrated in dysplasia, as their evolutivity is unknown. Similarly, cavernomas should not be left in place by disconnections as they may evolve, but also they may bleed even if they are not epileptogenic anymore. However, one might consider that the focal removal of a cavernoma associated to a disconnection of a larger parenchymal zone might be an option to consider in some circumstances.

The current work and its results, although preliminary, and together with the experience of other teams,[13] open the possibility for future more minimally invasive disconnective procedures.

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123 Corpus callosotomy

G Morrison and M Duchowny

Anatomy and physiology

The corpus callosum is a prominent cerebral midline interhemispheric commissural connection said to have approximately 180 million axons in humans[1] (Figure 123.1). The connections are homotopic and heterotopic[2] and the effects can be excitatory or inhibitory.[3] There is a differential pattern of callosal connection which may be the result of postnatal elimination of transitory callosal axons.[4] The corpus callosum participates in the interhemispheric integration of perception and cognition. The fibers of the corpus callosum principally connect associative regions of the cortex and are distributed in a rostrocaudal fashion.[5] Studies have tried to correlate the size of callosum with function. The splenium has been reported to correlate with intelligence, with a larger splenium being associated with higher intelligence.[6] The posterior third of the callosum is reported to be larger in dyslexic men.[7] This relationship between anatomy and physiology continues to unfold and requires additional study.

Concept and history

The concept of a corpus callosotomy for a patient with medically intractable epilepsy is palliation, not cure, and is based on the diminution of interhemispheric propagation of epileptic activity. This would then prevent/reduce bilateral synchrony of cortical epileptiform activity and thus interrupt secondary seizure generalization. This may also result in a global diminution of synaptic connectivity of the cerebrum. Thus, a corpus callosotomy should be effective in treating patients with seizures that require bilateral cortical activation for their clinical expression.

In 1940, Erickson reported that complete division of the corpus callosum in fourteen monkeys prevented the spread of discharges to the opposite hemisphere.[8] In the same year (and in the same journal), Van Wagenen and Herren reported the first series of callosotomies for seizure control in humans.[9] It is interesting that their rationale for the surgery may have been their observation that patients with tumors of the corpus callosum would have decreasing seizure frequency as the callosum was destroyed by the tumor. Additionally, the seizures seen early in these patients were generalized and, as the tumor grew, the seizures were often unilateral and without loss of consciousness.

Alternatively, it may have been their observation that epileptic patients who sustained a stroke involving the corpus callosum often had improvement in their seizure disorder. Regardless of their thought process, they probably did not know of Erickson's work. Erickson did fairly note previous experiments going back to 1914, including similar work reported by Gozzano in 1936.[8] Numerous investigators followed Erickson's initial observations[10,11] and it was established that the corpus callosum was primarily responsible for ensuring bilateral synchrony of spike and wave discharges, at least in the feline penicillin epilepsy model.[12]

Dandy may have had the first report of a corpus callosotomy but that was for access to pineal region tumors.[13] More then 20 years after Van Wagenen and Herren's report, Bogan reported on 'cerebral commissurotomy'[14,15] but the concept was not well received (utilized infrequently) until Wilson began reporting on callosotomy for seizure control in the late 1970s and early 1980s.[16–19] Wilson's first patient was a 9-year-old boy having 30 generalized seizures a day. Wilson did a complete commissurotomy (entire callosum, hippocampal and anterior commissure, and one fornix) and, remarkably, the boy became seizure free, off medications.[16] Luessenhop performed callosotomies on young children[20] but most early reports dealing with children were patients in the second decade.[21–26]

Indications

There has been a wide disparity of indications for a corpus callosotomy. Very few intractable epilepsy syndromes have not been recommended for callosotomy at one time or another. In fact, this operation has applied to virtually any refractory form of seizures where there is no possibility of a focal resection. Twenty years ago corpus callosotomy was recommended primarily for patients with secondarily generalized seizures or with infantile hemiplegia. In the latter case, it was as an alternative to a hemispherectomy.[27] Some patients with partial seizures (usually with rapid secondary generalization) were also treated with callosotomy as have patients with frontal lobe epilepsy or Rasmussen's syndrome. In all cases, the seizures could not be localized or an eloquent region was involved. Callosotomy has been recommended for patients with Lennox-Gastaut syndrome.[28,29] These seizures may be tonic, atonic, myoclonic, atypical absence, or generalized tonic-clonic in nature but it is the 'drop attack' seizure produced by either atonic or tonic seizures that is the most likely to respond to a callosotomy.[30–33] Callosotomy has even been reported as being beneficial in the treatment of tuberous sclerosis[34] and Sturge-Weber syndrome.[35] More recently, most comprehensive epilepsy centers are recommending callosotomy for patients with tonic, atonic, or 'drop attack seizures'.[31,36–41]

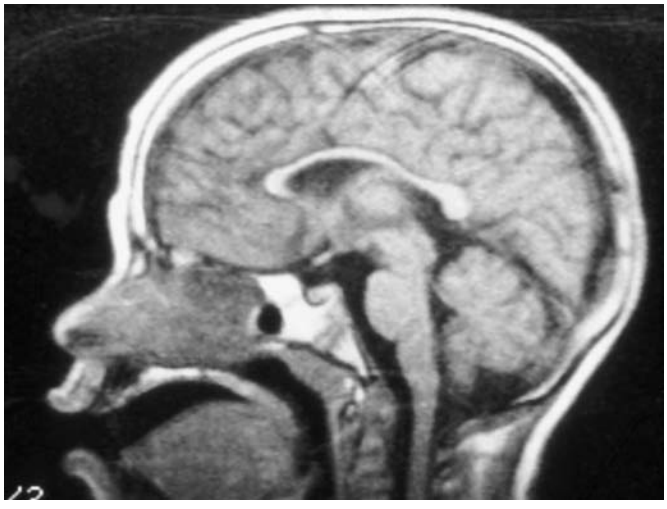

Figure 123.1 MRI of intact corpus callosum.

Patient selection

Similar to candidates for other epilepsy surgery procedures, candidates for corpus callosotomy should be experiencing frequent and debilitating epileptic seizures that have been determined to be medically intractable. Their quality of life should be seriously impacted by the seizures, i.e., affected patients would potentially be held back from employment options, operating a motor vehicle, achieving in school or participating in enduring social relationships.

Patients must have undergone extensive pre-surgical evaluation and have well documented seizure manifestations. For patients with multiple seizure types, the most debilitating seizure type should be the primary surgical target. Seizures that produce physical injury or life-threatening status epilepticus provide a strong rationale for intervention. When multiple seizure types exist in the same patient, it is reasonable to expect that secondary seizure types would not necessarily respond to corpus callosotomy as the primary target seizure type.

The principle goal of preoperative studies is to exclude localized seizure foci amenable to excisional procedures. EEG and video-EEG monitoring studies that document ictal capture are mandatory. If seizures are localized at onset, it is then necessary to document that there is subsequent spread and secondary generalization. It is also important to document independent seizure types that arise from both cerebral hemispheres.

There are no specific age-related criteria governing surgical intervention. Patients as young as 4 months[20] and as old as 55 years[26] have undergone the procedure. The majority of patients have been adolescent and young adults. It is advisable to consider corpus callosotomy as soon as the patient demonstrates and extablished seizure type that is not localized and would potentially benefit from callosal sectioning. Treating physicians should provide informative discussion emphasizing that the potential for complete seizure-freedom is limited, and that palliative goals are more realistic.

Seizure types

Seizure type is a decisive variable in the selection of epilepsy patients for corpus callosotomy. A comprehensive review of amenable seizure types has been carried out by Spencer.[42] Most centers perform corpus callosotomy for intractable generalized seizures including tonic, atonic, generalized tonic-clonic and absence seizures.[38] These seizures types would be expected to benefit from a procedure that would decrease bilaterally synchronous EEG abnormalities. As alternative subcortical pathways participate in bilateral EEG synchrony, complete abolition of generalized EEG activity is unlikely, but not required for improved seizure status.

The benefit of corpus callosotomy has repeatedly been shown for patients with disabling drop attacks. Reutens[41] reported a favorable outcome after corpus callosotomy in 64 patients, particularly for drop attacks in the setting of a unilateral focal lesion or true generalized epilepsy. Complete seizure suppression in 9/19 patients with falling attacks and an 80% reduction in 7/19 patients was noted by Rossi.[43] Generalized tonic-clonic seizures were less improved. Higher rates of seizure-freedom were reported by Shimizu[44] who found that 29 of 34 patients with drop attacks were seizurefree after callosotomy and four had only infrequent attacks. Only one patient did not show benefit. They additionally noted concurrent improvement in cognition and speech in 77% of their patients. Follow-up studies revealed that the cohort of children derived greater functional benefit than the adults.[45] Similarly favorable results were reported by Kim.[46]

The variation in outcome as a function of seizure type is notable. The superior outcome of patients experiencing drop attacks suggests that the corpus callosum may be of heightened importance in cases of bilateral synchrony associated with negative motor phenomena. In contrast, positive motor manifestations of generalized epileptic discharges appear less influenced. This would suggest the existence of different mechanisms for generalization for seizures that appear bilaterally sunchronous at seizure onset.[47]

Etiology

Corpus callosotomy has been advocated as treatment for a variety of neurological disorders associated with secondary bilateral synchrony. One of the earliest documented applications of corpus callosotomy was for patients with congenital hemiplegia.[20] Callosotomy was envisioned as a less aggressive procedure than hemispherectomy. Hemispherectomy could then be performed as a back-up procedure should corpus callosotomy prove ineffective.[48] Goodman[27] reported 'excellent' results in four of five patients with congenital hemiplegia and stressed the low incidence of complications in comparison to hemispheric ablation. Should anterior callosotomy prove ineffective, complete callosal sectioning may offer additional relief.

Selected patients with epilepsy due to cortical malformations have been treated with corpus callosotomy. Difficulties associated with localization of seizure origin and the extensive cortical involvement of some malformations has undoubtedly played a crucial role in candidate selection. Modest success after corpus callosotomy has been reported in three patients with subcortical laminar heterotopia.[49] Ambrosetto[50] reported amelioration of drop attacks in a retarded girl with the congenital bilateral perisylvian syndrome, Pallini[51] noted improvement in four patients with bihemispheric cortical dysplasia, and Landy[52] described improved atonic seizure status in a patient with band heterotopia. In contrast, anterior callosotomy offered no benefit to a patient with generalized seizures due to hypothalamic hamartoma.[53]

The experience with corpus callosotomy in young patients with epileptic encephalopathies has been mixed. Improvement in infantile spasms in West syndrome and cessation of drop attacks in patients with previous West syndrome was reported by Pinard.[54] Seizure reduction after callosotomy was reported in an 11-month-old patient with lissencephaly presenting as West Syndrome.[55] Improvement in patients with Lennox-Gastaut syndrome occurs predominantly for drop attacks.[56]

Corpus callosotomy has been advocated in a variety of clinical presentations where localization has been challenging, including frontal lobe seizures,[57] multifocal epilepsy and Rasmussen syndrome.[48] The advent of more sophisticated techniques for localization of seizure origin has largely rendered these indications obsolete.

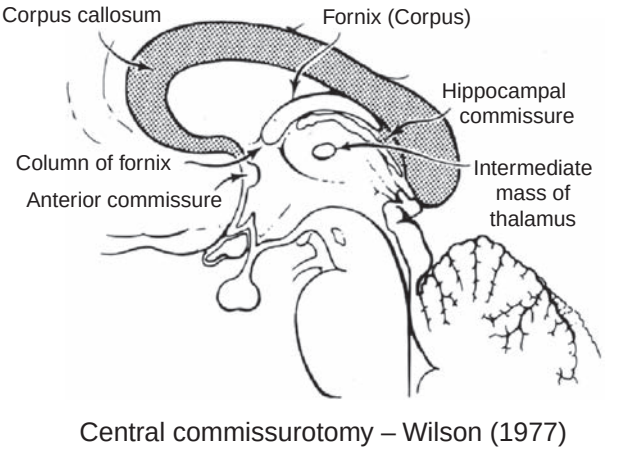

Figure 123.2 Diagram of the anatomy of early commissurotomy.

EEG

The preoperative EEG has been advocated as a tool for selecting candidates for corpus callosotomy. The degree of bilateral synchrony and the morphological similarity of generalized spike-wave discharges between hemispheres have been singled out as potential screening criteria. Matsuzaka[58] reported that a more favorable surgical outcome occurred in patients with the least variation in synchrony for bursts of spike-wave discharges. Prognostically favorable ictal EEG features include generalized slow spike-wave discharges, electrodecremental patterns and low amplitude fast frequencies.[59] It has also been suggested that posterior-dominant epileptiform discharges portend a poorer outcome after anterior callosotomy than anteriorly localized discharges.[60]

Others have been less inclined to attach significance to preoperative EEG patterns. In 36 patients undergoing anterior, posterior or two-stage callosotomy, Quattrini[61] observed a reduction in bilateral synchrony in the EEG but found no correlation with reduction in seizures. Similarly, the degree of lateralization of generalized epileptiform discharges did not correlate with reduction of tonic-atonic seizures as over 80% of patients obtain seizure reduction independent of their EEG patterns.[62] Blockage of bisynchronous discharges does not confer improved seizure status in children with Lennox-Gastaut syndrome.[63] It has also been shown from the postoperative EEG that a reduction in the number of epileptiform discharges or epileptic foci is not necessary for improved seizure status.[64] The persistence of bilaterally synchronous discharges in some post-callosotomy patients suggests that bilateral synchrony is also mediated via subcallosal pathways involving diencephalic or mesencepahlic structures.[65]

Technique

As with most surgical procedures, different techniques have been utilized by different neurological surgeons, usually with similar results. The very early procedures involved transecting the corpus callosum, the hippocampal commissure, the anterior commissure, and one fornix (Figure 123.2). The procedure evolved to a more limited sectioning of the callosum and the hippocampal commissure with rare sectioning of the anterior commissure. Centers also differed on how much of the callosum to transect at the first operation. Some (Minnesota) initially favored a total transection in one operation while most advocated (and still do – e.g., Yale) sectioning the anterior two-thirds to three-quarters during the first operation (Figures 123.3 and 123.4). One center (Dartmouth) staged the procedure with sectioning of the posterior half divided first.[66] Regardless of which part was sectioned initially, the callosotomy was only completed if the results were unsatisfactory after the partial transaction. At the present time, the only patients suitable for a complete transaction in one operation would be the very afunctional, globally developmentally delayed individual where a postoperative disconnection problem would not clinically alter the functional level.

Although most neurological surgeons favor an open approach, callosotomies have been performed with stereotactic radiofrequency[67] and with radiosurgery.[68] Some centers have used intraoperative EEG information to tailor the length of resection[23,69,70] but most groups use it, if at all, for investigative purposes and the authors have abandoned its use.

The two most popular positions are with the head lying on the side (so that gravity will help with the retraction) or brow up with the head elevated (the author's preference). If neuronavigation is to be utilized (which can be very helpful),[71] then 3-pin fixation is mandatory, otherwise it is optional. General anesthesia is similar as for other craniotomies with possible

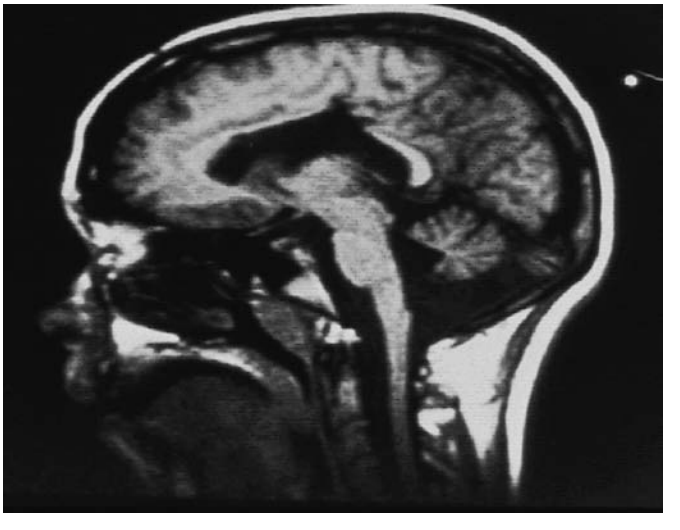

Figure 123.3 MRI of corpus callosum after an anterior two-thirds sectioning.

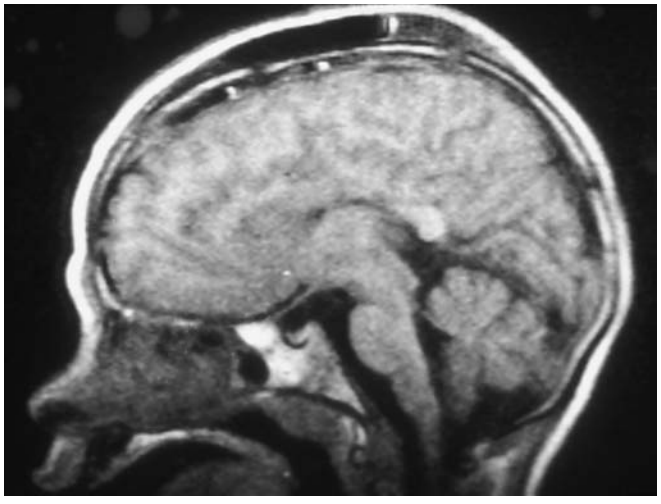

Figure 123.4 MRI of corpus callosum after an anterior three-quarters sectioning.

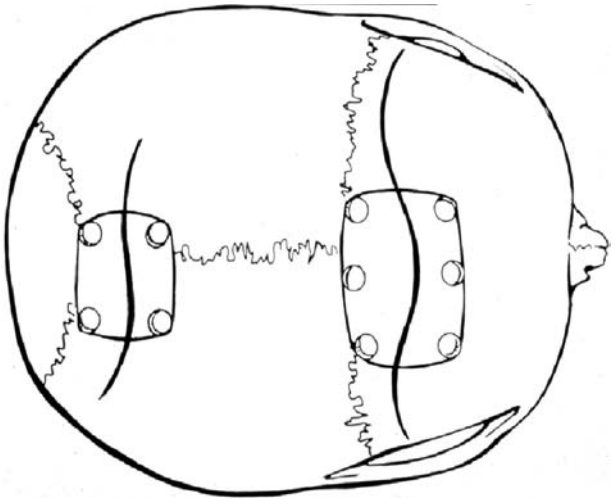

Figure 123.5 Diagram of head with a skin incision and craniotomy flap outlined. A complete callosotomy can be done from the anterior incision and the craniotomy flap may be safely extended slightly behind the coronal suture. The posterior incision is used if a second operation is performed to complete the callosotomy.

precautions for air embolism taken if the head is far above the heart. Dexamethasone and prophylactic antibiotics are used without scientific evidence of their efficacy.

A bi-coronal (or Soutar) incision is preferred (Figure 123.5) with the right sided limb a little longer. A bilateral craniotomy is then done at the level of the coronal suture (Figure 123.5). A callosotomy can be performed through a small craniotomy, but a larger opening gives the surgeon more flexibility in identifying the best corridor down the falx to the callosum. The venous anatomy will dictate the specific corridor as great lengths are taken to avoid sacrificing the bridging veins. Although a right-sided approach is often favored (right-handed surgeons and nondominant hemisphere), the anatomy may change the approach to the left side. This is arguable for left-handed patients but is sometimes dictated by the venous anatomy found at surgery. Theoretically this venous anatomy could be determined preoperatively (MRV) but, as of yet, this does not always show the required detail.

It is important to expose the midline and the sagittal sinus so that it can be retracted (by traction sutures on the dura or with a self-retaining retractor). This is also added by opening the dura based on midline. Mannitol (0.5–1g/kg) is usually given before the interhemispheric dissection is begun.

The dissection is then done with the aid of magnification (the author prefers the operating microscope) with careful separation of the midline structures. This is usually straightforward but can be confusing and there can be vessels not easily identified to one side or the other. If this occurs, it is wise to abandon this dissection and to dissect further anterior or posterior and the true anatomical nature of this vessel will usually become apparent. Although the cingulate gyrus has been confused with the corpus callosum, the adage of 'if it's not white, it's not right' is quite accurate. The white corpus callosum is visually unique. The vessels overlying the callosum are identified, separated, and preserved (Figure 123.6).

Dissection is performed anteriorly and posteriorly before the actual transection to identify and secure the boundaries of sectioning. The anterior boundary is the genu and the posterior boundary is approximately two-thirds of the callosum. This is usually easily identified as the location where the callosum begins to curve or slope inferiorly. Neuronavigational systems are a help as are measurements taken from the preoperative MRI. If a total callosotomy is to be done, the head may be moved to facilitate the posterior dissection.

After the dissection, the transection begins and is carried throughout the course (Figures 123.7 and 123.8) An attempt is made to stay exactly in the midline because, even in absence of a cavum septum, there is usually a small space or midline raphe to guide the surgeon and to facilitate staying out of the ventricular system. Most neurosurgeons use combination of suction and the bipolar forceps, but various microdisectors are helpful and some surgeons have used ultrasonic aspiration and even an endoscope (in cadaveric preparations).[72] An attempt is made to stay out of the ventricle but the author has not seen the difficulties described by others (e.g., hydrocephalus).[16,18] However, some blood in the ventricular system can produce postoperative fever. This may be ameliorated by the use of

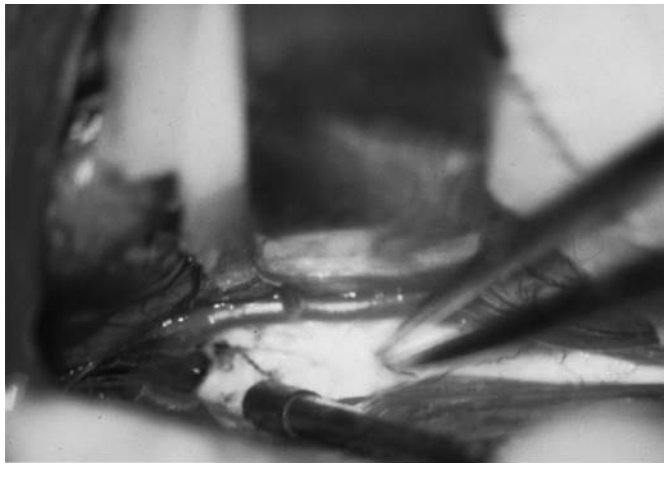

Figure 123.6 Operative photograph of corpus callosum exposed prior to transaction.

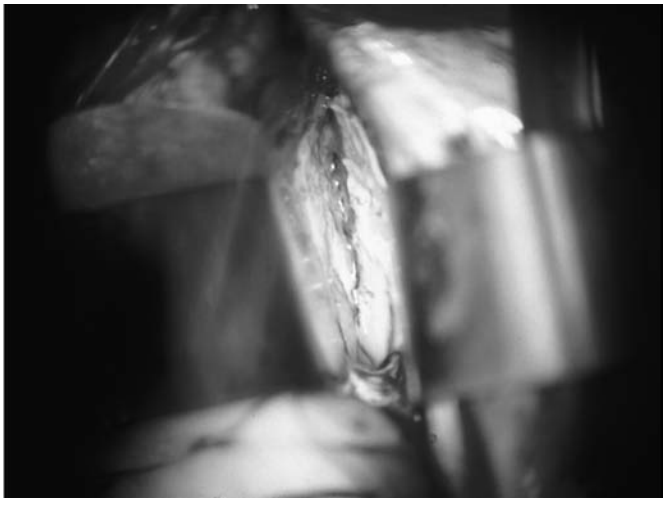

Figure 123.7 Operative photograph of transected corpus callosum.

dexamethasone. Some neurosurgeons have left a titanium clip at the posterior limit of the transaction to identify the boundary by neuroimaging and, as an aid for identification if further surgery is performed. This has not been the author's practice. Following the transaction and establishment of hemostasis, a standard closure is performed. In addition to steroids, patients are given a couple of doses of antibiotics and otherwise standard postoperative management.

If a second procedure is indicated, the neurosurgeon could go back through the anterior callosotomy incision, but scarring will make the dissection difficult and most would favor a separate, posterior, incision and craniotomy (Figure 123.5). Posteriorly, the falx goes to the callosum which makes its identification, and that of midline, easier. The same principles as outlined for the anterior procedure are followed and here, instead of identifying the anterior cerebral arteries after sectioning of the genu, the vein of Galen will be visualized as the splenium is transected and appropriate respect is given to it. The underlying arachnoid, beneath which lie the quadrigeminal cistern and the pineal, is preserved.

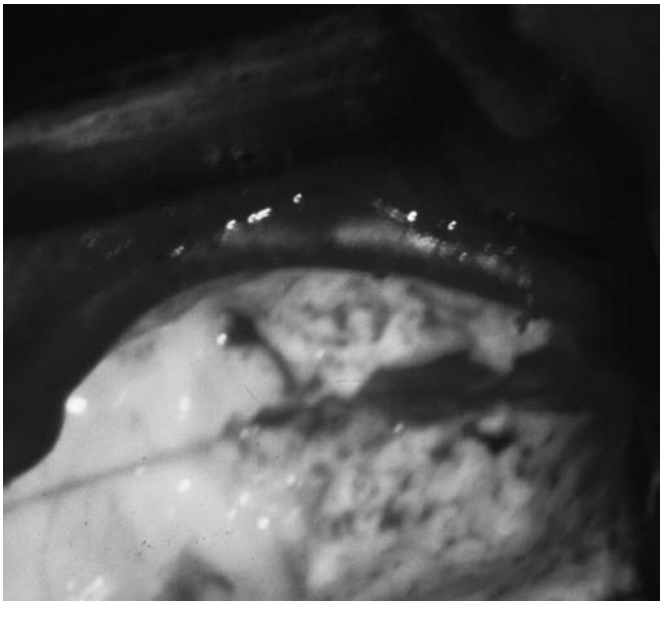

Figure 123.8 High powered operative photograph of transected corpus callousm.

Results

The first series of Van Wagenen and Herren included 10 patients reported in detail.[9] They operated on an additional 17 patients who were not reported in detail. They reported the conversion of generalized seizures to lateralized seizures with preservation of consciousness. Nine of the originally reported ten showed significant improvement.[9] It is difficult to make generalizations from subsequent reports since candidacy for callosotomy, technique, and the methods of quantifying outcome have been variable. It is difficult to compare the outcome of different published series of callosotomy patients because of variables that include: seizure type, patient's functional ability pre- or postoperatively, extent of pre- or postoperative investigation, and the definition of a 'good', 'satisfactory', or 'excellent' outcome. Indeed the variation is so extreme that some report complete, or almost complete, control of atonic, tonic, or generalized tonic-clonic in the majority of patients after callosotomy,[19,25,73] whereas others report a favorable response in less than 50% of operated patients.[26,32]

Several series have reported a significant reduction in bisynchronous discharges after callosotomy.[17,19,38,74,75] One related the EEG changes to the extent of transection.[65] Seven patients who underwent an anterior callosotomy showed a decrease in the quantity of epileptiform discharges.[76] Postoperatively, the total number of epileptiform burst activities, mean duration, and the total number of spike discharges decreased significantly.[76] There have been reports of increased partial seizure activity after callosotomy in humans[25,77–82] and in subhuman primates.[10,83] This worsening of seizure activity may be secondary to the loss of an inhibitory influence[84,85] and Spencer has described clinical seizures as being more intense.[66,84] Alternatively, postoperative partial seizures may represent a remnant of the patient's preoperative generalized seizures.[73]

Satisfactory outcomes have been reported to be between 50% and 80% where 'satisfactory' means a seizure reduction in frequency and/or severity of 50–80%.[29,66,85] Patients with atonic seizures have fared better than those with tonic seizures.[19,23,33,36,38–40,43,45,80,85–88] However, dichotomy exists. Madsen reported 80% significant improvement for drop attacks of either tonic or myoclonic origin, 69% for atonic drop attacks, 70% of atypical absence seizures, and 55% of generalized tonic-clonic seizures.[37] An early report from Dartmouth found excellent results in four or five patients who had a callosotomy instead of a hemispherectomy for congenital hemiplegia.[27] A report from Taiwan stated an 82% significant improvement (more than 50% reduction in seizure frequency) in patients with generalized tonic-clonic seizures, 73% with atonic seizures, and complete seizure freedom in 19%.[89] However, most reports continue to show better results for atonic seizures than for generalized epilepsy. A Japanese report found that 'total callosotomy is more effective for the treatment of drop attacks than partial callosotomy and that children receive more benefit than adults after callosotomy'.[45] They reported an overal 85% satisfactory outcome (90% or more seizure reduction).

Wilson reported that 16 of 20 patients had a greater than 50% reduction in overall seizure frequency.[17,19] Geoffroy had similar success in six of nine patients,[22] Luessenhop in three of four,[20] Amacher in four of four,[21] Rayport in seven of nine,[90] and Bouvier in six of six.[91]

Engel looked at the outcome of a large number of patients (197) from 16 centers and found that only 5% were completely seizure free, 71% improved, and 24% unimproved.[92] A follow-up survey in 1991 of 563 patients found that 8% reported seizure freedom with 61% improved.[93] Spencer reported a series of 22 patients, five to 39 years of age, in which complete control of seizures was seen in six of seven with tonic seizures, two of two with atonic seizures, 16 of 21 with tonic-clonic seizures, nine of 22 with complex partial seizures, and none with simple partial seizures.[25]

He also reported that complete callosotomy was twice as effective as partial section.[25] Spencer collected data on 330 patients and reported a success rate of 71% for atonic seizures following anterior section and 74% after total section; for tonic-clonic seizures the response was 56% and 75% respectively; for tonic seizures 47% and 75% respectively; and for absence seizures 33% and 64% respectively.[94] Roberts reported that for all seizures taken together, only 29% of patients undergoing anterior transaction achieved success (80% or greater reduction of seizures) but that this increased to 62% success following completion of the callosal section.[95]

Unfortunately, there has been much variability of reported success following callosotomy. Commonly, reports state results of 57% 'complete suppression of the generalized seizures associated with drop attacks' (12 of 21 patients and a 'seizure reduction of more than 75% in 6 of the 21.[46] Gates reported on 24 patients with 'a highly statistically significant reduction of postoperative tonic or atonic seizures'.[73]

One report stated that a very good outcome was present in 92% of patients more than ten years of age[96] and in a pediatric series where callosotomy was the predominant surgical procedure for intractable epilepsy (30% of the cases), a surgical cure for drop attacks was reported to be 91% following a total callosotomy and 67% after partial transection.[97] In the latter series, the most frequent preoperative EEG abnormalities were diffuse bilaterally synchronous epileptic discharges (72%). The neuropsychological consequences of the procedures are not clear, but improvement in quality of life was reported to occur in 77% of patients (97).

A small series of ten patients with bihemispheric malformations wherein a total callosotomy was performed reported cessation of drop attacks in eight (one patient subsequently relapsed).[98] Overall daily functional level was also reported to improve.

Completeness of resection

Although Spencer initially reported that outcome depended on the completeness of the transection,[25] other authors have shown no differences in seizure control between partial or complete sections.[41,23,99] Spencer later reported that a complete transection of the corpus callosum should be reserved for patients who did not respond to an anterior two-thirds section[82] but there is a clear benefit in proceeding to completion in patients with persistent generalized seizures after partial section.[94] An early report of 24 medically refractory seizure patients (a variety of seizure types) revealed a significant reduction in seizure frequency and severity in 75% after anterior two-thirds corpus callosum section.[100] In contrast, nine of 14 patients improved after a complete callosotomy in the treatment of West syndrome, while only two of 13 improved after an anterior callosotomy.[54]

Prognosis

The preoperative EEG has been used to predict outcome. It has been reported that the 'preoperative quantitative EEG analyses enabled ... to predict ... the surgical outcomes in patients undergoing corpus callosotomy'.[58] Another report stated that 'the ictal EEG but not other factors is able to identify a group of patients who have a better than 90% chance for total of nearly total resolution of seizures causing sudden falls'.[59] Better results may be obtained in patients with lateralized EEG abnormalities.[22]

Quality of life issues are more difficult to judge; while some have reported a favorable social outcome,[101,102] others have pointed out that overall clinical improvement or global measures of quality of life do not always correlate with seizure reduction.[103,104] However, eliminating drop attacks associated with craniofacial trauma, by corpus callosum section, is an extremely important goal, even if other seizure types persist.

In an early series, Ferrell did formal neuropsychological testing on eight patients and reported improvement in six.[105] Yang reported that 76% of families surveyed were satisfied with the surgical result and 72% were satisfied with the family's quality of life.[102] Positive behavioral changes, social skills, and attention spans were reported. Gillam noted similar results in that 15 of 17 families reported overall satisfaction with reported improved alertness and responsiveness.[104]

Complications

The usual complications of a craniotomy are seen but, fortunately, infrequently. Bone flap infection may be slightly increased because this is free bone flap and not an osteoplastic flap. Venous damage can result in an infarct as can damage to one of the deep arteries. Blood in the ventricle is to be avoided, but in the author's experience it has not been a problem and the development of hydrocephalus has not been observed. Contralateral weakness (if present) is usually transient and should be discussed pre-operatively. Long term neurological problems are rare but an exacerbation of previous lateralized deficits has been reported.[106]

Of concern are clinical situations particularly unique to a corpus callosotomy. There are possible acute and chronic sequelae of a callosotomy and these neuropsychological/behavioral changes have been well described[107–114] even though initial reports stated that callosotomy produced little alteration in cognition.[110] An acute disconnection syndrome may occur in some patients after an anterior two-thirds transection but almost always following complete transection. Affected patients are lethargic, apathetic, and mute,

a presentation that can be very disturbing to the family. This disconnection syndrome should also be discussed before surgery. Families should be informed that patients virtually always get better but that this recovery can take from days to weeks.

The problem of mutism following a callosotomy has been recognized for twenty three years.[115] Additionally, there may a hemiparesis (leg greater than arm), an apraxia and hemineglect (if testable), bilateral Babinski signs, urinary incontinence, and an increase in focal motor seizures.[29,85]

The chronic disconnection syndrome is often very subtle and identified only by careful neuropsychological testing. It is most often present when the splenium of the corpus callosum has been transected. Deficits in tactile transfer can exist which consist of poor naming of objects held in the nondominant hand and visual transfer problems which consist of poor naming of objects seen in the nondominant hemifield. Thus, it especially involves sensory and/or visual pathways and their connections for speech production. For example, with a posterior callosotomy an object seen only by the left visual field may be recognized but the information can not be transferred from the right hemisphere to the left dominant hemisphere for naming. In practice, this is rarely noticeable clinically because objects are viewed in both visual fields. An 'alien hand syndrome' has been reported wherein there is antagonistic or poorly cooperative behavior between the two hands.[108] This syndrome is usually transient but can, rarely, persist. Although poorer memory and concentration have been reported,[116,117] this may be more of an attentional impairment than actual memory dysfunction[118] or may occur when preoperative extracallosal damage exists, particularly involving the fornix.[119]

Although early reports stated that patients 'do not experience functionally significant intellectual, emotional, or social impairment',[105] deficits are possible in all patients after callosotomy and finding them may be a function of the index of suspicion. Most deficits are topographic in nature, must be carefully searched for, and are rarely clinical significant.[120] In fact, neuropsychological and psychosocial assessments are not significantly altered when compared with preoperative functional levels.[121] 'Deficits due strictly to callosal section can be almost completely predicted by the patient's preoperative behavior, cognitive deficits, and the presence of unilateral lesions resulting in interhemispheric dependence for function'.[66,106] Anterior sections result in disruption of sensory or motor integration functions as would be expected.[120] This is somewhat in disagreement with a report by Tassinari wherein only two of six patients undergoing an anterior callosal section demonstrated an impairment in intermanual transfer of tactile localization.[122] With careful testing it is apparent that effective binocular integration across the midline requires an intact corpus callosum.[123] Patients undergoing a callosotomy for seizure palliation may be different than other partial callosotomy patients, such as those who have a interhemispheric disconnection after traumatic brain injury where the deficits seem mild or transient.[124,125]

Long term problems are related to the amount of sectioning[25] with deficits almost doubled for a complete callosotomy compared to an anterior two-thirds transection.

Spencer reported motor difficulties in 15% vs. 8%, language impairment in 14% vs. 8%, and cognitive/behavioral impairments in 11% vs. 8%. Age may also be a factor, as the plasticity of the young provides for much better response and adaptation to any brain injury, including callosotomy.[66,126]

Some authors have reported that patients with low preoperative IQs are at greater risk of developing neuropsychological deficits following callosotomy,[41,126] but others report no relation between IQ and surgical outcome.[127,128,129] There are reports of improvement of psychomotor function, even after total callosotomy.[45,97,126]

Future

As noted, there are many conflicting reports regarding the indications for corpus callosotomy, the extent of transection, and, most importantly, on outcome. Outcome differs markedly, in part, because of the different interpretation of 'success', the methods and length of follow up and the degree to which neuropsychological, neurophysiological, or neurocognitive deficits were investigated.[130]

While our understanding of the indications and expectations for corpus callosotomy for the treatment of intractable epilepsy continues to evolve, the last decade has seen a sharp decline in the use of corpus callosotomy for intractable epilepsy. This may be partially due to the introduction of new anticonvulsant drugs and partially because of the increased ability to identify an epileptogenic zone with improved anatomic and functional neuroimaging and metabolic studies. However, even in 'nonlesional' cases, more aggressive investigation (e.g., increased use of implanted electrodes with extraoperative monitoring, increased use of ictal SPECT, PET, MEG) has allowed for more focally resective surgery.

New techniques might be of some benefit,[114] but are highly speculative at this time. The role of vagal nerve stimulation has yet to be determined. It can be stated that a microsurgical extraventricular division of the corpus callosum can help a number of patients and that staging the procedure remains a reasonable alternative approach as a complete callosotomy is not required in all patients. Behavioral and neuropsychological sequelae of commissurotomy are well-recognized, but are rarely of long term clinical consequence. In the majority of patients the potential benefits of the procedure outweigh the risks and, finally, callosotomy is currently an underutilized procedure, especially for children with intractable atonic seizures associated with recurring falls and injuries. Corpus callosotomy should remain in the surgical armamentarium of every comprehensive epilepsy program.

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124 Radiosurgical treatment of epilepsy

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Introduction

Radiosurgery is the precise application of focused radiation to a targeted volume area within the brain identified on magnetic resonance imaging.[1] Initially conceptualized by Leksell for use in functional neurosurgery, radiosurgical treatment for neurologic disorders has progressively widened its utility and is now also an option for several neoplastic and vascular indications.[2,3] Differing from standard dose-fractionated radiotherapy, radiosurgery allows the neurosurgeon to deliver precise and accurate radiation to a smaller volume without effecting large portions of normal parenchyma allowing for a powerful radiobiologic effect on the chosen targeted volume.[1,4–6]

Patients with epilepsy who are refractory to medical management may be referred for possible surgical management, and approximately half of them are found to be candidates for surgical resection of their seizure focus.[7] Focal partial epilepsies are typically responsive to surgical treatments and are increasingly being treated using 'structural' means.[2,8] The most common type of surgery performed is an anterior temporal lobectomy, resection of a portion of the temporal lobe.[7,8] Microsurgical resection of mesial temporal lobe structures can be performed with low morbidity and even lower mortality.[6] Open procedures have inherent risks including damage to the brain (either directly or indirectly by injury to important blood vessels), bleeding (which can require re-operation), blood loss (which can require transfusion), infection, and general anesthetic risks. In addition, surgical incisions can result in significant postoperative pain. Several clinical studies evaluating the morbidity of temporal lobe microsurgery report that 5–23% of epilepsy patients undergoing open surgery had a symptomatic neurologic deficit post operatively.[9–13] Furthermore, open procedures require several days of care in the hospital including at least one night in an intensive care unit which contribute to the economic costs of resective surgical treatment.[2] There also exists a population of patients with medically intractable epilepsy that is unsuitable for conventional resective surgery.[2] These patients may have their epileptic focus in eloquent regions of the brain which could result in irreversible language, motor, or visual impairment with surgical resection.[2,3]

Radiosurgery is now being evaluated as an alternative treatment to open resective surgery for intractable epilepsy. Specifically, radiosurgery is under study as a treatment of epilepsy associated with vascular malformations, gelastic epilepsy associated with hypothalamic hamartomas, and medial temporal lobe epilepsy associated with mesial temporal sclerosis.[1,3,4,6,14–37]

Preclinical evidence

Animal studies investigating focused radiosurgery in animal models of epilepsy have demonstrated the potential utility of radiosurgical treatment applied to epileptic foci to reduce seizure activity. Early animal experiments in cats indicated the potential of focused radiosurgery in a cat model of epilepsy.[2,14,17] Using doses between 10 and 20 Gy (one gray, Gy, is equivalent to one joule of energy per kilogram of tissue), cats with epileptic foci treated with an implanted cobalt source had reduced seizure activity. Histologic analysis of these animals revealed 'neuronal reafferentation' as the proposed mechanism of seizure amelioration.[14,17]

Recently, Sun *et al.* report that focused radiosurgical treatment successfully reduced seizure activity and raised the seizure threshold in a rat epilepsy model.[3] A linear accelerator was used to perform radiosurgery at doses of 10 or 40 Gy at the 90% isodose line using a 5 mm collimator. The seizure threshold to external electrical stimulation in these rats was significantly increased and the length of after-discharges was significantly decreased in the 40 Gy group. These antiepileptic effects were detectable 1 week after radiosurgery and continued for a three month follow-up period.[3]

Experiments from the University of Virginia were designed to evaluate the effects of radiosurgery on a chronic spontaneous limbic epilepsy model.[38] In this model, hippocampal electrodes were implanted utilizing a single 90-minute period of stimulation to produce a rodent spontaneous limbic epileptic model. Ten weeks later, Gamma Knife(r) radiosurgery with doses of 10 to 40 Gy, using a 4 mm collimator, was applied. While the lowest dose group (10 Gy) showed no decrease in seizures, the 20 Gy group did exhibit a gradual and continuous reduction in seizure occurrences from 2 to 6 months after radiosurgical treatment. Lastly, the 40 Gy group displayed a dramatic reduction in seizures by the second month. Histologic analysis of radiosurgical treated targets revealed no necrosis. Furthermore, penicillin induced epileptic activity was reduced in the brain slices of those rats that were treated with 40 Gy. Synaptically driven neuronal firing was found to be intact in these brain slices, suggesting that neuronal death was not responsible for the identified seizure resistance.[38]

Experiments at the University of Pittsburgh were designed to determine the dose of radiosurgery that was necessary to eliminate seizures in a kainic acid rat epilepsy model.[28] In this study rats underwent stereotactic injection of kainic acid into the right hippocampus to induce seizures. Ten days after the injections, the injection site was treated with Gamma Knife(r) radiosurgery using a 4 mm collimator over a range of 20–100 Gy.

The animals treated with a 20 Gy dose showed a reduction in the number of daily seizures during each week of observation after radiosurgery. Furthermore, three weeks after radiosurgery, all radiation groups – 20 Gy, 40 Gy, 60 Gy and 100 Gy showed a significant reduction in seizure activity confirmed with EEG evaluations. The authors report that histologic evaluation revealed no radiation-induced necrosis in any animals except for the 100 Gy cohort. However as the injection of kainic acid induces a loss of CA3 neurons in all animals, interpretation of histological findings may be difficult. Small areas of kainic acid necrosis were seen in 2/20 control animals and in 14/37 irradiated animals, but only in the 100 Gy radiosurgery treated group did the necrosis noted match the collimator size.[28]

A second study using the same kainic acid rat epilepsy model was undertaken to further evaluate the pathological and behavioral effects of 'subnecrotic' radiosurgery doses.[39] Stereotactic hippocampal kainic acid injections were followed by single isocenter radiosurgery using a 4 mm collimated Gamma Knife(r) with radiosurgery doses of 30 or 60 Gy. A significant reduction in seizures was noted in all animals, and this effect was seen earlier in the 60 Gy cohort than in the 30 Gy group (weeks 5–9 compared to weeks 7–9). Furthermore, rats treated with radiosurgery did not demonstrate a deficit in new memory attainment tasks with water maze testing compared with kainic acid injected animals, but both groups showing impairment compared to controls without kainic injection. Two blinded, experienced observers rated the histological specimens from all animals at 13 weeks following radiosurgery. Changes typical for kainic acid injections were seen in all animals including a loss of pyramidal cells in CA3-4. In 25/46 injected animals unilateral hippocampal atrophy with cell loss extending into CA1 and CA2 was noted. Although histologic assessment is difficult to assess given the use of kainic acid, necrosis matching the target volume of radiosurgery was not observed in any of the animals.[38] The authors again suggest that cessation of seizures following radiosurgery does not require concomitant loss of neurons.[39]

Two recent studies from the radiosurgery group in Prague report on their characterization of a 'subnecrotic' dose using radiosurgery in an animal model.[40,41] The investigators studied doses of 25, 50, 75 or 100 Gy delivered bilaterally to rat hippocampus. Memory function tests, MRI and histological examination were performed at 1, 3, 6 and 12 months following radiosurgery. A time and dose-dependent response was noted in memory function, T2 edema and necrotic histopathology. Animals dosed with 100 Gy died by 6 months following radiation and all had necrotic lesions. All animals treated at 75 Gy displayed memory impairment at 6 and 12 months, edema on MRI, and necrotic lesions, whereas only one of the animals treated with 50 Gy were effected by edema and necrosis. Otherwise, 25 and 50 Gy irradiated animals did not show any functional or structural impairment at up to one year after radiosurgery.[4] This finding of potential subnecrotic radiosurgery dose parameters prompted a second study where a 35 Gy radiosurgery dose was used and the animals were evaluated over 16 months.[40] By 6 months postirradiation, T2 edema was evident on MRI and this edema peaked at 9 months. By 17 months, two of six animals had postnecrotic cavities. The four animals without frankly necrotic cavities had severe atrophy of the corpus callosum, loss of thickness of somatosensory cortex and damage to the striatum oriens hippocampi.[40] These studies clearly indicate that the full radiobiologic and histological effect of radiosurgery may only be manifested after several months following treatment.

These preclinical studies report the amelioration of seizures as well as histologic neuronal changes associated with radiosurgical treatment in different animal epilepsy models. These animal studies suggest that the antiepileptic efficacy of radiosurgery is dose dependant.[6,28,38,39] Most of these studies suggest that a radiosurgery dose of approximately 25 Gy is required to see therapeutic antiepileptic effect, and that the full histological and other toxicity may require several months to fully develop.[2,3,28,38–44]

Clinical evidence

The first radiosurgical application for epilepsy surgery was utilized by Talairach in the 1950s with the implantation of radioactive yttrium in patients with MTLE without a lesion.[2,3,6] Further clinical experiences with Gamma Knife(r) radiosurgery and linear accelerator (LINAC) based radiosurgery for the treatment of arteriovenous malformations and low grade tumors also noted the incidental antiepileptic effects of radiosurgery.[6,18,20,23,25,26,37] Using Gamma Knife(r) and LINAC to treat arteriovenous malformations (AVMs), several groups have reported a supplementary improvement in seizure control.[27,35,42] Although it is not established whether reduction of tumor size or angiographic occlusion of the vascular malformation itself may reduce seizures, these reports of clinical seizure improvement with radiosurgery provided the impetus for investigating radiosurgery as an alternative treatment for medically intractable epilepsy.

Medial temporal lobe epilepsy

Medial temporal lobe epilepsy (MTLE) associated with mesial temporal sclerosis is perhaps the most well defined epilepsy syndrome responsive to surgical intervention. When temporal lobe epilepsy is due to underlying mesial temporal sclerosis (MTS), surgical cure can be expected in between 65 and 90% of patients.[2,7,8,43–49] This form of adult intractable epilepsy is particularly amenable to radiosurgery because 80–90% of these cases show changes on magnetic resonance imaging.[4,46]

Recently, radiosurgery has been explored as an alternative to open resective surgery for MTS associated medial temporal lobe epilepsy. In the first application of Leksell Gamma Knife® for epilepsy, Regis *et al.* utilized radiosurgery in a small number of patients showing amelioration of seizures with minimal morbidity and mortality.[31,34] A prospective, multicenter European study evaluating Gamma Knife(r) surgery for MTS showed comparable efficacy rates (65%) for seizure reduction by conventional surgery or radiosurgery after 2 years of follow up.[6] Using a marginal dose of 24 Gy, Regis *et al.* demonstrate that radiosurgery can be used as an alternative to conventional resective surgery to treat medial temporal lobe epilepsy associated with MTS and improve quality of life with favorable rates of morbidity and mortality (Figure 124.1).[6]

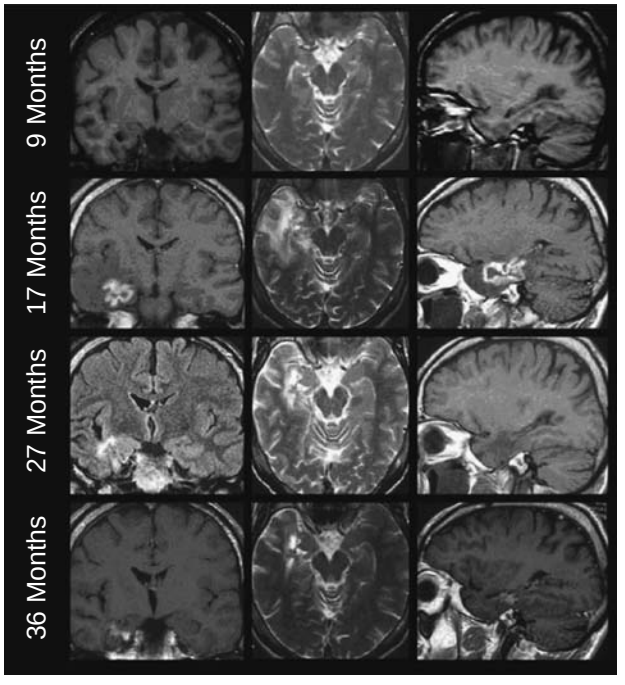

Figure 124.1 Representative radiographic changes on magnetic resonance imaging (MRI) after radiosurgical treatment of mesial temporal lobe epilepsy. Radiographic effects are not observed until after 1 year correlating with delayed clinical manifestation of therapy.[6]

In the US, a multicenter pilot trial is currently being conducted with initial results showing that 85% of patients treated with 24 Gy (to the 50% isodose line) to the medial temporal lobe, including the amygdala, anterior hippocampus and nearby cortex followed for at least 24 months are seizure-free with minimal morbidity (Barbaro *et al.* unpublished). This group is planning a larger, phase 3 trial comparing open surgery with radiosurgery for patients with clinically and radiographically defined MTS.

Although radiosurgery has proven effective and safe in ameliorating MTS associated seizures, the beneficial effects of radiosurgery are not displayed immediately. Most patients achieve seizure reduction at 9–12 months and complete cessation of seizures between 18–24 months after radiosurgical treatment. A transient increase in partial seizures (auras) is noted typically at approximately the same time as complex seizures decrease.[6] Greater than half of treated patients may require corticosteroids to treat the radiation-induced edema associated with the initial radiosurgical effect (10–15 months posttreatment) (6 Barbaro, personal observation).

One of the difficulties in applying radiosurgery broadly as an application for intractable epilepsy is the definition of the radiosurgical target. Because the MTS associated with MTLE is not well defined anatomically, the precise boundaries for radiosurgical treatment are not well known and hence is difficult to standardize amongst different treatment centers. Successful radiosurgical treatment has been shown to be target related. Recently, Regis *et al.* radiosurgically targeted the mesial temporal lobe structures in their series whereas Kawai *et al.* defined their treatment to the amygdala or hippocampus, and each series reported contrasting rates of successful amelioration of medial temporal lobe seizures with radiosurgery.[6,22,31,34] Although target definition may be variable amongst different neurosurgeons, radiosurgery for MTS associated MTLE is an attractive option because of its low morbidity and mortality. Furthermore, conventional open temporal lobectomy can also be pursued if the initial radiosurgical treatment is ineffective and sufficient time has been permitted for the delayed radiosurgical antiepileptic effect after 3 years.[6]

Recent dose studies have also indicated that a lower marginal dose of 20 Gy may be less effective in reducing seizures. Cmelak *et al.* report unsuccessful seizure reduction with radiosurgery using a 15 Gy marginal dose.[50] Kawai *et al.* also report two cases of radiosurgery with unsuccessful anti epileptic effect with a marginal dose of 18 Gy.[22] Finally, Srikijvilaikul *et al.* from the Cleveland Clinic report their series of failed radiosurgical treatment for seizure control with a 20 Gy marginal dose.[5]

The radiobiology of radiosurgery in the setting of MTS associated MTLE is not yet completely understood. While some animal studies have suggested an anti-epileptic effect of radiation with subnecrotic doses,[39] human studies indicate that a certain amount of tissue damage may be required to see a significant amelioration of seizures. The importance of this question is that radiosurgical treatment of eloquent brain regions would be possible if an effective subnecrotic dose could be found.

Histologic evaluation of radiosurgical treatment

Histological examination of radiosurgically treated human mesial temporal tissue for MTLE has been limited, but some histologic analysis of radiosurgically treated tissues involving patients who underwent resection due to lack of seizure control have been reported.[22,50,51] Using a subtherapeutic dose of 15 Gy, Cmelak *et al.* noted no radiation-induced histopathologic changes after radiosurgery.[59] In another two patients treated with 18 Gy, one patient was noted to have a necrotic focus with some prominent vascular changes consisting of vessel-wall thickening, fibrinoid and hyaline degeneration. The other patient treated with this subtherapeutic dose showed no necrosis or vascular changes.[22] Treated with a higher, yet subtherapeutic, dose of 20 Gy, all five patients from the Cleveland Clinic also showed necrosis, perivascular sclerosis, and macrophage infiltration upon resection and histologic evaluation.[51] These observations suggest that in humans, significant histologic changes may only be observed in radiosurgical doses greater than or equal to 20 Gy. These radiobiologic and histological changes may be required for a full antiseizure effect. Thus, a dose that produces some tissue damage without producing an excessive response, likely 24 Gy, is the optimal effective dose in the radiosurgical treatment of MTLE.[6,31,34]

Hypothalamic hamartomas associated gelastic epilepsy

Hypothalamic hamartomas are rare lesions with a prevalence of 1–2 in 100,000 commonly associated with precocious puberty, developmental cognitive delay, and gelastic epilepsy.[29,54] An overwhelming majority of seizures associated with hypothalamic hamartomas are gelastic in nature and are

medically refractory.[29,52,53] These hamartomas are ectopic tissue consisting of glia, neurons and fiber bundles.[24,52,53]

Surgical resection of hypothalamic hamartomas has been reported to improve control of gelastic seizure activity, but due to the technical difficulties of reaching this deep lesion in a critical area, open microsurgical resection is often difficult, incomplete and associated with a high risk of complications such as motor, visual and hypothalamic deficits.[24,52–55]

Unger *et al.* report two patients treated with low-dose radiosurgery for hypothalamic hamartomas with significant seizure improvement after 36 and 54 months.[36] This therapeutic delay is consistent with the radiobiological effects of radiosurgery.

In a recent retrospective multicenter study, Regis *et al.* report ten patients treated with 18 Gy that had improvement in their seizures after radiosurgical treatment of hypothalamic hamartomas.[29] In a larger series, 19 out of 30 patients were shown to have short-term improvements in 6 months of followup, but further follow-up data is still being evaluated in this series.[33] This alternative treatment holds great promise as an effective alternative treatment given the surgical morbidity associated with microsurgical dissection of hypothalamic hamartomas. Further investigations with larger series, longer follow-up in a prospective manner must be conducted to establish the true safety and efficacy of this treatment option.

Cavernous malformation associated epilepsy

The most frequent presentation of cavernous malformations is seizures. These congenital vascular malformations can cause hemorrhage and repetitive neurologic deficit, but more commonly manifest as repetitive seizures.[30,56] The incidence of medically intractable epilepsy associated with cavernous malformations is not yet established.[30]

Radiosurgical treatment for cavernous malformations is controversial because clear evidence for protection from hemorrhage has yet to be established.[21,24,30] Although resective, open microsurgical treatment of cavernous malformations remains the standard efficacious therapy, a recent series by Regis *et al.* suggest a role for radiosurgery in the treatment of seizures associated with cavernous malformations near 'highly functional cortex' that may preclude open resection.[30] Using a mean dose of 19 Gy, 53% of 49 patients with refractory seizures became seizurefree and 20% were significantly improved at 2 years after treatment,[30] demonstrating that epilepsy associated with cavernous malformations near eloquent cortex may be treated with radiosurgery to reduce seizure frequency. Given the low bleeding risk of cavernous malformations in cortical regions and common presentation with seizures,[57] patients seeking an alternative to microsurgical resection with decreased morbidity may opt for radiosurgical treatment of medically intractable seizures associated with these cavernous malformations. In addition to cavernous malformations near eloquent cortex, deep seated cavernous malformations which are not amenable to open procedures may also potentially be amenable to antiepileptic therapy with radiosurgery for medically intractable seizures. Unfortunately these deep seated lesions have a higher risk of clinical bleeding and poor neurologic outcome,[57] and the effect of radiosurgery on this risk is still unclear.[21,24,30] Without clear evidence of the effect of radiosurgery on bleeding risk, microsurgical resection remains the standard therapy for cavernous malformations.

Long term radiosurgical complications

Although the long-term complications of radiosurgery are not yet fully characterized, it appears that these risks are minimal. There are reported cases of radiosurgery associated 'radiation-induced' malignancies, but these reported cases are extremely rare.[6,58–61] Much longer periods of follow-up must be investigated to fully appreciate the possible long term complications, as the development of new radiation-induced neoplasms requires decades to develop. A conservative estimate suggests this rate as 3% in 30 years.

The antiepileptic radiosurgery mechanism

Although radiosurgery has been shown to reduce seizures in various forms of medically intractable epilepsies, the mechanism by which this abatement occurs is not clear. It has been suggested that radiation itself has a direct antiseizure effect. This effect has been purported to operate through several mechanisms. As glial cells are more radiosensitive than neurons, Barcia-Salorio proposed low-dose radiosurgery may reduce glial scar formation allowing increased dendritic sprouting, improved cortical reorganization and fewer seizures.[15] Elomaa proposed the antiepileptic effect of radiation is mediated through effects of somatostatin.[62] Although the clinical results of the most recent human studies suggest the therapeutic efficacy of radiosurgery is linked to necrosis of mesial temporal structures, proof for this concept would need to come from direct observation of tissue samples in patients where radiosurgery has controlled seizures. This is unlikely to occur, as only patients with persistent seizures are likely to undergo further open resective surgery.

Surrogate markers of radiation effect such as imaging changes on MRI have thus far shown mixed results. Radiation-induced edema has become evident in most patients 9–15 months following radiosurgery. These changes are usually time-limited, they are often followed by focal atrophic changes. Thus, MRI changes may not be diagnostic of true radiation necrosis. The actual mechanism by which high-dose radiation reduces neuronal hyperexcitability will not likely be found from human studies.

Although preclinical evidence and the results from two early human trials suggested control of seizures might be possible with doses of radiosurgery that were lower than those typically applied to tumors,[16,19] recent case reports also describe the failure of low-dose radiosurgery to control seizures.[22,50,51] While failure of seizure control is easy to identify, it is a much more difficult task to determine that this is due to an insufficient radiosurgery dose. The time dependence of radiosurgical effects is also a confounding factor that has not been fully explored. A consensus among different treating radiosurgical centers for when radiosurgical treatment has

'failed' has not yet been agreed upon.[32] As noted, recent, prospective results suggest that radiosurgery may have results very similar to resection where ~30% of patients will continue to have seizures.[6] The reported failures of low-dose radiosurgery are case reports and as of yet do not demonstrate a failure rate of 30%. Furthermore, radiosurgery patients who did not show adequate seizure reduction commonly had radiation doses of 20 Gy or less, and these patients showed little evidence of radiation-induced necrosis in their pathologic specimens.[22,50,51] Thus, the best evidence to date from human and animal experiments suggests that there is a steep dose-response effect for seizure reduction, that some neuronal damage is required to produce seizure abatement, and that the dose required to eliminate seizures is very close to the absolute tolerability of human brain tissue.

Conclusions

Recent data suggests radiosurgery is indeed effective at reducing epileptiform activity and seizures in several forms of medically intractable epilepsy. In animals, the low doses of radiation required to be therapeutic have not been shown to cause histologic changes, disruption of normal neuronal firing patterns or significant learning deficits. When multiple isocenters are employed, and animals are observed over longer time periods, the patterns of changes seen on MRI closely mimic those observed in human trials and histological analysis indicates that structural lesions are created. Animal studies have not yet proven if the antiepileptic effects of radiosurgery are due to tissue damage sufficient to cause functional ablation and necrosis or if seizure activity has been eliminated in still functional parenchyma. However, the available data suggest that it is necessary to produce changes on MRI consistent with tissue damage in order to eliminate seizures in humans.

Recent prospective trials suggest that radiosurgery may be an effective and safe treatment for medically intractable epilepsy associated with MTS. Prospective trials with larger numbers of patients will be required to establish radiosurgery as a standard therapy for MTLE. Further promise is shown in expanding the utility of radiosurgery for seizure control in medically intractable epilepsy associated with cavernous malformations and hypothalamic hamartomas. Radiosurgery may prove to be especially appealing in treating lesions near eloquent cortex or deep seated lesions when open microsurgical resection may not be feasible without significant morbidity. As the true long-term toxicity of radiosurgery is not known, patients treated with this modality should be carefully followed.

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125 Vagal nerve stimulation: experimental data

S Chabardès, I Najm, and HO Lüders

Introduction

Vagus nerve stimulation (VNS) is a worldwide applied technique for the treatment of intractable epilepsy that cannot benefit from resective surgery. Recent clinically-controlled trials have reported a 50% seizure control rate in about 30% of patients'. However, its efficacy seems to vary among teams and the type of patients who can benefit from this technique is so far unknown, despite more than 26,000 people treated worldwide. Moreover, the mechanisms of action are still not fully understood despite increasing interest in this field.

The purpose of this chapter is to give a critical overwiew of the experimental data existing in this field together with our experiments performed on rats at the Cleveland Clinic Foundation.

On the efficacy of VNS against seizures induced in animals

Original reports

At the end of the eighties, several teams reported the effect of repetitive VNS on seizure activities in generalized, or partial, secondary generalized models of epilepsy. It was based on preliminary observation[2,3] which indicated that low-voltage vagus nerve stimulation could significantly reduce spikes from a neocortical focus produced by topical application of strychnine. First, Zabara *et al*. reported[4,5] their experience in a chemically-induced generalized model of epilepsy using intravenous injection of strychnine in 20 dogs. They found that electrical stimulation of unilateral vagus nerve at a frequency that ranged from 30–80 Hz could abort seizures within usually less than 1 sec. This effect could last several minutes (up to 20 min) after the end of stimulation. These original very exciting results should be balanced at several levels: first, the seizure activity was not directly monitored by EEG recording, but only by EMG electrodes implanted bilaterally in both gastrocnemius muscles. Second, the authors monitored the EKG and respiration and used them as markers to asses that electrical current was properly delivered to the VN. They showed that in each case, there was a rapid but consistent bradycardia at the onset of the stimulation period together with hyperventilation. As the EEG was not monitored, one could easely argue that the powerfull cessation of 'EMG seizure' was in fact a nonspecific response to a severe vegetative dysfunction.

In 1990, Lockard *et al*.[6] were the first to report the effect of VNS on a monkey model in a robust, well-designed study. They used four animals, all equipped with an epidural EEG screw and who exhibited chronic, secondary generalized, spontaneous partial motor seizure obtained after subpial injection of alumina gel in the left central cortex. Seizure activity and severity was assessed for several months with chronic video-EEG monitoring. Left VN was stimulated in two animals, and right VN was stimulated in the remaining two. Each constant-current stimulation was delivered at the onset of every spontaneous seizure and lasted for the whole seizure. This stimulation period lasted 2–6 weeks preceded and followed by at least 2 weeks of no stimulation period (baseline). Stimulation parameters were as follows: frequency from 50–250 Hz, pulse width from 0.5–0.6 ms. Two monkeys became nearly seizure free during the stimulation period, while two others were not ameliorated. According to the authors, VNS had no consistent effect on either seizure severity or EEG interictal spikes and concluded that if VNS could influence 'the epileptogenic process', its efficacy was 'still in question'.

At the same time, Woodbury and Woodbury[7] reported the effect of VNS in the Pentylène-tétrazole (PTZ) and the 3-mercaptoproprionate (3-MP) model in rats which creates convulsive status. In an additional experiment they also used maximal electroshock seizure (MES) in wakeful rats. They showed that VNS was effective in preventing seizure, but that VNS could not terminate ongoing seizures in both PTZ and 3-MP models. They found that delay between onset of seizure, onset of stimulation, and seizure duration was significantly positively correlated. In the MES model, the authors found that VNS could not change the total duration of seizure but could prevent the tonic phase when C fibers of VN could be properly stimulated.[8]

The general conclusion of the authors was that VNS was effective in these three models, but the design of the study did not allow random stimulation periods. Moreover, the fact that rats which were not improved (number was not given) were all suspected not to have received the appropriate electrical stimulation properly because of technical problems is questionable as the anatomical study of VN integrity was not described in the paper.

Later, McLachlan[9] reported experimental data on anesthetized rats rendered epileptic by application of local penicillin (PG) in the motor cortex and ip injection of PTZ in an attempt to quantify the effectiveness of VNS on PG-induced

interictal spikes and the tonic-clonic phase of PTZ-induced seizure. The vagus nerve was stimulated using a grass system with biphasic square-wave pulses delivered at the onset of seizures. The stimulator was set at the following parameters: 0.01–1.2 mA, 20 or 50 Hz, 0.5 ms pulse duration, 1–20 s in duration. Mean spike frequency decreased significantly from 42 ± 11 to 28 ± 11 (mean reduction: 33%, $p < 0.001$) and the effect lasted 20 s after stimulation.

Amplitude of residual high voltage spikes was also reduced during and immediately after VNS. This effect appeared to be positively correlated with the current amplitude, while variation of frequency did not change the response. VNS could also decrease the duration of PTZ-induced seizure, and seemed to affect the clonic component of seizure which has been shown to involve the rostral mesencephalon, while tonic phase is more integrated in caudal brainstem structures. This point was not in agreement with the aforementioned study of Woodburry *et al.*[8] which reported that VNS was effective on the tonic phase in the MES model.

As in the study of Zabara *et al.*, VNS had strong effect on the heart with a mean 50% reduction in heart rate and caused immediate respiratory arrest for a maximum of 5 s. Interestingly, tail heating had the same effect on spike reduction compared to VNS, suggesting that stimulation of C-unmyelinated fibers could influence in a non specific manner the interictal spikes, independently from the type of stimulus (electrical or physical) and that the effect was not due to the location of the stimulation. The author concluded that this reduction in interictal spike frequency was real, but was probably due to a nonspecific arousal.

Recent studies

Cleveland clinic experience: VNS and kainic acid limbic seizure model in rats

Our group performed an experimental trial in the kainic acid limbic model of epilepsy in rats treated by VNS stimulation using the same parameters usually used in humans.

Materials and methods

Seven male Wistar rats were used in this study. Cervical surgery using microsurgery tools was performed under general anesthesia (ketamine) in order to implant one single-cuff electrode around the left vagus nerve. These electrodes were specially designed to be implanted in rats (Cyberonics). The diameter of the cuff electrode was 1.0 mm and the two contacts were 1 cm apart. Each electrode was placed around the VN after having isolated the VN itself from the carotid artery to minimize current linkage to surrounding structures (see Figure 125.1). VNS lead was secure with cement at the cranial level and was connected to the cyberonics stimulator during the trial. During the same surgical procedure, four epidural electrodes located bilaterally at the frontal and parietal level were inserted and two electrodes were stereotactically and bilaterally inserted into the posterior hippocampus according to the atlas of Paxinos. One week later, under continuous video-EEG monitoring, kainic acid was injected intraperitoneally in order to get reproducible limbic, secondarily-generalized status. The design of the study is illustrated

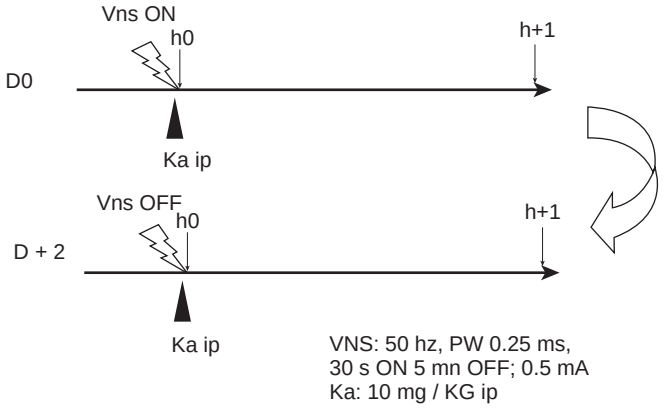


Figure 125.1 Design of the study.

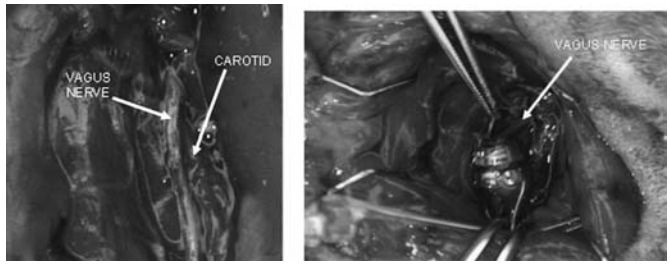


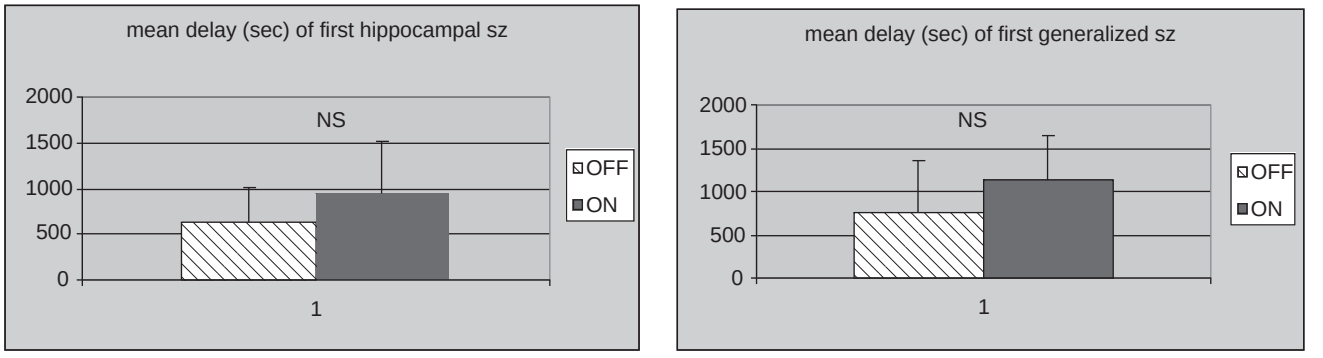
Figure 125.2 Surgical view of a VNS electrode surrounding the left VN in rat.

in Figure 125.2. Briefly, each rat received ip KA and at the same time, VNS was randomly turned on or off for 1 hour. Two days later, the same rat was again rendered epileptic using the same dose of KA and VNS was turned on or off depending on the previous randomisation. Each rat was then sacrificed after the experiment to assess the integrity of VN and the anatomical position of the VNS and hippocampal electrodes. EEG files were stored and reviewed offline. We particularly paid attention to the delay of first limbic and generalized seizures, the mean number and duration of limbic and secondarily generalized seizures. The off-period of each trial constituted the control situation.

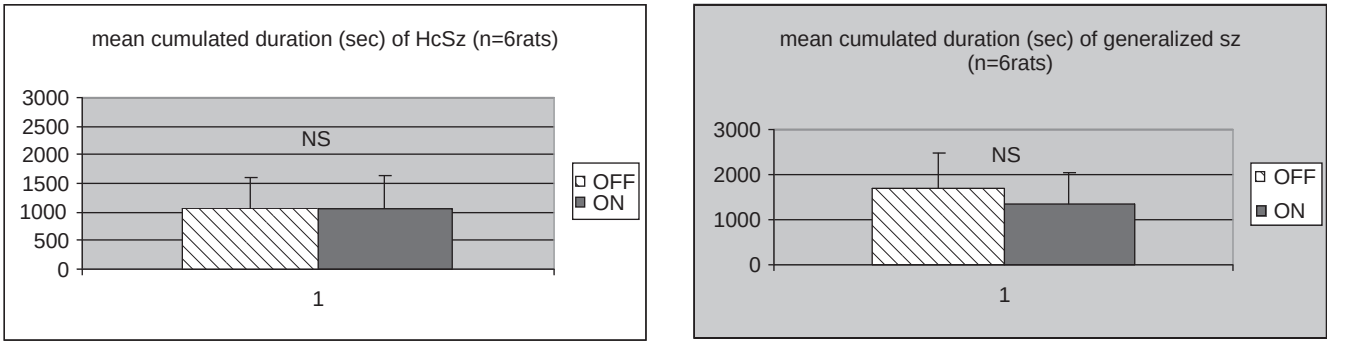
Results

Details are presented in Graphs 1–4 and Figure 125.3. No artefact was seen on epidural EEG during the ON period of stimulation. One rat died when the VNS was turned ON. In two rats out of six, there was a trend to delay the first occurrence of hippocampal or generalised seizure, but in one rat. this delay was shorter. In one rat out of six, VNS worsened the accumulated duration of hippocampal or generalized seizure, while in three animals, accumulated duration of generalized seizures tended to be smaller during the VNS period.

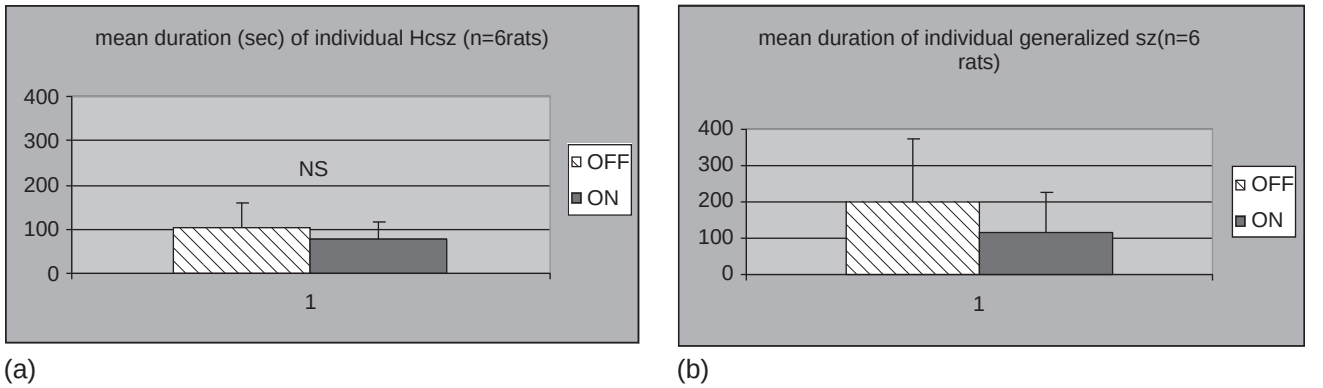
In our experimental conditions, when data were pooled, VNS did not change significantly mean delay of first hippocampal and generalized seizure, mean accumulated duration of hippocampal and generalized seizure, nor mean duration and number of individual hippocampal and generalized seizures for 1 hour following KA ip injection. At the individual level, VNS in our experiment had in some case both anticonvulsive or proconvulsive effects.



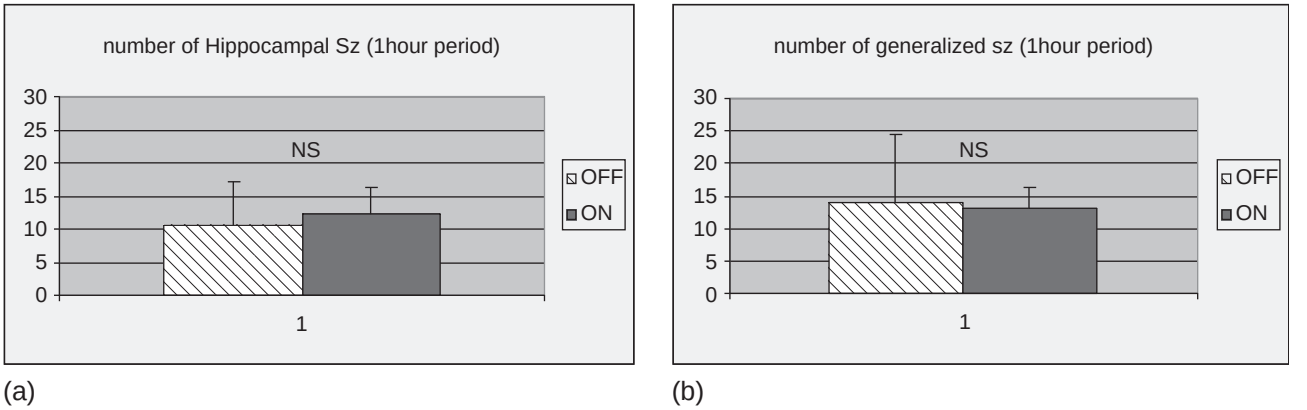
Graph 1 Mean delay of occurrence of the first hippocampal seizure (a) and generalized seizure (b).



Graph 2 Mean cumulated duration of hippocampal seizure (a) and generalized seizure (b).



Graph 3 Mean duration of individual hippocampal seizure (a) and generalized seizure (b).



Graph 4 Mean number of hippocampal seizure (a) and generalized seizure (b).

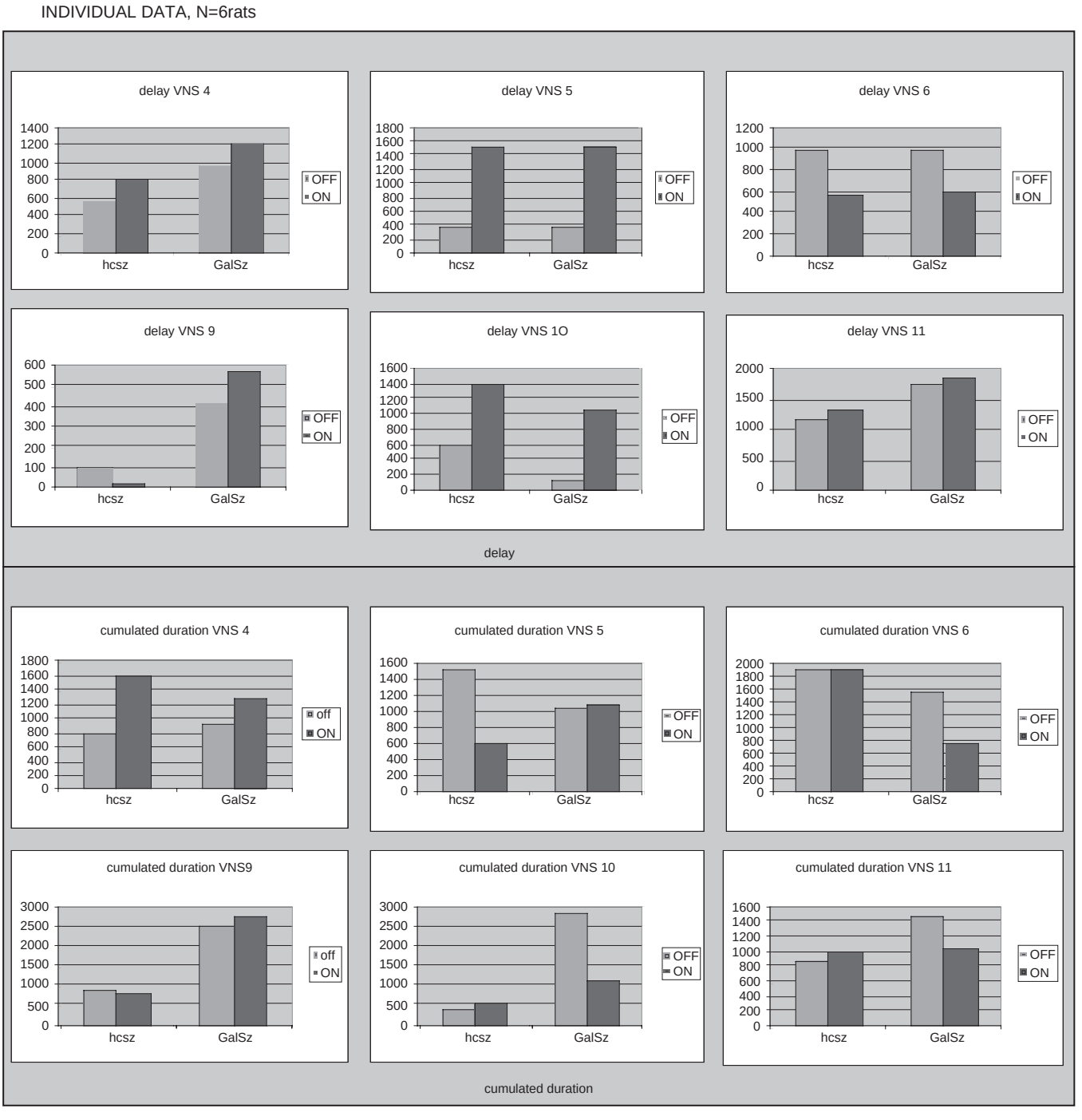


Figure 125.3 Graphs of all the six rats used in the experiment and showing the delay (upper part) and the accumulated duration (lower part) of limbic and secondarily generalized seizures. Note that both anticonvulsive or pro-convulsive effects can be seen.

VNS and amygdala-kindled seizures in rats

The group from Ghent in Belgium[10] have very recently reported the effect of VNS in amygdala-kindled seizures in rats. In a first paradigm, a group of eight rats received left-VNS 2 h prior to daily kindling stimulation. The result of this first experiment showed that VNS could not impact kindling epileptogenesis and had no prophylactic anticonvulsive effect on stage-5 seizures. Moreover, convulsive duration was significantly longer when VNS was applied prior to the kindling phase as compared to control situation. In a second paradigm, left VNS was applied 2 s after induction of the kindling stimulus that was determined to elicit a stage-5 seizures. The results of this experiment were as following: (1) the mean after discharge duration was significantly reduced after a 60 s VNS train compared to the control situation (50% reduction aproximatively). (2) However, only two out of six rats showed a complete suppression of stage-5 seizures. The authors concluded that VNS had both anticonvulsive and proconvulsive effects on amygdala-kindled seizures. This study is in accordance with our experiments described above in limbic seizure induced by ip injection of Kainic Acid.

VNS and absence seizures

The same group have also studied the effect of VNS in genetic absence epilepsy rats from Strasbourg (GAERS).[11,12] Briefly, 39 rats were used for this experiment in which VNS was applied acutely and chronically. In the first paradigm (acute experiment), a randomized cross-over design was used and VNS was applied when a spike and wave (SW) discharge appeared on the EEG and the stimulation was stopped at the end of the SW. The results of this experiment showed that mean duration of SW was significantly longer compared to the control situation and that VNS acutely applied worsened absence seizures. In the second paradigm (chonic stimulation), VNS was applied for 1 week after a first week of baseline. Compared to the control situation, VNS did not modify the number of SW or the mean and accumulated duration of SW. The authors concluded that a longer period of stimulation might be necessary to modify absence seizures in this model. This study does not confirm prior studies that showed that VNS was effective in another model of acute absence seizures induced by ip injection of PTZ.[13] In the PTZ model, Takaya *et al.*,[14] concluded that a preventive effect of VNS was seen in about 1/3 of rats and that this effect was better when the stimulation lasted 60 mn before the beginning of the PTZ injection.

According to the literature, PTZ-induced seizures are sensitive to VNS, whereas VNS appears to be ineffective on genetically determined absence seizures. The anticonvulsivant effect of VNS in this model is not related to the site of stimulation as demonstrated by Fanselow *et al.*,[15] who reported a 78% reduction of seizures in the same model using acute, trigeminal nerve stimulation.

VNS and maximal electroshock model in rats

Krahl *et al.*[16] have recently highlighted that the Locus Coeruleus was involved in the circuitry necessary for the anticonvulsivant effects of VNS. For this experiment, the authors used the maximal electroshock seizure (MES) model in rats and compared the severity of seizures during VNS, with and without chemical lesion of the locus coeruleus. They showed that VNS was effective on the severity of MES and that this effect was inhibited when the Locus Coeruleus was lesioned. In this report, VNS did not modify the number of seizures but their severity was expressed by a reduction of duration of hind limb extension.

Conclusions

VNS has complex effects on seizures and studies on animal models of epilepsy are difficult to analyze. It seems that, as in human studies, partial seizure might be influenced in approximatively 30% of cases, and that in cases of generalized epilepsy, studies can show improvement or at the opposite, no effect and sometime worsening.

Technical issues in animal experiments might explain in some part the difficulty to clearly demonstrate a consistent effect, like the difficulty to conduct chronic, long-lasting stimulation in animals, or the difficulty in stimulating specifically afferent fibres in the VN. Moreover, specific electrodes which allow better contact with fibres of VN should be designed in order to deliver current with much better efficacy. Animal experiments cannot so far answer the following question: does efficacy improve after chronic stimulation as compared to human pathology? Could the fibrosis surrounding the fibers of VN not explain in some part the heterogeneity of effects seen in animal experiments and in humans? Are we sure that the ratio of ON stimulation period compared to the OFF period is sufficient and can be applied in animal models?

We still believe that, as in other DBS techniques which are currently challenged, well-conducted animal experiments are mandatory to study the circuitry involved during VNS and that modulation of this circuitry either by lesion or activation could give to the scientific community strong experimental data supporting the antiepileptic effect of this therapy.

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126 Vagal nerve stimulation:surgical technique and complications

WE Bingaman

Introduction

Vagal nerve stimulation (VNS) is FDA approved for the treatment of medically intractable partial onset epilepsy in patients over 12 years old. Efficacy and safety issues have been addressed in several large clinical trials and will not be addressed here.[1–4] The current device is manufactured by Cyberonics (Houston, TX) and includes a pair of helical electrodes (2 mm or 3 mm diameter), a battery-powered generator (models 100, 101, and 102), a tunneling tool, software and programming tools, and supplies for the patient (Figure 126.1). The aim of this chapter is to review surgical technique and perioperative management.

Background and patient selection

Indications for VNS include patients with medically intractable partial epilepsy without resective surgical options or those where surgery is contraindicated for medical reasons. Contraindications to implantation include patients with history of previous left neck surgery or prior cervical vagotomy. Relative contraindications may include pregnancy, asthma, chronic pulmonary disease, active peptic ulcer disease, and insulin dependent diabetes mellitus. Additionally, implantation in patients requiring periodic magnetic resonance imaging (MRI) should be avoided because of safety concerns in the higher Tesla magnetic fields now commonly employed. Common adverse effects include coughing, hoarseness, dyspnea, and headache. These effects are seen during stimulation and tend to habituate with time. Serious adverse effects have been reported and include vocal cord paralysis, infection, Horner's syndrome, lower facial muscle paresis, and cardiac arrest. Sudden unexplained death has also occurred, but not at a rate different than the epileptic population.[5] Mechanical complications can occur such as lead fracture or failure and generator malfunction.

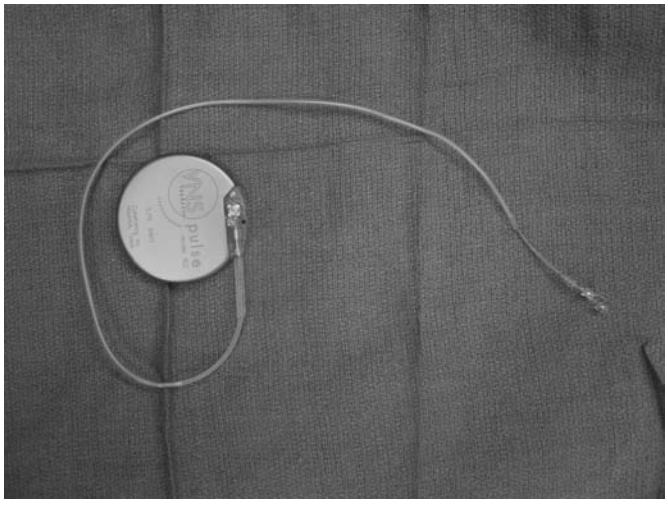

Figure 126.1 VNS Model 102 generator and electrodes. (Cyberonics, Inc. Houston, Texas).

Patients with epilepsy uncontrolled by anticonvulsant medications may be candidates for VNS. The definition of medically intractable generally includes a description of an adequate drug trial without unacceptable side effects. The exact definition of an adequate drug trial is not clear. Because the efficacy of VNS is similar to a new medication trial, it is the author's opinion that VNS candidates should exhaust medication options prior to consideration for VNS therapy.

Patients should also undergo a routine pre-surgical evaluation to exclude resective surgical options. This may include inpatient video-EEG monitoring and magnetic resonance imaging of the brain. Other studies might include positron emission tomography (PET) and ictal cerebral blood flow studies (SPECT). The patients are then presented at a multidisciplinary epilepsy conference and management options are discussed including VNS implantation. The patient is then instructed to keep a seizure diary for three months prior to implantation. Prior to surgery, the patient and family are counseled on post-operative expectations and side effects of stimulation. They are given a videotape of patient information published by Cyberonics.

Although not FDA approved for treatment in the pediatric population, there is growing evidence that VNS is safe and similarly effective in this population.[6–8]

Pre-operative discussion

The patient and family should be educated about the nature of the device being implanted. This includes a discussion of the expectations of the patient and the reality that they will likely not be seizure free. They should be counseled that the device will need a battery change in the future. They should be informed about the avoidance of MRI scanning while the VNS

electrode is in place around the vagus nerve. In addition, the use of diathermy is forbidden. Routine side effects are discussed (mainly hoarseness during VNS 'on times'). Complications such as the risk of infection and the risk of injury to the carotid artery, jugular vein, or vagus nerve should also be mentioned. The patient is also supplied with magnets from Cyberonics which enable the user to turn on or off stimulation. The use of these magnets is straight forward and should be explained to the patient and family members.

Finally, the patient should be counseled about the risks of revision surgery should the lead need to be removed or replaced. This includes an increased risk for vagus nerve injury from surgical trauma that is difficult to quantify as large numbers of revision surgeries have not yet been performed at many centers. At our institution, removal with or without replacement of the electrode has been done in ten cases with one case of transient hoarseness felt secondary to surgical manipulation.

Anatomy and surgical technique

The vagus nerve is a mixed cranial nerve containing approximately 80% sensory fibers. Efferent fibers innervate the larynx and provide parasympathetic control to the heart, lungs, and abdominal viscera. The right vagus nerve innervates the sinoatrial node of the heart while the left innervates the atrioventricular node. In the dog model, stimulation of the right vagus nerve caused more cardiac slowing then the left.[9] For this reason, the left human vagus nerve is implanted. Adverse cardiac complications have not been commonly seen, perhaps because stimulation of the nerve can be done on a segment away from the origin of the cardiac branches. The nerve is suited for implantation in the cervical region where it courses between the cervical carotid artery and the jugular vein. A segment of nerve approximately 3 cm in length is easily dissected in this region. It is our practice to begin with a segment low in the cervical region as patients may need another VNS electrode implanted on a different part of the nerve in the future.

The procedure itself is straightforward and is performed by any surgeon familiar with neck anatomy. Neurosurgeons are ideally suited because of the familiarity with epilepsy and their active roles in comprehensive epilepsy centers.

On the day of surgery, the electrode and generator are inspected and tested prior to the procedure. A spare generator and electrode should be available in case the primary device fails. Once verified that the equipment is functioning, preoperative antibiotics are given and the patient undergoes a general anesthetic.

A primary surgeon and assistant participate. The patient is positioned supine on the table with the anesthesia team at the head. The primary surgeon stands at the left side of the neck, his assistant opposite him. The patient's head is positioned on a donut and slightly extended and turned to the right. The surgeon may use a roll under the scapula to help extend the neck. After preoperative antibiotics are given, the neck and chest is prepped with betadine scrub and paint solutions. The electrodes are implanted in the left neck by either a 'carotid' incision or a transverse 'collar' incision. A 3–4 cm incision should be centered at mid-neck level (cricothyroid interval) and on the anterior border of the sternocleidomastoid muscle (Figure 126.2). The skin is incised with a #10 scalpel and the skin edges widely undermined with Metzenbaum scissors. The platysma muscle is divided in the direction of its fibers and the deep cervical fascia is opened to identify the sternocleidomastoid muscle. This muscle is mobilized and retracted laterally to expose the neurovascular bundle. This bundle is then incised to expose the carotid artery and jugular vein. The vein is retracted laterally and the main trunk of the vagus nerve is usually found deep between the artery and vein. Approximately 3–4 cm of nerve should be mobilized from surrounding loose connective tissue. Stay sutures in the carotid sheath can be utilized to deliver the nerve towards the surgeon. Mobilization and handling of the nerve should be done with fine forceps. Care must be taken to avoid injuring the main trunk or one of the branches.

Once the nerve dissection has been completed, the left chest incision is marked along the anterior axillary line and opened with a #10 scalpel. A subcutaneous pocket over the pectoralis fascia is created with sharp and blunt dissection. The pocket must be large enough to accommodate the generator while avoiding strain on the incision line.

The electrode array is removed from the sterile package and brought onto the surgical field. Skin edges should be isolated with sterile gauze and the electrode tunneling device passed from the neck incision to the chest incision in a plane just above the sternocleidomastoid muscle, being careful to pass superficial to the clavicle. Once the tunneler is passed, the metal rod is removed leaving the plastic sheath in place. The electrode cables are then inserted into the plastic sheath and the sheath pulled through to the chest. The ends of the cable are wrapped in a sterile towel until connected to the generator (Figure 126.3).

The electrodes are implanted on the vagus nerve by gently winding the electrode spirals around the nerve. The electrode array consists of three spiral coils. The first is not an electrode but a tethering coil, which is placed around the distal (caudal) portion of the nerve. The next is the cathode electrode and the most distal is the anode electrode, which ends up being placed on the most cranial portion of the nerve (Figure 126.4).

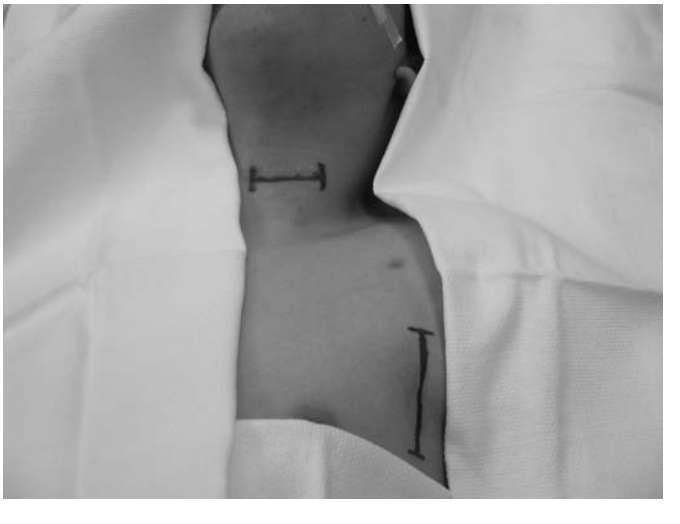

Figure 126.2 Location of incisions: left neck and left axilla.

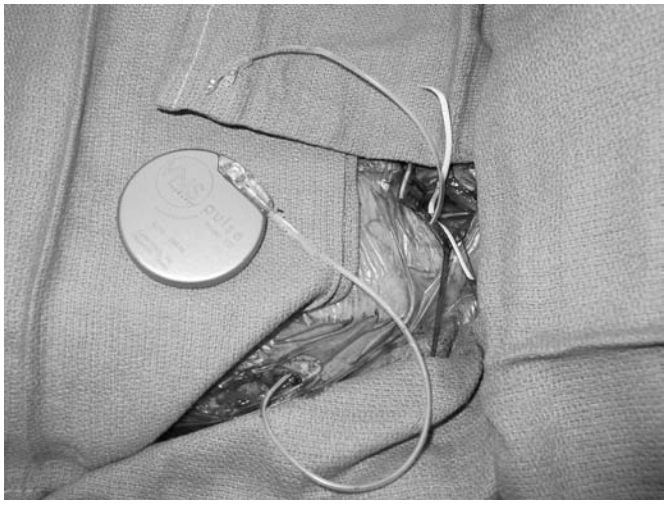

Figure 126.3 VNS electrode tunneled from neck to chest.

The actual electrode coils should be handled with care to prevent electrode breakage. Each coil has a small string attached, which is useful for deploying it around the nerve. The deployment of the electrode coils should be done with the primary surgeon and assistant surgeon working together to pass the electrode spirals around the nerve without placing undue tension on the electrodes or the nerve. Fine jeweler's forceps work well during this stage of the procedure. Once coiled properly around the nerve, a strain relief loop should be created above the carotid sheath with excess electrode cable. The loop is tied down with silicone ties provided in the electrode kit. These ties should be sutured to the cervical fascia deep to the platysma muscle. Avoid tying to muscle as the electrode may shift position when the patient moves their neck. Care should be taken to avoid inadvertently displacing the electrode from the vagus nerve during intraoperative manipulation and wound closure.

The pin is then connected to the generator at the chest incision, making sure to slide the connector all the way in and then tightening it with the wrench provided. This wrench will give way when the appropriate torque is reached. For older model electrodes with two pins, the cable marked with a white stripe is the positive electrode and should be placed into the model 102R generator in the positive receptacle. The other cable is the negative electrode and goes into the negative receptacle. Care must be taken to ensure the electrode pins are placed completely into the generator in the appropriate receptacle and tightened securely.

Figure 126.4 Electrode array deployed around nerve.

The neurologist or intraoperative neurophysiologist may assist you at this stage. The computer and hand-held wand are powered up. Make sure the batteries in the hand-held wand are new. Place the hand-held wand in a sterile drape and place it over the generator in the surgical field. During this programming, lead impedance and all connections are tested to verify integrity of the system. A 1-minute lead test is then performed with a stimulus delivered at 20 Hz frequency, output current of 1 mA, and a pulse width of 500 microseconds. During this test, the patient's vital signs and EKG are monitored for bradycardia. Some centers will then turn on the system at the lowest setting, while others prefer to wait 1–2 weeks before initiating stimulation therapy.

Once the system is tested, the generator is internalized and sewn to the pectoralis fascia with a permanent suture (prevents generator migration). Both incisions are then irrigated with antibiotic solution and closed anatomically with self-absorbing skin sutures. The patient is then discharged to home after a short period of observation in the recovery room. Prior to discharge, the patient should be assessed for vocal cord function.

Post-operative management and complications

Patients should be counseled to observe the wound for signs of infection. The sutures are self-absorbing and need not be removed. Return to normal preoperative activities is allowed after 48 hours. Patients should be warned that this therapy will not result in cessation of seizures and they should continue to practice seizure precautions and continue their prescribed anticonvulsant therapy. A return to care in two weeks with the treating neurologist is indicated to begin or increase VNS stimulation.

In 1994, Ben-Menachem *et al*. reported the most common side effects of VNS as hoarseness and throat pain.[10] Other reported adverse effects include dyspnea, coughing, and paresthesias. Importantly, the study concluded that VNS does not carry the CNS side effects associated with oral anticonvulsant therapy. The effects on vocal cord function have been reported in the otolaryngology literature with most studies reporting some effect on vocal cord function both related to implantation and ongoing chronic stimulation.[11,12] Additionally, rare cardiac complications have been reported.[13–15] In a 2004 report, Ali *et al*. described three patients who experienced asystole with complete heart block during intraoperative lead testing at a current of 1 mA.[13] The cardiac rhythm strips from these patients demonstrated a complete atrioventricular nodal block. In all patients this was transient and resolved with cessation of stimulation. One patient then went on to successful VNS implantation. Similarly, asystole and bradycardia were reported in 1999 by Asconape *et al*.[14] These cases also occurred during lead testing under anesthesia with no permanent sequelae. As Heck *et al* point out, 'occurrence of bradycardia is extremely rare when FDA-approved VNS parameters are used' (output currents in the range of 0.25–3.5 mA).[15]

The most common complication is wound infection. This occurs at the rate of 3–8%.[16–19] When identified early, antibiotic therapy should be initiated with the hopes of preventing device removal. Often however, both the generator and electrode need to be removed until the infection is cleared. Once cleared, the device can be re-implanted, typically 3–6 months later.

Rarely, injury to the vagus nerve may occur during implantation and will result in permanent voice change. Finally, mechanical device complications such as generator failure or lead breakage occasionally occur.

Revision surgery is necessary at generator battery end-of-life and usually involves opening the chest incision with replacement of the generator. Prior to revision surgery, consideration should be given as to which model VNS generator and electrode the patient has implanted, as the older electrode design (two pin) is not compatible with the latest generator (model 102, single pin). In the event of lead failure requiring lead revision, a second generator may need to be implanted. In this case, the hospital will lose the cost of the opened but not implanted generator. This scenario has been seen in the case of the patient with a model 100 or 101 generator and two-pin electrode who comes in the hospital for a battery change. Typically, a model 102R (two-pin compatible generator) would be connected to the existing electrode and the lead test carried out. If the lead impedance is a problem, then the electrode will need to be revised and perhaps the single-pin electrode implanted, which is not compatible with the 102R generator. Once a generator has been opened it is no longer a reusable item. Therefore, the surgeon needs to verify and check all components prior to opening the sterile packaging. We have found it useful to first check the existing electrode's impedance by disconnecting the existing generator and electrode and then reconnecting it tightly and running a lead test prior to opening any new VNS components (assuming some battery life is left in the existing generator). If the lead is a problem, the single-pin electrode would be implanted along with the 102 generator. If the lead is ok, the 102R generator would be implanted with the existing two-pin lead. Also, the surgeon should personally interrogate the patients implanted device to confirm battery life and lead impedance prior to the planned procedure. If any question exists as to which device is implanted or lead integrity then an X-ray of the device should be done prior to the revision surgery. In any case, informed consent should be obtained to include lead revision if necessary.

Occasionally the electrode lead will need to be replaced or removed due to breakage, high lead impedance, infection, necessity for MRI scanning, or patient desire. This can be undertaken, but entails risk to the vagus nerve. A recent series of seven patients underwent microsurgical removal without apparent injury; however the small number of patients makes it unclear exactly what the risk is.[20] As previously mentioned, the author has one case out of ten of transient vocal cord paralysis with electrode removal. Certainly, meticulous dissection of the electrode coils around the nerve is required, usually with loupe or microscopic magnification. Patients should be counseled on the risk of vagus nerve injury.

Summary

Vagal nerve stimulation therapy offers hope for highly select patients not responding to other more traditional epilepsy treatments. Despite initial high expectations, VNS therapy leads to a significant clinical response in only the minority of patients. Realistic outcomes and the necessity of avoiding MRI scanning once implanted should be carefully discussed with each patient prior to the operative procedure. Long term effects of VNS therapy remain unknown.

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127 Vagus nerve stimulation: human studies

T Loddenkemper and AV Alexopoulos

Introduction

History

Early reports of vagus nerve stimulation in patients with seizures date back to the early 1880s, when the New York neurologist James Leonard Corning (1855–1923) experimented with carotid artery compression and transcutaneous vagal nerve stimulation.[1] These methods were reinvestigated after further development of the EEG in the late 1930s, when first studies of VNS on EEG fast activity in cats were observed.[2] Suppression of interictal spiking in cats in a strychnine epilepsy model was first observed by Zanchetti in 1952,[3] and later confirmed in the same model by Stoica and Tudor.[4] Additional evidence of EEG desynchronization by VNS in cats was collected in the 1960s.[5] Evoked cortical potentials from VNS were first described in 1951 [6] and further characterized in rabbits, monkeys and cats in the 1970s.[7–9]

The effect of vagus nerve stimulation on epileptiform activity in humans was reexamined by Jacob Zabara.[10] Based on the theory that vagal nerve stimulation suppresses vomiting and gastro-intestinal motility,[11] Zabara hypothesized that VNS could have a similar effect on seizures and tremors. Zabara investigated seizures induced by pentylenetetrazol in dogs. Left vagal nerve stimulation was found to decrease seizure activity despite ongoing pentylenetetrazol infusion.[10] Several other investigators were able to reproduce these findings in other animal models, such as maximal electroshock and pentylenetetrazol-induced seizure models in rodents, and the alumina-gel model in primates.[12–14]

The first human patient, implanted in 1988 by Penry, became seizure free.[15] Further patients were implanted by Uthman *et al.*[16] The first randomized active control study was performed in 1992 and followed by five more studies that led to the FDA approval of the device on July 16th 1997 (Figure 127.1).

Anatomy and physiology of vagus nerve stimulation in humans

Anatomy of the vagus nerve

The vagus nerve consists of 80% afferent fibers, from the visceral organs – such as heart, lungs and gastrointestinal tract – from gustatory sensors in the mouth, and from a small skin area adjacent to the ear. Afferent fibers connect in the brainstem, in particular in the nucleus tractus solitarius and then project to higher centers, such as the thalamus, hypothalamus, amygdala, and insular cortex. Efferent fibers innervate the heart, lungs, and gastrointestinal organs, and also provide some motor innervation to voluntary muscles of the larynx and pharynx.

Efferents of the vagus nerve

Efferents include autonomic fibers to the visceral organs including heart, lungs, gastrointestinal tract and kidneys.[17] These efferent fibers originate from the medullary dorsal motor nucleus and the ambiguous nucleus and synapse with neurons of parasympathetic ganglia located in the periphery near the innervated structures. Interestingly, there is specialization of the left and right vagus nerve with respect to innervation of the heart. The right vagus nerve subserves the cardiac atria, whereas the left vagus is more closely related to the cardiac ventricles.[18] Consequently, the left vagus nerve is selected for stimulation in order to theoretically decrease the risk of cardiac side effects such as stimulation-induced dysrhythmias.

Additionally, efferent motor fibers originate from alpha-motor neurons in the nucleus ambiguous and supply the vocal cords as well as other laryngeal and pharyngeal muscles. These fibers are implicated in the generation of current dependent stimulation-induced side effects, such as hoarseness, vocalization and vocal stridor.

Afferents and projections of the vagus nerve

Afferents of the vagal nerve include information on visceral sensation from the larynx, pharynx, and visceral organs, somatic sensation from an area around the ear and taste from the lower pharynx. Cell bodies of these afferent neurons are mostly located in the superior and inferior vagal ganglia near the jugular foramen. Fibers connect in the dorsal medulla and synapse in the nucleus of the tractus solitarius (NTS), the nucleus of the spinal tract of the trigeminal nerve, the medial reticular formation, the area postrema, the dorsal motor nucleus of the vagal nerve and the nucleus ambiguus.[19–25]

The NTS is a bilateral tube-like structure within the rostral pons and the dorsal medulla oblongata. Each nucleus receives afferents from both the right and left vagus nerves. In addition to vagus afferents the NTS receives and processes multiple other projections originating from the spinal cord, other cranial nerves (V, VII, and IX), and brainstem structures, including the rostral ventrolateral medulla, the dorsal tegmental nucleus of the midbrain, the parabrachial nucleus, and others. These afferents are processed in order to compute the various visceral and motor efferents. The NTS in turn projects to the parabrachial nucleus,

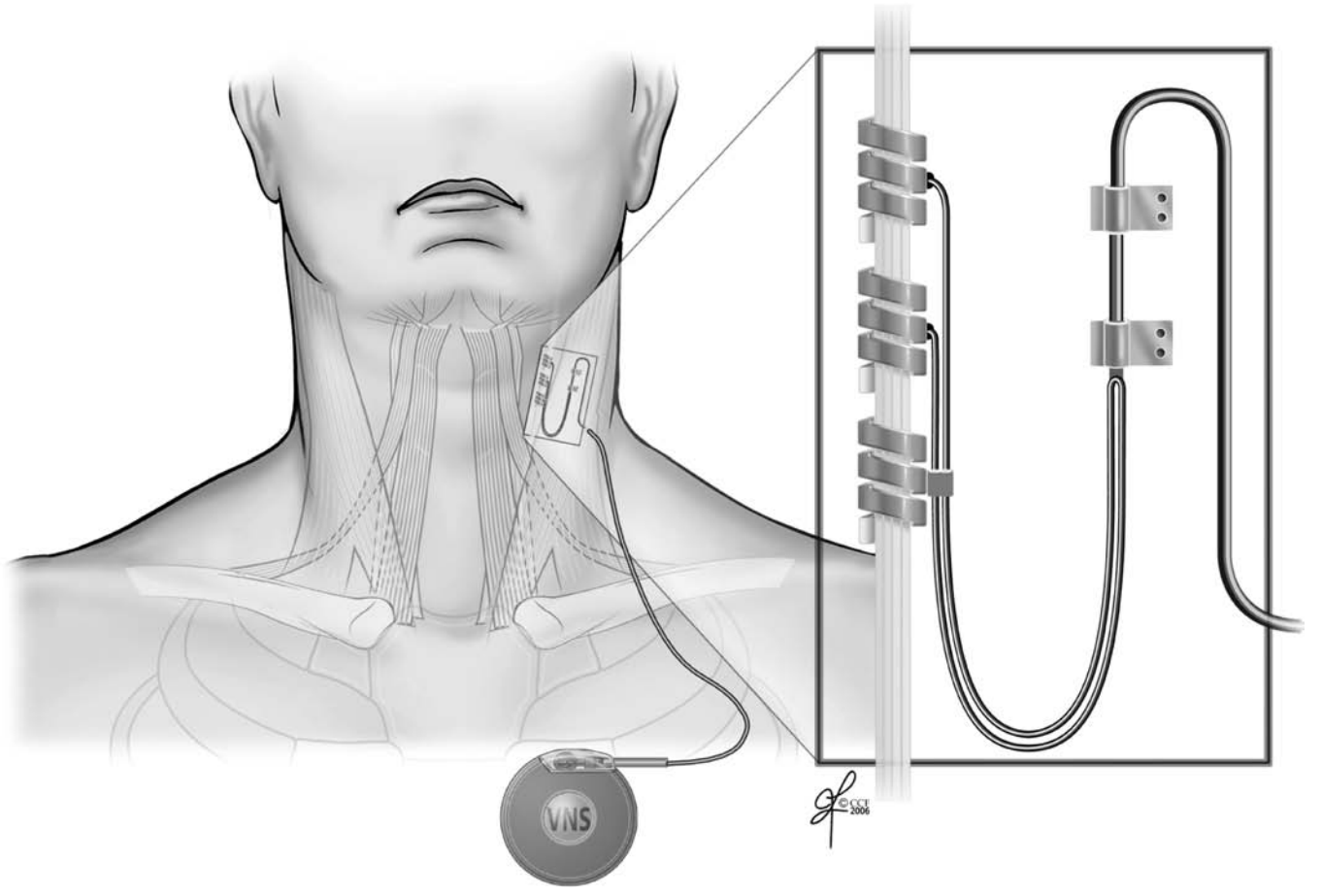

Figure 127.1 This schematic illustration demonstrates the left sided vagal nerve stimulator electrode placement and fixation.

the Kölliker-Fuse nucleus, the locus coeruleus, the raphe magnus nucleus, the inferior and medial cerebellar regions – including the vermis and cerebellar hemispheres – the periaquaeductal gray and other nuclei in the pons.[20,24,26–28] These connections allow influence on respiratory patterns and pain processing. Additionally, connections with the locus coeruleous allow either inhibitory (via the nucleus prepositus hypoglossi) or excitatory (via the nucleus paragigantocellularis) modulation of the noradrenergic system;[22,29] and connections to the raphe nuclei subserve the modulation of the serotonergic system of the brain. It has been speculated that this access to the adrenergic and serotonergic systems underlies the seizure modulating effects of VNS.[30] Afferents via the parabrachial nucleus connect to the thalamus, hypothalamus, amygdala, insula and other parts of the cortex, mediating gustatory and autonomic information.

The medial reticular formation of the medulla projects to the reticular and intralaminar nuclei of the thalamus along with other projections to the striatum and cerebral cortex.

Projections from the spinal trigeminal nucleus ascend unilaterally to somatosensory thalamic neurons, and then to the inferior postcentral gyrus and parietal lobe mediating pharyngeal and laryngeal sensation.

The area postrema is characterized by a high density of neuropeptide receptors and a capillary network with few tight junctions that facilitate neuropeptide diffusion. Afferent information to the area postrema is transmitted via blood neuropeptides. The area postrema also receives direct afferents from the vagus nerve, which project to the parabrachial nucleus and the NTS. This area is involved in controlling reflex function, such as the vomiting as well as the cardiovascular and respiratory reflexes.

The dorsal motor nucleus of the vagus and the nucleus ambiguous give rise only to efferent motor fibers targeting the larynx and visceral organs.

Cerebral projections of the vagus nerve encompass connections with the thalamus and hypothalamus (via the nucleus of the tractus solitarius, the parabrachial nucleus, the reticular formation and the spinal trigeminal nucleus), the amygdala, and various cortical areas including the insular and the prefrontal cortex (Figure 127.2).

Mechanism of action: human studies

Ictal and interictal EEG

Desynchronization of the EEG has been described as a potential mechanism in animal studies including cats,[5] rats,[12,13] dogs,[10] and monkeys.[14] However, the desynchronizing effects of VNS observed in animals could not be reproduced in human studies.[25,31,32] Hammond was not able to demonstrate suppression of interical epileptiform activity in humans.[33] Ictal EEG was modified in two patients out of five. No change in background activity was observed in this and in another study.[34]

More recent studies, however, suggest an effect of VNS on interictal EEG. Koo *et al.* followed 21 patients between 4 and 31 years at 3, 6, and 12 months after VNS implantation. Five patients with frequent interictal discharges at baseline showed

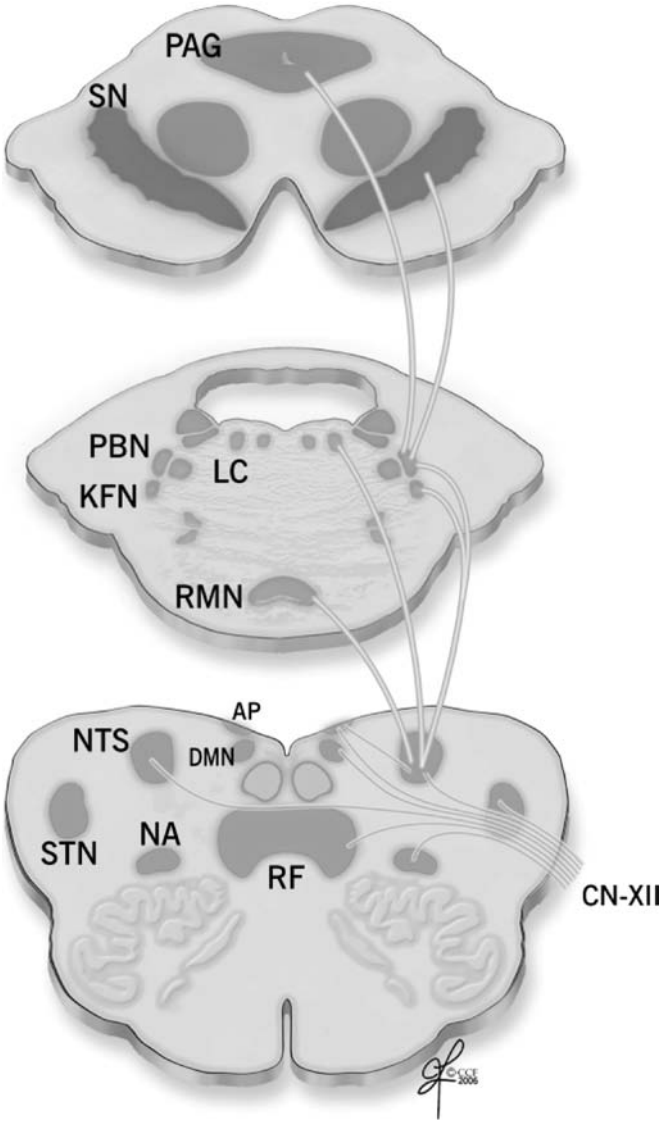

Figure 127.2 (a and b) This schema illustrates left vagus nerve afferents synapsing at several sites in the dorsal medulla, followed by projections from the pons via ascending vago-solitario-parabrachial pathways. Abbreviations: NTS – Nucleus tractus solitarius; PBN – parabrachial nucleus; PAG – periaquaeductal gray; CNA – central nucleus of the amygdale; PVN – periventricular nucleus of the hypothalamus; VPM – ventral posteromedial nucleus of the thalamus; STN – spinal trigeminal nucleus; VPL – ventral postero-lateral nucleus of the thalamus; PCG – post central gyrus; IPL – inferior parietal lobule; KFN – Kölliker-Fuse nucleus; LC – locus coeruleus; RMN – raphe magnus nucleus; PBN – parabrachial nucleus; AP – area postream; RF – reticular formation; DMN – dorsal motor nucleus of the vagus; NA – nucleus ambiguous.

synchronization of epileptiform activity, progressive increase in duration of spike-free intervals, and progressive decrease in duration and frequency of spike and wave activity with time. Patients with less frequent interictal epileptiform discharges also had a progressive decrease in the number of spikes on EEG with time, but did not show obvious synchronization or clustering of spikes. This alternating synchronization followed by more prominent desynchronization of EEG was felt to represent a potential mechanism for the action of VNS.[35]

Kuba *et al.* also reported reduction in the number of interictal epileptiform discharges (IEDs) during the period of stimulation and the interstimulation period – as compared to baseline – in fifteen patients with focal epilepsy. Interestingly, the reduction of IEDs was greater in patients, who responded to VNS (as defined by >50% reduction of all seizures).[36] These findings were reproduced by Hallbook *et al.* in children, where VNS was found to reduce IEDs, especially during REM, delta sleep, and EEG seizures. Again, there was evidence for a correlation between reduction of IEDs and effect on seizures.[37]

Evoked potentials

Animal studies showed that VNS could elicit evoked potentials in the cortex,[6,8,19,38] thalamus,[6,19,38] hypothalamus,[7] and cerebellum.[9] The effect of chronic VNS on brainstem auditory evoked potentials and somatosensory evoked potentials in humans was investigated by Naritoku *et al.* This study demonstrated interval increase between cervicomedullary and thalamocortical somatosensory evoked potentials in three VNS patients (as compared to baseline and to normal subjects). The authors suggested that vagus nerve stimulation alters neuronal networks outside of the brain stem vagus system, and highlighted the potential use of somatosensory evoked responses in titrating VNS therapy. However, it is difficult to draw meaningful conclusions from these series given the small number of VNS responders.[39]

Cerebral evoked responses following direct electrical stimulation of the vagus and esophagus were compared in eight epileptic subjects and with those recorded after esophageal stimulation in 12 healthy nonepileptic controls. Direct vagal stimulation was performed using a left cervical vagal pacemaker, which is used in the treatment of epilepsy. Esophageal stimulation was obtained with the use of an esophageal assembly incorporating two electrodes positioned 5 and 20 cm orad to the lower esophageal sphincter.

Another study compared evoked responses after direct electrical stimulation of the vagus nerve with a left vagal pacemaker and of the esophagus with two electrodes placed with a manometric assembly on the esophageal mucosa in eight patients with epilepsy undergoing esophageal stimulation and in 12 healthy nonepileptic controls.[40] Similar to the study by Naritoku *et al.* conduction velocity of the afferent response was found to be slower (7.5 m/s) in epilepsy patients as compared to healthy controls (10 m/s).[40] In contrast, a third study, which investigated the effect of VNS on visual, auditory brainstem, and long latency cognitive evoked potentials, did not detect any significant changes.[41]

Neurotransmitters

Hammond *et al.* reported increases in the metabolites of dopamine and serotonin – homovanillic acid and 5-hydroxyindoleacetic acid – in three out of six patients.[42] In addition a decrease in aspartate was seen in five of the six patients. Changes were associated with a decrease in seizure frequency.[42] Another study analyzed CSF neurotransmitters in sixteen patients before and 3 months after VNS. Decreases in the excitatory amino acid, aspartate, and increases in its inhibitory counterpart GABA were reported. Additionally, correlations between seizure reduction and increases in asparagine, phenylalanine, phosphoethanolamine, alanine and tryptophan concentrations were observed.[43]

Cerebral blood flow measurement by PET

Garnett *et al.* were the first to investigate the effect of VNS on cerebral blood flow by means of $H_2{}^{15}O$ PET in five patients

with epilepsy. Increased blood flow was demonstrated in the left anterior thalamus and the cingulate gyrus. These results may have been confounded by the fact that two out of the five patients had seizures during the PET scan.[44] As part of the manufacturer (Cyberonics) funded E04 trial, Ko *et al.* investigated three patients with $H_2{}^{15}O$ PET blood flow functional imaging. Left sided VNS resulted in activation of the right thalamus, right posterior temporal cortex, left putamen, and left inferior cerebellum.[45]

Henry *et al.* measured VNS-induced cerebral blood flow (CBF) effects after immediate and prolonged VNS in ten patients by performing $H_2{}^{15}O$ PET scans within one day after the onset of stimulation and by repeating the study after a period of 3 months.[32,46] Most subcortical sites activated during immediate stimulation were also activated after 3 months. During both times, VNS-induced CBF increases were found in similar locations in the bilateral thalami, hypothalami, inferior cerebellar hemispheres, and right postcentral gyrus. Cortical modification of CBF was less prominent after three months (including decreased CBF in bilateral hippocampal, amygdalar, and cingulate areas and increased bilateral insular CBF).[32] Interestingly seizures were found to be better controlled, when cortical blood flow decreased as a result of VNS.[32] These authors postulated a relationship between seizure reduction and decreases in cortical CBF.[32]

SPECT and perfusion

Ring *et al.* used (99m)Tc-HMPAO single photon emission tomography (SPECT) to investigate the effects of VNS on regional cerebral activity in seven patients, who had been receiving vagal nerve stimulation for a period of at least 6 months. VNS was found to be associated with decreased activity in left and right medial thalamus.[47] Vonck *et al.* investigated 12 patients by means of a 99mTc SPECT with a single-day split-dose protocol before and immediately after initial stimulation and noted a decrease in left thalamic CBF after the onset of stimulation. There was no evidence to suggest a correlation between hypoperfusion and seizure reduction.[48,49] Another study by the same group in a larger population of 23 patients showed evidence of deactivation in the left thalamus, right parahippocampal gyrus, and right hippocampus during initial stimulation with VNS.[50] In this latter study, a correlation between, initial stimulation changes in the right amygdala and therapeutic response was reported.[50] Another group confirmed the presence of decreased perfusion in the contralateral thalamus and cingulate and also reported additional areas of deactivation involving the ipsilateral brain stem, cingulate, amygdala and hippocampus.[51]

Functional MRI studies

Functional MRI studies during VNS in five patients demonstrated the most robust activation in both thalami (left greater right) and in the insular cortices bilaterally.[52] Additional activations of the ipsilateral basal ganglia, the postcentral gyri, the right posterior superior temporal gyrus, and the inferomedial occipital gyri were noted.[52] Liu *et al.* investigated five patients with complex partial seizures using blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI). Activation of the frontal and occipital lobes was seen in all patients. However, thalamic activation was only observed in the two patients with reduced seizure frequency.[53]

Stimulation paradigms

VNS parameters that can be manipulated include current intensity in milliamperes, frequency, pulse width, duration of stimulation and pattern of stimulation (stimulation paradigm). Therapeutic stimulation parameters for the E03 and E05 trials consisted of output current 0.5–3.5 mA, frequency 20–50 Hz, pulse width 500 μs, and stimulation on-time of 30–90 seconds followed by off-time of 5 minutes. The active 'control' group underwent 'low-dose' stimulation with output current 3.5 mA, frequency of 1–2 Hz, pulse width of 130 μs and stimulation on-time of 30 seconds with off-times ranging from 90–180 minutes.

Frequency

FDA recommended stimulation frequencies between 20 and 30 Hz. Lower frequency stimulation at 5 Hz is associated with reduced brain stimulation, as evidenced by fMRI studies comparing 5 Hz and 20 Hz stimulation protocols.[54] Furthermore, low frequency stimulation may facilitate stimulation of slow conducting C-fibers and lead to increased side effects.[55,56] Stimulation frequencies of 50 Hz and higher may result in irreversible vagal nerve fiber damage.[55]

Intensity

Currently available stimulation intensities range from 0.25 mA to 3.5 mA.[57] Currents between 0.8 mA and 2 mA are usually considered effective.[56] Stimulation can be increased incrementally by 0.25 mA – usually every 1–2 weeks – up to 2 mA. Stimulation (with a fixed pulse width) first produces depolarization of the large myelinated fibers with subsequent involvement of smaller myelinated and lastly unmyelinated fibers as intensity increases. Threshold for stimulation of fast, myelinated A fibers is 0.02–0.2 mA, for B fibers 0.04–0.6 mA and for unmyelinated C-fibers 2 mA and above.[58] The initial hypothesis that therapeutic VNS effects are related to depolarization of unmyelinated C-fibers has been disproved by Krahl *et al.*[59] Selective destruction of C fibers with capsaicin did not influence the antiepileptic effect of VNS in a pentylenetetrazol seizure model in rats.[59] Stimulation-induced side effects may increase with rising current delivery (either increased intensity or widened pulse width).

Pulse width

Available pulse widths include 130 μs, 250 μs and 500 μs. Usual settings include 500 and 250 μs. Increase of the pulse width leads to increased delivery of current, although this increase is not linear.[56] Comparison of different pulse widths (130 μs, 250 μs, or 500 μs) in fMRI studies showed that fMRI activations were greater with pulse widths of 250 and 500 μs – compared with the shorter pulse width of 130 μs – but not significantly different from each other; fMRI deactivation was greater for pulse widths of 130 μs and 250 μs as compared to the longer pulse width of 500 μs.[60]

Stimulation interval

Standard stimulation intervals consist of a 30 second on and a 5 minute off period. It is recommended that duty cycles do not exceed 50% of the complete stimulation paradigm in order to prevent nerve injury.[55,61] Some patients may experience better seizure control with faster cycles. DeGeorgio retrospectively

analyzed the effects of device parameter changes on seizure frequency in 154 subjects, who completed the long-term XE5 study. Comparisons were performed for the three most common off time periods of 3, 1.8, and 1.1 min. A change in off time to 1.1 min resulted in significant improvements in efficacy in a subgroup of VNS-resistant patients. A median seizure reduction from 21% before the change in off time, to 39% after the decrease in off time was observed in this subgroup of patients, who were initially felt to be VNS resistant.[62] However, other investigators have not observed improved seizure control with shortened off periods.[63]

Stimulation paradigms

These include open loop and closed loop stimulation. Open loop stimulation follows a certain stimulation pattern without consideration of seizures. Closed loop stimulation attempts to respond to the first warning symptoms of a seizure. In the preapproval studies (E03, E04, and E05) the device was programmed to deliver current to the treated group every 5 minutes for 30 seconds, regardless of seizure activity (open loop stimulation). Additionally, patients with a history of auras were encouraged to place a magnet over the VNS, when sensing that seizures were about to occur (closed loop).

Adjustment of parameters

After VNS implantation many centers do not start stimulation in the immediate post-operative period and for up to 5–14 days post-op. Other centers (including ours) prefer to program the device in the operating room. Initial settings usually include patterns of 30 second stimulation (on-time) every five minutes (off-time). Output current is usually increased in 0.25 mA steps.

Adjustment of stimulation parameters may be indicated in patients under the age of 12 years. Koo *et al.* performed intraoperative investigations during implantation of VNS in 21 patients aged 4–31 years and recordings made from the rostral end of the vagus nerve. These authors demonstrated that threshold current is higher in young children as compared to adults indicating that a higher current or larger pulse width is required in children in order to achieve equivalent effects.[64]

Efficacy of VNS

Randomized, double blind studies: E03 and E05

Two randomized placebo-controlled trials examined VNS prior to FDA approval, the E03 and the E05 trial. The first multicenter, double blind, randomized controlled trial, the E03 trial, included 114 patients over the age of 12 years with predominantly partial seizures and compared baseline seizure rates to those observed after stimulation in a 'high' and 'low' stimulation group.[31,65–67] The second multicenter, double-blind, randomized controlled study (E05) included 199 patients with complex partial seizures, who were followed for a period of 3 months. Again, patients were split into two groups with 'high' and 'low' stimulation: 28% of patients in the high stimulation group experienced seizure reduction as compared to 15% in the low stimulation group.[68]

Inclusion criteria

Patients were included in the two randomized, controlled, preapproval trials if they were between 12 and 60 years old, if they had at least six seizures per month and if they were being treated with zero to three AEDs. In the E05 study, patients were also required to have complex-partial seizures.

Stimulation paradigms

As mentioned above, both of these trials compared two different VNS stimulation paradigms, 'high' versus 'low' stimulation for the treatment of partial seizures. In the E03 trial settings in the high stimulation group included an output current of 0.5–3 mA, a frequency of 20–50 Hz (control=1–2 Hz), pulse width of 500 microseconds (control=130 microseconds), on time of 30–90 seconds (control=30 seconds), and off periods of 5 minutes (control=90 minutes). In the E05 trial, settings in the high stimulation group consisted of an output current of up to 3.5 mA, a frequency of 30 Hz (control=1 Hz), pulse width of 500 microseconds (control=130 microseconds), on time of 30 seconds and off periods of 5 minutes (controls=180 minutes).

Design and timeline

Baseline monitoring of seizure frequency was performed over a 12–16 week interval. During this baseline, preimplantation interval, seizure frequency was recorded and AED changes were only allowed in cases of toxicity or low levels. Eligible patients, who fulfilled all baseline criteria, were subsequently implanted. Randomization to either 'high' or 'low' frequency stimulation was completed 2 weeks after implantation. During the following 2 weeks after initiation of VNS treatment, therapeutic stimulator settings were increased as high as tolerated. On the other hand, the low-stimulation group received stimulation intensities that were increased to the level of perceptible stimulation. Treatment results and seizure frequency was monitored during the following twelve weeks.

Results

In E03, 125 patients were initially enrolled and 114 of those were implanted. Fifty-four patients were randomized to the high stimulation group, whereas 60 patients underwent low stimulation. In E05, 199 out of 254 initially enrolled patients fulfilled the eligibility criteria and proceeded to implantation. In the E05 trial, 95 patients were randomized to the high-stimulation group and 103 to the low-stimulation group; in addition one patient was excluded due to device infection.

The primary outcome parameter was change in seizure frequency during treatment as compared to baseline. Seizure frequency reduction in the E03 trial was 24.5% in the high stimulation group versus 6.1% in the low stimulation group ($p<0.01$). Seizure frequency reduction in the E05 trial was 28% in the high stimulation group as compared to 15% in the low stimulation group ($p<0.05$).

Secondary outcome parameters in the E03 trial were also in favor of the high stimulation group. 31% had >50% seizure reduction in the high stimulation group as compared to 13% in the low stimulation group ($p<0.05$). In the E05 trial, 11% experienced greater than 75% seizure reduction in the high stimulation group as compared to only 2% in the low stimulation group ($p<0.01$).

The E03 and E05 trials are the only studies included in a Cochrane library review and metaanalysis.[69] The overall odds ratio for 50% responders across both studies was estimated to be 1.93, by pooling the data from both the E03 and E05 studies. These results suggest that VNS may be effective as

additional treatment for patients with medically intractable partial seizures, who are older than 12 years of age at the time of implantation.

Problems with the E03 and E05 trials

A randomized trial with vagus nerve stimulation poses more problems than a pharmacological trial. In a pharmacological trial, patients can be treated with a placebo pill. In a VNS trial, randomization mandates implantation of the stimulator in both study groups. The active control group was also exposed to stimulation, delivered for a much shorter period of time and using lower frequency and pulse width. (high stimulation group 500 microseconds pulse width, 30 Hz, 30 s on, 5 min off; up to 3.5 mA versus low stimulation group 130 microseconds pulse width, 1 Hz, 30 s on, 90 or 180 min off, up to 3.5 mA). The fact that participants or physicians may have been able to detect current delivery in the treatment or placebo arm due to possible stimulation-related side effects constitutes a potential limitation of this study design. Further, unblinding or change in outcome may have resulted from lack of perceived VNS output after handheld magnet activation in the control group. Both trials were funded by the manufacturer and were limited to a relatively short period of observation post-VNS implantation. There are no randomized controlled data related to long-term VNS use. Other limitations include the lack of comparison to available pharmacological treatments. It is important to remember that the results of the E03 and E05 studies pertain to a certain patient population and that it is not possible to extrapolate these results to other groups such as patients with generalized epilepsy or children under the age of 12 years.

Non-double blind and long-term studies

The first patient received a vagus nerve stimulator in November 1988. Between November 1988 and September 1989 eleven patients were implanted. The first uncontrolled study with preliminary results on the use of VNS in humans was published in 1990.[15] Four out of the eleven patients with medically intractable epilepsy became seizure free in this first reported case series.[15] Additional early studies and uncontrolled observations documented seizure reductions by up to 50% in 30% of patients.[70–74] A first single blind pilot study by Uthman *et al.* [16,75] demonstrated a mean seizure frequency reduction of 46.6% after 14–35 months of VNS.

The first randomized active control study (E03) was completed in 1992 and the second one (E05) in 1996. Subsequent open label, non-blinded, longer term studies indicate that VNS treatment efficacy seems to further improve during the unblinded periods of follow up (after completion of the initial blinded treatment interval). Completion of the blinded 14-week long E03 period was followed by an open, non-blinded long term evaluation.[66] George *et al.*[66] reported long term follow up for 16 to 18 months after completion of the blinded E03 trial. All patients were treated with open label high frequency VNS. Twenty-six of the 31 patients initially randomized to high frequency VNS had a 52.0% seizure frequency reduction and 24 of the 36 patients initially randomized to low frequency stimulation experienced a 38.1% reduction of seizure frequency.[66] Salinsky *et al.* found similar results in 100 patients followed for a year after completion of the E03 trial.[76] In this series, response to VNS during the first three months predicted longterm outcome.[76]

Patients with six or more complex partial or generalized tonic-clonic seizures, who had been enrolled in the pivotal E05 study, were prospectively evaluated for a period of 12 months during the XE5 trial (long-term prospective efficacy and safety study = XE5).[62,71,77] In the E05 trial seizure frequency reduction of 28% was seen at three months. The vast majority of patients (195 out of a total of 199 patients) selected to continue treatment after this initial period. In the subsequent months 21 patients dropped out due to decreased efficacy and two patients died of unrelated conditions. After 12 months of follow up, 35% of remaining patients had a >50% reduction in seizures, and 20% had a >75% reduction in seizures.[77] After 15 months of follow up mean and median seizure frequency reduction was 37% and 45%, respectively.[71] An additional analysis of stimulation parameter changes suggested that the increased efficacy was not primarily related to changes in stimulation parameters.[62]

Morris *et al.* followed a total of 440 patients up to 3 years and found 50% seizure reduction in 36.8% of patients after 1 year, in 43.2% after 2 years, and in 42.7% after 3 years. Median seizure

Table 127.1 Adverse events of VNS in the E03 and E05 study

Adverse event	E03 *n*=114	E05 trial n=198 Number of patients (%)	Sum *n*=312
Voice alteration/hoarseness	28 (24.6%)	94 (47.4%)	122 (39.1%)
Increased coughing	9 (7.9%)	87 (43.9%)	96 (30.8%)
Pharyngitis (E03: throat pain)	13 (11.4%)	59 (29.8%)	72 (23.1%)
Pain (E03: muscle pain)	4 (3.5%)	58 (29.3%)	62 (19.9%)
Headache	6 (5.3%)	47 (23.7%)	53 (17%)
Paresthesias	5 (4.4%)	43 (21.7%)	48 (15.4%)
Dyspnea	4 (3.5%)	35 (17.7%)	39 (12.5%)
Nausea	NR	35 (17.7%)	N/A
Vomiting	NR	31 (15.6%)	N/A
Dyspepsia	NR	30 (15.1%)	N/A
Fever	NR	30 (15.1%)	N/A
Injury	NR	25 (12.6%)	N/A
Infection	NR	23 (11.6%)	N/A

*Only side effects in greater than 5% (E03) and greater than 10% (E05) were reported.

reductions were 35% after the first year, 44.3% after the second year, and 44.1% after the third year. Interestingly, about 25% of patients chose to discontinue VNS treatement.[78]

Similar sustained improvement have been observed up to 4[79] or 5 years.[80,81] Ben Menachem *et al.* followed 64 patients for up to 5 years. The average follow up in this series was 20 months. Twenty nine out of 64 patients had greater than 50% seizure reduction at their last follow-up.[80]

Five to 7 year follow up was available on 26 patients in the series reported by Spanaki *et al.* [82] Charts were reviewed after 1 year and after 5–7 years. Seizure frequency was decreased by 28% at 12 months and by 72% on final follow up.[82] Table 127.2 summarizes the findings of these long term follow up studies.

Currently, all long term studies are uncontrolled and data is usually collected during an open-label phase of the trial. In addition, medications and VNS parameters are allowed to vary and are commonly adjusted during the period of observation. Selection bias is a consistent limitation in these long-term studies, as patients with poor response to stimulation tend to exit early (accounting for a significant percentage of drop outs), leaving only patients with relatively good response to stimulation during longer follow up periods.

Vagus nerve stimulation in selected patient populations

Children

No randomized trials for pediatric patients are available. The E05 trial included 60 patients under the age of 18 years. Compared to baseline this group exhibited a 23% seizure reduction at 3 months and over 40% seizure reduction after a period of 6 months.[68] Nonrandomized pediatric case series were reviewed by Crumrine in 2000, who reported greater than 50% seizure reduction in 19 to 53% of pediatric patients followed for 3–24 months.[83]

VNS has been investigated in pediatric patients with epileptic encephalopathies,[84,85] Lennox-Gastaut syndrome,[86–88] tuberous sclerosis,[89] hypothalamic harmatomas [90] and Landau-Kleffner syndrome.[91]

VNS led to 17% median decrease in seizure frequency after 1 year in a study of 17 patients with epileptic encephalopathies.[85] In patients with Lennox-Gastaut syndrome, median seizure frequency reduction ranging from 52–58% has been reported after 6 months of VNS.[86,88] After 24 months, Aldenkamp *et al.* noted only a 20% average seizure frequency reduction in 19 children with Lennox-Gastaut syndrome.[87] Treatment effect was most prominent in the group with the highest mental age at baseline.[87]

Ten pediatric patients with tuberous sclerosis were reviewed in an open-label, retrospective study. Nine patients had at least 50% reduction in seizure frequency, and five achieved seizure frequency decreases that exceeded 90%. Comparison with medically treated tuberous sclerosis patients revealed improved seizure control with VNS. However, when the VNS-treated group was compared to patients with tuberous sclerosis undergoing epilepsy surgery better outcomes were observed in the surgically-treated group.[89]

In small series of patients with Landau-Kleffner syndrome and with hypothalamic harmatomas, half of the patients in each of the two series showed improvement in seizure frequency as compared to baseline. [90,91] Finally, a single case of interruption of status epilepticus has been reported after initiation of VNS in a 13-year-old.[92]

Elderly

Sirven *et al.* investigated vagus nerve stimulation for refractory epilepsy in 45 adults 50 years of age and older.[93]After 3 months, 12 out of 31 patients had greater than 50% decrease in seizure frequency, whereas after 1 year, 21 out of 31 patients had 50% or greater decrease in seizure frequency.[93] Additionally, patients experienced a significant improvement in quality of life (QOL) scores. These results suggest that VNS merits consideration as a treatment option in older individuals with epilepsy.

Safety and tolerability: complications and adverse effects

Infection

Infections due to the surgical intervention occur in 3 to 6% of patients and are usually controlled with oral antibiotics.[77,80,94] Fluid collection around the generator with or without infection can be managed conservatively with aspiration and antibiotics.[95] Irrigation with antibiotic solutions may be an alternative to explantation.[96] In the E05 trial, 1.5% of patients required device explantation due to infection.[68] The risk of infection may be higher in younger children and patients with developmental delay, because frequent drooling and inadvertent electrode and wound manipulation may predispose to infection.[97,98]

Hardware defects including breaks in the equipment at the electrode-wire junction were common surgical complications in early trials.[16,99] A recent study reported hardware failure in 2.7% of 74 patients with a minimum follow up of 1 year.[94]

Lower facial weakness was observed in a total of three patients enrolled in the E03 and E05 studies.[100] This was most likely related to high surgical incisions during early implantations; the risk of such adverse effect can now be neglected.[100]

Vocal cord paralysis and dysfunction can occur as a result of the surgery itself and/or as a result of the stimulation. Most frequent side effects include vocal cord dysfunction and hoarseness during stimulation.[31,68,99] Occasional cases of ipsilateral vocal-cord paralysis have also been described.[99] Delayed vocal cord paralysis may be related to post-operative nerve edema, which is a potentially preventable complication.[99] Post-operative vocal cord paralysis is frequently only temporary and patients may recover as swelling improves.[101] Laryngeal electromyography of the cricothyroid and thyroarytenoid muscles indicates that degeneration of the recurrent laryngeal nerve occurs in approximately 60% of patients after prolonged repetitive stimulation.[102] Self-inflicted vocal cord paralysis can also occur, when patients manipulate the leads under the skin.[103]

Other common side effects

In addition to hoarseness, patients enrolled in the E05 study complained of cough, throat pain and pharyngitis, muscle pain and pain at the insertion site, headache, paresthesias, and dyspnea.[31,68] Other less common symptoms reported in the same trial included nausea and vomiting, dyspepsia, fever, and infection (see Table 127.1). [68]

Table 127.2 Long-term follow up after VNS

Author	Year	n	Patient population (seizure types, epilepsy, or syndrome)	Design	Follow-up (maximum)	Outcome parameter	Completion rate/Drop-outs
George *et al.*[66]	1994	114 (67)	Complex partial seizures (EO3)	Prospective; open-label; not controlled	16-18 months	Seizure reduction by 50% in 50% of patients	67 out of 114 continued study; complete data on 50/67 (74.6%)
Salinsky *et al.*[76]	1996	114	Complex partial seizures (EO3)	Prospective; open-label; not controlled	1 year	Median seizure frequency reduction by 32%	14/114 (lack of efficacy)
Clarke *et al.*[130]	1997	10	Complex partial seizures	Prospective; open-label; not controlled	50 months	10 fold increase in the mean number of 14-day seizure–free periods	8/10 (80%); unchanged AEDs
Amar *et al.*[71]	1999	199	Partial seizures with alteration of consciousness; >12 y/o (XE5 trial)	Prospective; open-label; not controlled	15 months	Median seizure frequency reduction was 45%	164/199 (82.4%)
Vonck *et al.*[79]	1999	25	Complex partial seizures 17–44 y/o	Prospective	Average 29 months (up to 40 months)	Mean complex partial seizure frequency reduction 42.8%	15/25 (60%)
Morris *et al.*[78]	1999	454	Partial and generalized seizures (EO1–EO5 trials)	Prospective, open-label; not controlled	3 years	Seizure reduction by 50% in 43%; median seizure frequency reduction 44%	440 entered long-term trial; 93/454 at 3 years (20.5%)
Ben-Menachem *et al.*[80]	1999	64	47 focal epilepsy; 9 idiopathic generalized epilepsy; 8 LGS	Prospective, open-label; not controlled	Average 20 months (up to 5 years)	Seizure reduction by 50% in 45%	57/64 (89%)
DeGiorgio *et al.*[77]	2000	195	Partial seizures with alteration of consciousness; >12 y/o (EO5/XE5)	Prospective; open label; not controlled	1 year	Median seizure reduction 45%; seizure reduction by 50% in 34%	164/195 (84%)
Aldenkamp *et al.*[87]	2002	19	Children with LGS (6–20 y/o)	Prospective; open-label; not controlled	2 years	Mean seizure reduction was 20.6%	17/19 (89%)
Kawai *et al.*[131]	2002	13	Partial seizures; age 19–47 y/o	Prospective; open-label; not controlled	4 years (median 56 months)	Mean seizure frequency reduction 63%	13/15 (86.6%)
Tanganelli *et al.*[132]	2002	51	Focal or generalized seizures; age 7–49 y/o	Prospective; open-label; not controlled	6 months	Seizure frequency reduction by 50% in 46.8%	47/51 (92.1%)
Chavel *et al.*[133]	2003	30	Partial onset seizures; >12 y/o	Prospective; open-label; not controlled	2 years	Seizure reduction by 50% in 61%	23/30(76.6%)

Uthman *et al.*[134]	2004	48	Head trauma (10); encephalitis (4); febrile convulsions (1); unknown (33); 13–58 y/o at implant	Prospective; open-label; not controlled	12 years	Mean seizure frequency reduction by 52%	25/48 (52%)
Spanaki *et al.*[82]	2004	26	Partial epilepsy (24); 'atypical absence' epilepsy (1); generalized epilepsy (1)	Retrospective, chart review	5–7 years	Median seizure frequency reduction by 72%	26/28 records; Preselection; included only patients with follow-up
Huf *et al.*[135]	2005	40	Low IQ patients (<70);	Prospective; open label; not controlled	2 years	Seizure reduction by 50% in 27.5%	40/40 (100%)
Majoie *et al.*[81]	2005	19	Lennox-Gastaut Syndrome; 5–18 y/o	prospective	2 years	Seizure frequency reduction of 20.6%; seizure reduction greater 50% in 21%	19/19 (100%)
Halböök *et al.*[37]	2005	15	MCD (5); encephalitis (1); HIE (5); unknown (4); age 4–17 y/o	prospective	9 months	Mean interictal spike frequency reduction by 18%	15/15 (100%)
Rycklicki *et al.*[112]	2006	36	Children 18 mos to 18 y/o; 9 LGS; 27 focal epilepsy;	Prospective; open-label; not controlled	Mean follow up 30 months;	Seizure reduction by 50% in 71%	NR
Alexopoulos *et al.*[98]	2006	49	Tuberous sclerosis (3); MCD (6); encephalitis (2); mitochondrial disease (2); hypothalamic hamartoma (1); head trauma (1); generalized (4); unknown (34); 1–16 y/o	Prospective;	Median follow up 2 years	63% at 1 year; 83% at 2 years; 74% at 3 years	39/49 at 1 year (79.6%) 23/49 at 2 years (46.9%) 16/49 at 3 years (32.6%)

Less common stimulation-related side effects besides cough and hoarseness include outbursts of laughter, shoulder abduction, urinary retention, dysphagia, and torticollis.[94] A correlation between the intensity of the current and the degree of hoarseness has been described.[104]

Privitera *et al.* attempted to divide VNS side effects and complications to two groups: those attributed to implantation per se and those that were related to the stimulation. The authors reported that cough (OR 2.9), paresthesias (OR 6.3) and possibly pain (OR 2.2; nonsignificant trend) were associated with implantation of the device, whereas dyspnea was associated with stimulation (OR 2.65). Hoarseness was related to implantation, but additional hoarseness could be a product of stimulation (OR 14.5).[69]

Cognitive and psychiatric side effects

Side effects on mood and cognition as a result of VNS warrant further investigation. VNS usually leads to improvement of behavioral problems and has mood stabilizing effects.[85,86,105,106] Nevertheless, acute psychosis and depression have been described in relationship to VNS.[85,107,108] Effects on memory are variable. While some authors report improvement in word-recognition memory,[109] others have found decline in figural memory during VNS.[110] Additionally, central pain suppression has been reported with VNS. [111]

Respiratory changes and aspiration.

Dyspnea appears to be another stimulation-related side effect.[56] As demonstrated by laryngoscopy, dyspnea occurs due to adduction of the left vocal cord, which results from intensity dependent stimulation of the recurrent laryngeal nerve.[104]

Snoring, sleep apnea and gasping has been reported during sleep.[112–114] Due to its effect on breathing patterns, some authors consider obstructive sleep apnea syndrome as a relative contraindication to VNS. [115]In addition, an increase in respiratory rate has been documented during wakefulness.[116]

Rarely, aspiration during VNS has been observed in children with severe preexisting mental and motor disabilities.[117] Smyth reported that one of his patients died of aspiration pneumonia 30 days after VNS implantation.[94] Schallert *et al.* performed swallow studies in 8 children with VNS, which did not show any evidence of aspiration. Only one patient had laryngeal penetration of barium caused by VNS, but no aspiration was seen.[118] Increased drooling as a side effect of VNS has been reported in patients with Lennox-Gastaut syndrome.[86]

Cardiac asystole is a rare complication during testing of the vagus nerve stimulator at the time of implantation. Five patients have been reported up to date.[119,120] This complication seems to be exclusively limited to the intraoperative setting with an estimated frequency of one in 875 (0.1%). [121] Suspected causes include malfunction of the device, errors during surgery such as polarity reversion of the electrodes or atypical electrode placement, or possible indirect stimulation of cardiac afferents.[121] No major autonomic effects on heart rate variability have been described with chronic VNS.[122]

Death

Annegers *et al.* followed a cohort of 1819 patients for 3176.3 person-years from the time of VNS implantation. Twenty-five deaths were assessed for possible Sudden Unexpected Death in Epilepsy (SUDEP). Mortality and SUDEP rates were found to be equal to those seen in patients with severe pharmacoresistant epilepsy. Interestingly, the rate of SUDEP was 5.5 per 1000 during the first 2 years, but dropped to 1.7 per 1000 thereafter.[123]

VNS and pregnancy

Eight pregnancies during VNS have been reported by Ben-Menachem. Two patients had elective abortions, one experienced a spontaneous abortion and five pregnancies led to healthy, full term babies, including one twin delivery.[124]

Outlook

Advantages

VNS is an important addition to the currently available antiepileptic armamentarium. Its use in patients with pharmacoresistant seizures and may help decrease the number of antiepileptic medications and side effects associated with polypharmacy. Existent level one evidence supports the use of VNS in patients with focal seizures[69] and level two evidence is being collected in other patient populations.[121] About one third of patients experience seizure reduction of at least 50%[57] and similar results have been observed in adults and children, with additional improvement after longer stimulation duration.[98] The observation of positive VNS effects on mood, alertness and quality of life has ignited interest and ongoing study of VNS in other clinical areas such as depression and mood disorders,[125,126] anxiety,[58] migraines,[58] obesity,[127] and possibly conditions with memory difficulties and impaired alertness.[128]

Limitations

In most cases, however, VNS treatment provides a palliative and curative option for patients with seizures refractory to medications and ineligible for resective epilepsy surgery. Indications and criteria for VNS use have not been carefully defined nor have ideal stimulation parameters been clarified. No information on patients with less refractory epilepsy is available.[121] Additionally, there are no studies providing head to head comparisons with established antiepileptic drugs.

Furthermore, no randomized double-blind data exist for children younger than 12 years, for the elderly or for individuals with generalized epilepsies. Our current inability to predict responders prior to VNS leads to costly, unnecessary implantations. Observable benefit may be quite delayed in some cases.

All randomized preapproval studies have been funded by the industry. Furthermore, both the E03 and E05 trials are limited by the fact that randomization in stimulator trials is never completely blinded.[69] Patients and physicians may have been able to decipher stimulator settings and group allocation on the basis of the presence or absence of side effects related to the stimulation. Additionally, long-term follow up data are only available during periods of unblinded observation. Published long-term studies tend to be biased by drop-outs – patients who frequently discontinue VNS due to decreased efficacy leaving only the responders in the study.

Implantation of the metal stimulator limits future MRI scanning due to possible diathermy effects and manipulation

of stimulator settings by the magnetic field. Furthermore, the cost of the device and surgical intervention and the need for future battery replacements should be factored when making the decision for or against VNS.

Future perspective

Ideally future trials should address the variable stimulation paradigms and predictors for response to stimulation, should be independently funded, employ improved trial designs and target a broader patient population.

Improved trial designs

A randomized controlled trial including a sham or low-frequency stimulation that closer approximates side-effects of high frequency stimulation is needed. Prolonged periods of blinded randomized investigation and head-to-head comparisons with established antiepileptic drugs would be highly desirable.

Variation in stimulation paradigms and devices

Is it possible to define specific open or closed loop stimulation paradigms with stimulation frequencies and patterns tailored to certain types of seizures or patient populations? Such an approach may also lead to improvements in terms of side effect profile, battery life and MRI–compatibility of electrodes and stimulator.

Ability to predict outcome prior to implantation

Methods/studies that would lead to improved selection of favorable VNS candidates are eagerly awaited.

Expansion to different patient populations

Future trials should include a broader group of individuals with epilepsy such as patients with generalized epilepsy, patients with less advanced or less refractory epilepsies, elderly and children under the age of 12 years.

Financial issues

Independence from industrial funding. All major studies have been funded by industry that may have an interest in merchandising their product. Cost including the device, surgical intervention and maintenance is also a concern, although VNS treatment may lead to reduced costs over a longer period of time.[129]

VNS is the first FDA approved neurostimulation technique in epilepsy. Since its approval multiple other stimulation sites in the central and peripheral nervous system and techniques have been investigated for the treatment of epilepsy. Although VNS is not the ultimate treatment for seizures, it has opened the door for a burgeoning field of research in epilepsy and neurostimulation. VNS serves as a nonpharmacological, adjunctive and well-tolerated treatment alternative in selected patients with medically refractory epilepsy.

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128 Experimental evidence for the involvement of the basal ganglia in the control of epilepsy

C Deransart and A Depaulis

Introduction

Investigation of the basal ganglia (BG) circuits, shunt-connected to circuits for initiation and propagation of seizures, is essential in order to understand the chronic nature of the epilepsy, the episodic nature of the seizures and the phenomena underlying transition between interictal and ictal states. Over the past decades, the role of the BG system among the circuits involved in the genesis of different types of seizures has been mainly addressed in animal models. The development of rodent models with recurrent spontaneous seizures has greatly contributed to this investigation. Several data from different laboratories working with various models have led to the suggestion of a particular role for the BG circuits in epilepsy. In the present review, we will first briefly summarize the general functional anatomy of the BG before considering the possibility that BG circuits can generate or participate in the initiation and/or propagation of seizures, based on experimental data. In the second part of this chapter, data suggesting the involvement of the BG in the control of seizures will be discussed.

Functional anatomy of the basal ganglia circuits

The BG are connected to the cerebral cortex through several multisynaptic loop circuits. The cerebral cortex provides the main source of glutamatergic projections to the striatum and the subthalamic nucleus (STN), the two major input structures of the BG. As a consequence, the striatum processes information from all areas of the cerebral cortex, the midline and intralaminar thalamic nuclei, the amygdala, and the hippocampus. The inputs to the STN arise from a more restricted part of the cortex involving the motor, premotor, and prefrontal areas and from the parafascicular thalamic nucleus.

In turn, the two output stations of the BG, the substantia nigra pars reticulata (SNR) and the entopeduncular nucleus (the rodent equivalent of the internal segment of the globus pallidus), innervate a diversity of thalamic and brain stem nuclei through which they can influence cortical electrogenesis. In rodents, the projections to the thalamus mainly extends throughout the entirety of the ventral medial nucleus, but also the lateral and ventral parts of the medial dorsal nucleus, the intralaminar nuclei parafascicular, central medial, paracentral and restricted parts of the ventral anterior/ventral lateral complex and the lateral dorsal nucleus.[1–5] Through these thalamic nuclei, the BG influence the frontal cortex including the prelimbic and orbital prefrontal areas, the anterior cingulate and the sensory-motor areas. In addition, the BG also innervate by nigral GABAergic projections the intermediate and deep layers of the superior colliculus and the pedunculo-pontine nucleus from which arise major projections to the ventral medial and intralaminar thalamic nuclei.[6–9] Via the ascending projections of these brain stem structures, the BG can influence widespread areas of the cerebral cortex. Altogether, these anatomical data show that the BG are tightly connected to regions of the cortex playing a leading role in the generation of seizures and are in a privileged position to control the propagation of the paroxysmal discharges through multisynaptic loop circuits.

Based on anatomical and electrophysiological observations, a conceptual model of BG circuits and their relationships with the cerebral cortex has been proposed.[10,11] In this model, cortical information is transmitted from via three main pathways: (i) a direct striato-nigral pathway, (ii) a direct subthalamo-nigral pathway (also defined as the 'hyperdirect' pathway due to its fast conduction velocity), and (iii) an indirect striato-pallido-subthalamo-nigral pathway. Because the striatal projection neurons are GABAergic whereas STN neurons are glutamatergic, the trans-striatal and trans-subthalamic pathways exert opposite effects, respectively inhibitory and excitatory, on the output neurons like the GABAergic nigral projections. In accordance with this model, electrical stimulation of the cerebral cortex induces in these neurons a sequence of synaptic events consisting of an inhibition preceded or not by an early excitation and followed or not by a late excitatory event. The inhibitory event results from the activation of the direct striato-nigral neurons; the early excitation results from the activation of the hyperdirect subthalamo-nigral pathway and the late excitation of the indirect pathway.[12–14] In this indirect pathway, the inhibition of the GABAergic pallido-subthalamic neurons by the cortically-evoked striatal activation leads to a disinhibition of the STN cells. Because the BG output neurons are GABAergic and tonically active, their inhibition by the direct striatal pathway leads to a *disinhibition* of the BG targets in the thalamus and the brain stem.[15] Conversely, the trans-STN circuits (hyperdirect and indirect) reinforce the inhibitory influence that BG exerts on their targets.

Experimental evidence supporting the role of the basal ganglia in the control of seizure

The basal ganglia as a generator of seizures?

Although the BG circuits are known to generate spontaneous oscillatory activities in several physiological as well as pathophysiological conditions,[16–19] the possibility that they initiate or promote epileptic seizures appears quite unlikely. Indeed, oscillatory activities observed in BG circuits have very low frequencies and when recorded during seizures they appear to result from propagation processes. Furthermore, electrical or chemical stimulations of the BG structures rarely initiate seizures and their lesions never abolish the occurrence of seizures (for review see Deransart and Depaulis, 2002).[20] On the contrary, changes in neuronal activity revealed by EEG, glucose metabolism or expression of immediate early genes studies suggest that the BG circuits may rather 'detect' the beginning, localization and/or intensity of a seizure. It is thus conceivable that changes of activity of these circuits may have some consequences on the development of the on-going seizure.

Several lines of evidence have accumulated over the past 30 years to support the existence of a system involving the SNR and the BG which may control the propagation and/or the generation of different kinds of seizures in animals (reviewed in Depaulis *et al*. 1994).[21] Evidence has been mainly collected from pharmacological or electrical modulation of the BG circuits and more recently from electrophysiological recording of neuronal activity during spontaneous seizures as well as measures of long term modifications of the functioning of these circuits.

Effects of manipulations of the substantia nigra pars reticulata

In 1980, Gale and Iadarola were the first to correlate an increase of GABA in the SNR (induced by the systemic injection of an inhibitor of GABA-transaminase) with antiepileptic effects.[22] Later, they showed that the potentiation of the GABAergic neurotransmission within the SNR, by bilateral microinjections of GABAmimetic drugs, suppressed convulsions in various models of generalized seizures in the rat.[23] It was later shown that such local pharmacological manipulations also suppressed the EEG expression of seizures in a model of generalized nonconvulsive epilepsy.[24] Inhibition of the SNR could also be obtained by blockade of the glutamatergic input, which mainly arises from the STN. In particular, injection of different NMDA antagonists into the SNR suppressed absence-seizures in GAERS, whereas non-NMDA antagonists were without effects.[25] Since then, several studies have confirmed that pharmacological inhibition of the SNR suppresses different forms of convulsive and non-convulsive generalized seizures.[21] Recently, it was shown that 130 Hz stimulation applied to the SNR, also suppressed convulsions induced by fluorothyl inhalation.[26,27] The critical nigral projection involved in seizure suppression remains to be determined. However, disinhibition of neurons of the superior colliculus, one of the main targets of the SNR, appears to play a significant role in the mediation of these antiepileptic effects in some forms of seizures.[28,29] Within this structure, specific populations of neurons appear to be involved in the control of different forms of seizure.[30–32] This is in agreement with the fact that inhibition of nigral neurons was shown to be without effect on tonic seizures involving brainstem structures, as seen in audiogenic-sensitive rats suggesting that such manipulations are more efficient on seizures involving forebrain circuits.[33] Furthermore, a differential involvement of anterior *versus* posterior populations of the SNR was also suggested in adult male rats.[34] The circuits involved in the antiepileptic effects resulting from the inhibition of the SNR may thus differ according to the type of seizure under control, and remain to be characterized.

Involvement of the direct striatonigral pathway

The possibility that the direct GABAergic striato-nigral pathway could modulate seizures through inhibition of the SNR was first suggested by experiments showing that intranigral injection of GABAA agonists have antiepileptic effects in most models of seizure in the rat (see Depaulis *et al*., 1994[21] for review). Indeed, activation of cells in the striatum, either by glutamate or D1 agonists, increases the release of GABA in the SNR as measured by microdialysis,[35] and decreases SNR activity.[36,37] Several studies have shown that injection of either NMDA agonist[38,39] or a GABA antagonist[40,41] in the striatum can block convulsive seizures. The anticonvulsant effect was detectable throughout the entire extent of the striatum. However, the predominant suppression was elicited from sites located in the ventral and posterior part of the striatum. In addition, this suppression of seizures could be reversed by the subsequent injection of a GABA antagonist into the SNR.[41] We have confirmed and extended these findings in the genetic model of absence-epilepsy in the rat where activation of striatal neurons by NMDA or by a D1 receptor agonist, significantly suppressed spike-and-wave discharges.[42] These antiepileptic effects were obtained with doses that do not produce behavioral effects, and were mainly observed when injection sites were located in the core of the nucleus accumbens. Conversely, blockade of the D1 receptors in the nucleus accumbens or of the GABAA receptors in the SNR *increased* the occurrence of absence-seizures in GAERS, confirming the critical role of this ventral direct striato-nigral projection in the control of this form of seizure.[42] However, intrastriatal injection of a D1 agonist failed to suppress clonic seizures in the pilocarpine model,[43] suggesting that different circuits are involved depending on the type of seizures.

Involvement of the hyperdirect subthalamo-nigral pathway

The glutamatergic input from the STN appears to be critical in the maintenance of the SNR neuronal activity. Bilateral injections of a GABA agonist into the STN, or high-frequency stimulation of this structure, decrease the activity of nigral neurons.[44,45] We were the first to show that both ways of reducing the excitatory influence of the STN can also suppress epileptic seizures.[25,46] In both cases, the suppression of absence seizures in GAERS by STN inhibition was dissociated from behavioral side-effects such as dystonia or stereotypies. The antiepileptic effects of pharmacological STN inhibition were

also confirmed in generalized convulsive seizures induced by fluorothyl inhalation,[47] amygdala kindling,[48] intravenous bicuculline or by its focal application into the anterior piriform cortex.[49] More recently, 130 Hz stimulation of the STN was reported to protect against seizures induced by systemic injection of kainite,[50] injection of kainate into the amygdala[51,52] or fluorothyl inhalation.[53] It is also in agreement with previous findings showing that intranigral injection of NMDA antagonists have antiepileptic effects in several models (see above or Depaulis *et al*, 1994).[21]

The pallidum and the trans-subthalamic pathway

The involvement of the GABAergic input from the pallidum to the STN has been investigated only in a few models of convulsive epilepsy, supporting that pallidal structures could be involved in the seizure spread mechanism that occurs during secondary generalization.[54–57] In GAERS, disinhibition of the globus pallidus or the ventral pallidum by injection of a GABAA antagonist, suppresses absence seizures at doses without behavioral effects. This antiepileptic effect was correlated with a decrease in glutamate levels in the SNR as measured by microdialysis, suggesting that this effect is mediated, at least in part, through a reduction in activity of the STN.[58] Antiepileptic effects were more pronounced when the injection sites were located in the ventral part of the pallidum. Conversely, an *increase* in the occurrence of absence-seizures was observed following inhibition of the ventral pallidum,[58] The preferential involvement of the ventral aspects of the pallidum is in agreement with the stronger suppressive effects observed following pharmacological manipulations in the ventral striatum and was confirmed in amygdala kindling. In this model, disinhibition of the ventral pallidum by a GABAA antagonist reduced both the behavioral expression of seizures and the duration of the afterdischarge. Conversely, inhibition or disinhibition of the globus pallidus (i.e., dorsal part), failed to have any effect (personal observations). Further data obtained in other models of seizures are necessary to confirm the involvement of the ventral pallidum in the control of seizures.

Involvement of the indirect striato-pallido-subthalamo-nigral pathway

The involvement of the dorsal and/or ventral pallidum in the control circuit of seizures is somewhat in agreement with data obtained following intrastriatal injection of dopaminergic agonists of the D2 receptors. Several data have suggested that these receptors are preferentially located on neurons projecting to the globus pallidus.[59,60] Although such a segregation has been revised[61,62] activation of striatal D2 receptors results in neuronal inhibition and, among other things, leads to disinhibition of pallidal neurons.[63–65] Injections of D2 agonists into the dorsal striatum was shown to block seizures in different models of convulsions, whereas injections of D2 antagonists in the same region have proconvulsant effects.[43,66–69] Injections of D2 agonists at lower doses also significantly suppressed absence seizures in GAERS, whereas aggravation was obtained with antagonists (see Figure 128.1). In this model, antiepileptic effects were more selective when injections were located in the nucleus accumbens.[42] Furthermore, an additive suppression of absence-seizures was obtained when combined injections of low doses of a D1 and a D2 agonist were performed in the core of the nucleus accumbens.[42] This is in agreement with the potentiation of antiepileptic effects observed after combined injection of a GABAA agonist and an NMDA antagonist into the SNR, at doses shown to have no effect by themselves.[42] These data suggest that the trans-striatal and trans-subthalamic pathways could cooperate in the suppression of absence seizures, and that striatal dopaminergic transmission plays a key role in the modulation by the BG of this form of epilepsy (see below).

Electrophysiological evidence for an endogenous control system by the basal ganglia circuits

The pharmacological data reported either in the model of absence seizures or in other models of generalized epilepsy have raised the possibility that some BG circuits may act as an endogenous control system able to interrupt epileptic seizures and/or to modulate their occurrence,[21,70] According to such

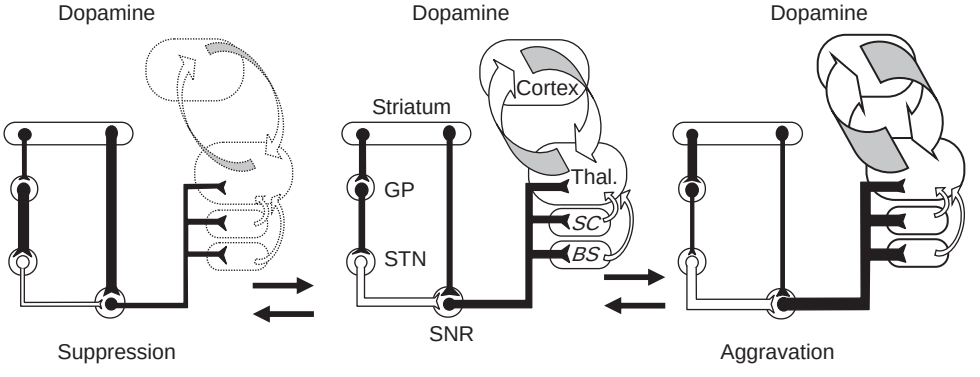

Figure 128.1 Effects of pharmacological manipulations of the basal ganglia structure. Schematic representations of the connectivity within the basal ganglia system thought to be involved in the control of absence-seizures in GAERS. Thickness of neuronal outputs is proportional to the activity of the projection, as modified following intracerebral pharmacological manipulations. An increased activity in the striatal dopaminergic tone has antiepileptic effects (left panel) whereas a decreased activity in the dopaminergic tone has proepileptic effects (right panel). For instance, dopamine at the striatal level is thought to simultaneously potentiate the inhibitory influence of the trans-striatal direct pathway and decrease the excitatory influence of the trans-striatal indirect pathway through D1 and D2 dopaminergic receptors, respectively. BS: brain stem; GP: globus pallidus; SC: superior colliculus; SNR: substantia nigra pars reticulata; STN: subthalamic nucleus; Thal: thalamus.

a hypothesis, changes of neuronal activity associated with the occurrence and/or interruption of seizures should be detected in some circuits of the BG. There is good evidence from electrophysiological recordings in both human patients and animal models, that changes in basal activity is observed in the BG concomitantly with an epileptic discharge.[71–77] In animal models, data were mainly collected during pharmacologically- or electrically-induced seizures, and the 'endogenous' nature of the observed changes of activity was thus difficult to determine. To investigate the possible relationships between unit activities in the BG and the cortical EEG during ictal and interictal periods, the genetic model of absence seizures was preferred for its spontaneous occurrence of frequent seizures and for the lack of motor components that could interfer with the recording procedure.[78,79] Single-unit recordings in GAERS maintained under neuroleptanalgesia indicated that SNR and STN neurons increase their firing rate, concomitantly with the occurrence of spike-and-wave discharges at the cortical level, whereas dopaminergic neurons of SNC tend to decrease their activity. Conversely, at the end of the seizure, SNR and STN neurons decrease their firing rate, whereas dopaminergic neurons of the SNC display a transient overactivity.[80] Because fentanyl and haloperidol used for neurolept-analgesia are known to interfere with neurotransmissions involved in the BG, we developed multi-unit recordings with a chronically-implanted movable tetrode in the freely-moving GAERS. Combined with off-line sorting of the tetrode data, this approach allowed to record single-unit activities in the SNR and showed no particular organization of the discharge mode during interictal periods, as compared to recordings performed in nonepileptic rats in previous studies.[81] However, when a spike-and-wave discharge occurred on the cortical EEG, the frequency of discharge of the SNR neurons increased and action potentials became organized in bursts (see Figure 128.2). These bursts always followed the spike component of each spike-and-wave element by a few milliseconds. In addition, a few seconds before the end of the EEG discharge, a decrease in SNR neuronal activity was often observed. These results, obtained in the freely-behaving animal, clearly showed that the spontaneous occurrence of epileptic discharges modifies the activity of SNR neurons.[78] The delay observed between the occurrence of the cortical EEG spikes and the burst of action potentials suggests that the SNR is involved in the propagation rather than the generation of the seizure. In addition, the decrease of unit activity observed before the end of the seizure, suggests that inhibition of SNR neurons could participate in the blockade of an ongoing seizure. The nature and the temporal pattern of these changes are in agreement with what could be predicted from the pharmacological data, and suggest that these events could contribute to the antiepileptic effects resulting from a physiological triggering of the control system.

The involvement of the BG is further supported by recent in vivo intracellular recordings showing that spike-and-wave discharges are associated with a transient interruption of striatal output neurons firing and a synchronized rhythmic bursting in STN neurons.[82,83] These distinct changes in activity during absence-seizures in the striatonigral and subthalamonigral pathways are likely to produce an imbalance between excitation and inhibition within the SNR and lead in turn to synchronized burst firing of SNR neurons in phase with the spike-and-wave complexes in the EEG, thus providing an endogenous mechanism controlling positively the maintenance and the duration of the seizure. Hence, the rebound of excitation observed at the end of a spike-and-wave discharge in most of striatal output neurons[82] and consistent with the decrease of SNR activity[78] might have a negative modulatory effect on spike-and-waves and thus contribute to the interruption of an ongoing absence-seizure.[83]

Role of the dopaminergic transmission

Both pharmacological and electrophysiological approaches have revealed a critical role of the striatal dopaminergic neurotransmission in the control of seizures. It suggests that this part of the BG circuit is involved by seizure propagation and/or triggering of the control circuits. Indeed dopamimetic

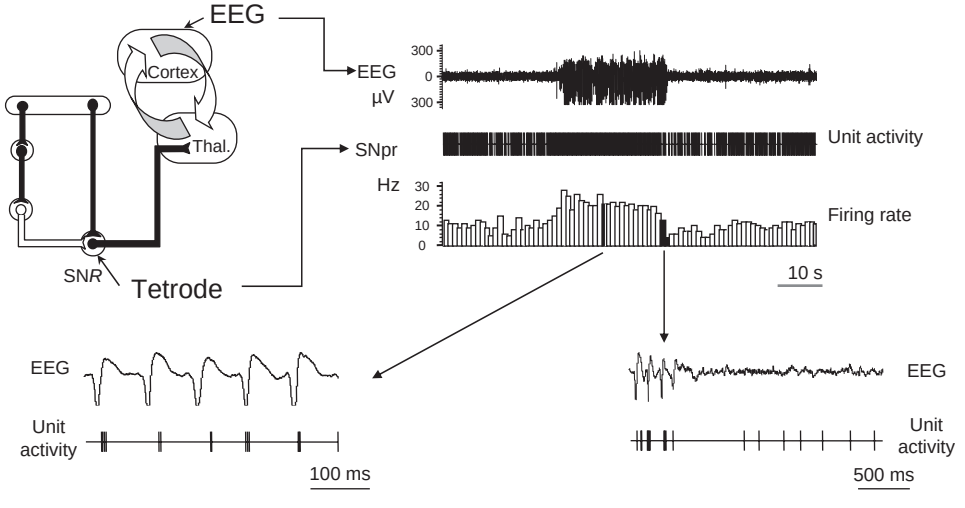

Figure 128.2 Changes in extracellular unit recordings in the SNR in a freely behaving GAERS. Cortical EEG and unit activity obtained from a freely behaving rat equiped with a movable tetrode chronically implanted within the substantia nigra pars reticulata. The lower panels display an enlargement of spike-and-wave complexes with simultaneous bursts of action potentials (left panel) and changes occuring at the end of an absence-seizure (right panel).

drugs have been reported in both human and in animals to have antiepileptic effects (for review, see Starr, 1996).[84] For example, a suppression of absence-seizures in GAERS was reported following systemic injection of dopamimetics, whereas aggravation was observed after injection of dopamine antagonists.[85] The critical influence of dopamine in the control of absence-seizures was also confirmed by experiments showing that local 6-OHDA lesion of dopaminergic neurons within the ventral mesencephalon (pars compacta of the SN and ventral tegmental area) temporarily aggravates absence seizures in GAERS (personal observations). In addition, the recurrent involvement of this neurotransmission by the repetition of seizures may result in long term modifications as evidenced in both rats and humans.[75,86,87] In fully amygdala-kindled rats, a decreased presynaptic dopamine turnover has been demonstrated in the ipsilateral nucleus accumbens, by microdialysis,[88] as well as an increase in D2 receptor binding and mRNA expression.[87,90] These changes may represent a compensatory process for the seizure threshold-lowering effects of the kindling process.[84] However, the motor patterns of the convulsive seizures (i.e., clonic or tonic movements), as well as the secondary behavioral effects e.g., stress, anxiety[91–93] learning impairment[92,94] observed in kindling are likely to also interfere with the dopaminergic neurotransmission.

Investigation of the expression of different dopaminergic transcripts in the striatum of GAERS revealed an increased level of D3 mRNA expression in neurons of the core of the nucleus accumbens in adult GAERS as compared to nonepileptic control rats, whereas no differences were observed in the shell or in other regions (dorsal striatum, olfactory tubercles, islands of Calleja). This was specific to D3 receptors since no change in the expression of mRNAs coding for other neuronal dopaminergic markers (tyrosine hydroxylase, membraneous and vesicular dopamine transporters) or D1, D2, and D5 receptors were observed. Interestingly, D3 transcripts were not increased in 21-days juvenile GAERS[95] where no absence seizures had yet occurred.[96] Our data thus suggest that this transcriptional change is likely to represent either a part of the epileptogenesis process or an adaptive response to repeated seizures. Its localization in the core of the nucleus accumbens is in line with the dopamine-sensitive antiepileptic sites in the ventral striatum and further supports the involvement of ventral structures of the BG system in the control of absence seizures.[42] Although the functional consequences of an up-regulation of D3 receptors on neurons of the n. accumbens are still unknown, it is likely to be related to the overactivity of the dopaminergic neurons observed at the end of the absence seizure (see above).

Altogether, our results and data from the literature, support the hypothesis that epileptogenesis and/or recurrence of generalized seizures induce persistent, transcriptional changes of striatal dopaminergic neurotransmission. Whether these changes represent an alteration of the controling capacities of the BG, as suggested by some clinical data,[75] or an adaptive attempt to reinforce control of seizures, remains to be examined.

Conclusion and perspectives

Although it is clear that the BG circuit cannot generate seizures and are unlikely to be involved in their initiation, numerous experimental data presented in this review have revealed that changes in the activity of the BG system influence the occurrence and/or cessation of epileptic seizures. In addition, the dynamic of changes observed in BG neuronal activity during seizures suggest that these structures stand at a nodal point not only to detect but also to interfere with an on-going seizure. Electrophysiological approaches allowing a more acute space- and time-resolution in order to simultaneously follow changes in seizure activity and changes in the activity of the BG are expected to provide further evidence for this hypothesis. In particular, it will be necessary to further investigate how this remote control system is triggered endogeneously and to determine how changes in SNR activity affect the thalamo-cortical circuit.

The collection of pharmacological and electrophysiological data in animal models of epilepsy has led to the emergence of the BG as a possible control circuit of the seizures. These experimental data have already led to initial clinical trials using high-frequency stimulation of the STN in epileptic patients.[52,97–99] These preliminary data, as well as clinical observations involving BG activity in epileptic patients[75,77,86] encourage further research in chronic models of epilepsy, to better determine the exact output circuits involved in seizure interruption, the mechanisms triggering SNR inhibition and whether the same circuits are involved in the control of different types of seizures.[100] This will allow identification of the optimal target structures and the forms of epilepsy likely to benefit from this new therapeutic approach.

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129 Repetitive transcranial magnetic stimulation

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Introduction

Transcranial magnetic stimulation (TMS) was introduced in 1980[1] as a technique for noninvasive stimulation of the brain and other parts of the central nervous system[2] and has been quickly developed as a standard procedure in clinical neurophysiology to investigate conduction properties of the pyramidal tract.[3,4] When technical limitations had been overcome it soon became clear that repetitive application of magnetic pulses to the brain was capable of modulating the excitability of cortical neurons.[5,6] Moreover, it was very soon discovered that repetitive transcranial magnetic stimulation (rTMS) could be used to induce plastic changes of cortical excitability that last beyond the period of stimulation itself. Since it had been described that rTMS may improve patients with major depression,[7] this technique is continuously in discussion as a therapeutic tool in various neurologic and psychiatric disorders.[8,9] In particular, for epilepsy rTMS seems to have the potential of evolving as a promising therapeutic alternative since there is still a substantial proportion of patients in whom – despite numerous newly-developed drugs and improved surgical techniques – seizures are not sufficiently controlled. Even more so since rTMS is a noninvasive, nondestructive technique that could fulfil substantial prerequisites for a treatment strategy in drug-resistant epilepsy syndromes with epilepogenic focus in eloquent cortical areas that can not be treated by resective surgery.

Obviously, the concept of stimulating the brain to treat epilepsy is not new. Early in the 20th century attempts were started to develop different techniques of electrical stimulation in different parts of the brain to reduce epileptic activity and to treat epilepsy. The most promising electrical stimulation procedures for epilepsy treatment are discussed in detail in an earlier chapter of this book section.

Technical considerations

Magnetic stimulation differs from electrical stimulation in several aspects: First, all electrical stimulation techniques used in epileptology so far are invasive and need surgical procedures to place the stimulation electrodes either on the brain surface or into deep brain structures. With TMS a coil with windings of a strong copper wire held against the surface of the head induces a magnetic field of up to 2 Tesla by short but strong currents of about 4000 amps delivered from high-voltage capacitors. The magnetic field penetrates the skull without diminution and, by rapid change of field strength, induces an electric current in any conductive tissue, thus also in the brain. The electrical current when flowing through the brain leads to activation of neuronal axons and induces action potentials that run along physiological pathways and connections within the brain. At that site the rTMS effects share some common aspects with electric stimulation but the stimulation effect should largely depend on the direction of the stimulating current. While with electrical stimulation the current runs from anode to cathode and current density depends on the electrode size, with magnetic stimulation the induced current runs parallel to the wire of the coil that produces the magnetic field and the current density depends on the coil shape and the distance from the coil.[10]

It should be noted that there are magnetic stimulation types other than rTMS that are also mentioned in the literature but which are not discussed here. While in rTMS studies pulsatile stimulation of high intensities are used (200 μs, 1–2 Tesla, 20–50 Hz repetition rate), for example the workgroup of Dobson[11,12] investigated the effect of constant DC magnetic fields with intensities of about 1–2 milliTesla (10^3-fold less than rTMS) on spike frequency in epilepsy patients. The electromagnetic field of power line (1–2 microTesla, 10^6-fold less than rTMS, 50–60 Hz) was investigated in many studies and also in animal models of epilepsy.[13,14] Finally, effects of a so-called magnetic field therapy were described in epilepsy[15,16,17,18] using continuous or sine-wave fields mostly with intensities in the picoTesla range (10^{12}-fold less than rTMS).)

Parameters of stimulation

As indicated above, there are some crucial factors that influence the effect of TMS and rTMS. The impact of these factors has been largely studied at the motor cortex where the effects can easily be evaluated by measuring the size of the motor-evoked potentials induced in a target muscle of which the area of cortical representation is stimulated.[9,19] It may be assumed that most of the experience from the motor cortex may hold true for other cortical areas although this has not been shown so far. The main parameters of TMS will be introduced as follows:

Coil shape

The shape of the copper wires formed into a coil has great impact on the intensity, orientation, and depth of penetration of the magnetic field. Two major types of coils are used: the circular or round coil has a circular winding of about up to

9 cm diameter. The induced magnetic field and additionally the induced current in the brain is circular, as well, which means that the magnetic field covers a great target area with similar intensity although orientation of the current is different at any point. In contrast, the so-called figure-of-eight coil consists of two adjoining circular windings of about 7 cm (and more) in diameter. With the current running in opposite directions in the two ends of the figure-of-eight, superimposition of the magnetic fields produces a focal magnetic field beneath the joint with an approximately linear orientation and, compared to the round coil, with increased penetration depth.[20,21] For the brain it seems most likely that with these coil types TMS only reaches the cortical surface of the brain, intensity strongly attenuates with depth and may not activate neurons more than 5–6 cm below surface of the scalp.[22] Field strength and penetration depth increase with stimulation intensity and with coil size but focality weakens and vice versa: the smaller the coils and the lower the stimulus intensity, the more focally it stimulates but also the more its field strength decreases.[23]

More recently, other, more complex types of coils have been designed with the advantage of improving penetration depth. The most promising is the so-called H-coil[24] which has been designed with the aim of reaching areas 3–4 cm deeper than the figure-of-eightcoil and is probably capable of activating the mesial temporal lobe, though this has not been investigated yet.

Stimulation site and coil orientation

As indicated above, the coil shape is important for the direction and orientation of the induced current. To stimulate a certain brain region it seems important where and how focal the stimulation takes place and what the orientation of the induced current is. For the motor cortex a strong dependency on coil orientation has been described.[25,26]

Pulse shape

For a long period of TMS research little attention was paid to the shape of the magnetic pulse. Mainly for technical reasons, manufacturers designed TMS devices with widely different pulse shapes: monophasic as well as biphasic pulses were used, some with asymmetrical polarity and time course. However in recent years it was shown that for single pulses as well as for rTMS, the pulse shape has great impact on the effect of brain stimulation.[27–29]

Intensity

Since the magnetic field is not homogenous, it is impossible to provide exact information about the intensity of stimulation in a specific part of the stimulated brain area.[22] Researchers have therefore opted for taking the percentage of maximal stimulator output as a measure of the stimulation intensity. For better adaptation to individual subjects and patients, intensity was adjusted according to an individual's motor threshold; this is a biological parameter and is defined by the minimal stimulus intensity needed to elicit a motor evoked potential in a target muscle when stimulating the motor cortex.

Stimulus frequency

The rate at which rTMS pulses are applied is vital for the type of induced after-effects, since rTMS can be used to induce both elevation and reduction of cortical excitability. Whether the excitability of the stimulated cortical network is up- or down-regulated and therefore is facilitated or inhibited seems to mainly depend on the stimulation frequency.[19,30] From studies on rTMS applied to the human primary motor cortex, evidence exists that rTMS frequencies of 5 Hz and above lead to an increased excitability,[5,31] while frequencies of 1 Hz or less result in reduced motor cortical excitability.[32,33]

Number of stimuli and number of repetitions

From the motor cortex, evidence exists that the after-effects of rTMS depend on the number of repetitive stimuli.[9] In treatment studies, trains consisting of 500–2000 stimuli were used on a arbitrary basis. So far, there is no evidence for a rational prediction of the number of stimuli needed to induce long-term effects and there is also no evidence regarding whether a correlation exists between the number of stimuli and the strength or duration of the after-effects.

However, there is strong evidence that daily repetition of the rTMS train leads to a magnification or consolidation of the after-effects.[34]

Physiological basis of rTMS

From a historical point of view the antiepileptic effect of TMS and rTMS was discovered somewhat by chance as described later in this chapter. When rTMS effects were first studied in humans and even when pilot studies on epilepsy treatment with rTMS in patients had started, there was still no clear idea of the physiological mechanisms behind the long-term effects and the processes that would render repetitive stimulation beneficial in epilepsy. For a better understanding it may therefore be useful to outline the main ideas regarding the physiological mechanisms thought to be involved in the rTMS effects. Although only little is proven, it seems nevertheless reasonable to build on established hypotheses regarding the physiological basis of electrical brain stimulation that were derived from the observation that long-term modulation of synaptic strength can be induced by high-frequency repetitive electrical stimulation.[35] Some time passed after the discovery of the so-called *long-term potentiation* (LTP) before a contrary phenomenon, *long-term depression* (LTD) was demonstrated, at first in the cerebellum[36] and later in hippocampal slices.[37] Furthermore, it was shown that LTP and LTD could be induced in the same neuronal structures, depending on the stimulation frequency: while high-frequency stimulation induces LTP, LTD was obtained by low-frequency stimulation[38] – but this strong dichotomy may not always hold true since the order of different stimulation types has great impact.[39] When similar phenomena were induced in neocortical neurons they were considered to be LTP-like and LTD-like phenomena, and it could be shown that these mechanisms largely share similar mechanisms.[40–42]

In several studies mainly on hippocampal tissue, mechanisms of LTP and LTD were found to contribute to

epileptogenesis[43,44] and it could be shown that low-frequency electrical stimulation is capable of reducing spontaneous as well as induced epileptogenic activity in hippocampal tissue.[45] The interaction of electrical stimulation and epileptogenesis has been largely investigated and, moreover, important animal models of epilepsy are based on kindling and other effects of electrical stimulation that enhance or induce epileptogenicity.[46,47–49] In contrast to the large body of literature on epilepsy and electrical stimulation in animals, there are far fewer studies on magnetic stimulation in animals or in tissue slices. This is probably due to technical problems with the coil dimensions needed to stimulate sufficiently (see above). Coils may be too large or brain and slices too small for stimulation focal enough to investigate particular aspects of the rTMS effects. This may be the reason why rTMS in humans was not preceded by animal studies but vice versa.

Animal studies of rTMS

When it became clearer that low-frequency rTMS, like low-frequency electrical stimulation, may have antiepileptic effects, the effect of rTMS was also studied in different animal studies. Seizure induction by intraperitoneal injection of pentylenetetrazole, a GABA antagonist, as a model for generalized seizures in the rat was investigated by Akamatsu *et al.*[50] They found that 1000 pulses at 0.5 Hz led to a prolonged latency for seizure development. Moreover, rTMS effectively prevented the development of status epilepticus of pentylenetetrazol-induced convulsions. Already investigating the effects of high-frequency rTMS some years earlier, Jennum and colleagues[51] showed that a series of 1 or 5 seconds of 50 Hz rTMS did not alter seizure induction after pentylenetetrazole injection, but that repreated rTMS over 30 days reduced the time for inducing seizures after pentylenetetrazole injection. This is well in accordance with the frequency-dependency of proepileptic and antiepileptic effects of repetitive stimulation, although in this study seizures were not directly induced neither under acute rTMS nor after repeated application.

Nevertheless in another animal model, the amygdala kindling model for mesial temporal epilepsies, the results were the opposite. A single rTMS train of 20 Hz for 3 sec resulted in elevation of after-discharge threshold[52] 2 weeks after rTMS but did not affect the kindling process itself. The interpretation of these findings is not clear. So far, complementary studies of low-frequency rTMS on the amygdala kindling model has not been performed; also a proepileptic effect of any kind of high frequency rTMS in amygdala kindling model has not been shown directly. Nevertheless, there is evidence for an antiepileptic effect of low-frequency rTMS shown indirectly in an animal model of epilepsy: using a rat flurothyl kindling seizure model, intraventricular injection of cerebrospinal fluid (CSF) of humans after 1 Hz rTMS and after 10 Hz rTMS led to a decreased kindling rate with CSF after low-frequency stimulation and tended towards a higher kindling rate, which supported the hypothesis that CSF after rTMS has antiepileptic or proepileptic properties, depending on the stimulation frequency.[53]

Nevertheless, the biological basis for the long-lasting effects of rTMS is not well understood and further studies are still needed.[54,55]

Safety aspects of TMS and rTMS

Even before repetitive application techniques of TMS were introduced, it was debated whether TMS applied as single pulses or as a series of a few pulses could produce side-effects and, in particular, provoke seizures. In order to deal with this apprehension appropriately, we studied the literature extensively.

Provided the exclusion criteria are followed (cardiac pacemakers, intracranial electronic devices, intracranial metal objects), single pulse TMS is regarded as safe in normal subjects, even in epilepsy patients.[56] Nevertheless, in a few cases epileptic seizures were observed in patients with neurological disorders,[57–59] though it was unclear whether TMS was directly responsible for them.

Single TMS also seems to be safe for patients with single seizures or epilepsy. Liepert and colleagues[60] did not observe any seizures when investigating motor pathways with TMS in 21 patients who had previously had a single seizure. In a study of 53 epilepsy patients in which motor-evoked potentials were investigated with TMS, only two patients developed complex-partial seizures of their typical semiology.[61] In another study using TMS for monitoring the conduction properties of central motor pathways in 58 epilepsy patients, seizures were not induced and the epilepsy was made worse.[62] When trying to activate the epileptic focus in 48 epilepsy patients, only six patients developed seizures, although 22 patients did develop seizures after-discharges following activation of the epileptic focus.[63] In another study of 140 epilepsy patients, only six ictal events occurred immediately or shortly after TMS.[64] Nevertheless, during verbal working memory testing, 20 patients with intractable epilepsies experienced three auras and two seizures.[65] Only one study published so far has described reproducible induction of focal seizures by TMS in one patient suffering from a focal epilepsy originating from a documented epileptic focus in the left supplementary motor cortex.[66] The semiology of seizures triggered by TMS was identical to the spontaneous ones. From a meta-analysis, overall risk of induction of seizures in epilepsy patients by single or double pulse TMS studies seems to be no higher that 3.6%.[67]

Repetitive TMS

When rTMS is used with high frequencies, epileptiform activity and seizures are more likely. Even in normal subjects, a spread of excitation was observed under high intensities of high-frequency rTMS and a seizure occurred in one subject.[68,69] In a depressed patient under rTMS antidepressant treatment, a complex-partial seizure presumably of the frontal lobe was induced.[70] When stimulating the assumed epileptic focus, Hufnagel *et al.*[71] were able to induce after-discharges in 12 of 13 epileptic patients and a complex-partial seizure in one patient, but failed when stimulating other brain areas. Trying to replicate these findings under identical conditions, Schuler *et al.*[72] only found activation of the epileptic focus in three out of ten patients while hyperventilation was more often provoked (six patients). Dhuna *et al.*[73] were unable to induce any seizure when performing rTMS on the hemisphere containing the presumed epileptic focus in intractable epilepsy patients for presurgical evaluation, but induced a seizure in one patient

after applying maximal intensity rTMS on the other hemisphere. Another group[74] was not able to induce any seizure in epilepsy patients with 30 Hz and 50 Hz rTMS, but observed reduction in spike frequency over 10 minutes after rTMS. In a more recent study on 21 epilepsy patients for presurgical evaluation, rTMS of the assumed epileptic focus was not sufficient to induce any seizure.[75] Thus, it was concluded that TMS and rTMS do not seem to be helpful in lateralization during presurgical evaluation in intractable epilepsies.[75,76]

The question of safety with rTMS was addressed in several other studies[68,77–79] and recommendations from the *International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation*, June 5–7, 1997, Bethesda, USA, are available.[80] From all studies known so far it can be concluded that the risk of inducing seizures increases commensurate with the intensity and frequency of an individual's seizures? Additionally, the intertrain interval of several rTMS trains is an important safety criteria.[77] A seizure has never been seen with rTMS at intensities below 100% resting motor threshold or at frequencies below 1 Hz. In patients with severe epilepsy, seizures may occur under low-frequency rTMS although the causative role is unlikely. Moreover, the opposite effect is assumed (see below).

Several other studies were also unable to detect side effects from TMS and rTMS. No cognitive impairment was found after TMS in normal subjects nor in patients.[81–85] Only little is known on possible morphological changes in human brain tissue after rTMS, but no lesions were found in human hippocampal tissue of two patients who received 2000 pulses of 25 Hz rTMS trains before undergoing epilepsy surgery.[86] Although it was described that electrodes may heat under rTMS and may cause tissue damage,[87] such a case has so far never been reported.

In summary, rTMS when applied according to the safety criteria appears to be relatively safe in patients with epilepsy, since conclusive evidence of TMS being a trigger of ictal events has only been found in a very few cases (see above). However, not all possible side effects have yet been thoroughly addressed and long-term side-effects are still possible.[88] High-frequency rTMS studies in epilepsy are only justified for diagnostic reasons, and the patient must be informed of the potential risk of seizure induction.

Antiepileptic effects of rTMS in humans

As indicated above, the antiepileptic effect of TMS was discovered unintentionally when attempts were made to elicit epileptic activity. When Hufnagel and Elger[63] tried to activate the epileptic focus in 48 patients with intractable epilepsies by using single-pulse TMS, they found enhancement but also suppression of epileptiform potentials in seven patients with continuously spiking epileptic foci. Additionally, they described temporary interruption of epileptiform paroxysms for 1–3 sec. in nine cases, and found persistent suppression of spontaneous spikes in one patient. These results were early evidence that TMS pulses may inhibit epileptiform activity. When applying single TMS pulses repetitively every 3 to every 10 seconds (0.3–0.1 Hz) – before the term repetitive stimulation was coined and before repetitive stimulators were built – Steinhoff and colleagues noticed a decrease in spike frequency for at least 5 min after stimulation, most prominently bilaterally when TMS was applied contralateral to the epileptic focus in seven patients with medically intractable complex-partial seizures of mesiobasal limbic onset.[89] These results may represent evidence that TMS influences cortical network excitability across the hemisphere.

In 1997, preliminary data on three patients with cortical action myoclonus were presented showing that 1 Hz rTMS over 30 min was able to reduce action myoclonus. Although applied over several days, the effect always decayed two hours after rTMS.[90]

Based on these experiences, several studies with different designs were performed to evaluate the antiepileptic efficacy of rTMS in patients. These studies are described in a short summary below, and the table gives an additional overview.

Open, uncontrolled studies

Based on the evidence of antiepileptic effects of low-frequency rTMS, an open study on nine patients with intractable temporal and extratemporal focal epilepsy was performed in order to investigate long-term therapeutic effects.[91] Seizure frequency during four weeks before and then after rTMS treatment was compared. During five consecutive days, 1000 pulses (100% motor threshold intensity, 0.33 Hz) from a repetitive magnetic stimulator were applied by an unfocal round coil (9 cm diameter) placed over the vertex. All patients tolerated rTMS treatment well and worsening of epilepsy did not occur. Eight of nine patients reported a reduction in seizure frequency or reduced severity of seizures. In all nine patients, average seizure frequency (seizures per week) was significantly reduced by approximately 39%. Two patients did not show any seizure reduction; the other patients showed decreases of less than 20% ($n=1$), 20–50% ($n=3$) and more than 50% ($n=3$). The effect decayed over 4–8 weeks.

In another open study of eight patients with drug-resistant epilepsies due to malformation of cortical development, focal rTMS with 600 pulses of 0.5 Hz led to a reduction of epileptiform activity by 46.4% and 42.1% at 15 and 30 days, respectively, after the single rTMS session. This electroencephalographic effect was accompanied by reduction in seizure frequency by 57.3% and 51.2%, respectively.[92]

Seizure reduction by 19.1% over 2 weeks after rTMS was found in seven patients with different types of extratemporal epilepsies when treated with rTMS (90% motor threshold stimulus intensity), 0.9 Hz over 15 min twice a day over 5 days, described by another group.[93] When analysed separately, they found a 35.9% reduction of complex partial seizures compared to a 7.4% reduction of simple partial seizures. Moreover, patients with smaller differences in resting motor threshold and active motor threshold showed higher reductions of complex partial seizures. However, all effects were not significant.

Most recently, the effect of hemispheric cerebellar rTMS was investigated in an open study of 6 patients with single and multiple epileptic foci.[94] During a 4-week period of 5 Hz rTMS with 100 stimuli per day and 95% motor threshold stimulus intensity, five of six patients showed a reduction in

seizure frequency by 34.8%–100%; the seizure rate returned to pre-rTMS level directly after the treatment period.

Case report studies

These positive group effects were supported by a few case reports. In a patient with focal dysplasia, biweekly treatment with one hundred stimuli at 0.5 Hz and 95% motor threshold intensity using an unfocal coil placed over the area of dysplasia reduced seizure frequency by 70% over a 4-week period of treatment.[95] With a similar protocol (0.5 Hz rTMS biweekly over 4 weeks, focal stimulation but 90% motor threshold stimulus intensity) another group found a reduction in seizure frequency of up to 42% in two patients with single focus while there was no benefit in patients with multiple foci.[96] Myoclonus-related epileptic activity could be shown to be reduced when treated with 15 min 1 Hz focal rTMS in a patient with cortical dysplasia in the primary motor cortex and continuous positive myoclus of the contralateral forehand.[97] In another patient with epilepsia partialis continua due to a cortical dysplasia in the motor cortex, rTMS (0.5 Hz, 90% motor threshold intensity, 100 pulses) nearly abolished seizure activity for a period of almost 2 months and the effect was reproduced.[98] In contrast, high-frequency rTMS with 20 Hz (50% stimulator output stimulus intensity) in two patients with epilepsia partialis continua interrupted epileptic activity for up to 24 h after rTMS and, moreover, was accompanied by a decrease in perfusion measured by SPECT.[99]

Placebo-controlled studies

Nonblinded, uncontrolled therapeutic trials and single case studies in epilepsy should be interpreted with caution since placebo effects may play a substantial role. In a trial studying 24 patients with focal epilepsy, randomized to either active or sham stimulation with 15 min 1 Hz-rTMS twice a day at 120% motor threshold stimulus intensity applied focally over the epileptic focus, the group by Theodore and colleagues[100] found a mean seizure reduction of 16% for actively treated patients and of 1% for sham-stimulated patients over a post-stimulation period of 2 weeks and a reduction of 4.5% and –0.4% over 8 weeks, respectively. The difference did not reach significance.

From a second placebo-controlled trial only an interim analysis has been published so far.[101] They carried out a placebo-controlled, cross-over design 1.0 Hz and 0.33 Hz rTMS treatment with 1000 pulses per day (100% motor threshold stimulus intensity) over 5 consecutive days with an unfocal stimulation coil placed over the vertex. For the placebo condition, stimulation with 0.66 Hz was applied using a specially designed coil with a reduced output that was ineffective in reaching the cortex. For the 17 patients who completed the study in this analysis, there was no significant difference between the 1.0 Hz, the 0.33 Hz and the placebo stimulation types. Only for the week in which stimulation was performed was there a significant reduction by approximately 40% of seizure frequency when compared to baseline – and a 2-week post-stimulation period still shows significant reduction in seizure frequency when referred to baseline. When compared to placebo, the 0.33 Hz condition fell slightly short of significance. However, the preliminary analysis of the full data set on the 23 patients who completed the full study (Tergau *et al.*, in preparation) does not show any significant effect at all for either condition, not even for the week during which stimulation was performed.

Another study [112] on 43 patients with a similar design using 0.3 Hz stimulation verum and placebo did not show any significant effects although there was a slight reduction in seizure frequency (15%) in verum group versus 9% reduction in the placebo group; additionally frequency of epileptiform EEG discharges neither showed any significant effects, only 12 patients of 38 patients showed spike reduction by >50%. With a stimulation protocol slightly changed (1 Hz) 5×1200 pulses, Fregni and colleagues (2006) reported significant reduction in seizure frequency when stimulated focally the focal lesion. EEG pattern were also reduced.

There is another study in which four subgroups were compared without a placebo condition: patients with focal epilepsies and patients with non-focal epilepsy were treated with focal stimulation and unfocal stimulation, respectively, both subgroups were subdivided in two groups with long stimulation procedure (total pulses 3000) and short stimulation (1500 pulses). There was a non-significant reduction in seizure frequency by 13.9% with a non-significant differences between long and short stimulation (−23 vs. −3%). But there was no difference at all between focal and non-focal stimulation types.

rTMS for treatment of epilepsy – where are we now?

So far, only some 80 patients with epilepsy have been included in studies using rTMS as a treatment strategy. This is far below the critical number of patients needed for drawing substantial conclusions on the antiepileptic efficacy of rTMS. Most of the uncontrolled studies indicate a positive effect showing reduction in seizure frequency either during or for a short time after rTMS of up to several weeks. Mainly low-frequency rTMS with 0.3–1.0 Hz was used, mostly with stimulus intensity just below motor threshold; the number of stimuli and the period over which treatment was performed showed large variation. However, the two controlled trials existing so far failed to confirm these positive results or showed only mild and short-lived effects. In the following, with the hope of learning from disappointments in the past, we discuss some aspects that might be important for optimization of rTMS trials in the future.

Why did controlled studies fail to show a therapeutic effect of rTMS in epilepsy patients?

The antiepileptic effect of rTMS does not exist?

The worst and simplest possible explanation for the failures of rTMS studies would be that the assumption of an antiepileptic effect from rTMS is wrong. Although a large number of animal studies and slice studies showed that repetitive electrical stimulation is capable of modulating neuronal activity and

that a special type of repetitive stimulation can reduce epileptic activity, this need not hold true for magnetic stimulation ... and need not hold true in humans. Moreover, LTP and LTD are physiological phenomena demonstrated in small and circumscribed neuronal network areas, but they might only play a minor role in epileptogenesis and 'antiepileptogenesis'. These phenomena may in humans be counterbalanced in the intact, albeit epileptic, brain if induced by rTMS at all. However, although a number of scenarios could be drawn to explain a nonexistent antiepileptic effect of rTMS, there is a large body of evidence that the effect actually exists. For the future, more studies are needed to find and explain the exact physiological mechanisms of the missing links between animal and human studies.

The stimulation type was not optimal

Two basically different rTMS techniques have been used in the studies described above. On the one hand, focal stimulation can be used to affect the epileptic focus, while on the other, unfocal stimulation may be chosen to reduce the cortical excitability of the neuronal network involved in the propagation of seizure activity. Taking into consideration the technical aspects discussed at the beginning of the chapter for both paradigms, we must conclude that there is no definitive answer so far to what direction and what orientation is needed to obtain optimal effects. From the majority of the treatment studies mentioned above, focal stimulation appears more advantageous, even in view of the two unsuccessful controlled studies by Theodore *et al*. and Tergau *et al*.[100,102] A positive effect could have been missed due to incorrect orientation and/or incorrect direction of the focal stimulation.

Another aspect may support the advantage of focal stimulation. It is known that focal stimulation at threshold intensities only activates a small area of cortex lying some 3 cm beneath the skull. It may be assumed that a mesial epileptic focus cannot be achieved effectively. This could be an explanation for the lack of better results in the study by Theodore *et al*., in which 10 of the 24 patients had a temporo-mesial epileptic focus. A subgroup analysis showed that neocortical epilepsies responded much better (24±22% seizure reduction) than mesial epilepsies (–11±28%). This difference, however, was not significant, probably due to the small sample size. Support for the hypothesis of superiority of focal stimulation is presented by the two placebo-controlled studies where focal stimulation showed seizure reduction[110] while unfocal did not (Cantello *et al*.). Nevertheless a direct comparison of those two stimulation types failed to show significant effects.[111]

But also the unfocal stimulation concept may have some support. Brain imaging as well as neurophysiological studies showed that brain areas remote from the TMS stimulation site can be modified.[103–106] However, it must be admitted that induced remote effects could lead to more contrary effects than intended, since inhibition of inhibitory neurons in the vicinity of the epileptic focus could boost epileptic activity regardless of focal or unfocal stimulation. Such a proepileptogenic effect has not been obtained so far but it may be discussed whether under certain circumstances there is a counterbalance of antagonistic effects. Specific study protocols need to be performed on suitable epilepsy syndromes to investigate further the influence of stimulation type.

The stimulation parameters were not optimal

In most of the studies, low-frequency stimulation between 1.0 and 0.3 Hz has been used with trains of up to 1000 stimuli per session and with several sessions over days and even weeks. While selection of the frequency is based on observation of rTMS effects on motor cortex excitability, the number and intensity of stimuli was chosen arbitrarily. No systematic studies have been performed to compare stimulation protocols that differ in these parameters. Regarding the repetition of sessions, there is evidence that a consolidation and/or magnification of long-term effects might occur when trains are repeated the next day, but further studies are needed to evaluate protocols with daily, biweekly stimulation or any other repetition rate. Optimal protocols might be different for different individuals.

Moreover, it is fairly unknown whether the separation between the two obviously contradictory modifications of cortical excitability, facilitation and inhibition, is fixed at a certain stimulation frequency. Indeed, a couple of studies demonstrated a possibly large inter-individual variability with regard to susceptibility to inhibitory and excitatory rTMS.[107] In addition, it is not clear whether the results with the motor cortex can be seen as generally valid for all brain regions. Nevertheless, it is well accepted in general that activation is more likely induced when higher frequencies are used and inhibition is yielded by low frequencies. This seems to be confirmed by a PET study, showing that high-frequency led to an increase of regional cerebral blood flow (rCBF) in the stimulated brain areas, whereas under low-frequency the rCBF decreased.[108,109]

The patient selection was not optimal

The epilepsy syndrome and related factors such as focus localisation, pathology, medication, duration of disease, and seizure types may be of importance for the success of rTMS treatment. Studies so far indicate that patients with focal epilepsies due to cortical dysplasias represent and optimal patient population for rTMS. This could be explained by technical characteristics (see above) but it could also be a matter of the type of cortical lesion. To investigate this further, different types of epilepsies with circumscribed cortical pathology should be compared using identical stimulation protocols.

Furthermore, the patients treated so far have been mostly drug-resistant, which means that they are a negative selection of subjects who had failed any other treatment strategy. To discover the true potential of rTMS, patients who are not drug resistant should also be studied.

Finally, the number of patients was much too small to demonstrate significant effects.

The expected effects could have been overestimated

The impression derived from initial studies is that rTMS induces long-term effects outlasting the stimulation by days and weeks. There is, however, no evidence that any other intervention – not pharmacological treatment nor stimulation procedure – can induce therapeutic after-effects of such duration. So, why should rTMS be an exception? Moreover, physiological studies on the motor cortex showed after-effects of much shorter duration. For most of the other types of brain stimulation, even for the vagus nerve stimulator (see Chapter 127),

Table 129.1 Survey on rTMS studies in epilepsy patients

Authors	Num.of pat.	Stimulation site	Coil	Pulse	Intensity (% of motor threshold)	Frequency (Hz)	Duration	Number of pulses per session	Number of sessions	Treatment period	Total num. of stimuli	Effect
Open trials												
Tergau *et al.*[91]	9	Over vertex	9 cm-round	Monophasic	100%	0.33	25 min	1000	5	5 days	5000	38.6% reduction in seizure frequency, four week post rTMS, significant
Fregni *et al.*[92]	8	Over dysplasia	Figure-of-eight	?	100%	0.5	20 min	600	1	1 day	600	46.4% and 42.1% significant reduction in epileptic discharges at 15 and 30 days post rTMS57.3% and 52.1% significant reduction in seizure frequency at 15 and 30 days post rTMS
Kinoshita *et al.*[93]	7	Over focus	9cm-round	?	90%	0.9 Hz	15 min	810	10	5 days	8100	Overall seizure reduction by 19.1% over two weeks post rTMS, with 35.9% reduction of complex-partial seizures and 7.4 reduction of simple-partial seizures. No significant effect
Brighina *et al.*[94]	6	Over cerebellar hemisphere	Figure-of-eight	Monophasic	90%	5 Hz	2 x 10 sec	100	20	Four weeks	2000	54.1% seizure reduction over four weeks during rTMS but no effect after rTMS
Case reports												
Menkes *et al.*[95]	1	Over dysplasia	9 cm-round	Monophasic	95%	0.5	3.33 min	100	8	Four weeks	800	70% reduction in seizure frequency; 77% reduction of spikes

Daniele *et al.*[96]	4	Over dysplasia	Figure-of-eight	Monophasic	90%	0.5	3.33 min	100	8	Four weeks	800	Reduction by 31–42% in two patients with single focal dysplasia during as well as after rTMSNo seizure reduction in two patients with multiple foci
Rossi *et al.*[97]	1	Over perirolandic area	Figure-of-eight	Biphasic	90%	1.0	15 min	900	1	Once	900	Number of myoclonic jerks was was reduced to 33%, jerk-related spikes were reduced in amplitude; number of jerk-related spikes did not change
Graff-Guerrero *et al.*[99]	2	Over epileptogenic region	Figure-of-eight	Monophasic	128%	20	15 x 2 sec	600	1	Once	600	Reduction of hyperperfusion in of epileptogenic focus in the two patients with epilepsia partialis continua; In one patient seizure stopped for 24 h, one patient showed only minimal improvement
Misawa *et al.*[98]	1	Over dysplasia	Figure-of-eight?		90%	0.5	3.33 min	100	1	Once	100	Epilepsia partialis continua in hand and arm was abolished over 2 months after single rTMS trial. Results were reproduced in the same patient
Controlled trials												
Theodore *et al.*[100]	24	Over focus sham	Figure-of-eight?	?	120%	1.0	15 min	900	14	1 week	12600	Over 2 weeks post rTMS: 16% (active), 1% (placebo) seizure reduction; not significant Over 8 weeks post rTMS: 4.5% (active), –0.4% (placebo) seizure reduction; not significant

Continued

Table 129.1 Survey on rTMS studies in epilepsy patients—cont'd

Authors	Num.of pat.	Stimulation site	Coil	Pulse	Intensity (% of motor threshold)	Frequency (Hz)	Duration	Number of pulses per session	Number of sessions	Treatment period	Total num. of stimuli	Effect
Tergau *et al.*[102]	17	Over vertex	9 cm-round	monophasic	100%	0.33 1.0 0.66 sham	50 min 16.6 min 25 min	1000	5	5 days	5000 5000 5000	Approx. 40% seizure reduction during stimulation for 0.33Hz condition, no seizure reduction for any other type or time period; no significant difference to placebo
Fregni *et al*. 2006	21	Over lesion (cortical malfor-mation)	Figure-of-eight	?	100%	1 Hz	20 min	1200	5	5 days	6000	Significant reduction of seizure frequency over two months and significant reduction of epileptiform EEG discharges over 2 weeks
Joo *et al*. 2007	35	Fokal over lesion	Figure-of-eight	? ? ?	100% 100% 100%	0.5 Hz 0.5 Hz 0.5 Hz	5 min 10 min 5 min	300 600 300	5 5 5	5 5 5	1500 3000 1500	Non-significant reduction in seizure frequency compared to baseline (–13.9%); long stimulation showed unsignificantly more reduction(–23%) compared to short (-3%); focal was not different from unfocal Significant reduction in spike frequency
		Unfocal	Round	?	100%	0.5 Hz	10 min	600	5	5	3000	
Cantello *et al*. 2007	43	Vertex	Round	Bipghasic	100%	0.3 Hz	55.5 min	1000	5	5	5000	Non-significant reduction –15%) in verum group (placebo –9%); non-significant reduction in spike frequency (–50% in 12/38 patients)

a higher repetition rate is described as effective. Long-term studies are needed in which rTMS treatment is performed over weeks and months, like other treatment strategies.

Conclusion

Repetitive TMS is a promising tool to modulate cortical excitability. Under certain circumstances rTMS seems to have antiepileptic properties strong enough to reduce epileptic activity in humans. rTMS at present is certainly not a procedure that could replace pharmacological or surgical treatment if applicable. Nevertheless, rTMS is safe, is a noninvasive technique and can be administered easily. Thus rTMS in the future may broaden the spectrum of therapeutic alternatives in epilepsy treatment. To achieve this goal, optimized protocols need to be developed, patient selection has to be improved and therapeutic effects should be confirmed in large controlled trials.

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SECTION 17

Surgical outcome

130 Mesial temporal lobectomy: post-surgical seizure frequency

L Jehi

Introduction

Temporal lobe epilepsy (TLE) is the most common type of partial epilepsy in adults.[1] Seizures arise from the mesial temporal structures (amygdale, hippocampus, and perhaps parahippocampal gyrus) in >90% of patients with TLE.[2] Hippocampal sclerosis (HS) represents the pathological substrate in 44–65% of mesial TLE,[3–6] with mesial TLE related to HS (MTLE-HS) recently proposed as an isolated syndromic diagnostic entity.[7] Surgical removal of the mesial structures, either in isolation via a selective amygdalohippocampectomy (SAH) or in addition to varying segments of the temporal neocortex via an anterior temporal lobectomy (ATL), was shown to be of invaluable benefit for the large patient population with pharmacoresistant TLE.[8–10] Seizure freedom after ATL correlates with reduced mortality[9,11–17] and a better quality of life, as reflected by improved psychosocial measures and employment rates.[12,18–20] Mere reduction in seizure frequency is not enough to improve most of those measures.[12] It is therefore essential to optimize our understanding of the various factors impacting postoperative seizure freedom.

Since Bengzon published the first article on outcome in 1968,[21] thousands of studies have addressed the degree and stability of postsurgical seizure freedom while attempting to identify useful prognostic factors. This chapter will review the available outcome measures, discuss the pitfalls of outcome studies, provide an overview of the published success rates, suggest proposed prognostic factors, and finally elaborate on special issues pertaining to postoperative seizure freedom.

Available outcome measures

Definitions of 'seizure-free' vary. Two major classification systems are currently available to assess postoperative seizure freedom.

Traditionally, most studies have used Engel's classification (Table 130.1), reporting favorable seizure outcomes as being either 'excellent' reflecting freedom from disabling seizures (Engel Class I), or 'good' with the additional inclusion of patients having rare seizures (Class I and II). Disadvantages of this system include the following: (a) certain outcome criteria, such as 'worthwhile improvement', are very ambiguous, leading to variation in interpretation among different centers; (b) comparison to AED drug trials is virtually impossible as those typically use '≥50% seizure reduction' as their outcome measure; (c) the 'seizure free' category (Class I) is not restricted to patients who are truly completely seizure free after surgery (Class IA); it also includes those with persistent auras, simple partial seizures, and generalized convulsions upon AED withdrawal (Classes IB–D). Since studies do not usually report outcome using Engel's classification subcategories, the independent evaluation of truly seizure free patients is not always possible.

To address the above issues, the International League Against Epilepsy (ILAE) recently issued a commission report proposing a new outcome classification scheme (Table 130.2). Completely seizure-free patients are classified separately; seizures are quantitated in each category and compared to a well-defined baseline frequency, and results can be easily compared to AED drug trials. To date, only one study[23] compared both systems in its outcome assessment, and found similar results at the last available follow-up.

Some centers reported their outcomes using internally validated scoring systems.[23–25] Others chose a pre-specified period of seizure freedom – usually 12–24 months – as reflecting a favorable outcome.[26–29]

This wide variation in outcome measures is only one of many pitfalls complicating the interpretation and comparison of the results among different outcome studies.

Pitfalls of outcome studies

First, the evaluated patient cohorts are heterogeneous with differing demographic characteristics, epilepsy duration, and pathological substrates. Some studies included patients with temporal and others with extratemporal epilepsy in the same outcome analysis.[30–33] This is problematic as certain prognostic variables may have completely different implications in different populations: febrile seizures for example may represent a good prognostic indicator for TLE patients[34–38] while conferring a grim outcome after surgery in frontal lobe epilepsy.[39] Outcome evaluations in 'non-pure' cohorts may then produce misleading conclusions.

Second, few studies were done in the era of high resolution MRI, and even less accounted for evolving pathological classifications of entities like hippocampal sclerosis and cortical dysplasia. Many 'non-lesional' patients from earlier cohorts may actually have subtle MRI lesions on current imaging.

Third, significant issues exist in the statistical methods used. We know now that cross-sectional studies[40–43] depict outcome at a snapshot in time, usually at 12 or 24 postoperative months, missing late recurrences and not adjusting for the

Table 130.1 Engel's classification of postoperative outcome

Class I: Free of disabling seizures[a]
- A: Completely seizure free since surgery
- B: Nondisabling simple partial seizures only since surgery
- C: Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
- D: Generalized convulsions with AED discontinuation only

Class II: Rare disabling seizures ('almost seizure free')
- A: Initially free of disabling seizures but has rare seizures now
- B: Rare disabling seizures since surgery
- C: More than rare disabling seizures since surgery, but rare seizures for the last 2 years
- D: Nocturnal seizures only

Class III: Worthwhile improvement[b]
- A: Worthwhile seizure reduction
- B: Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 years

Class *IV: No worthwhile improvement*
- A: Significant seizure reduction
- B: No appreciable change
- C: Seizures worse

[a] Excludes early postoperative seizures (first few weeks).
[b] Determination of 'worthwhile improvement' will require quantitative analysis of additional data such as percentage seizure reduction, cognitive function, and quality of life.

variation in the rate of recurrence over time. Univariate methods of analysis, in contrast to multivariable regression methods, do not account for the interaction among the various potential prognostic factors.[31] Studies using multivariable regression methods[30,33,43–46] do not typically account for variation of the rate of recurrence with time, nor in the duration of follow-up among patients: the significance of the prognostic factors thus evaluated only applies to seizure freedom at one point in time, the study's particular follow-up time. This may explain why studies evaluating outcome at 1 versus 5 years after surgery may have identified completely different predictors of seizure freedom. Only a handful of studies[45,47–51] used longitudinal methods of analysis better suited to analyze recurrence at various follow-up intervals.

Fourth, few prospective studies were performed.[12,52–54] Current data is largely derived from retrospective studies where multiple sources of bias compromise the validity of definitive conclusions.[55]

Rates and stability of seizure remission

Table 130.3 summarizes the results of most major TLE surgery outcome studies. Criteria for selecting those studies were publication after 1991, a minimum of 25 patients evaluated, cohorts of either exclusively or predominantly mesial temporal

Table 130.2 Proposal for a new classification of outcome with respect to epileptic seizures

Outcome classification	Definition
1	Completely seizure free;[a] no auras
2	Only auras;[b] no other seizures
3	One to three seizure days per year; ± auras
4	Four seizure days[c] per year to 50% reduction of baseline seizure days;[d] ± auras
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras
6	More than 100% increase of baseline seizure days; ± auras

[a] 'Neighborhood seizures' in the first postoperative month are not counted.
[b] Auras are only counted if they are short in duration, and similar or identical to the preoperative ones.
[c] A 'seizure day' is a 24-h period with one or more seizures. This may include an episode of status epilepticus.
[d] 'Baseline seizure days' are calculated by determining the seizure-day frequency during the 12 months before surgery, with correction for the effects of AED reduction during diagnostic evaluation.

Table 130.3 Surgical outcome in major studies evaluating pure cohorts of patients with HS

Author	Study period	Years of follow-up: mean (range)	N	Surgery	Outcome measure used		Percentage of favorable outcome at 1 yr	2 yr	5 yr	>5 yr	Date of last follow-up
Paglioli *et al.*[53]		6.7 (2–11)	80	ATL	Engel I						72%
		4.5 (2–11)	81	SAH	Engel I						71%
Sindou *et al.*[89]	1994–2003	4.4 (n/a–n/a)	100 (69 with MTS)	ATL, TL or SAH	Engel I (All)						85%
					Engel I (MTS)						91%
Kelemen *et al.*[66]	1985–2001	6.1 (2–17)	94 (46 with MTS)	ATL	Engel I		72%	66%	59%		56%
Erickson *et al.*[166]	1986–2000	4.2 (1–n/a)	84	ATL	Engel I		78%	67%			
Jeha *et al.*	1990–2000	5.5 (1–14.1)	371 (219 with MTS)	ATL or SAH	ILAE 1	All		78%	66%	53% at 10 yr	63%
					ILAE 1	MTS		71%	64%	55% at 10 yr	70%
Jeong *et al.* [44]	1994–2000	4.6 (1- n/a)	227	ATL	Engel I		81%		75%		
Spencer *et al.*[52]	1996–2001	4.6 (2–7.3)	339 (297 with MTS)	ATL	2 year remission from seizures ±auras.			46%	69%		MTS 68% Neocortical 50%
Janszky *et al.*[27]	1993–2002	n/a (0.5–n/a)	171	ATL	Complete seizure freedom to last follow-up or for ≥2 yrs at time of outcome assessment'			71%	58%		
Salanova *et al.*[16]	1984–2002	n/a	262	ATL	Engel I						65%
Kelley *et al.*[13]	1965–1974	29.9 (±4.9)	56	ATL	Seizure freedom ±auras (completely seizure free or since 5 yrs postop)		56%		52%	50% at 30 yrs	
Urbach *et al.*[79]	2000–2001	n/a (1-n/a)	45	SAH	Engel IA		51%				
					Engel IB-D		22%				
Paglioli *et al.*[57]**	1992–2000	5.47 (2–11)	135	ATL or SAH	Engel IA		85%	77%	74%	66% at 10 yrs	
Urbach *et al.*[54]	1999–2000	2	209	n/a	Engel IA		73%				
McIntosh *et al.*[14]	1978–1998	9.6 (0.7–23)	325	ATL	Engel I[a,b,d]	All	61%	55%	48%	41% at 10 yrs, 37% at 15 yrs.	
						HS	68%	62%	54%	47% at 10 yrs, 43% at 15 yrs.	
Lowe *et al.*[18]	1993–1999	5.8 (2–9.2)	48	ATL	Engel I		83%	76%	64%[a]		
Stavem *et al.*[46]	1988–1992	n/a(2-n/a)	63	ATL	Engel I			44%			
Kobayashi *et al.*[41b]	n/a	4.8 (1.6–9.8)	20	ATL or SAH	Engel I						85%
Hardy *et al.*[40]	1991–1998	3.8 (1-n/a)	118	ATL	>75% reduction in seizure frequency						92% (of those 62% seizure free except auras)

Continued

Table 130.3 Surgical outcome in major studies evaluating pure cohorts of patients with HS

Author	Study period	Years of follow-up: mean (range)	N	Surgery	Outcome measure used	Percentage of favorable outcome at 1 yr	2 yr	5 yr	>5 yr	Date of last follow-up
Yoon et al.[47†]	1972–1992	8.4 (3.1–20)	175	n/a	'Continuously seizure-free'	51%				
Kilpatrick et al.[104††]	1993–2002	5.9 (n/a)	80	n/a	Engel I All MTS					75% 76%
Jutila et al.[58]	1988–1999	5.4 (3 months–10.5 y)	140	ATL or SAH	ILAE 1	64%	58%	50%	50% at 9 yrs	58%
Wieser et al.[75]	1975–1999	7.2 (1–24)	369 (with MTLE, 151 with HS)	SAH	Engel I ILAE Class 1a	71% 56%	70% 50%	65% 38%	62% 34% at 10 yrs	66.9% 57.1%
Hennessy et al.[28]	1975–1995	5.2 (n/a)	116	ATL	12 consecutive months of absolute seizure freedom ± auras			67%		
Wiebe et al.[9]	1996–2000	1	80	ATL (in all except one with SAH)	Freedom from seizures impairing awareness	58%				
Foldvary et al.[45]	1962–1984	14 (2.1–33.6)	79	ATL	Seizure free	63%	53%	52%	45% at 10 yrs	65% Engel I 35% ILAE 1a
Kilpatrick et al.[42]	n/a	3.2 (1.7–5)	56	ATL	Seizure freedom ± auras					86%
Salanova et al.[15**]	1984–1995		145	ATL		66%	63%	60%	55% at 10 yrs	
Assaf et al.[114]	1989–1995	n/a (2–n/a)	75	ATL	Seizure free or auras only					69%
Hermann et al.[159]	n/a	0.5–0.7	30	ATL (± superior temporal gyrus resection)	Seizure free without auras or simple partial seizures					55–60%
Schuh et al.[106]	1990–1996	n/a (1–n/a)	102	ATL	Engel Ia Engel Ib-d					55% 15%
Radhakrishnan[43]	1988–1991	3.6 (2–5.7)	175	ATL	Seizure free or nondisabling seizures at last follow-up					77%

Chung *et al.*[167]	1989–1996	n/a (1–n/a)	50	ATL	Engel I				78%
Lancman *et al.*[98]	1992–1994	n/a (1–n/a)	108	ATL	Engel I				69%
Blume *et al.*[29]	1978–1992	5.5 (1–16)	100	ATL	Seizure free for ≥2 years				58%
Silander *et al.*[168]	1980–1990	n/a (2-n/a)	62	ATL	'Seizure free'		53.2%		
Zentner *et al.*[169]	1987–1993	3 (1–6)	178	ATL or SAH	Engel I				62%
Sperling *et al.*[12]	1986–1990	5	89	ATL	Engel I			70% (55% ILAE1)	
Arruda *et al.*[105]	n/a	2.8 (1–n/a)	74	ATL or SAH	Engel I and II				72%
Mihara *et al.*[170]	n/a	5.7 (2–11.9)	132	ATL or SAH	Engel I				70%
Holloway *et al.*[171]	1989–1992	n/a (1–n/a)	28	ATL	Engel I				75%
Loring *et al.*[172]	1988–1992	n/a (1–n/a)	55	ATL	'Seizure free'	80%			
Liu *et al.*[173]	1987–1990	1.1 (0.2–3)	35	ATL	'Seizure free'				28.5%*
Chung *et al.*[139]	1980–1986	n/a (2–n/a)	59	ATL	Seizure free ± auras during the second postoperative year				62%

[a] Assessed at 63 months.
[b] Familial MTLE.
[c] Bold prospective studies.
[d] Italic: all TLE (not distinguishing MTLE from neocortical).
[e*] Those were SF since discharge. An additional 34.2% became SF 'after early attacks'... so maybe included patients with immediate postop sz.
[f**] Included in cohort published in 2005.
[g†] includes extratemporal (temporal only 140).
[h††] includes Kilpatrick 1999.

lobe epilepsy (MTLE) cases, and clear outcome measures and description of the statistical design. When cohorts from the same center were evaluated twice, we only show the most recent evaluation.

In general, outcomes are favorable. One randomized controlled trial[9] showed that only two patients need to be treated surgically for one patient to become free of disabling seizures. This is superior to most interventions in neurology. Several meta-analyses using retrospective studies,[31,32,55,56] and few prospective studies[12,52–54] showed comparable results with about two-thirds of the patients becoming seizurefree postoperatively, compared to 5–8% with medical therapy. Similar outcomes were shown in cohorts of pure HS.[18,27,28,40–42,44,54,57] Favorable outcomes of more than 50% are still seen more than 10 years after ATL reflecting a sustained benefit.[13–15,45,47,51,57,58]

Outcomes are usually stable. If a patient is seizure free at 1 year postoperatively, the likelihood of remaining seizure free is 87–90% at 2 years, 74–82% at 5 years, and 67–71% at 10 years.[13–15,43,45,47,59–61] If a patient was seizure free for 2 years postoperatively, chances of seizure freedom increase up to 95% at 5 years, 82% at 10 years, and 68% at 15 years.[14,23,45,60,62,63] So, seizure-freedom for 2 years might be a better predictor of long-term outcome, although both the 1-year and the 2-year states correlate fairly well with future outcome.

Timing of seizure recurrence: early versus late relapse

Most recurrences happen early during the postoperative course with more than half of first recurrences occurring within 6 months,[12,45,64] 62–86% within the first year,[15,45,51,58,65] and up to >95% within 2–5 postoperative years.[12,15,45,51,65]

An initial phase of steep seizure recurrence is followed by a relapse rate of 2–5% per year for 5 years with subsequent more stable seizure freedom.[14,45,47–51] Recent data suggest that prognostic factors affecting those two phases of recurrence are distinct,[27,47,51,66] possibly reflecting different mechanisms for early versus late relapses.

Multiple factors have been implicated in early recurrences, mostly attributed to incomplete resection of the epileptogenic zone. However, the factor most consistently associated with late relapses (beyond 2–5 years) is lack of abnormal pathology,[47,51] suggesting possibly an underlying diffuse functional abnormality at the molecular or cellular level.[51] An underlying 'age-dependent etiology' of surgical failures was proposed in a recent prospective multicenter study where delay to remission predicted later relapse in medial TLE patients.[52] Long epilepsy duration,[27] increasing age at surgery,[52,61] preoperative bilateral interictal spiking(<80% from one side) with early ictal contralateral propagation (>5 sec) and postoperative ipsilateral spiking[66] were also implicated. Many of the above risk factors are actually seen with long-standing HS. Knowing that HS is likely a progressive disease as suggested by animal studies,[67] increase in the incidence of bilateral spiking with time,[68] the progression to temporal lobe atrophy in chronic epilepsy,[69] and the proven bilaterality in most cases on MRI[70] and pathology[3,4] might make this entity an ideal 'age-dependent etiology' where both genetic[41,71,72] and environmental factors lead to surgical refractoriness after years leading to medical refractoriness.[27]

'Running-down' phenomenon

The counterpart of late seizure relapses also exists. The 'running-down' phenomenon, defined as the late remission of postsurgical seizures,[73] occurs in 3.2–20% of TLE surgery cases.[22,23,44,66,73,74] The frequency of seizures during the running-down interval may be up to several per month,[35] but a seizure-free state is usually achieved within two years.[35,60,62] The most accepted explanation for this phenomenon is a dekindling effect, an opposite process to secondary epileptogenesis, where the induced synaptic dysfunction gradually declines in the surrounding epileptogenic cortex after pacemaker resection, and eventually 'runs itself down'.[35,73,74] Patients in this group are more likely to have a history of febrile seizures,[35] normal neurological examination,[35] unilateral interictal EEG preoperatively,[23,35] etiologies other than head trauma or encephalitis,[35] and a smaller and more anterior epileptiform preresection EcoG,[35] i.e., findings consistent with a more localized anterior epileptogenic focus when compared to those who continue with refractory seizures. Furthermore, this phenomenon occurs more in SAH patients compared to ATL (12% vs 20%)[35,73,75] with seizure freedom being achieved earlier in ATL compared to SAH (2 yrs vs 2.6 yrs). This supports the notion that patients patients who experience the 'running-down phenomenon' have foci of 'intermediate epileptogenicity' between restricted epileptogenic zones in those who immediately go into remission, and larger, often more posterior epileptogenic zones of refractory cases who never remit.[35]

Possible predictors of recurrence

Clinical variables

Age at onset of epilepsy

Patients with an earlier age at onset of epilepsy (usually <5 years)[57,58] or at the initial, often febrile, precipitating insult[76,77] were up to three times[58] more likely to have a favorable postoperative outcome. Some investigators proposed that this variable actually predicts HS which is the actual good prognostic indicator.[28,42] This theory is supported by the observation that those patients were more likely to have features typical of HS such as unilateral hippocampal atrophy on MRI,[76] focal ictal EEG[58] and predominantly partial seizures,[58] and by the fact that age at onset per se was of no prognostic value in studies evaluating pure cohorts of HS[28,40,42] or controlling for pathology.[14,51,52] One study, however, showed that the age of occurrence of remote CNS infection was predictive of outcome regardless of the finding of MTS on MRI suggesting an independent correlation between the age of infection and the resultant cerebral injury.[77]

Duration of epilepsy

Many studies found no correlation of epilepsy duration with outcome.[12–15,28,35,42,43,45,46,51,52,57,58,78,79] A long history of seizures correlated with worse outcome in multiple studies on univariate analysis.[12,23,49,80–83] In some of those same cohorts,

this influence disappeared when multivariate analysis was performed adjusting for other more solid indicators of outcome.[14,44] Janszky found that epilepsy duration predicted long (at 5 yrs) but not short-term (at 2 yrs) outcome.[27]

Multiple theories attempted to explain those findings. One hypothesis relates epilepsy duration to secondary epileptogenesis as some data proposed a link of longer seizure history in patients with TL tumors to a higher incidence of bilateral independent EEG foci.[84,85] However, a similar incidence of secondary discharges have been described with illness of shorter length.[86] A second hypothesis may be that different epileptic foci mature at different rates, possibly in relation to original pathology or genetic predisposition.[47] In one study, the influence of epilepsy duration disappeared after adjusting for the occurrence of generalized seizures which remained as the only independent predictor of outcome. The authors hypothesize that a long history of seizures may then just correlate with the development of generalized seizures.[14] This may be possible since prior literature suggests that seizures may evolve and become more complex with time.[87,88]

Age at surgery

Most studies found no correlation between age at surgery and seizure outcome.[13,14,23,28,33,34,40,42,43,45,46,51,57,76,79,89] One longitudinal study in HS patients found that cases who were ≤24 years old at surgery were about four times more likely to be seizure free at 5 postoperative years when compared with the older surgical group (36 years or older).[44] Few other studies found similar results.[12,35,90]

One should note here that successful and safe ATLs have been performed in the elderly (>50 years old), although chances of achieving seizure freedom are not as high as in younger patients (3/6 SF in Cascino *et al.*,[91] 6/20 in Mclachlan *et al.*,[92] 16/30 in Sirven *et al.*[93]) versus 75% in younger individuals.[93] Older patients however were not more likely to have neuropsychological deficits from surgery and enjoyed the same benefits as young patients with regard to driving.[93] Therefore, older age by itself should not be a deterrent from surgery.

Absence of secondarily generalized tonic-clonic seizures (SGTCS)

Only 57% of MTLE-HS patients with SGTCS achieved a 1-year remission compared to 80% remission rate in those who had only partial seizures in one study.[28] Patients who had no GTCs were 2.2 times more likely to be seizure free 5 years after surgery in another study.[44] This effect may be most significant when GTCs are frequent (>2/year) and occurring within 3 years of surgery.[14] It correlates with early (by 2 years) but not later recurrences.[27,51] Although many studies of mixed TLE subgroups identified a prognostic role to GTCs,[33,51,58,82] one recent prospective multicenter trial found that their significance is restricted to outcome of MTLE patients.[52] No correlation to outcome was found in smaller or cross-sectional studies.[42,46,83,94]

SGTCS are not typical of MTLE-HS.[7,87] Their occurrence correlates with more extensive hippocampal sclerosis[95] and with multifocal irritative areas.[96] MTLE patients who had SGTCS prior to PET examination have an extended hypometabolism compared to those who have no SGTCS.[97] All those findings suggest that SGTCS may affect outcome through reflecting a diffuse epileptogenic zone or secondary epileptogenesis.

Preoperative seizure frequency

While multiple studies found no correlation between seizure frequency and outcome,[23,33,42,44,52,79,82,83,98] frequent seizures (>20/month) were associated with lower rates of seizure freedom: 50, 44, and 28%, and 17% vs 72, 67, 56%, and 50% SF estimates at 6 mo, 1 yr, 5 yr, and 10 yrs in one study[45] and 80, 74, 67% vs 89, 84, and 79% SF at 6 mo, 1 yr, and 2 yr in another study.[51]

History of febrile seizures

Data regarding the prognostic significance of febrile seizures are again contradictory. Multiple studies found no effect.[27,28,42,43,52,58,99] Some suggested that any proposed beneficial effects of febrile seizures found in many studies[34–38,52,100] simply reflects their association with HS.[43] The differing view argues that complex febrile convulsions, in contrast to simple febrile convulsions, correlate with a more restricted epileptogenic zone and constitute the main favorable prognostic indicator[15,27,52] and that failure to distinguish between the two types of febrile convulsions in analyzing outcome would miss this interaction. In fact, Janszky found in 2003 that complex febrile convulsions predicted a 91% SF rate at 2 years in MTLE (versus 64% if absent).[36] Re-evaluating the same cohort of patients 2 years later but without differentiating between simple and complex febrile convulsions, this effect could not be re-confirmed.[27]

Preoperative auras

No correlation between occurrence of auras and outcome was proven.[15,35,44,51,83]

Imaging variables

Magnetic resonance imaging

Multiple studies[24,43,48,52,83,101–105] and a recent meta-anlaysis[56] concur that a unilateral MRI abnormality is one of the strongest predictors of a good surgical outcome. Patients with MRI evidence of HS had a 54% chance of seizure freedom at 10 years after ATL compared to 18% if MRIs were normal in a recent longitudinal study.[14] However, the presence of ANY unilateral temporal MRI lesion also confers a good prognosis.[14,43,46,58,89,101,104,106,107] Recent data suggests similar outcomes regardless of the nature of the MRI lesion, although more research is needed to clarify this point.[14,54]

Concordance of imaging with ictal and interictal EEG improves outcome,[56] up to 94% at last follow-up in certain studies.[43] In fact, concordance of interictal EEG and MRI represented the test combination of closest association with outcome in MTLE.[108,109] The traditional view that a normal MRI is an automatic correlate to surgical failure[43,48,110] has recently been challenged by several studies showing seizure freedom rates of 41–48% as far as 8 years after ATL.[40,51,111–113] The pathologic substrate of this category of patients remains open to debate. Some findings suggest that successfully treated patients with normal MRIs actually represent undetected HS. This is supported by better seizure freedom rates of 78%[111]–100%[112] when presurgical evaluation is consistent with a mesial temporal focus: a history of febrile seizures,

anterior interictal discharges and a unilateral regular theta temporal ictal rhythm predicted better outcomes in 17 patients with normal MRI.[111] Those findings have all been correlated with HS on pathology.[114,115] In one study, all patients with a good outcome and normal MRI had pathologically confirmed HS.[105] Conversely, another study concluded that most cases of normal appearing hippocampi on high-resolution MRI have neocortical TLE since they had less febrile seizures, more delta rhythms at ictal onset and more extensive lateral neocortical changes on PET with surgical outcomes still comparable to those of MRI obvious HS[113] It should be emphasized that surgery was successful in nonlesional patients only when performed in context of concordant EEG and PET data.[51,113] 'Normal' MRIs correlating with bad outcomes in older studies using lower quality imaging may have included patients with extratemporal or contralateral pathology, findings that would currently exclude viable surgical options.[51,113] Focal epileptogenic zones may arise from tissue with microscopic or cellular dysfunction that is too subtle to be visible on MRI, but may still be amenable to surgical treatment.[51] A normal MRI should not therefore preclude a presurgical evaluation because an ATL performed with concordant presurgical data may still offer major benefits in refractory patients where with other treatment modalities such as AEDs and VNS, the chances of seizure freedom for more than 1 year are still less than 5%.[116,117]

Bilateral MRI lesions, including grossly bilateral HS, reflect multiple potentially epileptogenic foci and correlate with a worse surgical outcome: 58% seizure free at 2 years compared to 78% when compared to unilateral lesions or even normal MRI.[51,101,103,118] Subtle hippocampal asymmetries in studies using volumetrics were less predictive of outcome.[70,119]

Nuclear imaging

Unilateral temporal hypometabolism on FDG-PET predicts a good surgical outcome in patients with MTLE.[107,120–123] This effect is independent of pathological findings and is observed regardless of whether MRI is normal or not. In a recent review of the literature,[120] Casse found that 86% of patients with unilateral temporal hypometabolism ipsilateral to the side of surgery had a good outcome as defined by more than 90% reduction in seizure frequency or Engel Class I or II. This number was slightly reduced to 82% if the MRI was normal. Chances of successful outcome, similarly defined, dropped to 62% when PET was normal and to 50% when it showed bitemporal hypometabolism.[120] With extratemporal hypopmetabolism, chances of seizure freedom are even worse: complete seizure freedom at last follow-up (mean 6.1 years) was seen in 45% of patients with extratemporal cortical hypometabolism confined to the ipsilateral cerebral hemisphere, and only 22% with contralateral cortical hypometabolism.[124]

Abundant data supports the usefulness of ictal SPECT in localizing the epileptogenic zone in TLE[125–130] with 70–100% of ictal being correctly localising and only 0–7% incorrectly localizing.[130] Clear correlations with postoperative outcome, however, need further clarification. Atypical perfusion patterns on ictal SPECT correlated with lack of pathology in the surgical specimen and with a poorer surgical outcome (33% SF after 2 years of follow-up) when compared to typical (60% SF after 2 years), typical with posterior extension (69%) and even bilateral temporal hyperperfusion pattern (67%).[131] Multiple other studies have also suggested that a correct localization of the epileptogenic focus by ictal SPECT correlates with a favorable seizure outcome.[132–136] This conclusion was not confirmed though when a multivariate analysis was performed evaluating the predictive value of multiple noninvasive modalities: Son *et al*. found that while MRI, EEG, and PET had comparable predictive values for Engel Class I, SPECT had less predictive value.[137] Results for interictal SPECT suggest that it is relatively poor at localising the seizure focus.[130] Further research is needed to clarify the role of SPECT in TLE.

Electrophysiological variables

Noninvasive EEG

Focal interictal EEG predicts a favorable outcome when lateralized to the side of surgery,[35,43,57,138,139] or when highly localized to the resected temporal lobe.[28,30,35,57,66,94] Patients whose interictal EEGs showed ≥90% predominance on the operated-on side had an 80% chance of complete seizure freedom after a mean 5.5 years of follow-up versus 54% in those with lesser degrees of lateralization in a recent prospective study.[57] In general, interictal evidence of a diffuse irritative zone predict a worse outcome: postoperative seizure freedom is worse when interictal spiking was posterior temporal,[35,114] extratemporal,[28,43] or bitemporal[35,43,66,94] in multiple studies. Posterior temporal and extratemporal spiking in patients with pathologically confirmed HS may reflect diffuse epileptogenicity, or 'dual pathology' with associated neocortical epileptogenic zones thereby explaining the associated worse prognosis.[28,35,43] However, prognostic implications of bilateral interictal spiking on surface EEG deserve more careful consideration, as they do not automatically preclude postoperative seizure freedom. One study found that if ≥90% of surface interictal bitemporal spikes arise from one temporal lobe, excellent outcome is possible (92% seizure-free in the second postoperative year vs 50% if <90% lateralization), and further evaluation with depth EEG electrodes may not even be indicated.[139] In the presence of a unilateral temporal structural MRI abnormality (HS or other lesion),[94,140,141] and with lateralizing WADA or neuropsychiatric testing,[141] up to 64% of patients with bilateral interictal spikes achieved complete seizure freedom at ≥1 year postoperatively[141] when seizure onset was strictly unilateral on invasive evaluation. A history of febrile seizures or early onset of epilepsy (prior to age 3–6 years)[94,100] also correlated with favorable outcome in patients with bitemporal interictal spikes. Such a constellation of findings (clear unilateral HA on MRI, unilateral predominance of spikes, lateralized Wada, history of febrile seizures) are consistent with unilateral HS: contralateral spiking may be spread from a surgically treatable hippocampus. If, however, MRI is normal or shows widespread abnormalities, then seizure recurrence is the rule[140–142] as an extratemporal focus spreading to both temporal lobes or bitemporal epilepsy become likely.

Many recent studies failed to show a correlation of lateralization or localization of interictal EEG with outcome.[24,27,40,52,83,99] This is felt to reflect a selection bias as one study found that unilateral interictal epileptiform discharges occurred more frequently in patients who underwent TLE compared to those who had a presurgical evaluation but ultimately did not undergo surgery, suggesting that patients with unilateral discharges are more likely to be chosen for surgery.[27]

Similar concepts apply to the prognostic value of ictal EEG. Again, focal[58] or anterior[114] ictal EEG correlates with a more favorable outcome, and patients who had bitemporal ictal onsets on surface EEG still achieved seizure freedom rates of up to 64%[141] at one postoperative year if seizures were exclusively unilateral with depth recordings and imaging or neuropsychological testing were also consistent with unilateral temporal dysfunction.

Absence of epileptiform activity on postoperative EEG at 3 months,[43] 6 months,[51] or 1 year[143,144] all correlate with seizure freedom.

Invasive EEG

Depth electrode evaluations have traditionally been used to clarify lateralization of the epileptogenic zone, whereas subdural recordings may help define its extent. Those modalities are therefore reserved for patients with a poorly defined epileptogenic zone, which may explain poorer outcomes seen in patients who required invasive recordings preoperatively compared to those who did not.[13,16,30,51,145] Specific findings obtained with those evaluations also help to predict postoperative seizure frequency. During depth recordings, exclusively unilateral seizure onset,[94,141,146,147] and ictal spiking as opposed to low-voltage fast activity, electrodecrement, or any other rhythmic sustained activity at seizure onset,[148] represent well-documented predictors of surgical success, whereas evolution into distinct contralateral electrographic seizures lowered seizure freedom from 84% to 47% at one postoperative year.[149–151] Short interhemispheric propagation times, ranging from <1 sec[152] to <8 sec[147] correlate with seizure freedom. Favorable prognostic variables with subdural evaluation include a short duration between EEG and clinical seizure onset,[153] and anterior and/or middle basal temporal ictal onset group[154] as opposed to diffuse or posterior temporal onset.

Surgical technique and outcome

The side of surgery does not correlate with outcome.[13,35,36,42,46,51,57,89] Similar seizure freedom rates have been observed with SAH and ATL.[22,51,53,57,105] Many studies failed to correlate the extent of temporal resection,[40,58,89] the extent of hippocampal resection,[13,33,155,156] nor having a mesial versus neocortical resection[51,52] to outcome. Those studies, however, did not evaluate patients with MTLE separately. In the presence of unilateral MTLE with HS, the extent of mesial resection becomes a very important predictor of postoperative seizure freedom.[7,46,56,99,157,158] In a prospective, randomized, blinded clinical trial, Wyler *et al.* found that only 38% of patients where the hippocampal resection was limited posteriorly by the anterior edge of the cerebral peduncle (partial hippocampectomy) were seizure free at 1 year, compared with 69% of those where the hippocampus was removed further, to the level of the superior colliculus (complete resection).[10] Using intraoperative electrocorticography may limit the extent of hippocampal resection without compromising outcome for both MTS and non-MTS patients.[155] The amount of amygdala that must be resected to achieve seizure freedom is unclear, although one study found no correlation between residual amygdalar tissue and outcome.[99] The ideal extent of lateral temporal resection also remains to be defined. Evidence from several retrospective,[25,46] and one prospective[159] study suggest it has no relation to outcome, while older studies reported better outcomes with more extensive lateral resections.[29,160]

In the presence of a well-circumscribed lesion, such as a tumor or a vascular malformation, a lesionectomy might suffice unless there is associated hippocampal atrophy.[7,161–163] In such cases of dual pathology, complete seizure freedom at last follow-up was lowered from 73% with lesionectomy plus mesial temporal resection to 20% with mesial temporal resection alone, and 12.5% with lesionectomy alone.[164]

Etiology, pathology, and outcome

When pathological findings in the resected temporal lobe were restricted to gliosis, worse short and longterm outcomes have consistently been observed.[47,48,51,81] In a recent longitudinal study of 371 patients, 44% of cases who only had gliosis were completely seizure free at 8 years, compared to 64% if a specific pathological diagnosis was identified.[51]

Furthermore, many,[14,33,43,52] but not all[30,47,51,61,66,83,123] studies described more favorable outcomes if either HS or any other clear lesion was identified in MTLE. It is not clear, however, whether the specific type of pathological abnormality affects outcome. Seizure-freedom rates were similar between HS and other types of lesions in many recent,[14,51] or prospective[52,54] studies, although the older literature[48,59] had suggested higher rates of late recurrence for MTLE-HS. This was thought to reflect a progressive quality of MTLE-HS. It is also possible that outcome depends not only on the presence of HS, but also on its severity: worse disease may predict better outcome. One group found that 84% of patients with classical HS, as defined by neuronal loss and sclerosis in CA1, CA4, and the granule cells of the dentate gyrus, achieved at least 95% seizure reduction at last follow-up, compared to only 29% of those where cell loss was restricted to the dentate gyrus and/or CA4.[165] Another group also found that rates of Engel Class I outcomes at last follow-up increased from 60 to 76 to 89% as the pathological severity of HS ranged from mild to moderate to severe.[22]

Conclusion

Epilepsy surgery is an essential treatment modality for patients with pharmacoresistent MTLE. Our knowledge about the predictors of postoperative seizure freedom and the mechanisms of recurrence is still evolving. Multiple factors seem to influence outcome. The ideal surgical candidates are those with concordant presurgical evidence suggestive of focal, and well-localized epileptogenic foci. Clinical, electrophysiological, or imaging findings suggestive of bilateral or diffuse pathologies tend to predict worse outcomes. Further research is needed to evaluate the implications of our current knowledge on the mechanisms of seizure recurrence.

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131 Resective surgery in children

T Loddenkemper and E Wyllie

Introduction

Surgery has become an established therapy for selected patients with pharmacologically intractable epilepsy.[1] Since the report of the first cases early in the 20th century,[2] advances in neuroimaging and surgical techniques have made this treatment option also available to children and infants. Seizure outcomes have been favorable in adolescents and children,[3–5] and even in infants.[5–11]

The first randomized prospective study comparing medical treatment with epilepsy surgery in adult epilepsy patients demonstrated a higher percentage of seizure-free patients in the surgical group and a higher quality of life following surgery. Additionally, one patient in the medical group died of sudden unexplained death.[12]

Advances in the areas of medical refractoriness, localization of the epileptogenic zone, functional cortical representation and mapping, and plasticity and adaptability of the developing brain as well as postoperative seizure outcome allow us now to use epilepsy surgery in more and more carefully selected children and even infants. Candidate selection has to be guided by seizure semiology and frequency, age-related variation in etiology, localization of the epileptogenic zone in relationship to functional cortical areas and has to consider possible risks and benefits of surgical intervention.

Candidate identification and selection

Medically intractable seizures

In theory medical intractability means resistance of seizures to any antiepileptic medication without major side-effects from medications. Practically, and in order to determine intractability of seizures, ineffectiveness of antiepileptic drug treatment needs to be demonstrated. Trials of combinations of all drugs and drug combinations may take several years. Adequate pharmacological treatment needs to be monitored by serum drug levels. Despite of the development of many new antiepileptic drugs, the percentage of patients with pharmacologically intractable epilepsy has remained stable. Children that do not respond to older antiepileptic drugs are therefore also less likely to respond to newer medications.

Kwan and Brodie studied 525 patients (including adolescents and children, median age 29 years) that were not being treated for epilepsy at the time of referral.[13] Among 470 patients that had never received and antiepileptic drug before 47% became seizure free after treatment with the first antiepileptic drug, 13% responded to the second drug and additional 4% responded to a third or multiple antiepileptic medications. Despite inclusion of newer antiepileptic drugs, 36% of patients remained unresponsive to AED treatment, and predictors for persistent treatment were symptomatic or cryptogenic epilepsy and patients with more than 20 seizures prior to initiation of treatment.[13] Patients who did not respond to the first drug were also less likely to respond to a second drug, if treatment was discontinued due to ongoing seizures. Multiple clinical medication trials will only indicate medical intractability asymptotically, but never with absolute certainty.

Reasons for apparent intractability may include treatment of non-epileptic seizures with AEDs[14] or noncompliance in adolescents. A review of 21 pediatric cases referred for epilepsy surgery revealed drug treatment omissions, and two children with structural lesions improved significantly with carbamazepine treatment.[15] Confirmation of medical intractability is therefore always important. However, this should take place in a timely fashion as ongoing recurrent seizures pose a threat to the child's overall wellbeing and to the developing brain, including cognitive decline[16] and neuronal structural changes and injury.[17,18]

Referral for epilepsy surgery is warranted in patients with focal epilepsy. The decision may therefore also be influenced by the probability of seizure control in case of a surgical intervention. In excellent surgical candidates, e.g., in patients with a circumscribed benign tumor on imaging and congruent seizure semiology and EEG findings, the decision for surgery may be made earlier than in less surgically remediable cases. Definition of medical intractability and the decision for epilepsy surgery is therefore also a balance between probability of seizure freedom after medical and after surgical treatment. Nevertheless, even seizure semiology and EEG findings may be misleading in predicting the outcome after surgical intervention in children. There is evidence that patients with generalized seizure semiology have become seizure free after epilepsy surgery.[8] Based on our own experience, selected patients with presumably generalized epileptiform discharges may also be candidates for resective epilepsy surgery.

Identification of the epileptogenic zone

Resective epilepsy surgery aims towards complete removal or disconnection of the epileptogenic zone without removing eloquent cortical areas. The epileptogenic zone is "defined as

the area of cortex indispensable for the generation of clinical seizures."[19] At this point the gold standard and proof of identification of the epileptogenic zone is therefore resection of this cortical area followed by seizure freedom. Prior to surgery, several techniques can be used in conjunction in order to estimate the epileptogenic zone prior to surgical intervention, such as history and physical examination, seizure semiology as documented by history taking and video recordings, (Video-) EEG, neuroimaging and functional tests.

History and physical examination

History and physical examination in the presurgical evaluation of children with epilepsy includes the time of onset of seizures and identification of different seizure types, detailed description of seizures according to the patient and according to observers with respect to clinical semiology[20] and lateralizing features,[21] seizure duration, frequency and longest seizure-free interval, occurrence of last seizure, generalized seizures and history of status epilepticus, possible injuries due to seizures, and postictal presentation. Risk factors for epilepsy, such as head trauma, CNS infections, tumors or vascular disease, family history of seizures, developmental history and possible delay or retardation, febrile seizures, and other important medical conditions need to be documented. Additionally, a detailed history of previous work-up and all previous and current antiepileptic medications including maximum doses, duration, possible drug levels and side effects is important to determine pharmacological intractability of seizures. Although more difficult to elicit in children, complete examination will highlight clinical deficits indicating a focal structural lesion such as impaired visual fields, hemiparesis, or language deficits.

Video-EEG and seizure semiology

Video-EEG monitoring is an important tool in the determination of the epileptogenic zone. The goal is the exclusion of generalized epilepsy and non-epileptic paroxysmal events. Additionally, video-EEG provides information on seizure semiology including a vast amount of localizing and lateralizing clinical features.[21] Furthermore, a large sample of interictal abnormalities such as background changes and generalized slowing indicating encephalopathy, focal slowing and asymmetry indicating a structural lesion, and interictal epileptiform activity as localizing evidence for epilepsy are also helpful information. Finally, the correlation of ictal onset patterns with clinical seizure semiology is important and can supply localizing information. However, some of this data may not be as reliable as in adult epilepsy patients. Especially in younger children and infants inability to communicate specific features of auras and limitations to clinical testing during seizures require attention. Recent nonpublished data from the Cleveland Clinic also suggests that diffuse or generalized EEG may be neglected in the setting of a focal lesion on neuroimaging in infants and young children. Electrophysiological findings may therefore be less important than the actual imaging findings in children.

Structural neuroimaging and functional tests

Identification of a structural lesion on neuroimaging is one of the most important prognostic factors in epilepsy surgery, in particular in extratemporal lobe epilepsy. The most important neuroimaging technique is MRI and this has been indirectly demonstrated by improvement of surgical outcomes before and after the introduction of MRI.[22] Results in patients with a focal lesion such as focal malformation of cortical development, low grade neoplasm, or mesial temporal sclerosis indicate more commonly seizure freedom after epilepsy surgery in lesional as compared to nonlesional cases.[23–25]

2-[^{18}F]fluoro-2-deoxyglucose positron emission tomography (FDG-PET) can be helpful in the identification of lesional epilepsy cases. Prior to the advent of high-resolution MRI, Chugani *et al.* reported five children with infantile spasms and decreased cerebral glucose metabolism as demonstrated by PET.[7] Results were concordant with EEG findings. Four out of five patients underwent epilepsy surgery and became seizure free. Pathology demonstrated cortical dysplasia.[7] These results have later been confirmed in a larger series.[8] Although MRI imaging and resolution improved over the last decade, FDG-PET remains a helpful localization tool in the diagnosis of MRI negative cases providing additional information on placement of intracranial electrodes.[26]

Single-photon emission computerized tomography (SPECT) can also assist in the localization of the seizure focus in children.[27–30] Rapid injection of a radioactive tracer during seizures allows subtraction of ictal and interictal blood flow images. Simultaneous electrophysiological confirmation of habitual seizures is necessary to ensure that the actual seizure in question has been imaged.

Using a modified protocol, intracarotid amobarbital testing can also be successfully applied in children over the age of 5 to 6 years old in order to lateralize language function and memory.[31] In selected cases, intracarotid amobarbital testing may also assist in unmasking bilateral hypersynchrony on EEG.

Neuropsychological evaluation

Neuropsychological evaluation of younger children and infants is more difficult and less objective than in adults. Most reliable features in infants include the evaluation of developmental milestones. Neuropsychological test results in older children and adolescents may reflect those in adults including differentiated IQ assessment, memory evaluation and lateralization of other cortical functions. Plasticity and ability to transfer or relocate cortical functions within the first decade and even beyond this age represents an unique opportunity and window for surgery in childhood epilepsy.[32,33] Nevertheless, these patients remain at risk for a general reduction of cognitive development due to a 'crowding effect'.[34]

Patient management conference

Results of the presurgical evaluation are discussed in a multidisciplinary meeting including specialists from epileptology and neurophysiology, neurosurgery, neuroradiology and nuclear medicine, neuropsychology and psychiatry, and if warranted from the ethics committee. Information will be presented by specialists in the team and then weighed towards localization of the epileptogenic zone and anticipated chances of seizure freedom. This will be compared to risks of loss of eloquent cortex and function, and possible complications. Finally, timing and type of surgery or additional workup and investigations will be recommended.

Types of surgeries in pediatric patients

More than 90% of epilepsy surgeries in infants are extratemporal resections, hemispherectomies, or resections of multiple lobes.[5,8,9] This changes in older children and adolescents,[5,35] in whom temporal resections become more frequent. Temporal resections are with 70% the most frequent epilepsy surgery in adults.[1]

Extratemporal focal resection

Extratemporal resections are more frequent in children than in adults. Indications for extratemporal resections include either a cortical extratemporal epilepsy focus or a lesion. Electrocorticography or subdural electrode recordings can assist in the determination of the extent of the resection. Damage to nonepileptic cortical regions should be limited and spare function if possible. Based on the underlying etiology, either lesionectomies, lobectomies or multiple lobar resections can be performed. Results from extratemporal resections have not been as good as temporal lobectomies.

Temporal lobectomy

The first adult cases of temporal lobectomy in epilepsy patients were reported by Bailey and Gibbs in 1951,[36] and the first series on surgical outcome after temporal lobectomy in 40 children under 15 years of age was published by Davidson and Falconer in 1975.[37] Types of procedures include resection of the mesial temporal structures, lesionectomy in the mesial or lateral temporal lobe, or lateral neocortical resections.[38] The pathology in children with temporal lobe epilepsy varies from adults. Whereas mesial temporal sclerosis is the predominant cause in adults, children frequently present with temporal neocortical lesions, including malformations of cortical development and neoplasms.[39]

Hemispherectomy

The first cases of improvement of seizures after hemispherectomy have been reported by Krynauw in 1950,[40] and additional cases followed in 1951 by Cairns and Davidson,[41] and 1952 by Penfield.[42] Several types of hemispheric removal techniques exist, with anatomic and functional hemispherectomy being the most frequent ones. Although hemispherectomy leads to contralateral hemiplegia and hemianopia, the increased plasticity of the maturing brain allows many patients to ambulate after several months. The *anatomic hemispherectomy* involves a complete resection of the whole hemisphere excluding the basal ganglia.[43] Anatomic hemispherectomy can lead to superficial hemosiderosis seen in up to 25% of patients and to hydrocephalus occurring in up to 30% of patients.[43] A *functional hemispherectomy*[44] is a physiologically complete hemispherectomy, but anatomically incomplete. After a temporal lobectomy, the central fronto-parietal cortex is resected, the insula is removed, and the remaining frontal and parieto-occipital lobes are disconnected. A modification of this procedure includes a suprasylvian window, which reduces postoperative hydrocephalus rates down to 18% as compared with 30% in patients with anatomic hemispherectomy.[43] Other complications such as infection, and hemorrhage may also occur less frequently after functional hemispherectomy. Additional options include hemispherotomy,[45] hemidecortication,[46] and the Oxford modification of anatomic hemispherectomy.[47]

Multiple subpial transections

Frank Morrell introduced the technique of multiple subpial transections based on the observations that epileptogenicity is potentiated by horizontal connections between cortical neurons and functional elements are depend on vertical connections and columnar structure of the cortex. The technique of multiple subpial transections is the selective interruption of horizontal intracortical fibers within the suspected epileptogenic zone. Interruption of the horizontal connections impairs the cortical ability to generate synchronous discharges while maintaining physiological activity that is mainly mediated via the vertical cortical columns. This technique is predominantly used if the epileptogenic zone lies within eloquent cortex, i.e., resection of this cortical area would lead to an unacceptable clinical deficit in language, motor or sensory function. It differs from other disconnection procedures such as corpus callosotomy by disconnection within the epileptogenic zone. Other disconnection procedures attempt to disconnect the epileptogenic zone from the symptomatogenic zone.[48] In the first clinical patient series of multiple subpial transections, complete seizure control has been observed in 11 out of 20 cases and recurrence of epilepsy in different cortical areas was only seen in patients with underlying progressive diseases, such as Rasmussen's encephalitis, tumors and subacute sclerosing panencephalitis.[48]

Multiple subpial transsection in conjunction with resective surgery lead to seizure freedom in up to 46% of children.[49] Although the exact extent of the effect is unknown, Spencer *et al.* demonstrated in a metaanalysis of 211 adult and pediatric patients efficacy of the procedure itself.[50]

Corpus callosotomy

Corpus callosotomy was first described by Van Wagenen and Herren in 1940.[51] Currently, it is used as a palliative procedure in patients with predominantly atonic seizures. Anterior callosotomy aborts atonic seizures in 100% and decrease generalized tonic-clonic seizures in 83% of patients.[52] Total callosotomy may decrease seizure frequency in patients that fail partial callosotomy. In patients with total callosotomy the largest seizure reduction was seen in tonic-clonic (68%) and tonic (57%) seizures.[52] Ictal EEG patterns after callosotomy became more focal. Seven out of 18 patients with anterior callosotomy and five out of ten patients with complete callosotomy had a more focal seizure onset after disconnective surgery.[53] However, this procedure is strictly palliative and does not cure seizures. The main advantage is the abortion of atonic seizures in order to decrease the number of falls and to enable patients to reduce injury by a more focal seizure onset.[43]

Selection of the type of callosotomy (complete or anterior) is dependent on (anticipated) language function. Complete disconnection leads to neuropsychological deficits including dissociation of both hemispheres (split brain syndrome) with lack of the language dominant hemisphere to access information in the nondominant hemisphere. Additionally, patients may develop apraxia of the nondominant hand to verbal commands and present with difficulties with bimanual coordination.[54,55] Anterior callosotomy, alternatively, leads to fewer deficits with slowing of speech and decreased use of the dominant limbs and

may be the first choice in intellectually higher functioning children, with the option to expand the procedure to a complete disconnection.

Vagus nerve stimulation is discussed separately in Chapter 127.

Frequent etiologies in pediatric epilepsy patients

Sturge-Weber syndrome

Sturge-Weber presents sporadically and is in up to 80% of patients associated with seizures.[56] Besides epilepsy, leptomeningeal angioma and associated cortical changes, patients present with a facial port wine stain in the area of the first trigeminal branch, and with glaucoma.[57] Kossoff *et al.* reviewed the literature on hemispherectomy in 45 patients with Sturge-Weber syndrome and 36 (80%) became seizure free.[56] This number is very similar to the 81% seizure free patients in 32 additionally reported patients in this series.[56]

Tuberous sclerosis complex

Tuberous sclerosis is an utosomal dominant phakomatosis with variable penetrance.[58] Initial presentation consists of seizures in 92% of patients.[59] Additionally, patients usually present with mental retardation. Main pathological substrate are hamartomatous tubers that can present in multiple organs, and frequently multiple tubers are seen within the brain. Other pathological manifestations include giant cell astrocytomas. Patients may be candidates for epilepsy surgery, if a single circumscribed epileptogenic lesion can be identified. PET may be helpful to identify the epileptogenic zone.[60] Multiple cerebral tubers are not a contraindication and seizure freedom is still possible if the epileptogenic tuber can be identified and resected.[61–63]

Malformation of cortical development

First described by Taylor *et al.* in 1971,[64] malformation of cortical development now accounts for up to 25% of patients undergoing epilepsy surgery.[65] Predominantly focal, multilobar or hemispheric malformation patterns such as hemimegalencephaly may be considered for epilepsy surgery, whereas patients with more diffuse malformations such as lissencephaly are less likely surgical candidates. Several neuroimaging features, such as blurring of the gray-white matter junction, focal cortical thickening and aberrant gyral cortical patterns, and white matter hyperintensity on T2 weighted or flair images or hypointensity on T1 images may or may not be present on MRI.[66]

Rasmussen's encephalitis

Focal chronic encephalitis (Rasmussen's syndrome) is characterized by progressive hemiparesis, hemianopia, and pharmacologically intractable seizures.[67] Seizures may progress to epilepsia partialis continua. Neuroimaging reveals progressive unilateral hemispheric atrophy and pathology is suggestive of inflammation. The etiology of this condition is not known, but an autoimmune disease is suspected, and this is supported by temporary improvement of symptoms with immunomodulatory treatment. However, the only curative treatment is hemispherectomy in patients with unilateral symptoms.[68]

Mesial temporal sclerosis

The first focal resections besides hemispherectomies in children were performed in temporal lobe epilepsy patients.[69] In this series of nine patients, mesial temporal sclerosis was found in seven out of nine patients, with four out of nine patients becoming seizure free and additional two patients that were almost seizure free.[69] Seizure freedom after temporal lobe epilepsy surgery in children ranges from 54–83%, with many of these patients presenting with mesial temporal sclerosis.[5,70–73] However, long-term seizure freedom declined on long-term follow up from 80% after two years to 66% after 15 years.[74] A similar decline has been observed in adult patients.[75] Nevertheless epilepsy surgery in temporal lobe epilepsy remains superior to medical therapy.[12]

Developmental tumors

Epileptic seizures are frequently the first presentation of developmental tumors such as gangliogliomas, gangliocytom as, and dysembryoplastic neuroepithelial tumors (DNET). Interestingly, in DNETs the epileptogenic zone is frequently not the tumor itself but surrounding malformation of cortical development associated with the DNET.[76] In a series of children with gangliogliomas, initial presentation consisted of seizures in 50% of patients. They are also frequent etiological findings in patients undergoing epilepsy surgery ranging from 0–40%.[9,11,77–81] Surgical intervention in patients with gangliogliomas rendered 78% of patients seizure free and additional 18% had reduced seizure frequency after surgery.[82] In a series of nine pediatric patients with DNETs, seven became seizure free after resection and the other two had markedly reduced seizure frequency.[76] Low-grade gliomas may also have an excellent prognosis with seizure freedom in up to 96%, if tumors can be completely resected.[83] Shorter duration of seizures may be predictive of good outcome in these patients.[83]

Hypoxic-ischemic injuries

Pre- and perinatal hypoxia and unilateral vascular insults frequently leads to infarction with or without porencephaly. Patients often present with seizures, hemiparesis and varying degrees of developmental motor or speech delay depending on the site of the lesion. Patients presenting with pre-existing hemiparesis were among the first candidates considered for epilepsy surgery, although no pathology has been provided in this series.[40] Seizure free outcome after hemispherectomy ranges from 73–84%, with a better outcome in patients undergoing functional hemispherectomy as compared to anatomical hemispherectomy.[84–87]

Vascular malformations

Up to 40% of patients with vascular malformations present with seizures as initial symptom.[88] Cavernous angiomas are the most epileptogenic vascular malformation, whereas data on pediatric patients with venous angiomas and capillary teleangiectasis is rare.[88] On MRI, cavernous angiomas present as typical round or oval lesions with mixed signal intensity ('popcorn' lesions) and with a surrounding hypointense parenchymal ring on gradient-echo and T2-weighted images related to hemosiderin deposition.

In a series of 11 children undergoing resection of the cavernous angioma because of intractable epilepsy, all became

seizure free.[89] Another series of 51 children reports seizure freedom in 70%.[90]

Seizure outcome after epilepsy surgery

Infants

Although infants were included in the first reported series of hemispherecomies,[40] it took another 40 years until the first experience with epilepsy surgery in infants was reported in detail.[6,7] In 1993, Chugani *et al.*[8] report 23 infants and children with cortical resection ($n = 15$) or hemispherectomy ($n = 8$) due to infantile spasms. At follow-up after on average 28 months, 15 children became seizure free, four had major reduction in seizure frequency and seizure frequency did not change in four children after epilepsy.[8] Out of 12 infants reported by our center, six became seizure free and another three had only rare seizures after on average 32 months of follow-up.[10] Duchowny *et al.* followed 26 infants for at least 1 year after epilepsy surgery and found 16 seizure free, four with greater than 90% seizure reduction, and six with some improvement in seizure frequency.[9] Most recently our center analyzed results of epilepsy surgery of patients under the age of 6 months.[91] Eleven out of 15 patients were seizure free (Engel class I), and three additional infants were much improved. Epilepsy surgery cmplications in this high-risk group included aseptic meningitis in three and a middle cerebral artery stroke in the region of the epileptogenic zone in a patient with pre-existing hemiparesis. Overall outcome was favorable and antiepileptic medications were significantly reduced.[91]

Children and adolescents

Few epilepsy surgery series focus specifically on this age group, but several studies include patients in this age range. The largest series to date reported 136 patients, of which 68% of patients were seizure free after a mean follow-up of 3.6 years.[5] Of note, this series also included infants. Patients with temporal lobe resections (78%) had better outcomes than patients with extratemporal resections (54%). This series demonstrated that etiology and not location of surgery was most important for seizure freedom, with higher rates of seizure freedom in patients with low-grade tumors (82%) than in patients with malformation of cortical development (52%).[5] This is also supported by Gilliam *et al.* who reported 33 patients between 1 and 12 years of age and an overall seizure freedom rate of 57%. Postoperative seizure freedom rate in patients with temporal lobe resections was lower as compared to frontal lobe resections, suggesting other influences on seizure freedom than resection site.[3] Other series including children and adults demonstrate similar results (Table 131.1).[4] Based on different patient populations other studies with fewer patients found similar results, with some variation in percentage of seizure frequency based on etiology, age group, duration of follow up, outcome parameters and resection site (Table 131.2). These results are more encouraging than response to newer antiepileptic medications leading rarely to seizure freedom and reducing seizure frequency by 50% in only 30% of patients.[92] Additionally, the chances of improvement after failure of two or more antiepileptic medications is 5% or less.[13]

Preoperative predictors of seizure outcome

Paolicchi *et al.*[35] followed a cohort of 75 patients under the age of 12 years and tried to determine predictors for outcome at least one year after focal resection. The only significant predictor of good outcome was completeness of resection of the epileptogenic lesion. This was defined as resection of a structural lesion and of an area with interictal and ictal intracranial EEG findings. 92% of patients undergoing complete resection of the epileptogenic lesion subsequently became seizure free. Patients with multilobar resections had a worse outcome as compared to the rest of the cohort with only 22% seizure free patients.[35]

Tonini *et al.* performed a metaanalysis of 47 selected articles in adults and children. Studies after 1984 with a sample size of at least 30 patients, at least 90% of cases with MRI, follow up for at least one year and outcome parameter defined as seizure remission were included. Positive predictors for seizure remission included febrile seizures, mesial temporal sclerosis, tumors, abnormal MRI, EEG/MRI concordance and extensive surgical resection, whereas intracranial monitoring and postoperative epileptiform discharges were negative predictors (Table 131.2).[4] Based on this meta-analysis, neuromigrational defects, CNS infections, vascular lesions, interictal spikes, and the side of the resection did not predict outcome.[4]

Mani *et al.* found acute postoperative seizures within 24 hours after epilepsy surgery predictive of recurrent seizures. Patients with acute postoperative seizures were 73% less likely to be seizure free after 6 months, 78% less likely to be seizure free at 12 months, and 87% less likely to be seizure free after 24 months.[93] Acute postoperative seizures were seen more frequently after extratemporal resection as compared to hemispherectomy.[93]

Age-related risks and contraindications of epilepsy surgery

Mortality

Due to their smaller body weight and lower blood volumes and due to usually more extensive resections, such as hemispherectomies or multilobar resections epilepsy surgery in children has some significant risks. Mortality in pediatric epilepsy surgery series ranges between 1 and 2%. In the Cleveland Clinic series, two out of 149 patients died immediately after surgery (1.3%).[5] Another series reports one death in a case series of 83 patients (1.2%).[35] Earlier series in younger children from established epilepsy centers had even higher mortality rates with one death in eight reported cases in a study from 1988.[6] Other series from established pediatric tertiary epilepsy centers report slightly higher numbers in children undergoing hemispherectomy (4 perioperative deaths in 58 children undergoing hemispherectomy).[94] Mortality from epilepsy surgery should be weighed against risks of injury or SUDEP due to ongoing uncontrolled seizures. In a study on SUDEP in children with learning difficulties, the incidence of sudden death was estimated at 1:295 per year.[95]

Table 131.1 Selected epilepsy surgery series in children

Author	Year	N	Types of surgeries	Pathology, imaging, or presumed etiology	Design	Age at surgery (y/o)	Follow up	Seizure free (%)	Comments
Krynauw[40]	1950	12	Hemispherectomy	NR	R	2–21 y	Few wks to 4 y	100% (10/10)	10/12 with seizures; one death
Cairns and Davidson[41]	1951	3	Hemispherectomy	NR	R	7–20 y	1 y	100% (3/3)	
Penfield[42]	1952	4	Hemispherectomy	NR	R	NR	1 y (?)	3/3 (100%)	No follow up reported on remaining case
Ignelzi and Bucy[46]	1968	4	Hemidecortication	Gliosis and atrophy (4)	R	6–20 y	1–11 y	4/4 (100%)	One patient with two isolated breakthrough seizures (controlled with medication)
Wilson[117]	1970	50	Hemispherectomy	37 cases examined in detail: Localized arterial lesions (21); diffuse arterial lesions (14); SWS (2)	R	NR	NR	68%	1 postoperative death
Falconer[69]	1970	9	TLE	MTS (7) Nonspecific (2)	R	9–14 y	3–10 y	4/9 (44%); 2/9 'almost fit–free'	
Davidson and Falconer[37]	1975	40	TLE	MTS (22); MTS & hamartoma (2); hamartoma (7); tumor (3); encephalitis (1); nonspecific (7)	R	0–15 y	1–20+ y	23/40 seizure–free (57.5%)	Two patients with ongoing seizures died (suicide & pneumonia)
Whittle[81]	1981	16	8 TLE 8 ETLE	Normal (2); nonspecific (1); GG (3); arachnoid cyst (2); porencephaly (5); MTS (2); AVM (1)	R	9–17 y	1–7.5 y	3/16 'fit–free' (18.75%); 5/16 'rare fits'	
Blume *et al.*[77]	1982	16	FLE (4); PLE (1); OLE (1); TLE (10);	Astrocytoma (12); oligo (2); GBM (1); GGL (1);	R	<21 y	8–45 m	7/16 seizure free;	7/8 with complete resection seizure free
Lindsay *et al.*[118]	1984	50	TLE (32); ETLE (8); hemispherectomy (10)	MTS (20); astro (4); oligo (3); GGL (1); mixed astro/oligo (1); hamartoma (4); angioma (1); cyst (1); gliosis (1); TSC (1); normal (3); stroke (1); MCD (1); hemispheric sclerosis (8)	R	Median 14 y	<2 y to >10y y	34/50 seizure free (68%)	
Meyer[71]	1986	50	TLE	NR; except for tumors in 6 patients: astro (2); oligo (2); GGL (2)	R	7–18 y	Mean 4.5 y (0.6–10 y)	27/50 seizure free (54%); 12/50 with rare auras (24%)	
Lindsay *et al.*[119]	1987	17	Hemispherectomy (17)	NR	R	Median 11.5 y (7–17 y)	Mean 12.5 y (1–36 y)	11/17 seizure free (65%)	

Continued

Table 131.1 Selected epilepsy surgery series in children—cont'd

Author	Year	N	Types of surgeries	Pathology, imaging, or presumed etiology	Design	Age at surgery (y/o)	Follow up	Seizure free (%)	Comments
Harbord and Manson[70]	1987	15	TLE	Gliosis (3); microhamartoma (1); cerebral dysplasia (1); myelin breakdown products (1); normal (2); tumors/cysts (7)	R	2–15 y	1–16 y	11/15 (73%) less than 1 seizure per month	Comparison with 38 medically managed TLE patients
Drake[120]	1987	16	TLE (16)	Tumors (12): GGL (4); astro (3); oligo (3); meningeoma (1); mixed oligo/astro (1); vascular malformation (3); cyst (1); 9/10 concomittant MTS	R	6–16 y (mean 12.6 y)	Average 2 y	9/16 (56%) seizure free	
Chugani *et al.*[6]	1988	5	Hemispherectomy (3); MLB (2)	NR (on neuroimaging: hemimegalencephaly (1); possible MCD (1))	R	18 d–5 y	5–9 m	3/4 seizure free (75%)	One death in immediate postsurgical period; focus on PET
Chugani *et al.*[7]	1990	5	MLB (4)	MCD (4)	R	14–33 m	4–20 m	4/4 seizure free(100%)	Focus on PET hypometabolism
Duchowny *et al.*[121]	1990	5	Frontal (4); temporal (1)	GCT (1); gliosis (2); hamartoma (1); NR (1)	R	2–11 m	Up to 2 y	3/5 seizure free (60%)	
Adelson *et al.*[122]	1992	33	(Extended)TLE	14 cases with more than one pathology; Neoplasm 16; MCD 12; 'reactive changes' 15; MTS 5	R	0–17 y	1.5–6 y (in 30 patients)	23/30 seizure free (77%)	
Fish *et al.*[123]	1993	118	Frontal lobe excisions (45); temporal resections (73)	Cyst (2); abscess (4); gliosis (4); stroke (3); trauma (3); angioma (1); infection (15); TS (2); MCD (6); SWS (1); chronic encephalitis (4); unknown (36); foreign tissue (2); febrile convulsions (22); MTS (6); trauma (6); AVM (1)	R	0.6–15 y	2–31 y (median 15 y)	3/45 FLE seizure free 19/73 TLE seizure free	Febrile seizures predict good outcome in TLE; Lesions predict good outcome, limited imaging
Chugani *et al.*[8]	1993	23	Cortical resection (15); hemispherectomy (8)	MCD (16); Gliosis (6); Normal (1)	R	5 m–3 y	4–67 m; mean 28 m	15/23 seizure free	
Caplan *et al.*[124]	1993	13	Hemispherectomy (13)	NR	R	5–16 y	8–142 m	7/13 seizure free	Focus on neuropsychological outcome
Wyllie *et al.*[73]	1993	18	TLE	MTS (4); MCD (1); neoplasm (9); 4 NR	R	16 m–12 y	6 m	15/18 seizure free (83%)	

Guldvog *et al.*[79]	1994	64	Temporal 38, frontal 15, other 11	MTS (2); gliosis (11); hamartoma (2); tuber (2); Vasc. malformation (7); chronic inflammation (1); nonspecific (1); glioma & GGL (9); no change (20); missing (9)	R	4–19 y	Median follow up 7 years (data missing in 10 patients)	56.1% seizure free	Tumor patients included
Wyllie *et al.*[11]	1996	12	Frontal (3), temporal (2), TPO (2), funct. Hemispherectomy (5)	MCD (5); SWS (3); GGL (3); Hemimegalencephaly (1)	R	2.5–29 m (mean 15.3)	4–86 m (mean 32)	6/12 Engel I	
Goldstein *et al.*[125]	1996	33	TLE	MCD (23); DNET (6); ganglioglioma (2); gliosis (1); encephalomalacia (1)	R	0–15 y	Mean 56 m (24–120 m)	15/33	
Gilliam *et al.*[3]	1997	33	TLE, ETLE/FLE	Arachnoid cyst (1); gliosis (2); GGL (6); DNET (4); normal (2); MCD (11); chronic encephalitis (1); MTS (1); MTS & MCD (1); Oligo (1); glioma (1); remote stroke (1); angioma (1)	R	1–12 y	6 m	19/33 (57%) seizure free; FLE 6/10 (60%); TLE 9/17 (53%)	Two patients with neurological deficits after surgery
Vining *et al.*[94]	1997	58	Hemispherectomy	Rasmussen (27) MCD (24) Vascular (7)	R	6.8 y (0.2–20.6)	Mean 6.2 y (0.5–27.3 y)	29/54 (54%)	Four perioperative deaths
Szabo *et al.*[80]	1998	14	TLE (14)	DNET (2); MTS (4); GGL (3); Astro (2); MCD (2); atrophy (1)	R	7–12 y	mean 34 m (23–48 m)	10/14 Engel I	Focus on neuropsychological outcome
Williams *et al.*[126]	1998	9	TLE (9)	MTS (5); gliosis (2); TSC (1); normal (1)	R	8–15 y (mean 13 y)		6/9 (66%) seizure free	Focus on neuropsychological outcome
Wyllie *et al.*[5]	1998	136	TLE (72), ETLE/MLB (48), hemispherectomy (16)	Tumor (44); MCD (34); MTS (18); Other (27); SWS (5); infarction (5); Rasmussen (3)	R	3 m–20 y	1–7.5 y (mean 3.6 y)	92/136 (68%) Engel I	
Duchowny *et al.*[9]	1998	31	Hemispherectomies (14), LB (14); MLB (3)	MCD (21); DNET (3); PPA (3); GGL (2); GCT (1); GNH (1)	R	0–3 y	1 y (available in 26 patients)	16/26 seizure free (61%)	Better outcome with lesion; tumors excluded
Dlugos *et al.*[127]	1999	8	TLE (8)	MCD & gliosis (3); MTS & MCD (2); MTS & gliosis (2); MCD (1); gliosis (1)	R	11–18 y (mean 13 y)	NR	6/8 (75%) Engel I	Focus on neuropsychological evaluation
Paolicchi *et al.*[35]	2000	75	TLE (29); ETLE (37); Combined (9)	MCD (42); tumor (25); acquired lesion (6); normal (1); no pathology (1)	R	0–12 y	at least 1 y	59% seizure free	77% class I/II;
Westerveldt *et al.*[111]	2000	82	TLE (82)	Structural lesion other than MTS in 42/82	R	14.3 y (6–17 y)	Average 14 m; at least 5 m	NR	Assessment of neuropsychological outcome after right and left temporal resection

Continued

Table 131.1 Selected epilepsy surgery series in children—cont'd

Author	Year	N	Types of surgeries	Pathology, imaging, or presumed etiology	Design	Age at surgery (y/o)	Follow up	Seizure free (%)	Comments
Robinson *et al.*[112]	2000	22	AHS (22)	MRI: hippocampal changes (12); normal (7); lesion (1); bilateral abnormal (2)	R	9–21 y	1 y	Engel I: 15/21 (71%); 11/17 (65%) at 2 yrs	IQ improvement
Miranda and Smith[113]	2001	50	TLE (50)	Dual path (10); no additional information	R	6–18 y (mean 13.3 y)	Mean 9 m (0.5–79 m)	33/50 seizure free	Focus on neuropsychological changes
Kuehn *et al.*[128]	2002	26	TLE (20); ETLE (6)	NR	R	Mean 12.9 y	0.4–1.25 y	15 seizure free (58%)	Focus on neuropsychological changes
Sherman *et al.*[129]	2003	22	Hemispherectomy (2), TLE (11), frontal (6), parietal (2), CC (1)	Cryptogenic (15); MCD (4); infection (2); tumor (2)	R	6–17 y	NR	11/22 Engel I (50%)	IQ comparison between surgical and nonsurgical group
Pulsifer *et al.*[130]	2004	71	Hemispherectomy (71)	Rasmussen (37); MCD (27); Vascular (7)	R	0.25–20.6 y	2.4–37.5 y	46/71 seizure free (65%)	Neuropsychological assessment
Smith *et al.*[72]	2004	30	TLE (18), ETLE (8), MLB (4)	MCD (7); MTS/MCD (6); tumor (7); gliosis (4); TSC (2); Rasmussen (1); arachnoid cyst (1); normal (2)	P	1 y	6–18 m	17/30 Engel I (56.7%)	Focus on cognitive and psychosocial function
Sinclair[100]	2005	15	Posterior resections (parietal 9, occipital 6)	MCD (4); stroke (2); normal (2); Astro (2); TSC (2); GGL (1); cyst (1); DNET (1)	R	1.5–16 y	Mean 15.9 m for NP (NR)	7/15 Engel I	9/15 Engel I or II
Gleissner[78]	2006	66	AH (8), LB/LX & AH (21); LB/LX (33); MST (4)	MTS (9); Tumor (27); MCD (16); venous malformation (2); other (8); normal (4)	R	4–16 y	1 y	67–78% seizure free	Comparison of three different IQ groups
Riney[131]	2006	29	Hemispherectomy (27); MLB (2)	MCD (12); Vascular (15); Rasmussen (2); Dual path: MTS (21/29)	R	4.5–204 m	NR	NR	Focus on hippocampal abnormalities

Abbreviations: AH – amygdalohippocampectomies; CC – corpus callosotomy; LB – lobectomies; LX – lesionectomies; MST – multiple subpial transections; MCD – malformation of cortical development; DNET – dysembryoplastic neuroepithelial tumor; GGL -ganglioglioma; GCT – gangliocytoma; GNH – glianeuronal hamartoma; HS – hippocampal sclerosis; PPA – peri/postnatal lesion; SWS – Sturge-Weber syndrome

Table 131.2 Predictors of epilepsy surgery outcome (adapted from Tonini *et al.*, Epilepsy Research, 2004[4])

Positive predictors for seizure remission	Odds ratio	Confidence interval
Febrile seizures	0.48	0.27–0.83
Mesial temporal sclerosis	0.47	0.35–0.64
Tumors	0.58	0.42–0.80
Abnormal MRI	0.44	0.29–0.65
EEG/MRI concordance	0.52	0.32–0.83
Extensive surgical resection	0.24	0.16–0.36
Negative predictors for seizure remission		
Postoperative discharges	2.41	1.37–4.27
Intracranial monitoring	2.72	1.60–4.60

Morbidity

Several complications may be related to the surgical intervention, such as hemorrhage, infection, and hydrocephalus as well as neurological deficits. In an epilepsy surgery series on 708 patients, approximately 3% of patients had postoperative surgical complications.[96]

Additional morbidity may be related to loss of eloquent cortex. Resection of the primary motor area in the precentral gyrus and perirolandic region leads to contralateral motor deficits, but due to bihemispheric innervation, facial motor function and contralateral proximal motor function can recover.[97] Although sensory lesions rarely lead to disability, removal of the primary sensory area in the postcentral gyrus, in particular the hand area, may cause loss of fine finger movements[98] and should therefore be avoided if possible. However, even in patients after hemispherectomy, secondary somatosensory areas and other cortical regions in the intact hemisphere continue to mediate sensory function.[99] Visual field defects occur after parieto-occipital resections or after resection of Meyer's loop in the posterior temporal lobe.[100]

Memory decline after temporal lobe epilepsy surgery has been described, and patients with normal mesial temporal structures on presurgical MRI and high baseline memory function may be at a higher risk.[101] Postsurgical memory outcome is most likely dependent on the reserve capacity of the contralateral not resected hippocampal structures and the functional adequacy of the hippocampus that will be resected, as evidenced by pathology and volumetric studies.[101]

Resection of language dominant areas is rare, but partial or complete resection may be warranted in highly selected patients with brain tumors and Rasmussen's encephalitis. Plasticity of the language cortex in children is an advantage and partial language transfer to the intact hemisphere may be possible in particular in patients with Rasmussen's encephalitis and in patients with initially bilateral language until teenage years.[32]

Additional benefits of epilepsy surgery in infants and children

Development and cognition

Cognitive development may be vulnerable to side effects of seizures and antiepileptic treatment, especially at an early age. Patients with epilepsy are considered to be at threefold higher risk of cognitive or mental problems as compared to the general population.[102] In a population based study, learning disability has been detected in 76% of adult patients with childhood onset epilepsy.[103] In addition to effects on cognition, childhood-onset temporal lobe epilepsy also seems to be associated with white-matter tissue volume loss and other structural brain abnormalities.[104] Several authors report a relationship between the severity of the intellectual disability and the seizure outcome.[103,105–108]

In a series of 12 infants undergoing focal resections or hemispherectomies at our center marked 'catch-up' developmental progress was noted after epilepsy surgery in almost all patients.[10] This was confirmed in a larger series on 24 infants undergoing epilepsy surgery.[109] Pre- and postoperative Bayley Scales of Infant Development were documented and a developmental quotient as compared to biological age was calculated. All children had some degree of developmental delay prior to surgery. Developmental quotient improved after surgery, and improvement was predicted by developmental function prior to epilepsy surgery.[109] Similar results were also found by Asarnow *et al.*,[110] who assessed developmental outcome with the Vineland Adaptive Behavior Scales after 2 years. Developmental outcome was best for infants undergoing surgery at a younger age and who had better developmental baselines prior to surgery.[110] An early epilepsy surgery intervention is also associated with better long-term psychological outcome, and may be warranted in order to utilize the greater amount of plasticity in infants and children and to prevent secondary epileptogenesis.

Review of intellectual outcome in older children and adolescents after temporal lobe epilepsy surgery demonstrated several studies demonstrating an increase of the nonverbal intelligence quotient as compared with verbal intelligence after surgery.[34,111–113]

Cost

The overall direct cost of epilepsy is usually higher in children than in adults.[114] Two studies analyzed the cost of epilepsy surgery in children. In a Swedish study conducted 1980–1992,[115] in the year after surgery annual costs per case were reduced by $11 525 US in direct costs and $42 000 US in indirect costs. Additionally, number of physician contacts and emergency room visits decreased in all patients, even in the patients with ongoing seizures.[115] In a Canadian study, Keene *et al.*[116] analyzed cost efficacy of cortical resection in 64 children with medically intractable epilepsy. The costs of the patients undergoing surgical resection were higher as compared to the medically treated group during the first 14 years, but then slowly declined and after 14 years the surgically treated group was cheaper.[116]

Conclusion

Overall seizure freedom after epilepsy surgery is approximately 60% (Table 136.1) and is comparable with outcome in major adult epilepsy surgery series. Advantages of epilepsy surgery in children include a greater amount of plasticity and improvement of behavioral deficits with impact on neuro-development. Timing of epilepsy surgery is important and risks versus benefits of an early surgical intervention have to be weighed in every patient separately. Further advances in diagnostic tools such as functional imaging and genetics as well as surgical techniques may well lead to improved surgical candidate identification and diagnosis of the epileptogenic zone, with reduction in complications and improved seizure outcome. Other less invasive surgical techniques such as brain stimulation and microcatheter and electrode applications may also gain additional importance in the future.

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132 Hemispherectomy: post-surgical seizure frequency

I Tuxhorn, H Holthausen, P Kotagal, and H Pannek

Introduction

Postoperative seizure control following cerebral hemispherectomy (CH) for intractable seizures is similar to that in cases of pediatric temporal lobe epilepsy. The good seizure outcome after CH has been well documented since it was first introduced for the treatment of severe seizures arising from one hemisphere over 50 years ago. In recent years surgical technique has focused less on brain resection and more on disconnection of the epileptogenic cortex to improve perioperative complications and long-term morbidity.

Although most patients benefit with improved seizure control after CH, seizure-free outcome is only reported in 60–80% in most studies which raises the question of which factors are prognostically significant for good outcome. The surgical technique and pathologic substrate causing the epilepsy probably are the two most important factors that will affect surgical outcome.

In this chapter we will give a brief historical review of the development of surgical technique and present the available data from various studies of large CH series from different US and international centers that have looked at the question of which factors influence postoperative seizure frequency.

In addition we will present some individual case material from our centres illustrating some of the anatomical, surgical and epilepsy-related factors that may contribute to post-surgical seizures after CH.

History of hemispheric surgery for epilepsy

Hemispherectomy has been termed the ultimate focal resection and has become an established neurosurgical procedure to treat seizures arising diffusely from one hemisphere.[1] After McKenzie performed the first successful hemispherectomy in 1938 for seizure control in a patient with infantile hemiplegia which was followed by a hiatus of 12 years Krynauw, a South African neurosurgeon in 1950 reported his series of 12 hemispherectomies achieving 80% seizure-free outcome in his patients with infantile hemiparesis.[2] These initially positive experiences were duplicated by other authors in larger patient series and by 1968 the results of 420 hemispherectomized patients were published.[3] In addition the good seizure outcome (80% seizure free, 14% substantial seizure reduction, 5% no change and 32% off medicine) of 50 further hemispherectomy cases from a single center were reported by Wilson in 1970.[4]

At the same time, first reports of mortalities associated with late complications of hydrocephalus secondary to superficial, cerebral hemosiderosis (SCH) transiently dampened further enthusiasm for this procedure to treat hemispheric epilepsy.[5,6] These reports led to successive modifications of the neurosurgical technique from the extensive anatomic excision of the hemisphere (anatomic hemispherectomy) to sparing of most of the white matter by only excising the epileptic cortex (hemidecortication), followed by various disconnective techniques disrupting all afferent and efferent fibres but essentially leaving in place most of the cerebral structures including cortex and white matter, which has been termed a functional hemispherectomy.[7]

Nowadays most centers perform modifications of the functional technique which has undergone further refinements to minimize tissue excision which is usually limited to the temporal lobe including the mesial structures and central insular cortex. Recently new approaches and techniques to optimize the functional disconnection (hemispherotomy) of the hemisphere via two different approaches – the vertex approach[8] or the peri-insular approach – have been published.[9,10] In the latter approach the operculum is excised and the white matter is transected perpendicularly through the circular sulcus of the insula and a complete parasaggital callosotomy is performed from within the lateral ventricle.[7]

Results post hemispherectomy

The overall seizure outcome after hemispherectomy has been reported from various centers and generally ranges between 50–80% seizure-free outcome and significant reductions of seizure frequency and intensity (Engel II and III) in up to 90% of the operated groups. Only a small proportion of patients do not benefit from the procedure. The main pathologies described from most centers include hemimegalencephaly and other hemispheric malformations of cortical development e.g., schizencephaly, unilateral pachygyria/polymicrogyria, Sturge-Weber syndrome, Rasmussen's encephalitis and a variety of acquired encephaloclastic lesions.

The hemispherectomy surgical techniques vary from center to center but may be grouped as anatomic resections, functional hemispherectomies and the newer modifications termed hemispherotomy with either a lateral or vertex approach to disconnect the epileptogenic hemispheral cortex.

Table 132.1 Common etiologies in hemispheric epilepsy

Sturge-Weber Syndrome
Rasmussen's Encephalitis
Porencephaly – Hemiatrophy after ischemia and vascular insults
Hemimegalencephaly
Non-hemimegalencephalic migrational disorders

A large meta-analysis of 333 hemispherectomied patients was analysed in 1997 and published in the proceedings of the Bethel-Cleveland International Symposium on pediatric epilepsy surgery.[11] The data from 11 centres were pooled and an attempt was made to stratify prognostic factors most likely affecting seizure control after hemispherectomy.

Overall, the newer techniques with emphasis on disconnection were as good as or slightly better than the older large resective techniques with the clear additional benefit of improved perisurgical morbidity. In the same analysis it could be shown that postoperative seizure outcome was influenced by the underlying pathology. Sturge-Weber syndrome patients were seizure free in up to 82%, whereas only 56% of dysplasia cases became seizure free. In the study no postoperative imaging data was available to assess the degree of disconnection but the relevance of a meticulous disconnection of the frontal and posterior regions was emphasized in this analysis. Improved seizure frequency with a 68% seizure-free outcome in cases with hemimegalencephaly who underwent a complete paracallosotomy as part of the hemispherotomy procedure without entry into the ventricular system was reported from the Bethel series.[11] Analysis of the preoperative parameters including age of onset, duration of epilepsy, as well as electrographic data with widespread interictal sharp waves and evidence of ictal spread to the good hemisphere did not show any influence on the outcome results.[11]

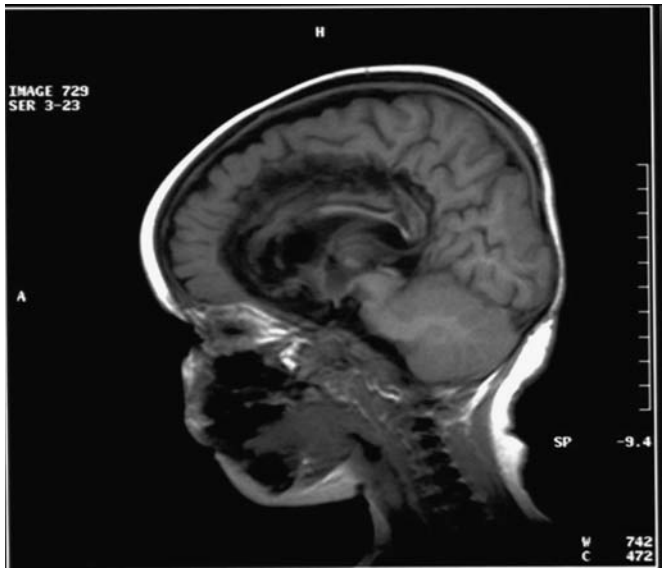


Figure 132.1 Sagittal MRI post-hemispherotomy in HMG showing complete anterior to posterior paracallosal disconnection. The infant had catastrophic epilepsy and APOS in the first postoperative week and is now seizure free for 1 year.

Hemispherectomy for catastrophic epilepsy in infants

Severe hemispheric epilepsy frequently manifests in the first 2 years of life and ideally hemispherectomies should be performed as soon as possible in this young group of patients to reduce medical morbidity and the risk of status-related mortality. In a newer systematic study of 18 infants operated under the age of 3 years incompleteness of dissection was the only variable statistically associated with persistent seizures after surgery. The type of surgical procedure, pathology category, persistence of insular cortex and bilateral interictal epileptiform activity was not associated with persistent seizures after surgery.[12] Although only a small patient group of 18 children was studied, pre- and postoperative MRI data was available to methodically look at the degree of disconnection with each applied surgical procedure which included anatomic hemispherectomy, functional hemispherectomy and modified hemispherectomy. In this study hemispherotomy with emphasis mainly on dissective technique was not perfomed.[12]

Further analysis of the group of patients (37%) with persistent seizures demonstrated that the presence of fronto-basal brain tissue was a clear source of persistent seizures and two patients subsequently became seizure free after reoperation to complete the disconnection. All patients had surgical

Table 132.2 Types of hemispherectomy techniques

Anatomic hemispherectomy and modifications
Hemidecortication
Functional hemispherectomy (disconnective hemispherectomy
Hemispherotomy: peri-insular, vertical parasagittal

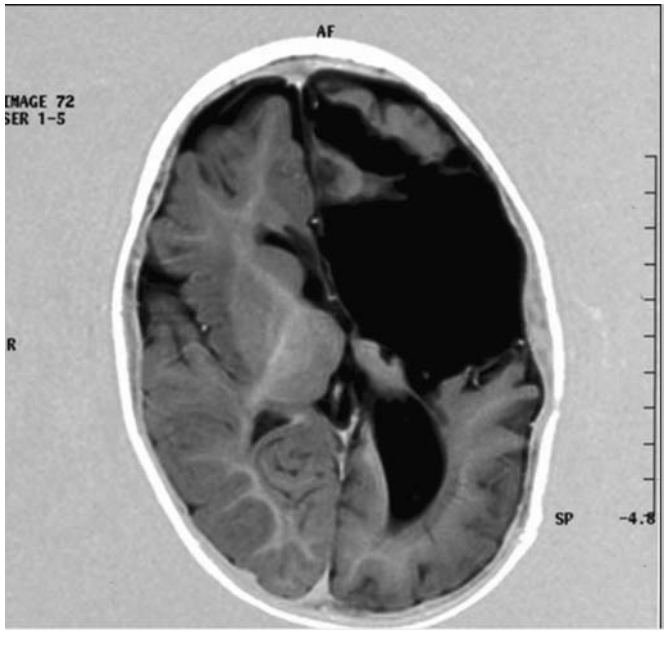
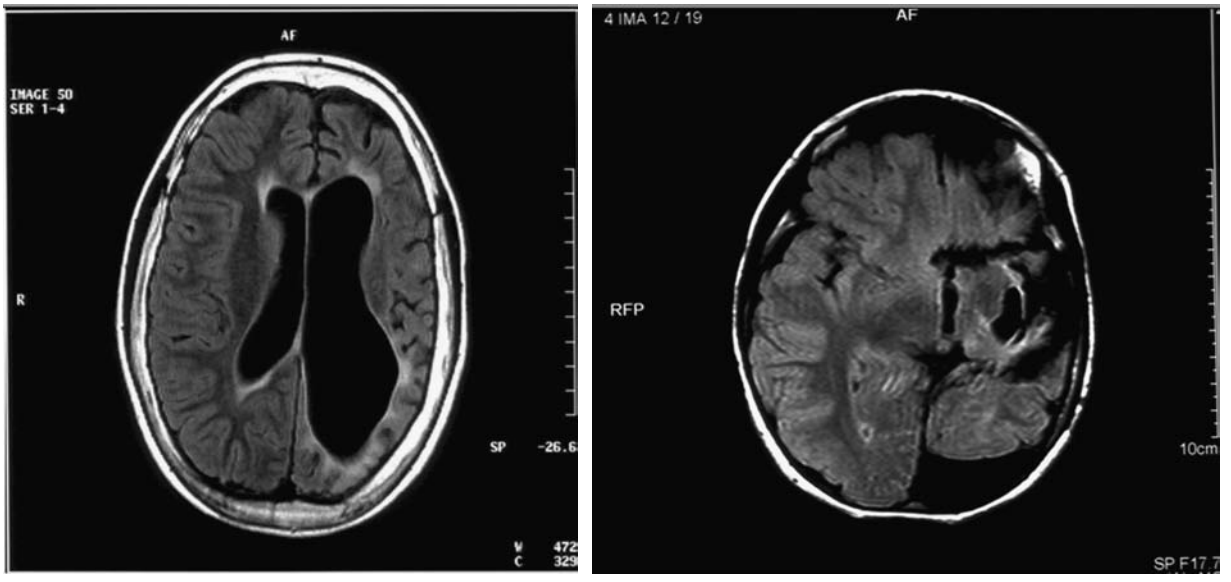


Figure 132.2 Axial MRI post-hemispherectomy showing incomplete left frontal disconnection. Reoperation with complete disconnection led to seizure-free outcome.



(a) (b)

Figure 132.3 Axial MRI showing progressive left hemispheric atrophy caused by Rasmussen's encephalitis and post left functional hemispherectomy MRI with complete disconnection and seizure-free outcome.

procedures with disconnection through the lateral ventricles. The authors emphasize the difficulty of performing complete disconnections of the frontal horizontal fibres in children with large distorted hemimegalencephalic malformations and that disconnection of the frontal cortex from the mesial structures of the temporal lobe is the most challenging step to achieve in this neurosurgical procedure. Incomplete disconnection of the corpus callosum was only noted in one of 12 incompletely disconnected procedures reported in these series while no incomplete posterior disconnections were reported.

The authors comment on the potential value of intraoperative imaging for these cases but clearly point out the anatomic limitations leading to incomplete fronto-orbital disconnections: the fronto-basal region is intimately related and limited in its posterior aspect by the hypothalamus and the anterior perforated substance which is the exit and entry site for the lenticulostriate arteries and veins and also marks the site of the most anterior inferior portion of the basal ganglia. If these functionally critical structures which do not differentiate well from the cortical gray matter of the frontal lobe are disrupted by the surgeon, resection may result in severe morbidity or death. Therefore the anterior cerebral artery which unfortunately shows anatomic variation is a highly respected anatomic landmark that prevents the surgeon from disrupting these cerebral structures and therefore any 'frontal lobe' brain tissue lying posterior to a more 'anterior variant' of the ACA will be left behind and lead to an incomplete resection. This leads the authors to conclude that in some cases a complete disconnection cannot be performed safely for anatomical reasons and further attempts to remove the remaining frontal cortex can lead to unsuccessful results.[12]

The sequential stages in the surgical method, technical pitfalls, and complications of peri-insular hemispherectomy are characterized by Villemure *et al.* in a recent paper reporting on the outcome in 43 children[13] – 90% were classified as Engel 1 and the incidence of vascular complications and hydrocephalus was very low due to preservation of the cortical vessels and minimal disturbance of the subarachnoid space.

The results reported in these studies emphasizes the importance of accurate patient selection of cases with clear unilateral hemispheric disease and the crucial role of the surgeon's experience for improving surgical strategy and technique.

Prognostic role of acute postoperative seizures

Acute postoperative seizures (APOSs) have been defined as seizure events occurring early within the first 7–10 days after surgery. These have been studied quite systematically in patients with temporal lobe epilepsy as prognostic events determining long-term seizure control. In 114 patients undergoing hemispherectomy APOSs were studies retrospectively and found to occur in 22.6% of patients.[14] Patients with >5 APOSs after hemispherectomy had a more prolonged and complicated hospital course and worse postsurgery seizure control, more AED use and higher reoperation rate than patients without or up to 5 APOSs. Thus the number of APOSs was found to be a valuable predictor of postsurgery seizure control and a useful parameter to counsel patients or families about prognosis after hemispherectomy. In the same study the seizure types observed were described as focal tonic-clonic, unilateral tonic head and eye movements, staring and eye rolling, mouth twitching, myoclonic shoulder twitching, and tonic extension of both extremities. In addition, extensive spasms and a frightened look were also described. In general, the APOSs compared to the pre-surgical seizure type in over 78% of the patients examined. The clear predictive value of the number of APOSs (>5) for post hemispherectomy seizure control may be related to the fact that the younger patients undergoing CH have multiple seizures every day before surgery compared to adult temporal lobe patients who usually only have a few seizures per week. In addition, APOSs tended to occur more in patients with lower pre-surgical Vineland DQ scores. The authors recommend that video-EEG telemetry after hemispherectomy should document whether patients

have a habitual seizure versus a non-seizure event, whether the seizure was typical of the pre-surgical events and whether abnormal EEG findings were noted over the non-resected brain or hemisphere that might support the concept of induced secondary epileptogenesis.[14] These findings were duplicated in a more recent study in which APOSs were analysed in extratemporal resections and hemispherectomy patients.[15] Only 13% of the hemispherectomy patients had APOSs compared to 37% of the extratemporal resective cases and similar to the previous study the presence of APOSs was highly predictive for long-term seizure control which was only seen in 15% of children with APOSs compared to 63% of those without APOSs.[15]

Post CH seizures – newer studies analyzing the influence of pathology and surgical technique

Postoperative seizures were reported in a recent study of 30 patients operated over a time span from 1987 to 2003 in which the effect of surgical technique and pathology on seizure frequency and general morbidity were analyzed.[16] Of 21 patients who could be followed-up for one year 17 remain seizure free or had a 90% seizure reduction and the four patients who continued to have seizures had a recurrence within the first few days after surgery. Two of these patients were reported to have an incomplete disconnection of the corpus callosum, the etiologies were Rasmussen's encephalitis and malformation of cortical development. In the total series only two patients did not improve significantly after surgery.[16]

The authors discuss the relevance of pathology and surgical technique as main factors for postoperative seizure control based on their study and further series in the literature.[17–20] The authors found incomplete disconnections in 18.5% of their cases which is the same incidence reported previously from the UCLA series.[21] In another series using modified perinsular hemispherotomy 9% incomplete disconnection was reported,[22] while Mittal reported no incomplete disconnections in their series of transsylvian keyhole functional hemispherectomy.[20] In a large series reported from Johns Hopkins[18] five out of 111 patients who underwent hemidecortication had repeat surgery for persistent seizures as residual tissue could be identified on MRI. In the Bethel series of 105 hemispherectomies 9 patients (9%) had reoperations for incomplete disconnections, however the rate of incomplete disconnections is higher as only children that had poor postoperative seizure control had a second surgery.[11] Incomplete disconnections may occur with all techniques and relate to the pathology and specific anatomical features of malformed hemispheres so that thick cortical mantles and large distorted hemispheres require good surgical technique and experience of the neurosurgeon to achieve complete disconnection so that the expertize of the neurosurgeon is very important for outcome.[13] The authors concluded that hemispherectomies are procedures where pathology and surgical technique interact narrowly to determine post-surgical prognosis and morbidity.

The UCLA series spanning surgeries from 1986 to 1995 reports excellent seizure control and motor function in 50 patients with more than 1 year follow-up of 90% of seizure reduction.[21] Late postoperative seizure breakthrough required reoperation and further disconnection in five of 27 functional hemispherectomy patients and three of 27 anatomical hemispherectomy patients. In more detail 74% (37) were completely or nearly seizure free with no more than occasional seizures after one year, seven additional patients (14%) showed a greater than 90% reduction in seizure frequency and 10% had a moderate reduction, while one patient showed no improvement. Therefore 88% of the patients had extremely favourable results with greater that 90% seizure reduction. The study presents no MRI data. The authors also discuss technique issues and based on their results and experience they recommend anatomical hemispherectomy in patients with a small lateral ventricle on the affected side because this small window of access increases the difficulties in the disconnection portion of the functional technique. They also state that the presence of large cysts or very marked atrophy is an argument for an anatomic procedure as there is much less disconnection through brain tissue. An anatomic hemispherectomy is also favoured in patients with dysplastic syndromes in which the tissue may become hemorrhagic. They counterbalance the increased risk of hydrocephalus in their argumentation and recommend that functional hemispherectomy should be favoured in patients with a large lateral ventricle present on the affected side, because this facilitates an access for disconnection. By this argument children with middle cerebral artery infarcts are good candidates for the hemispherotomy procedure and particularly where adhesions and scar tissue may obstruct access to the large cerebral arteries which is necessary when performing an anatomic resection. From their experience and data analyses these authors conclude that anatomical functional and modified anatomical hemispherectomy provides an excellent seizure control in young hemiplegic children with intractable epilepsy. They do suggest that the choice and type of hemispherectomy should be individualised with safety and efficacy with regard to seizure control being the primary factors to be considered.

In a follow-up study from the same centre 2-year postsurgery seizure control is reported for a larger series of 115 patients as follows: 78.6% were seizure free at 6 months ($n=112$), 76.3% at one year ($n=97$), 70% at 2 years ($n=88$), and 58% at 5 years ($n=50$). There is a decline in seizure-free patients between 2–5 years postsurgery, which is quite similar to that reported in other cases of extratemporal pediatric epilepsy surgery. The authors note that fewer HME patients were seizure free in follow-up compared to other pathology categories but the differences were not statistically significant, age at surgery and duration of seizure did not correlate with seizure control. The authors comment that the HME cases were surgically the most challenging and of the pathology groups undergoing surgery had the lowest post surgery seizure control which however was higher (58.3%) than in previously reported studies (37%).[23]

In a parallel study from the same centre a comparison of three techniques by pathologic substrates was evaluated in the same group of patients and the factors stratified in the way they affected seizure control: heir conclusion was that the pathologic substrate is less influential with regard to post-hemispherectomy seizure control than other factors such as follow-up length, duration of seizure at surgery, completeness of disconnection of cortex and subcortical structures in patients with cortical dysplasia and Rasmussen's encephalitis.[24]

Long-term seizure control post-hemispherectomy

Seventeen patients treated with hemispherectomy from 1950 to 1971 with a seizure-free or near seizure-free outcome in half of 16 patients (94%) who were followed up long-term up to 38 years were reported by Davies.[25]

Similarly, the long-term follow-up[26] of eight patients showed excellent seizure control, improved neuropsychologic functioning, but a relatively high rate of early postoperative hydrocephalus and CT scan was found valuable to diagnose late complications. The authors emphasize the marked reduction in seizure frequency and improved behaviour, however, with little change in intellect or postoperative hemiplegia.

Seizure-free rates between 50–65% have been reported in studies with 5 or more years follow-up after hemispherectomy, compared with 67 to 88% in reports with shorter follow-up periods.[25] Late recurrences of seizures between 2–5 years are known to occur in pediatric patients after extratemporal resections, however the reasons for late seizure recurrence are not well studied but the phenomenon needs to be considered when comparing seizure control in different clinical series – follow-up duration is an important factor that needs to be considered. The authors, in addition, discuss the effect of including the basal ganglia and thalamus in the resection/disconnection for post-hemispherectomy seizure control, especially in patients with cortical dysplasia and Rasmussen's encephalitis. Studies clearly show that in patients where the basal ganglia and thalamus are preserved the seizure-free rates are lower, reported between 31–67%.[27–29] In studies where deeper structures were removed or disconnected the seizure-free rates are higher, 67–87%.[22,24,30,31]

Recently the favourable long-term seizure outcome results and low complication rate of 83 children who had vertical parasagittal hemispherotomy were reported by Delalande.[32] Similarly the first adult series of 9 patients with follow-ups of up to 30 years was reported with 83% remaining seizure free in the long term and no mortality reported over this period.[33]

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133a Psychiatric outcome of epilepsy surgery

AM Kanner and AJ Balabanov

Introduction

Patients with medically intractable epilepsy are at risk for mood, anxiety, psychotic, and attention deficit disorders (ADHD) (see also Chapter 94). For example, lifetime prevalence rates of depressive disorders range between 30–50%, those of anxiety disorders between 10 and 30% and those of ADHD between 20 and 30%.[1–4] It is not surprising that prevalence rates of these psychiatric disorders are relatively high in patients being considered for epilepsy surgery. In a review of the literature Koch-Stoecker found prevalencerates ranging from 43 to 80% among seven case series.[5] In the case series from the Bethel Epilepsy Center, 43% of patients met criteria for a psychiatric syndrome according to the criteria described in the *Diagnostic and Statistical Manual of Mental Disorder*, Third Edition, Revised, while an additional 29% met criteria for a psychiatric syndrome and a personality disorder.

Recognition of post-surgical psychiatric complications of epilepsy surgery goes back to more than 50 years. For example, in 1957, Hill *et al*. described post-surgical depressive episodes occurring independently of seizure outcome and remitted within 18 months.[6] For a long time, most of the data were obtained in case series at The Guy Maudsley Hospital in London, United Kingdom;[6,7] nonetheless, in the last 15 years there has been a marked increase in the number of published studies.

Psychiatric issues related to epilepsy surgery are complex and can be grouped into four main questions: (1) What are the prevalence rates and clinical manifestations of post-surgical psychiatric complications and what is their relation to post-surgical seizure outcome? (2) To what degree do pre-surgical psychiatric comorbidities contribute to post-surgical psychiatric complications? (3) What is the impact of pre-surgical psychiatric comorbidities on post-surgical seizure outcome and psychosocial adjustment? (4) What is the impact of epilepsy surgery on the course of pre-surgical psychiatric comorbidities? The purpose of this chapter is to address these four questions.

Post-surgical psychiatric complications

Post-surgical psychiatric complications can be the expression of (i) a de novo psychiatric disorder, (ii) a *recurrence* of psychiatric disorder that had been in remission for a period of time prior to surgery, (iii) an *exacerbation* in severity of a psychiatric disorder that was present in a subclinical form or that was mild enough in severity that had gone unrecognized by patient, family and clinician or that was identified because of a more careful evaluation of the patient.

The most frequent post-surgical psychiatric complications include; (i) depressive and anxiety disorders, (ii) psychotic disorder, (iii) psychogenic nonepileptic events (PNEE) and other types of somatoform disorders. A study completed at the Rush Epilepsy Center will serve to illustrate the various forms in which post-surgical psychiatric complications present.[8] The study included 99 consecutive patients, 59 men and 40 women that had undergone an antero-temporal lobectomy and had a minimal post-surgical follow-up period of 2 years (median follow-up duration: 7 years; range, 2–13 years). Their mean age was 31±10.7 years (range, 8–59 years) and the mean duration of their seizure disorder was 19.9±8.8 years (range, 4–40 years). A post-surgical psychiatric complication was rated as; (i) a *de novo episode/disorder*, (ii) an *exacerbation* in severity, or (iii) a *recurrence* of a pre-surgical disorder. Any of these complications were rated as *persistent* if they had failed to remit despite several treatment strategies that included pharmacologic trials and psychotherapy. Psychiatric disorders that were present before and after surgery and did not change in their severity after surgery were rated as *unchanged*, while those that remitted after surgery were rated *improved*.

Among the 99 patients, 62 had temporal lobe epilepsy (TLE) secondary to mesial temporal sclerosis (MTS), 18 had lesional TLE and 19 idiopathic TLE, documented with volumetric measurements of mesial structures. Fifty-five patients (55.6%) had a lifetime psychiatric history before surgery, 46 of whom had a mood disorder which consisted of depression alone in 22 patients, and mixed depression and anxiety disorders in 24 while three had in addition ADHD. Among these 46 patients, 26 had experienced a major depressive disorder, 14 a dysthymic disorder and six bipolar illness. Nine patients had other psychiatric disorders that included ADHD or pure anxiety disorder. Among the 99 patients, 44 (44.5%) met our criteria for post-surgical psychiatric complications: nine patients (11%) with de novo depressive/anxiety disorders and four patients (4%) with de novo psychotic episodes. Thirty one patients experienced an *exacerbation* in severity of pre-surgical depressive/anxiety disorders; these complications occurred during the first 12 months after surgery in all patients. In addition, seven of these 31 patients developed de novo PNEE. At the last contact, the post-surgical psychiatric

complication of 14 patients (13.5%) had failed to remit despite multiple pharmacologic trials; two of these patients had developed a de novo post-surgical depressive disorder.

Univariate analyses identified persistent seizures, pre-surgical psychiatric history and a left temporal seizure focus as predictors of post-surgical psychiatric complications. Multivariate regression models, however, identified a pre-surgical history of depression and a left sided seizure focus as predictors of post-surgical psychiatric complications, but not post-surgical seizure outcome. Interestingly enough, having failed to obtain gainful employment after surgery was not a predictor of post-surgical psychiatric complications (see below).

Post-surgical depressive and anxiety disorders

The prevalence rates of post-surgical depressive disorders vary widely among the different studies ranging from 5% up to 63%, with a mean of 26%. In a study of 274 patients, Bruton *et al*. found a 20-fold increase in the prevalence rate of depression after surgery[9] varying in severity from mild dysphoric to major depressive episodes associated with suicidal attempts. More often than not, these post-surgical complications are an expression of a *recurrence* or *exacerbation* of pre-surgical comorbid disorders. Furthermore, de novo psychiatric disorders are less frequent and are also likely to occur in the first six months after surgery. Here are some examples.

Wrench *et al*. published a study of 62 patients who underwent epilepsy surgery; 43 had an ATL and 19 an extratemporal lobectomy ETL.[10] Both groups had comparable pre-surgical histories of depression and anxiety (33% and 23% respectively for ATL and 53% and 18% respectively for ETL). At 1 month after surgery, symptoms of anxiety and/or depression were reported by 66% of ATL patients and 19% of ETL. At 3 months, 54% of ATL and 33% of TL patients were still symptomatic with 30% of ATL and 17% of ETL patients still experiencing a depressive episode. Furthermore, at the 3-month evaluation 13% of ATL patients had developed a de novo depression and 15% a de novo anxiety disorder, while 18% had developed other type of de novo psychiatric disorders. In contrast, only 17% of ETL patients had developed de novo anxiety, but not depression or other psychopathology. At 3 months follow-up, there was no significant association between post-surgical psychopathology and seizure outcome. Glosser *et al*. published a study of 44 patients who underwent an ATL; in the first month after surgery, 12 patients (31%) developed de novo depression and/or anxiety disorders or recurrence of a disorder that had been in remission during the six months preceding the surgical procedure.[11] By 6 months, they were still symptomatic but significantly improved and by 1 year, all but two patients had become free of symptoms. In a study of 49 patients who underwent an ATL and were followed for a period of almost 11 years, Altshuler found that five (10%) developed de novo depressive episodes, four within the first post-surgical year.[12] Similar findings were reported by Ring *et al*. in a study of 60 consecutive patients who underwent an ATL and had a psychiatric evaluation prior to surgery, at six weeks and three months after surgery.[13] At 6 weeks, 45% of all patients were experiencing emotional lability that reflected a de novo psychiatric complication in half of the patients. By 3 months, the emotional lability and symptoms of anxiety had remitted or improved significantly but not so the depressive states. Blumer *et al*., reported a much higher prevalence rates of de novo psychiatric complications in a study of 50 consecutive patients, 44 of who underwent an ATL and six a frontal lobe resection;[14] 14 patients (32%) developed de novo psychiatric disorders presenting as an interictal dysphoric disorder in six patients, depressive episodes in two and a psychotic disorder in six, while only three patients (7%) experienced an *exacerbation* of a pre-surgical interictal dysphoric disorder. In all but two patients the psychiatric complications occurred within 2 months after surgery. All psychiatric complications remitted with psychotropic treatment. Blumer *et al*. associated the development of post-surgical psychiatric complications with persistent seizures.

The role played by the side of surgery on the risk of developing post-surgical depressive disorders has been also investigated. Quigg *et al* studied the relation between the laterality of the seizure focus and the risk of depression before surgery and 1 year post-surgically among 107 patients, 90 of who underwent an ATL and 17 an ETL.[15] Higher pre-surgical depressive comorbidity and right-sided surgery were significant predictors of more severe postoperative depressive symptoms. Worse preoperative depressive traits predicted worse postoperative scores on scales measuring symptoms of depression. Although the side of surgery did not predict worse post-surgical symptoms of depression, there was a trend for patients with right-sided foci. Findings for the ATL subgroup ($n = 90$) were similar to those of the overall sample. These authors concluded that patients undergoing epilepsy surgery in the right hemispheric, especially those with high pre-surgical depression-related morbidity, may be particularly susceptible to clinical depression. These data differ with the findings of our study in which left-sided focus was a predictor for post-surgical depressive episodes.[8]

Pre-surgical *ictal* fear or panic has been also associated with post-surgical psychiatric complications. For example, Kohler *et al*. studied the association of ictal fear with mood and anxiety disorders before and 1 year after ATL.[16] They compared 22 patients with ictal fear with two matched groups of patients with other type of auras and no auras at all. Pre-surgical and post-surgical evaluations at one to two months and one year after ATL were carried out to identify mood and anxiety disorders and the use of psychotropic medication. The majority of patients in the three groups experienced mood and anxiety disorders before surgery with comparable frequencies. Mood and anxiety disorders declined in the two control groups, but not in the ictal fear group after surgery. Postoperative mood and anxiety disorders were more common in patients with persistent seizures and in those in the ictal fear group who were seizure free. Furthermore, a majority of patients with ictal fear required the use of psychotropic medication after surgery.

In addition, Kanemoto *et al*. have identified an association between pre-surgical postictal psychotic episodes (PIPE) and post-surgical mood disorders in a study of 52 patients who underwent an ATL. Post-surgical mood disorders presented as manic and depressive episodes during the first two post-surgical years.[17]

Post-surgical psychosis

The prevalence rates of post-surgical psychotic complications have been estimated to range between 1% and 10% among patients undergoing ATL. Unfortunately, the data of post-surgical psychotic studies are significantly less robust than those of post-surgical mood and anxiety disorders and consist more often than not of small case series or anecdotal reports. Several case series have include a mixture of patients with pre-surgical and de novo post-surgical psychotic disorders.

De novo post-surgical psychotic episodes may present as schizophreniform-like disorders, manic episodes and postictal psychotic episodes. In the study carried out at Rush Epilepsy Center cited above, Kanner *et al.* identified a de novo psychotic episode in four patients within the first 6 months after surgery consisting of a manic episode in two and a paranoid episode in the other two patients.[8] Symptoms remitted in two patients with pharmacotherapy without the need of hospitalization while the other two had to be hospitalized in a psychiatric unit. In one patient, symptoms remitted after the first admission, while the second patient had to be hospitalized twice. Two of these patients had lesional epilepsy caused by dysembrioplastic neuroepithelioma (DNET) in one and a ganglioglioma in the second.

Shaw *et al.* identified 11 patients who developed de novo post-surgical schizophreniform psychosis among 320 consecutive patients (3.2%) who underwent an ATL.[18] Psychotic symptomatology became apparent within the first year in all patients. These 11 patients were compared to a control group of 33 patients. Psychotic patients were more likely to have bilateral epileptiform activity, a smaller amygdala in the nonoperated side and pathologies other than MTS.

Stevens identified a de novo psychotic disorder in two patients within the first 12 months after surgery among a group of 14 patients who had undergone an ATL and who were followed for a period of 20–30 years.[19] Both patients were seizure-free. In a study of 57 consecutive patients who underwent an ATL, Leinonen *et al.*, identified five (8.8%) who developed postoperative psychotic episodes.[20] Two (3.5%) patients had experienced PIPE before surgery which they continued to have post-surgically. Among the other three patients, two (3.5%) experienced a definite and one (1.8%) a probable de novo schizophreniform psychotic disorder. Among 74 patients who underwent an ATL, Jensen and Larsen identified nine who developed a de novo psychotic disorder.[21] Six of the latter nine patients began experiencing psychotic symptoms after they became seizurefree.

Some investigators, have associated the risk of post-surgical psychotic episodes with a right temporal seizure focus. For example, Mace *et al.*[22] reported seven consecutive patients who developed a de novo psychotic disorder following an ATL, six in the right: one developed a delusional depression and four a schizophrenic-like psychosis, while one patient was diagnosed with Capgras' syndrome. Nonetheless, the relation between side of seizure focus and the risk of developing post-surgical psychosis cannot be established on the bases of these small case series.

As in the study by Kanner *et al.*[8] other authors have associated the presence of gangliogliomas or dysembrioplastic neuroepitheliomas with the development of de novo post-surgical psychotic disorders. Andermann *et al.* reported six patients who experienced a de novo psychotic disorder in six patients from four centers.[23] The psychotic disorders consisted of schizophreniform-like episodes with paranoid and depressive symptomatology. These investigators estimated a risk of 2.5% for the development of de novo psychosis (1 of 39) in patients with this type of lesions that undergo an ATL. Such association remains to be established in larger studies, however.

As stated above, *post-surgical manic* episodes can be psychiatric complications of ATL. For example, Carran *et al.* reported 16 patients who developed a de novo manic episode following an ATL.[24] These patients were identified from a case series of 415 consecutive patients (i.e., 3.8% of patients) who had undergone an ATL at the Comprehensive Epilepsy Center of Jefferson University Medical Center. These patients were compared to a control group of asymptomatic patients matched for age and gender and a second group of 30 patients who experienced a post-surgical depression. The manic episode occurred within the first year after the ATL and was short-lived in all but one patient. Compared to the two control groups, patients with post-surgical mania were more likely to display bilateral electrographic abnormalities, to have a right temporal seizure focus, though this difference did not reach significance when compared to the depressed group. Both post-surgical symptomatic patients were more likely to have experienced GTC seizures before surgery and to fail to achieve seizure freedom post-surgically.

Postictal psychotic episodes can also occur de novo after ATL. Christodoulou *et al.*[25] reported three cases (1%) among 282 consecutive patients who had undergone an ATL. All three patients had seizures predominantly from the contralateral (nonsurgical) site or had bilateral independent seizures, while none of the patients who failed surgery but continued to have seizures from the site of the surgery developed de novo PIPE. This supports the conclusion that patients with PIPE (chronic or de novo) have bilateral independent temporal lobe dysfunction.[26] Manchanda *et al.* identified four patients (1.3%) who developed a de novo PIPE among a group of 298 consecutive patients who had undergone an ATL.[27] All four patients had a right sided resection and had no preoperative psychiatric history.

It has been established in several studies that patients with PIPE are at significantly greater risk of having bilateral independent ictal foci.[26,28–30] In a study completed at the Rush Epilepsy Center, the occurrence of PIPE predicted the presence of bilateral independent ictal foci with an 89% probability.[26] By the same token, patients with recurrent PIPE are at significant risk of developing interictal psychosis. To minimize this risk, clinicians must carefully weigh the possibility of offering 'palliative' surgery to patients with PIPE and bilateral ictal foci, particularly those with MTS, provided that most seizures originate from the side of the MTS and the neuropsychological data are concordant with the intended surgical target.

Post-surgical psychogenic nonepileptic events

Ferguson and Rayport were the first authors that described the occurrence of post-surgical de novo PNEE in1965.[31] The development of these events has been attributed to the 'stress' associated with a 'seizure-free' life in patients with chronic epilepsy that are not 'emotionally, physically or economically ready' to face their own or their families increased expectations.

While this 'hypothesis' makes intuitive sense, the available data does not seem to support it. Here is some of the evidence.

The prevalence rates of post-surgically PNEE are relatively low, ranging between 1.8–10% among the different case series. For example, in the study carriedout at the Rush Epilepsy Center cited above, 7% of the patients developed de novo PNEE[8] (Kanner *et al*., submitted). A pre-surgical (lifetime) psychiatric history was associated with the development of post-surgical PNEE but was not found to be a predictive variable in univariate analyses. Interestingly enough, PNEE were not reported in seizure-free patients; in fact, persistent seizures were significantly associated with the development of de novo PNEE. Furthermore, failure to obtain gainful employment was not associated with the development of PNEE.

Ney *et al*. reported the occurrence of post-surgical PNEE among 96 patients who underwent epilepsy surgery over a period of 11 years.[32] Five patients (5.2%) developed de novo post-surgical PNEE. Low full-scale IQ, preoperative psychiatric comorbidity and major surgical complications were identified as risk factors. Glosser *et al*. identified 22 patients with post-surgical PNEE corresponding to a prevalence rate just below 10%.[33] Most of these patients were women with primary right-hemisphere seizure foci and onset of their epileptic seizures after adolescence. In this study, preoperative psychiatric diagnoses were not related to increased risk of PNEE. Reuber *et al*. identified 13 patients with both epileptic and PNEE and investigated their post-surgical outcome:[34] 11 of the 13 patients had significant clinical improvement post-surgically. However, in two out of 13 patients the severity of the PNEE (including pseudo-status epilepticus) increased postoperatively despite a significant improvement of their epileptic seizures. Both patients had a pre-surgical psychiatric history. V-EEG monitoring is required in order to make the diagnosis. Once diagnosed, the PNEE are usually self limited, however psychiatric help with cognitive therapy and counseling might also be needed.

Post-surgical somatoform disorder

This type of psychiatric complication is either rare or underrecognized. To-date there has been one case series of ten patients who developed somatoform disorder (other than PNEE) after ATL.[35] Seven of the ten patients developed an undifferentiated somatoform disorder, one had pain and body dysmorphia, another had pain disorder, and another had body dysmorphia alone. Somatoform disorder was significantly more common among patients who underwent a right ATL ($n = 9$).

Treatment of post-surgical psychiatric complications

Depression and anxiety disorders

The treatment of post-surgical depression includes the use of pharmacotherapy, psychotherapy, particularly cognitive behavior therapy or a combination of both treatment modalities can be considered. In patients with de novo depressive disorders, it is of the essence to rule out any prior history of manic or hypomanic disorder or a family history of bipolar illness before starting an antidepressant drug, as these agents may worsen the course of a bipolar disorder if given without concomitant mood stabilizing agents.[36] The use of antidepressant drugs of the selective serotonin reuptake inhibitor (SSRI) family are the agents of choice in the management of depressive and anxiety episodes in patients with epilepsy.[37] The use of SSRIs in the treatment of anxiety disorders includes panic, generalized anxiety and obsessive compulsive disorders.[37] Some of the depressive disorders can be very severe and may not respond to pharmacotherapy. In such cases, the use of electroshock therapy (ECT) can be considered. Krahn *et al*. reported one such case of a 25-year-old woman who developed a psychotic depression one year after undergoing a left ATL.[38] ECT resulted in symptom remission without any impact on the seizure disorder.

Psychotic disorders

These require the use of antipsychotic drugs; this class of drugs can lower the seizure threshold and thus, should be started at low doses, titrated up slowly and kept at as low a dose as possible. Among the older antipsychotic drugs, haloperidol remains the safest with respect to the risk of seizure occurrence.[39] Among the newer antipsychotic drugs (also known as atypical antipsychotic agents) all have a lower risk of causing seizures with the exception of clozapine.[40] Quietapine is a drug favored by many clinicians as being the safest; although, no controlled data is available. Of note, quietapine has been one of the antipsychotic drugs not to have been found to cause slowing of the electrographic recordings' background activity.

Impact of epilepsy surgery on pre-surgical psychiatric disorders

Anxiety and depressive disorders following ATL and ETR

Epilepsy surgery appears to decrease the prevalence of psychiatric comorbidities at follow-up evaluations. In the study carried out at the Rush Epilepsy Center, a lifetime psychiatric history prior to surgery had been identified in 55 patients of whom 51 were symptomatic at the time of the psychiatric evaluation.[8] At the last contact, 14 continued to be symptomatic despite multiple treatment strategies and an additional 14 patients were symptomfree on psychotropic medication. Thus, epilepsy surgery resulted in total remission off psychotropic medication in 45% of patients. Among the 44 patients reported by Glosser *et al*., six (15%) were symptomatic before surgery and became asymptomatic post-surgically.[11] Twenty-one patients were unchanged in their psychiatric status: eight who were symptomatic and 13 who were asymptomatic before surgery. While the overall prevalence of psychiatric disorders had not changed 6 months after surgery, the symptom severity measured with the Brief Psychiatric Rating Scale had improved significantly. In the study reported by Altshuler *et al*., 17 of 49 patients (35%) had a lifetime history of at least one major depressive episode.[12] Eight of these patients never experienced another major depressive episode post-surgically. In this study, like in our study, the only predictor for post-surgical depressive disorder was a pre-surgical history of depression. Devinsky *et al*. reported the results of a study of 360 patients from seven epilepsy centers in the USA

who underwent epilepsy surgery; 89% had an ATL.[41] Psychiatric syndromes were identified at baseline and two years after surgery with the structured interview Composite International Diagnostic Interview (CIDI). Pre-surgically, 75 patients (22%) met criteria for a diagnosis of depression, 59 (18%) of anxiety disorders and 12 (4%) of other psychiatric disorders including bipolar illness and schizophrenia. At the two-year post-surgical evaluation, only 26 patients (9%) met diagnostic criteria for depression and 20 (10%) for anxiety, while three patients (1%) met criteria for other psychiatric diagnoses. Thus epilepsy surgery had resulted in symptom remission in more than 50% of patients. In this study, the presence of an anxiety or depressive disorder post-surgically was not associated with seizure outcome.

Psychotic disorders

The decision to consider epilepsy surgery in patients with refractory epilepsy and comorbid psychotic disorders has been the source of much controversy. Indeed, some epilepsy centers consider the existence of a psychotic disorder as a contraindication for epilepsy surgery while others do not, as long as the patient can cooperate during the pre-surgical evaluation and has a clear understanding of the therapeutic expectations and risks of the surgical procedure. The impact of ATL on the post-surgical course of the psychotic disorder has varied from unchanged (in a majority of cases) to improved psychotic status and/or level of functioning.[42–47] Yet, several reports have suggested that, in the long term, psychiatric symptoms such as irritability and aggressive behavior can improve following ATL. For example, in a study of 74 patients who underwent an ATL, Jensen and Larsen identified 11 with a psychotic disorder *pre-surgically*.[21] The surgical procedure had no impact on the psychotic disorders that were present pre-surgically. In a study of 52 patients, Kanemoto *et al*. reported recurrence of psychosis in more than two-thirds of the patients with preoperative history of interictal psychosis. Some of the patients (7/12) remained in acute psychosis for a long time.[44] In a series of five patients with a chronic psychotic disorder who underwent an ATL, Reutens *et al*.[45] reported an excellent seizure outcome in all patients. The surgical procedure did not modify the psychotic disorder post-surgically, but the absence of seizures facilitated their level of functioning. Marchetti *et al*. reported six patients with pre-surgical interictal psychosis who underwent an ATL.[46] Five of the six patients achieved a seizure-free outcome and there was no worsening of their psychotic disorder, with relative improvement in the mental conditions of five patients. These same authors reported an additional case of a 45-year-old female patient with a 30-year history of epilepsy and recurrent postictal psychotic episodes since the age of 35 which evolved to a chronic refractory interictal psychosis.[47] Following a right ATL she became seizurefree with remission of the psychotic disorder. All of these case series exemplify that patients with interictal psychosis can successfully complete a pre-surgical evaluation.

Epileptic encephalopathies

The term of 'epileptic encephalopathies' is used to refer to psychiatric and cognitive disturbances whose onset can be traced back to that of the seizure disorders and which can be expected to improve and at times totally remit with the abolition of the epileptic activity. In some epileptic encephalopathies, clinical seizures are rare or not identified but EEG recordings display abundant epileptiform activity. One example of this type of encephalopathy is the acquired epileptic aphasia of childhood (also known as Landau-Kleffner syndrome (LKS), in which severe language and psychiatric disturbances are the major expression of the epileptic disorder and cure of the seizure disorder often is followed by their *partial to full* recovery[48] (see also Chapter 43). Hypothalamic hamartomas with gelastic epilepsy (HHGE) is another example of an epileptic encephalopathy but which is associated with a pharmacoresistant seizure disorder. It presents characteristically with severe psychiatric and cognitive disturbances associated with the onset of a variety of epileptic seizures but particularly gelastic seizures, and also including complex partial, secondarily generalized tonic-clonic seizures, and at times atonic or tonic seizures.[49] Epilepsy surgery has become one of the treatment modalities of these two epileptic encephalopathies and the severe psychiatric and cognitive disturbances appear to remit or improve significantly with the successful cessation of epileptic activity. Unfortunately, the pre and post-surgical psychiatric disturbances have not been evaluated in a systematic manner in either of these two disorders and in most patient series the reports of improvement have been based on parents' reports and not on structured interviews or diagnostic instruments. Thus, the absence of such data precludes a totally objective assessment of the impact of surgical treatment on the pre-surgical psychiatric manifestations and post-surgical changes of these disorders but some data are available and worth reviewing.

Landau–Kleffner syndrome

The surgical technique employed in LKS has consisted primarily of multiple subpial transection (MST) of the epileptogenic area, which typically involves intra and perisylvian cortex.[50] Kanner *et al*. reviewed the post-surgical outcome of 22 children with LKS who underwent epilepsy surgery at the Rush Epilepsy Center between the years 1990–2003 (for more details see Chapter 43).[51] Among the 22 children, 14 were boys and eight girls who were 6.95±1.95 years old at the time of surgery. The mean age of onset of LKS was 4.3±1.4 and the mean duration of the disease before surgery was 2.5±1.3 years; 21 had nonfunctional language for a period of at least 18 months; one child had functional language but had been experiencing frequent and recurrent language regressions that failed to be prevented with pharmacotherapy that included multiple AEDs trials and steroids. Behavioral problems were reported in 19 children; clinical seizures were also identified in 19 patients. In 14 patients (63.6%) only MST of intra and/or perisylvian cortex was performed. In seven (32%) a combination of MST and resection of temporal lobe structures was carried out, while one child underwent a resection of the planum temporale in the right hemisphere of a right-handed boy. Among the 19 children with clinical seizures before surgery, 15 (79%) became seizure free, two had rare seizures, one had >90%, and one had >90% seizure frequency reduction. The presence of epileptiform activity (but not a CSWS pattern) in the last EEG was not associated with a worse post-surgical

language recovery. On the other hand, recurrence of language disturbances occurred in three patients who had a recurrence of a CSWS pattern after surgery.

Post-surgical neuropsychological and speech evaluations were carried out after a mean period of 34.1±19.9 (7–75 months). The mean *baseline* score of the language test used for evaluation of expressive vocabulary, the Expressive One Word Picture Vocabulary Test-Revised (EOWPVT-R, expressed as age equivalent in months old) was 12.8±9.0 months, while the mean *baseline* score of the Peabody Picture Vocabulary Test-Revised (PPVT-R) which is used for evaluation of receptive language was 14.6±12.9 months. At the last formal speech evaluation, the mean EOWPVT and PPVT scores displayed significant increments to 144±72.9 months and 144±73.8 months, respectively with mean gains of 124±60.1 months and 129±59.2 months respectively. In addition, there was a significant correlation between the duration of post-surgical follow-up and the gains made on the PPVT ($r = 0.56$, $p = 0.02$) and a statistical trend for the EOWPVT ($r = 0.4$, $p = 0.09$). At that time, 20 of the 22 patients were still receiving speech therapy. Following a mean post-surgical follow-up period of 48.3±30.2 months, 16 children (72%) had regained functional language as defined by the ability to use complex sentences and understand what was being said to them. Despite these significant gains, only nine of these children (41%) were in a regular class without a need of assistance or further speech therapy. Finally, behavioral improvement was reported in 17 of the 22 patients (77%) by the parents, though there was no significant association between recovery of functional language and reported behavioral improvement.

Encephalopathy due to HHGE

Three surgical techniques have been advocated for the treatment of HHGE, including resection of the hypothalamic hamartoma, radiation with gamma knife and disconnection or destruction of the hamartoma with stereotactic radiofrequency.[49,52–54]

The behavioral and cognitive changes reported in these patients are quite variable. In most patients, behavioral difficulties are characterized by aggressive behavior, uninhibited tendencies, and clinical pictures indistinguishable from attention deficit with hyperactivity, and irritability. Up to 30% of patients may have autistic features. In those patients who appear to have normal cognition, insidious changes often develop before puberty.[49] In most patients, gelastic events often are the only seizure manifestation during the first 5–10 years of life. However, most patients develop other seizure types before puberty. The frequency of the gelastic seizures may be as high as 100 attacks per day. The frequency of other seizures is variable, but often they occur weekly. Of note, some patients who have frequent gelastic seizures do not deteriorate, whereas others with other types of epileptic seizures have worse outcome. The association between seizures and behavioral changes is not clear as the number of seizures in this syndrome often is difficult to estimate. However, depth EEG recordings from the hamartoma often demonstrate almost continuous discharges with or without secondary spread. It is possible that this almost continuous epileptic activity causes considerable cortical and subcortical dysfunction. For parents, the behavioral and cognitive problems often become more important than the seizures.

At least 11 case series of patients with HHGE treated with one of the three techniques cited above and totaling more than 120 patients have been published in the literature in the last 10 years. There is a consensus among the various investigators that successful lesioning or removal of the hamartoma leads to major improvements in cognitive performance and behavior. Most astonishing is the rapid cognitive and behavioral changes observed in these patients. Of the 11 case series published, data from seven are included in Table 133a.1 and presents cognitive and behavioral information on cognitive and behavioral changes post-surgically.[55–61] Five of the series consisted of resection of the HH and one of stereotactic surgery with gamma knife and one with interstitial radiation. Improvement of cognitive and psychiatric disturbances was observed in a majority of patients.

Impact of pre- and post-surgical psychiatric illness on post-surgical seizure outcome

Most of the studies that have investigated the relationship between post-surgical psychiatric disturbances and seizure outcome have found a significant association between persistent post-surgical seizures and post-surgical depressive disorders. Furthermore, Vickery *et al.* have also demonstrated an

Table 133a.1 Surgical case series with data on post-surgical cognitive and psychiatric changes

		Pre-surgical disturbances		Improvement post-surgically			
Authors	N	Cognitive disturbances	Psychiatric disturbances	Cognitive disturbances	Psychiatric disturbances	Seizures	Surgical procedure
Rosenfeld (2003)	5	5	5	5	5	5	Resection
Fohlen (2003)	18	18	18	17	17	17	Resection
Palmini (2002)	13	13	13	13	13	13	Resection
Bonhage (2003)	8	8	8	5	5	5	Interstitial Radiation
Freeman (2003)	12	12	12	12	11	11	Resection
Striano (2005)	6	6	?	3	?	3	Resection
Regis (2005)	25	25	0	9	9	18	Gamma knife

association between persistent seizures, including persistence of only auras and poor quality of life post-surgical.[62,63] Indeed, compared to patients who are completely seizurefree including free of auras had significantly higher scores on the Quality of Life in Epilepsy Inventory-89 (QOLIE-89) than those with only auras. The negative impact of persistent auras on the quality of life may be mediated by the need to be kept on AEDs or even the use of higher doses of AEDs to assuage the concern of recurrent seizures. Nonetheless, these data are counterintuitive since patients with auras but no disabling seizures can function normally in all areas. In fact, in a study by Kanner *et al.*, a pre-surgical lifetime psychiatric history of depression was the strongest predictor of persistent auras (in the absence of disabling seizures) on the one hand, and of post-surgical psychiatric complications, particularly depression on the other[64] and (Kanner *et al.*, submitted). Thus, these data raise the question of whether the worse QOLIE-89 scores in patients with persistent auras are driven by a concurrent mood disorder and not (only) by the auras.

A few studies have suggested that a *pre-surgical* psychiatric history is associated with a worse post-surgical seizure outcome. For example, in a study of 121 patients who underwent an ATL, Anhoury *et al.* reported a worse post-surgical seizure outcome for patients with a lifetime psychiatric history compared with those without.[65] Koch-Stoker investigated the post-surgical seizure outcome among 100 consecutive patients who underwent an ATL; 78 had a pre-surgical lifetime psychiatric history. Among patients without comorbid psychiatric history, 89% were seizure free after surgery while this occurred in only 43% of patients with pre-surgical psychiatric history (unpublished data). In the study cited above, Kanner *et al.*[64] used a logistic regression model to identify predictors of post-surgical seizure outcome in the 99 consecutive patients who had undergone an ATL. Covariates included: (i) cause of TLE (MTS, lesional TLE and idiopathic TLE); (ii) history of secondarily generalized tonic-clonic seizures (never, only at the onset of the seizure disorder, 1–2/year, >2year); (iii) duration of seizure disorder; (iv) lifetime history of depression (may have included major depressive disorder, dysthymia). As already mentioned above, a lifetime history of depression was the *sole* predictor of persistent auras in the absence of disabling seizures. In addition, the cause of the temporal lobe epilepsy and a lifetime history of depression were both significant predictors of failure to achieve freedom from disabling seizures. When the outcome variable was no disabling seizures in the last 2 years, the cause of TLE was the strongest predictor, while a lifetime history of depression yielded a statistical trend. These data raise another question – 'Is it possible that a psychiatric history, particularly depression is an 'indicator' of a more severe form of epilepsy?'

Psychosocial outcome

Family dynamics

Epilepsy surgery is expected to have a positive significant impact on the patient's life. With the achievement of seizure freedom, patients can become more independent, not only as it pertains to their ability to drive but in other areas of their life. Paradoxically, in some cases seizure freedom can have a negative impact on family dynamics. Indeed, some family members become accustomed to the patients' limitations and dependency on others and have difficulties allowing the patient to become more independent and see their role in life (unconsciously) as that of a 'caretaker' without which they cannot 'function'. Unfortunately, these dysfunctional family dynamics are not rare in families of patients with a chronic illness like epilepsy and invariable are bound to lead to conflict when patients try to become more independent. In fact, divorce is not an uncommon 'complication' of successful epilepsy surgery. Thus, all couples and families need to be evaluated for the eventual risk of this type of family problems.

Gainful employment

Obtaining gainful employment or getting a better job are some of the obvious goals of a successful surgical treatment. Unfortunately, such is not always the case. A review of the literature reveals that the main factors associated with post-surgical employment are: reduction of seizures or seizure freedom, pre-surgical cognitive ability, psychiatric comorbidity, pre-surgical employment and improvement of neuropsychological function.[66] In a study of 88 adult patients who underwent an ATL at the Rush Epilepsy Center, the predictors of post-surgical gainful employment included: working before surgery, achieving a seizure-free state, a negative lifetime history of depression and being a woman.[67] Lendt *et al.* found that a young age at the time of the surgery and improvement of the general neuropsychological functioning and especially attention are associated with employment after the surgery.[68] In another study, Reeves *et al.* found that being a student or working full time within a year before the surgery, driving after the surgery and obtaining further education after the surgery were associated with full time work postoperatively.[69] Clearly, these data are indicative of the need to carry out vocational evaluations before surgery among unemployed patients.

Disclosure of post-surgical psychiatric complications

As shown above, epilepsy surgery is associated with post-surgical psychiatric complications which should be openly discussed with patients and family members with as much detail as the other surgical risks. Indeed, patients should be advised of the risk of post-surgical depressive and anxiety episodes occurring within the first 12 months, with a higher symptom incidence in the first 3–6 months and a tendency to remit by 12 to 24 months. This is especially true when the patient has a previous history of mood disorder and the symptoms are actually an expression of a recurrence or exacerbation of pre-surgical depressive and/or anxiety disorders, while de novo mood/anxiety disorders are significantly less frequent. In patients undergoing ATL de novo depressive and anxiety disorders can be expected in 10–15% and a risk of 10–15% of persistent mood and anxiety disorders should be disclosed. Patients undergoing extratemporal resections have a lower risk of developing post-surgical psychiatric complications compared to patients undergoing an ATL, though the data available on post-surgical complications after ETL are rather sparse and more studies are needed to establish the

actual risk. With respect to the potential risk of post-surgical psychotic complications, patients and family members should be advised that while de novo post-surgical psychotic complications have been estimated to range between 1–10% following an ATL, the actual frequency remains to be established.

Concluding remarks

The data reviewed in this chapter clearly indicates that patients undergoing epilepsy surgery are at risk of developing psychiatric complications during the first post-surgical 12 months. While in a majority of patients, symptom remission is expected, 10–15% of patients may continue experiencing psychiatric symptoms that may fail to respond to multiple treatments. On the other hand, epilepsy surgery is expected to improve the course of psychiatric disorders, particularly anxiety and depressive disorders in more than 50% of patients. This is another advantage of epilepsy surgery which is rarely discussed with patients and families, in part because of a failure to include a psychiatric evaluation in most pre-surgical evaluations. Finally, the suggestion that pre-surgical psychiatric disorders may be predictive of post-surgical seizure outcome requires further research as it may help identify common pathogenic mechanisms between psychiatric and epileptic disorders.

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133b Sudden unexpected death in epileptic patients after epilepsy surgery

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Introduction

People with epilepsy have a reduced life expectancy.[1] Mortality has been consistently shown to be 2–3 times higher in people with epilepsy than in the general population (for a review see Tellez-Zentano and Wiebe, 2005)[2] and even higher in populations with more severe epilepsy or associated disorders.[3–5] This increased mortality is attributable to both the underlying disease and to epilepsy itself, and, in rare cases, to fatal side effects of medical or surgical treatment. Common causes of death include pneumonia and other medical illnesses, suicide, seizure-related death and sudden unexpected death (SUDEP). The latter two causes account for between one–fourth and two-thirds of all deaths,[6] making SUDEP the most common cause of death in patients with epilepsy.[7] Reducing mortality is an important aim of epilepsy management.[8] Given that epilepsy surgery is the only intervention to render large proportions of patients with drug resistant epilepsy seizurefree with or without antiepileptic drugs,[9] it is of interest to examine the potential of epilepsy surgery to reduce seizure-related mortality. In this chapter, we focus on the question if epilepsy surgery is able to reduce the incidence of SUDEP in refractory epilepsy.

Definition of SUDEP

To establish the presence of SUDEP, an expert panel in 1997 [10] suggested all of the following criteria: (a) a diagnosis of epilepsy; (b) death occurring unexpectedly while in a reasonable state of health; (c) death occurring suddenly; (d) death occurring during normal activities and benign circumstances; (e) not finding an obvious medical cause of death during postmortem examination; (f) death not resulting from trauma, asphyxia due to aspiration or intractable status epilepticus. SUDEP is considered 'definite' when all criteria are met, and 'probable' when there are no postmortem data. Other definitions of SUDEP exist.[11,12] Some authors use Nashef and Brown's definition of SUDEP,[11] i.e., 'sudden, unexpected, nontraumatic and drowning death in an individual with epilepsy with or without evidence for a seizure and excluding documented status epilepticus, where postmortem examination does not reveal a cause of death'. All definitions share the problem of accurate classification due to insufficient information about the circumstances surrounding death, and to the infrequent practice of postmortem examinations.

SUDEP in surgical candidates and operated patients

A review of 19 studies looking at overall mortality in epilepsy determined that the proportion of SUDEP among all causes of death in surgical candidates or operated patients ranged from 40–77%.[2] The annual incidence of SUDEP was highest in studies of patients who had epilepsy surgery or were surgical candidates (2.2:1000–10:1000) or were undergoing vagus nerve stimulation therapy (4:1000), with a median of 3.6:1000 patient-years.[2] Accordingly, in a review pooling data from all drug-resistant epilepsy series providing detailed numbers of SUDEP and patient-years of follow-up, we found a total of 154 SUDEP among 41, 439 person-years, resulting in a mean annual SUDEP incidence of 3.7/1000.[13] A high number of AEDs, high frequency of seizures, and long duration of epilepsy were found to be more commonly found in high-risk than in low risk populations.[2] In addition, uncontrolled tonic-clonic seizures have been associated with a higher risk of seizure-related death and SUDEP.[6,14] The role of seizures in the pathophysiology of SUDEP is therefore briefly discussed in the next paragraph.

Seizures and SUDEP

Although a detailed account of the pathophysiology of SUDEP is beyond the scope of this chapter, a large body of evidence suggests that SUDEP, although unexpected, is not fully unexplained any more.[15] SUDEP is seizure related in the majority of witnessed cases.[14,16–19] Two major mechanisms have been implicated, one is obstructive or central apnea and neurogenic pulmonary edema.[11,18,20–24] The other is ictal cardiac dysfunction, either through ictal asystole, or ictal cardiac ischemia.[25–29] The cardiac hypothesis of SUDEP has been strenghtened by the detection of potentially fatal asystole in three out of 20 patients with drug-resistant partial epilepsy when examined by implantable loop EKG.[31] Furthermore an

incidence of 0.4 % of ictal asystole has been documented in 1244 video-EEG recordings.[31] Thus, it is not unreasonable to expect that improving seizure control or disease changes associated with better seizure control after epilepsy surgery might reduce mortality. In the following paragraph, we briefly review the evidence that the incidence of SUDEP is actually reduced after surgery for epilepsy.

Does epilepsy surgery lower the incidence of SUDEP?

The impact of resective epilepsy surgery on mortality has been evaluated in several series comparing pre- and postoperative mortality rates (Table 133b.1). Three of these series have concentrated on temporal lobe surgery and demonstrated that the postoperative mortality rate was normal in seizure free patients, whereas it was significantly higher, and comparable to that observed in drug resistant epilepsy cohorts, in patients with poor seizure outcome after surgery.[6,32–33] The authors implied that had surgery not been performed, the patients would have continued to suffer excess mortality, dying at rates similar to patients whose seizures persisted.[6,32–33] This result suggests that successful surgery is associated with dramatic reduction of the risk of epilepsy-related death. However, the authors cautioned that they cannot exclude the possibility that the different responses of their patients to surgery could indicate underlying biological differences that are related to mortality rates.[6,32–33] In fact, other series could not confirm the above findings, and reported comparable death rates in patients with and without postoperative seizure control.[34,33]

In addition, a number of confounding factors need to be considered when examining the relationship between seizure control and mortality after epilepsy surgery. If, for example, mortality is reduced after surgery only in those with complete seizure control, or epilepsy surgery increases mortality in those who remain uncontrolled or the minority with worse control after surgery, the net group effect of surgery on mortality may be small. Furthermore, if the subgroup that responds to surgery had no increased seizure-related mortality to begin with, surgery may have had no effect on mortality even when improving seizure control. Also, theoretically, all-cause mortality may be related to the underlying cause of the epilepsy, and surgery might not be able to completely remove the cause and thus be not able to lower mortality. Finally, reports of survival after epilepsy surgery have been heterogeneous in sample selection, observation periods, analytic methods, choice of comparison groups, and based on small numbers of deaths.[6,34–37] Also, patients were not stratified according to their pre-surgical risk factors for SUDEP or seizure-related death.

Another attempt to study the impact of resective epilepsy surgery on mortality, is to compare cohorts of surgically and medically treated patients. Seven studies have addressed this issue, using various methodologies, and again providing controversial results (Table 133b.2). Only two of the seven series reported a significantly lower death rate in operated patients as compared with those medically treated.[35,39] However, the result by Vickrey and co-workers could be partly explained by preoperative differences between the two populations, including the type of epilepsy (mainly nonlocalized in the medical group and temporal in the operated patients) and the baseline seizure frequency which was significantly higher in the non operated patients.[35] Furthermore, the other five series failed to demonstrate a difference in mortality between operated and nonoperated patients.[37,32,38–42] In the next paragraph we examine the evidence that surgery was in fact responsible for the lower mortality rate reported in some studies.

Table 133b.1 Impact of resective surgery on mortality: seizure-free versus not seizure-free patients

Study population (no. of patients)	SMR: seizure-free patients	SMR: not seizure-free patients	Authors
596 total, 355 TLE	228 at 2 years: 5 died, SMR=3.8 (3 SUDEP);	255 at 2 years: 6 died, SMR=4.3 (3 SUDEP)	Nilsson *et al*. (2003) (ns)
196 total, 106 TLE	69 at 2 years, SMR = 6; no difference	100 at 2 years, SMR = 7.8	Stavem and Guldvog (2005) (ns)
393 TLE	199, no death; significantly lower	194, 11 died, SMR = 4.7 (9 epilepsy related)	Sperling *et al*. (1999) ($p = 0.05$)
215 TLE	148 patients, follow-up: 1–15 years: 3 died, SMR = 1.7 (CI: 0.35–5.0), 1 SUDEP, 1 cancer, 1 suicide; significantly lower	67 patients follow-up: 1-15 years: 8 died, SMR = 7.4 CI: 3.1–14.5); 5 Seizure/ SUDEP, 3 accident/ suicide	Salanova *et al*. (2002) (no Overlap of CI, significant difference)
299 surgical patients	11/13 who died were not seizure free (4 SUDEP (definite and probable), 7 seizure-related)	3/13 who died were seizure free (2 SUDEP, 1 killed by vehicle, seizure-related)	Hennessey *et al*. (1999) (difference)
398 surgical patients	313 with Engel outcome score I, death and SUDEP rate per person-year: 1/535, 0	85 patients with Engel outcome score II–IV, death and SUDEP rate per person-year: 1/81.3, 1/97.6	Sinha *et al*. (2005), ($p = 0.36$)

Abbreviations. SMR = standard mortality ratio per 1000 patient years, SUDEP = sudden unexplained death I epilepsy, TLE = temporal lobe epilepsy.

Table 133b.2 Impact of surgery on mortality: operated versus nonoperated patients

Study population (no. of patients)	SMR: operated patients	SMR: nonoperated patients	Authors
202 surgical vs. 46 nonsurgical patients	14 died (7%) at 6 yr. follow-up	9 died (20%) at average follow-up of 6 yr.	Vickrey *et al*. 1995 ($p<0.01$). Reviewer commentary: cause of death not rigorously ascertained, higher proportion of ongoing seizures in those who died.
196 total, 106 TLE	69 at 2 years, SMR = 6	100 at 2 years, SMR = 7.8	Stavem and Guldvog (2005) (ns)
596 operated patients and 212 nonsurgery patients	596, 14 died, 6 in SUDEP. SMR 4.9 (CI 2.7–8.3). SUDEP incidence 2.4 per 1000 person-years	212, 5 died, 4 in SUDEP, SUDEP incidence: 6.3 per 1000 person-years. SMR for all causes: 7.9 (CI 2.6–8.1)	Nilsson *et al*. (2003) (ns). Reviewer commentary: None of the SUDEP patients was seizure free.
324 TLE	316 at 4.5 years: 12 died, SMR = 1.7 (2 SUDEP, 2 status/seizure related, 1 head injury after falling, 2 medical illness, 2 suicide, 3 cause unknown)	116 at 2 years: 8 died, SMR = 7.4 (2 SUDEP, 1 status, 1 homocide, 1 drowning and medical illness, 2 unknown cause)	Radhakrishnan *et al*. 2005 (abstract) (ns) All cause mortality, $p = 0.218$, for seizure related death only $p = 0.416$)
201 surgical vs. 185 nonsurgical patients			Guldvog *et al*. (1991) (no difference in proportion of patients alive in both groups)
398 surgical vs. 707 patients rejected for surgery	313 with Engel outcome score I (Group A), death and SUDEP rate per person year: 1/535, 0 (Group A). 85 patients with Engel outcome score II–IV, death and SUDEP rate per person year: 1/81.3, 1/97.6 (Group B)	707 patients rejected for surgery (Group C), death and SUDEP rate per person year: 1/59.7, 1/77.2 (Group C)	Sinha *et al*. (2005) Group A vs. C: $p = 0.001$
775 surgical patients vs. non surgical patients (number not given)	SUDEP rate 0.79/1000 patient years	SUDEP rate 1.1/1000 patient years	Walczak *et al*. (1999) (ns).

Is epilepsy surgery responsible for lower SUDEP rates after surgery? post-hoc or propter-hoc?

It is apparent from the above studies that no consensus emerges regarding the impact of surgery on mortality. As already pointed out, several differences in methodology, type of control population and surgical candidates, are likely to explain the discordant findings observed in the literature. Taking all available data into account, it appears that the main effect which might hold on is the lower risk of seizure-related death in seizure-free patients after temporal lobe surgery, as compared to those who failed to respond to such surgical procedure. However, other series could not confirm the above findings, and found comparable death rates in patients with and without postoperative seizure control.[34,33] Is the lower long-term mortality, in particular SUDEP, reported in some studies, compelling evidence that surgery is in fact responsible for lowering mortality? The attribution of the mortality-lowering effect of surgery rests on the implicit assumption, that prior to surgery, responder and nonresponder to surgery carried a similar risk of mortality. If, for example, those who respond to surgery have a priori a lower mortality, a better postsurgical mortality outcome in surgical responders is no proof for the effect of surgery on mortality. Theoretically, clinical predictors of unfavorable postoperative seizure outcome might also be associated with a higher risk of death, preoperatively. Is there any suggestive evidence that responders may have a lower mortality risk to begin with? In fact, secondary generalized seizures, for example, appear to represent a risk factor for both SUDEP and surgical failure in TLE.[18,19,43–45] Another piece of indirect evidence that patients with a favorable outcome regarding seizures after surgery may have a priori a lower risk of SUDEP comes from Sweden.[46] The authors studied autonomic cardiac control by measuring the heart rate variability prior to surgery and correlated their finding with surgical seizure outcome. Before surgery, the heart rate variability was significantly lower in the patients with ultimately poor outcome (Engel class II–IV) compared with patients with good outcome (Engel Class I). Reduced heart rate variability is a known risk factor for sudden death in nonepileptic patients

with various cardiovascular conditions,[47] and might also be associated with an increased risk for SUDEP.[46] According to these data, surgery candidates with a good outcome may a priori have a lower risk of SUDEP and further suggest that the lower incidence of SUDEP reported after successful surgery may not necessarily be a consequence of the operation.[46]

Support for the view that preoperative differences in risk for cardiovascular death or for SUDEP might exist in patients undergoing resective surgery, comes form a series of publications by Hilz and coworkers.[48,49] They reported that following temporal lobe surgery, there is a reduction of sympathetic cardiovascular modulation and baroreflex sensitivity.[48] More specifically, they suggested that temporal lobe surgery seems to stabilize the cardiovascular control in epilepsy patients by reducing the risk of sympathetically mediated tachyarrhythmias and excessive bradycardiac counter-regulation, both of which might be relevant for the occurrence of SUDEP.[48] In a subsequent publication, Hilz and co-workers studied 16 patients before and after temporal lobe epilepsy surgery and found that sympathetic modulation decreased after surgery in eight patients with good outcome, defined as no seizures in the 10 months after surgery, while it further increased in the group of eight patients with poor surgical outcome.[54] These data support the hypothesis that patients with good seizure outcome (which have been shown to have an improved mortality risk after surgery, as reviewed above) may have had a lower preoperative risk for SUDEP to begin with, and as a consequence it is difficult to attribute the postoperative benefit in mortality outcome to the epilepsy surgery.

The authors have proposed at least two mechanisms to explain the differences in autonomic modulation between patients with good and those with poor outcome of surgery.[49] One, central relay areas of autonomic control areas, such as the amygdala, hippocampus, fronto-orbital cortex, insular cortex, paraventricular or hypothalamic regions are either in close proximity to the epileptogenic zone or part of the pathologic tissue accounting for seizure generation and/or epileptogenesis. Two, interictal EEG activity spreading towards neighboring centers of autonomic control may also interfere with autonomic modulation.[49] The first hypothesis is consistent with the concept of temporal-plus epilepsy which refers to an epileptogenic zone that primarily encompasses the temporal lobe but extends outside the boundary of a standard resection, thus displaying electro-clinical and MRI features highly suggestive of TLE, including signs of hippocampal sclerosis, while usually not responding to anterior temporal lobectomy.[50] The perisylvian region is often involved in this form of epilepsy,[50,51] including two brain structures that might play an important role in the pathophysiology of SUDEP, the insula and the frontal operculum. Electrical stimulation of the precentral operculum has proved to elicit apnoea in patients with epilepsy,[52] whereas insults to the insular cortex appear to promote cerebrogenic sudden death.[53] However, despite clear indications that the insular cortex regulates cardiovascular function in animals and humans,[26,53] only scarce data are yet available regarding its implication in severe ictal arrhythmias or SUDEP.[54–56]

Coming back to our discussion that preoperative differences in risk for SUDEP might exist, it is of particular interest that the eight patients with good outcome of surgery had shown better results in spectral powers of autonomic heart rat modulation *prior* to surgery than those with poor outcome.[49] Although the number of patients was small and the postoperative follow-up was short, these results seem to support our hypothesis that postsurgical reduction in SUDEP rates might be preferentially seen in those with a lower risk for SUDEP prior to surgery. Conversely, augmented sympathetic modulation was seen in patients with persistent seizures after surgery.[49] The authors also suggest that these data indicate an increased cardiovascular risk or risk in SUDEP in patients with poor outcome of epilepsy surgery.[49] Furthermore, anecdotal reports of SUDEP after successful anterior temporal lobectomy suggest that the mechanism leading to SUDEP cannot be halted by successful epilepsy surgery in all cases.[57] In the series by Hennessy *et al.* (1999), the mortality including SUDEP rate of patients with right sided mesial temporal sclerosis remained considerably elevated after surgery (SMR 32, 95% confidence intervals: 24.7–40.5, SUDEP 1: 134 patient-years). In that respect it is of interest to note that in a series from Austria, surgical candidates with right mesial temporal sclerosis had the highest rate of ictal and postictal tachycardia.[58]

If, in fact, the preoperative risk of death is higher in patients who will eventually fail to respond to temporal lobe surgery as compared to the other patients, one could reconcile the positive findings reported in temporal lobe surgery series and the negative results of studies which have compared surgically and medically-treated patients. However, it remains unclear if epilepsy surgery contributes to improved long-term survival in cohorts with severe epilepsy. This controversy has recently been underscored in a review article.[13] Unfortunately, testing this hypothesis remains elusive at the present time mainly for two reasons. One, we cannot precisely anticipate the postoperative seizure outcome prior to surgery as discussed by Ryvlin and Kahane (2005). Two, no large series of surgical outcome exist which have included a stratification for low or high pre-surgical risk for SUDEP.[50]

Neurostimulation and SUDEP

In a cohort of 1819 patients drawn from the pre-FDA approval clinical research trials and the manufacturer's records undergoing vagus nerve stimulation (VNS) for treatment of refractory epilepsy. In the 1819 patients who were followed for 3176 patient-years from implantation, the SUDEP rates were 4.1 per 1000 patient years.[59] The mortality and SUDEP rates are similar to those reported from clinical trials of new drugs and cohorts of severe epilepsy. However when the authors stratified the data by duration of use, the rate of SUDEP was 5.5 per 1000 over the first two years, but only 1.7 per 1000 thereafter.[59] The authors concluded that the lower SUDEP rates after two years of VNS were intriguing, but required further study.[59] If responders to VNS carry a lower risk of SUDEP prior to implantation they have not been examined, to our knowledge.

Conclusions and summary

Several, but not all, series have reported reduced death and SUDEP rates in patients rendered seizure free by epilepsy surgery, whereas those who continue to suffer recurrent seizures postoperatively had an increased mortality comparable to that

observed in medically-treated drug resistant epilepsy or patients rejected for epilepsy surgery. However, in view of many confounding factors, most notably the emerging evidence that those with good seizure outcome after surgery may have lower death and SUDEP risk to begin with, i.e., prior to surgery, the exact contribution of epilepsy surgery for the lower rate of SUDEP observed after surgery needs to be determined. Another unresolved issue is whether some surgical patients will have an increased risk of SUDEP compared to nonsurgical controls with refractory epilepsy. Finally, it is tempting to speculate that the mechanisms responsible for surgical intractability may also regulate the risk of seizure-related mortality, particularly of SUDEP. Once we are able to better predict surgical seizure outcome, we may also gain a better understanding of the mechanism(s) involved in lowering the risk of SUDEP after surgery.

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134 Psychosocial outcome and quality of life outcome

NK So and CB Dodrill

Introduction

Common questions asked by patients before epilepsy surgery can be separated into those on the potential for a positive outcome and those on the risk of an adverse effect. Positive outcomes include seizure control, the possibility of a reduction or withdrawal of antiepileptic medications, retention of employment or the hope of new employment and a better job, the ability to drive, improvement in independent function in the community, and a better social relationship with family and friends. Adverse effects include pain and suffering, neurological deficits, impairment of memory and cognition, negative change in mood and personality, loss of independence and death.

This chapter deals with one of the most important outcomes of epilepsy surgery, the impacts of this surgery upon one's quality of life (QOL), especially in a social context. So important is this area, that one could even argue that if the surgery does not have a positive impact upon the quality of the patient's life that indeed it has failed.

We begin this chapter with a review of some of the most salient studies dealing with epilepsy surgery and quality of life overall. We then go on to specific topics of interest within the psychosocial and QOL domains, and we present some of our own data, not heretofore published, to support the conclusions we have drawn. Finally, we offer some guidelines to where research in this area might profitably go in the future.

Basic studies of general interest

What do we know of the concerns of patients with epilepsy outside of the routine clinical encounter? In particular, what do we know about psychosocial and QOL concerns? A Concerns Index has been developed with the Epilepsy Foundation of America, and studied in patients both before and after epilepsy surgery.[1] The Concerns Index was developed in two parts. First 81 patients with chronic epilepsy listed concerns in order of importance. Then experts selected items to construct a 20-item questionnaire. There are pertinent questions on driving, injury from seizures, job status, cognitive function, mood state and social function. Sixteen of 20 concerns were significantly reduced in a group of patients who had received anterior temporal resections, against a comparison group of patients awaiting surgery. However, the Concerns Index does not answer what epilepsy surgery patients actually seek out as the desired goals of surgery.

In fact, the desired goals expressed by patients about to undergo epilepsy surgery seem both logical and consistent across the world. One study from Australia specifically asked epilepsy surgery candidates 'What is the main reason you have sought surgical intervention?'[2] In order of descending rank, patients ranked firstly seizure control (62%), then driving (45%), new activities (38%), employment opportunities (35%), as the main goals for seeking surgery. In the Bonn series,[3] the top 4 motives for surgery in descending order were: seizure control, independence, medication reduction, and improvement in vocational performance. In an Irish study,[4] the most frequently cited aims for surgery in 69 preoperative patients were: gains in employment, driving, independence, improved socialization, and medication reduction.

In a study from the United Kingdom, the expectations of 70 presurgical candidates were studied by asking how they believed they would be on several self-report scales if surgery were successful in stopping their seizures.[5] Preoperative patients had expectations that they would be in better control, and have better memory, more happiness, more independence, more interest in life, more hope, and to be more skillful and to be of greater value after successful surgery. The preoperative profiles were then compared to the self-ratings of 22 seizure-free patients 1 year after actual surgery. It showed that the presurgical expectations exceeded that reported by successful surgery patients 1 year after operation for several areas, such as interest in life, happiness, independence, and memory. This is a reminder that as in many areas of human psychology, expectations may exceed actual experience and that it could be important to counsel patients accordingly.

Outcomes after surgery can be divided into those based on observable measures, and those that are self-perceived. To understand the full impact of epilepsy surgery, both are needed. By observable measures we mean a quantity or status that some person other than the patient can appreciate. They include the core outcomes of seizure control, vocational and educational status, driving status, neuropsychological performance, neuropsychiatric behavioral changes, morbidity, and mortality.

However, other aspects of outcome, such as a patient's own sense of independence, or success in social relationships, are not so easy to quantify in the eyes of an observer. Similarly, the sense of self-worth is one that can only be made by the subject. Hence the measurement of self-perceived health status has become an important science.[6,7] Separate from numerical measures of disease burden, health-related quality of life

(QOL) scales look at self-perceived sense of wellbeing in the major domains of physical health, mental health, social function, and general health. These are based on self-report questionnaires as distinct from classifications by an observer or investigator. It is beyond the scope of this chapter to discuss the background and processes leading to the development of the major measuring instruments in use except to point out that they need to satisfy the requirements of reliability, validity, and practicality. Reliability is the ability to measure variance that is not due to random error. Validity is the degree that the measure reflects the quality being assessed and not some other. Practicality or feasibility concerns the application of the instrument in real life, and includes the use of questions that can be clearly understood, and a form of administration that is not too burdensome.

The different measurement instruments and scales in use for assessing quality of life outcome after epilepsy surgery can be broadly separated into three groups. First, generic scales used in general health research which are not disease specific. Probably the most well known is the SF-36 of the RAND General Health Scales. Others include some of the instruments developed by the World Health Organization, such as the Quality of Life Assessment (WHOQOL) in its various forms. Second, are epilepsy specific scales. The first to be developed and used extensively was the Washington Psychosocial Seizure Inventory (WPSI).[8] Adapted with epilepsy-specific questions, but built on the RAND SF-36 is the Epilepsy Surgery Inventory (ESI-55),[9] containing 11 subscales covering a range of functions. Of the 55 items, 36 belong in the RAND SF-36, while 19 are specific to epilepsy concerns. Another more extensive instrument is the Quality of in Life in Epilepsy (QOLIE)-89,[10] which contains 89 questions. It includes the RAND SF-36 items, as well as selected items from ESI-55, and further expanded with additional questions. Others are sometimes specific to established use in different countries or regions, such as the Quality of Life Assessment Schedule (QOLAS), or EuroQol (EQ-5D).[11] Third, are those borrowed from other disciplines but thought also important in patients with epilepsy. Many are from the mental health world, such as the Beck Inventories for Depression (BDI), and for Anxiety (BAI), Hospital Anxiety and Depression Scales (HAD), Katz Adjustment Scales (KAS), Minnesota Multiphasic Personality Inventory (MMPI), the Brief Psychiatric Rating Scale, and numerous others.

Course of postoperative change

Changes in psychosocial and QOL functioning as demonstrated on any of the measures, whether observable or self-perceived, can certainly be expected to evolve over time. At what time point or points, should we gather the data? Is there a necessary time latency before changes become evident? The preoperative to postoperative interval over which measures were compared varied tremendously from as short as 2 weeks[12] to more than 30 years.[13] More commonly, intervals chosen were at 1, 2 and 5 years, when patients were contacted both for information on seizure control and psychosocial outcomes.

At 3 months after surgery, some patients still have not completed basic healing, may have headaches and other symptoms related to surgery, and may still lack stamina to return to all customary activities. This may seem too short an interval to determine postsurgical outcomes. Nevertheless, some studies had shown a divergence from preoperative quality of life even 3 months after surgery.[14,15] It is unclear whether expectations for a positive outcome rather than actual life changes could have accounted for that. It is clearly too early to talk about gains in employment or independence just 3 months after surgery. Even at 6 months, while surgical healing is likely complete and most patients have resumed customary activities, there is question whether it may be premature to determine psychosocial outcome. For instance, while the commonest seizure-free interval required by driving licensing authorities in the US is 6 months, some require 12 months of seizure control before driving is permitted. Successful employment is another area that can take a longer time frame. The study by McLachlan *et al.*[16] looked at QOL (ESI-55) at 6, 12, and 24 months in a group of patients who had undergone anterior temporal resection as compared to a medically managed group with similar disease severity. The study showed that significant differences in mean and several subscales in self-reported QOL between surgical and medical groups were greater at 24 months follow-up than at 6 or 12 months. A group time effect was also reported by Markand *et al.*[17] There was greater improvement at 2-years than at 1-year follow-up. It is possible that changes in psychosocial status can continue after 24 months. By 5 and 10 years after surgery, a period of stability is more likely to have been established. At the other extreme, when follow-up extends to 30 or more years, new uncontrolled variables can be introduced, such as the appearance of new comorbid conditions that can contaminate the effect of surgery. In the case of children who received surgical treatment while still at school and receiving vocational training, there is a need for longer follow-up studies to learn of the impact of surgery on the maturing brain and personal development.

Bladin and Wilson in Australia,[18,19] have stressed that the patient undergoes major adjustments after a major medical intervention that epilepsy surgery represents. The very relief obtained after seizure control is attained, transforming a life of chronic illness to one of relative well-being, can itself lead to new challenges. This challenge, 'the burden of normality', can lead to maladaptive psychosocial changes that are not anticipated. They reported that 35% of patients rendered seizure free experienced problems related to changing family dynamics, sometimes resulting in divorce. Another 20% of patients and families reported behavioral problems in dealing with the seizure-free state. Indeed, for many patients in whom epilepsy started relatively early in their life, their whole life had been on hold or constrained. Educational learning and life skills have been frequently compromised, and it may or may not have been possible to develop normal social relationships or work habits in the years of intractable epilepsy. Many have in addition to intractable epilepsy significant cognitive impairments that affect performance and judgment. The loss of disability income and social support can become a stressor. What has passed for the presurgical fabric of life may be a construct rather different from that in normal individuals without chronic illnesses. When that presurgical fabric of accommodation is transformed by complete seizure control, the set of complicated adaptations may unravel.

Seizure relief and other predictors of outcome

A reasonable expectation is that any improvement in psychosocial functioning and QOL after epilepsy surgery will reflect relief from seizures. Indeed, relief from seizures has been posited to be so important that unless there is complete relief, significant improvement in psychosocial functioning cannot be expected.[20,21] As can be seen in Table 134.2 and in a later section, this relationship has been repeated affirmed in many studies. Furthermore, when seizure-outcome groups are stratified, the changes in QOL are graduated, with the best outcome in the completely seizure-free (and aura-free) group, next in those with residual auras, who in turn do better than those with a few seizures each year.[15,17,22]

Other presurgical factors that might influence postoperative psychosocial outcome have not been consistently examined. In particular, the strong correlation between neuropsychological measures of mood and QOL measures[23] makes one wonder how premorbid mood status determines outcome after surgery. The reverse has been studied. One study found that preoperative scores on the emotional adjustment scale of the WPSI were highly correlated with subsequent depression.[24] Higher age at surgery was found to be negatively correlated with QOL measures in one study,[15] but not in another.[22] A single study reported that a higher presurgical IQ score correlated with better psychosocial outcome.[25]

It is also of interest to ask if subjects with high self-ratings in function are the ones most likely to report continued wellbeing. This seems to be trend in employment, those already in employment before surgery are most likely to remain employed or to make gains in work status.

Long-term outcome 5 and 10 years after surgery at University of Washington

The University of Washington (UW) Regional Epilepsy Center prospectively performed neurological, neuropsychological, psychosocial, and EEG evaluations on 108 adults (age 16 and over; 55 women, 53 men; 94 right-handed, 14 left-handed; 107 Caucasian) with surgery on the left in 55 cases and on the right in 53 cases. Seventy-four of these patients were re-evaluated 5 years (± 6 months) after their surgeries and the remaining 34 patients were evaluated 10 years (± 6 months) after their surgeries. Preoperatively and at follow-up, patients were administered the Washington Psychosocial Seizure Inventory. Patients were divided across seizure outcome groups (Seizure free – no seizures whatever in the last 2 years of follow-up (n=53 total for both 5- and 10-year groups); significantly improved – at least a 75% improvement in the last 2 years of follow-up in comparison with the 2 years prior to surgery (n=30); not significantly improved – less than a 75% improvement in seizure frequency (n=25).

With the 5-year and 10-year groups combined, the preoperative and postoperative scores for the seizure-free patients on the WPSI are shown in Figure 134.1 using the paired Student *t* statistic applied to each variable independently with

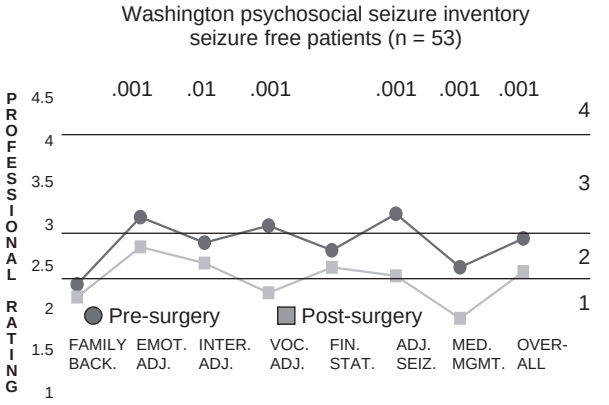

Figure 134.1 Preoperative and 5–10-year postoperative scores on the WPSI for the 53 patients who became seizure free. Improvements (lower scores) were noted on six of the eight clinical scales of the WPSI at the.01 level or better.

statistical significance set at the.01 level or better. Statically better (lower) scores were obtained on six of the eight WPSI scales with substantial differences noted in all psychosocial areas except for family background and financial status. As would be expected, these are the areas that would be most difficult to change after surgery.

Figure 134.2 presents the results on the significantly improved patients. As can be seen, there are fewer statistically significant changes demonstrated on the WPSI and they were at levels less confidently associated with change from a statistical viewpoint. Nevertheless, they are convincingly greater changes than those of the not significantly improved group which are presented in Figure 134.3 where the changes seem to be little more than random fluctuations from one time to the next.

One can see that the results presented here are at deviance from other studies which showed no improvement in psychosocial function after surgery unless relief from surgery was complete. Several factors may be operative here, illustrating the complexity of their interactions. Those studies that have argued for complete seizure relief as the only important determinant have tended to lack the numbers to do detailed

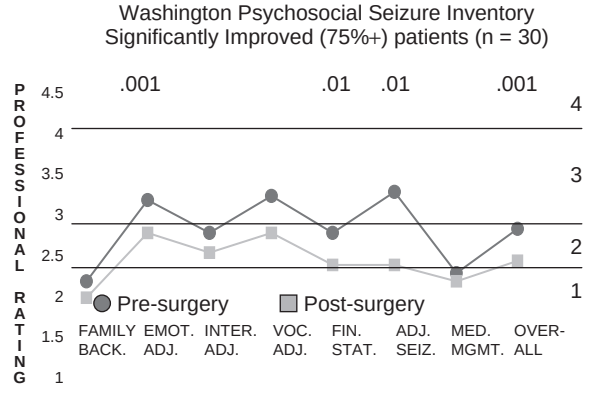

Figure 134.2 Preoperative and 5–10-year postoperative scores on the WPSI for the 30 patients who had significant improvement in their seizure frequencies (at least 75%). Improvements (lower scores) were noted on four of the eight clinical scales of the WPSI at the.01 level or better.

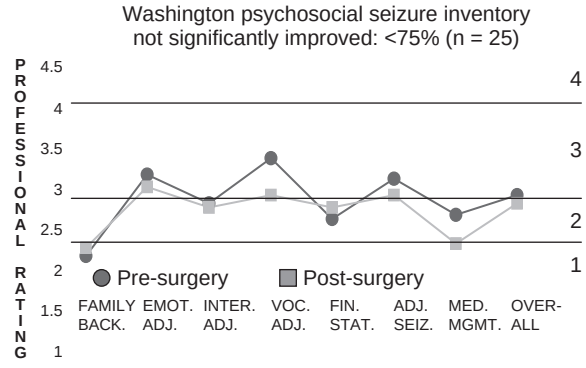

Figure 134.3 Preoperative and 5–10-year postoperative scores on the WPSI for the 25 patients who had no significant improvement in their seizure frequencies (less than 75%). Improvements (lower scores) were not observed on any of the eight clinical scales of the WPSI at the.01 level or better.

stratification of seizure status or did not take the extra steps to do so. We already mentioned other studies which showed that QOL improvements were incremental over a range of seizure outcomes.[15,21,22] Two other factors are specific to the UW study. One is the extended length of postoperative follow-up of 5 and 10 years. This is anticipated to produce a more stable state that takes into account some earlier years of adjustment. Another is the type of psychosocial measure used. The WPSI was developed on an empirical basis, with every item anchored in performance in everyday life as judged by professionals.[8] It was specifically not developed on the basis of an approach whereupon items are placed in groups based upon apparent content. It was also not developed on the basis of factor-analysis, a subjectively-based procedure which is not externally anchored, with factor names which are also not empirically anchored. As a consequence, less obvious changes in functioning may be missed.

Medication status after surgery

In general, patients who have had surgery, are either receiving fewer antiepileptic medications or are more likely to be on no medications in the postoperative period (Table 134.1). This is not too surprising, and undoubtedly strongly biased by patients who have been able to stop medications after becoming completely seizure free. Even though there is no set common protocol to discontinue antiepileptic drugs, particularly in light of follow-up information which showed that medication discontinuation carries a real risk of seizure relapse in those who initially appeared seizure free, many patients would nevertheless act on their own and taper and go off medical therapy when they judge themselves to be free of seizures. Even cautious clinicians who might not suggest to their patients that they should discontinue medications would still agree to a reduction in the number or dosage of drugs when patients are doing well.

Employment

Many but not all studies reported gains in employment status after epilepsy surgery. The most compelling were those that also compared surgically treated patients with a nonsurgical control group.[1,13,25,27,30,32] Whenever additional enquiries had been made on the determinants that may influence employment after surgery, two have consistently been affirmed. One is that the employment status after surgery is correlated to whether the individual has been working, full-time or at least part-time before surgery.[3,26,29] The other is that a gain in employment is strongly influenced by the seizure outcome, and that only seizure-free individuals are likely to maintain or gain new employment (Table 134.1). One study not only looked at improvements in employment and psychosocial status, but also at deterioration and reported that 94% of

Table 134.1 Effects of epilepsy surgery on antiepileptic medication (AED) status and employment status

Study	Medication status	Employment status
Augustine *et al*. 1984[26]	(not studied)	Improved employment Unemployment related to preoperative unemployment, disability payments, psychiatric disease
Guldvog *et al*. 1991*[13]	More likely off AEDs	Improved working ability in surgery group
Vickrey *et al*. 1995*[27]	Reduced AED	Non-significant trend towards improved employment
Sperling *et al*. 1995[28]	(not studied)	Improved in seizure-free patients And younger age at surgery
McLachlan *et al*. 1997*[16]	Reduced AED	(not studied)
Reeves *et al*. 1997[29]	(not studied)	Trend for improvement, correlated with ongoing education and full-time employment before surgery
Lendt, *et al*. 1997[3]	(not studied)	Overall improvement, Correlatied with seizure-free status
Kellet *et al*. 1997*[30]	(not studied)	Improved in surgery group if seizure free
Gilliam *et al*. 1999*[1]	Seizure-free more likely off AED	No significant improvement
Markand *et al*. 2000*[17]	Reduced AED	(not studied)
Jones *et al*. 2002*[25]	(not studies)	Improved in surgery group Best when seizure free
Lowe *et al*. 2004[31]	Seizure-free more likely off AED	(not studied)

*with a non-surgical comparison group

patients who suffered deterioration had continued seizures after surgery.[3]

In one study,[29] being a student before surgery or obtaining further education after surgery were factors associated with employment after surgery. In two studies,[3,28] age at surgery influenced outcome in that patients who remained unemployed after surgery were more likely to have been operated on later compared to those who became employed. This is a pointer perhaps to the importance of early intervention to permit not only the restoration of physical wellbeing, but also to allow a younger person the chance to gain or regain the educational and social skills that are a prerequisite to successful employment. By contrast, those already on disability payments before surgery were less likely to be employed afterwards.[26] It is not clear if those on disability payment before had more severe disease, more severe limitation in skills, or whether being established on disability payment itself served as a disincentive to return to the workforce.

School and education

Long-term studies of children or adolescents who received epilepsy surgery are relatively small in number and very different in design.[33] It is difficult to draw conclusions on the effect of surgery on the educational and psychosocial outcome of children and adolescents based on these reports. Only two used a QOL questionnaire with both preoperative and postoperative assessments but did not specifically discuss educational outcomes.[34,35] The largest series of 50 patients who had temporal lobectomy in childhood from Mayo Clinic reported that 34 were either in school or employed at the time of follow-up.[36] Guldvog reported on the educational attainments of a cohort from Norway who had epilepsy surgery, as compared with a matching medically treated group.[13] In looking just at patients who were still receiving education at the time of intervention, there was no significant difference in the length of education attained in the two groups. If anything, more surgically treated patients dropped out of school before having completed 7 years of education as compared to medical controls.

The lack of clarity in the literature more likely reflects on deficient data rather than lack of an effect. Many who have guided youngsters through successful surgery have been impressed by the transformation in behavior and attention that makes for enhanced learning at school. For those treated at a later stage in formal education, it could mean the difference between success or failure in graduation and certification.

Driving

Several studies specifically gathered information on driving status before and after surgery. This might be considered a relatively trivial matter in parts of the world where public transport is the norm. However, the privilege of driving is a vital part of independent living and a basis for work in most parts of North America. The Mayo Clinic series reported that the percentage of patients driving went from 20% preoperatively to 79% postoperatively.[29] Gilliam reported that 60% of patients were driving after surgery, while only 27% were able to do so preoperatively.[1] Again the seizure outcome after surgery is the major determinant, since all driving authorities base the decision to issue a license on establishment of seizure control. Thus while 64% of patients who were seizure free successfully got a license postoperatively, none of the patients who continued to have seizures were able to do so.[37]

Neuropsychiatric status

The Multi-Center Study on Epilepsy Surgery has provided the largest cohort of patients followed for psychiatric status before and after epilepsy surgery.[38] A total of 360 patients made self-reports using the Beck Depression Inventory, and the Beck Anxiety Inventory, and were administered the Composite International Diagnostic Interview, before surgery, and at 3, 12, and 24 months after surgery. The study confirmed significant overall improvement in symptoms of depression and anxiety after surgery, in keeping with prior reports. The decline in self-reported depression and anxiety was apparent as early as 3 months after surgery. Symptoms of depression and anxiety, present in 22.1% and 24.7% of preoperative patients respectively, declined by almost 50% postoperatively. Seizure control was significantly ($p=.02$) correlated with rates of postoperative depression: moderate to severe depression was present in 8.2% of seizure-free patients as against 17.6% of patients with continuing seizures. There is a similar but not statistically significant trend ($p=.09$) for postoperative anxiety. Localization or lateralization of the seizure focus were not correlated with depression or anxiety before or after operation.

The overall improvement in depression and anxiety after surgery can yet overlook two developments. First, a transient increase in symptoms in the first few weeks to months after surgery which fortunately resolve just as rapidly, with or without the use of psychotropic medications. Second, development of de novo psychiatric illnesses. One study reported that close to 50% of patients developed depression, anxiety, or mood lability in the the first few weeks after surgery. Bladin reported that 54% developed anxiety in the postoperative period.[17] Many of the patients improved within the first year. Certainly patients should be counseled before surgery that depression and anxiety can arise in the postoperative period, and offered treatment when indicated.

The literature on the de novo development of major psychiatric illness after epilepsy surgery is a long one. It includes historical hypotheses that are controversial. One is the concept of 'forced normalization' that describes the emergence of psychosis after the cessation of seizures, and others relate to the correlation of psychopathology to brain laterality, with schizophreniform symptoms linked to the dominant hemisphere, while mania and depression were linked to the nondominant hemisphere. Many of the observations were in the form of uncontrolled case series. Thus the frequency or incidence of such problems was unclear in the earlier reports. The latest Multi-Center Study yielded a de novo rate of 7.9% for depression, 9% for anxiety, and 1.1% for psychosis (mania, schizophrenia) in postoperative patients who did not have these manifestations before.[38] However, another series of 100 consecutive patients who had temporal lobe resections at a major center in Germany,[39] gave a somewhat higher incidence of de novo psychosis (11%), although the rate of

major depression (9%) was similar to that in the Multi-Center Study. The patients who developed postoperative psychosis were all rated to have had personality disorders before surgery, and some had persisting seizures while others were seizure free.

In the Norwegian study that compared 201 surgical patients to a medical control group of 185 patients, 6.7% of the surgical group developed de novo psychosis, while none occurred in the medical group. It is not clear whether the lower rate of postsurgical psychosis in the Multi-Center Study from the USA reflects different patient selection criteria between the USA and Europe, or differences in methodology in psychiatric evaluation.

Mortality

Patients with refractory epilepsy such as those who are candidates for surgical treatment are known to be at an increased risk for death. Often these are in the form of sudden unexplained death (or SUDEP) in addition to known accidents, suicide, or concurrent illness. Although the range of estimates for mortality can be large, the standard mortality ratio for patients with uncontrolled seizures at referral centers is close to 5, translating into an overall mortality of 1.3 per 100 person-years.[41]

In the Norwegian study, the survival of surgery patients was compared to those of medical controls.[40] There was no difference between the groups. However the effect of complete seizure control was not analyzed. A UCLA cohort of surgical versus non-surgical patients showed that surgically treated patients had significantly reduced mortality.[42] The most complete follow-up data on mortality after epilepsy surgery had been that reported by Sperling over the years.[43,44] In both the 1999 and 2005 reports, patients with recurrent seizures had significantly higher mortality (1.14–1.37 per 100 person-years) as compared with those who were seizure free (except for auras). Seizure-free patients had a mortality rate similar to that of the age- and sex-matched population at large. In short, persistent seizures after surgery are associated with an increased mortality rate similar to that of medically refractory patients, while successful epilepsy surgery normalized the risk.

Outcomes from quality of life scales

There has been a growth of interest in the assessment of quality of life by self-report questionnaires in the last decade. Selected findings from studies reporting on larger sample sizes are included in Table 134.2.

Table 134.2 Effects of epilepsy surgery on quality of life (QOL) measurements

Study	Surgery (n)	Control (n)	Measure	Follow-up	Results
Dodrill 1987[45]	60	–	WPSI	1 yr	Improvement in 5/8 scales
Vickrey 1995a[27]	202	46	ESI-55 KAS	Mean 5.8 yrs	Improvement in 5/11 scales
Vickrey 1995b[21]	133	–	ESI-55	> 1 yr	Improvement: seizure-free aura-free > aura-free > continuing seizures
McLachlan 1997[16]	51	21	ESI-55	6, 12, 24 months	Improvement in 6/11 scales at 24 m, better than at 6 or 12 m. Improved when seizure free or 90% reduction. Decline in others
Kellet 1997[30]	94	36	Various	> 1 yr	Improvement when seizure free v 10 seizures a year or no surgery
Malmgren 1997[46]	103	–	SF-36 HAD	> 2 yrs mean 4 yrs	Correlation with seizure outcome Seizure free: improved 7/8 scales
Wheelock 1998[21]	79	–	MMPI WPSI	2 m 1 yr	Improved only when seizure free
Gilliam 1999[1]	125	71	ESI-55	> 1 yr	Improved 8/11 scales Correlation with mood, employment, driving, AED use but not seizure status
Selai 2000[11]	25	15	QOLAS ESI-55 EQ-5D	Mean 1 yr	Improved 2/3 ESI-55 composite scores and QOLAS when seizure free or >75% seizure reduction
Markand 2000[17]	53	37	QOLIE-89	1, 2 yrs	Improved 10/17 scales Greater improvement at 2 yrs v 1 yr Seizure free aura free best outcome
Wiebe 2001[14]	40	40	QLIE-89	1 yr	Surgery group improved more than medical group
Spencer 2003[15]	231	–	QOLIE-89 BAI, BDI	> 2 yrs	Improvement apparent at 3 mo's Correlation with seizure outcome
Lowe 2004[31]	50	–	QOLIE-89	>2 yrs	Improvement when seizure free

For abbreviations of QOL instruments, see pages 5,6

All studies have shown an improvement in usually more than one quality of life domains. Some have shown an improvement as early as 3 months,[14,15] while two reports noted that improvement was greater at 24 months than at earlier time points.[16,17] Half of the studies employed a 'control' or comparison group of patients who did not have surgery: either because they did not have a localizable epileptogenic zone amenable for surgery, or because candidates declined surgery or were still awaiting surgery. All except one study[1] that specifically looked at the relationship between postoperative seizure control and QOL outcomes revealed a correlation between postoperative seizure status and QOL measurements: namely that a seizure-free status, or very few seizures, were correlated with higher QOL scores. The most detailed analysis of postoperative seizure outcome status with QOL measurements was that by Vickery based on UCLA data.[22] It showed significantly higher QOL scores in patients who were completely free of seizures and auras (Engel Class Ia), as compared to those who had residual auras, who in term were separable in QOL measures from those with 2–12 seizures a year, and from those with >12 seizures a year. The latter had the lowest scores. Of interest, the study found no difference in QOL measure amongst seizure-free patients whether they remained on antiepileptic medications or not. That seizure-free and aura-free patients had the most pronounced improvement in QOL was confirmed by another study.[17]

There have been gratifyingly few indicators pointing to deterioration in psychosocial functioning after surgery, but it could be that this has not been looked into carefully. In order to answer this and other questions an ideal study would comprise both a surgery and medical treatment arm, with sequential QOL measures over time, starting at baseline before intervention. The one study that satisfied this design did not have the details to address this issue.[14] Anecdotal clinical experience suggests that deterioration in psychosocial function does unfortunately occur in a minority of patients, usually in those who have failed to obtain satisfactory seizure control sometimes with compounding neurological or cognitive deficits. Partial support comes from the Bonn series that found socioeconomic deterioration when it occurs to be related to insufficient seizure control.[3] Markand[17] found the only significant decline in QOL scores from baseline in patients with persisting seizures (not including auras) and that was in the social support domain of the QOLIE-89.

Summary

There is now a wealth of data that can be called on when counseling patients going through surgical evaluation and treatment. In addition to and in consequence of an improvement in seizure control, patients can rightfully anticipate an improvement in the potential to participate in the full range of life activities, which can extend to work and driving. As would seem to be obvious, seizure-free patients would no longer be exposed to the risk of sudden death as compared to those with continuing seizures. How long it takes for the positive benefits of epilepsy surgery to become apparent remains a subject of enquiry. Although some studies showed an improvement as early as 3 months after surgery, gains in life functions and employment will likely take much longer. Despite the consensus for positive change after successful surgery, we need to be mindful that there are others who can be unsettled or challenged by changes that come about after surgery.

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135 Neuropsychological outcome

WB Barr

Introduction

It is known that up to 60–80% of those patients undergoing surgical treatment for partial epilepsy with a well-defined seizure focus will become seizure free following surgery.[1] However, it is also acknowledged that 25–40% of these individuals will also experience a postoperative decline in memory, language, or some other aspect of cognitive functioning. This chapter will review an evolving literature demonstrating how results from presurgical neuropsychological testing, combined with demographic variables and other neurodiagnostic findings, are useful for predicting which patients are at greatest risk for developing a postoperative drop in neuropsychological functioning. The current review will, in a manner that is consistent with the available literature, emphasize findings from studies of adults undergoing temporal lobe resection.

Neuropsychological testing, as a methodology, has provided valuable information regarding the effects of epilepsy surgery. This type of testing has proven critical to the operation of any epilepsy center. Findings from the original Maudsley series, published over 50 years ago, demonstrated postoperative memory changes in a subset of patients undergoing temporal lobectomy.[2,3] More details regarding the nature of these memory changes have described in an elegant series of studies performed by Brenda Milner and her colleagues at the Montreal Neurological Institute.[4,5] These studies brought attention to the fact that not all patients experience the same cognitive outcome from surgery and that a number of surgical variables, such as side and extent of the surgical resection, can be used to predict what types of deficits might be observed afterwards. Studies from the 1970s and 1980s demonstrated that the degree of postsurgical deficit often related to surgical outcome, as defined by a reduction in seizure frequency.[6] An interesting finding provided by Novelly and colleagues at Yale University, indicated that postsurgical deficits associated with functions of the surgical hemisphere were, in some cases, accompanied by concurrent improvement in functions in the opposite hemisphere.[7]

The fact is that most types of epilepsy surgery involve resection of brain areas considered important for normal memory processing. Emphasis has thus been placed on predicting memory outcome, with results indicating that a considerable number of patients may experience a decline in some aspect of language or cognitive functioning following standard procedures for anterior temporal lobectomy (ATL). Development of global amnestic syndromes was reported in some early series[8,9], but the occurrence of such devastating impairments in memory is now estimated to appear in less than 1% of cases after utilizing a number of methods to prevent its occurrence.[10] Predicting other types of neuropsychological deficits is generally based on brain topography and what is known about the functional neuroanatomy of the brain. Changes in executive functions and behavior are generally predicted when surgery is performed on the frontal lobes. Deficits in other functions, such as perception and higher-order sensory functions are seen in some cases involving surgery of more posterior brain regions.

Postoperative deficits in language and related functions are a natural concern when one is performing surgery on traditional 'language zones' of the dominant hemisphere. Many surgical centers make great efforts to ascertain the site and nature of cortical language representation using procedures such as the intracarotid amobarbital procedure (IAP) or intracranial language mapping either intraoperatively or through stimulation of subdural grids. Many are now also using newer techniques such as functional magnetic resonance imaging (fMRI) and magnetoencephalograpy (MEG) for evaluating hemispheric representation of language.

The prediction of postoperative memory decline has received the most attention and has been guided by two basic theoretical approaches, with both based on findings from neuropsychological research. One is based on Milner's[11] initial observation that material-specific memory deficits in verbal and nonverbal memory will be observed following surgery on the left (dominant) and right (nondominant) temporal lobes respectively. The second is based on a model developed by Chelune,[12] predicting that the degree of postoperative memory deficit, as well as seizure outcome itself, will be determined by the 'functional adequacy' of the tissue to be resected.

An analysis of material-specific memory findings, as predicted by Milner's model, is included in nearly every neuropsychological study of postoperative outcome. The conclusion drawn from recent reviews of the literature is that there is strong empirical support for the link between surgery on the left temporal lobe and postoperative deficits in verbal memory.[13] However, there is substantially less support for the proposed relationship between nonverbal memory impairment and surgery on the right temporal lobe.[13,14] Effects sizes from a recent meta-analytic study of verbal and nonverbal memory scores from Wechsler Memory Scale are depicted in Figure 135.1. The findings from a variety of sources thus demonstrate that patients undergoing surgical resection of the language dominant hemisphere are at the greatest level of

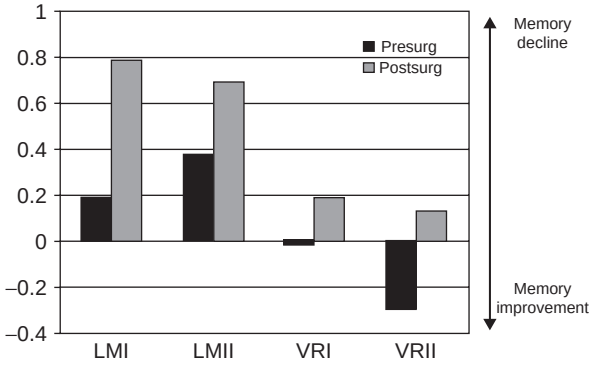

Figure 135.1 Effect sizes from 33 studies assessing verbal and nonverbal memory performances before and after temporal lobectomy (Adapted from Lee, Yip, and Jones-Gotman).[13]

risk for undergoing an identifiable decline in postoperative memory functioning.

For years, it was unclear whether prediction on postoperative cognitive outcome should be based on observation of the functioning of the side that was to be resected or the side that would remain following surgery. Initial studies using the IAP focused on information on functioning from the side contralateral to surgery to predict whether a patient was at risk for developing a postsurgical amnestic syndrome. However, results from subsequent studies using neuropsychological testing in conjunction with information from the IAP, neuroimaging, and histological analyses, has indicated that the functions of the side to be resected is an important factor to consider in predicting a patient's postoperative level of functioning. According to Chelune's functional adequacy model, the degree of postoperative memory decline can be predicted by examining the integrity of the proposed surgical zone, as defined by integration of a number of predictive variables.[12]

Initial evidence for the functional adequacy model was based on findings that significant decrements on memory testing following temporal lobe resection were observed in those patients with higher levels of performance on presurgical testing.[15,16] Results of subsequent research[17] demonstrated that patients with the highest levels of memory performance, in particular, showed greater decline in memory performance in the 6 months following surgery. Less significant decline in functioning was observed in patients with lower levels of presurgical memory functioning. The authors argued that these findings were not simply the result of a statistical 'regression to the mean', but rather a tendency for the most functional patients at baseline to be more vulnerable to experiencing postoperative memory loss.

The functional adequacy has now been supported by findings from a number of other neuropsychological studies.[18–21] The theory has also received support from a number of neuroimaging and IAP-Wada studies, which will be reviewed below. It is now generally accepted that this model, combined with other factors, is effective in predicting a patient's neuropsychological outcome from surgery.[22] A brief listing of these factors is provided in Table 135.1. The following sections will review further characteristics of neuropsychological functioning following epilepsy surgery as well as other factors that can be used to predict outcome.

Table 135.1 Factors important for predicting outcome from epilepsy surgery (from Elger, Helmstaedter, and Kurthen)[22]

1. The 'functional adequacy' of the tissue to be resected, as determined by EEG, neuroimaging, and neuropsychological testing.
2. The degree of 'mental reserve', as reflected by patient's age, educational attainment, and level of presurgical intellectual functioning.
3. The degree of postoperative seizure control, particularly the frequency of generalized tonic-clonic seizures.

Profile of change in postoperative neuropsychological functions

Clinicians and patients are interested in knowing which cognitive functions are at risk for decline following surgery. The following section provides a review of what is known about changes in various aspects of neuropsychological functions following surgery:

General intelligence

One of the earliest findings from neuropsychological studies is that epilepsy surgery results in very little change in overall intellectual functioning.[23] Some studies have found an IQ increases in some patients following surgery, particularly in those that become seizure free. However, from a psychometric standpoint, changes in 6–8 IQ points are required to constitute a significant change, and changes of that magnitude are rarely observed after surgery.

The view that patients with lower levels of intelligence do not benefit from surgery has been dispelled by research findings showing similar levels of seizure reduction in both low and high IQ groups.[23,24] Patients with higher levels of preoperative intellectual functioning and memory performance do tend to experience a greater degree of net decline following surgery, although they also continue to exhibit a higher level of postoperative functioning than do patients with lower levels of presurgical functioning.[25] This finding has been considered supportive of the model of 'cognitive reserve' that has gained acceptance in the research fields of dementia and traumatic brain injury.[26,27]

Memory

Memory decline is a primary concern when considering neuropsychological outcome from epilepsy surgery. A number of studies have shown that memory change is commonly reported in patients following surgical resection of the temporal lobe and such change exerts a significant impact on a patient's perception of quality of life.[28] Studies using neuropsychological testing have demonstrated that if a patient undergoes a decline in functioning after surgery, it is most likely to occur in the realm of verbal memory.[13,17] Similar to what has been observed in IQ studies, the findings generally show that patients with higher levels of memory performance before surgery will undergo a greater degree of decline afterward.[23]

There has been some evidence of improvement in some memory skills following surgery, particularly for those functions associated with the hemisphere contralateral to the surgery.[7]

Decrements in postoperative memory functioning have been observed using a range of verbal memory tasks. Several studies have shown that the paragraph-recall (Logical Memory) subtest from the Wechsler Memory Scales (WMS) provides one of the most sensitive measures of postoperative memory change.[13,29,30] Other studies have demonstrated that measures of acquisition and delayed recall from measures, such as the California Verbal Learning Test, Rey Auditory Verbal Learning Test, and Selective Reminding Test, are also sensitive to identifying postoperative changes in memory performance.[17,31,32] Additional success has been obtained from testing the ability to learn and retain word pairs, as provided in Paired Associate subtest from the WMS.[16,28,33,34]

Using findings based on the study of Patient H.M. as a prototype, it was initially thought that memory disturbance resulting from unilateral temporal lobectomy was characterized primarily in terms of 'rapid forgetting' or as a deficit in memory 'consolidation'.[33,34] However, findings from contemporary studies using more refined assessment techniques have determined that the decline in verbal memory following left anterior temporal resection is more multifaceted, as it is also characterized by prominent impairments in encoding and retrieval stages of memory processing.[35] Others have described a specific effect on relational memory.[36] Deficits in memory processing are also known to occur in patients undergoing frontal lobe resection, although the pattern of disturbance is qualitatively different as these patients are more prone to having difficulties with selection or retrieval processes and more prone to making intrusion or perseverative errors than patients undergoing temporal lobe resection.[37,38]

As mentioned above, there has been much less support for the presence of visual memory impairment resulting from surgery performed on the nondominant hemisphere. It has been thought that a number of factors contribute to the lack of findings of a decline in nonverbal memory functioning following right ATL, including limited theoretical knowledge of the right temporal lobe's role in memory processing as well as the sensitivity of most commonly used measures for assessing visual memory.[39,41]

Little success has resulted from using traditional measures of figural memory, such as the WMS designs or Rey's complex figure, to identify memory changes in patients undergoing surgical resection of the nondominant hemisphere.[13,14,42] However, findings from recent studies have indicated that the latest version of the Wechsler Memory Scale (WMS-III) may be more sensitive than other commonly used measures to identifying material specific memory impairment following unilateral ATL,[43] although it does not appear sensitive to identifying lateralized deficits in patients prior to surgery.[44] This study demonstrated that a combination of findings from the Verbal Paired Associates, Faces, and Family Pictures subtests can be used to discriminate right and left ATL patients with 81.3% accuracy.[43] Mixed findings have been obtained from studies using figural learning paradigms, analogous to verbal list-learning tasks, where designs ranging in complexity are reproduced after viewing them over repeated trials.[14,45–48]

Some success in identifying material-specific decline in nonverbal memory functions has been demonstrated using specialized test methods. Based on findings from the primate literature, it has been hypothesized that memory dysfunction following resection of the nondominant temporal lobe will reflect a disturbance of the ventral processing stream, which has related to processing object, as opposed to spatial, information.[39] Given the proximity to the fusiform face area,[49] processing and retaining facial information would be expected to be particularly affected. In fact, studies using facial recognition paradigms have shown the emergence of subtle deficits in facial perception following right temporal lobe resection.[50] Difficulties with remembering unfamiliar faces, both before and after right temporal lobe resection, have been reported in numerous studies.[14,39,51–53] It has been shown that the primary impairment is related more to memory than to perceptual processing of the faces.[54] One study has demonstrated the specificity of this deficit, as demonstrated by a decline in facial, but not spatial, memory following right temporal lobe resection.[55] However, in spite of these observations, a number of studies have demonstrated spatial memory deficits using a variety of innovative paradigms.[56–58]

While most attention is placed on postsurgical evaluation of possible deficits in new learning, a number of studies have demonstrated difficulties with recalling remote knowledge following anterior temporal lobe resection. Several studies have shown deficits in recognizing and naming familiar faces, such as those of celebrities such as politicians, actors, musicians, and athletes.[59–62] A recent study has shown that patients undergoing left ATL may develop difficulties with naming famous individuals depicted in pictures, while those undergoing right ATL appear to have a more basic difficulty with the perceptual aspects of identifying those depicted in the photograph.[60]

Recent interest has also turned to the examining changes in processing and retaining emotional stimuli in patients undergoing temporal lobe resection.[63] Studies have shown that patients undergoing right ATL may develop a specific reduction in their startle response or in their ability to perform in a fear conditioning paradigm.[64,65] These observations have carried into memory paradigms, where is has been demonstrated that patients undergoing resection of the amygdala exhibit a specific reduction in the ability to learn and retain emotionally charged information.[66–70]

Language

Prevention of postoperative language impairment is a concern, particularly when surgery involves the language-dominant hemisphere. Surgery performed on the dominant temporal lobe is most commonly associated with postoperative naming deficits, as typically measured by tests of confrontation naming and verbal fluency. While impairments on other language tasks, such as sentence repetition or auditory comprehension may be encountered, they are seen far less often.

A decline in naming performance is thought to occur in approximately 30–40% of patients undergoing surgery on the language dominant hemisphere.[71,72] Naming decline is not limited to those undergoing extensive resection of the lateral cortex as a relationship between naming impairment and excision of the hippocampus has been demonstrated.[73]

Surgical studies have placed far less emphasis on assessment of naming deficits than on changes in verbal memory functions. Demographic predictors of naming decline appear to be similar to those used for evaluating the risk of memory loss. A specific risk to postoperative naming abilities has been found for those patients undergoing left hemisphere surgery with a later age of onset or an absence of early risk factors for seizures and negative findings on neuroimaging.[73,74]

Assessing changes in naming performance following surgery is typically performed through use of a picture recognition paradigm, such as the Boston Naming Test. However, results from recent studies have indicated that naming changes might be identified more accurately using auditory naming tasks as opposed to visual naming paradigms.[75–77] Results of studies attempting to characterize the type of postoperative naming impairment have been somewhat conflicting. One study found that left ATL is associated with a category specific impairment in naming nonliving as opposed to living things, whereas another study showed the opposite findings.[78,79] Other studies have found that retrieval of object names is affected more than verb naming and words learned at a later age are more likely to be affected those acquired early in life following left temporal lobe surgery.[80,81]

Studies on postoperative language change have also shown decreases in verbal fluency following both left and right unilateral temporal lobectomy.[82] Fluency, as defined in these studies, is assessed through paradigms requiring a generation of word lists beginning with either a specific letter of the alphabet or coming from a predefined semantic category, such as animal names. A decrease in verbal fluency is observed in some patients following surgery to the dominant frontal lobe.[83] Improvement in verbal fluency has been observed in some patients following frontal lobe resection, particularly in cases obtaining good postoperative seizure control.[81,84]

Other neuropsychological functions

Studies using standard neuropsychological measures of motor and sensory functions have found very little change in patients undergoing resection of the temporal lobe. Findings from one study found presurgical baseline impairment in somatosensory functions, with some apparent improvement observed in a subset of patients following surgery.[85] Changes in olfactory functions have been observed after anterior temporal lobectomy, with no consistent association with the side of the resection.[86] Patients undergoing right temporal lobe excision exhibit less accurate recognition of emotion and less change in response to emotional stimuli than do left temporal lobe patients.[66,87]

There are no consistent findings demonstrating deficits in visual perceptual or spatial functions associated with right anterior temporal lobe resection.[88,89] Specific impairment in facial recognition has been observed in one study, although the size of the overall effect was mild.[50] Patients undergoing right temporal lobe surgery have been found to have greater difficulty integrating spatial information while walking a linear path.[90] Development of spatial neglect is rarely seen following temporal lobe resection. However, it has been observed following surgery to the parietal cortices of the right hemisphere.[91] Other studies have demonstrated changes in auditory perception, most notably directional pitch and spatial location, following surgical resection of the right temporal lobe.[92–94]

Greater attention has been placed on assessment of executive functions before and after surgery. In general, patients undergoing frontal lobe resection generally exhibit decline on measures of executive functions.[37] Those with resection of premotor or SMA regions exhibit specific decreases in response maintenance and inhibition, while those with surgery on the left hemisphere also exhibit some decline on language tasks.[23,83] Studies using newer measures of frontal lobe functioning from the Delis-Kaplan Executive Functioning System have demonstrated particular deficits in set-shifting, nonverbal fluency, and response inhibition in frontal lobe surgical patients.[95–97] A decline in spatial working memory has also been reported in patients undergoing frontal lobe surgery.[98]

A number of studies have found impairment in executive functions in patients with temporal lobe epilepsy, contrary to predictions based on early studies finding a double dissociation between frontal and temporal lobe resection groups.[99] Deficits in performance on the Wisconsin Card Sorting Test, a traditional measure of 'frontal lobe functions' has been observed in patients with temporal lobe dysfunction presurgically, with some of these patients exhibiting a normalization in performance following anterior temporal lobe resection.[100,101] It has been hypothesized that the postsurgical improvement is related to a removal of nociferous cortex affecting remote frontal lobe functions.[102] A recent observation if improvement in verbal fluency performance following temporal lobe resection is interpreted supports that hypothesis.[84]

Predictors of neuropsychological decline

It is clear that a number of factors are required to accurately predict postoperative changes in cognitive functioning. The level of evidence has now reached a point where one can use information from neuropsychological tests, obtained presurgically, combined with other surgical and neurodiagnostic values, to predict which patients are at risk for neuropsychological decline.[22] A listing of some of the most commonly known factors for predicting decline are listed in Table 135.2. More details regarding demographic, surgical, and neurodiagnostic predictors of cognitive decline are provided below.

Table 135.2 Predictors of poor cognitive outcome from surgery on the language-dominant hemisphere (from Elger, Helmstaedter, and Kurthen)[22]

1. Persistent seizures.
2. Intact memory performance preoperatively.
3. Extent of surgical resection.
4. Notable collateral brain damage after surgery.
5. Low reserve capacity.

Demographic variables

Developmental factors, including age at the time of surgery and the stage of development at the time of seizure onset, are important factors for predicting postoperative cognitive decline. Most of what is known about postoperative outcome is based on studies of individuals ranging in age from 20 to 45 years, which is the group most likely to undergo surgical intervention. The risk of cognitive decline following surgery appears to be lower in children below the age of 16 years than in adults.[103] At the other end of the age spectrum, older individuals appear to experience greater memory loss, consistent with a profile of accelerated aging.[25] Continuing decline in memory performance may be seen in some individuals ten years or more following surgery.[28] The postoperative deficit in verbal memory in patients rendered seizure free is similar to what is observed over time in nonsurgical patients that are continuing to experience seizures.[25]

Age of onset of epilepsy is thought to interact with both functional and structural indices in a manner consistent with predictions of the functional adequacy model.[12,104] Those with a younger age of onset will have experienced pathology at an earlier stage of development and will have experienced seizures for a longer period of time. This will lead to a greater state of neurological compromise accompanied by more severe and widespread cognitive impairment. However, this would also cause a redistribution of function to other brain areas, which would lead to a less severe deficit following surgery.

In contrast, individuals who develop epilepsy later in life are not as compromised from a neurological standpoint and do not exhibit the same degree of cognitive dysfunction preoperatively. In these individuals, surgery would involve removal of more functional brain tissue, leading to development of a greater level of deficit postoperatively. Support for these findings with age was present in some early studies, but at least one recent study has failed to find a link between severe hippocampal pathology, memory decline, and early onset of seizures.[104]

Another general finding is that, with increasing age, cognitive deficits become more specific and less reversible with surgery. It has been suggested that the pattern of findings involving age of onset are more consistent for cognitive functions associated with neocortical zones than for those associated with the mesial temporal lobe.[23] For example, findings have suggested that more severe naming deficits are observed in older patients. Other studies examining demographic factors have suggested that women, in general, exhibit less severe cognitive decline following surgery than men.[105]

Surgical variables

A relationship between postoperative memory decline and continued seizures has been observed inconsistently across studies.[28] However, the general finding is that postoperative improvement in memory is seen most frequently in patients with greater than 75% seizure reduction.[7,16,106]

The type of surgical procedure has not borne out as a consistent influence on postoperative memory functioning in temporal lobectomy patients. A number of studies have found that a more selective resection of the anterior temporal lobe leads to less severe postoperative deficit than a standard anterior temporal lobe resection.[48,106–109] However, one study has shown that there is no difference in outcome between various surgical approaches.[48] Another multicenter study demonstrated no influence of tailored temporal lobe resections for preventing naming changes in surgical cases involving the language dominant hemisphere.[110] Surgical removal of the superior temporal gyrus during left temporal lobe surgery has been found to have no specific influence on postoperative naming performance.[111]

Much less is known about the neuropsychological outcome of other types of epilepsy surgery. One study found that patients undergoing frontal lobe resection are prone to developing deficits in executive functions after surgery, whereas patients undergoing temporal lobe resection experience relative improvement in these functions.[37] Mild changes in performance IQ, as measured by the WAIS-R, has been reported following surgery to the posterior cortices, irrespective of side.[112] Preliminary data have indicated that a reduced risk of postoperative neuropsychological decline is not associated when gamma knife surgery is used as a treatment for temporal lobe epilepsy.[113]

In cases of callosotomy, one must be prepared for the possible emergence of the well-described 'split-brain' syndrome, particularly features of the alien hand syndrome. However, it has been shown that language is more likely to undergo a decline following callosotomy than any other function.[23] The occurrence of severe language impairment, in the form of postoperative mutism, is known to occur in some patients with atypical patterns of hemispheric language dominance.[114] It is thus critical to ascertain a candidate's pattern of language dominance through the IAP or fMRI prior to surgery. Improvement in social functions has been observed as a positive finding in some cases following callosotomy, with the greatest level of improvement observed in patients that were younger at the time of surgery.[115]

Hemispherectomy has been demonstrated to be an effective treatment for patients with hemimegalencephaly or with Rasumussen or Sturge-Weber syndromes. It is generally assumed that in surgeries involving the left hemisphere, language has moved to the right side, making postoperative language changes unlikely. Research findings have shown that this is most often the case, but some children do continue to be prone to language changes following surgery.[116] Improvements in IQ and attention following hemispherectomy have been reported in some series.[23]

Neurodiagnostic variables

Many studies have demonstrated that a multidisciplinary model, using a combination of neurodiagnostic, demographic, and performance-based factors, is most effective for predicting neuropsychological outcome from epilepsy surgery.[19,117,118] Results from neuropathological studies have consistently demonstrated that memory outcome is impacted significantly by the preoperative presence of hippocampal sclerosis (HS) on the side to be resected.[71,119,120] Individuals with severe unilateral HS tend to exhibit lower levels of preoperative memory functioning and are likely to exhibit less decline in memory performance following surgery.[121]

Neuroimaging findings

The functional adequacy model has been supported by results of studies using MRI measures of hippocampal pathology.[122,123] The findings show that removal of a nonatrophic left hippocampus is generally associated with the greatest degree of memory decline, although it is also possible to observe memory loss in some patients with the most severe presurgical levels of HS.[35] It is now known that surgery performed on individuals with bilateral hippocampal pathology does not necessarily cause global amnesia. However, greater rates of memory decline are seen in those patients with bilateral hippocampal atrophy who undergo surgery on the dominant left temporal lobe.[35] These and other findings indicate that the functional integrity of the left temporal lobe plays a critical role in predicting memory outcome, independent of the presence of structural pathology.[124,125]

Functional adequacy has been predicted through results of magnetic resonance spectroscopy (MRS).[126,127] Functional MRI (fMRI) has been shown to be useful for predicting postoperative naming.[128] Studies using functional imaging methods have indicated that both FDG-PET and fMRI can be helpful in predicting postoperative memory impairment.[129,130] In the case of FDG-PET, a lack of left side hypometabolism predicted the onset of memory loss in patients undergoing left ATL.[131]

Intracarotid amobarbital procedure (IAP)

IAP memory scores, combined with MRI measures of hippocampal volume, have been shown together to be related to the degree of memory change following temporal lobectomy.[132] However, it has been suggested that these variables are used most optimally for prediction of verbal as opposed to nonverbal memory changes.[133] A recent study has demonstrated a significant negative correlation between IAP scores ipsilateral to the surgical resection and postoperative memory change, consistent with predictions based on the functional adequacy model.[134] There has been some suggestion that, in cases with right hemisphere language dominance, verbal memory functions might also shift to the right hemisphere, resulting in the observation of less severe memory decline after surgery.

Language mapping

While an emphasis has been placed on language mapping prior to dominant hemisphere surgery,[135] results from studies using both grid and intraoperative brain mapping procedures have been variable. Some studies have shown that standard ATL without stimulation mapping is safe for long-term language functions.[136] One multicenter study found that the rate of postoperative naming decline was not influenced by the availability of mapping data.[110] Removal of basal temporal zones found to be patent for language functioning on mapping have not been associated with consistent decrements in postoperative language abilities.[137] However, others have recently found that identification of mapping sites critical for auditory descriptive naming is important for predicting both auditory and visual naming outcome.[138] A more distributed region of language functions has been described in patients with decreased intelligence and lower levels of educational attainment.[139] Results from mapping studies using magnetoencephalograpy (MEG), have suggested a reorganization of hemispheric language representation following dominant hemisphere resection.[140]

Recent methodological advances

One of the criticisms of neuropsychological research is that it has typically focused on results of group analyses, making it difficult to translate the results into manner that can be useful in counseling patients. There has also been a view that focusing on analysis of group differences following surgery may mask many of the differences between patients undergoing left and right temporal lobe resection.

There has been a recent trend moving from group methods of analysis towards predicting the risk of postoperative change in individual patients. To optimize the prediction of individual risk, investigators have been using statistical methods, such as the reliable change index (RCI) and standardized regression-based (SRB) methods to control for the reliability of the instruments, practice effects, and regression to the mean. These measures are readily obtained through studies of test-retest changes observed in non-surgical patients.[30,141–144]

Experience shows that RCI's are the most easy to use in a clinical setting, with a level of expected change observed on retesting translated into 95% confidence intervals. Modifications to the original RCI formula are made, correcting for practice effects.[144] Values for some of the most commonly used neuropsychological tests are provided in Tables 135.3 and 135.4. Clinicians are encouraged to use these values to determine whether significant changes in neuropsychological test scores are observed in individual patients following surgery.

Results from postsurgical studies using RCI and SRB methodology are summarized in Table 135.5. When patients are considering surgery, they can now be informed, on the basis of results from these studies, that the risk for postoperative decline in verbal memory ranges from 28–49% in patients undergoing left temporal lobe surgery while the risk for decline patients undergoing right temporal lobe surgery ranges from 7–33%, depending on the memory measure that is used to assess outcome.[72]

Other studies have revealed greater degrees of risk in patients undergoing left anterior temporal lobe resection with minimal evidence of hippocampal sclerosis on MRI.[104] Another study found that bilateral hippocampal atrophy, in the presence of left temporal lobe seizures, increases the risk of memory decline following left temporal lobectomy.[35] Bilateral hippocampal atrophy did not provide a risk to patients undergoing right temporal lobectomy. One study has shown that patients with MTS and normal preoperative memory performance are still at risk for developing memory changes following surgery.[124] Using indices from the CVLT, 17% exhibited a drop on acquisition scores, while 65% experienced a decline in verbal retrieval. This point was made again in a case report where intact preoperative memory performance in the presence of numerous signs of hippocampal sclerosis resulted in a significant postoperative decline in memory.[125] The results from the studies using methodology for assessing change have thus provided evidence that results from presurgical testing provide a critical predictor of

Table 135.3 Reliable change index (RCI) values for the WAIS-III, WMS-III, and other neuropsychological tests

Neuropsychological test	Adjusted 90% RCI*	Reference
Wechsler Adult Intelligence Scale–III (WAIS-III)		29
•Full Scale IQ	≤ –6, ≥ +8	
•Verbal IQ	≤ –8, ≥ +8	
•Performance IQ	≤ –7, ≥ +13	
•Verbal Conceptual Index (VCI)	≤ –7, ≥ +9	
•Perceptual Organization Index (POI)	≤ –8, ≥ +14	
Wechsler Memory Scale–III (WMS-III)		29
•Auditory Immediate Memory Index	≤ –14, ≥ +16	
•Auditory Delayed Memory Index	≤ –19, ≥ +15	
•Visual Immediate Memory Index	≤ –15, ≥ +21	
•Visual Delayed Memory Index	≤ –13, ≥ +23	
Tests of Executive Functions		
•Wisconsin Card Sorting Test		141
Total Errors (Raw Score)	≤ –40, ≥ +22	
Perseverative Errors (Raw Score)	≤ –22, ≥ +16	
•Trailmaking Test		140
Part A (Time in seconds)	≤ –14, ≥ +10	
Part B (Time in seconds)	≤ –37, ≥ +44	
Language and Visuospatial Functions		
•Boston Naming Test (Raw Score)	≤ –5, ≥ +5	141
•Controlled Oral Word Association Test (Raw Score)	≤ –12, ≥ +14	141
•Benton Facial Recognition Test (Raw Score)	≤ –6, ≥ +6	140
•Judgment of Line Orientation Test (Raw Score)	≤ –3, ≥ +7	140

*Corrected for practice.[143]

Table 135.4 Reliable change index (RCI) values for commonly used tests of verbal and nonverbal memory

Test	Adjusted 90% RCI*	Reference
Verbal Memory Tests		
•California Verbal Learning Test		140
Total Learning (5 Trials, Raw Score)	≤ –11, ≥ +15	
Long Delayed Free Recall (Raw Score)	≤ –3, ≥ +7	
Discriminability (Raw Score)	≤ –17, ≥ +23	
•Rey Auditory Verbal Learning Test		141
Total Recall (5 Trials, Raw Score)	≤ –15, ≥ +5	
Delayed Recall (Raw Score)	≤ –7, ≥ +5	
•WMS-III Verbal Paired-Associate Subtest		29
Verbal Paired-Associates I (Scaled Score)	≤ –3, ≥ +3	
Verbal Paired-Associates II (Scaled Score)	≤ –4, ≥ +4	
•WMS-III Logical Memory Subtest		29
Logical Memory I (Scaled Score)	≤ –3, ≥ +3	
Logical Memory II (Scaled Score)	≤ –4, ≥ +4	
Nonverbal Memory Tests		
•Rey Complex Figure Test		142
Delayed Recall (Raw Score)	≤ –11, ≥ +12	
•Recognition Memory Test		141
Faces (Raw Score)	≤ –5, ≥ +9	
•WMS-III Faces Subtest		29
Faces I (Scaled Score)	≤ –3, ≥ +5	
Faces II (Scaled Score)	≤ –3, ≥ +5	
•WMS-III Family Pictures Subtest		29
Family Pictures I (Scaled Score)	≤ –3, ≥ +3	
Family Pictures II (Scaled Score)	≤ –4, ≥ +4	

*Corrected for practice.[143]

Table 135.5 Rates of memory decline in dominant and nondominant temporal lobectomy patients using RCI and SRB methodology

Test measure/study	*Dominant ATL*	*Nondominant ATL*	
Wechsler Memory Scale – Logical Memory II			
A. Martin *et al*. 1988[71]			
•Improved	9%	9%	
•Unchanged	42%	58%	
•Declined	49%	33%	
B. Stroup *et al*., 2002[19]			
•Improved	3%	7%	
•Unchanged	60%	82%	
•Declined	37%	11%	
California Verbal Learning Test			
Delayed Recall			
A. Stroup *et al*., 2002[19]			
•Improved	0%	0%	
•Unchanged	54%	89%	
•Declined	46%	11%	
Total Learning–Five Trials			
B. Martin *et al*. 1988[71]			
•Improved	2%	2%	
•Unchanged	71%	91%	
•Declined	28%	7%	
	Left ATL Patients		
	Mild HS	Mod HS	Sev HS
California Verbal Learning Test			
Total Learning – Five Trials			
C. Martin *et al*. 2002[103]			
•Improved	20%	0%	0%
•Unchanged	20%	78%	77%
•Declined	60%	22%	23%

neuropsychological outcome independent of information obtained from neuroimaging.

Conclusion

A number of important advances have been made over the past 50 years in assessing neuropsychological outcome from epilepsy surgery. Most attention is place on the prevention of declines in naming and verbal memory, which are most likely to be seen in a sizeable minority of patients following surgical procedures conducted on the language-dominant hemisphere. Current practices involve a model utilizing presurgical neuropsychological testing, along with information obtained from neuroimaging and the IAP, to assess a given patient's risk for postoperative decline. Patients with evidence of intact cognitive functions on the site to be resected are considered at greatest risk for postoperative memory decline, independent from structural imaging findings. Studies using newer statistical approaches to evaluating neuropsychological change are providing clinicians with information that makes it easier to counsel individual patients on the risk of developing postsurgical changes in memory and language.

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136 Temporal lobe epilepsy surgery: surgical complications

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Introduction

No professional man gets greater pleasure from the record of his successes than a surgeon. How delightful when the uninformed refer to them as miracles! And how inaccurate! But no one regrets his failures more ...[1]

Surgical complications are perhaps the most humbling of all mistakes. The role of this chapter is to delineate the most frequent complications encountered in surgery for temporal lobe epilepsy. In addressing the potential pitfalls of this surgical procedure, perhaps one can hope to determine means to avoid them. During the last century, a considerable amount of general knowledge has been gained in surgical evaluation for temporal lobe epilepsy. The implications and outcomes have been fine tuned over the past 50 years at many epilepsy centers to make temporal lobe resection for medically intractable disease the most common surgical procedure for epilepsy worldwide.[2–11] The benefits of this surgery have revolutionized the prospect of epilepsy being a potentially curable disease. Surgical resection for medically refractory seizures has demonstrated very promising results with respect to seizure control. A multitude of studies have estimated a 60–70% rate of seizure freedom and up to an 85% rate of significant reduction in seizure frequency.[3,4,11] A prospective randomized controlled trial found 64% of patients who underwent surgical resection were seizure free compared to only 8% in the medical group on optimal medical therapy.[11] They concluded that surgery was superior to prolonged medical therapy. However, one must remember in counseling patients for surgical intervention, that complications do occur and can be life altering.

The temporal lobe performs a myriad of functions including integration of such higher level functions as language, musical appreciation, emotion, and memory. Its location bordering the frontal, parietal, occipital lobes makes it ideal for acting to coordinate and process multivariate information. Likewise, its mesial structures, including the hippocampus, are deeply involved in episodic memory processing. Additionally, one must remember that the temporal lobe borders the vascular supply of essential relay stations including the thalamus, internal capsule, and basal ganglia. Interference of these pathways, either by temporal lobe pathology or surgical intervention, can result in significant loss of function. The optic tract and visual pathways traverse the temporal lobe making a visual field deficit a possible outcome to disturbance of this area. Lastly, several cranial nerves approximate the mesial portion of the temporal lobe as is evidenced by the typical sign of a third nerve palsy with uncal herniation.

The temporal lobe acts to coordinate sensory information and synthesize it as it relates to higher level cognitive function. For example, in recalling a memory, one can often remember the specific situation in fine detail. With such an integral processing station, it is no surprise that surgery in this region can be associated with a multitude of complications. Temporal lobe epilepsy, in its natural progression, is often associated with many of the neuropsychological complications described here. Patients with longstanding temporal lobe epilepsy often will demonstrate a cognitive decline with difficulties in language, memory, and psychosocial functioning.

The chapter will begin by discussing the intricate anatomy of the temporal lobe and providing a brief overview of the various surgical approaches. An understanding of the resection bed's proximity to a multitude of essential anatomical pathways and structures will assist in explaining some of the various complications that are commonly encountered. We will then embark on a brief overview of the most commonly described surgical complications associated with general craniotomy. The remaining portion of the chapter will focus on the various neurological complications that have been documented. The neurological sequelae will be subdivided into motor, sensory, visual field, and cranial nerve deficits. We will then discuss neuropsychological complications including language, memory, and general cognitive disturbances. Lastly, we will address various psychiatric complications which have been observed following temporal lobe surgery for epilepsy.

Anatomy

The anatomy of the temporal lobe, including the mesial structures, is quite complex and requires a three dimensional understanding of its relationship to the rest of the brain before embarking on surgical intervention.[12] It is separated from the frontal lobe superiorly by the Sylvian fissure. One can follow the Sylvian fissure medially until it ends at the circular sulcus. This structure separates the insula from the temporal stem which comprises the white matter outflow tracts of the temporal lobe. Inferior and medial to the temporal stem lies the temporal horn of the lateral ventricle. The mesial structures of the temporal lobe reside along the medial aspect of the ventricle.

The complex anatomy of the mesial temporal structures and their proximity to the brain stem and other critical vascular and neuronal structures makes surgery in this region challenging. The mesial structures start at the parahippocampal gyrus and extend medially curling upwards contiguous with

the hippocampus. The hippocampal sulcus separates the parahippocampal gyrus from the hippocampus proper. The ambient cistern lies between the mesial temporal lobe and the brain stem. The posterior cerebral artery, posterior communicating artery, basal vein of Rosenthal, and the third nerve pass through this cistern. The hippocampus and the limbic lobe are C-shaped structures which extend posteriorly and follow the course of the lateral ventricle and corpus callosum. The hippocampus comprises the medial wall of the temporal horn of the lateral ventricle. The fornix, which is the outflow tract of the hippocampus, extends posteriorly and follows the course of the ventricular system to the mammillary bodies. The choroidal fissure delineates the hippocampus and fornix from the diencephalon, optic tract, and basal ganglia medially. The amygdala is contiguous with the basal ganglia and lies just anterior to the head of the hippocampus. Please see Wen and Rhoton's section describing surgical anatomy for more detail.[13]

Approaches

In the context of temporal lobe surgery for epilepsy, most surgical strategies are aimed at resection of the hippocampus and associated mesial structures. Hippocampal exposure is usually accomplished via the ventricular system and access to the ventricle has been described through multiple approaches.[8,14–19] Each approach necessitates some type of tissue disruption and each has its described advantages and disadvantages. These are described in detail elsewhere in this book.

Surgical complications

Surgical complications in this chapter include those complications associated with general craniotomy for all indications. Many centers quote different complication rates with respect to postoperative hematoma, infarct, retraction injury, wound complications, and infection as have been observed in their individual institutions.[2,3,9–11,20] These types of complications vary with the experience of the center, the resources of the institution, and the degree to which these are reported and recorded. Generally, infection is felt to be the highest surgical risk estimated in 1–5% of cases with the risk increasing with prolonged intracranial monitoring.[2,20] In a study evaluating risk of craniotomy and postoperative infection and role of antibiotic prophylaxis in 4578 craniotomies, it was found that the overall rate of infection was 6.6%.[20] Several studies have been done to correlate increased risk of infection with chronic invasive subdural grid and subdural electrode monitoring.[21,22] In a review and prospective analysis of 38 patients who underwent craniotomy for electrode implantation, clinical infection was observed in 7.9% of patients, with a 13.2% positive culture rate indicating that laboratory results do not always correlate with clinical outcome.[22] In a retrospective analysis of 198 monitoring sessions in 187 patients, the overall rate of infection was found to be 12.1%.[21] These studies suggest that the risk of infection increases significantly with preresection craniotomy for intracranial monitoring. Hematoma and infarct are seen far less often; in less than 3 % of cases.[2,9,21] Upon review of the 449 therapeutic procedures performed in Sweden between 1990 and 1995, infection was observed in 5.1%, hematoma in 0.4%, deep venous thrombosis in 0.4%, hydrocephalus in 0.7%, and CSF leak in 0.7%.[9] In a retrospective analysis of a series of 429 consecutive patients operated on during 6.5 years in the University of Bonn epilepsy program, a total of 33 surgical complications were encountered, 7.5% stemming from temporal lobe resections.[2] Of those described, deep vein thrombosis and pulmonary embolism were observed in 2% of patients. Postoperative meningitis was observed in 1%, with postoperative wound infection seen in 2.8%. A retrospective analysis of 215 patients who underwent temporal lobectomy for medically intractable epilepsy found no surgical mortality, but 1.3% of the patients harbored an infection of the bone flap.[10]

In summary, when considering the general risks associated with craniotomy in this region, one must appreciate the individual experience of the home institutions where these operations are performed as well as the unique nature of these procedures. The risk of infection is often higher than that for a routine craniotomy as many of these patients undergo placement of subdural grids for prolonged intracranial monitoring prior to the definitive surgical resection. In routine craniotomy without subdural grid monitoring, the risk can be estimated for most centers as between 1 and 3%. This risk increases with preresection monitoring to 8–12%. The risk of serious complications such as hematoma and infarct appear to occur on the order of 1–2%, but may vary according to the home institution's individual experience. Preoperative medical evaluation and perioperative monitoring are essential in reducing risk for developing such complications as deep venous thrombosis, pulmonary embolism, and perioperative myocardial infarction and should be utilized routinely. Additionally, perioperative antibiotic prophylaxis should be considered in an effort to reduce infection risk as well as strict adherence to a wound care regimen.

Neurological complications

Motor deficits

Hemiparesis of the contralateral side following surgery for temporal lobe epilepsy has been well described in the literature. In the manuscript, "Manipulation Hemiplegia", Penfield, Lende, and Rasmussen eloquently describe this complication and propose various theories for its etiology.[23] All operations carried out in the temporal regions by Penfield between 1948 and 1955 were retrospectively reviewed to include 161 in total with 8 incidents of hemiparesis accounting for 5%. Additionally, complete homonymous hemianopsia was also produced in all cases. Hemihypesthesias were also present. The hemiplegia improved to some extent in all cases. It was hypothesized that this triad of symptoms was attributable to injury of the internal capsule and associated structures where the corticospinal tracts, optic radiations, and thalamic radiations could be affected. It was proposed that this injury was likely vascular. It was further felt to be the result of injury to the anterior perforating arteries. It has since been attributed to injury to the anterior choroidal artery which supplies the optic tract, ventral thalamus, part of the striatum, and part of the posterior limb of the internal capsule.

Since Penfield's intial observations, numerous other institutions have documented postoperative motor deficits following temporal lobe surgery for medically intractable epilepsy. In 1975, Jensen reported his results from a survey covering 2,282 published temporal lobe resections around the world performed from 1928–1973 with respect to seizure control outcome and complications.[24] They found persistent hemiparesis in 2.4% and transient hemiparesis in 4.2% of temporal lobe resections respectively. In a retrospective analysis reviewing complications in 654 procedures recorded in the Swedish National Epilepsy Surgery Register between 1990 and 1995, hemiparesis was observed in 2.2%.[9] Of the 247 temporal lobe resections, one patient was observed to have hemiparesis after a temporal lobe resection excluding the hippocampus and four occurred after temporal lobe resection including the mesial structures. This was felt to support the theory that hemiparesis occurred as a result of injury of the anterior choroidal artery.

In Behrens' report, hemiparesis was the most frequent neurological complication being observed in 1.8% of the temporal lobe resection group.[2] Upon review, it was found that in two cases, manipulation of the anterior choroidal artery led to infarction of the internal capsule as documented on postoperative computed tomography scans. In a cohort of 215 patients, two patients suffered from a postoperative hemiparesis.[10] A regression analysis was performed in an attempt to identify potential risk factors for this potential complication. These two patients were greater than the mean age of 34 suggesting the possibility of advanced age as a risk factor for developing this complication.

In review of the above studies, hemiplegia and associated deficits following injury to the anterior choroidal artery and perforant vessels appears to occur on the average of 2%. Long-term studies have not been conducted to determine the percentage of patients with this complication who develop improvement. Subjectively, upon gross review of the literature, it would appear, that in a majority of cases of this type of complication, the hemiplegia is transient and tends to improve over several months to a year. Whether advanced age could be a risk factor for the development of this complication remains unclear.

Visual field deficits

Surgery for temporal lobe epilepsy afforded a new outlet for studying the route of optic radiations through the middle cranial fossa. Prior to temporal lobe resections for epilepsy, anatomical studies of visual field defects were limited to surgery for neoplastic resection as illustrated in Cushing's series, or by Meyer's studies of secondary degeneration following vascular or traumatic lesions.[25,26] Soon after the initial descriptions of temporal lobe resections for epilepsy were published, several case series examining the effect of the surgery on visual fields were presented. In the initial reports, it became evident that a majority of patients demonstrated a partial homonymous contralateral visual field defect limited to the upper quadrant. This was felt to be a reflection of the degree of the surgical resection and likely attributable to injury to Meyer's loop; the lateral most portion of temporal optic radiations. Penfield in 1954 stated, that if the excision was limited to less than 6 cm of the temporal lobe, no visual field defect was observed and resection of greater than 6 cm was associated with a partial visual field defect and greater than 8 cm was associated with a complete homonymous hemianopsia.[8] In contrast, Falconer's experience in 40 patients did not demonstrate a clear association with the degree of visual field defect with respect to the extent of the temporal lobe dissection.[5,27]

In 1958, two case series were published from Montreal Neurological Institute and Guy's de Maudsley Neurosurgical Institute in London.[28,29] In the former, 41 patients who underwent temporal lobe resection in an effort to elucidate the architecture of the optic radiations in the temporal lobe were examined pre- and postoperatively with perimetry visual field testing.[27,28] They found that there was no increased risk to central vision, visual acuity, or blind-spot margins. They found visual field defects in 82% of the patients. All were found to be quadrantic in nature. Ten were found to be congruous and 23 were incongruous with the defect closer approaching the fixation point in the eye on the side of the surgery. Additionally, they noted a slanting inferior margin of some of the defects expanding to a homonymous hemianopsia rather than a pure quandrantanopsia. They then embarked on a review of the existing literature describing the optic radiations of the temporal lobe. They concluded that the visual defects encountered were due to the effects of surgical ablation and not edema of the temporal portion of the visual radiation, as the deficits persisted 4 and 9 months postoperatively. Falconer and Wilson from London studied the visual field changes in 50 consecutive patients treated by anterior temporal lobectomy.[27] They found the chances of developing an upper quadrantic defect was on the order of 5 to 1. They determined that there was no significant difference in the range of the extent of the hemianopsia with regard to the extent of the dissection between 4.5 and 8 cm from the temporal pole extending posteriorly. All of their results demonstrated a congruous visual field defect, in contrast to the results reported by Van Buren and Baldwin.

Ten years following these two illustrative manuscripts, Marino and Rasmussen performed a more detailed review examining 50 patients operated upon for temporal lobe epilepsy at the Montreal Neurological Institute between 1962 and 1967.[30] Preoperative perimetry and tangent screen tests were normal in all patients in this series. It was found that 58% of the patient exhibited partial or complete quadrantic defects. The smallest defect being a small triangular sector near the vertical meridian with the most severe being a complete homonymous hemianopsia. It was found that in 34% in whom no field defects were noted, temporal lobe removals extended between 4 and 8 cm. They found a poor correlation between the extent of the defects and the extent of temporal lobe resection. This lended support to the idea of the presence of considerable variability in the formation of the optic radiations between patients. They reported the visual field defects were congruous in 79% of patients.

More recently, several large reviews have been undertaken to study the various complications associated with the procedure. In the review of the Swedish National Epilepsy Surgery Register of 449 procedures performed between September 1990 to 1995, two patients were found to have experienced hemianopsia.[9] In Jensen's review of 868 cases, visual field deficits reported ranged from 2.9–93% with an average of 50.9%.[24] After the two extremes reported were eliminated, it was found that visual field defects occurred at a frequency of

46% with the majority being partial hemianopsias and only 4% were complete homonymous hemianopsias. In a study of 215 patients, only one patient demonstrated a hemianopsia equaling 0.4%.[10] In Wiebe's prospective randomized trial quadrantic visual field defects occurred in 55% of patients in the surgical group.[11] However, these were asymptomatic and were only evident on detailed visual field testing. A recent study was carried out at the National Hospital in London to evaluate the extent of visual field defects and to discuss its implication in passing the British driving examination.[31] Of patients who had undergone temporal lobe surgery,[24] underwent postoperative evaluation with both Goldmann and Humphrey perimeter testing. It was noted that a field deficit was found in 54% of patients using the Goldmann test and 46% using the Humphrey analysis. In 25% of these patients, the defect was large enough to fail the vision criteria set forth by the British driving regulations, prompting the role of preoperative discussion of this side-effect prior to surgical resection.

The majority of these studies thus far have attributed the visual field defects to an injury to the optic radiations which traverse the temporal lobe. The superior quadrantanopsia appears to be associated with a primary injury to Meyer's loop, whereas a complete homonymous hemianopsia has been attributed to removal of a greater extent of the temporal lobe as well as disruption of the optic radiations as they course medially and inferiorly. It would make sense that there would be a variance in the incidence of visual field deficits with respect to differing surgical approaches. A study comparing the standard anterior temporal lobectomy (ATL) approach with selective amygdalohippocampectomy (SAH) with respect to visual field deficits was carried out by Egan *et al.*[32] Twenty-nine patients were enrolled, with 14 undergoing SAH and 15 ATL. The patients were tested using Goldman perimetry 1 month postoperatively. Approximately 75% were found to have a superior quandrantanopsia. There was no statistical difference between the two approaches. It was postulated that the visual field defect occured during ATL when the temporal tip is removed. In SAH, it was explained that visual field defects occurred as the suction device and retractors are driven through the optic radiations en route to resection of the medial temporal lobe.

In conclusion, visual field defects following surgery for temporal lobe epilepsy range from minor triangular defects to complete homonymous hemianopsias. In the majority of cases, the patients demonstrated a superior quadrantanopsia and were unaware of their deficit as it was diagnosed only with detailed visual field testing. The range of patients to exhibit visual field defects ranges from 46% to 82% in earlier studies. A quote of a 50% chance of possibly incurring a visual field defect is reasonable when counseling patients for this procedure. The extent of the visual defect does not appear to clearly correlate with the degree of dissection or approach of the surgery. The optic radiations, which make up the most lateral aspect of Meyer's loop appear to be most susceptible to injury. However, in the majority of cases, the patients who were found to have a superior quadrantanopsia on detailed testing were unaware of their deficit. In those few cases of patients who suffer a more extensive hemianopsia, it may be related to the amount of resection or individual variance on the course of the optic radiations as they encompass the temporal lobe and appears to with a frequency of 4–12%.

Cranial nerve deficits

The cranial nerves most often implicated in potential complications following surgery for temporal lobe epilepsy are the oculomotor CN III and the trochlear CN IV nerves. The oculomotor nerve passes through the ambient cistern bordering the medial aspect of the temporal lobe en route to the cavernous sinus. The trochlear nerve innervates the superior oblique muscle of the orbit. It exits the brain stem dorsally and decussates in the superior medullary velum. It then courses lateral to the cerebral peduncles and passes between the posterior cerebral and superior cerebellar arteries just lateral to CN III as it runs medial to the temporal lobe before entering the cavernous sinus.

Several studies have demonstrated cranial nerve palsies following temporal lobe surgery.

Rydenhag *et al.* documented two trochlear nerve and two oculomotor nerve palsies following mesial temporal lobe resections upon their review of 247 temporal lobe resections.[9] Third nerve palsy was seen transiently in four of 279 cases reviewed by Behren's *et al.*[2] In Salanova's study of 215 patients, seven manifested transient cranial nerve palsies with nerves III or IV following temporal lobectomy.[10] This accounted for 3.2% of their series and was observed to have resolved in several weeks. Jacobsen *et al.* reviewed 22 cases of patients who underwent anterior temporal lobectomy for treatment of epilepsy at the Marshfield clinic between 1987 through 1993 and found three cases of transient postoperative diplopia.[33] Detailed neurological examination was performed which demonstrated ipsilateral trochlear nerve palsies. Postoperative imaging did not demonstrate any evidence of infarction. It was felt that this complication was likely secondary to traction. The trochlear nerve is the thinnest cranial nerve residing in the lateral wall of the cavernous sinus and may be vulnerable to mechanical distortions of the lateral wall which may occur during temporal lobe resection. The authors felt that trochlear nerve palsies may be underdiagnosed due to their difficulty in diagnosis and that the prevalence may be higher than initially supposed. Thus, after review of the literature, it would appear that the risk for developing a cranial nerve palsy of either the oculomotor or trochlear nerve is on the order of 1.5–3%. Additionally, this deficit appears to be transient in the majority of cases which would correlate with a possible retraction injury as opposed to direct injury to the nerve or vascular compromise.

Language deficits

The role of language in the temporal lobe can be appreciated by observing certain seizure semiologies. Often persons are completely aphasic during a seizure or exhibit abnormal language with perseveration and paraphasic errors. The posterior superior portion of the temporal lobe has been mapped as Wernicke's area; with lesioning of that area associated with a receptive aphasia. The inferior frontal gyrus overlying the superior temporal lobe is implicated in Broca's area, the lesioning of which is associated with an expressive aphasia. The two are believed to be connected via the arcuate fasciculus where lesions have been characterized as producing a conductive aphasia. Numerous studies have demonstrated language difficulty following surgery of the temporal lobe. Many centers report a transient aphasia characterized by

dysnomia following temporal lobectomy for epilepsy.[34–38] However, the more long-term impact on temporal lobe resection on language function has been less clearly elucidated. The role of this section will provide a broad overview of the temporal lobe's function in language and to outline the most common complications encountered following surgery in this area.

In the initial surgeries for temporal lobe epilespy, intraoperative language mapping was employed routinely as well as an attempt to avoid the superior temporal gyrus secondary to the risk of injury to Wernicke's area. In recent years, the role for language mapping has been debated. Hermann conducted a prospective analysis of 29 patients who underwent partial resection of the anterior temporal lobe utilizing intraoperative mapping.[35] No significant loss in either dominant or nondominant-sided resections with respect to language function was observed. Anecdotally, improved seizure control was observed in patients from this study who were unable to tolerate intraoperative mapping for various reasons. As a result, Hermann carried out a follow-up study with 64 consecutive patients who underwent anterior temporal lobe resection without intraoperative language mapping.[36] The patients were administered the multilingual aphasia test preoperatively and 6 months postoperatively. A median of 4.25 cm of lateral dominant temporal cortex or 4.5 cm of nondominant temporal cortex was removed including resection of the superior temporal gyrus. No measurable compromise was appreciated when comparing preoperative and postoperative scores. In fact, dominant temporal lobectomy patients were seen to have gained in language comprehension function postoperatively.

The surgical approach has been implicated as a means for protecting language function. It has been argued that sparing the superior temporal gyrus results in less postoperative dysnomia. It has also been implied that preoperative or intraoperative language mapping results in less difficulty with language post operatively. In a large multicenter study, four surgical approaches were examined with respect to visual confrontation naming following Wada proven language dominant left temporal lobectomy for epilepsy.[39] A total of 217 patients underwent surgery either via tailored resection with intraoperative mapping, tailored resection with extraoperative mapping, standard resection with sparing of the superior temporal gyrus, and standard resections including excision of the superior temporal gyrus. They found that in all surgical groups there was significant decline in visual confrontation naming as assessed by the Boston Naming Test by an average of 8%. They saw no significant change between naming outcomes as a function of surgical approach.

Contrastly, Ojemann conducted a study of 117 patients undergoing Wada proven left language dominant hemispheric resections for various reasons where language mapping was undertaken.[40] It was found that essential areas for language were often organized in a 1–2 cm mosaic pattern of discrete areas of language function. Mosaics essential for language were usually located in the frontal cortex or in the temporoparietal cortex. These findings were often highly localized and reproducible within a given patient but were not found uniformly in a group analysis. These findings imply a great degree of variability within localization of essential naming and language function to suggest a role for language mapping. Since its inception the role for intraoperative mapping and partitioning of the superior temporal gyrus has been debated. Currently, temporal lobe epilepsy surgery has expanded so that many centers no longer perform tailored resection according to language mapping nor do they routinely spare the superior temporal gyrus.

Dysnomia appears to be the most common deficit encountered in language function following surgery for temporal lobe epilepsy. Hermann published a study to evaluate the presence of dysnomia following dominant anterior temporal lobectomy.[41] Patients with Wada proven left hemisphere speech dominance with intractable nonlesional epilepsy and full-scale IQ > 69, underwent anterior temporal lobectomy without functional mapping at the University of Tennessee, and were evaluated with respect to language. These patients were administered a standard aphasia battery preoperatively and 6 months postoperatively. The primary area of interest was a visual naming subtest. The extent of lateral dominant resection averaged 4.3 cm from the temporal tip. No significant difference in the mean preoperative to postoperative score was seen for the right temporal lobectomy group. Left temporal lobectomy patients experienced a 23–27% decline from their preoperative performance. A study by Martin *et al.* showed in a total of 101 Wada proven left language dominant patients who underwent anterior temporal lobectomy for medically intractable epilepsy showed that nearly 50% of the left-sided resected patients experienced clinically meaningful declines with respect to the Boston Naming Test.[42] This contrasted with right-sided resected patients who showed no significant decline on the Boston Naming Test.

Following, these and other studies which demonstrated a clear decline in postoperative naming ability after resection of the Wada proven language dominant temporal lobe, many studies have been aimed at predicting risk factors for developing this difficulty. Stafiniak *et al.* evaluated 45 patients who underwent anterior temporal lobecomy for medically refractory epilepsy.[38] All patients received comprehensive neuropsychological evaluations preoperatively and 3 weeks after surgery. After left dominant lobectomy 60% of patients with no early risk factors such as early neurologic insult via infection or trauma, or febrile seizure demonstrated a > 25% decline in naming. However, none of the patients without early risk factors experienced a postoperative decline in naming. None of the patients who underwent right-sided surgery experienced a naming decline postoperatively. This study would suggest that perhaps patients with a neurological insult early in life are able to collateralize language ability to some extent allowing for decreased risk for dysnomia postoperatively. Bell studied 26 patients with Wada proven left-sided language dominance who underwent left anterior temporal lobectomy with respect to naming performance.[43] The age of onset of epilepsy was the only predictor of postoperative dysfunction. Patients who developed epilepsy at an earlier age were more likely to exhibit less difficulty with naming postoperatively. Patients who had felt that they had learned the particular word in question at a later age were more likely to have difficulty naming it in the time prescribed during the Boston Naming Test on their postoperative evaluation. In a multicenter trial to compare surgical approach with language difficulty postoperatively, one risk factor which was identified was the age at onset of epilepsy. Patients who developed seizure onset at a later age demonstrated increased difficulty in naming.[44]

The above studies demonstrate a postoperative decline in naming ability following dominant temporal lobe resection. However, the stability of this deficit over time has been less clearly observed. Stafaniak *et al.* evaluated 41 patients with respect to dysnomia following surgery for temporal lobe epilepsy and found that four of the six patients who experienced an average decline of 61% in naming ability pre- to postoperatively improved to a mean decline of 18% at 1 year follow-up.[38] This finding suggests that this naming deficit often shows significant improvement over time. In a prospective study by Davies *et al.*, 95 consecutive patients undergoing standard anterior temporal lobectomy for intractable complex seizures were studied with respect to language functioning.[34] Patients underwent a neuropsychological evaluation to assess naming of objects preoperatively and 1 year postoperatively. Comparison of the preoperative scores showed a significantly lower score for the left-side dominant group for several of the language measures. At the 1 year follow-up, left-sided lobectomy patients demonstrated a significant improvement in verbal fluency and performance IQ. Right-sided temporal lobectomy patients also showed a significant improvement with respect to verbal fluency and performance IQ. In these resections, the superior temporal gyrus was resected without evidence for detriment to language function. In fact, this study seemed to support that the surgical resection allowed for improvement in language fluency and performance IQ. This may be a result of improved seizure control, or perhaps, the idea of relieving abnormal circuitry to allow normal circuitry to develop and progress.

Functional magnetic resonance imaging has prompted a new cadre of non-invasive means to study language organization. In one study designed to evaluate reading skills in patients who underwent left-sided language dominant temporal lobectomy for medically intractable epilepsy compared patients to age matched controls.[45] Those patients who demonstrated higher level reading skills postoperatively were more likely to recruit right hemispheric activity, specifically the in the right inferior frontal gyrus, right hippocampus, and right inferior temporal gyrus. The introduction of magnetoencephalograms has also added to the abundant studies underway to determine language localization. In a recent study by Pataria *et al.*, 12 patients were examined using MEG who underwent left temporal lobectomy.[46] They found that patients who exhibited bihemispheric recruitment preoperatively for language tasks were more likely to show increased right hemispheric activity postoperatively.

The temporal lobe's function in language has long been recognized as is evidenced by Wernicke's and Brodman's mapping studies. Temporal lobe epilepsy is often associated with semiology whereby the patients demonstrate language difficulty during seizures. The implications of temporal lobe resection on language ability have been somewhat surprising. Initially, it was felt that resections should be undertaken with intraoperative mapping and careful preservation of the superior temporal gyrus. Numerous studies have demonstrated no significant difference between outcomes in language function when intraoperative mapping is not utilized or the superior temporal gyrus is resected. However, there may exist individual variance between patients to support utilization of intraoperative mapping per Ojemann's argument which must be considered when counseling patients of surgical risk of language difficulty. Additionally, though many studies have demonstrated a significant problem with dysnomia following surgery, it would appear that this is often a transient deficit which resolves in the first 12 months postoperatively. It was also found that patients with Wada proven language dominance on the side of the resection were more likely to suffer language difficulty postoperatively than those who underwent non-language dominant resections. Additional risk factors for language difficulty aside from dominant hemisphere resections included later age of epilepsy onset. New imaging analyses have shown that possibly patients who recruit the opposite hemisphere are better able to compensate for language difficulty postoperatively. Taken together, these data may lend support to the idea that patients who develop epilepsy at a younger age and who may exhibit a higher degree of plasticity, are at an advantage as they may be able to develop bihemispheric projections to support language function. This would argue proposal of surgical intervention in the younger population with medically intractable epilepsy. In conclusion, patients considering surgery for temporal lobe epilepsy need to understand the risk of language difficulty postoperatively. This risk appears to be increased in patients undergoing resection in the Wada proven dominant hemisphere, later age of onset of epilepsy, and absence of childhood neurological insult such as infection, trauma, or febrile seizures. Additionally, it would appear that, in a majority of patients, perioperative language difficulty is a transient phenomenon which demonstrates significant improvement 1 year following surgery.

Memory deficits

Since the inception of temporal lobe epilepsy surgery, a correlation has been observed between resection of the mesial structures and memory. Unfortunately, much of the knowledge that has been gained in this regard has been at the expense of surgical complications. Penfield and Scoville described several case reports of patients who underwent either unilateral hippocampal resection for temporal lobe epilepsy or bilateral resection for psychiatric illness, and developed severe anterograde amnesia.[47,48] In all of these patients, there was evidence of difficulty in acquiring new memories to the extent that these patients were no longer able to carry out their activities of daily living. In those patients who underwent unilateral resection, it was found postoperatively that the opposite hippocampus exhibited a destructive lesion. After careful analysis of these patients, it was concluded that bilateral hippocampal dysfunction was correlated with this severe form of amnesia.

The Wada test was introduced in Japan by Juhn Wada in 1949 and initiated into Western medical literature in 1960.[49] The test involves injection of sodium amytal into each carotid artery to induce a temporal loss of function in the injected hemisphere. Lanugage is then assessed by monitoring the EEG-slowing and associated hemiparesis. Memory is assessed 10 minutes following injection and following return of EEG behavior to baseline. This test was initially utilized in 20 patients being evaluated for epilepsy surgery in Japan in an effort to determine language hemisphere dominance. However, after it was determined that memory likely also demonstrated some degree of lateralization, Branch and Milner published a retrospective analysis of 50 patients being evaluated for surgical resection at the Montreal Neurological Institute.[50] They hypothesized that no memory defect should

be seen after unilateral amytal injection unless there was a poorly functioning hippocampal formation on the contralateral side. They found memory disturbance in 13% of patients. This study led to the idea of utilizing the Wada test as a means of assessing the ability of the contralateral hemisphere to support memory independently when planning for resection of ipsilateral mesial temporal structures. The Wada test is employed on a routine basis in most epilepsy centers in an effort to prevent devastating memory loss following hippocampal resection. Rausch describes outcome data for 214 patients at UCLA who underwent anterior temporal lobectomy.[51] All patients underwent Wada testing prior to procedure and demonstrated 67% of correct responses when sodium amytal was injected on the side ipsilateral to the resection. No significant postoperative memory decline was demonstrated after resection. Jones-Gotman evaluated the results of patients who failed Wada memory tests compared to those who had passed (found to support memory in the contralateral hemisphere) and who had undergone temporal lobectomy.[52] Seventy-two patients were included in the sample; 11 who had failed the preoperative Wada test contralateral to the planned resection. Substantial postoperative losses with respect to long-term memory deficits 1 year after surgery were observed in those patients. In conclusion, the Wada test aids in determining whether or not memory can be adequately supported by the hemisphere contralateral to the planned resection.

The hippocampal formation appears to correlate with episodic memory functioning used in day-to-day living as opposed to semantic memory which refers to knowledge of a more encyclopedic variety. Patients with temporal lobe epilepsy have been found to have progressive memory decline with respect to normal controls.[53,54] Likewise after surgical resection, further decline has been reported. Despite a great deal of progress, the pathways of memory formation, consolidation, and retrieval have not been completely elucidated and appear to demonstrate considerable variability between subjects. Regardless, numerous studies implicate the neocortex of the temporal lobe in short-term or working memory functioning. Contrastly, the hippocampus has been implicated in memory consolidation.[53–55] Hermann *et al*. report on a series 57 patients with full scale IQ > 69, medically resistant temporal lobe epilepsy, with Wada proven left hemisphere dominance.[55] All subjects were given the California Verbal Learning Test preoperatively and 6 months postoperatively. This test provides information on overall recall ability, rate of learning, and indices of forgetting in addition to characterizing between different types of memory consolidation. This test involves oral presentation of a 'shopping' list of 16 items followed by five immediate recall trials. They found that patients who underwent a right-sided resection showed greater recall of words from the middle of the list, were able to utilize semantic clustering and demonstrated an overall greater ability to recall verbal material after a short delay. The patients undergoing left-sided temporal resection showed a lower proportion of words recalled from the middle of the list and exhibited more errors in free recall. The left-sided resected patients were more inefficient in their memory strategy. Given a list of 30 or more words, they were less able to remember words towards the top of the list and appeared to try to remember them by serial connection rather than semantic clustering. This means that they would attempt to recall the words by remembering the order in which they were presented rather than making associations to connect the various words together. This study lends support to the theory that the language dominant hemisphere hippocampus is important in allowing the person to cement memories into functional quanta.

Multiple studies including volumetric as well as histologic analyses have been done to demonstrate the role of the hippocampus in verbal memory functioning. A study by Trenarry *et al*. compared preoperative MRI-based hippocampal volumes with pre- and postoperative performance on an assortment of memory tests in 80 patients who underwent temporal lobectomy for medically intractable epilepsy.[56] The average hippocampal volume was noted to be smaller on the side ipsilateral to the resection which correlates with the numerous patients exhibiting mesial temporal sclerosis as a pathologic entity. They found that greater atrophy of the left hippocampal formation when compared to the right was associated with improved verbal and visual memory following a left temporal lobectomy. Contrastly, resection of a non-atrophic normal sized hippocampus resulted in verbal and visual memory decline. This data lends support to the idea that the hippocampus may be involved in both verbal and visual memory consolidation. Previous studies have shown that hippoampal cell loss in the CA1 region is observed reliably in patients with hippocampal sclerosis. Rausch and Babb evaluated 25 patients who underwent temporal lobe surgery for medically intractable epilepsy and found that the degree of hippocampal neuron loss was significantly related to memory function.[57] Preoperatively, patients with left temporal lobe seizures with severe neuron loss, defined as greater than 80% cell loss when compared to controls, performed worse than those with less than 80% cell loss. Postoperatively both sets of patients with left-sided resections decreased their performance on word pair tasks and delayed recall.

Numerous studies have been done to demonstrate postoperative memory decline following surgery for temporal lobe epilepsy. Chelune *et al*. conducted a prospective analysis of 42 patients with medically intractable epilepsy who underwent temporal lobectomy with Wada proven left-sided language dominance.[58] The patients were tested 3 months prior to their surgeries and at 6 months postoperatively. They found a significant decline in verbal memory tasks with those patients scoring the highest preoperatively demonstrating the most significant decline. A decrease in 1.5 standard deviations was evident in the verbal memory score. Rausch *et al*. compared 44 patients who underwent temporal lobectomy with eight patients who were found not to be surgical candidates.[54] All participants underwent cognitive testing preoperatively, 1 year postoperatively, and at least 9 years later. All patients had language dominance in the left hemisphere confirmed by Wada testing. Ninety Percent of patients were found to exhibit hippocampal sclerosis on pathologic analysis. They found that the group of patients who underwent left temporal lobectomy demonstrated decreased performance in verbal memory scores when compared with preoperative scores. Patients who underwent right temporal lobectomy showed increases in verbal memory scores. Long-term follow-up demonstrated progression in decline in verbal memory for both patients undergoing right- and left-sided resections as well as those patients who did not undergo surgery. These results support that left-sided temporal lobectomy for left-sided language

dominant patients is associated with a decline in verbal memory functioning postoperatively. However, the study implies that patients with temporal lobe epilepsy may exhibit a more rapid decline in memory functioning than would be expected in the general population. Helmstaedter *et al.* enrolled a total of 144 patients who underwent temporal lobectomy.[53] Participants were matched with respect to sex, age, seizure frequency, and IQ. Patients who failed the Wada test or who showed right hemisphere language dominance were not included. They found that left-sided temporal lobe epilepsy patients did significantly worse on preoperative performance measures of short and long delayed recall than patients with epilepsy localized to the right temporal lobe. Short and long delayed recall were impaired in only 34–40% of patients with right temporal lobe epilepsy compared to 70–80% of patients with left temporal lobe epilepsy. Postoperatively, no significant change was appreciated in any measure of verbal memory in right temporal lobe resections. Left temporal lobe resections by contrast showed marked negative effects on learning, recognition, and recall. The deficits observed were most pronounced in tests of memory acquisition and recognition.

The lateral neocortex has been implicated more in naming and short-term working memory tasks. The mesial temporal lobe and hippocampus specifically has been associated with long-term memory consolidation and retrieval. A study by Helmstaedter *et al.* sought to confirm this representation by comparing the type of memory deficits suffered by persons undergoing lateral versus mesial resections for epilepsy surgery.[54] They examined 47 patients with medically intractable temporal lobe epilepsy localized to the left hemisphere who underwent standard anterior temporal lobectomy, cortical lesionectomy, and selective amygdalohippocampectomy. Memory was assessed preoperatively and 3 and 12 months postoperatively using a variant of the Rey Auditory Verbal Learning Test. This test was designed to assess different aspects of declarative memory including working memory by means of immediate recall as well as long-term aspects such as consolidation and retrieval by asking for free recall following distraction, delayed recall, and recognition. The results were compared to 175 matched controls with no history of a central nervous system disease. A significant decrease in delayed free recall and an increase in recognition errors in patients who underwent anterior temporal lobectomy and selective amygdalohippocampectomy when compared to the cortical lesionectomy group. They also found a significant effect in patients who underwent temporal lobectomy with respect to selective amygdalohippocampectomy with a further deterioration in total immediate recall. A repeat analysis 12 months postoperatively was consistent with 3-month data to suggest stability of the outcome over time. These data support the hypothesis that the mesial temporal structures are correlated with long-term memory retrieval and consolidation while the lateral temporal lobe is more implicated in working memory. This study implies that perhaps anterior temporal lobectomy results in a deficit in both working memory and long-term memory whereas selective amygdalohippocampectomy may offer some preservation of working memory. However, a study of 140 patients who underwent selective amygdalohippocampectomy demonstrated a significant decline in all aspects of verbal learning and memory.[60] The results were standardized according to normative data of 200 healthy controls. Patients underwent a neuropsychological examination of verbal and visual memory functions preoperatively and 3 months postoperatively. Left-sided resected patients scored 2–3 standard deviations below the mean postoperatively. These deteriorations involved verbal memory learning, delayed free recall, and recognition. The authors found no recovery of postoperative verbal memory declines as clinically meaningful losses were evident in 33–50% of patients at the 1 year follow-up.[61]

Tailored resection for temporal lobectomy has been proposed in patients to preserve both language and memory function. A study by Ojemann and Dodrill demonstrated memory centers localized in the lateral neocortex of the temporal lobe.[62] In a study of 14 adults who underwent left temporal lobectomy with intraoperative mapping, the Weshler Verbal Memory Scale was employed to study memory function pre- and postoperatively. The score decreased an average of 22% at 1 month and 11% at 1 year. In the mapping studies, they found the presence of temporo-parietal zones of memory sites which largely bordered naming sites. They then correlated the presence of these sites with the proximity to the resection bed. They found that the presence of these sites within the resection zone was present in five of six patients who demonstrated a significant memory decline postoperatively indicative of an 80% predictive ability.

Numerous studies have been done in an attempt to elucidate which patients may be at greater risk for postoperative memory decline. One study found that later age at onset of epilepsy and older chronologic age were risk factors for memory deficits.[63] Two hundred three patients were assessed using the California Verbal learning Test preoperatively and 6 months postoperatively following anterior temporal lobe resection. In this study, higher postoperative scores correlated with higher preoperative scores, younger chronologic age, higher full-scale IQ, female sex, and right-sided resection. To explain the variance in higher preoperative scores being associated with higher postoperative scores, they suggest that, when all other preoperative variables are held constant, a person with higher intelligence is better able to compensate. In a multiple regression analysis performed on 144 patients who underwent anterior temporal lobectomy several factors were felt to be predictors of postoperative deterioration.[53] High presurgical performance level, older age, longer duration of epilepsy, extensive en bloc resection, preexisting deficits in memory performance and preoperative secondarily generalized seizures were all associated with a decline in memory function postoperatively. The effect with respect to age appeared to correlate well with an age of 30 years at the time of surgery. Only 17% of patients aged > 30 demonstrated stable or improved memory performance postoperatively. A further analysis to evaluate the role of regression based outcome methodology was employed on a cohort of 101 patients found a significant performance decline in 25–50% of patients with left-sided resections.[42] However, they noted a significant range of memory outcome within groups to support the great deal of variability found in numerous other studies. In a study by Hermann *et al.*, 60% of patients with left anterior temporal lobectomy experienced postoperative decrease in verbal memory but 38% showed improvement illustrating the great deal of individual variance between patients with respect to functional outcomes.

In summary, the role of the temporal lobe in memory function is both complex and critical. The Wada test is an important tool which has been developed to determine the ability for the contralateral hemisphere to adequately support memory following temporal lobe and hippocampal resection. However, even when one is careful to offer surgery only to those patients who have favorable Wada test results, memory deficits remain a significant complication observed following this surgery. In patients with left-sided language dominance, the risk of memory dysfunction postoperatively appears to be greater than those who undergo right-sided resection. The presence of preoperative memory deficit in setting of mesial temporal sclerosis may mitigate the risk of a decline in verbal memory postoperatively. The deficits that are observed following temporal lobectomy are characterized by difficulty with working memory and memory consolidation. Resection of the lateral neocortex appears to result in a deficit of working memory whereas resection of the mesial structures results in difficulty with memory consolidation. These deficits often require the patient to adopt different strategies for memory consolidation such as outward documentation to assist them in their day-to-day living. Postoperative neuropsychological testing, in addition to studying the types and degree of memory difficulty observed following temporal lobe resection, provides a tool for the patient and patient's family to identify particular weaknesses which then may be addressed. Older age at epilepsy onset, older chronologic age, higher preoperative functioning, and left-sided resections appear to be risk factors for memory deficits postoperatively. Taken together, these data illustrate particular trends which may correlate to predictive analysis of postoperative memory decline but that for each individual there exists a great deal of variance.

Cognitive deficits

Cognitive difficulty has been noted in patients with temporal lobe epilepsy when compared to controls. Progression of the disease is associated with progressive cognitive impairment prompting a role for medical or surgical control of seizures. The question of whether the extent of the neocortical resection correlated to the degree of cognitive impairment was addressed by Lutz *et al*. comparing 80 randomized patients who either underwent transylvian approach or transcortical approach for mesial resection.[64] All patients received comprehensive neuropsychological testing of verbal, non-verbal memory, attention, and executive functions before and 6 and 12 months following surgery. It was found that 75% of patients became seizure free with no appreciable difference observed with regard to surgical approach. Repeated multivariate analysis of variance measures demonstrated no statistical difference between cognitive outcomes with the exception of phonemic fluency which was improved after transcortical but not after transsylvian approach. This improvement in verbal fluency with the transcortical approach has traditionally been attributed to seizure freedom postoperatively. However, the authors felt that the improvement with the transcortical approach may be a reflection of this function being more closely associated with frontal lobe manipulation. Verbal fluency could be regarded more as an executive function and, as such, has its seat in the frontal lobe. The frontal lobe is manipulated with retraction more with the transylvian approach than with the transcortical approach.

In a study by Wachi et. al., 26 patients who underwent anterior temporal lobectomy including excision of the hippocampus were evaluated with a battery of neuropsychological tests pre- and postoperatively.[65] They found a uniform improvement in cognitive functioning following resection. A significant increase was observed in verbal IQ from 85.1 to 89.3. Performance IQ also increased from 89 to 95 1 year postoperatively. Full-scale IQ scores also were observed to increase at 1 year after surgery from 85.5 to 88.5. There was no significant difference between memory function as determined using story recall test, Benton's visual retention test, Rey-Osterreith complex figure test, and the WMS-R between preoperative analysis and postoperative analysis. These improvements were felt to be reflective of an overall decrease in seizure frequency with 62% of the patients being seizure free. However, the study was made of a small sample size and statistically significant comparisons could not be made between left- and right-sided resection.

The role of tailored resection with respect to cognitive preservation was undertaken by Leitjen *et al*.[66] Eighty patients with pathologically proven mesial temporal lobe sclerosis underwent surgery. These patients underwent a standard neuropsychological test battery 6 months prior to and 6 months after the surgery including verbal IQ (VIQ), performance IQ (PIQ), visual naming, and a complex figure test. Sixty-one percent of the patients demonstrated neocortical spikes on the intraoperative ECoG. Interestingly, patients with left-sided resections with neocortical spikes demonstrated a slightly improved VIQ preoperatively than their counterparts without spikes. They found an improvement in PIQ in patients who underwent tailored resection, but not in any other modality. It was felt that this was in contrast to their initial hypothesis that neocortical spikes were indicative of dysfunctional tissue and that removal of such spikes would allow for a better cognitive performance outcome, especially in regard to language function thought to be harbored in the neocortex of the temporal lobe.

Taken together, these studies support that improved seizure frequency results in overall improvement in visual and performance IQ following surgery for temporal lobe epilepsy. A complete resection of the mesial structures without regard to intraoperative mapping may allow for greater seizure control and thus correlate with improved outcome in cognitive functioning.

Psychiatric deficits

Epilepsy in itself has been associated with a higher incidence of a major depressive illness and suicide. It is estimated that the suicide rate in epilepsy patients is five times that of the general population.[67,68] One study found that up to 50% of patients with epilepsy suffer from depressive syndromes.[69] Patients with temporal lobe epilepsy have been found to have an even higher risk of depression.[63] Temporal lobe epilepsy, in particular, has been associated with a variety of psychological disturbances both before and after resective procedures. The proximity to the limbic structures has been implicated as a possible reason for higher incidence in mood and psychiatric disturbances. The amygdala in particular has been associated with processing of fear response. In one study of 28 patients who had undergone anterior temporal lobectomy, a postoperative impairment was found in recognizing facial expressions

of fear, anger, sadness, and disgust.[70] In a prospective randomized controlled trial of 80 patients who either underwent temporal lobectomy or received optimal medical therapy the rate of depression was fairly equally represented between both groups.[11] Eighteen percent of patients were diagnosed with depression in the surgical group compared to 20% of patients in the medical groups indicating the increased prevalence of this problem in this population. Since the landmark study by Kluver and Bucy describing a state of hypersexualuality, loss of fear, hyperphagia, and generalized apathy following bilateral temporal lobectomy, various psychiatric derangements have been attributed to the temporal lobe.[71] Disturbances in mood, emotional responses, and even schizophrenic-type illnesses have been localized to the temporal lobe. Blumer's report, based on a series of 50 patients who underwent temporal lobectomy and were followed for an average of 17 years sought to examine the type of psychiatric sequelae of the surgery.[68] Fifty patients experienced an exacerbation or onset of a chronic schizophrenia-like psychosis. Ten percent also demonstrated angry and aggressive behavioral outbreaks. Many patients preoperatively demonstrated hyposexuality. These patients were observed to have developed normal sexual arousal and occasional hypersexuality postoperatively. Fenwich *et al.* conducted a literature review and circulated a questionnaire to multiple centers around the world to study the current practice and outcomes of surgery with regard to psychiatric complications.[72] In comparing three separate series, there was a rate of developing a schizophrenia-type psychosis in 15.4%, which is greatly increased from the stated 1% lifetime incidence documented for the general population. A retrospective analysis was performed by Inoue and Mihara to assess the presence of psychiatric morbidity in association with epilepsy surgery.[73] Their subjects consisted of 226 patients who underwent surgical therapy between 1983 and 1997. Seventy-eight percent of the patients exhibited psychiatric disorders before and after surgery. Of those 61 patients who demonstrated psychiatric disturbances before surgery, one-third of them resolved following surgery. Nine patients were found to have transient affective disorder immediately postoperatively which resolved in 1–2 months. Eight patients developed a chronic psychiatric disorder de novo following surgery. Of these, six were found to have psychosis and two developed behavioral disorders. This study suggests that about a third of persons with psychiatric disorders prior to surgery will experience resolution of their symptoms postoperatively, while the rest will persist. It also suggests, that in a select minority of patients, a de novo psychiatric disturbance will become manifest after surgery. Shaw, interested in the association between temporal lobe surgery and postoperative schizophrenia-like psychosis, performed a retrospective analysis of a series of 320 surgical patients.[74] They identified 11 patients who developed a schizophrenia-type psychotic illness postoperatively and compared them with 33 control subjects who remained free of psychosis. The psychotic illness was characterized by the presence of persecutory delusions and auditory hallucinations. They found no clear association between postoperative seizure activity and the development of psychotic symptoms. However, they did find that those patients were more likely to demonstrate pathologies other than mesial temporal sclerosis as five of the 11 had lesions such as vascular hamartoma, DNET, ganglionglioma, and abscess. Additionally, they found that the psychotic patients were more likely to demonstrate bilateral EEG abnormalities.

Christodoulou *et al.* made an interesting observation in reviewing a case series of 282 consecutive patients who underwent temporal lobe resections for epilepsy.[75] Fifty-six patients demonstrated persistent or recurrent seizures postoperatively. Three of these patients developed a chronic psychotic illness. Upon further study, it was found that all three of these patients demonstrated a new seizure type postoperatively arising from the side contralateral to the resection. This appears to support the theory that patients prone to psychotic breaks may have some inherent involvement of both hemispheres, perhaps brought out by resection of one side of the mesial temporal structures.

Epilepsy surgery has also been associated with a higher predisposition to somatic-type disorders. A retrospective review of 325 anterior temporal lobectomies performed between 1991 and 2000 at New York University Hospital found 10 patients (3%), who developed somatoform disorder.[76] These were characterized by body dysmorphia and pain disorder. Nine of the ten had undergone right resections which correlate with previous data implicating the right temporal lobe in psychotic corrolaries. It is difficult to assess objectively the psychiatric complications of temporal lobectomy for epilepsy as many of these patients demonstrated abnormal psychiatric profiles preoperatively. In general, it is felt that a majority of patients develop stronger emotional ties, family relationships, and become more functionally independent following the procedure likely secondary to its improvement in seizure control. However, for a select few, it may predispose them to developing a severe psychotic illness similar to schizophrenia. It is recommended that potential candidates for resective surgery be considered for a psychiatric assessment prior to the procedure to ensure that they are receiving optimal therapy prior to any potential surgical intervention.

Conclusion

In conclusion, surgery for medically intractable temporal lobe epilepsy is associated with a broad variety of complications. When counseling prospective candidates for this procedure, one must keep in mind the intricate structure and relationship of the temporal lobe with its surroundings as well as the variety of functions intrinsic to the temporal lobe itself.

The surgical complications most frequently encountered include hematoma and infection. The risks of craniotomy vary between institutions and should be quoted as such. In general, a risk of postoperative infection is on the order of 2–5%. Risk reduction is achieved by employing sterile technique and perioperative antibiotics. The risk of a clinically significant hematoma is on the order of 1–2% which may necessitate a need for a repeat craniotomy for hematoma evacuation. Wound complications such as dehiscence, superficial wound infections, and CSF leak all have been seen with routine craniotomies as well as with temporal lobe epilepsy surgery. Wounds should be monitored closely postoperatively and a strict wound care regimen should be followed.

In consideration of the potential neurological complications, one must recall the more rare deficits such as injury to

the anterior choroidal artery and resultant hemiplegia as well as the routinely observed contralateral upper quadrantanopsia seen postoperatively. Motor deficits postoperatively appear to be secondary to vascular injury. Risk factors for vascular disease such as increasing age, hypertension, hypercholesteromia may all be considered not only for risk to specific vessels but also in regard to the patient's overall surgical risk. The risk for a potential visual field defect is on the order of 50%. The majority of patients are unaware of this deficit, but in up to 12% of patients, a more significant and disabling defect such as a complete homonymous hemianopsia may develop. Cranial nerve palsies of the third and fourth cranial nerve can occasionally be observed postoperatively. These may be quite bothersome for the patient but usually are transient in nature.

The potential adverse effects on language and memory were discussed in detail. The temporal lobe harbors various regions associated with language function such as Wernicke's area and other regions identified with intraoperative mapping studies, and resection of the language dominant temporal lobe can result in a significant dysnomia. This appears to improve with increasing postoperative period and may resolve entirely. Older age at onset of epilepsy appears to be a risk factor which may be associated with poorer postoperative language function. Many patients demonstrate improvement in language which is likely multifactorial but may be associated with overall seizure control. The possible detriment to memory function is significant and can be severe. The ability for the contralateral hippocampal formation to independently support memory should be evaluated preoperatively and surgical resection planned accordingly. The type of memory most affected appears to be episodic memory consolidation. Patients who develop postoperative memory deficits appear to exhibit difficulty with employing strategies for recalling information attributable to the events of daily living that is not in their immediate memory banks. This type of deficit appears to be stable with time. Patients may benefit from learning various means to cope with this outcome.

Lastly, the psychological sequelae of this surgery were discussed. Temporal lobe epilepsy of its own right is associated with an increased incidence in psychiatric morbidity including mood disorders, somatic disorders, as well as psychotic disturbances. The risk of introducing a new psychiatric illness is fairly rare, but there is a clear association between development of a postoperative psychotic illness similar to schizophrenia and surgery for temporal lobe epilepsy. Neuropsychological analysis should be considered prior to surgery to ensure that the patient is enrolled in optimal treatment paradigms.

This chapter serves as a basic outline of the potential pitfalls associated with surgery for temporal lobe epilepsy. One must remember that in addressing the risks and benefits of this surgical procedure, each patient should be assessed as an individual. The percentages and data presented here serve only as guidelines. The neurosurgeon and neurologist involved will need to balance each patient with respect to individual risk for surgery, potential neurological complications, potential cognitive complications, as well as psychiatric complications. The surgical approach and the use of mapping need to be considered on an individual basis. In doing so, one can hope to provide the best hope for a good surgical outcome unfettered with complications.

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137 Neocortical focal epilepsy surgery: surgical complications

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Introduction

The main goal of the pre- and intraoperative evaluation for epilepsy surgery is to identify possible candidates in whom surgical intervention will totally or partially control seizures without increasing neurological deficits or general morbidity. The neurosurgeon is dependent on this evaluation, to identify potential candidates for epilepsy surgery, for developing a safe operative strategy, and to minimize complications. For that reason, this chapter will concentrate on the topic 'surgical complications in neocortical focal epilepsy surgery' addressing complications from diagnostic and therapeutic procedures.

In general, we can divide complications in focal neocortical epilepsy surgery based on pathophysiological mechanisms:

Surgical complications
- Infection
- Hematoma
- Brain swelling
- Hydrocephalus
- Vascular compromise (arterial or venous)

Injury to eloquent areas of the brain causing neurological impairment
- Hemiparesis
- Hemiplegia
- Visual field defect
- Aphasia
- Alexia
- Neuropsychological impairment (deficits in cognition, memory, language, attention, and concentration).

Psychosocial impairment
- Family and interpersonal relationships
- Self esteem
- Vocational/educational

Psychiatric impairment
- Depression
- Anxiety
- Psychosis

In regard to surgical procedures related to neocortical focal epilepsy, we can additionally classify complications due to focal neocortical resections in:

Diagnostic procedures
- Complications associated with subdural grid and strip electrodes, depth electrodes and stereoelectroencephalography (SEEG).

Therapeutic procedures – resective surgery
- Complications associated with frontal (mesial and lateral) resections
- Complications associated with temporal lobe resections
- Complications associated with parietal and occipital resections.

Procedural complications

Diagnostic procedures: subdural grids/strip electrodes, depths electrodes, and SEEG complications

When noninvasive studies remain nonconcordant or inconclusive regarding the localization and the extent of the seizure onset zone and/or the eloquent cortex, invasive studies using subdural grids, strips or depths electrodes may be needed.[1–3] Jayakar and colleagues proposed the following relative indications for the evaluation with invasive monitoring: normal structural imaging, extratemporal location, divergent noninvasive data, encroachment on eloquent cortex, tuberous sclerosis, and cortical dysplasia.[3] Rosenow and Lüders[4] recommended the use of invasive monitoring only in patients with focal epilepsy (single focus) in whom there is a clear hypothesis regarding the location of the epileptogenic zone (derived from noninvasive studies).

The intracranial placement of subdural grid electrodes via craniotomy has received increasing acceptance over the past decade. Invasive electroencephalogram (EEG) monitoring by subdural grid electrodes facilitates prolonged electrographic assessment as well as extraoperative functional brain mapping. Also, it is particular important in pediatric cases in which awake surgery and intraoperative functional mapping is often difficult.

The principal complications of grid electrode implantation include infection and subdural hematoma formation

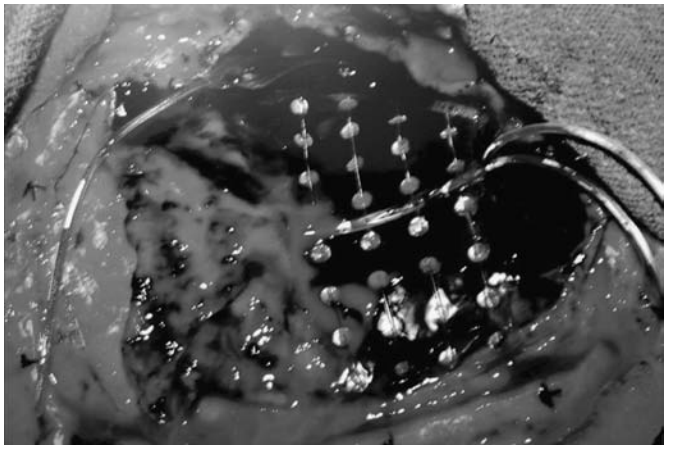

Figure 137.1 Intraoperative aspect of large subdural hematoma located underneath the subdural grid.

(Figure 137.1), which may be associated with neurological deficits, elevations of intracranial pressure, and even death.[5–7]

Other complications may include brain swelling and arterial or venous infarctions (Figure 137.2). In a recent series, of the two hundred twenty-eight cases from nine centers, the reported complications included infection, hemorrhage with transient deficit, increased preexisting hemiparesis, aseptic necrosis of the bone flap, and transient elevations in intracranial pressure.[8] In an individual series from the Cleveland Clinic, an initial infection rate of 22% declined to 7% when subcutaneous tunneling of electrode cables was instituted.[9] More recently, routine use of perioperative antibiotics and water-tight dural closure with sutures at cable exit sites has been advocated in our group.[10] Since these modifications were introduced, the infection rate has declined markedly.

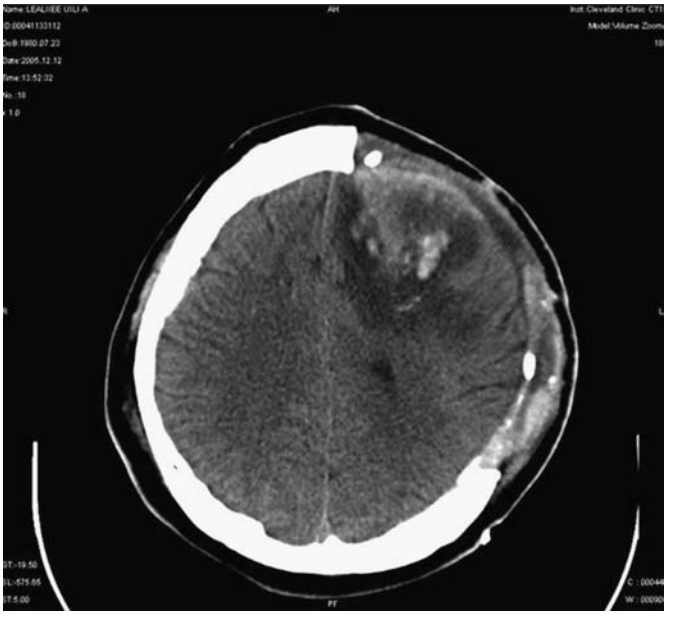

Figure 137.2 Complication of subdural grid placement: Venous infarction located in the left frontal lobe region after subdural grid placement. Postoperative CT after subdural grid removal and bone decompression.

In the absence of a multicenter, prospective complications survey, anecdotal reports of subdural hematoma formation, increased intracranial pressure (ICP), and death following grid placement have been documented in the literature.[11] Some centers recommend routine, perioperative decadron and mannitol administration over the 2–3 days after surgery, dural grafting, or leaving out the bone flap during the period of monitoring as responses to the threat of increased intracranial pressure. Circumferential dural incision, linning of the outer grid surface with hemostatic agents, and tapering of valproic acid are also recommended to reduce hematoma formation.[12] There is no data with respect to the relative value of any of these practices in preventing individual complications.

Regarding subdural strip implantation, the epilepsy surgery literature suggests that subdural strip electrode insertion may be safer than depth electrode placement.[7,13–15] No examples of significant hemorrhagic complications associated with prolonged neurological deficit or death have been reported so far. Localized infections occur at a slightly lower frequency when compared with depth recordings and usually respond to antibiotic therapy alone. In a recent series of three hundred fifty patients, two cases of meningitis, one brain abscess associated with hemiparesis, and three superficial wound infections were reported.[16] In two additional reports studying 122 patients, no hemorrhagic, neurologic, or infectious complications occurred following strip electrode placement.[17,18]

Different techniques of invasive monitoring exist and each has its advantages and disadvantages. Chronically implanted subdural electrodes allow recording from large superficial cortical areas, but they provide limited coverage of deeper structures, such as the hippocampus, the interhemispheric region or cortex within sulci. Intracerebral electrodes have the advantage of excellent sampling from mesial structures and from deep cortical areas, with the disadvantage of providing information from a limited volume of tissue. Combined use of subdural and intracerebral electrodes also has been advocated. In a recent publication, Cossu *et al.*[19] presented a retrospective study of a large series of patients (211 patients) who underwent stereoelectroencephalography (SEEG) evaluation. SEEG provided additional guidance towards epileptic focus resection in 183 patients (87%), resulting in a seizure-free outcome in 44% of the cases, and an overall significant improvement in 82%. Major complications occurred in less than 1% of the patients, with an overall hemorrhagic event risk of 4.2%. Other complications included one brain abscess, not resulting in permanent deficit, one episode of focal cortical edema, and one retained broken electrode. The authors concluded that SEEG is a useful and relatively safe tool in the presurgical evaluation of focal epilepsy.[19]

As highlighted by others, important issues relating to depth electrode placement and associated complications include: (1) the relative safety of lateral, parasagittal, and tangential methods of insertion, (2) the relative safety of flexible versus rigid electrodes, (3) the role of computer-assisted work-stations in the improvement of stereotactic accuracy and the reduction of vessel injury, and (4) the effect upon infectious complications of length of monitoring, antibiotic prophylaxis, tunneling of electrode leads, and methods of electrode removal.[19]

Resective surgery complications: temporal neocortical focal resections

In general, there are at least four different surgical approaches to treat mesial temporal lobe epilepsy. These approaches include: (a) en bloc temporal resection or standard temporal lobectomy, (b) awake temporal lobectomy with tailored resection, (c) amygdalohippocampectomy, and (d) radical hippocampectomy. Each technique represents a different approach to the identification and resection of the epileptogenic zone. Because this chapter is focused on complications in neocortical epilepsy surgery, complications related to mesial temporal lobe resections will not be discussed.

In an extensive review of the literature performed by Pilcher and Ojemann regarding complications of anterior temporal lobectomy, mortality occurred in less than 1%, mainly caused by hemorrhage, infarction, pulmonary complications and sudden death. Other complications included hemiparesis (transient or permanent) in 2–4%, minimal visual field defects in more than 50%, and severe field defects (hemianopsia) in 2–4%. Infections (meningitis, abscess), epidural hematoma, and III nerve palsy (transient) occurred in less than 2%. Neurobehavioral complications included transitory anomia (less than 1 week) in 20% of the patients, persistent dysphasia in 1–3%, and transitory psychosis/depression in 2–20%.[12]

Penfield reported a 2.5% hemiplegia in an early Montreal Neurological Institute (MNI) series. He attributed this complication to excessive manipulation of branches of the middle cerebral artery (MCA) during the trans-sylvian resection of insular cortex.[20] Alternative explanations included direct capsular injury with insular resection as well as compromise of the lenticulostriate vessels and the anterior choroidal artery.

Visual field deficits occur following temporal lobe resections in approximately 50% of operated patients. These deficits are often incongruous or worse in the ipsilateral eye, due to the anterolateral location of ipsilateral fibers overlying the anterior portion of the temporal horn (Meyer's loop). Severe visual field deficits considered disabling by patients are less frequent and were reported in 8% in our previous series.[9] Rasmussen *et al*. suggested that by limiting the extent of the superolateral ventricular opening to 1 cm, quadrantic deficits could be avoided entirely.[21–23] Other studies also suggested that the magnitude of the visual field deficit was entirely related to the extension of the ventricular opening, mainly in the ventricular roof in the temporal horn. Alternatively, direct surgical injury to the optic tract, lateral geniculate nucleus, or optic radiation in the posterior temporal lobe white matter can also cause visual field deficits.

Postoperative anomia or dysphasia is not uncommon following dominant temporal lobectomy. These aphasias are largely resolved after 1 week. Transitory dysphasias are reported in up to 30% of operated patients in the setting of awake surgery with intraoperative language mapping. Removal of the anterior temporal or inferior-basal language sites may explain this phenomenon.[12] Other explanations include resection of cortex within 1–2 cm from essential language areas, brain retraction, and disruption of white matter pathways connecting language areas.

According to Crandall and colleagues, persistent language disorders were found in three of 53 patients undergoing temporal lobe resection.[24] In another series, five of 25 patients were aphasic at the time of discharge (Katz *et al*. 1989).[25] In the MNI series, using intraoperative language mapping, two of 250 patients were reported to have long-lasting aphasia after surgery.[21–23] In both cases, aggressive resection near essential speech areas was performed. In the Seattle series, removal of brain within 1–2 cm of essential sites established by intraoperative mapping was associated with mild language deficits.[26–28]

The 'tailored operation' is designed to use language mapping techniques to identify and protect neocortical language sites. In a comparison of 'standard' versus tailored temporal lobectomies performed by a single surgeon, a slight increase in postoperative dysnomia was identified 6 months after surgery following a 'standard' operation.[29]

Therapeutic procedures: extratemporal neocortical focal resections

The extratemporal epilepsies considered for resective therapy are less frequent, more variable in their presentation, and are associated with a less favorable seizure outcome postoperatively than is the temporal lobe epilepsies. Additionally, the epileptogenic zone is more likely to involve eloquent cortex and intraoperative or extraoperative brain mapping is often necessary. All of these factors have a direct impact upon the complications of extratemporal neocortical focal resections, especially the functional consequences of adequate removal of the epileptogenic zone in eloquent cortex. In a systematic fashion, we can divide extratemporal focal resections into frontal, central, parietal and occipital resections.

Frontal resections

The frontal lobe encompasses one-third of the cerebral cortex volume, yet, despite its large size, the frequency of surgically treated frontal lobe epilepsy is small as compared to temporal lobe epilepsy. This varies between 18%[30,31] and 5.5% in larger series. This may be due to the inherent complexity, variable presentation, presence of eloquent cortex, and difficulty with EEG localization often seen with frontal lobe epilepsies.

The manifestations of frontal lobe epilepsy can be divided into three major subgroups:[32–34] Supplementary motor seizures, complex partial seizures and focal motor seizures. The localization of an ictal onset area is difficult in frontal lobe epilepsy and is facilitated when a lesion is present on imaging.[30]

Anatomically, Broca's area is located in the inferior frontal gyrus at *pars triangularis* and *pars opercularis* of the dominant frontal lobe, and this region is generally avoided when dominant frontal resections are performed under general anesthesia. The cortical representation of essential language sites may be quite variable and brain mapping techniques are often utilized to tailor frontal resections and avoid language complications. These investigations may identify zones of language cortex quite separate from Broca's area within middle,

superior, and even parasagittal frontal cortex in the region of the supplementary motor area.

Transitory aphasic syndromes are often caused when resections are carried within 1–1.5 cm of these essential language areas.[26,27] Long lasting expressive aphasia can follow resection or operative injury (vascular compromise) to language sites in the posterior inferior frontal gyrus. Any resection involving frontal cortex, but especially parasagittal cortex (superior frontal gyrus), may cause compromise of draining frontal veins with associated postoperative edema and potentially venous infarction leading to postoperative language and motor deficits.

The supplementary motor area (SMA), defined by Penfield and Welch[35] is located in the mesial superior frontal cortex of the lower extremity, superior to the cingulate gyrus. Functional studies have shown that this area is activated during initiation of movement and vocalization. Stimulation of this area leads to a fencing posture with bilateral motor movement. The SMA is extensively and somatotopically connected to the corpus callosum, resulting in fast spread of the ictal discharges to the contralateral side, making lateralization of the ictal onset zone difficult.[36] Resection of the supplementary motor area may produce a supplementary motor cortex syndrome characterized by mutism (dominant SMA cortex), and contralateral neglect with a hemiparesis characterized by diminished spontaneous movement which gradually resolves over several weeks.[37,38] On long term follow-up, gross motor deficits are rare.

The orbito-frontal area is limited laterally by the orbitofrontal sulcus, medially by the olfactory sulcus, anteriorly and superiorly by the frontomarginal sulcus, and posteriorly by the anterior perforated area. The orbito-frontal cortex is extensively connected with the anterior and mesial temporal lobe, cingulum, and opercular area and thus frequently misdiagnosed as anterior temporal seizures.[39] Adequate sampling of these structures using invasive electrodes is recommended. On the nondominant side, extensive resection of the orbitofrontal cortex can be performed without deficit. The intersection of the optic nerve and the olfactory nerve and the anterior face of the M1 segment of the middle cerebral artery are used as the posterior anatomical landmarks of the resection. On the dominant side, mapping of Broca's area should be performed.

The cognitive effects of extensive frontal resections are clinically insignificant with minimal consequences in daily life activities.[40] Furthermore, provided that a careful subpial technique is employed with preservation of the vascular supply to motor cortex, frontal excisions may be safely carried up to the pial bank of the precentral gyrus. Care must be taken, however, not to undermine the motor cortex if the resection is extended into the white matter.

Central resections (perirolandic)

Central type epilepsy or seizures arising from the primary motor and sensory area are relatively infrequently encountered in surgical series. In patients with preserved motor function, these epilepsies present considerable challenges. A more aggressive approach to the perirolandic epilepsies is gaining acceptance with improved surgical techniques such as extraoperative functional mapping of central cortex, intra-operative mapping by direct cortical stimulation, and microsurgical technique.

Resection of the face motor cortex

The partial resection of the nondominant face motor cortex may be safely performed, resulting in a transitory contralateral facial asymmetry. Complete removal may be associated with perioral weakness and dysarthria in some patients. The superior resection margin should extend no higher than 2–3 mm below the lowest elicited thumb response. In the dominant hemisphere, some surgeons report postoperative dysarthrias and dysphasias following face motor cortex excision. Nevertheless, Rasmussen *et al*. reported that complete removal of dominant face motor and sensory cortex may be safely performed provided that manipulation of underlying white matter or ascending vascular supply is avoided.[21–23] It is our experience that essential motor language sites may be found just anterior to motor tongue cortex in the inferior or even middle frontal gyrus. Certainly, mapping of these areas is mandatory to avoid a postoperative deficit after dominant frontal lobe resections involving the lower perirolandic cortex.

Resection of the hand/leg motor cortex

The resection of the primary hand motor cortex produces a permanent deficit of fine motor control and should be avoided if useful hand function is present preoperatively. Resection of the primary leg motor cortex will elicit an immediate flaccid leg paralysis followed by gradual partial recovery of ambulatory capacity over months.[21–23] Proximal limb function is likely to recover however distal ankle and foot permanent weakness are often present, requiring use of orthoses for safe ambulation.

Resection of the sensory cortex

The resections of leg or face sensory cortex cause permanent but clinically insignificant deficit of proprioception in the leg or two-point discrimination in the lower face.[41] In contrast, resection of hand sensory cortex is followed by important functional impairment, with the majority of patients showing deficits of pressure sensitivity, two-point discrimination, point localization, position sense, and tactual object recognition, which makes functional use of the involved hand difficult.[41]

Parietal resections

Seizures originating in the parietal lobe account for up to 6% of reported series but very few articles reporting complications in parietal resections are available in the literature. A large proportion of patients exhibit an aura, most commonly somatosensory.[33] Pain, vertiginous sensation, aphasia, or disturbance of body image is suggestive of parietal origin. The ictal manifestations are varied and reflect the quick spread to the frontal lobe in superior parietal epilepsies and to the temporal lobe in inferior parietal cases.[42] Interictal and ictal scalp EEG recordings were not reliable markers for parietal lobe epilepsy. In two recent series, surgery resulted in

satisfactory seizure control. Salanova *et al.* reported the MNI experience of 79 patients with nontumoral parietal lobe epilepsy. Of these, 45.5% were seizure free, 19% had rare seizures, and 21.5% had worthwhile improvement. Persistent dysphasia was noted in two patients, a Gerstmann's syndrome in one, and contralateral weakness in three cases.

Large parietal resections may be undertaken posterior to the central cortex in the nondominant hemisphere without causing a sensorimotor deficit and with a rate of hemiparesis of approximately 0.5%.[21–23] A non-dominant parietal syndrome may follow these resections in some individuals. In the dominant hemisphere, language mapping must be used to avoid postoperative language deficits. When resections are extended into the parietal operculum, contralateral lower quadrantic or, hemianopic visual field deficits (rare) may occur as resections are performed beyond the depths of the sulci into the white matter.[8,21–23]

Occipital resections

Occipital lobe seizures are rare, representing just 1% of epilepsy surgery patients in the MNI series.[33] Early clinical manifestations of elementary visual hallucinations, ictal amaurosis, eye movement sensations, and blinking are highly suggestive of an occipital origin.[42] In infra-calcarine cases, quick spread to the temporal lobe can produce symptomatology typical of mesial temporal lobe epilepsy. An imaging abnormality is found in a large proportion of cases.[42] In patients with hemianopsia, resective surgery carries minimal risk. On the dominant hemisphere, the speech related cortex should be identified and spared. The management of patients with intact vision is challenging. When a circumscribed lesion is found, lesionectomy can yield satisfactory results. In non-lesional cases, the ictal onset area should be precisely localized using invasive electrodes.[43] These are used in addition to mapping of the calcarine cortex and speech related cortex. With this strategy, visual deficts can be minimized. Resections of the dominant basal temporal lobe should be carefully planned as this can yield an alexia without agraphia deficit.[1,2]

Contralateral homonymous hemianopsia often follow resections in this area, despite careful extraoperative mapping of cortical function. If vision is intact preoperatively, calcarine cortex and optic radiations must be spared as much as possible if the occurrence of an hemianopsia is to be avoided. The use of intraoperative visual evoked potential (VEP), intraoperative direct stimulation, and radiological techniques to map the geniculocalcarine projections (diffusion tensor imaging or DTI) are still under investigation.

If adequate data from invasive monitoring is available to suggest that the superior calcarine gyrus may be spared, an inferior calcarine gyrus resection with or without an aggressive resection of mesial temporal lobe structures will result only in a superior quadrantic deficit associated with minimal disability. Excision to within 2 cm of Wernicke's area in the domimant hemisphere may elicit persistent dyslexia.[21–23] Therefore, exposure at craniotomy should be adequate to provide access to the postcentral gyrus and parieto-temporal language areas, which will serve as the anterior limits of resection.

Conclusions

A valid appreciation of the complications of epilepsy surgery is fundamental to balance the risks and benefits of diagnostic and therapeutic procedures. Unfortunately, the medical literature available on this topic does not reflect contemporary surgical practice. Available data is derived from the surgical experience of a few highly experienced surgeons working in well-established comprehensive epilepsy centers and used patient selection criteria and operative approaches which have since been modified or radically changed.

Although a prospective trial to study the risks of invasive monitoring and other surgery related complications is not feasible, more literature on contemporary outcomes and complications using modern day surgical techniques is necessary. As the number and complexity of patients referred for epilepsy surgery continue to increase, surgeons are obligated to accurately report complications occurring from surgical treatment. As this chapter has outlined, complications are quite variable depending largely on the region of the brain operated. Armed with this knowledge, the surgeon and patient can truly make informed decisions regarding the risks and rewards of cortical resections to treat medically intractable epilepsy.

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SECTION 18

Post-surgical management

138 Early post-surgical management of patients with epilepsy

I Melamed and AA Cohen-Gadol

Introduction

Post-operative management of patients who have undergone epilepsy surgery should be tailored based on the needs of each individual patient but is similar to those who have undergone other types of major craniotomies. There are certain common factors that should be considered in the early post-operative management of patients who undergo epilepsy surgery. These include prevention and control of post-operative seizures, infection, cerebral swelling, and new expanding mass lesions such as a hematoma. Thorough communication with the patient and family is especially important to decrease their anxiety and make them comfortable about the need for additional interventions and the prognosis.

The patients undergoing surgery for intractable epilepsy also form a unique subset of patients with very specific needs that should be addressed in the immediate post-operative period. One of the specific needs of major importance pertains to prevention and control of post-operative seizures. Therefore, the major portion of this chapter is dedicated to management of early post-operative seizures for patients who undergo epilepsy surgery. We will also briefly discuss the relevant post-operative psychosocial issues among this patient group.

Management of post-operative infection and hematoma

With recent advances in epileptogenic focus localization and microsurgical techniques, epilepsy surgery has become relatively safe. In the report for temporal lobe and localized neocortical resection for epilepsy, Engel and his associates summarized a total of 556 patients from seven institutions in whom the morbidity and mortality of resective procedures were addressed.[1] In this group, there were two deaths (0.4%). These were not a direct result of surgery but occurred within 1 month of surgery. Two subdural hematomas were reported but those did not lead to a permanent morbidity. There were 34 patients with new neurological deficits (6%). These included 17 mild aphasias, five 3rd or 4th cranial nerve palsies, ten visual field deficits, greater than a quadrant, and 12 instances of hemiparesis. Sixteen (3%) of these 34 patients had deficits that were transient, resolving within 3 months, while 18 (3%) had permanent deficits. There were 26 (5%) instances of infection, nine (35%) of which were wound infections.

The use of prophylactic antibiotics to prevent infection is routine and an intravenous antibiotic of choice (usually Kefzol) is continued for 24 hours after surgery. The use of glucocorticosteroids to prevent and control cerebral swelling is less routine and is tailored according to the preference of the surgeon. It is interesting to note that one of the first studies to note the use of steroids in reducing post-operative cerebral edema was conducted among patients who had undergone temporal lobe resective epilepsy surgery.[2] Most patients would benefit from gastric ulcer prophylaxis (especially if they are taking steroids), as well as deep vein thrombosis prophylaxis.

Patients who undergo an intracranial monitoring study using subdural grids, strips or depth electrodes may be at increased risk of infection. Intravenous antibiotics are most commonly continued during the course of their study until the electrodes are removed and resective surgery is conducted (antibiotics are usually continued for an additional 24 hours after the last surgery). For patients who harbor intracranial electrodes, signs of infection including persistent fever, cerebrospinal fluid drainage from the wound, and decreased level of consciousness require work-up to rule out CSF infection. If the suspicion for infection is high, removal of electrodes urgently is indicated.

Expanding hematomas may form around or underneath subdural grids or strips causing mass effect and an altered neurological status. Is this case, a head computed tomography (CT) imaging may assist with the diagnosis; however, the artifact caused by the electrodes on this form of study may interfere with an adequate visualization of the hematoma. If mass effect and distortion of ventricles/midline structures is noted and is responsible for the neurological decline, emergent evacuation of hematoma is indicated.

If the patient has signs of CSF space infection more than a week post-operative ly, a head CT with contrast to rule out cerebritis (early cerebral abscess) or subdural empyema is reasonable. In addition, a lumbar puncture will exclude post-operative meningitis. An acutely decreased level of consciousness will certainly make the performance of the work-up more emergent.

Management of acute post-operative seizures

Acute post-operative seizures (APOS) (those occurring within 7–10 days of surgery) occur in 20–28% of patients who undergo epilepsy surgery.[3–5] Up to 12.6% of patients who undergo a

craniotomy may suffer from an APOS despite not having any seizures before surgery.[6] The APOS are defined as 'early' if the seizures were present in the first 24 post-operative hours or 'late' if the seizures occurred between post-operative days 2–7. Others have called acute post-operative seizures as 'neighborhood' seizures within one month post-surgery (Commission on Neurosurgery of the International League against Epilepsy, 2001).[7]

Possible etiologies for APOS include: subtherapeutic drug levels, fevers, metabolic disturbances such as acidosis or hyponatremia and/or residual unresected epileptogenic focus.[5] Such seizures can also signify the presence of a post-operative complication such as hemorrhage or infection. The seizure itself should be treated and a search for reversible etiologies such as those listed above should be initiated.

In the absence of any underlying acute structural and metabolic post-operative etiologies that is remediable, acute post-operative habitual seizures (same seizure semiology as the pre-operative period) can be distressing psychologically to the patient, family and surgeon and therefore an understanding of their prognostic influence on long-term seizure control is of great importance. Several studies have shown that patients with seizures within the first week after surgery have a greater likelihood of suffering from recurrent seizures.[4,8–10] However, others state that APOSs have no significant bearing on the overall outcome from seizure surgery.[11,12]

Malla and co-workers,[4] in their paper on acute post-operative seizures following anterior temporal lobectomy, suggested that only patients who had APOS similar to their pre-operative habitual seizures were less likely to have an excellent outcome than patients without APOS. In this study, 160 consecutive patients who underwent an anterior temporal lobectomy and amygadalohippocampectomy at the Mayo Clinic (Rochester, MN) for nonlesional temporal lobe epilepsy were included. The patients were divided into groups based on the type of seizure they experienced, presence of risk factors, and whether the seizure occurred early (within 24 hours) or later (day 2–7) in the post-operative course. Thirty-two patients developed APOS. Five of these patients had identifiable risk factors for APOS such as subtherapeutic drug levels or infection. During the last follow up visit 20/32 (62.5%) patients had excellent results (they were seizure free or had experienced one seizure after the discontinuation of medication), while 96/128 (75%) of the patients without APOS had excellent results. Seven of the patients with early APOS had habitual seizures. Of those seven, only one (14.3%) had excellent outcome at the last follow-up. Interestingly there were no statistically significant differences in outcome between early and late APOS, or between patients with and patients without precipitating factors identified for their APOS. Therefore recurrent habitual seizures during the acute post-operative period may indicate that the epileptogenic focus has not been adequately resected. Such information may be used for patient counseling. On the other hand, patients suffering from APOS which are not the same as their habitual pre-operative seizures should therefore be reassured of a good long-term chance of seizure freedom.

In the pediatric population,[5] another study of patients 18 years or younger who underwent epilepsy surgery documented a 63–78% lower chance of seizure freedom among patients who suffered from APOS as opposed to those who did not. In this study, a multivariate analysis showed that APOS was an independent predictor of a less-favorable outcome. Nevertheless, 51% of the patients with APOS were seizure free at the last follow-up. In this study, subtherapeutic drug levels were not a significant risk factor for the occurrence of APOS, however; fever was a 'key post-operative risk factor', defined as two consecutive readings (taken every 4 hours apart) if >38 degrees. A history of febrile seizures was not associated with an increased chance of APOS.

In another study of pediatric patients at UCLA who underwent hemispherectomy, Mathern[3] found that the incidence of five or more acute post-operative seizures predicted longer seizure duration before surgery, longer hospital course, later oral food intake, more frequent lumbar punctures, worse overall seizure control at 0.5 and one year after surgery, more antiepileptic drug use at 2 and 5 years after surgery, and higher reoperation rate. The authors in this study did not find any difference between the patients with 0 and 1–5 APOS. The timing of the APOS did not predict outcome. The cause of recurrent post-operative seizures in these patients may have been the capability of the opposite intact hemisphere to generate seizures that were not appreciated before surgery.

The relationship of APOS and long-term seizure outcome may also be dependent upon the epilepsy syndrome and resection location. The incidence of APOS may be slightly higher among adult extratemporal resections (average 42%; range 26–46%) as compared with pediatric and adult temporal lobe epilepsy patients (average 30%, range 17–49%.) For the patients who have undergone extratemporal resections, the importance of APOS in predicting long-term seizure freedom is less clear. A study reported that APOS among patients who have undergone frontal lobe resection has no prognostic significance [13] while others have found less favorable seizure outcome among patients who have undergone extratemporal resection and have suffered from APOS.[5,8]

Lüders[8] found that seizure recurrence was significantly higher when seizures occurred during the first week after surgery. Although seizure recurrence increased progressively with longer follow-ups, the 6-month post-operative seizure outcome was an excellent predictor of long-term outcome. Lüders therefore recommended that, seizure frequency should be reported at fixed follow-up periods, e.g., at 6 months and 1, 2, 5, and 10 years. This reporting strategy will allow comparison of outcomes between different studies.[9]

Others have suggested that early APOS (within 24 hours of surgery) may be less important in long-term prognostication of seizure outcome. This is the time when the effect of anesthesia and surgical manipulation on cerebral physiology is greatest, increasing the risk of a seizure.[14] In general, the occurrence of APOS should be interpreted cautiously and individually for each patient. Although the presence of seizures post-operatively may signify a lower chance of long-term seizure freedom, one must remember that a significant majority of these patients do become seizure free.

Several limitations are present in the majority of the studies which have studied the importance of APOS. Video-EEG monitoring is not routinely performed subsequent to surgery.

The care takers who report the ictal behavior may not be qualified for such purpose. Often, the family member may observe an APOS and may not be able to adequately identify the post-operative seizure semiology.

Post-operative management of antiepileptic drugs

The effects of anesthesia, stress of surgery as well as missing doses of medications have been known to cause varying changes in the blood levels of antiepileptic drugs (AEDs) in patients who have recently undergone epilepsy surgery. This phenomenon exposes the post-operative patient to an increased risk of a seizure. The seizure may cause uncontrollable spikes in blood pressure, causing intracerebral hemorrhage in the resection bed during the early post-operative period as well as prevent rapid patient's post-operative recovery and mobilization. Therefore, prevention of post-operative seizures is of special importance.

Effstorm, Friel and their associates have demonstrated a reduction in drug levels following surgery among the patients on stable doses of medications.[15,16] Friel *et al.* followed drug levels of 12 patients treated with phenytoin, carbamazepine and valproate. In the six patients on phenytoin and the six on carbamazepine, there was a significant reduction in serum levels at 48 hours post-operatively compared to those immediately pre-operatively.[16] However, in the five patients treated with valproate there was no significant change. In another study, the toxic levels of carbamazepine observed after surgery for subdural grid placement may suggest that the metabolism of carbamazepine can actually become slower following surgery.[17] It is thus recommended that the levels of AED medications be followed closely during the first 48 hrs after surgery to avoid sub- and/or supratherapeutic drug levels which in turn can lead to post-operative seizures or toxic reactions, respectively.

AEDs should not be tapered during the immediate post-operative period despite a lack of seizures. The time-line for tapering or discontinuing AEDs after successful surgery is not clear. The patients who undergo epilepsy surgery typically require fewer AEDs than those who did not have surgery.[18] Schiller *et al.*[19] retrospectively studied 210 patients after temporal and extratemporal resections for epilepsy at the Mayo Clinic (Rochester, MN). In this group of patients, the medications were tapered sequentially with a varied taper typically lasting 6–25 months. The medications were altered in 180 of the 210 patients. AEDs were tapered and discontinued in 84 (40%) and reduced in 96 (46%). Discontinuation of the AED treatment was associated with recurrent seizures in 22 of the 84 patients. Reinstitution of the AED treatment resulted in seizure control in 20 of the 22 patients. The remaining two patients developed medically refractory epilepsy despite AED therapy. Thirteen of 96 (14%) who reduced the number or dose of AED medications had recurrent seizures. In trying to define the patients who would be at an increased risk of seizure recurrence after medication adjustment, these authors investigated numerous factors. Patients with a normal pre-operative MRI study showed a tendency for higher seizure recurrence. Nevertheless, this difference did not reach statistical significance. No difference was observed in seizure relapse between patients with and without epileptic spikes in the post-operative EEG studies. Furthermore, reviewing the length of medical therapy after surgery, the authors could not find any correlation between the duration of seizure-free post-operative AED treatment and seizure recurrence after AED withdrawal. Thus, this study could not find a way to predict who would have recurrent seizures after AED adjustments. It would seem wise to wait at least 6 months in order to allow the patient to recover from surgery and assure successful surgical outcome before discussing tapering medications.

Post-operative psychosocial issues

Epilepsy has had a long historical association with psychiatric and behavioral disturbances. It has been estimated that about 20% of temporal lobe epilepsy patients have depression. Wrench *et al.* studied the effects of seizure surgery on mood disturbances.[20] This study included 43 patients who underwent temporal resections, and 17 patients who underwent extratemporal resections. Prior to surgery, each patient was seen by a psychiatrist, while after surgery each patient was screened by the treating clinical neuropsychologist and referred for psychiatric assessment where indicated. Before surgery 57% of the patients had previous psychiatric history to include depression, anxiety, postictal psychosis, personality disorder, anorexia nervosa, dysthymia, substance dependence, and delusional disorder. At discharge from the hospital, 32% of the patients were experiencing psychiatric difficulties. At one month, reports of psychiatric difficulties increased to 52% among patients who underwent temporal resections, significantly greater than extratemporal patients. No association was found between the outcome of the surgery and general psychopathology, depression or anxiety. Other studies have also documented that temporal lobectomy patients have a tendency to develop symptoms of mood disturbance within six weeks of their post-operative period.[21,22] The patients who are at a higher risk for such disturbances might benefit from pre- and post-operative counseling.

Conclusions

Acute or early post-operative seizures can be emotionally devastating to the patients and their families due to the possible negative impact of these acute seizures on long-term seizure outcome following epilepsy surgery. The precise impact of acute post-operative seizures on the long-term outcome of epilepsy surgery has remained controversial. The available studies have predicted a negative or no impact on final outcome of surgery in patients who suffer from acute post-operative seizures compared to those who remain seizure free early in the post-operative period. The appropriate post-operative care can help in the management of these patients and assist them on their way to recovery from this epilepsy disorder.

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139 Post-surgical pharmacotherapy: discontinuation of anticonvulsants

AS Tanner and D Schmidt

Introduction

Resective surgery for epilepsy is currently offered to a wide variety of patients with different kinds of focal medically refractory epilepsy in centers around the world. Specifically, temporal lobectomy is now well established as effective in patients with intractable temporal lobe epilepsy.[1] The body of literature on resective epilepsy surgery, heavily concentrated on temporal resections on adult patients, has shown a wide range of seizure-freedom rates for all procedures, (33–90%)[2] with the highest rates after anterior temporal lobectomy for medial temporal lobe epilepsy.[1] While several series reported in the literature have included small numbers of patients and have used different follow up periods, methodologies and study designs[2] most of them agree on the long-term benefit of temporal lobectomy for the treatment of refractory epilepsy. Reported figures show rates of seizure freedom that range between 53–80% during the first year postoperatively, 53–58% at year two, and 52–55% at year five.[2]

For patients that have undergone neocortical resections this figure is shown to be somewhat lower than for temporal resections, and around 50% at two years.[3] For children, studies report that around 70% of pediatric patients with temporal lobe epilepsy[4] and 54–82% of patients with pathologies such as Rasmussen's encephalitis, hemiplegia, or Sturge-Weber are seizure free after surgery[5]. Many patients (anywhere between 10% and 60%), however, relapse after epilepsy surgery and evidence shows that most of these relapses occur early after surgery (within the first two years)[6,7] although later recurrences have been reported.[7,8] Some of the factors cited as predictors for relapse include longer preoperative illness, normal pathology[8] and the presence of secondarily generalized seizures before surgery.[7] A factor that has only recently been explored is the role that antiepileptic drugs (AEDs) play after epilepsy surgery especially in relationship to the risk of relapse.[9] This is an extremely important and relevant variable not only because of obvious importance when counseling patients and planning therapeutic decisions after surgery, but because of the expectation from patients that freedom from drugs follows surgery.[10] The literature on these topics is unfortunately not as abundant as in other areas of epilepsy surgery. Reasons for this may include the inherent difficulties in assessing outcomes after discontinuation AEDs, in designing adequate clinical trials that address this particular issue and the lack of universal guidelines. We will review the relevant literature in this chapter.

Discontinuation of AEDs: relevant literature

Most of the literature in AED discontinuation after resective surgery again relates to temporal lobe epilepsy.[1,2,6,7,11–16] Few papers address this issue on neocortical, extratemporal and all types of resections in children.[3–5,17–24] Schiller and his colleagues[21] reported in 2000 a series of 210 patients that underwent either a taper or discontinuation of AEDs after epilepsy surgery. The majority of these patients were adults, and most of them underwent temporal lobe resections. After 1 year of seizure freedom (including patients with isolated auras), patients were divided into a group that reduced but not withdrew AEDs, and a group that tapered and discontinued AEDs; they were compared to a 'control group' of patients that were seizure free after surgery and did not alter their medication regimen. Their retrospective study revealed seizure recurrence in 14% and 36% of patients by the end of 2 and 5 years respectively after complete AED withdrawal, and recurrence of 9% and 14% of patients who partially reduced AED treatment by the end of 2 and 5 years. (Table 139.1) There were no statistical differences on the clinical features between the groups that partially discontinued AEDs with the control group. Reinstitution of AEDs resulted in seizure control in 91% of patient who relapse after complete AED withdrawal. Among the variables that they studied abnormal preoperative MRI carried a higher tendency for seizure recurrence. They did find that seizure recurrence was unrelated to the duration of the seizure-free post-operative AED treatment.

In a recent publication, Kim[13] and his colleagues reported on a series of patients that underwent AED discontinuation. They included patients of all ages and a majority undergoing temporal lobectomy for hippocampal sclerosis. Altogether, 33% of patients who attempted AED tapering experienced seizure relapse in the course of discontinuation. The seizure recurrence rate was not different in patients that had become seizure free immediately after surgery than on those who became seizure free sometime after surgery. The majority of patients (70%) regained seizure freedom after reinstitution of AEDs.

Schmidt *et al.*[22] analyzed six retrospective series of patients undergoing planned AED discontinuation under medical supervision. Their review showed an average relapse rate of 34% for all surgeries, most often temporal lobe resections with recurrence rates increasing with the length of follow-up.

Table 139.1 Discontinuation of antiepileptic drugs: relevant literature

Study (Reference number)	Number of patients age/ gender	Procedures included	Design	Follow-up	Proportion of surgical patients seizure free after discontinuation of AEDs
Schiller *et al.*[21]	*N* = 210 Age mean: 31.9; range: 9–55. 107 f; 103 m	Temporal lobe resections: 89.5% Extratemporal resection: 10.5%	Retrospective	Mean: 5.1±0.3 range: 3–8 Years	57/84 (67%) after complete discontinuation; 83/96 (86%) after partially reducing AEDs
Kim *et al.*[13]	*N* = 88 Age mean: 27.3; range: 11–41 49 f; 39 m	Temporal lobectomy: 100%	Retrospective	Mean: 77.4 months range: 36–144	37/66 (56%)
Wieser *et al.*[15]	*N* = 376 Age mean: 32±11 166 f; 210 m	Temporal lobe resections: 100% (selective amygdalohippocampectomies)	Retrospective	Median: 7.5±05.7 Range: 1–25	92/111 (82.9%)
Berg *et* al.[25]	*N* = 129 Age median: 36 years	Temporal lobe: neocortical and medial temporal	Prospective	Not stated	88/129 (68%)
Lachhwani *et al.*[18]	*N* = 97 Age mean: 11 Range: 3 months –18 years	Temporal and extra-temporal resections	Retrospective	Median: 37 Range: 1–134 months	57/68 (84%)

Interestingly, among all patients analyzed, only 48% of seizure-free adult patients discontinued AEDs, whereas 71% of seizure-free children did so. Their findings suggested that there was no benefit in waiting to attempt AED tapering (1 year in children and 2 in adults), and that the occurrence of rare seizures or auras did not preclude successful AED discontinuation. In accordance with other studies and observations, more then 90% of adult patients with seizure recurrence regained seizure control after reinstitution of AEDs. This study failed to find a strong association between relapse after AED withdrawal and factors such as age of onset of epilepsy, duration of epilepsy and preoperative MRI findings.

Wieser and Häne[15,16] reported retrospectively on patients that had undergone amygdalohippocampectomy. In their study the overall risk of relapse associated with AED tapering and withdrawal was 17%; they concluded that in this population monotherapy was an adequate option, and therefore AED reduction to monotherapy could be advisable as early as 1 year postoperatively with discontinuation at year two. In a recent report, Berg and her colleagues from the Multicenter Study of Epilepsy Surgery[25] analyzed the impact of reducing AEDs in subjects who attained a 1-year seizure remission after surgery. The authors found that 41 of 129 patients (32%) relapsed after reducing AEDs. No difference was found between reducing from two to one AED or from one to no AEDs. Delayed remission after surgery was significantly associated with an increase rate of relapse, while continued auras were marginally associated with relapse. Of note, in the series of patients reported by Berg, 45% of patients (73 of 162) in the nonreduction arm also recurred. Overall, 39% of all patients who attained seizure freedom for one year recurred (114 of 301).

The literature addressing AED discontinuation after epilepsy surgery in children is scarce. As indicated earlier, anywhere between 50% and 80% of pediatric patients become seizure-free after surgery for temporal lobe epilepsy, seizures associated with infantile hemiplegia or seizures accompanying tumors.[4,5]

The report by Lachhwani[18] (included in the analysis by Schmidt cited earlier) showed that 16% of patients that underwent AED discontinuation had seizure recurrences. No significant differences were found based on etiology. The majority of these patients regained seizure control after the AEDs were reinstituted.

One related question that patients and physicians have is the long-term seizure prognosis following epilepsy surgery in patients off AEDs.

Long-term surgical seizure outcome off AEDs: relevant literature

Although surgery is often seen as a curative treatment for patients with drug-resistant temporal lobe epilepsy, little information is available regarding how many cases are seizure free for at least five years without taking AEDs. This question was reviewed by Schmidt *et al.*[26] The review included 13 retrospective and five prospective clinical observations published since 1980 provided data on long-term seizure control off AEDs in a total of 1658 patients (Table 139.2). No randomized studies were found. Following temporal lobe surgery, approximately one in four adult patients and approximately one in three children or adolescents were shown to be seizurefree for 5 years without AEDs (25%, mean of eight studies in adults, 95% CI: 21–30%, and 31%, mean of three studies in children, 95% CI: 20–41%). The rate of seizure control off AEDs seemed to be stable after 2 years of follow-up. However, as 55% of patients free of disabling seizures preferred not to discontinue their medication completely as late as 5 years after surgery, it is impossible to know if more patients could have been seizure free, if all had discontinued their medication. No features predictive of surgical cure were detected except for better outcome in children versus adults with hippocampal sclerosis and in patients with typical versus atypical Ammonshorn's sclerosis or tumor in one small study each. In conclusion, the available evidence on seizure outcome off AEDs after temporal lobe surgery is based on nonrandomized studies and, in part, data were collected retrospectively.[11,15,19,26–41] In a single–center study of long-term seizure outcome off AEDs following temporal lobe surgery, which appeared after completion of the above review, Kelley and Theodore[42] reported a similar result. In their analysis one in three patients were seizure free of AEDs when reexamined 10–30 years after surgery.

Discussion

The importance of the quality, quantity and length of AED treatment in patients that have undergone epilepsy surgery goes beyond the pure consideration of seizure freedom versus seizure recurrence: AEDs influence quality of life because of side effects, interactions with other drugs, issues related to contraception, pregnancy, lactation, menopause, bone health as well as financial issues.[43–46] Therefore, understanding their role after epilepsy surgery is vital when treating and counseling these patients for more than one reason.

The current relevant literature suggests that a significant minority of patients (about a third of adults, perhaps a lower percentage in children) will have seizure recurrence upon AED discontinuation after resective surgery for epilepsy. In addition, based on long-term studies, one in three patients can expect to be free of seizures without taking AEDs anymore. Because the goal of many patients considered for epilepsy surgery is to be free of medications, this literature becomes an important tool for discussing this issue after surgery. Fortunately, the literature shows that the vast majority of these patients will regain seizure control once AEDs are restarted, with only a small minority of up to 10% going on to have intractable or recurrent seizures.

Many important issues, however, remain unanswered. Most of the relevant papers addressing AED discontinuation have included in their analysis both patients undergoing temporal and extratemporal resections, and in some cases children and adults alike. This 'lumping' of cases does not allow us to make specific determinations for these different groups, and it can, as a matter of fact, confound the results. Are patients with nonlesional MRIs and neocortical resections at higher risk of recurrence than are patients with lesional cortical epilepsies? Are patients with classical mesial temporal epilepsy at a different risk? If we control for other variables, do all groups have the same risk? Future research has to address this issue in different cohorts of patients. Another point that ought to be considered is whether or not there was bias in

Table 139.2 Long-term surgical seizure outcome off antiepileptic drugs: relevant literature

Study (Reference number)	Number of patients age/gender	Procedures included	Design	Follow up
Adams *et al.*[27]	*N* = 44 Age median: 12.7, range: 2.5–15.8	Anterior temporal lobectomy	Retrospective	
Bien *et al.*[11]	*N* = 148 Age mean: 31.5; range 8.8–63	Temporal lobe resections: anterior temporal lobectomy and amygdalohippocampectomy	Prospective	4.8 years (mean)
Derry *et al.*[28]	*N* = 30 18f; 12m	Temporal lobectomy	Prospective	8.5 years
Elwes *et al.*[29]	*N* = 101 Age median: 23; range 3–53 48f; 54m	Anterior temporal lobectomy	Retrospective	61 months
Gilliam *et al.*[30]	*N* = 196 Age mean:33. 110f; 86m	Anterior temporal lobectomy	Cross-sectional	n/a
Li *et al.*[32]	*N* = 23 Age mean: 29.7	Anterior temporal lobectomy	Prospective	
King *et al.*[31]	*N* = 23 Age mean: 31.5	Anterior temporal lobectomy	Retrospective	1 year
Maher *et al.*[33]	*N* = 93 Age mean: 32 48f; 45m	Temporal lobe resections	Retrospective	2 years
Mathern *et al.*[19]	*N* = 198 (TLE=31) 87f; 111m	Hemispherectomy; lobar and multilobar resections, temporal lobe resections	Retrospective	2 years
McLachlan *et al.*[34]	*N* = 51 Age mean: 31.9 27f; 24m	Anterior temporal lobectomy	Prospective	2 years
Mizrahi *et al.*[35]	*N* = 22 Age mean: 21 11f; 11m	Anterior temporal lobectomy	Retrospective	
So *et al.*[37]	*N* = 184 Age median: 31; range:7–86 years 100f; 84m	Anterior temporal lobectomy	Retrospective	3.4 years (median) Range: 1.1–5.7
Sperling *et al.*[38]	*N* = 89 Age mean: 31.9, range 10–60 years 44f; 45m	Anterior temporal lobectomy	Prospective	5 years
Wieser *et al.*[15]	*N* = 376 Age mean: 32 165f; 211m	Amygdalohippocampectomy	Retrospective	5 years
Williamson *et al.*[40]	*N* = 67 Age and gender n/a	Temporal lobe resections	Retrospective	5.7 years (mean) Range 2–14 years
Oxbury *et al.*[36]	*N* = 50 Age: children group median 14 (8–15), adult group: 22 (16–36) Gender: n/a	Temporal lobe resections	Retrospective	5 years
Velasco *et al.*[39]	*N* = 22 Age mean: 32, range: 15–48 11f; 11m	Anterior temporal lobectomy	Prospective	2 years
York *et al.*[41]	*N* = 145 Age mean:27.9, range: 7–57 82f, 63m	Anterior temporal lobectomy	Retrospective	1 year

selecting the patients that have undergone AED tapering or withdrawal. Were the 'high-risk' patients excluded? Are the risks of recurrence actually higher? Only prospective, carefully designed trials will answer this question as well as issues such as the identification of other predictors of seizure recurrence and of patients 'pre-determined' to recur after surgery regardless of AEDs.

One further consideration is whether different techniques of tapering have confounded the results. Does reduction carry a different risk than discontinuation? A constant among most studies is the lack of unified way to taper and discontinue: the majority will cite that tapering and discontinuing was done at the direction of the treating neurologist. What is the best way to taper? Does this influence recurrence? Again adequately designed trial may answer this. Although some investigators have suggested timelines for tapering, an issue that remains inconclusive is how long AEDs should be kept after surgery.

In conclusion, we now know that a subset of patients initially seizure free after surgery will relapse after AED taper and/or discontinuation, and that upon reinstitution most of them will regain control of their seizures again. However, numerous other issues are yet to be elucidated and future research should focus on addressing this vital information.

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140 Post-surgical rehabilitation

R Thorbecke and B Hötger

Why rehabilitation in the context of epilepsy surgery?

For the majority of patients undergoing epilepsy surgery this intervention effects a dramatic change in the course of their illness, i.e., they reach ultimate freedom of seizures. It seems that patients anticipate this and generate expectations respectively aims going beyond the aim of mere seizure relief – e.g., they plan to get a driving license or to begin a new professional career, etc.[1,2]

From the early times of epilepsy surgery in the 1950s until today (also on the professional side) the goal of epilepsy surgery has not only been to stop seizures but in consequence to improve the patient's wellbeing, functioning and their social situation especially with respect to employment and independent life.[3,4]

However, from the first reports on social outcome until today it is obvious that not all patients gain from the procedure as might be expected from the excellent prognosis after surgical intervention. There may be barriers to the attainment of the preoperatively defined goals – e.g., neuropsychological deficits[5,6] or psychiatric disturbances already existing before surgery, or a low potential to discard a sick role with low expectations held over many years.[7–9] There might also be barriers in the patient's environment not perceiving the new possibilities for growth and for taking over more demanding roles.[10]

Rehabilitation in the context of epilepsy surgery means supporting the patient to attain their goals when they decide to have surgical treatment. This may be psychological support for adaptation to a new situation with new and more expectations than during the years before surgery. It may also include social work, counselling to improve one's employment situation. It must however be kept in mind that the expectations connected to the surgery might be unrealistic in relation to the patient's capabilities or formulated not concrete enough to work at their realization.[1] Here rehabilitation means to shape expectations into a more realistic form with the patient – in the best already before surgery.

Plan of this chapter

In the first part the patient's aims tied to surgical interventions are depicted. In the second part the knowledge on outcome of surgical interventions in relation to these aims is reported, discussing at the same time relevant prognostic factors. In respect to rehabilitation, it is important to understand that postoperative seizure status is not the only, and not always the most, important prognostic factor for social outcome. Rather we have to account for the patient's cognitive and behavioral resources to adopt new roles. The Bethel Epilepsy surgery programme has existed for more than 15 years now and, from the beginning, there was a focus on social outcome, its determinants, and how to optimize it. Therefore a section with the Bethel experiences from 1990 – 2004 will be included. In the third part, finally, practical advices for rehabilitation interventions in epilepsy surgery patients stemming from the literature and from the experiences in the Bethel epilepsy surgery program will be reported.

Aims/expectations of patients associated with epilepsy surgery

Several studies have preoperatively investigated expectations with respect to the postoperative psychosocial situation. Baxendale *et al.* asked patients to rate themselves with a self-concept scale, first in a general way and second under the presupposition that the proposed surgery would be successful in eliminating their seizures. It appeared that the patients were expecting to be happier, more in control, and more hopeful, independent and interested in life.[11] Thorbecke, in a similar way asked for expected changes in several social domains. The greatest expectations were present for elimination of seizures followed by improved mobility, employment opportunities, sports, leisure time activities, and more social contacts, and the hope to find a partner. In fact the perception of difficulties in any social domain correlated consistently and highly with the strength of the expectation of change after surgery.[12] Wheelock *et al.* asked patients and significant others for expected life changes following epilepsy surgery. Having more friends, being less dependent on others, others worrying less about the patient, improved marital/family relationships, ability to drive, ability to work, and ability to do more things independently were mentioned most often.[13,14] Taylor *et al.* asked 69 patients who already had decided to get surgery, and who were able to depict their postoperative aims with respect to their cognitive and psychiatric status. The mean number of statements was three (range 1–5). Improved work situation, driving, independence, socializing, relief from taking medication/relief of side effects were the five most often-mentioned aims. Surprisingly there was little expressed interest in improving cognitive functioning.[2]

An interesting question addressed in these studies is what type of expectations have the best chances to be fulfilled. From Wheelock's study comes the finding that those patients whose expectations were fulfilled, postoperatively were more satisfied, and this was associated with better psychosocial functioning.[13,14] Wilson *et al.* asked the patients preoperatively about their expectations in respect to surgery and postoperatively to rate

the success. 'The successful subgroup primarily reported expectations that led to a practical or clearly identifiable result, such as seizure ablation, driving, employment and the initiation of new activities'. In contrast, the unsuccessful subgroup reported less practical expectations (difference for expectations to become employed < 0.05) but more expectations of psychosocial nature and the expectation that the operation would generally enhance their QOL.[1] In Wheelock's and Thorbecke's studies it was the opportunity to do these practical things now which was delineated as postoperative changes.

In all three studies[1,12–14] no differences with age or gender are reported and in all three studies persons who had not become completely seizure free reported less changes. Wheelock *et al.*, and in a similar way Wilson *et al.*, showed that the expectations of those whose seizures were not completely eliminated but improved were only slightly or moderately fulfilled. It is evident that these findings should have practical consequences for pre- and postoperative counselling especially for a better adaptation of those improved but not completely seizure free. An interesting comment in this context comes from Wheelock *et al.* when they compare preoperative evaluation of risks with the behaviour in a game of chance: '… on hearing from their physicians that they have a 70–75% chance of becoming seizure free, patients may automatically place themselves in the positive outcome category rather than acknowledge that they may be among the patients who continue to experience seizures.'[14]

Factors determining social prognosis

Outcome might be very different for different social domains, and different outcomes might be affected by different factors, e.g., seizures having stopped might influence the capability to drive or the possibilities to do certain types of sports in a very direct way, whereas living independently or starting a new career might be much more determined by age, cognitive abilities, and social skills than by mere seizure status.

Overview from the literature

Employment

The majority of studies in the early years of epilepsy surgery between 1960 and 1980 showed dramatic improvements in employment rates after epilepsy surgery.[3,15,16] Up to the eighties such effects were less obvious[17,18] or there were no effects at all.[19–21] In the US multicenter study of epilepsy surgery in a cohort of 396 patients followed for at least 2 years after surgery, there was only a not significant increase of employment from 45–52%.[22] A somewhat different picture evolves in studies using a control group. A Norwegian study demonstrated that persons who are employed at the time of surgery stay longer in the work force than controls,[10] and in a study from the U.S. the rate of persons in full time employment was significantly higher in the surgery group compared with a medical management group.[23] Nevertheless in the surgery group there remained 31% without full-time employment.

In the early studies it seemed clear that improved seizure status was predictive for improved employment situation.[2,16] However, in the more recent studies there is not such a clear picture and it seems that additional factors must be accounted for. In a study by Jones *et al.*, the employment rate of those having become seizure free was higher than for persons who were not seizure free, the difference, however, did not reach significance.[23] Lendt and colleagues found four factors relevant for postoperative employment – preoperative employment, low age at surgery, improvement in general neuropsychological functioning especially attention, and good seizure outcome.[18] Reeves *et al.* observed that being a student or working full time within a year before surgery, driving after surgery, and obtaining further education after surgery were associated with full-time work postoperatively.[20]

These results are not as favourable as expected in view of a patient group in which about 70% of the patients have become seizure free at the time of follow-up. So it is not surprising that the need of rehabilitation efforts, especially in the vocational domain, is underlined in the more recent studies. 'Vocational rehabilitation efforts should be enhanced and should include those who were working prior to surgery but unemployed at follow-up.'[27] To make progress in this direction, however, would need a careful analysis of barriers to gainful employment in the patient such as already preoperatively existing cognitive deficits and psychiatric disturbances as well as barriers in the environment, e.g., when the patient's enlarged work abilities after surgery are not perceived.[10]

Independent living

To live more independently is one aim expressed by patients in all studies addressing aims/expectations (see above). Also, professionals are interested in the effects of epilepsy surgery on independent living for economical reasons. There is, however, a dearth of data allowing some conclusion in this direction. In older studies highly significant gains with respect to independent living were reported.[24] There were, however, no control groups. A study from Norway showed a strong decrease in the need to be looked after in the surgically-treated patients at the end of the mean follow-up interval of 17 years. In the control group however the same course could be observed although seizure frequency at follow up was significantly higher.[10] Thus the decrease in supervision reflected rather a general attitude change towards independent living of persons with disabilities or the subjects simply growing older than true changes resulting from surgery. There are also difficulties in finding a definition of independent living which is independent from cultural norms.[25–27]

> In the controlled study of Jones *et al.* independent living was defined as not requiring assistance in any of three activities of daily living (e.g., organizing and taking medications, keeping appointments, and showering) and as living alone, with a roommate(s), or with significant other(s) (not living with parents or living in an assisted-living arrangement). The proportions living independently were, for the surgery group pre 53%, post 85%, for the control group pre 39%, post 48% ($p < 0.001$). Possible prognostic factors were not evaluated.[23]

The Bethel experiences are reported below. For rehabilitation purposes some general findings on independent living in PWE might be helpful (delineated in Thorbecke's review 2001):[26,27] epilepsy might only be of importance if there are frequent and severe (grand mal) seizures. Decisive factors seem to be additional disabilities, e.g., physical limitations like hemiparesis and cognitive deficits.

Driving

Reeves *et al.* reported that in their series 79% of 112 patients were driving postsurgically which is in good accord with 80% having an excellent seizure outcome. In this study driving after surgery was one important predictor for full-time work at follow-up.[20] In the study of Jones *et al.* 67% of the patients were driving 5 years after surgery in contrast to only 22% of the controls ($p<0.001$), freedom of seizures being a significant predictor.[23]

Although to overcome driving restrictions is one of the most important aims of patients deciding to undergo surgery, there may be complications which prevent them postoperatively from driving. In a study on effects of visual field defects and epilepsy control seven out of 13 patients were seizure free and also seven out of 13 had visual fields that would allow them to drive. However only five met both criteria, significantly altering the percentage of patients who were actually eligible to drive.[28] The authors concluded that the probability of driving should be discussed at length prior to any temporal lobe surgery (see also).[29]

At least in countries were a formal examination is necessary to get a driving license it might be that already preoperative or postoperative cognitive deficits may hinder the patient to pass it successfully. This should be discussed with patients at risk prior to surgery.

Family relationships, social contacts and significant others

There is only little information on this domain. Mihara *et al.* asked patients and families to rate satisfaction with different social domains pre- and postoperatively independently from each other and then computed change scores. The assessments of patients and their families concurred well. About 2/3 of the patients and somewhat less of the family members rated emotional wellbeing and leisure time activities as improved 2 years after surgery. There were, however, much lower changes in respect to social contacts, family relations and in respect to financial status.[30,31]

Bladin *et al.*, when doing a rating together with patients and families found nonfamilial relationships improved nearly at the same degree as Mihara *et al.* Changes in family relationships were reported however much lesser, the majority of the 107 interviewed saying that relations remained unchanged.[19] In both studies changes were influenced by seizure outcome. In both studies, however, it was not clear if the quality of preoperatively already-existing relationships had improved or new postoperative contacts had been initiated. Anyway, from both studies it can be inferred that 10–15% of the patients also postoperatively had major difficulties in nonfamily relationships, respectively social contacts.

Langfitt *et al.* in an extensive study in which the family interactions of 43 patients 2–3 years after surgery were videotaped, looked for family predictors of social adjustment i.e., functioning in the areas of work/school, social/leisure time, and family relationships. Predominant affect in the family and, to a lesser degree, seizure outcome explained 50% of the variance in social adjustment. The correlations were especially high for the group of patients who had not become seizure free. The authors underline the importance of family support for this patient group, which has much more difficulties, to rely on a social network outside their family.[32]

Bladin, in his study on psychosocial difficulties after TLR, observed 4 years after surgery a level of 6% divorce which was unremarkable against a general divorce rate of 1:3.[19] Carran *et al.* reported the proportion of married patients pre- and postoperatively not to differ significantly from each other – 37% versus 43%. However 33 of 190 patients had changed marital status postoperatively with 21 who became married, and 12 who became divorced.[33] Although the divorce rate seems to be low the divorces reported might be related to surgery, e g., if the patient preoperatively had sustained the relationship only because of the dependency in consequence of the seizures and, after having become seizure free, escapes.[19]

Psychological wellbeing

It is now well established that TLR improves HRQL.[34] However this hold only for those patients who have become completely seizure free. In patients who still have auras (Engel class IB) no improvements could be observed[35–38] although there was substantial seizure reduction. However such a

> Failure is a judgement based on preoperative expectations. To reduce the seizure frequency by half, or to eliminate one of two seizure types could be seen as favourable outcomes if they had been agreed-upon goals prior to surgery.[39]

These authors contend that these problems could be prevented by formulating clear and realistic expectations preoperatively.

There are other factors apart from seizure status decisive for postoperative quality of life. Personality traits like neuroticism,[40,41] learned helplessness, a measure closely related to depression,[35,36] and learned resourcefulness which refers to a personality style that not only buffers negative effects of stress, but which also prompts the initiation of corrective personal change strategies such as the use of thoughts to control emotion, application of problem solving strategies, and delaying immediate gratification influence HROL independently from seizure outcome.[42] Depression is the strongest predictor for HRQOL explaining up to 45% of HRQL independently from seizure status.[43] Depressive syndromes (dysthymic disorders, major depression) may be found up to half of the patients preoperatively, and de novo mood disorders in about 10% postoperatively, the latter mostly being of transient nature[44] (see Chapter 95). From this it becomes obvious that apart from seizure outcome a close psychiatric follow-up in the first 2 years postoperatively may be decisive for the outcome as judged by the patient in quality of life terms.

Finally there is the small group of patients with no improvement at all. This group may deteriorate in HRQOL in comparison to the baseline preoperatively.[4] A surprising finding is that the overwhelming majority of patients who did not become seizure free say that they would have surgery again in a comparable situation[23] i.e., they are not at odds with the unsuccessful therapeutic trial. Nevertheless this is the group needing the most intensive medical, psychiatric/psychotherapeutic, and social-work support postoperatively.

Difficulties to adapt to a situation without seizures (burden of normality)

Bladin and Wilson in recent years repeatedly reported on difficulties associated with the cessation of seizures after surgery,

e.g., inability to cope with a new situation imposing less social constraints but at the same time making new demands – inappropriate, self-indulgent behavior in consequence of this, or being at odds with ones fate because surgery came too late.[9] Such phenomena have loas been observed and gave the starting point for rehabilitation in epilepsy surgery.[7,15,45] Wilson *et al*. observed these phenomena with an increasing frequency in up to 30% of the patients until 2 years postoperatively.[46] From the features described it is, however, not clear for what proportion of the patients they are of clinical relevance. Wheelock also reported such difficulties in seizure free patients but the frequency was low. She conceded however that her sample ($n = 32$) might have been too small to give an adequate estimation.[13,14]

A further difficulty is that from the newer reports of Wilson *et al.* it is not clear who is especially prone for the described difficulties in adaptation. In the older reports[45] it seemed that patients with preoperative personality disorders and/or extremely unrealistic expectations were especially susceptible to such reactions. In our experience, patients with few resources for adaptation i.e., a dearth of social skills and cognitive impairments preoperatively especially with an IQ in the range of a learning disability preferably develop these maladaptive reactions.

Experiences from the Bethel epilepsy surgery programme

In the preceding section it was shown that there is a lack of studies dealing with the social situation of epilepsy patients after surgery. Especially pre- and postoperative changes in the patients' objective social situation have not often been analyzed. We did a follow-up on social outcome in our program twice – for patients getting ATL between 1991 and 1996 [26,27] and between 1998 and 2004.[47] Here we report some results of the second follow-up.

Patients and methods

This study was undertaken in 115 patients with temporal lobe epilepsy who were treated in the epilepsy surgery program Bethel between 1998 and 2004. The patients' demographic features are presented in Table 140.1.

All patients were interviewed by a social worker pre- and postoperatively and were asked to fill out the PESOS-Questionnaire before surgery and two years after that. The PESOS-Questionnaire (PESOS = Performance, Sociodemographic aspects, Subjective evaluation/estimation) is a tool which was developed in the Epilepsy Center Bethel to assess the impact of epilepsy, the epilepsy related quality of life and the psychosocial problems of epilepsy patients.[48] Additionally patients rated their quality of life on a seven point Lickert-Scale 6 months after surgery.

Neuropsychological testing was conducted pre- and 6 months postsurgically. The standard test battery consisted of tests which are indicators for verbal and nonverbal memory, attention, ability to explore, spatial constructive abilities, short-term and working memory, cognitive flexibility and intelligence. Sixty-five patients were included in a specific rehabilitation programme focusing on work related integration. The focus on rehabilitation in Bethel has existed from the beginning, but a special rehabilitation unit was not installed before 1997.

Table 140.1 Bethel program – basic data

Sex m/f	53/62
Right temporal lobe epilepsy/ left temporal lobe epilepsy	68/47
Age mean years (SD); range	35.04 (10.6); 15–60
Duration of epilepsy mean years (SD); range	21.97 (12.0); 1–53
Surgery: right TLE/left TLE/ lesionectomy	62/46/7
Seizure outcome: Engel class I/II/III/IV	79/17/11/8

Patients who suffered from a progredient tumor were excluded from the study.

Results

Changes in specific social domains

To be able to analyze postoperative changes in the above-defined categories we dichotomized patients' answers. There was a significant improvement of the patients' objective social situation in most domains (Table 140.2). In comparison to the results observed in our first follow up[26,27] the results were even more promising.

Table 140.2 Differences prepost for the whole group

Social domain	Pre		Post		*p*	
Accidents	22.3%	(31%)	2.7%	(8%)	< 0.001	(< 0.001)
Not driving	91.0%	(96%)	59.3%	(70%)	< 0.001	(< 0.001)
Not leaving without accompanying person	10.6%	(23%)	2.7%	(7%)	0.006	(0.0002)
No sports	51.5%	(65%)	34.8%	(58%)	0.001	(n.s.)
Unemployment	19.8%	(19%)	8.9%	15%	0.013	(n.s.)
Disability pension	13.9%	(15%)	14.9%	(23%)	n.s.	(n.s.)
Unsatisfactory employment situation	49.5%	(64%)	15.7%	(34%)	< 0.001	(0.0008)
Living with parents	27.0%	(39%)	15.7%	(26%)	0.002	(0.0002)
Social contacts < 1/week	33.3%	(29%)	24.1%	(32%)	n.s.	(n.s.)
No partner	34.9%	(48%)	28.1%	(46%)	< 0.001	(n.s.)

( ): Results Thorbecke (2001).

After describing differences prepost a stepwise logistic regression analysis was done including neuropsychological, social, and clinical variables as predictors for the postoperative score in the analyzed domain. We also included the patients' presurgical score in every domain as a predictor.

Employment

Surgery did not cause a significant change in the amount of people who were in disability pension. In fact only one more person received a disability pension after surgery.

The pre-postsurgical comparison however shows that there was a significant decrease in the unemployment rate after surgery. While about 20% of all patients were out of work before surgery less than half of them (9%) were unemployed afterwards ($p = 0.013$). Furthermore the perceived employment situation improved a lot: while 49.5% called their working situation unsatisfactory presurgically only 15.7% felt the same 6 months after surgery ($p < 0.001$).

To gain a better objective judgement of the patients' employment situation social workers grouped it into four categories: as good as before (employed before and after surgery), as bad as before (out of work before and after surgery), improved (unemployed presurgically, employed postsurgically) and deteriorated (employed before surgery, out of work postsurgically). Housewives were excluded from these categories.

About half of the patients (52.3%) were employed before and after surgery (as good as before), in 5.4% of the cases the negative employment situation had not changed (as bad as before), 22.5% had been out of work before surgery but were employed afterwards (improved) of all patients 19.8% had to cope with a more negative employment situation, e.g., they had been employed before surgery but were out of work or in pension after it.

Work-related problems which epilepsy patients have to deal with decrease after surgery. The PESOS-Questionnaire contains a scale concerning different aspects of problems at work (days on sick leave, slow working speed, memory and attention problems, staying a whole work day, seizures at work). Before surgery 59.1% of the patients said to have such problems, postsurgically comprised only 24.6% ($p = 0.002$)

In the logistic regression analysis (Cox and Snells-$R^2 = 0.405$; Nagelkerkes-$R^2 = 0.723$) the preoperative status was proved as a significant predictor, e.g., patients who received disability pension before surgery were more likely to be still in pension afterwards ($p < 0.001$). An additional predictor was the age at first seizure, a greater proportion of patients with epilepsy onset later than 20 years receiving early disability pension ($p = 0.023$).

The postsurgical employment status and also the subjective perception of the work situation can be best predicted by the presurgical work situation ($p = 0.010$, Cox and Snells-$R^2 = 0.103$; Nagelkerkes-$R^2 = 0.168$).

Mobility

The majority of patients (more than 85%) were independent before and after surgery (i.e., patients left their home without an accompanying person). After surgery even more people were able to leave home without company ($p = 0.006$). In the logistic regression analysis only the presurgical situation was a significant predictor ($p < 0.001$, Cox and Snells-$R^2 = 0.155$; Nagelkerkes-$R^2 = 0.292$).

Sports

In contrast to Thorbecke's results a significant increase in the percentage of people doing sports regularly (48.5% preoperative vs. 65.2% postoperative) could be observed. The analysis for predictors (Cox and Snells-$R^2 = 0.145$; Nagelkerkes-$R^2 = 0.204$) showed an effect of the seizure outcome ($p = 0.042$) and the preoperative frequency of doing sports ($p = 0.004$). Persons who had already been active in sports before surgery and who were seizurefree postsurgically did sports more often.

Independent living

The pre-postsurgical comparison showed that postsurgically fewer patients lived with their parents (27% vs. 15.7%, $p = 0.002$). After surgery more patients called their living situation satisfying: presurgically 15.3% were not satisfied with their living situation, postsurgically only 8.1% thought their living situation was not satisfying.

Significant factors for predicting (Cox and Snells-$R^2 = 0.346$; Nagelkerkes-$R^2 = 0.593$) the postoperative living situation were the patient's age ($p = 0.004$), the presurgical living situation ($p < 0.001$), and the neuropsychological parameter 'nonverbal memory' ($p = 0.013$). Patients who lived independently were significantly older ($F(40) = 2.19$; $p = 0.002$) than patients still living with their parents. Additionally patients who lived at home presurgically were at a greater risk to still live with parents after surgery ($F(1) = 63.97$; $p < 0.001$). People with a poor nonverbal memory performance were more likely to live with their parents.

Social contacts

No significant change in the frequency of social contacts could be observed after surgery. Respectively 76.7 and 85.9% of the patients had social contacts outside the family pre- and postoperatively at least once per week. In contrast there was a significant change in the number of friendships ($p = 0.004$). While preoperatively 29.4% of all patients reported to have very few or no friends, postoperatively only 15.9% made this statement.

There was also a positive change in the subjective evaluation of social contacts. Postsurgically significantly more patients called the quality and number of friendships satisfying ($p < 0.001$). Only 11.6% were not satisfied with their social life after surgery while presurgically 19.5% were not pleased with their social contacts.

Two factors were suitable to predict the postsurgical situation with respect to social contacts: the presurgical frequency of social contacts ($p = 0.024$) and the extent of epilepsy-related fear ($p = 0.046$). Patients who had had more social contacts before surgery and who had a lower level of epilepsy-related fear were more likely to have a high frequency of social contacts (Cox and Snells-$R^2 = 0.095$; Nagelkerkes-$R^2 = 0.143$).

Partnership

In contrast to the results from 2001 there was a significant increase in the percentage of people having a partner

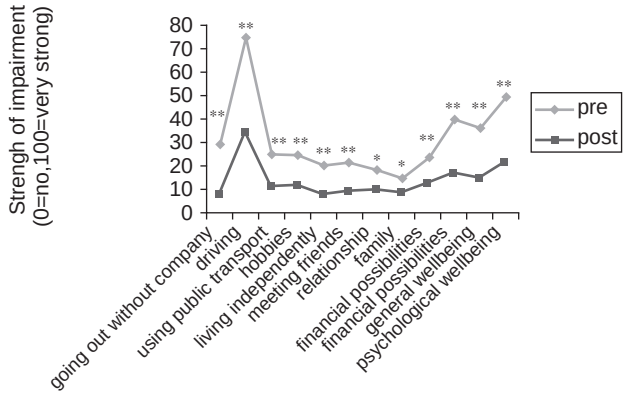

Figure 140.1 Differences pre-post in subjective impairment due to epilepsy.

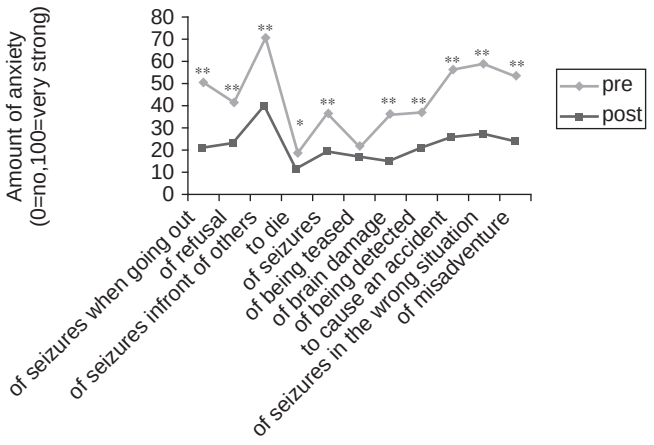

Figure 140.3 Differences pre-post in epilepsy related fear.

($p<0.001$). While presurgically 34.9% of our patients had no partner, only 28.1% had no partner after surgery. In addition to that, less people reported epilepsy-related problems in their relationship (35.3% postsurgically vs. 13.8% presurgically). However, the presurgical status was the only predictor (Cox and Snells-$R^2=0.238$; Nagelkerkes-$R^2=0.352$).

Subjective social situation

The patients' subjective situation was assessed with four scales: impairment due to epilepsy, emotional adaptation to epilepsy, stigmatization and epilepsy-related fear. The pre-postoperative comparison of these scales is presented in Figures 140.1 to 140.3.

Figure 140.1 shows the comparison for the subjective impairment due to epilepsy. A significant reduction of impairment could be observed in every single item of this scale. Thus patients' felt, less restricted in domains such as going out without company, using public transport, etc. Additionally the change in the scale sum score became highly significant ($p<0.001$).

Figure 140.2 shows the results of the pre-postsurgical comparison of two scales: the underlined items belong to the scale 'stigmatization', the other items are part of the scale 'emotional adaptation to epilepsy'. While all pre-postsurgical comparisons became significant ($p<0.001$) with respect to the latter scale only one significant change could be observed when looking at the stigmatization scale: Patients felt more accepted after the surgery ($p<0.001$).

Figure 140.3 shows that the patients did not suffer from epilepsy-related fear as strongly as they did presurgically. Nevertheless the fear of being teased remained.

To conclude, in general quality of life indicators improved significantly. There was however little change in perceived stigmatization.

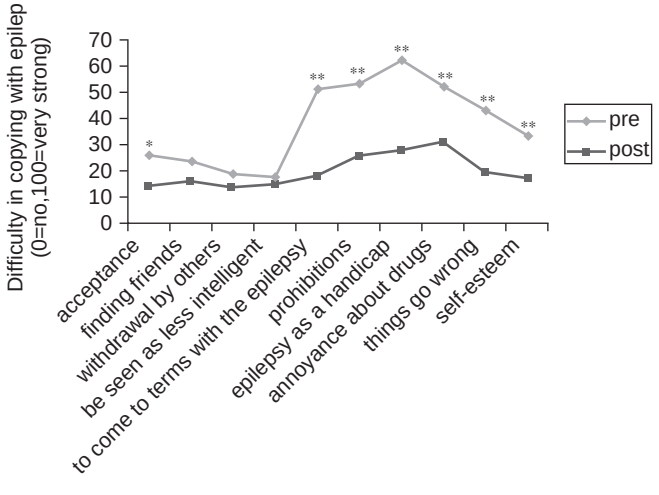

Figure 140.2 Differences prepost in coping with the epilepsy.

Conclusions

The results from our second follow up are in good agreement with our former results[26,27] as well as with results reported by others (see the second section). The patients' objective and subjective social situation in most domains improves after epilepsy surgery. No significant change, however, can be observed in felt stigmatization.

In comparison with our former results, especially the outcome on work related variables is more positive than before. While no difference in the postoperative employment situation could be found in 2001, there is a significant improvement in the second cohort. This improvement could be due to the establishment of a special rehabilitation unit in our centre in 1997 (for a description of the rehabilitation unit see below.

Nevertheless, there are persisting restrictions. First of all, no significant improvement can be observed in the frequency of social contacts. Possibly this result is coherent with the finding that patients still feel stigmatized after surgery. Thus patients with a high degree of felt stigma could be lacking the self-certainty to take the first steps to build up new relationships. Changes in social behaviors perhaps may need more time to have measurable effects. The same holds true for changes in the work situation. While a significant decrease in the unemployment rate can be observed in the second follow-up, the percentage of people who receive a disability pension remains stable.

All in all the studies presented in the previous section and also our own results show that there is a need for rehabilitative

interventions because even surgically-treated patients with a good seizure outcome suffer from social difficulties. The Bethel experience gives hints that rehabilitative care is indeed important and can positively influence patients' social situation after surgery.

Rehabilitation interventions

Pre and postoperative rehabilitation

Preoperative rehabilitation

As we have demonstrated in the second section, the evaluation of outcome by the patient and also individual motivation to work for postoperative improvements of the psychosocial situation depends strongly on preoperative expectations/aims set in connection with the surgical intervention. Therefore rehabilitation should always begin preoperatively with working out realistic expectations together with the patient and family. This seems essential in view of the high proportion of patients with psychiatric and neuropsychological deficits already existing preoperatively. In both follow-up studies from Bethel, about 60 % of the patients had personality disorders (Koch-Stoecker 2001,[44] unpublished data 2005). Preoperative neuropsychological deficits were reported repeatedly by Helmstaedter.[5,6]

In our experience, expectations with respect to social outcome should not be discussed with the patient immediately before surgery because at this time the patient is involved in evaluation of the medical risks informed by the neurosurgeon. An ideal time is after the patient management meeting (see Chapter 104 this volume) because then medical, neuropsychological, psychiatric, and psychosocial work-up is finished so seizure prognosis, and the patient's rehabilitation potential can be assessed. Working out expectations should not only be done by the neurologist, and the patient, but also other team members (neuropsychologist, social worker) should be consulted if their knowledge is relevant. Wilson *et al.*,[1] suggest the following questions to tap expectations:

1. What is the main reason you have sought surgical intervention?
2. Do you see the operation as a chance to change your life?
3. Have you made any postoperative plans?
4. Do you plan engaging in any new activities/hobbies postoperatively?

In our center we discuss expectations with two open-ended questions.

1. What changes in your life do you expect postoperatively if you do not become seizure free, your seizure status however improve strongly?
2. What changes in your life do you expect postoperatively if you become completely seizure free?

In our experience the first question makes it easily possible to single out those patients who assess the surgery a failure if there is not complete seizure relief. Furthermore answers to both questions are a very good starting point for working on concrete expectations.[2] Taylor *et al.* learned from their interviews that people vary greatly in their capacity to formulate an answer when posed a question such as 'How shall you know 2 years from now, that you are better?' and propose an individualized approach without preformulated questions.[2] Anyway, it is important to document the expectations/aims because there might be phases later in which the patient may feel overburdened by new expectations and then it might be helpful to remind him of his own plans from the preoperative workup.

The topics to be addressed when discussing expectations would be:

1. Inform the patient and relatives regarding expected seizure outcome. Also when the patient's chances to become seizure free are very high it should be made clear that there is a possibility, even if small, that seizures may persist after surgery.
2. Discussion of the patient's and his family's individual expectations/aims in relation to surgery. Relying on neuropsychological assessment and the patient's history, e.g. patient's employment career, realistic expectations must be discussed. When the patient, and his family's expectations are unrealistic, e.g., a patient with a learning disability who believes that he can successfully accomplish a high-level professional training postoperatively, first steps of vocational rehabilitation should be done already *before* surgery. Otherwise the difficulties will be masked after unsuccessful operation ('because I have not become completely seizure free it does not work') or he will be frustrated although successfully operated because his expectations are not fulfilled.

Postoperative rehabilitation

Horowitz *et al.*[8] delineated a rehabilitation model with five phases in which the patient detaches himself from his chronic disease. The first phase is described as a *moratorium* during which the old roles are continued or unrealistic expectations arise. It is followed by *reappraisal*, a phase during which new behaviors are tried out or new restrictions arise directed by the fear to provoke seizures. The next phase is called *great expectations*, Excessive expectations may lead to the perception of failure in the patient; the persons in his environment on the other side may react with removal of support or with a rigidification of the role structure. It is the authors' contention that in this phase psychotherapeutic support and support by a social worker is crucial. In the next two phases named *turbulent period with the self* and *gradual adaptation* the authors describe two different endpoints of rehabilitation, one in which the role of the chronically ill person is reinstalled and made permanent; this happens when the construction of a new identity does not succeed and may be accompanied by severe psychiatric reactions; the other in which the person gradually gains more autonomy, and needs less support by his family.

Although this model was designed from experience with only 17 patients in the sixties it also seems to give a frame for understanding the postoperative psychosocial development today. In our experience the first three phases–moratorium, reappraisal, and trying going in new directions–are passed in the first 6–12 months post-surgery, and only in rare cases it takes longer, and it seems that the situation 24 months postoperatively can be taken as the 'outcome of surgery'.

Wilson *et al.*, when describing different ways of postoperative adaptation as 'outcome trajectories' noted early anxiety as a marker for a poor psychosocial outcome and no vocational changes in the first 12 months as indicators for a poor employment outcome 24 months post-operatively.[49]

Situations which require special rehabilitation efforts

We feel that a team composed of the neurologist, psychiatrist, neuropsychologist, and social worker, who have met the patient already preoperatively, is essential for successful rehabilitation.

Situation immediately after surgery

If the patient is seizure free, and there are no neurological complications or noticeable neuropsychological deficits, and emotional adaptation seems adequate, the most important thing is to advise the patient when to return to the workplace or when to takeup duties as a homemaker. It is the experience of other centres (*Wilson trajectories*) and also our own that premature return to work may be followed by complications such as a long sick leave, etc. We inform our patients preoperatively that it may take 3 months until they are able to return to work, and then make an individualized plan postoperatively. It seems that age at surgery is the most important factor for the time needed for postoperative recovery. If possible it may be very helpful to re-enter work stepwise i.e., to start with less hours than normal and then gradually increase the number of work-hours per day.

There are, however, patients who have relapsed immediately after surgery or who have a high risk to do so. Furthermore there are patients who have a high level of anxiety or other psychiatric complications, or who are at risk to deteriorate psychiatrically (see Chapters 144 and 150), patients who had neuropsychological deficits already preoperatively, or whose performance has deteriorated postoperatively, and patients who had preoperatively social or employment difficulties or who are at risk to deteriorate. In our centre in 1997 a short-term inpatient rehabilitation program lasting about three weeks was installed for this group. Medical treatment, psychiatric support, psychotherapeutic counselling, neuropsychological training to learn compensatory strategies for word–finding difficulties, visual field or memory deficits, occupational therapy, sports and recreational therapy, intensive counselling, and a structured patient education program especially designed for postoperative patients are offered.[50]

Continuing psychosocial difficulties several months after surgery

We feel, that at about 6 months after surgery it is possible to assess whether a patient is not progressing according to expectations. This includes patients who have become seizure free and have no psychotic disturbances, but in whom one of the following complicating factors can be indicated: persisting mood disturbances, psychosomatic complaints (see Chapter 144), neuropsychological deficits which may or may not have been present preoperatively, occurrence of role conflicts in the family, work situation having become more difficult because the improved seizure situation is not accounted for by colleagues, and patients who apparently do not use their improved mobility and their new possibilities for leisure-time activities.

We offer an intensive team counselling these patients during a 3-day intake 6 months after surgery. We also offered a weekend workshop for couples in which one partner had had surgery twice. Patients and partners complained about different problems, and conflicts were mostly reported by the partners. Psychoeducational methods including role-play were employed. From this resulted the experience that solutions for conflicts could be found, although this might be difficult. All couples said at the end that they would try out the new ways of communication they had learned to solve conflicts.[51] There are also patients who have not yet returned to their work-place 6 months after surgery, who continue to be unemployed, or who have not become seizure free and now plan to apply for early disability pension. Furthermore there are patients whose early disability pension now finishes, and who need support for work reintegration. If we cannot solve these difficulties during the 3-day intake, we try to get funds for a second intake in our short-term rehabilitation unit. During the intake immediately after surgery the patients get medical treatment, psychiatric support, psychotherapeutic counselling, and neuropsychological training, which are extended to occupational assessment and real work-experience in companies downtown where professions similar to those the patient intends to return to are found. There are also intensive contacts to employers and to the agencies responsible for labour mediation and vocational rehabilitation. In our series with 115 patients with TLR (see section above) we had nine second intakes 6 months after surgery. Five had a successful rehabilitation outcome: two young adults received afterdischarge vocational training, one adult received vocational retraining, two patients were able to return to their workplace, one of them not being seizure free and having severe neuropsychological deficits. The four patients with a negative rehabilitation outcome all had not become seizure free, additionally one had a severe psychiatric complication, and two had deteriorated in their neuropsychological abilities. For one patient the reasons were not clear.

Patients with late relapses

There is a significant risk for late relapses. In a recent study about half of these patients remitted, the others continued to have seizures although in low frequency.[52] Unfortunately there is little research on the social prognosis of this group. From clinical experience we know that there are patients who become resigned, giving comments like 'now I am again an epileptic and must bear the consequences'. Apart from a thorough medical assessment those patients need social-work support and sometimes also psychiatric counselling to prevent their situation from destabilizing.

Conclusions

By going through the literature and by presenting results from our own program we tried to show that a need for rehabilitation interventions before and after epilepsy surgery is consistently described. This review also identifies a number of predictors for social outcome that allow the planning of targeted pre- and postoperative rehabilitation interventions. Depending on the special outcome domain the predictors vary. The results from our program as well as from other studies show

that the majority of the patients postsurgically remain in the same situation as before. However, this is not only true for the well adapted but also for those in an unsatisfactory situation. From our experience it is the small number of patients who are able to improve postoperatively, and the also small group which deteriorates postoperatively which must be the target group for rehabilitation interventions. If there is a thorough preoperative work-up and a close follow-up during the first 6 months postoperatively these patients can be identified and addressed for rehabilitation interventions.

These interventions should rely on the prognostic factors known from literature (third section) and on the practical experiences reported in the fourth section.

Timing would be one important aspect. From the literature it seems that a great deal of rehabilitation counselling has to be done preoperatively to shape the expectations of the patient and relatives and to develop the individual's potential for rehabilitation. In the postoperative course we delineated three occasions for considering rehabilitation support:

1. Immediately after surgery if there is a high risk for psychosocial complications or complications have already occurred.
2. About 6 months after surgery when there are hints that the patient did not profit as much as would have been possible.
3. When the patient relapses after some time without seizures.

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SECTION 19

Neuropathology and research related to epilepsy surgery

141 Neuropathology of mesial temporal sclerosis

I Blümcke

Introduction

Mesial temporal sclerosis (MTS) is the major finding in patients with temporal lobe epilepsies (TLE) and histopathologically characterized by segmental neuronal cell loss and gliosis within the hippocampal formation (syn. hippocampal sclerosis, Ammon's horn sclerosis). The majority of hippocampal specimens also reveal alterations within the dentate gyrus, i.e., granule cell dispersion. In addition, variable cell loss can be detected within adjacent cortical regions, including the subiculum, entorhinal cortex, and amygdala. Cortical dyslamination and increased numbers of ectopic white matter neurons within the ipsilateral temporal lobe may also occur in MTS. Neuropathological evaluation of surgical specimens is, therefore, an important diagnostic tool to characterize the morphological substrate of the epileptogenic region. In most patients, clinical histories point to an early onset, such as precipitating events before the age of 4 years, and recent molecular studies targeted developmental pathomechanisms of hippocampal architecture to play a role in the formation of MTS, i.e., loss of Reelin and granule cell dispersion. In contrast, surgical treatment is usually carried out at an end stage of the disease and make any sequential relationship of mesial temporal pathology in TLE patients difficult to obtain. In order to better address underlying etiologies in the heterogeneous group of TLE patients and to stratify post-surgical outcome, a novel clinico-pathological classification system is proposed, which point to early preceding events, respectively the developmental state at which such an event compromises mesial temporal lobe maturation, as a reliable predictor for severe hippocampal pathology.

Clinico-pathological findings in MTS

Histopathological studies in patients with pharmacoresistant TLE have identified mesial temporal sclerosis (MTS, syn., Ammon's horn sclerosis, hippocampal sclerosis) as major pathological finding[1,2] MTS can be detected in approximately 65% of patients with MTLE[1] and 24.8% of a consecutive cohort of 3319 epilepsy patients undergoing surgical resection for various etiologies in Germany (Table 141.1). Although the pathogenesis of MTS remains to be identified, clinical histories follow a characteristic schedule in most patients. In our series of 824 patients obtained from major German epilepsy centers, including the Universities of Berlin, Bonn, Erlangen, and Freiburg as well as the Bielefeld-Bethel clinics, three periods were identified. Approximately 50% of patients presented with an initial precipitating injury before the age of 4 years.[1] In this cohort, complex febrile seizures are the most frequently noted findings. Birth trauma, head injury or meningitis were other early childhood lesions observed in TLE patients. The mean age at onset of spontaneous complex partial seizures is 11.1 years (Table 141.1). As a matter of fact, structural, molecular or functional analysis cannot be obtained during this early and clinically silent period. The diagnosis of MTS can be verified in surgical specimens mainly after a long period of frustrane antiepileptic medication. The mean age at the time of surgery is about 34 years with a medium history of epileptic seizures of almost 23 years (Table 141.1). As in most other series reported so far, both genders were equally affected and a familial history of TLE was very rare indicating that hereditary genetic factors do not play a major role in MTS associated TLE.

Histopathologically, MTS is characterized by segmental pyramidal cell loss in CA1 (Sommer's sector), CA3 and CA4 (endfolium), whereas CA2 pyramidal and dentate gyrus granule cells are most seizure resistant (Figure 141.1). Notwithstanding, several interneuronal cell populations were also affected, i.e., neuropeptide Y- and somatostatin-immunoreactive interneurons and/or mossy cells in the CA4 sector.[3,4] Neuronal cell loss is invariably associated with reactive astrogliosis, which results in stiffening of the tissue and established the traditional term of Ammon's horn sclerosis.[5] An intriguing question relates to the mechanisms of selective neuronal vulnerabilities between these morphologically similar neuronal cell populations. Notwithstanding, this topic is matter of ongoing studies and will not be further discussed in this chapter. Major pathomechanisms include, besides many others, abnormal neuronal circuitries (aberrant mossy fiber sprouting)[6] and molecular rearrangement/plasticity of ion channel and neurotransmitter receptor expression.[7]

Clinico-pathological classification of MTS

Clinical studies assume mesial temporal lobe epilepsies as a heterogenic entity with different etiologies and clinical histories.[8–10] Hence, neuropathological investigations described different patterns of neuronal cell loss within hippocampal subfields and adjacent temporal lobe structures.[4,11,12]

Table 141.1 Clinico-pathological findings in MTLE patients

		Hemisphere					
		Number	Age OP	Gender		Onset	Duration
MTS		824	34.0	343 L/356 R	407 M/418 F	11.1	22.9
DUAL		127	21.7	30 L/73 R	80 M/47 F	8.7	13.5
	with LEAT	53	26.0	15 L/33 R	34 M/19 F	11.2	15.6
	with Malformation	31	13.7	15 L/15 R	20 M/11 F	3.2	10.7
	with scars	17	28.2	4 L/12 R	10 M/7 F	13.4	15.9
	with vasc. Lesion	13	20.2	6 L/6 R	9 M/4 F	5.7	14.6
	with inflammation	9	16.2	2 L/5 R	6 M/3 F	10.9	5.3
	NOS	4	16.0	2 L/2 R	1 M/3 F	1.3	14.8
No MTS	LEAT	76	25.5	30 L/27 R	38 M/38 F	12.5	13.1
	Malformation	62	13.7	23 L/30 R	34 M/28 F	5.4	9.5
	No lesion	41	25.8	13 L/21 R	21 M/20 F	12.9	14.2
	Scars	24	23.4	8 L/9 R	15 M/9 F	7.4	16.4
	Vascular lesion	12	30.9	4 L/5 R	9 M/3 F	16.7	12.5
	Inflammation	9	21.1	6 L/3 R	7 M/2 F	14.6	6.4

Evaluation of 1175 patients with mesial temporal lobe epilepsies and surgical resection including the hippocampal formation. All data were obtained from the German Neuropathological Data Base for Epilepsy Surgery. Histopathological evaluation and clinical histories are as following:

MTS: mesial temporal sclerosis; DUAL: dual pathologies; LEAT: long-term epilepsy associated tumors; Vasc.: vascular; NOS: not otherwise specified; Age OP = age of patients at surgery (in years); Hemisphere: L (left), R (right); Gender: F = female, M = male; Onset = age at onset of spontaneous seizure activity (in years); Duration = duration of seizure disorder before surgical treatment (in years).

An intriguing issue is, therefore, to identify determining factors on hippocampal pathology patterns. A reliable neuropathological classification system will also be most helpful to separate distinct pathological subgroups and to better predict post-surgical outcome. A first systematic attempt was published in 1992 by Wyler[11], referring to percentages of neuronal cell loss within identified hippocampal subfields CA1-CA4 (Table 141.2). The Wyler-Score is well established in the neuropathological work-up of MTS and threshold values are defined either by 10% (Wyler score 1 = mild MTS) or 50% of neuronal loss. Classification includes five grades (W0 = normal, W1 = mild, W2 = moderate, W3 = classical hippocampal sclerosis and W4 = severe hippocampal sclerosis). End folium sclerosis is subsumed into W2. In previous investigations, certain difficulties evolved using the Wyler-Score to identify mild hippocampal sclerosis on the basis of 10% neuronal cell loss within CA1 and CA3/CA4. Our own analysis even identified 10% neuronal loss within the first standard deviation of age-matched control individuals. An extension and revision of the Wyler-Score was then published by Proper *et al.*[13] including mossy fiber sprouting. Mossy fiber sprouting as well as reactive gliosis are frequently associated with long-term mesial temporal lobe epilepsy, and were confirmed in a variety of different animal models.[12,14–19] However, any histopathological classification system should be deliberately based on general histopathology techniques and staining protocols applicable in any pathology laboratory worldwide, without further time and cost-intensive or capricious neuroanatomical techniques, i.e., Timm staining for aberrant mossy fiber sprouting.[9]

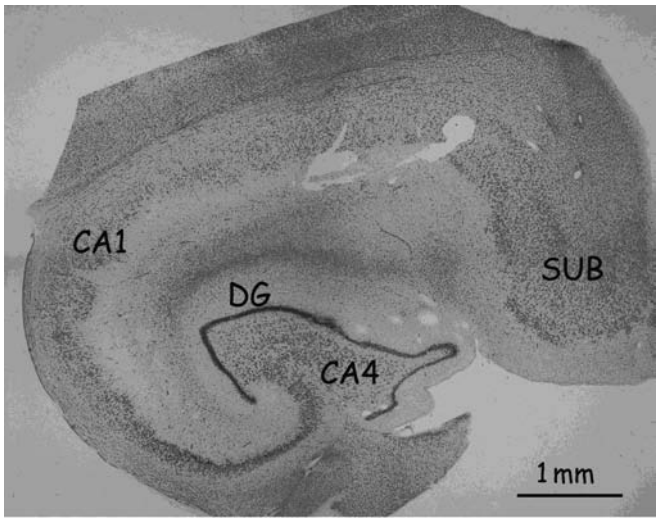
We propose, therefore, a novel clinico-pathological classification system for hippocampal cell loss in patients suffering from mesial temporal lobe epilepsies (MTLE). Five distinct patterns were recognized (Table 141.2) and associate with specific clinical histories and/or post-surgical outcome.[20]

No MTS

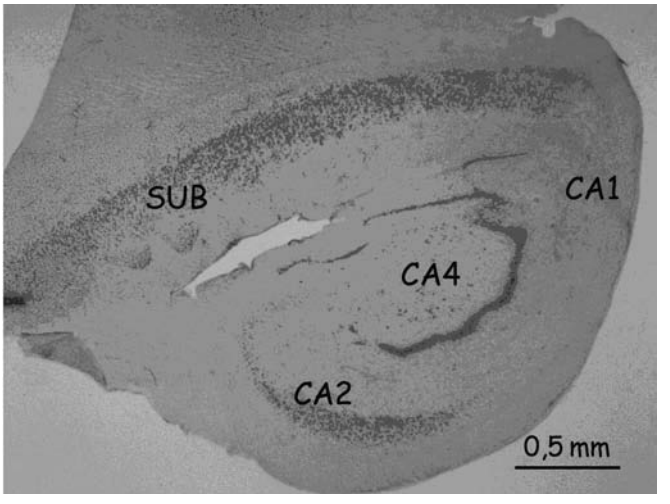
Despite electrophysiological evidence for mesial temporal lobe generation of seizures, a cohort of approximately 19% of MTLE cases do not show microscopical features of neuronal cell loss (Table 141.1; Blümcke *et al.*, 2007)[20] and cell density measurements were not significantly different from age matched autopsy controls (±10% difference in neuronal cell densities are explicable only by the standard deviation obtained from human control values !). We designated this group as no mesial temporal sclerosis (no MTS; Table 141.2). This observation has been frequently reported in neuropathological surveys of similar MTS series.[1,2] The epileptogenic pathomechanisms of hippocampal seizure generation remains to be further determined, and we suggest a mechanism similar to the kindling animal model. Indeed, focal lesions adjacent to the hippocampus can be frequently identified in this cohort of TLE patients (Table 141.1).

MTS type 1a and 1b (classical and severe hippocampal sclerosis)

With 70% of MTS cases, the largest group present with a classical or severe pattern of segmental neuronal cell loss affecting CA1 and CA4. Due to considerable similarities of neuronal cell loss patterns and clinical histories, we designated these two groups as MTS type 1a (20%) and 1b (50%). In our hands, the degree of CA3 and CA2 pyramidal cell loss is likely to differentiate between MTS type 1a (with moderate CA2 cell loss) and MTS type 1b (with severe CA2 cell loss). This distinction is reasonably similar to that described by Wyler *et al.*[11] Correlation with clinical data pointed to an early age of preceding events (< 3 years) as important predictor of this classical and severe hippocampal pathology pattern.



(a)



(b)

Figure 141.1 Neuropathological findings in mesial temporal sclerosis (MTS). Neuropathological hallmarks of MTS represent segmental pyramidal cell loss affecting the CA1 and CA4 sectors (b). In contrast, CA2 pyramidal and dentate gyrus (DG) granule cells are most seizure resistant. a: Histograph of a human hippocampus obtained from autopsy. SUB: Subiculum. Pigment-Darrow Red Staining. Scale bars = 1 mm in a and 0.5 mm in b. Note the significant atrophy of the MTS specimen in b. (See Color plates.)

Atypical MTS type 2 (CA1-sclerosis) and type 3 (endfolium sclerosis)

We identified two atypical variants characterized either by severe neuronal loss restricted to sector CA1 (MTS type 2; 6%) or to the hilar region (MTS type 3, 4%). In MTS type 2, preceding events were documented at a later age (mean six years), whereas in MTS type 3 and normal appearing hippocampus (no MTS) the first event appeared beyond the age of 13 and 16 years, respectively.

The novel MTS classification system allows some prediction of post-surgical outcome (Table 141.3). In our large cohort of TLE patients, the overall six months outcome revealed a rate of 78% seizure freedom, which is in the well-recognized range of earlier reports.[8,10,22–26] The best outcome was achieved, however, in patients presenting with MTS type 1a and MTS type 1b (> 83% seizure freedom), whereas only half of patients with atypical MTS patterns (type 2 and type 3) became seizure free (Table 141.3). Notwithstanding, TLE patients without hippocampal neuronal loss have also a proven benefit from epilepsy surgery.

An intriguing challenge for any neuropathological classification system of CNS diseases is the relationship between cellular/molecular lesion patterns and clinical parameters as well as its predictive value for post-surgical outcome. The age of the first preceding event such as birth trauma, febrile seizures, head trauma, encephalitis or first seizure in the absence of a preceding event was significantly different in the neuropathology groups. Early events occurring in pre-school age under age of 7 years came along with severe neuronal loss in hippocampal subfield CA1. Moreover, earlier events under the age of 3 years presented with more widespread hippocampal damage comprising all hippocampal sectors as well as the dentate gyrus. Occurrence of an event or epilepsy onset (in the absence of an event) during early adolescence did affect only the hilar region and spared also other hippocampal subfields to a greater extent. Events occurring even at later adolescence were associated with a rather normal appearing hippocampal formation. Many reports emphasize the association between initial preceding events and development of MTS. The frequent association with febrile seizures in early childhood supports this hypothesis. Seizures during early childhood are associated with aberrant mossy fibre axon connections without evidence of seizure-induced cell death.[27] Moreover, prolonged seizure discharges stimulate dentate granule cell neurogenesis as a potential repair mechanism, leading to aberrant connections.[14] Such alterations may affect normal brain development and further promote epileptogenesis, whereas seizure activity during later adolescence may strengthen recurrent excitation and induce excitotoxic cell damage, i.e., MTS.[19]

Granule cell dispersion

The population of dentate gyrus granule cells is pathologically affected in the vast majority of patients with MTS (Figure 141.2). Lesional patterns in this anatomical distinct compartment range from granule cell dispersion, which occur in almost 50% of patients[1] to severe cell loss in MTS type 1a and 1b (Table 141.2). Neuropathological criteria for granule cell alterations have not been firmly established.[9] We consider any increase in granule cell lamination above 10 layers with smaller perikarya and larger intercellular gaps as pathologic and compatible with GCD. Ectopic cluster and bilamination within the molecular layer can also be identified, although to a smaller extent. Since granule cell pathology is not internationally standardized by a classification system, clinicopathological studies yielded complementary results. Granule cell dispersion may be associated with early seizure onset or status epilepticus at an initial stage of the disease.[28,29] On the other hand, Mathern *et al.* failed to establish a correlation between dentate granule cell densities and onset of seizures.[30] A positive correlation was found between the presence of granule cell dispersion and the severity of hippocampal neuronal loss.[2,16,31] This finding suggests that the processes of granule cell dispersion and MTS are closely linked. Furthermore, the occasional observation of granule cell dispersion in the absence of

Table 141.2 Histopathological classification systems for MTS

Reference	Pattern	CA1	CA2	CA3	CA4	DG
(Blümcke *et al.*, 2007)						
no MTS	normal	no loss	no loss	no loss	no loss	no loss
MTS type 1a	classic	80%	30%	30%	40%	55%
MTS type 1b	severe	85%	49%	70%	85%	60%
MTS type 2	atypical	80%	20%	20%	25%	20%
MTS type 3	atypical	20%	25%	30%	45%	35%
(Wyler *et al.*, 1992b)						
Wyler Score 0	normal	no loss	no loss	no loss	no loss	–
Wyler Score 1	mild	10%	–	10%	10%	–
Wyler Score 2	moderate	10–50%	–	10–50%	10–50%	–
Wyler Score 3	classic	>50%	<50%	>50%	>50%	–
Wyler Score 4	severe	>50%	>50%	>50%	>50%	involved

Comparison between two MTS classification systems proposed by Wyler *et al.*[11] and by Blümcke and *et al.*[20] Neuronal cell loss is expressed as percentage from control values within hippocampal subfields (CA1–CA4) and dentate gyrus (DG). Semi quantitative analysis should be applied to determine the extent of pyramidal cell loss. Values represent mean percentages of persisting neurons. It is important to note, that standard deviations need to be applied for scoring individual numbers (data not shown). A software analysis system will be available upon request from the author to automatically calculate the new MTS score.

hippocampal cell loss but with widespread cortical malformations would also point towards a malformative origin.[32]

Dual pathologies

In a proportion of patients with MTS, depth electrode recordings and intraoperative electrocorticography characterize more widespread areas of epileptiform activity involving both mesial and lateral temporal lobe regions.[33–35] From neuroimaging and neuropathological studies it is well established that MTS can occur in combination with a second temporal lobe epileptogenic pathology such as cortical dyslamination (i.e., Focal Cortical Dysplasia type I), ectopic white matter neurons or low-grade glio-neuronal tumors.[1,33,36–41] There are also occasional reports of distinct hippocampal malformations occurring with MTS[42] and structural hippocampal abnormalities on MRI which appear to preceed MTS.[43,44] In the German Neuropathological Data Base for Epilepsy Surgery, dual pathologies were identified in approx. 10% of cases (Table 141.1). There is some evidence for less severe hippocampal neuronal loss when a 'dual pathology' is present (i.e., MTS type 3). In these cases, 'kindling' of the hippocampus by the adjacent temporal lobe lesion may play a role. There is some evidence to support the notion that progressive hippocampal atrophy occurs with longer duration of seizures.[45–47] It has been shown, however, that surgical removal of both lesions results in the best post operative seizure outcome for dual pathologies[40] indicating that each component contributes to the genesis of seizures. The coincidence of dual temporal lobe pathologies also raises the important question of a common predisposing malformative process for both lesions. Furthermore, in a larger proportion of TLE cases, less well defined, subtle microscopic malformations may be identified. Such alterations lend further evidence for underlying temporal lobe dysgenesis which renders it more vulnerable to seizures, neuronal injury and ultimately MTS.[48,49]

A major difficulty, however, reflect the poor interrater concordance for the neuropathological classification of dual pathology in MTS patients. We propose, that the term 'dual pathology' is restricted to a combination of MTS and those lesions, which are likely to represent a distinct pathogenic etiology, i.e., MTS and LEAT, MTS and vascular lesions, MTS and glial scars/trauma. White matter neuronal ectopy and cortical dyslamination of the temporal lobe may not inevitably fit to this assumption and need, therefore, careful attention. The same holds true for the frequent association between LEAT and cortical dysplasias, which may not arise from different pathogenic mechanisms.

Table141.3 Correlation between pathology patterns and post-surgical outcome

		Engel 1	Engel 2	Engel 3	Engel 4
no MTS	n	71.0	12.9	9.7	6.5
MTS type 1a	n	85.7	10.7	3.6	–
MTS type 1b	n	83.3	8.9	7.8	–
MTS type 2	n	50.0*	20.0	20.0	10.0
MTS type 3	n	42.9*	14.3	28.6	14.3
Total	n	77.7	10.8	9.0	2.4

Outcome according to Engel's classification was determined with a minimum period of six months after epilepsy surgery. A total of 166 patients were included in this analysis (Blümcke *et al.*, 2007).[20]
*Note the better outcome in MTS type 1a and 1b, whereas only 50% of patients with atypical MTS type 2 and 43% with atypical MTS type 3 became seizure free ($p = 0.051$).

A pathogenetic model for MTS – associated TLE

Molecular-neuropathological studies of surgical specimens obtained from patients with chronic TLE have focused on different pathogenetic mechanisms, such as (i) structural (axonal/dendritic) and molecular reorganization patterns

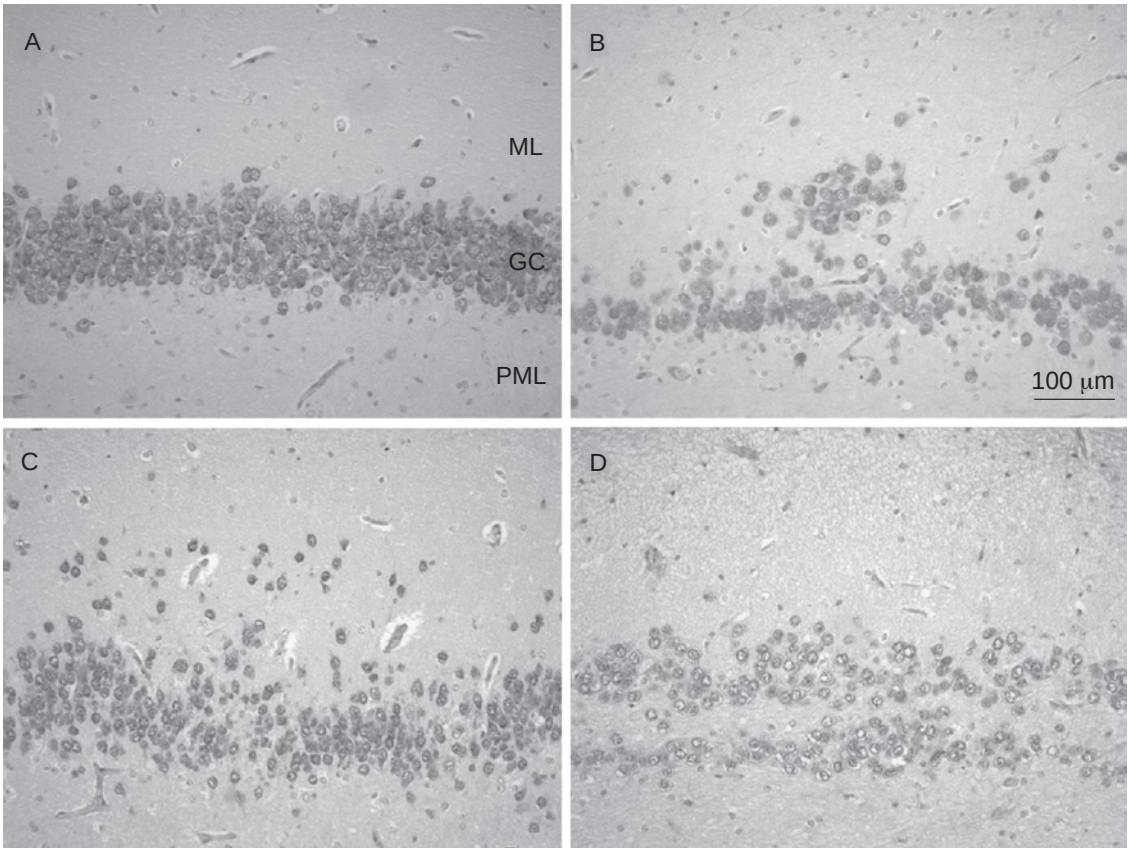


Figure 141.2 The spectrum of granule cell pathology in MTS. Different patterns of granule cell pathologies can be observed in surgical MTS specimens. A: Normal, densely packed granule cell layer of the dentate gyrus (ML – molecular layer; GC – granule cell layer; PML – pleomorphic cell layer). B: A cluster of ectopic granule cell displaced into the molecular layer is depicted. C: A frequent finding comprises granule cell dispersion with a broader thickness of GC and increased gaps between individual neurons. D: In a few patients the granule cell layer present as bilayered structure. Compared to controls, borders to adjacent layers are always less distinguishable in GC pathologies. Scale bar in B = 100 μm (applies also to A, C, and D).

(neurotransmitter receptors, extracellular matrix), (ii) selective neuronal vulnerability (CA1 pyramidal cell loss), (iii) activity dependent changes in neuronal function/synaptic plasticity (voltage dependent ion channels), (iv) gliosis (spatial ion buffering capacity/glutmate receptor expression/gap junctions) as well as (v) epilepsy-associated neurogenesis. A comprehensive model encompassing the chronic disease history in individual patients has, however, been difficult to obtain. Considering the major clinical milestones and molecular-pathological and pathophysiological changes that can be observed at the end stage of the disease (when neurosurgically resected hippocampal specimens are available) the following pathogenic model of MTS associated TLE will be discussed.

We conclude that MTS is an early disorder compromizing normal development of mesial temporal lobe organization with the dentate gyrus as the primarily target.[1] Whether a somatic genetic component plays a role, i.e. affecting neurodevelopmental signaling pathways such as the reelin cascade, can not be excluded yet. However, increased neurogenesis and/or persistence of Cajal-Retzius cells in TLE patients with MTS point towards a prolonged and abnormal maturation period[50,51] and may be regarded as predisposition/susceptibility factor to seizures and neuronal cell loss. This hypothesis is supported by the notion that long-term epilepsies per se do not inevitably damage the hippocampus (repetitively shown in cohorts of TLE patients with poorly controlled seizures).[2]

During a latency period, which usually extends into the 'teenager period', a number of structural and molecular reorganization mechanisms can be assumed. This model is difficult to address in human surgical tissue specimens obtained from an end stage of the disease. However, there is ample evidence from animal models of limbic epilepsy indicating a number of activity dependent reorganization events preceding the onset of spontaneous seizure activity. In particular, neurotransmitter receptor complexes dramatically change their molecular composition in a region-specific manner. Such modulatory changes can functionally reduce seizure threshold levels in the dentate gyrus.[52–54]

Following onset of spontaneous seizure activity within the hippocampal formation and mesial temporal lobe structures during adolescence, secondary changes associated with excitotoxic cell damage may lead to the full-blown pattern of MTS.[1] This model does not rule out that segmental neuronal cell loss can occur already during an earlier period. We do, however, propose that limbic seizure activity on its own cannot induce MTS without preceding anatomical and functional alterations in the hippocampus/dentate gyrus network. This assumption is supported by our studies in lesion-associated TLE, in which patients suffer from low-grade tumors, malformations or vascular lesions (Table 141.1). In these patients, the hippocampus does not unequivocally reveal neuropathological changes (Table 141.2) although seizure semiologies and clinical histories can be very similar to MTS-associated TLE patients.[1]

Our new MTS classification systems fits very well into this model, since most patients with classic or severe MTS (type 1a/1b) suffer from early precipitating injuries. In contrast, atypical patterns with cell loss restricted either to CA1 (MTS type 2) or to the hilus (MTS type 3) associate with later seizure onset.[20] Further studies will be warranted to extend and confirm MTS classification systems and to better stratify the heterogeneous group of TLE patients.

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142 Pathology of neocortical epilepsy

M Thom and S Sisodiya

Introduction

A range of focal developmental brain disorders and other cortical abnormalities are now recognized to be highly associated with intractable seizures. Diverse and subtle structural lesions can be identified by neuroimaging and further localized with regions of abnormal activity on EEG and functional imaging and in many cases they may be amenable to surgical resection. One goal of neuropathological examination and study of the tissue removed, above providing a tissue diagnosis, is to investigate more precisely the relationship between the abnormal neuronal and glial cell types identified, and their connections between the lesional and perilesional cortex. This can be correlated with preoperative studies and will continue to improve our knowledge of the cellular basis for seizure onset, which may lead to more directed surgical resections and further improve postoperative quality of life.

Neuropathology methods

Tissues from surgical resections carried out for the treatment of neocortical epilepsy are in general rapidly transported to the neuropathology laboratory fresh from theater in order to allow optimal tissue sampling. Where electrophysiological studies are being carried out on single cells or tissue slices, immediate immersion of the identified cortical region for study into cold, oxygenated, artificial CSF is necessary, from which thick (200–300 μm) vibratome sections are rapidly cut. Neuronal electrophysiological properties, can then be investigated and correlated with cell morphology and local connectivity.[1] Intraoperative marking of electrically abnormal areas identified by subdural grids also allows study of particular histopathological features in the seizure-onset zones in comparison to functionally more normal regions.[2] For structural abnormalities seen on MRI, reliable co-registration and mapping of the pathological changes in the resected specimen also requires careful tissue handling. Following removal, resected brain tissues naturally undergo distortion as well as significant volume changes when subjected to standard tissue fixation, processing and tissue sectioning methods. However, careful orientation and precise slicing of the specimen (Figure 142.1) with reformatting of volumetric MRI images may allow reasonable registration between the specimen and in vivo images.[3] Such methods will become particularly important when investigating more subtle pathological features, for example those in mild dysplasias.

Tissue sampling protocols for neocortical resections in epilepsy will vary between laboratories and with the type of tissue resection carried out. For example the availability of adjacent perilesional or more electrically and structurally 'normal' cortex depends on the underlying condition, operative approach, localization of lesion and functional eloquence of that cortical region. For many epilepsy pathologies, eg., low-grade tumors, complete resection may be more desirable rather than biopsy for the best post-operative outcome and for other lesions (e.g., cavernomas), additional resection of marginal tissue may be beneficial. Ideally, samples for freezing, routine formalin fixation and for electron microscopy should be taken from both the abnormal regions as well as 'more normal' regions. Such archiving of tissues is important both for future diagnosis and molecular research. In most neuropathology laboratories, standard histological stains for the routine diagnosis of neocortical lesions in epilepsy include cresyl violet (Nissl stain) with luxol fast blue to demonstrate abnormalities of the cortical laminar and myeloarchitecture and the presence of abnormal cell types. Immunohistochemistry panels are selected appropriate to the suspected pathology but neuronal markers such as NeuN, phosphorylated and nonphosphorylated neurofilament proteins, glial markers as GFAP and markers of interneuronal groups are more widely used as routine cellular markers in epilepsy neuropathology.

Neocortical neuropathologies in epilepsy

Common neocortical pathologies encountered in some reported epilepsy series, (not including the more frequent temporal lobectomy series reports), are listed in Table 142.1. The most common pathologies include cortical malformations (also discussed in Chapter 148), vascular malformations (Chapter 149), low grade tumors (Chapter 150), inflammatory lesions, in addition to cortical scarring and gliosis.

Focal neocortical malformations

The neuropathology of generalized malforma-tions due to abnormal cortical development are covered in Chapter 148. The main types of focal malformations encountered in epilepsy surgery are divided into three main groups: focal cortical dysplasis, mild dysplasias (mild MCD), and hamartomatous lesions.

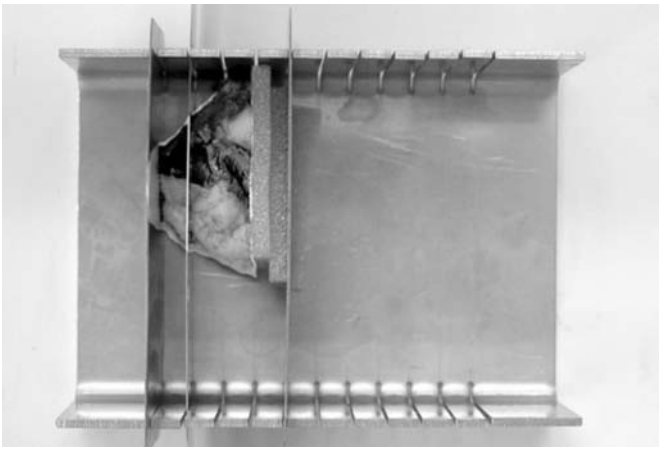

Figure 142.1 Simple metal cradles (7 × 5 cm) can be designed for the handling and slicing of cortical resection specimens in epilepsy to allow even slicing of blocks to correlate with preoperative MRI. In addition, particular regions of the specimen (as shown) can be linked intraoperatively for further localisation of abnormalities.

Focal cortical dysplasia

Focal cortical dysplasia (FCD) describes a type of malformation of cortical development where the abnormality is largely restricted to a region of the cortical plate and characterized by distinctive cyto-architectural changes. These lesions are easily recognized in histological sections but in the past the terminology used has lacked consistency between centers. Recent reappraisal of the nomenclature[4] has resulted in a widely adopted classification system of these lesions in most epilepsy centres which will facilitate their further study. In this system FCD is divided into two types, type I and II, based on the presence of specific neuropathological features as outlined in Table 142.2. Type II FCD, for example is characterized by the presence of abnormal cell types including *dysmorphic neurones* and *balloon cells*.

Macroscopic abnormalities may be present in surgical resections from FCD cases. There may be apparent thickening of the cortical gray matter, blurring of the gray-white border and the tissue may appear firmer. The overall lesion size varies and can be up to several centimetres broad, involving both sulci and gryri. On histological examination, abnormalities of cortical laminar architecture (also called 'dyslamination') are common to all types of FCD with loss of distinction between cortical layers, more easily visualised with Nissl stain or NeuN immunohistochemistry (Figure 142.2). Cortical layer I may often remain relatively cell-free and better defined than other laminae in the region of dysplasia, but may be broader or narrower than normal. The junction between the deep cortical layers and white matter is also typically ill-defined. A lack of radial alignment of neurones compared to normal cortex may also be present in FCD type II. However in FCD I, particularly in childhood epilepsy, an exaggeration of columnar neuronal arrangement has been reported.[5,6] Care should obviously be taken with the interpretation of any perceived cytoarchitectural abnormality in relation to normal regional variations.

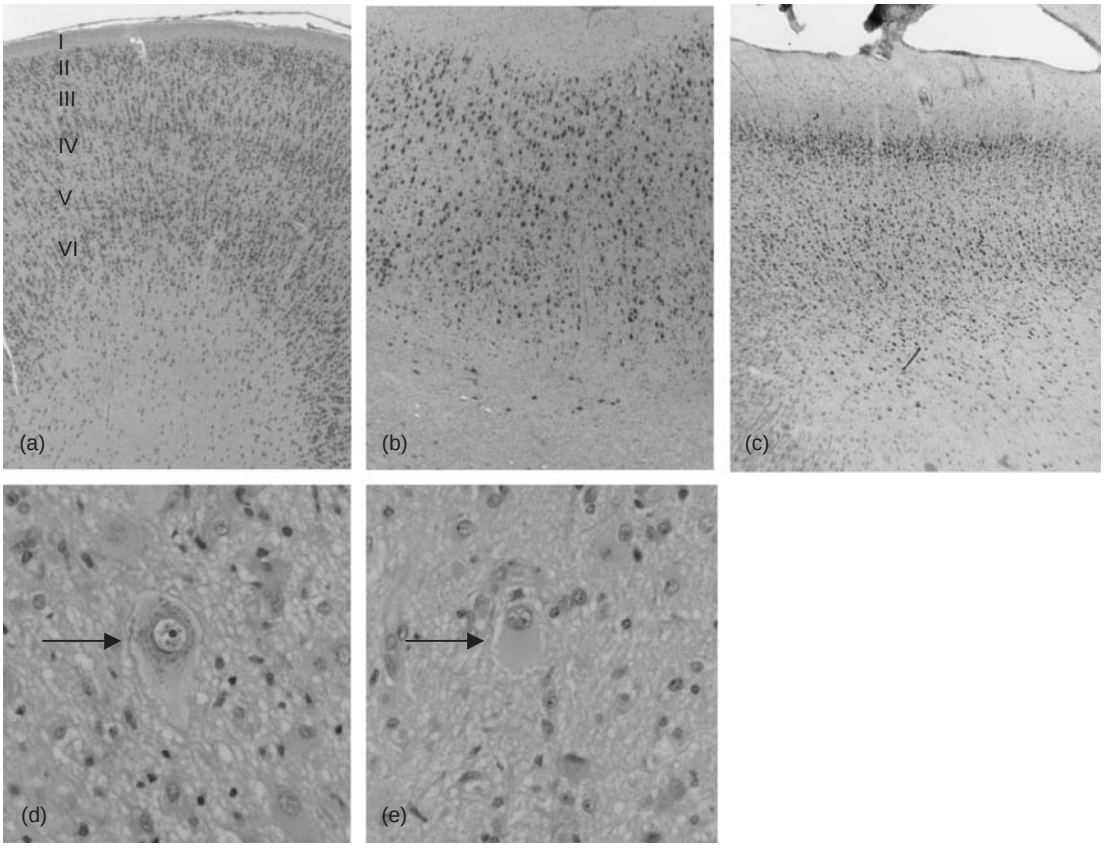

Figure 142.2 FCD type II highlighting changes in the cortical cytoarchitecture as seen with NeuN immunostaining. (a) Normal cortex with distinction between cortical laminae and in (b) in FCD although layer I remains well defined, clear distinction between deeper cortical layers is lost and in (c) a pediatric FCD case, dysplastic neurnones predominate in upper and lower cortical laminae and layer I appears broader than normal. (d) A dysplastic neurone in FCD in H&E preparation and (e) a balloon cell.

Table 142.1 Range of common neuropathological diagnosis in some larger reported epilepsy surgical series which included extratemporal resections (results shown in %)

Series (Ref)	Types of resection	Age of patients	Number of cases (time period)	Major MCD	Focal dysplasias: FCD Mild MCD Hamartomas	Vascular malformations	Low-grade tumours	Hippocampal sclerosis	Old scars/ gliotic/ atrophic lesions	Rasmussen's encephalitis/ others
Goteborg, Sweden 1999[1]	T (25%), F (21%), M (21%)	Children (0–18 years)	108	6%	22%	1%	8.5%	5.5%	53%	0.5%
	T (75%), F (15%)	Adults (18yrs+)	128 (8 years)	1.6%	12.5%	8.5%	10%	14%	51%	2.4%
London, UK 2001[2]	En bloc temporal lobe resection (excluding HS alone)	50% less than 20 years	80 (20 years)	3%	6% 2.5% hamartoma	6. 2%	75% (65% DNT 7.5% GG)	33% (a dual pathology – HS in isolation not included in this series)	–	9.8%
Cleveland, Ohio 2000[3]	Extratemporal neocortical resections	Mean age 21years; range 3 months – 57 years	133 (17 years)	-	37.6% 44.4% (neuronal heterotopia in white matter) 4.5% hamartoma	3%	20.9% (4.5% DNT 5% GG)	–	18%	RE=1.5% No pathology identified= 17%
Grenoble, France 2002[4]	Lesionectomy (11.6%) Corticectomy (49.5%) Combined (38.8%) 81.6% included temporal lobe	Mean age 24.5 years (range 2.5 to 61.2 years).	327 (10 years)	–	18%	4%	28% (18% DNT 8.8% GG)	31% (dual pathology in 5.5%)	5%	RE=1.2% No pathology identified = 15.6%
Bonn, Germany 2002[5]	Focal frontal lobe resections	Adult	68	–	26%	14%	35% (1.4% DNT 11% GG)	–	20%	5%

T = temporal, F = Frontal, M = Multilobar, DNT = dysembryoplastic neuroepithelial tumour, GG = ganglioglioma, HS = hippocampal sclerosis, EFS = end folium sclerosis, RE = Rasmussen's encephalitis, 'en-bloc temporal lobe resection' includes hippocampus and amygdala.

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Table 142.2 Pathological features of FCD subtypes as outlined in the system by Palmini *et al.* (2004)

Type	Subtype	Pathology features	MRI	Useful immunohistochemistry panel to aid lesion characterization
FCD type I	IA	Architectural cortical abnormalities ± features of mild MCD	Structural imaging – not usually identified	NeuN – to demonstrate cortical architecture
	IB	Architectural abnormalities and giant (hypertrophic) or immature neurones	Structural imaging – not always identified	*Hypertrophic neurones* Neurofilament proteins; Phosphorylated and nonphosphorylated heavy and light chain (enhanced expression), NeuN
FCD type II	IIA	Architectural abnormalities with dysmorphic neurones but no balloon cells	(May be normal) Increased cortical thickness Blurring of the gray-white junction	*Dysmorphic neurones* Neurofilaments NeuN Developmental proteins; Doublecortin, PSA-NCAM, Nestin, MAP1B
	IIB	Architectural abnormalities with dysmorphic neurones and balloon cells	Above plus Increased signal on T2 or FLAIR (extending toward ventricle in some cases)	*Balloon cells* Variable expression: GFAP, vimentin, neurofilaments, synpatophysin, CD34, CD133, nestin, doublecortin, MAP1B

MCD = Malformation of cortical development.

Abnormalities of the cortical myelo-architecture may also be striking features in FCD, with the presence of excessive and abnormally-orientated cortical myelinated fiber bundles. Myelin rarefaction of the immediate subcortical white matter is also a common finding.

The identification of abnormal cortical neurones and glial cells in FCD define the subtypes (Table 142.2). *Dysmorphic neurones* have an abnormal orientation, dendritic branching pattern and cytoskeletal structure (Figures 142.2 and 142.3). In Cresyl violet stained sections, the Nissl substance of these neurones appears abnormally clumped and eccentric thickening of nuclear membranes is seen. Such neurones may be present in any cortical lamina or may predominate in pyramidal cell layers III and V and are occasionally seen as single cells within apparently normal cortex away from the main lesion, or in clusters trailing into the underlying white matter. The abnormal orientation of these neurones ranges from slight rotation to complete inversion.[1] The dendrites show increased tortuosity but decreased spine density. *Balloon cells* have large round cell bodies with eccentric nuclei and pale pink, glassy cytoplasm on H&E. Multinucleate or giant cell forms are frequent. Cells with mixed balloon cell/ dysmorphic neuronal appearances may also be identified as indeterminate or transitional cell forms. Balloon cells lack axons and dendritic spines and tend to be located in deeper cortical layers, spilling into the white matter, but can be present throughout the cortex, including layer I (Figures 142.2 and 142.3). *Giant or hypertrophic pyramidal neurones* differ from dysplastic neurones in that they retain an overall pyramidal morphology and orientation but may present in any, or throughout all, cortical layers. These cells have abnormally tortuous but shorter dendrites, with increased branching. Their cross-sectional area is significantly larger than normal pyramidal cells.[1] *Immature neurones* are less frequently identified in FCD lesions. These are round or oval cells (diameter 10–12 μm) with a thin rim of cytoplasm and rudimentary dendrites and they may aggregate in clusters.

Although these abnormal cell types are readily recognizable in routine sections, immunohistochemistry may aid their further characterization and classification (Table 142.2 and Figure 142.3). Neurofilament gene expression has been shown to be augmented in FCD neurones[7] and immunopositivity may highlight abnormal morphology, alignment and laminar position (Figure 142.3). Dysmorphic neurones are also highlighted with silver stains, such as Bielchowsky (Figure 142.3) although tau-positive Alzheimer disease-like tangles are only rarely present in these neurones and usually in older patients. In addition, in many abnormal cell types in FCD there is aberrant expression of developmentally-regulated proteins (Table 142.2). Strong cytoplasmic immunopositivity of abnormal neurones in FCD may be seen for nestin[8] whilst balloon cells show variable expression of nestin, vimentin, GFAP, neurofilaments, and MAP1B, an immature MAP isoform.[9] More recent studies have also shown membranous expression of stem cell markers CD34 and CD133 in balloon cell populations located predominantly in the white matter.[10,11] Co-expression of both neuronal and glial markers by abnormal cell types is also another common finding,[9,12] confirming aberrant glial-neuronal differentiation. These findings reflect the likely mal-developmental origins of FCD.

How these abnormal cell types may be involved in the generation of seizure activity is under study. Single cell recordings from dysplastic neurons have demonstrated abnormal intrinsic membrane properties and ion channel functions.[1] Using current clamp techniques in in vitro slice preparations however, no spontaneous epileptiform depolarisations

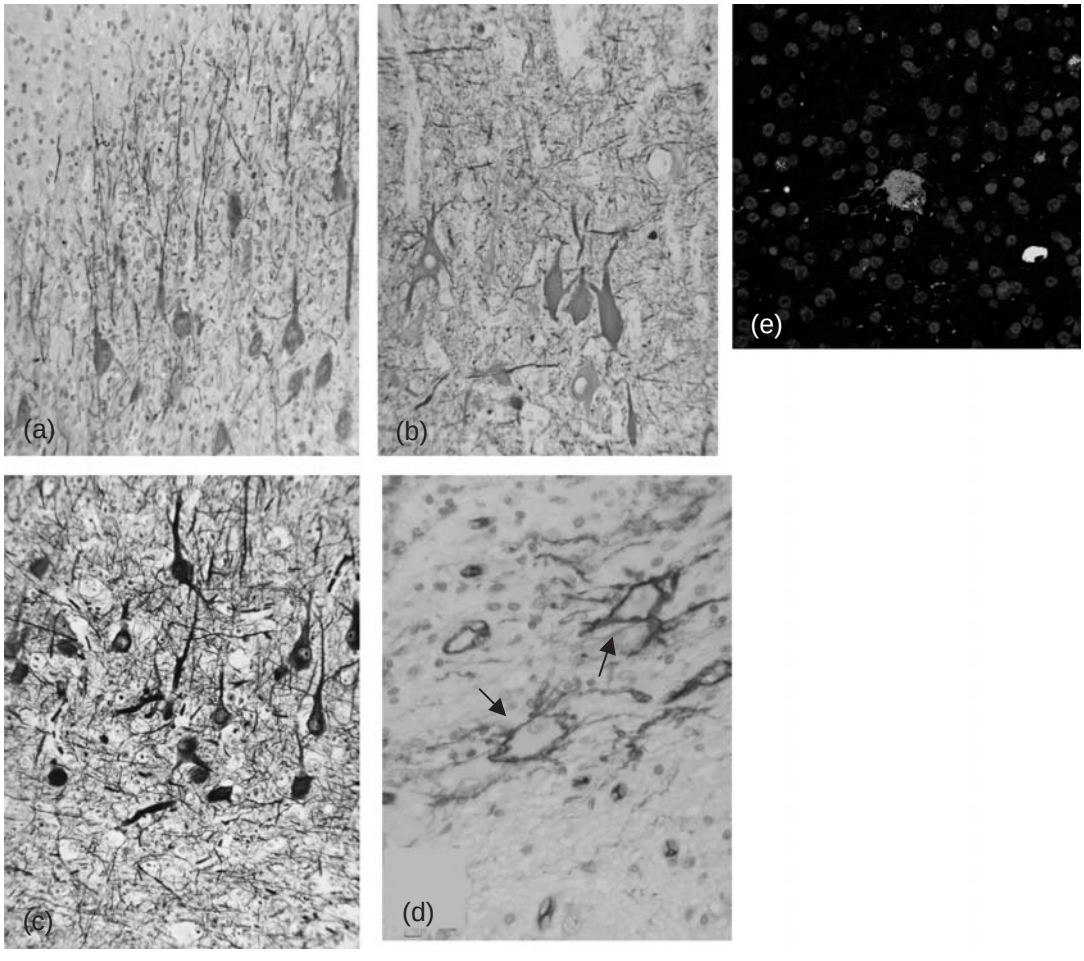

Figure 142.3 Cell types in FCD type IIB. (a) Hyertrophic pyramidal neurones in layer III show strong immunolabelling with nonphosphorylated neurofilament antibodies (SMI32) and in (b) labelling of dysmorphic neurones and numerous processes in the cortex is shown with phosphorylated neurofilament epitope (SMI31). Dysmorphic and hypertrophic neurones in FCD II can also be highlighted with silver stain methods (c). Membranous expression of CD34 on balloon cells in the white matter is a common finding in FCD IIB (d). Proliferative potential of balloon cell populations in FCD type IIB is demonstrated by double labelling for cell cycle marker Mcm2 (nuclear stain, green) and nestin (red) (e). (See Color plates.)

in cytomegalic neurons were noted, suggesting they are unlikely to operate as 'pacemaker' neurons.[13] Balloon cells do not display spontaneous synaptic current or action potentials[1] and lack synaptic contacts[14] suggesting they are relatively inert bystanders. Direct electrocorticographic recordings also support that the centre of the FCD lesion containing balloon cells are less epileptogenic than other regions.[2] In these patients the epileptogenic regions mainly reside in the surrounding regions that are dysplastic but relatively devoid of balloon cells.

The dysmorphic neurons in FCD show increased expression for glutamate receptor subunits, including NMDA receptors.[15] These are heteromeric receptors assembled from NR1, NR2A-D and NR3 subunits and the composition confers specific physiological properties, for example sensitivity to Mg^{2+} blockade. Normal cortical neurons mainly express NR1 and NR2A NMDA receptors. Studies of NMDA receptor subunit expression in large dysmorphic neurons show increased NR1 and NR2 immunolabelling, indicative of a greater number of receptors per cell, although overall receptor density may not be increased.[14] Reports also suggest varying alterations in subunit composition and assembly of NMDA receptors in these cell types in FCD, considered likely to influence their electrophysiological output[16–18] as well as synaptogenesis and possibly neuronal migration during development. AMPA receptor mRNA is also increased in dysplastic neurons.[16,19] A potential role for the differential expression of NR2B in dysplastic neurons was validated in recent in vitro electrophysiological studies in freshly resected human slices; Ifenpordil, a specific inhibitor of the NR2B subunit of the NMDA receptor almost completely suppressed epileptiform discharges in FCD types I and 2A but had no effect on control tissue.[18]

In further support of a local excitatory-inhibitory imbalance in FCD lesions there is evidence for a reduction of number of local inhibitory interneurons and terminals in FCD type II lesions using labelling for GAD, parvalbumin and calbindin.[20,21] $GABA_A$ receptor subunit ($\beta1$, $\beta2$, $\alpha1$, $\alpha2$) mRNAs are decreased in abnormal neurons of FCD[19] as well as in TSC lesions[17] and a reduction in GABA transporter 1 (GAT1) has also been shown in FCD.[20] This potential deficit in inhibitory input may have a role in intrinsic bursting of excitatory neurons. However, other studies propose preserved GABAergic activity in the region of dysplasia[13] and hypertrophic, inhibitory synaptic terminals are often seen to surround dysplastic neurons in ultrastructural studies.[14,20,22] Indeed, recordings from in vitro slice preparations of FCD have implicated a role for GABAergic synchronisation of ictal discharges.[23]

The pathogenesis of FCD is unknown. It is widely considered to represent the result of arrested neuronal migration, abnormal differentiation, progenitor cell proliferation or programmed loss of neurones during cortical development possibly following some localised insult. Abnormal numbers of cortical neurones have been shown in FCD lesions[24,25] with preservation of the proliferative potential of balloon cells (Figure 142.3). FCD is not familial and there is no animal model that exactly resembles the human counterpart. It is plausible that FCD results from a somatic mutation in precursor or progenitor cell populations during development. Single cell analysis has shown that the cells within FCD are not clonally derived but probably arise from mixed populations of progenitor cells.[26] As the histological features of FCD IIB are similar to neocortical tubers of the tuberous sclerosis complex (TSC) (see Chapter 156) several research programs have sought to identify a common genetic link. Sequence alterations (polymorphisms) in the *TSC1* locus and loss of heterozygosity have been identified in FCD type IIB[27] but not in FCD IIA samples[28] potentially implicating TSC genes in balloon-cell containing FCD lesions as distinct from other FCD types. The TSC gene products interact with several intracellular signalling pathways, including Rap1 (binding with ezrin which effects cell adhesion, migration, polarity and cell cycle progression), dysregulation of the insulin signalling mTor/p70SK-S6 pathway (influences cell size and proliferation) and the wnt-1/β-Catenin pathway (implicated in cell survival, cell shape and differentiation, polarity and migration). Molecular studies utilising single cell capture, however, have also disclosed differences between balloon cells and giant cells in FCD and tubers suggesting that the pathological mechanisms in operation are not identical in these lesions.[29–32] Furthermore histological and molecular similarities also exist between FCD and more extensive malformation causing hemimegalencephaly (HME). HME is often sporadic and associated with epilepsy, but occasional linked with syndromes such as linear sebaceous neavus syndrome, proteous syndrome and rarely TSC. Like FCD, activation of the wnt-1/β-catenin pathway has been shown in HME.[29] The reelin and cdk5 signalling pathways have also been implicated in the pathogenesis of FCD, as mice deficient in these proteins display marked cortical laminar abnormalities. Finally there is also an alternative hypothesis, although with relatively less evidence to support it, that FCD is a localised lesion that occurs as a result of cortical structural re-organisation and plasticity following a prior cerebral-cortical insult, for example early cerebral trauma.[33–35]

Mild MCD (malformation of cortical development) in neocortical epilepsy

Mild MCD in epilepsy encompass the more subtle end of the spectrum of focal cortical malformations. These lesions were previously labelled microdysgenesis or architectural dysplasias. Microdysgenesis (or microscopic dysplasia) has been used to cover a wide variety of microscopic minor cyto-architectural cortical abnormalities, including poor distinction between laminar boundaries, an excess of cortical neuronal clusters, an excess of layer I and white-matter neurones and prominent perivascular oligodendroglia-like cell aggregates among others.[36–38] Mild MCD is a term used more discriminately and in the updated Palmini classification, they are divided into two categories: *type I* with ectopic neurones placed in or adjacent to layer I and *type II* with microscopic neuronal heterotopia outside layer I (Figure 142.4). Cortical laminar abnormalities are now included under FCD type IA.

Excess single or 'ectopic' neurones in layer I in mild MCD type I may have varied origins including residual preplate cells from earlier developmental stages (for example, reelin-secreting Cajal-Retzius cells),[39] other early neurones of the marginal zone, abnormally persistent subgranular cell layer neurones, radial migrating GABAergic neurones from the ganglionic eminence or heterotopic cortical plate neurones. In some cases, layer I hypercellularity is readily apparent on qualitative inspection of resected tissues, with occasional formation of nodular aggregates. Quantitative evaluation to distinguish Mild MCD type I from normal cortex may prove of practical value but is time consuming.[21,24,25,39,40] As yet there is no established immunohistochemical panel that can distinguish 'ectopic' from normal layer I neuronal populations and therefore in many cases the diagnosis based on routine stains may be difficult.

Similarly with Mild MCD type II, which includes ectopic single white matter neurones, there are practical diagnostic issues in the separation of pathological 'ectopia' from normal interstitial neurones of the white matter, particularly in the temporal lobe where such cells are more numerous. Possible origins of white matter neurones in mild MCD type II include an excess of residual subplate cells or 'true' heterotopic cortical plate cells. White-matter neurones have mixed morphologies and include pyramidal and small inhibitory interneurones. Several quantitative studies have been carried out, mainly in temporal lobe epilepsy, and confirm higher white matter neuronal densities compared to controls but diagnostic criteria differ between these studies regarding the types of neurones included and the method of quantitative analysis.[38,40–42] Furthermore, in epilepsy, processes such as atrophy and gliosis affect tissue volume and may falsely exaggerate cell number.

Consequently there is less consensus agreement on the diagnosis of mild MCD compared to histologically more easily-recognized forms of FCD. The frequency of mild MCD, in both temporal lobe and neocortical epilepsy is uncertain, with reports suggesting figures of between 16.7–43% in surgical series.[37,43,44] Furthermore as both type I and II mild MCD are typically not visible using current neuroimaging techniques, neuropathology remains the only method of detection. The pathogenesis of mild MCD is unknown. There are some animal models, such as the Ihara rat, which show microdysgenetic features reminiscent of the human trait. As to an underlying genetic basis for Mild MCD, a recent study demonstrated TSC1 genomic sequence polymorphisms in surgical epilepsy specimens showing single white matter neuronal heterotopia and lesions of FCD type I.[28] In contrast to FCD type II, there is as yet little evidence confirming a direct link between mild MCD and cortical epileptogenesis. An excess of layer I neurones with cell hypertrophy was particularly associated with infantile spasms in one study.[24] However, mild MCD-like pathologies have also associated with other behavioral and cognitive conditions without seizures.[4]

Dysplasias adjacent to low grade tumors in epilepsy

Focal dysplasia has also been reported in the context of epileptogenic low-grade glioneuronal tumours, such as DNT and

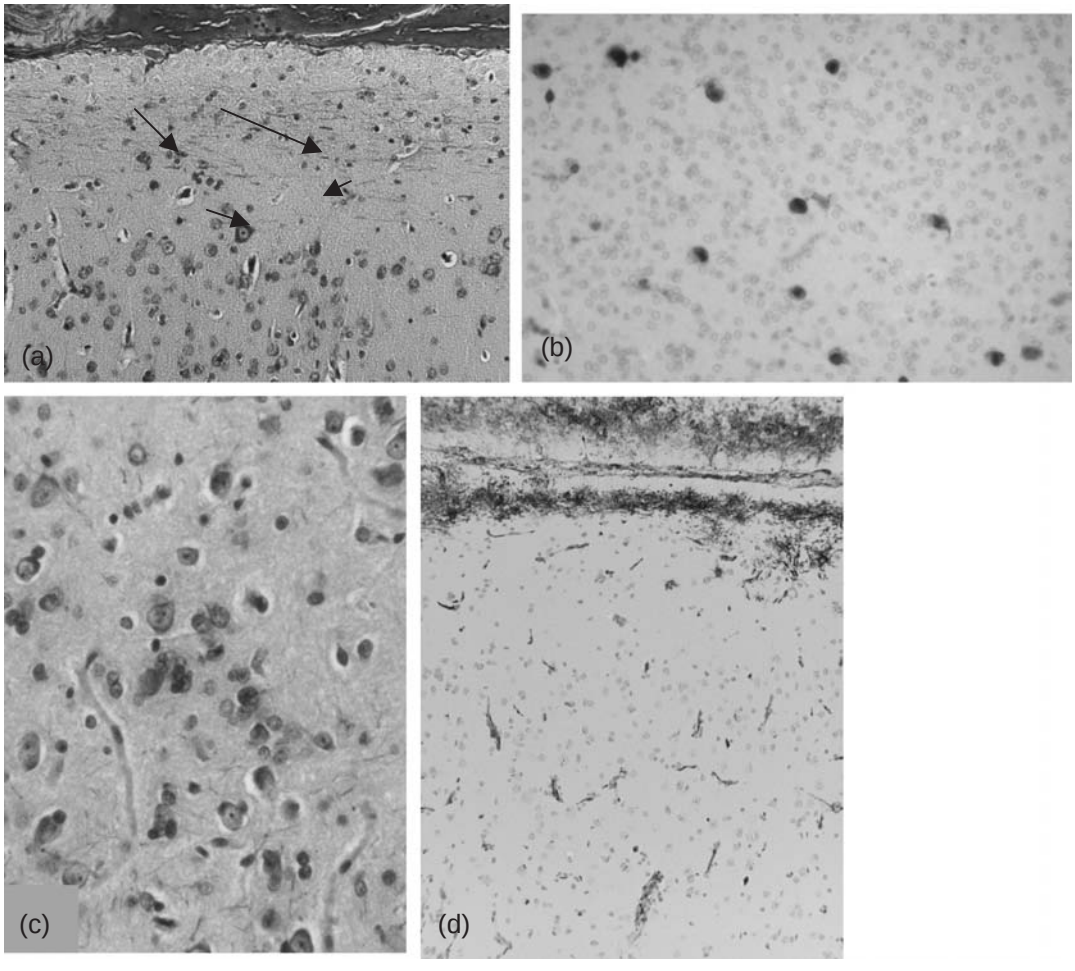

Figure 142.4 Mild MCD. (a) Subtle changes in cortical cytoarchitecture described in Mild MCD include and excess of ectopic neurones in layer I as seen in this Nissl stained section showing a cluster of small neurones (long arrow) and a single large ectopic neurone (short arrow). (b) An excess of single mature neurones in the white matter is one feature of Mild MCD type II, as shown here with NeuN staining. The cortex adjacent to epileptogenic glio-neuronal tumours may show dysplastic features including hamartia like aggregates of immature neurones (c) and an excess of small cells and immature neurones in layer I as highlighted with CD34 staining (d). (See Color plates.)

ganglioglioma, possibly indicating a common biological origin. The type of cortical dysplasia reported varies but is usually cortical/dyslamination (corresponding to FCD type IA). Layer I hypercellularity or a 'subpial cellular band' (mild MCD type I) is also commonly reported[45–47] (Figure 142.4). Clusters of immature neuronal cells mixed with mature neurones and glial cells forming aggregates around 0.2–1 mm across are also common findings in the cortex adjacent to these tumours. These are often referred to as hamartias or 'microdysgenetic nodules'.[48] They may represent tumour precursor lesions and can escape detection on routine H&E but are highlighted with immunolabelling for nestin or the stem cell marker CD34, particularly when in the temporal lobe.[49,50] More severe types of cortical dysplasia, such as balloon cell types of FCD, are rarely reported in association with DNT or ganglioglioma.[47]

The diagnosis of additional cortical dysplasia must be distinguished from disturbance to the cortical architecture resulting from local tumour infiltration. The presence of of cortical dysplasia in the vicinity of glioneuronal tumors raises the possibility of a common biological origin and furthermore the question of the source of the intrinsic epileptogenicity, which is important for surgical management. Intracerebral EEG recordings in ganglioglioma suggest that ictogenesis resides in the itself.[50] The exact mechanisms resulting in hyperexcitability remain to be determined; the prominent mature and immature neuronal component of these tumours is one obvious explanation and expression of several glutamate receptors subtypes on both the neuronal and glial component have been shown[51] and may contribute to proepileptogenic circuits integrating with the adjacent cortex.

Hamartomata in neocortical epilepsy

Hamartomata occurring in epilepsy are a relatively poorly-defined pathological group compared to cortical dysplasias and tumors, being less well represented in epilepsy surgical series. *Glio-neuronal hamartomata* have been described in various cortical locations, particularly temporal and frontal lobes. They are composed of circumscribed masses of mature, but haphazardly arranged, cell types.[52] The imaging characteristics are variable[53,54] but their lack of growth and mitotic activity help to distinguish these lesions from low grade tumors.[52] Following resection recurrence is unusual. The *hypothalamic hamartoma* is a distinct lesion that has a strong association

with intrinsic subcortical epileptogenesis, particularly manifesting with gelastic seizures and may be associated with the development of secondary cortical epileptogenesis[55] and is further discussed in Chapter 43. Unlike the tuberous sclerosis complex, hamartomas or malformative cortical lesions are relatively rarely reported in neurofibromatosis type 1 (NF1) a syndrome in which epilepsy occurs in up to 6% of patients. Neurofibromatosis type 2 (NF2) can be associated with multiple cortical glial micro-hamartomata that are often incidental findings at post mortem, in addition to meningioangiomatosis. *Meningioangiomatosis* (MA) is a presumed hamartomatous developmental lesion, as distinct from meningeal tumours. It is associated with epilepsy, more commonly in sporadic MA (over 80% of patients) than for MA associated with the NF2 complex.[56] MA more commonly occurs in the frontal or temporal lobes forming a superficial or plaque-like hemispheric mass. Histologically it is composed of an intracortical and leptomeningeal collection of small blood vessels and perivascular spindle cells. The intervening cortical parenchyma can appear disorganized and gliotic and neurofibrillary tangles may be present. The more common sporadic form of MA is typically solitary and EEG suggests the epileptogenicity is confined to the adjacent cortex. Indeed, seizures may persist in over half of patients following surgical treatment.[57] It is unexplained as to why patients with MA in NF2 typically do not manifest with seizures.[56]

Rasmussen's encephalitis

Rasmussen's syndrome or encephalitis is a rare, progressive unilateral neurological disorder, typically presenting in childhood with intractable focal seizures (see Chapter 44). Cortical inflammation, neuronal loss and gliosis of one hemisphere are the typical pathological findings in surgical resection specimens, including hemispherectomies. The inflammation is often patchy even in a localized region of the brain. It appears to proceed through various stages of activation representing the presumed immunological destruction of the cortical parenchyma. The early stages are marked by infiltrates of T lymphocytes, microgliosis and astrocytosis (Figure 142.5). In end stages, there is marked neuronal loss, and pan-laminar cortical cavitation.[58] There is a correlation with the pathological stage and the duration of the illness, although within a single specimen regions at non-contiguous stages may be in close proximity. In addition the pathology may be more severe in patients with younger age of onset, suggesting brain maturity may modulate the inflammatory response.[59] The aetiopathogenesis of Rasmussen's encephalitis remains unknown; T-lymphocyte cytotoxicity is currently favored over viral infection.

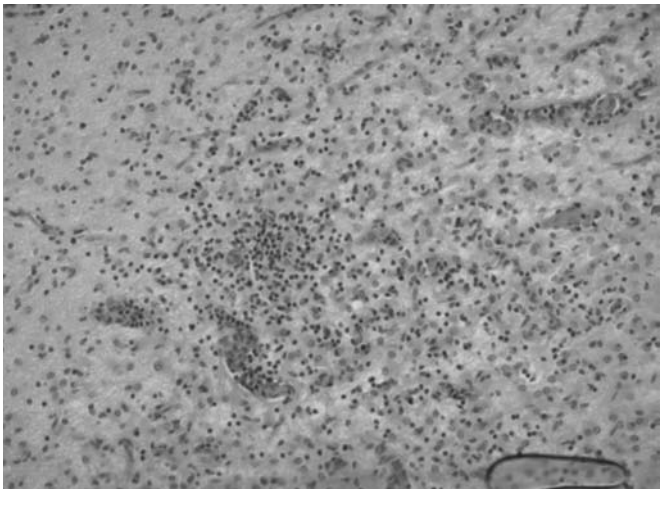

Figure 142.5 Active stage of Rasmussen's encephalitis with infiltrates of lymphocytes in the cortex and early cortical neuronal loss, cavitation, and gliosis.

Nonspecific cortical scarring

The neuropathology of old traumatic scars and cerebral injuries are discussed in Chapter 156. In some neocortical resection specimens subtle degrees of cortical scarring are present and do not appear to be directly attributable to cerebral trauma or perilesional changes and more likely represent tissue changes as a result of seizures themselves. Recurrent generalized seizures or episodes of status epilepticus can result in laminar cortical neuronal loss (Figure147.6) typically involving pyramidal neurones with a corresponding laminar gliosis. Gliosis may also be marked in the subpial region and in the white matter, where perivascular atrophy, vascular degenerative changes and deposits of corpora amylacea are not infrequent findings. The cause of these 'nonspecific' degenerative changes is unknown. Recent studies, however, highlight the importance of not dismissing glial cell proliferations in epilepsy as a mere structural scarring reaction as these cells have important physiological properties. Glutamate released from glial cells can activate neuronal NMDA receptors with the capacity for epileptiform discharges[60] and through establishing local pathological networks, could be a mechanism for synchronising local neuronal activity.[61] Glutamate receptors are also expressed on astrocytes[62] which may also form an extensive syncytium via gap-junctional coupling. Astrocytes have roles in neurotransmitter transport and regulation of levels in the extracellular space. Therefore, proliferation of these glial cells in regions of scarring may potentially play a functional role in neocortical epilepsies and seizure spread.[63]

Molecular and genetic research in epilepsy neuropathology

Access to well-preserved human brain tissue with a detailed history of insults, seizures, and drug exposure, through surgical programs for the treatment of drug-resistant epilepsy, is one of the great advantages researchers in epilepsy have compared to those working in other neurological diseases. Mostly such material consists of varying amounts of tissue, usually including hippocampus, from the temporal lobe, but focal or lobar extratemporal or even hemispherectomy material is sometimes also available. Studies have been undertaken on fresh and fixed tissues, at macroscopic, microscopic, immunohistochemical, electron microscopic, molecular and genomic and functional levels, mainly in hippocampal sclerosis, but also to lesser extents in tumors, brain malformations (including vascular malformations), traumatic brain injury and other pathologies. The range of research is enormous, and

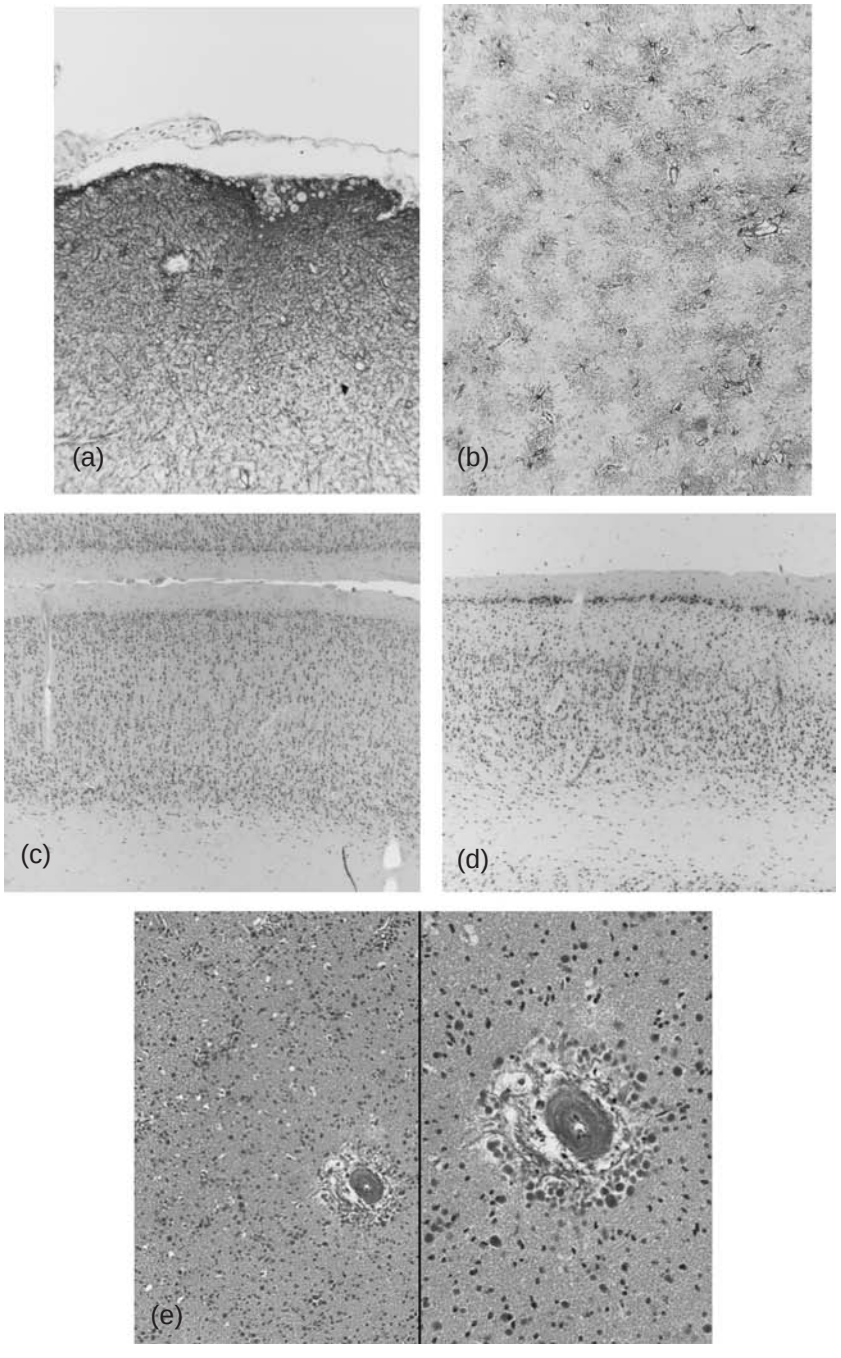

Figure 142.6 Nonspecific cortical changes in patients with epilepsy include regions of superficial cortical and subpial gliosis as seen on GFAP stain (a), areas of cortical gliosis (b). Neuronal loss may be identified in superficial cortical layers (d) compared to normal cortex (c). Marked accumulation of corpora amylacea may be present in the white matter and around small vessels (e) as well as the cortex. (See Color plates.)

only general principles and illustrative brief examples can be given. The interested reader is referred to detailed texts and reviews.[63]

Investigation has revealed a gamut of changes in the two most common surgically-resected pathologies, hippocampal sclerosis (HS) and focal cortical dysplasia (FCD), ranging from changes in entire cell populations, loss of specific immunophenotypic subtypes, alterations in cell morphologies, distributions and processes, disruptions to cellular architecture, genomic expression,[31] protein signatures, processing and function:[16] most of this work has been immunohistochemical, but electron microscopic and functional studies have also contributed.

Genomic investigations are only beginning to be undertaken, and are well illustrated by work from Peter Crino's group. Thus, for example, the possible clonality of origin of cells in FCD has been considered; more recent data raise the possibility of somatic mutation underlying FCD[29] and hemimegalencephaly, with extensive changes in entire cellular pathways such as the mTOR cascade.[30] The use of single-cell laser capture microdissection and single cell mRNA amplification and analysis will become more widely applied, and

integrated with examination of variation in germline DNA, to produce comprehensive pictures of pathophysiology using neuropathological material.

There remain problems. Completely normal comparable brain tissue is very difficult to obtain; most studies that include control tissue use adjacent histologically-normal tissue, but this has its detractors. Almost universally, only a single time point can be examined from one individual, in comparison to animal models: cause and effect, and disease progression, can only be inferred or separated with additional information. There are threats to the availability of tissue from issues of consent, misuse, and legislation, but there is also recognition that these tissues are invaluable for advancing understanding. Undoubtedly, there is still much to be learnt from modern neuropathological analyses of epilepsy brain material.

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143 Pathology of malformations of cortical development

R Spreafico and AJ Becker

Cortical development

At the end of the 18th century Camillo Golgi described glial fibers 'radiating' from the central canal towards the periphery of the spinal cord suggesting that '... the key for the solution of many questions is enclosed in the embryogenesis of the nervous central organs'.[1]

Santiago Ramón y Cajal, aware of the works of Golgi, published his first report on the developing cerebral cortex in 1889 stating that cell division occurred preferentially in the 'vicinity of the epithelium', that neuroblasts migrated beneath the outer part of the developing cortex and that radial glia served as scaffold structure for embryonic development.[2]

A particular hallmark regarding mechanisms of cortical development is represented by Rakic's work[3] who clarified the intercellular neuron-glia relationship demonstrating that 'late-generated cells find their way to the cortex by assuming a bipolar shape and moving outward in direct and constant apposition to radial glial processes that span almost the entire width of the telencephalic wall'.

More recent findings provided evidence for distinct nonradial migration routes of certain cell cohorts that migrate parallel to the pial surface. Further novel data indicate that radial cells are capable, by asymmetric division, to give origin to neurons and glial cells, thereby pointing towards the neurogenic potential of radial glial cells.[4–8]

Cell proliferation, migration, differentiation, maturation, as well as programmed cell death represent the fundamental events involved in the developmental shaping of the cerebral cortex.

At the beginning of cortical development, a homogeneous population of undifferentiated cells is present, organized as a pseudostratified columnar epithelium, and called the ventricular zone (VZ). From these undifferentiated cellular population, the neocortex is generated through successive and partially irreversible steps and the final laminated cortex of mammals, including humans, is generated through the formation of transient structures.

After the appearance of the VZ, a new area, called the marginal zone (MZ), is formed just below the pial surface. This area is supposed to be the first functionally active zone of the developing cortex. It constitutes the site of initial synapses formation with brainstem-derived afferents. The MZ also promotes the maturation of early generated neurons in the subpial region, presumably triggering the subsequent migratory events.[9] Thus, the appearance of the MZ marks the initial event of cortical neurogenesis and precedes the formation of all the other cortical layers. The superficial lamina containing the first differentiated neuronal elements is termed primordial plexiform layer (PPL).

Subsequently, after a mitotic cycle, the neuroblasts from the VZ migrate upward and by arrival of the first migratory neurons the PPL is split into two regions. The most dorsal one, close to the pial surface, becomes the prospective layer I; the second one, named the subplate (SP), lies below the newly arrived cohort of neurons forming the cortical plate (CP). The SP is considered the area recipient of fibers incoming from subcortical structures, which establish synapses with the neurons of SP, and represents the waiting compartment for these afferents during CP development. SP neurons are destined to die later on through a process of programmed cell death, and the fibers will then be released to reach their appropriate and final cortical target.

During further developmental stages, the thickness of the CP progressively increases due to the arrival of subsequent waves of migrating neuroblasts. This process follows an inside-out sequence, i.e., the early generated and migrated neurons will form the deep layers of the future neocortex, displaced downward by the neurons generated later and forming the most superficial layers.[9,10] By these mechanisms, layers II through VI are formed.

As mentioned above, two main trajectories, a radial and a tangential route, have been identified for neuronal migration. The process of radial migration implies that newly generated neuroblasts from the proliferative zone migrate to the CP climbing along radially oriented fibers that extend from the ventricle to the pial surface.[6–8,10] Radially migrating neurons give rise primarily to pyramidal neurons (i.e., projection neurons), which are excitatory and utilize glutamate as main neurotransmitter.

Nonradially migrating neurons are generated in the ganglionic eminence, the primordium of the future basal ganglia, located in the ventral forebrain. The cells generated in the ganglionic eminence follow a long tangential migratory route to reach the CP and constitute the majority of non pyramidal neurons (i.e., cortical interneurons), which are GABAergic.[4–6]

These two migratory mechanisms have been extensively studied in animal models; although in principle they are present also in humans, recent data suggest that the population of GABAergic neurons reaching the cortex through tangential migration is only 20–30% of the total inhibitory population resident in the adult neocortex.

Thus, during cortical development, a spatially and ordered sequence of migratory events is accomplished to construct the cerebral cortex. Although the intimate processes leading to the mature cortical structure are not yet completely understood it is evident that both intrinsic (genetic) and environmental mechanisms are involved in corticogenesis and that disturbances of these processes can result in a wide range of alterations, from severe brain malformations to local disruption of cortical structure.

Malformations of cortical development (MCD), recognized as pathologically since the end of the 19th century, constitute a heterogeneous group of focal or diffuse anatomical derangement with pathological features more largely depending on the timing of the defect within the developmental process than on its cause.

The advent of high-resolution imaging techniques, particularly magnetic resonance imaging (MRI), made it possible to diagnose MCD in vivo and, several types of partial epilepsies previously defined as cryptogenetic are now recognized as secondary to cortical lesions. As a consequence correlations between imaging and electroclinical data have increased the number of patient that appear as candidates for surgical treatment.

Neuronal migration disorders (NMDs) are generally considered a subgroup of MCD, and their definition may imply that disruption of migration is the only mechanism on which the malformation is based. However, not all the so-called NMDs have been shown to be due directly to impaired neuronal migration, and other mechanisms are therefore involved.

The cortical malformations previously grouped under the general term of NMDs are currently diversified to reflect the improved knowledge of the pathological substrate, the possible aetiological factors and the relationship between altered structural features of the malformation and type of epilepsy.[11–15]

Lissencephaly

Abnormalities related to cortical development may either affect proliferation and lead to abnormally sized and shaped neuronal and glial cells or be associated with aberrant neuronal migration, which results in abnormal neuronal positioning and compromized cortical architecture.[12] Migration of virtually all cortical neurons is severely affected in lissencephaly. This alteration goes along with an abnormally smooth cerebral surface.[16] Classic lissencephaly shows a prevalence of 11.7 per million births.[17] However, the prevalence of milder forms of the disorder remains undetermined. Initially thought to be an extremely rare disorder going along with severe epilepsy, retardation and early death, MRI reveals individual patients to survive until adulthood.

In normal brain development, the even, agyric cerebral surface, which is present until the 11th week of gestation, is replaced by gyral architectures developing from the area of the sylvian fissure during the following weeks. Gyration is physiologically terminated around the 32nd fetal week. The determination stage for pathological manifestation of a lissencephalic compromised brain development is between fetal weeks 11–13.[18] Transitional forms between lissencephaly/agyria and pachygyria occur. In pachygyria, the cortical architecture appears more advanced compared to agyria.

Different genetic causes underly lissencephalic brain abnormalities, which can lead to substantial alterations with respect to the distribution of the pathological alterations as well as the aberrant cortical architecture. Linkage studies have particularly pointed towards alterations in two genes, i.e., doublecortin (*DCX*) on the X chromosome[19] and *LIS1* on chromosome 17.[20–22] Mutations in *DCX* cause lissencephaly (XLIS) in hemizygous male individuals and subcortical band heterotopia (SBH) in heterozygous females.[23,24] DCX is a microtubule-associated phosphoprotein maintaining cytoskeletal plasticity during axonal outgrowth, neuronal maturation and cell migration.[25] Impaired DCX function in vitro results in interruption of microtubuli. Thereby, the cellular shape and cytoskeletal function as well as cell migration are compromised in vivo.[19,26,27] The combination of high resolution MRI and genetics has recently shown that women with nonsydromical mental retardation, epilepsy and normal MRI may have *DCX* mutations. Women were identified due to male relatives with subcortical band heterotopia or lissencephaly. Therefore, *DCX* may be regarded as candidate gene for women with cryptogenic epilepsy and retardation in the absence of male relatives or a known relevant family history.[28]

Heterozygous deletions of the chromosomal region 17p13. containing *LIS1* underlie extensive phenotypical alterations, summarized as Miller-Dieker syndrome, which comprises severe lissencephaly, craniofacial defects, substantial EEG abnormalities. The syndrome generally is associated with a reduced lifespan. Intragenic deletions or mutations of *LIS1* cause isolated lissencephaly. *LIS1* codes a subunit of the acetylhydroxylase and is expressed by Cajal-Retzius cells.[29,30] Other genes located on chromosome 17p are likely to be involved in the phenotype of the Miller-Dieker syndrome. A recent study has identified at least one gene in this region that influences neuronal migration, YWHAE, which encodes a protein termed 14-3-3ε.[31] It has been pointed out, that the pachy- or a-gyral alterations associated with *LIS1* are pronounced in the posterior occipital area, whereas the structural abnormalities in XLIS are more pronounced in the anterior occipital brain.[23]

LIS1 is expressed and may have a structural role in the adult human brain. It is differentially activated by seizure activity in animal models.[30] *DCX* is regarded to be expressed in the human brain only during development. For both genes, an immediate link between the mutational event and a causative, phenotypic effect has not been shown and does not appear very likely. Epileptic seizures may more probably occur due to complex functional changes resulting from disruption of the normal development of the cortex and white matter and an aberrant neuronal network architecture.

Another form of lissencephaly with an autosomal-recessive transmission mode is caused by deletions in the reelin (*RELN*) gene.[32] In the affected individuals, moderately severe pachygyria is associated with extensive cerebellar hypoplasia. In addition to seizures, severe hypotonia and developmental delay constitute clinical hallmarks of the syndrome.

Type-II-lissencephaly is represented by alterations described as 'pachygyric micropolygyria'.[33] The cerebral surface appears agyric but not smooth. Histologically, abundant and confluent microgyri are present. In the cerebellum multiple cortical

heterotopias are present. Type-II-lissencephaly is frequently associated with oculocerebellomuscular anomalies including the Walker-Warburg-syndrome.[34] or the Fukuyama-type congenital muscular dystrophy.[35,36]

Pathological hallmarks of the lissencephalic brain are absence (agyric) or decreased presence (pachygyric) of convolutions. In pachygyria, the gyri appear flat and smoth. The border between gray and white matter appears unsharp and the cortical organization is severly compromised. With respect to histopathological alterations, two types of lissencephaly are distinguished (Figure 143.1)[37]: *type-I* reveals a thick, only rarely differentiated cortex under a smooth, rather agyric cerebral surface. White matter appears rather thin. The cortical area is composed by four layers:

- A marginal (molecular) layer
- An outer neuronal layer
- A cell-depleted layer with tangentially orientated myelinated fibres
- An inner neuronal layer.

This architecture is typically present in the Miller-Dieker syndrome. The neurons that are compromised in migration may form an additional cortical layer in the white matter, which may result in a double cortex.

The *type-II* lissencephalic phenotype relates to pachygyric alterations, reduced gyration of the cerebral surface and increased width of gyri. The claustrum in most cases is absent. Additional alterations occur in the medulla-cerebellum area, where impaired neural migration in the cerebellar cortex as well as heterotopias of the nucleus olivaris may be present.[18] At the conversion zone of the pachygyric to the normal cortical architecture, the outer neural layer shows a transition to the normal cortex. In contrast, the inner neural layer does not show

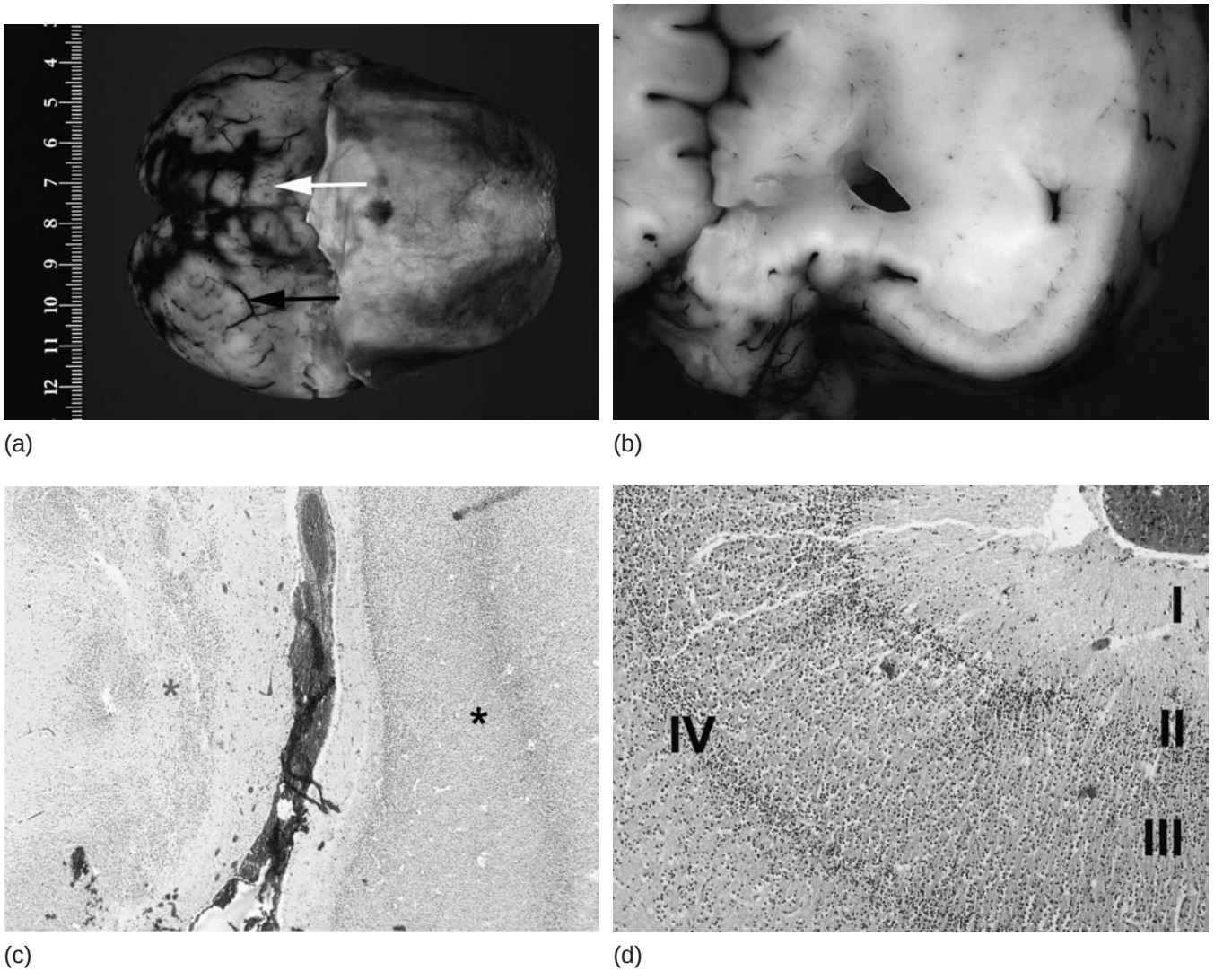


Figure 143.1 Neuropathological findings in lissencephaly. In lissencephaly, the gyri can be flat and smooth, an appearance termed pachygyria (white arrow), or absent, i.e., agyric (black arrow) (a, kindly provided by Volkmar Hans, MD, Bielefeld-Bethel, Germany). On the macroscopic section, a compromised cortical architecture becomes manifest in the agyric areas of the brain (b, kindly provided by Volkmar Hans, MD, Bielefeld-Bethel, Germany). On histological sections, the aberrant architecture of the lissencephalic cortex becomes visible, i.e., lack of cortical organization (gray asterisk) as well as pathological four-layer structure (black asterisk) (c, hematoxilin and eosin, ×100). The characteristic four-layer structure in lissencephaly can differentiated according to a marginal (molecular) layer (I), a outer neuronal layer (II), a cell-depleted layer with tangentially orientated myelinated fibres (III) and an inner neuronal layer (IV) (d, hematoxilin and eosin, ×400).

continuity to the normal cortex. This histological finding may help to differentiate pachygyric alterations from polymicrogyria.

Polymicrogyria

The presence of an excess number of abnormally small gyri that lead to an irregular cortical surface is described by the term polymicrogyria. The outermost cortical layer, i.e., molecular layer, commonly fuses, which results in the appearance of a rather smooth cortical surface. At least two general histological types are observed, the four-layered and the unlayered type. Clearly, a variety of intermediate neuropathological phenotypes exist.

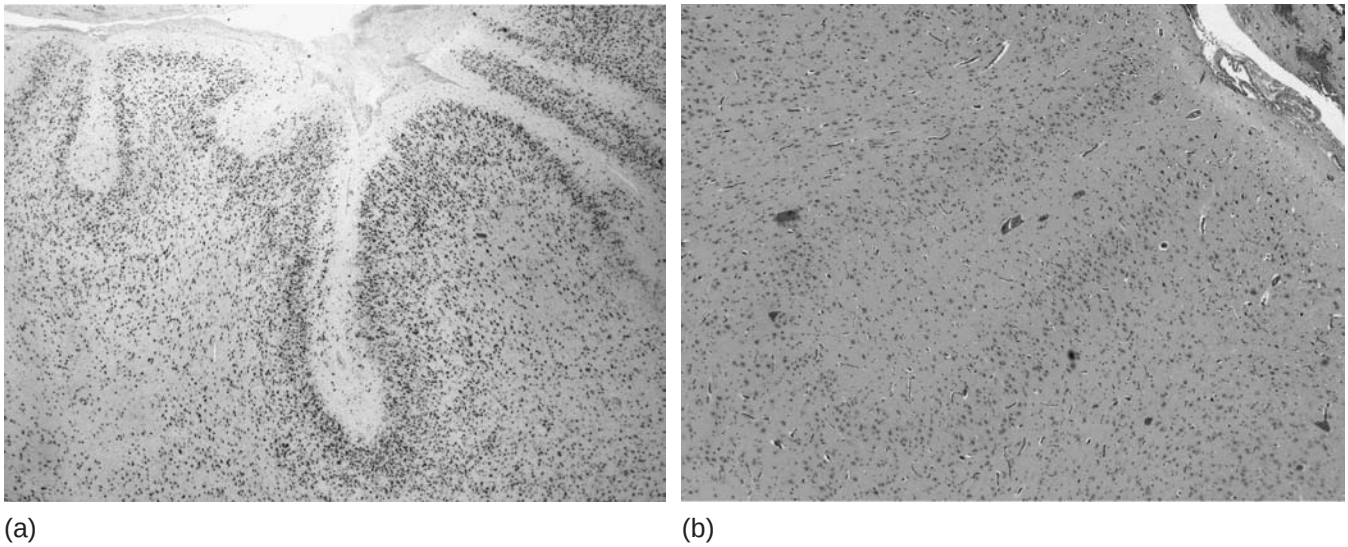
Polymicrogyria may be identified on MRI by excessive cortical gyration in the absence of significant cortical volume and an irregular border between gray and white matter.[15] An important aspect of polymicrogyria is the regional distribution. The malformation may occur unilaterally as well as bilaterally. The manifestation of polymicrogyria at variable brain regions refers to a variety of specific subsyndromes.[38–40] A subsyndrome with distinct clinico-pathological findings and familial recurrence is bilateral perisylvian polymicrogyria, in which the individuals suffer from parallel pseudobulbar palsy, spastic quadraparesis, learning disability and epilepsy.[39,41] There is substantial variation with respect to the extent of polymicrogyria with a wide range of clinical manifestations, from severe encephalopathy with intractable epilepsy to only selective impairment of cognitive function.[42]

Various patterns of inheritance have been described for the different subtypes of polymicrogyria.[41] No individual genes have been linked to any of the bilateral forms with isolated polymicrogyria, although a mutation in *MECP2* was observed in a male patient with bilateral perisylvian disorder and severe neonatal encephalopathy.[43] Further, various linkages to distinct chromosomal regions have been reported.[44,45] A recent hybrid genetic-MRI approach led to the identification of the homeobox gene PAX6 as a factor, in which mutations can result in unilateral polymicrogyria.[46] As observed frequently for other types of cortical malformations, polymicrogyria may be part of multiple congenital anomaly syndromes.[15]

The mechanisms of epileptogenesis related to polymicrogyria are not entirely understood. An experimental model has been used, where a single or few microgyri are generated by a freezing insult. Recent data indicate a widespread region of functional impairment, which extends the visual-ized abnormality in the model.[47,48] Also in patients with polymicrogyria, surrounding cortex appears be involved in epileptogenesis. Therefore, surgical resection of an area of polymicrogyria alone is rarely likely to substantially attenuate or abolish recurrent epileptic seizures.[49,50] Polymicrogyria is, however, not inevitably associated with epilepsy, and it may present as developmental delay or congenital hemiparesis.

In contrast to agyria or pachygyria, gyri are formed in polymicrogyria. However, gyri are atypically organized and lack the physiological laminar cytoarchitectural structure. Polymicrogyria is frequently observed in the vicinity of encephaloclastic lesions such as schizencephaly.[51,52] Exogenic causes of polymicrogyria comprise infections including cytomegaly, toxoplasmosis, rubeola as well as impaired haemodynamic with predelection to the perfusion area of the middle cerebral artery.

Histologically, polymicrogyric lesions show a variety of alterations. On the one side of the spectrum (*type 1*), unlayered polymicrogyria can be observed (Figure 143.2). The molecular layer is continuous and does not follow the convolution profiles. The neurons have a radial distribution and do not show a laminar organization.[53] Microscopically, polymicrogyria (*type 2*) shows a laminar structure composed of four layers:



(a) (b)

Figure 143.2 Neuropathological findings in polymicrogyria. Histopathologically, polymicrogyria comprises a spectrum of alterations. The molecular layer commonly fuses. Polymicrogyria (*type 2*) shows a laminary structure composed of four laminae, i.e., molecular layer, outer neuronal layer, nerve fiber layer, inner neuronal layer (a, NeuN, ×100). In polymicrogyria (*type 1*), the molecular layer is continuous and does not follow the convolution profiles. The neurons have a radial distribution and do not show a laminary organization (b, hematoxilin and eosin, ×400).

- Molecular layer
- Outer neuronal layer
- Nerve fiber layer
- Inner neuronal layer

Apparently, the third layer (nerve fiber) is a result of cellular necrosis and subsequent myelinisation. Occasionally, in the neuronal cell layers granular as well as pyramidal neurons can be observed resembling residuals of the normal six-layer cortical architecture. These two histopathological subtypes do not necessarily have a distinct origin, as both may coexist in contigiuous cortical regions.[54,55]

A main differential diagnosis of polymicrogyria and lissencephaly is given by ulegyria.[56,57] Ulegyria has a prominent scar character with substantial fiber gliosis. Polymicrogyria and lissencephaly lack this extensive astrogliosis. In contrast to ulegyria, there is a dense network of tangentially orientated myelinated fibres in the subpial outer areas of the molecular layer in polymicrogyria.

Schizencephaly

Porencephaly or schizencephaly constitute cystic cortical lesions, which result in open connections between the lateral ventricles and the subarachnoidal space. Schizencephaly is currently grouped with polymicrogyria among the malformations of cortical development (MCD; group IIIA 1,2).[15] Schizencephaly represents a lesion presenting with a transcortical cleft, open or closed (with unapposed or apposed cortical lips, respectively), lined by cortex. Schizencephaly may be further related to regional absence of proliferating neurons and glia or to abnormal cortical organization. Local failure of induction of neuronal migration or focal ischemic necrosis with destruction of the radial glial fibers during early gestation has been hypothesized.[55] Recent studies have pointed to molecular alterations in schizencephaly, suggesting germ line mutations in the EMX_2 homeobox gene in approximately 70% of the cases.[58–60]

With respect to the areas affected, there is a predelection for the central region as well as areas perfused by the middle cerebral artery. Hypoxic damage manifests during fetal development until the end of cortical maturation. There is combination of schizencephaly with polymicrogyria[53] (*type 1*) as well as co-occurrence of schizencephly with radial orientation of the gyri in the vicinity to the cortical defect (*type 2*).[54,61,62] Frequently, schizencephaly occurs bilaterally. However, substantial pathological alterations including the morphological manifestation in form of a porus, is often present only unilaterally. In such cases, abnormal gyration may be observed on the side contralateral to the porus. In some cases the inner glioependymal surface may extend to the external cortical surface, which can appear as a membranous, pale cover. Clefts may be associated with a range of other malformations of, for example, the septum, optic nerve, callosum or hippocampus.[63] Surgical therapy of refractory epilepsy due to schizencephaly has been reported, but is rarely considered in the most number of cases.[49]

In congenital porencephaly, there is a parallel amygdala-hippocampus-atrophy in a high number of cases. With respect to the differential diagnosis of schizencephaly, cystic necroses that are due to inappropriate perfusion at peri- and postnatal stages have to be differentiated. Frequently, these cystic lesions do not exhibit a communication between the inner and outer liquor spaces.

Hemimegalencephaly

Hemimegalencephaly (HME) is a rare, complex brain malformation characterized by enlargement of one hemisphere. In the past it has been included into one of the three major forms of megalencephaly[64,65] and considered as a consequence of aberrant neuronal migration. Although its etiology remains unknown recent molecular genetic studies, imaging and neuropathological data have provided insights in the pathogenesis of this malformation which is actually considered either an early, genetically programmed developmental disorder related to cellular lineage and establishment of symmetry[66] or a primary disorder of proliferation.[67] Barkovich *et al.*[15] include HME among the non-neoplastic malformations due to abnormal neuronal and glial proliferation; two major subgroups are identified: the isolated forms and those associated with neurocutaneous disorders. Sarnat and Flores-Sarnat[68] differentiate, on the basis of morphological and molecular genetic criteria, three main subgroups partially overlapping the Barkovich classification:[15] isolated HME, syndromic HME (associated with other diseases mainly neurocutaneous syndromes) and total HME characterized by associated enlargement of the ipsilateral half of the brain stem and cerebellum.

Being a rare congenital malformation, despite many cases or small series reports, reviews of large cohort of patients is rare in English literature. Tinkle *et al.*[69] in a retrospective study of 15 patients of identified HME reported 53% of nonsyndromic cases and 47% associated with known or suspected syndrome. In a nationwide survey of 44 patients Sasaki *et al.*[70] reported that 36% of the patients had underlying disorders. In their cohort the right hemisphere was mainly affected (66%) with male predominance and no familial cases.

Neurological symptoms are similar in the syndromic and isolated forms[66,70] and characterized by epilepsy, contralateral hemiparesis and psychomotor retardation. Severe epilepsy, often refractory to medical treatment and thus suitable for surgical treatment, is occurring in the vast majority of patients.[71]

Imaging studies are fundamentals for the in vivo study of HME although no substantial differences are present between isolated and syndromic forms. In addition to the evident asymmetry of hemispheres, unilateral thick cortex with broad, flat gyri associated with pachygyria or micropoligyria are evident in the affected hemisphere. Schizencephaly, asymmetry of corpus callosum, heterotopia in white matter can also be observed. White matter abnormalities with loss of gray-white matter differentiation are also present.[66,70,72,73]

Few autoptic cases are reported and the majority of neuropathological studies derive from specimens obtained from multilobar resections or hemispherectomies (Figure 143.3) performed for epilepsy treatment.[73–77] The neuropathological features, like clinical, EEG and MRI aspects, do not allow a differentiation between syndromic and isolated cases and strictly overlaps the gross anatomical abnormalities depicted by imaging studies. Gross specimen inspection shows areas with sulci and gyri of variable configuration (Figure 143.3); thickened gray matter as well as white matter larger than normal volume with blurring of gray-white matter are constantly found.

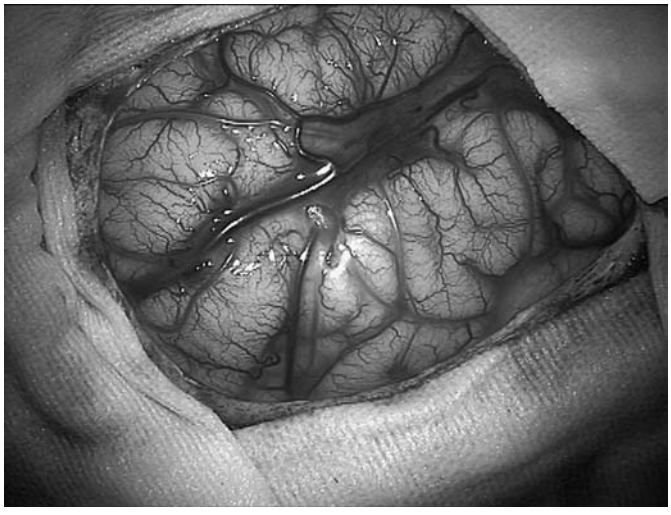


Figure 143.3 Hemimegalencephaly as appears before surgical hemispherotomy; note the broad and irregular gyri. (kindly provided by Prof. G. Broggi).

The lateral ventricle of the enlarged hemisphere is frequently straightened and corpus callosum is frequently asymmetric and thin. At histopathological level a wide spectrum of morphological alterations with combination of different aspects of malformations of cortical development (pachygyria, polymicrogyria and cortical dysplasia with heterotopic neurons in the white matter) can be observed. Dysplastic cortical areas are characterized by cortical dyslamination with columnar arrangement. Large and small neurons are mixed randomly with many disoriented cells. Neuronal cytomegaly with enlarged axons is usually observed so that morphometric analysis demonstrates a significant increase, over controls, in neuronal profile area.[75] The co-occurrence of balloon cells associated with giant dysmorphic neurons are similar to the histopathological findings observed in Taylor's type focal cortical dysplasia (Type IIB in the classification by Palmini *et al.*).[12] Astrocyte proliferation, demonstrated by GFAP immunostaining, is present in both gray and white matter. In some cases dysmielinization is also present in the white matter as suggested by MRI findings. Some ultrastructural data are available but no vascular abnormalities, metabolic storage material or mitochondrial alteration have been observed.[75,77]

Some neurons in HME are expressing markers of cellular immaturity such nestin, MAP1B and vimentin suggesting a defect of cell differentiation or proliferation. Thus its is likely that this developmental malformation may results from somatic gene mutation affecting progenitor cells in one hemisphere during brain development. Recently Crino and coworkers have addressed the molecular pathogenesis of HME.[78,79] by assaying, in eight patients, the expression of 200 cell signalling, growth, angiogenic and transcriptional factor genes with targeted cDNA arrays. The authors found altered expression of 31 mRNAs from four gene families that may lead to aberrant cell growth and hemispheric enlargement in HME.

Heterotopia

The term heterotopia comprises malformations of cortical development characterized by the presence of apparently normal neurons in abnormal position and in general in the subcortical hemispheric white matter. Three main categories are recognized: individual misplaced neurons in the white matter (neuronal heterotopia), nodules of gray matter within the white matter (nodular heterotopia) and band heterotopia (double cortex). In the original classification by Jacob[80] neuronal heterotopia was not considered and only subependymal nodular and band (laminar) forms were included. In the recent classification by Barkovich *et al.*[15] conditions of abundant neurons in the white matter are considered as being due to abnormal neuronal migration. However, classification issues of neuronal heterotopia are still matter of intense debate and authors indicate that the presence of exceeding neurons in the white matter (frequently associated with different forms of MCD) can be ascertained only after accurate morphometric analysis of surgical specimens.[81,82] In this chapter we will focused on the neuropathological aspects of nodular and band heterotopia.

Periventricular nodular heterotopia (PNH)

The incidence of PNH in the general population and in patients with epilepsy is unknown. In a large cohort of 132 epileptic patients with different forms of cortical dysgenesis at the Montreal Neurological Institute, 15% had PNH while Raymond *et al.*[13] reported that 20% of the cases with MCD presented PNH. At the C. Munari Epilepsy Surgery Centre approximately 7% of the patients operated on for intractable epilepsy presented PNH. Only a few autoptic cases are reported however, recent high-resolution imaging techniques allow a precise definition of the macroscopic morphology and extent of nodular heterotopia. Surgical specimens were rare since it was generally considered that epileptic patients with PNH did not respond to surgical treatment; however recent reports suggest that in patients with unilateral heterotopia, surgery can be highly beneficial when epileptogenic zone is carefully identified by refined electroclinical presurgical assessments including invasive recordings.[83,84] The increasing data from genetic studies and MRI (Figure 143.4a) as well as the availability of surgical specimens are determining a continuous refinement of the sub classification system for PNH. Barkovich *et al.*[15] subdivided the PNH into subependymal and subcortical groups. Tassi *et al.*[83] on the basis of their surgical and neuropathological experience proposed a three subgroups: unilateral, bilateral symmetric and bilateral asymmetric. Battaglia *et al.*[85] further refined the classification recognizing two main groups: the bilateral and unilateral. Three subgroups have been distinguished in the bilateral form and two in the unilateral.

In familial bilateral PNH an X-linked dominant inheritage has been established also characterized by a high incidence of spontaneous miscarriage in male foetuses; linkage analysis mapped this disorder to Xq28. Sporadic cases of bilateral PNH both in female and male have also been described. Nodular heterotopia may also been observed in other conditions for with multiple causative genes and environmental aetiologies are suggested.[86] As noted before, neuropathological studies on tissue from epileptic patients with nodular heterotopia are rare and an autoptic study of a patient with genetically proven FLN1 mutation has been recently published.[87] In all cases the nodules consist of masses of neurons, without laminar organization, with well defined boundaries, surrounded by white matter

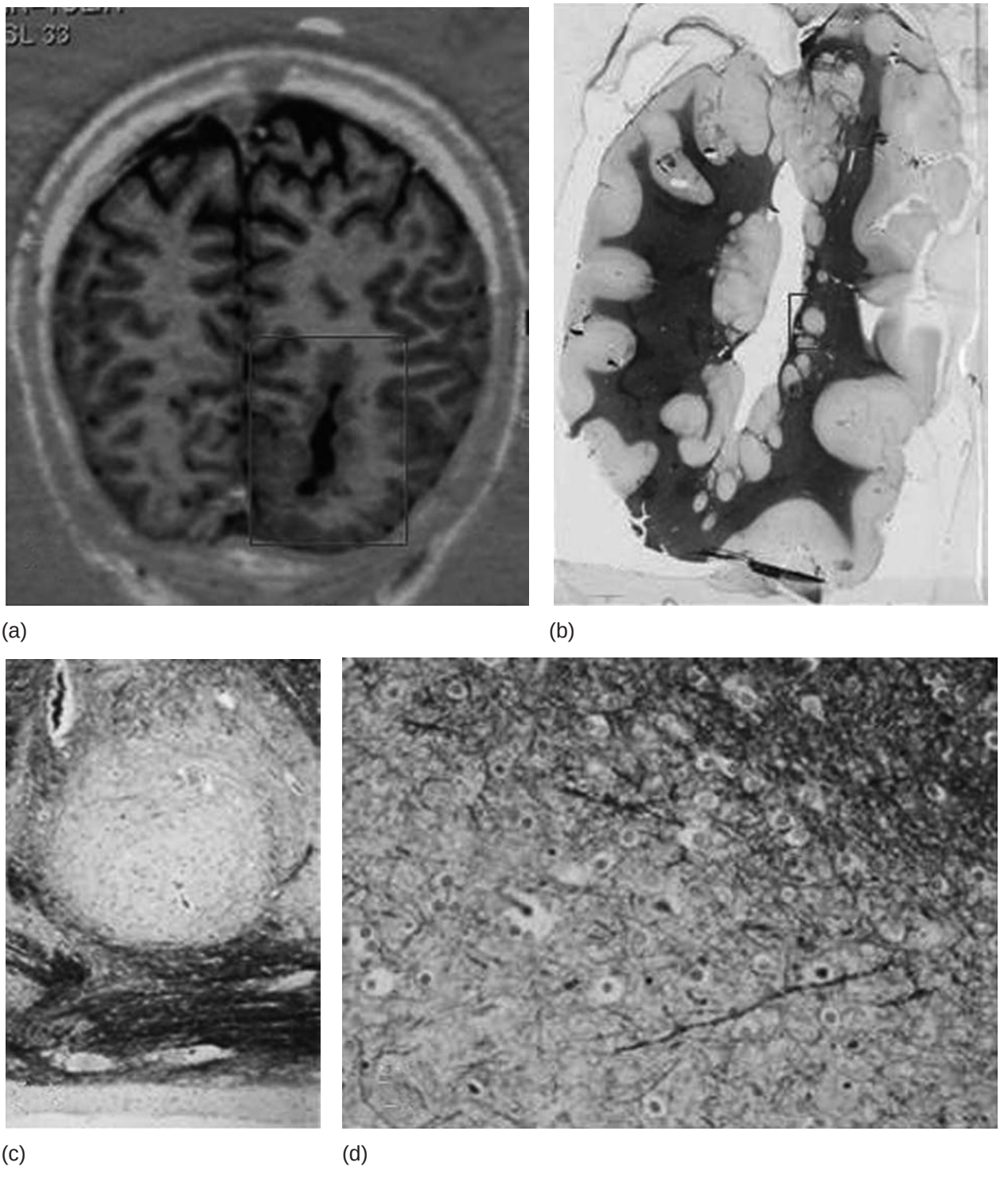


Figure 143.4 Periventricular nodular heterotopia. a. MRI showing large asymmetrical nodular heterotopia. b. Luxol Fast Blue stained section from specimen obtained after surgical resection. Note the large number of irregular nodules one of which (boxed area) can be observed at higher magnification in c. and showing aggregates of neurons with different size and morphology surrounded by white matter fibres. Some fibers penetrate within the nodule (d).

fibres some of which infiltrate the nodules (Figures 143.4b–d). Within the nodules aggregate of small pyramidal neurons, with some immature features and with haphazardly oriented dendrites, appear intermingled with neurons positive for calcium binding proteins suggesting the presence of different subpopulations of GABAergic interneurons.[83,87,88] Taken together these data suggest that the final structure of nodules seems to be independent from their etiology and unrelated to whether the heterotopia is unilateral or bilateral, subependymal or subcortical.

With regard to the neocortex overlying the nodular heterotopia, although MRI frequently suggests polymicrogyria, recent neuropathological data reported abnormal gyration but without histological abnormalities consistent with the typical four-layered or unlayered polymicrogyria.[83] In most, although not in all, of the reported neuropathological studies various degrees of cortical dysplasia are described with reduced expression of calcium binding proteins suggesting an impairment of GABAergic system. In other cases a normally layered cortex can be found although cortical disruption can

be noted in areas where nodules impinge on the cortex. In cases when nodular heterotopia involve the temporal lobe hippocampal sclerosis can also be present.[13,89]

Band heterotopia

This malformation is classified by Barkovich *et al.*[15] among those due to abnormal neuronal migration and included in the subgroup called lissencephalies/subcortical band heterotopia spectrum. However from the neuropathological aspect laminar heterotopia, also defined as band heterotopia or double cortex, is frequently included within the broad group of 'heterotopia'. The genetic aspects of this malformation has been reviewed in the 'lissencephalies' paragraph.

Being a diffuse cortical malformation, frequently genetically determined, only few neuropathological reports are available mainly on sporadic autoptic cases.[65] Although laminar heterotopia can be associated to intractable epilepsy, focal surgical resections have been reported to yield inadequate results.[90] However case reports on surgically treated patients with satisfactory postsurgical outcome have been published.[91,92] Despite the reduced number of neuropathological specimens an increasing number of evidences and careful anatomical descriptions are available thanks to the high resolution imaging also providing genotype/phenotype correlations of this malformation.[50,51,93]

The gross anatomical aspect observed on both MRI and neuropathological specimens is characterized by a continuous bilateral, roughly symmetrical, band of gray matter located between the cortical mantle and the ventricles. The thickness of the band varies among patients and seems to be correlated with the degree of associated mental retardation. The outer cortex may be normal although a slight reduction in number of gyri and pachygyria can be observed. The histological aspect of the cortex is generally normal with a regular six layers (Figures 143.5a and b) and normal distribution of neuronal elements with no cytological alterations.[91,94] Beneath the outer cortex a zone of white matter of variable thickness is present containing abundant heterotopic neurons frequently arranged in columns (Figure 143.5b).

The heterotopic band consists of unlayered small and medium sized rounded or pyramidal neurons (Figure 143.5b). Although macroscopical (as also observed at MRI) the heterotopic band appears as a continuous aggregate of neurons. At microscopic level it appears discontinuous and interrupted by radially oriented fibers. Within the white matter and in the heterotopic band the pyramidal neurons appear haphazardly oriented and nonpyramidal neurons express different calcium binding proteins suggesting the presence of different subpopulations of GABAergic interneurons.

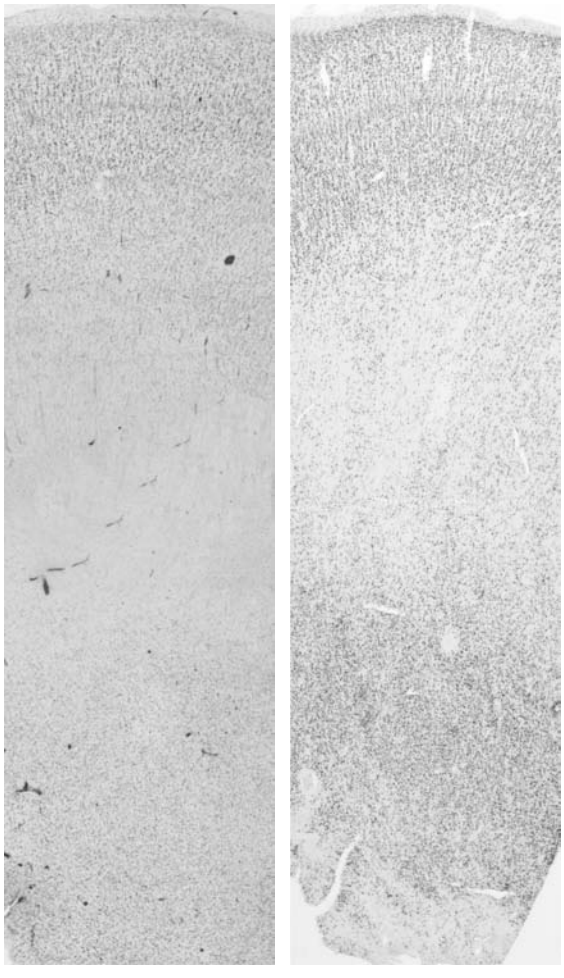


Figure 143.5 Laminar (band) heterotopia. Low power photomicrographs showing two adjacent sections from specimen obtained after surgical resection. a. Nisll stained section showing a regularly layered outer cortex and the heterotopic unlayered bend. In the white matter between the two cortices aggregates of heterotopic neurons arranged in columns are evident b. with NeuN immunostaining. (modified by Mai *et al*. Neurology 2003;60:1834–8).

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144 Pathology of neurocutaneous abnormalities, vascular abnormalities: post-infectious and post-traumatic pathologies associated with epilepsy

I Blümcke and M Hildebrandt

Introduction

With recent advances in high-resolution brain imaging, focal lesions became increasingly detectable in patients suffering from chronic, intractable epilepsies. Tailored resection strategies emerged as a beneficial therapeutic option in many of these patients. Increasing access to lesional brain tissue allows systematic neuropathological investigation as well as molecular-biological and genetic studies. This comprehensive approach will further improve our understanding of specific pathomechanisms as well as enhanced seizure susceptibility of focal lesions. In this chapter, the spectrum of neoplasms and malformations associated with neurocutaneous syndromes as well as epilepsy-associated vascular, post-infectious or post-traumatic lesions will be discussed. Genetically determined neurocutaneous syndromes are particularly challenging. Often, multiple lesions are identified, i.e., cortical tubera, subependymal nodules, or subependymal giant cell astrocytomas in patients suffering from tuberous sclerosis complex (TSC). Sturge-Weber syndrome, another phakomatosis frequently associated with focal epilepsies, manifest with proliferation of leptomeningeal veins (meningoangiomatosis) of the subarachnoidal space and/or superficial neocortex. Progress in molecular-genetic analysis highlighted compromized developmental signaling pathways as underlying pathogenic mechanism whereas enhanced seizure susceptibility appears to result from axonal and molecular reorganization of adjacent brain tissue. Besides genetically determined pathology, post-traumatic and post-infectious lesions are other frequent findings in focal epilepsies. Astroglial cell populations transform into scarring tissue and altered molecular expression patterns, i.e., glutamate transporter versus receptors or other molecules associated with ion homeostasis may contribute to the generation of spontaneous seizure activity. In addition, axonal reorganization in brain tissue adjacent to a specific lesion as well as immunogenic mechanisms tackling affected neurons appear to play a major role. During postnatal development, progressive cortical dysplasia in the vicinity of affected brain regions also contribute to enhanced epileptogenesis. Vascular malformations will also be covered in this chapter. Cavernomas, arterio-venous malformations as well as rare hamartomatous lesions with a prominent vascular component can be histologically identified as underlying morphological substrate, whereas molecular pathomechanisms and enhanced epileptogenicity remain to be determined.

Neurocutaneous syndromes

Two distinct neurocutaneous syndromes typically associate with severe seizures, i.e., tuberous sclerosis complex (TSC) and Sturge-Weber syndrome (SWS). TSC manifests clinically with a triad of seizures, mental retardation, and facial angiofibroma (adenoma sebaceum).[1] However, presence of hamartomatous lesions in the brain, i.e., multiple cortical tubera, periventricular nodules, and subependymal giant cell astrocytomas (SEGA) or other organs, e.g., periungual angiofibromas, retinal tumors, angiolipomas in the kidneys or rhabdomyoma in the heart as well as dermal depigmentation ('white spots' as identified during Wood-light inspection) are hallmarks of the clinical diagnosis.[2]

Sturge-Weber syndrome usually presents with facial 'port wine haemangioma' (flame naevus) associated with the ophthalmic division of the trigeminal nerve, ipsilateral leptangiomatosis and glaucoma. Typical clinical manifestations are intractable seizures, stroke-like episodes, headaches, cognitive impairment, hemiparesis, and homonymus hemianopsia. Often mental retardation occurs. Other frequent findings include glaucoma, which affects nearly half of these patients. Brain manifestation usually shows unilateral venous angiomas, preferential within the occipital and parietal lobes. However, all lobes could be affected, occasionally both hemispheres are involved.

Macroscopic and microscopic findings in tuberous sclerosis complex (TSC)

Brain manifestations of TSC include cortical tubera, presenting as round hyperdense lesions in cortical gyri.[3] They occur

multifocal, are firm to palpation and extend into the white matter. The most characteristic feature of cortical tubera is the presence of giant cells (Figure 144.1). They are five to ten times larger than cortical pyramidal cells, present with an opaque cytoplasm and are often multinucleated. Distinct features of neuronal and/or astrocytic differentiation can only rarely be identified.[4] However, some giant cells express immunohistochemically either neuronal or glial antigens, occasionally coexpression occurs. More importantly, expression of immature markers can be observed in the majority of surgical

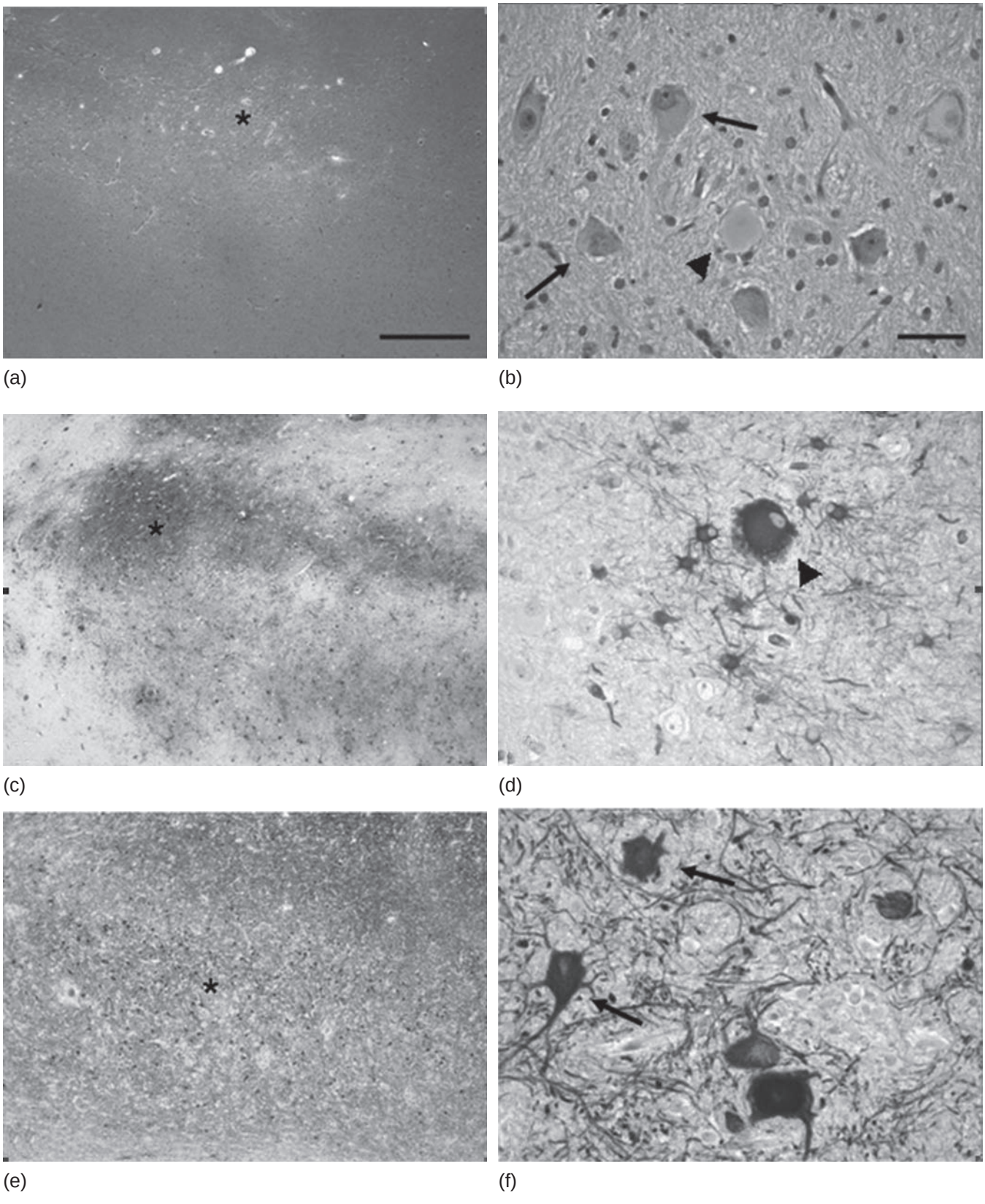

Figure 144.1 A cortical tuber (indexed by asterisk in a) was identified in this epilepsy patient suffering from tuberous sclerosis (serial sections in a = HE, c = Vimentin and e = Neurofilament; 12.5×, scale bar = 1000 µm). Higher magnification in b (HE), d (Vimentin) and F (Neurofilament) demonstrated a biphasic composition with dysplastic neurons (arrows in b and f) and opaque giant cells (arrowhead in b; scale bar = 50 µm) immunoreactive for vimentin (d).

specimens, including vimentin, nestin or the stem cell epitope CD34, which is compatible with an arrested differentiation of compromized progenitor cells.[4,5] Although the surrounding non-affected neocortex demonstrates usually with a normal cytoarchitecture, calcifications, either within or adjacent to the lesion, are frequently encountered in TSC patients.

Other typical features occurring in TSC are periventricular nodules, well-circumscribed masses containing giant cells as described above and subependymal giant cell astrocytomas (SEGA; Figure 144.2). The latter occur in 6–16% of patients with TSC and can occur at various localizations. SEGA is a benign, slowly growing tumor typically arising in the wall of the lateral ventricles corresponding to WHO Grade I. Histopathologically SEGA presents as a well circumscribed, often calcified tumor, mainly composed of large, plump cells resembling astrocytes. Perivascular pseudopalisading (Figure 144.2B) and clustering of tumor cells are common features. Cellular pleomorphism and occasional mitosis are common and do not indicate a malignant behavior. Anaplastic tumor progression has never been reported in TSC patients, although exophytic growth may reach extensive masses associated with severe clinical symptoms.[6] Recent microarray analysis identified similar expression profiles between cortical tubers, SEGA and conditional *Tsc1* knock-out mice, indicating pathogenic origin from related defects in progenitor cell differentiation during brain development.[7]

Molecular-genetic findings and enhanced epileptogenesis

TSC is a autosomal dominant inherited genetic disorder with a prevalence of approx. 9/100 000.[8] Despite its high penetrance considerable phenotypic variability can be observed, even within affected family members. The mechanisms remain, however, to be specified. Sixty percent of patients suffer from spontaneous de novo mutations. Two genetic loci are characterized. TSC1 is mapped on 9.q34, includes 23 exons, and encodes for the protein hamartin, which is strongly expressed in brain, heart, and kidney.[9] The transcript contains 8.6 kb. Hamartin consists of 1164 amino acids and has a molecular weight of 130 kDa. It inhibits tumor formation possibly by regulating cellular adhesion through ezrin-radixin-moiesin family proteins and the small GTP-binding protein Rho.[10]

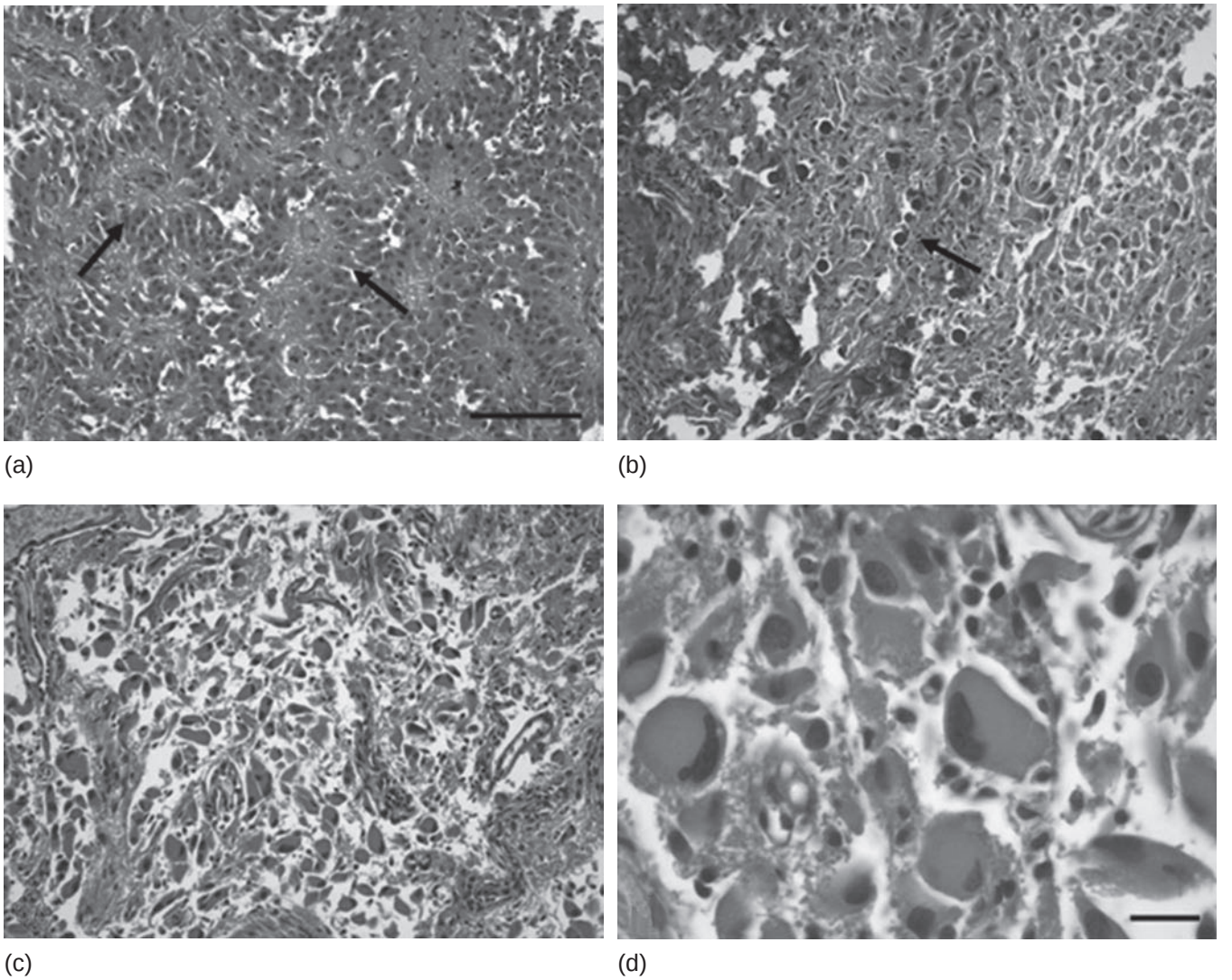

Figure 144.2 Subependymal giant cell astrocytoma (SEGA) in a patient with tuberous sclerosis. Tumor cells formed perivascular pseudopalisading (arrows, HE, scale bar = 1000 µm). Microcalcification can be frequently encountered (arrow in b, HE). Higher magnification characterize pleomorphic and multinucleated eosinophilic tumor cells (c and d, scale bar = 20 µm), frequently expressing vimentin (e) or neuronal marker proteins (arrowheads in f Microtubule associated protein MAP2).

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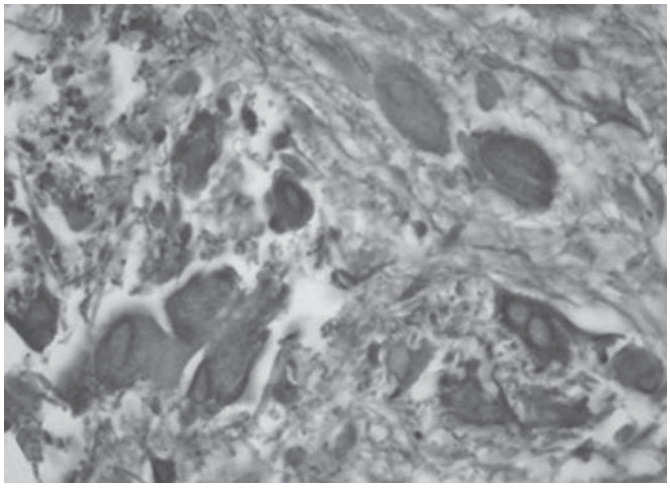

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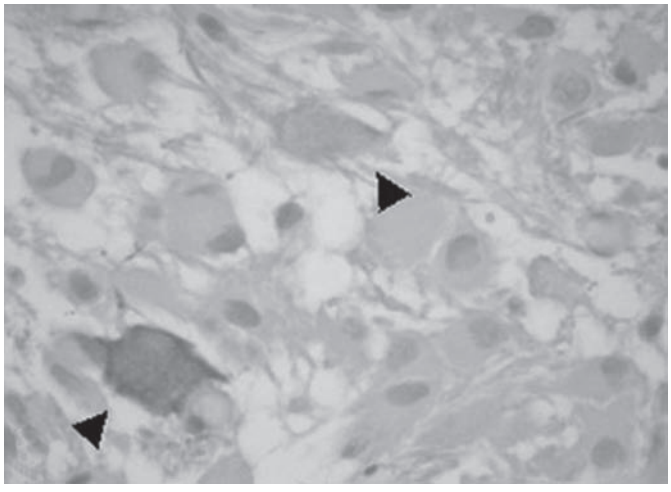

(f)

Figure 144.2—cont'd

The immunohistochemical pattern overlaps with tuberin, the gene product of TSC2, which is mapped to chromosomal region 16p13.3 and includes 41 exons.[11] The transcript contains 5.5 kb. Alternative splice variations are common. Tuberin contains 1807 amino acids with a molecular weight of 180 kDa. It bears significant homology with the catalytic domain of the GTPase-activating protein Rap1-GAP, a member of the ras family. It regulates cell cycle by inhibiting the G1/S transition and promoting entry to the G0 phase.[12]

A two-hit model is assumed for the clinical manifestation of TSC. Inactivating germline mutations of TSC1 or TSC2 is followed by a later somatic mutation in hamartomatous cells, explaining the clinical variability in an autosomal dominant inheritance. Loss of second TSC1- or TSC2-allels, i.e., loss of heterozygosity (LOH) leads to a homozygote negative state. LOH of TSC1 or TSC2 also occurs in sporadic tumors, e.g., carcinomas of mamma or bladder. Therefore both genes are likely to represent tumor suppressor genes. The recent finding that the TSC1/TSC2 complex is involved in the insulin growth factor receptor signaling pathway[13] is compatible with variable histomorphological phenotypes including defects in proliferation (SEGA), differentiation (occurrence of giant cells) and migration (missing lamination and heterotopic immature cells in the white matter).

The Eker rat with hereditary kidney cancer presents with germline mutations of the TSC2 homologue and functions as an animal model of human TSC. In Eker rat brains, lesions occur as cortical tubers, subcortical hamartomas, subependymal hamartomas, and anaplastic gangliogliomas.[14] Even though anaplastic gangliogliomas are not part of human TSC, the animal model demonstrates the similarity of glioneuronal lesions suggesting a comparable origin. Furthermore, TSC in humans shares histopathological features of glioneuronal tumors, especially gangliogliomas and dysembryoplastic neuroepithelial tumors (DNT) and tuberous form of focal cortical dysplasia (FCD) type IIb providing the hypothesis of a common origin.[15] The epileptogenicity of TSC associated brain lesions have been addressed in various clinical and molecular studies. Cortical localization, disrupted lamination, cytoarchitectural disturbances and possible altered synaptic connectivity of dysplastic neurons may account for intrinsic epileptogenicity of tubers, whereas giant cells are likely to be physiologically inert (Cepeda *et al.*, 2003).[16]

Sturge-Weber syndrome (SWS; macroscopic and microscopic findings)

Imaging and gross examination reveals widespread, usually unilateral leptomeningeal angiomatosis, cortical calcifications in a 'railroad track' pattern and less frequently atrophy of the underlying neocortex (Figure 144.3). White matter abnormalities are common and may be linked to chronic ischemia and reactive gliosis. Angiography demonstrates an overall lack of superficial cortical veins, non-filling of the dural sinuses and tortuous course of veins towards the vein of Galen.[17] Functional brain imaging has demonstrated decreased glucose metabolism and hypoperfusion of the affected neocortex.[18] Focal epilepsies are frequent clinical symptoms observed in almost 80% of SWS patients.[19]

Microscopically, leptomeningeal angioma in SWS presents with large tortuous and abnormal venous structures in thickened leptomeninges (Figure 144.3). The underlying brain tissue may be atrophic and displays neuronal loss, reactive astrogliosis, and microcalcifications. Laminar cortical necrosis may occur, suggesting ischemic damage secondary to venous stasis in leptomeninges and cerebral vessels. The underlying cortical vessels are increased in number, typically thin-walled and narrowed by hyalinization and subendothelial proliferation. Repeated stroke-like episodes and thrombosis may result in disease progression and neurological deterioration.

Molecular findings and enhanced epileptogenesis in Sturge-Weber syndrome

SWS occurs sporadically with a frequency of approximately 1/50 000. Inheritance is so far not established. Non-Mendelian genetic hypotheses, including chromosomal instability have been suggested. Spontaneous somatic mutations in a common progenitor cell line of dermal, neuronal and ocular tissue in the first trimester of development may lead to genetic mosaicism of the affected areas.[20] A case report about one of two monozygotic twins presenting with SWS supports this hypothesis.[21]

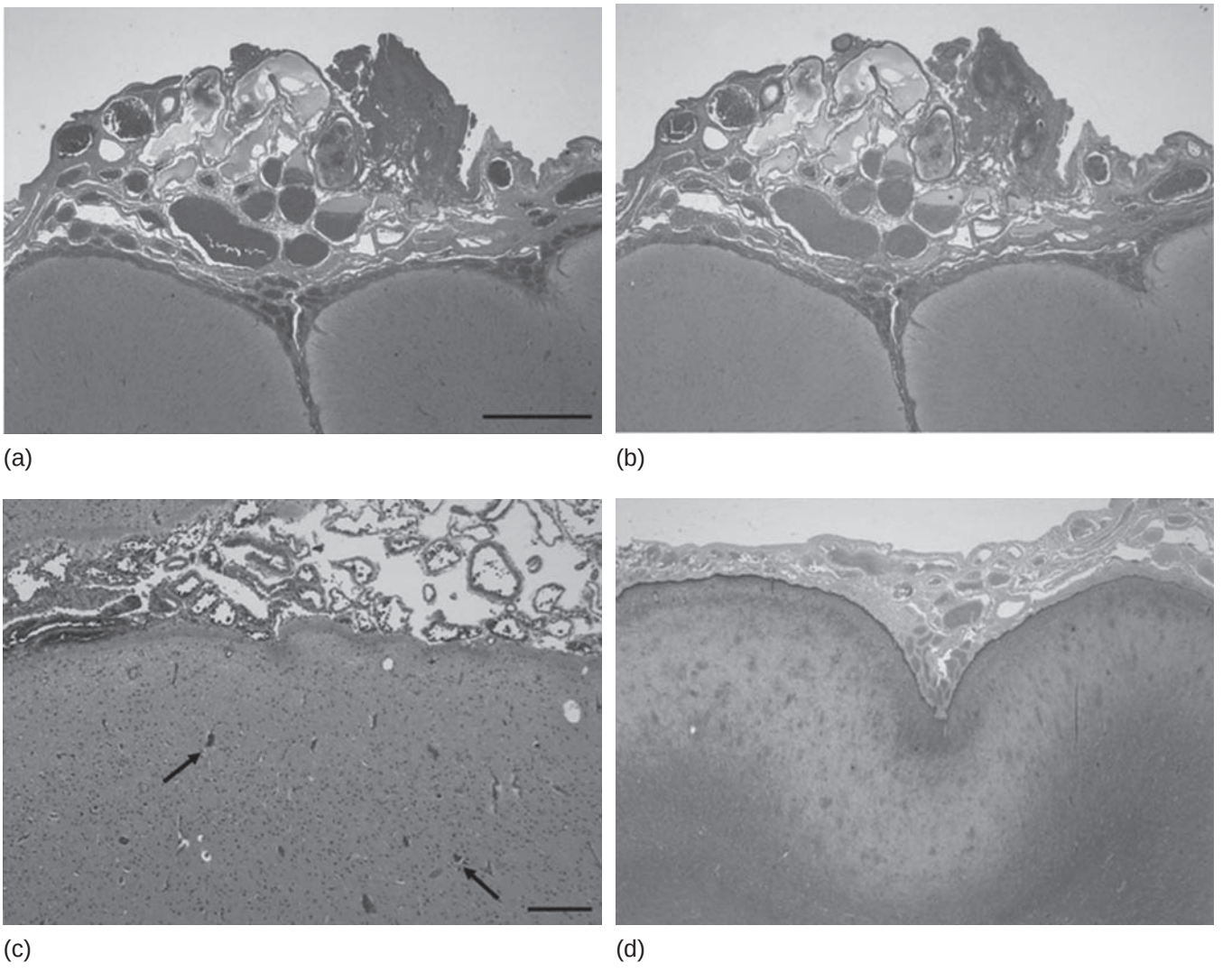

Figure 144.3 Leptomeningeal angiomatosis in a Sturge-Weber patient presenting with focal seizures (a HE, b Elastica van Gieson; 12.5×, scale bar in a = 1000 µm, applies also to b and d). The underlying neocortex demonstrates cortical atrophy with microcalcifications (arrows in c; HE 40×, scale bar = 200 µm) and reactive astrogliosis (d; GFAP).

Another possibility refers to a two-hit model combining hereditary and spontaneous factors. Excessive vascular proliferation of the angioma diverts blood flow from parenchyma and creates an anoxic environment in the surrounding brain, leading to cellular damage. As a result, the underlying cortex becomes atrophied, calcified, and eventually dysfunctional,[22] leading to seizures. The endothelial basal lamina contains an extracellular matrix composed of glycoproteins and proteoglycans including laminin, fibronectin, and tenascin. Fibronectin has been identified as a key regulator in angiogenesis and vasculogenesis and plays a crucial role in brain tissue response to ischemia and maybe to seizures.[23] Increased fibronectin gene expression levels were indeed observed in fibroblasts obtained from port-wine hemangiomas compared to normal skin samples. Moreover, there was a trend towards increased fibronectin protein expression in SWS brain samples compared to postmortem controls. Therefore, fibronectin is supposed to be a likely candidate for SWS.

Furthermore, analysis of families with hereditary port-wine stain identified RAS1 mutation on chromosome 5q.[24] The RAS1 gene product is p120-RasGAP, a negative regulator of the Ras-mitogen-activated protein kinase signaling pathway. It may also be a candidate for involvement in vascular abnormalities of SWS.

Vascular malformations associated with focal epilepsies

Vascular malformations are classified with regard to caliber and configuration of the blood vessels, their continuity with the normal cerebral vasculature and the amount of intervening brain parenchyma. They are assumed to represent congenital lesions as a result of disturbed mesodermal differentiation between the third and eighth week of gestation. Vascular malformations may be part of a distinct syndrome but also occur in combination.

Cavernomas

Cavernous hemangiomas (cavernomas) occur within the brain parenchyma or the leptomeninges. MRI usually reveals a well circumscribed superficial lesion with surrounding hemosiderine deposit. The lumen is occasionally occluded; therefore they

did not fill on angiography. Histologically, they are composed of closely apposed dilated vascular channels without intervening brain parenchyma (Figure 144.4). Elastica van Gieson (EvG) staining discovers thin blood vessel walls, containing endothelium and a collageneous adventitia. Calcification or even ossification can be microscopically detected. A peripheral rim of hemosiderin-storing macrophages may be identified in the surrounding tissue.

Molecular findings and enhanced epileptogenesis associated with cerebral cavernous malformations (CCM)

The prevalence of cavernomas is 0.02 up to 0.5%. Approximately 4–6% of pharmacoresistant epilepsies are caused by cerebral cavernous malformations (Table 144.1). There is no evidence that space occupying mass effect leads to epileptogesis. Rather repeated microhemorrhages and hemosiderin deposits in the surrounding cortical tissue may cause hyperexcitability by iron ions, providing free radicals and lipid peroxides. Furthermore, reactive glial proliferation may be epileptogenic. In some cases, dual pathology with Ammon's horn sclerosis occurs.[25]

Cerebral cavernous malformations (CCM) can occur in a sporadic form as well as a familial form. Familial CCM are inherited in the autosomal dominant mode, and three genes have been localized to chromosome 7q11.2-21 (CCM1), 7p15-13 (CCM2) and 3q25.2-27 (CCM3).[26] KRIT1 (Krev interaction trapped 1) is likely to represent the disease causing gene in CCM1.[27] Approximately 40% of families with cerebral cavernous malformations carry KRIT1-mutations. KRIT1 encodes a protein with a four ankyrin repeat domain at the N-terminus and C-terminal domain for interaction with Krev-1 (Rap1a, ras-related protein 1A). Most KRIT1 mutations are loss of function mutations leading to increased interaction between ICAP1α and β1 integrin, which influences integrin β1-dependent cell adhesion, migration and angiogenesis. Mutation of CCM2 gene occurs in 20% of patients with familial CCM. It contains a phosphotyrosine-binding domain (PTB), but its function is unknown.[28,29] Approximately 40% of CCM families are linked to the CCM3 locus, so-called PDCD10 (programmed cell death 10). Its role in vascular morphogenesis remains to be investigated.[30]

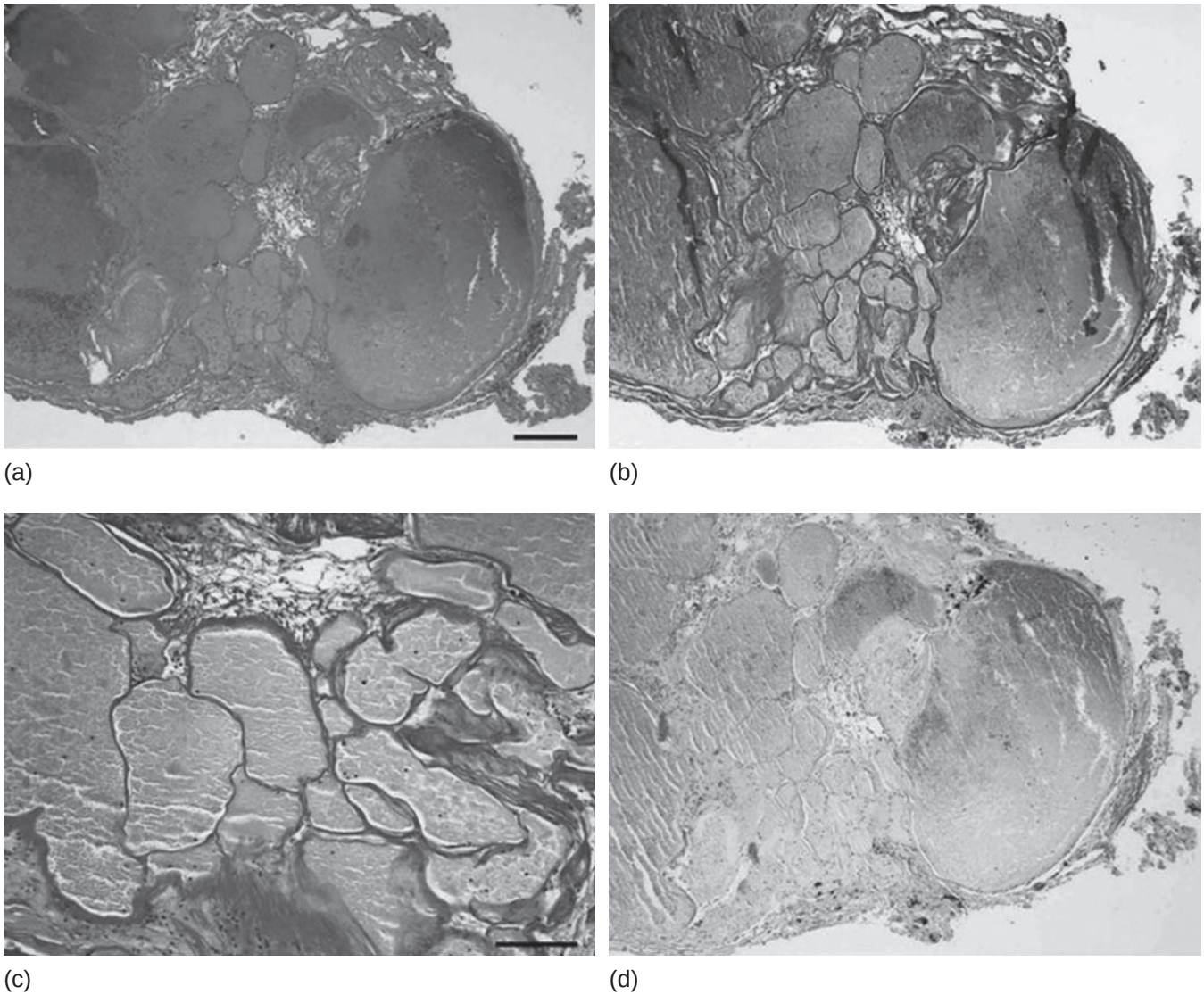

Figure 144.4 A cavernoma showing thin-walled vessels without intervening brain parenchyma is depicted in a (HE, scale bar = 200 µm, applies also to b, d). b: Elastica van Gieson staining (EvG) of a serial section to a; c: EvG staining at higher magnification fail to show regular lamination of vessel walls; scale bar = 100 µm. d: Hemosiderin storing macrophages are recognized using Berliner-blue reaction.

Table 144.1 Summary of 2386 epilepsy associated focal lesions (German neuropathological data base for epilepsy surgery)

	DIAGNOSIS	NUMBER	AGE	DURATION
MTS	AHS	902	33,9	22,8
	DUAL	137	22,8	12,6
TUMORS	GG	423	25	13,6
	DNT	129	26,9	12,9
	ASTRO	112	32,4	13,1
	OLIGO	36	36,6	11,1
	PXA	22	30,7	17
	SEGA	14	19,3	14
MALFORMATIONS	FCD Type II	160	17,3	13,1
	HETEROTOPIA	50	29,2	17,6
	FCD Type I	37	12,4	8,6
	HAMARTOMA	30	23,7	16,9
	PMG	24	6,4	2,9
	HEMI	7	1,7	1,7
VASCULAR	CAVERNOMA	161	36,8	13
TRAUMA	SCAR/PORUS	98	25,9	15,8
ENCEPHALITIS	VARIOUS	29	24,9	10,3
	RASMUSSEN	15	11,6	3,4

NUMBER of patients included in the neuropathological database; AGE at operation (years); DURATION of epilepsy (years); MTS: mesial temporal lobe sclerosis; AHS: Ammon's horn sclerosis; DUAL: dual pathology presenting with AHS and another distinct histomorphological lesion (i.e., tumor, vascular lesion); GG: ganglioglioma (WHO grade I–III); DNT: dysembryoplastic neuroepithelial tumor (WHO grade I); ASTRO: astrocytoma (WHO grade I–III); OLIGO: oligodendroglioma or mixed glioma (WHO grade II–III); PXA: pleomorphic xanthoastrocytoma (WHO grade II); SEGA: subependymal giant cell astrocytoma (WHO grade I); FCD: focal cortical dysplasia (Type I or Type II according to Palmini *et al.*, 2004); HETEROTOPIA: ectopic neurons in white matter (single or neuropil islands) or nodular heterotopias; HAMARTOMA: glio-neuronal hamartomas or hamartias; PMG: Polymicrogyria; HEMI: Hemimegalencephaly; ENCEPHALITIS, VARIOUS: summary of lesions associated with bacterial, viral or parasitic infections.

Arterio-venous malformation (AVM)

AVMs may occur in all parts of the CNS but most commonly in the territory of the middle cerebral artery. AVMs range in size from grossly invisible to those which involve a large part of the entire hemisphere. They may enlarge over time by recruitment of contiguous blood vessels.

MRI shows vascular lesions with abnormal vessels and surrounding hemosiderine deposits. Angiography reveals arterio-venous shunting. Histological examination discovers vessels of irregular size, shape, and degree of muscularization. Besides venous appearing vessels with thin amuscular walls, arteries with intact media and lamina elastica could be observed (Figure 144.5). Arterio-venous shunts with disruption of arterial vessel wall architecture are visible using Elastica-van-Gieson staining. Interposed brain parenchyma is usually gliotic and frequently contains hemosiderin storing macrophages after recurrent bleedings. Remnants of preoperative embolisation may be incorporated into vessels.

Molecular findings and enhanced epileptogenesis associated with arteriovenous malformation (AVM)

AVMs arise congenital during embryogenesis and account for 70% of all cerebral vascular malformations in children. Immature developing veins and arteries contact with each other before development of capillaries. Lack of development of a capillary bed leads arterio-venous shunts and consecutive dilatation of the receptive venous system. AVM become symptomatic at any age but most commonly present in the second to forth decade with recurrent subarachnoidal bleeding. Seizures may be related to brain ischemia caused by 'stealing' of blood from surrounding brain parenchyma into the malformation.[31,32] As well as in cavernomas iron deposits after bleeding or reactive gliosis could also cause seizures.

AVMs seem to be sporadic lesions, and familial intracranial AVMs are rare.[33] However, recent studies identified possible candidate genes related to angiogenesis. Microarray analysis revealed increased mRNA of vascular endothelial growth factor A (VEGF A) and its protein product as well as increased expression of integrin $\alpha v\beta 3$ protein, leading to a possible role of integrins in AVMs.[34] An earlier study demonstrated a markedly decreased Tie-2 and also VEGF-R2 expression in AVM vessels, which may contribute to the pathogenesis of AVMs. Some arteriovenous malformations (AVMs) are associated with hereditary hemorrhagic telangiectasia type 1. Endoglin, the gene mutated in this disorder, is expressed at reduced levels on blood vessels of these patients. Endoglin is a component of the transforming growth factor-beta receptor complex critical for vascular development and homeostasis. Even though it seems not to be involved in the generation of AVMs, the presence of endoglin on fibroblasts in the perivascular stroma suggests an active role for this protein in vascular remodeling in response to increased blood flow and shear stress.[35]

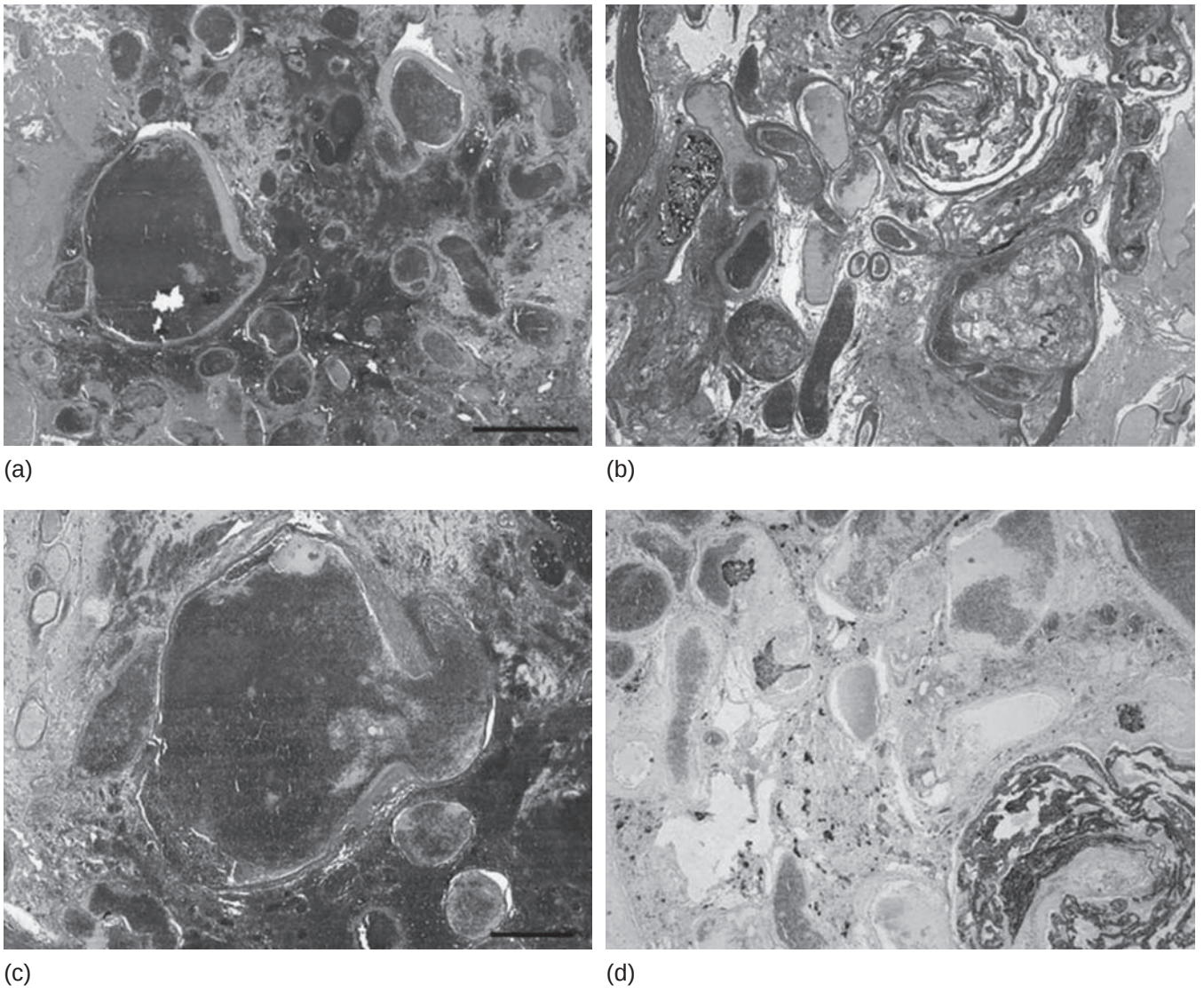

Figure 144.5 a: Arterio-venous malformation with vessels of irregular size (HE, scale bar = 1 mm, refers also to b). b: Occurrence of preoperative embolisation (EvG). c: Arterio-venous shunt vessel (EvG, scale bar = 500 µm, refers also to d). d: Hemosiderin saving macrophages, Berliner-blue reaction.

Capillary teleangiectasia

Capillary teleangiectasias are often an incidental finding during brain autopsy and cannot be detected by imaging unless the lesions are confluent or hemorrhagic. They are composed of dilated blood vessels separated by relatively normal brain parenchyma, which often shows reactive astrogliosis (Figure 144.6).

Molecular findings and enhanced epileptogenesis associated with capillary teleangiectasia

Capillary teleangiectasia have a high prevalence and are usually asymptomatic. Beeding is rare. If capillary teleangiectasias occur in distinct brain regions, e.g., within the hippocampus, or in association with other vascular malformations, seizures may occur. However, hereditary hemorrhagic teleangiectasias (HHT), an autosomal dominant vascular malformation of skin, mucosa and viscera can also manifest in brain vessels. Three gene loci are known: HHT1 on chromosome 9q34.1, HHT2 on chromosome 12q11-14 and HHT3 on chromosome 5q31.5-32.[26] HHT1 is caused by mutations in endoglin which encodes a TGFβ binding protein expressed predominantly in endothelial cells and lays an important role in vascular remodeling and the maintenance of vessel wall integrity.[36] HHT2 results from mutations in the ALK1 gene which encodes a type1 serine-threonine kinase receptor in endothelial cells. Alk1 binds to TGFβ1 and activin-A, and signal through phosphorylation of SMAD1 and SMAD5.[37] A third genetic locus, HHT3 was recently identified in a family without linkage to endoglin, ALK1 or SMAD4 on chromosome 5. However, the specific gene of HHT3 has not been identified yet.[38] There exists also an association with juvenile polyposis (JP), caused by mutations in the MADH4 gene on chromosome 18q21.1 which encodes SMAD4. SMAD4 is an integral downstream effector on the TGFβ signal transduction pathway.

Inflammatory lesions

Bacterial infections

The risk to develop epilepsy after cerebral infection is likely to dependent on the type of infection rather than on age. No obvious increase in risk to develop epilepsy is seen after

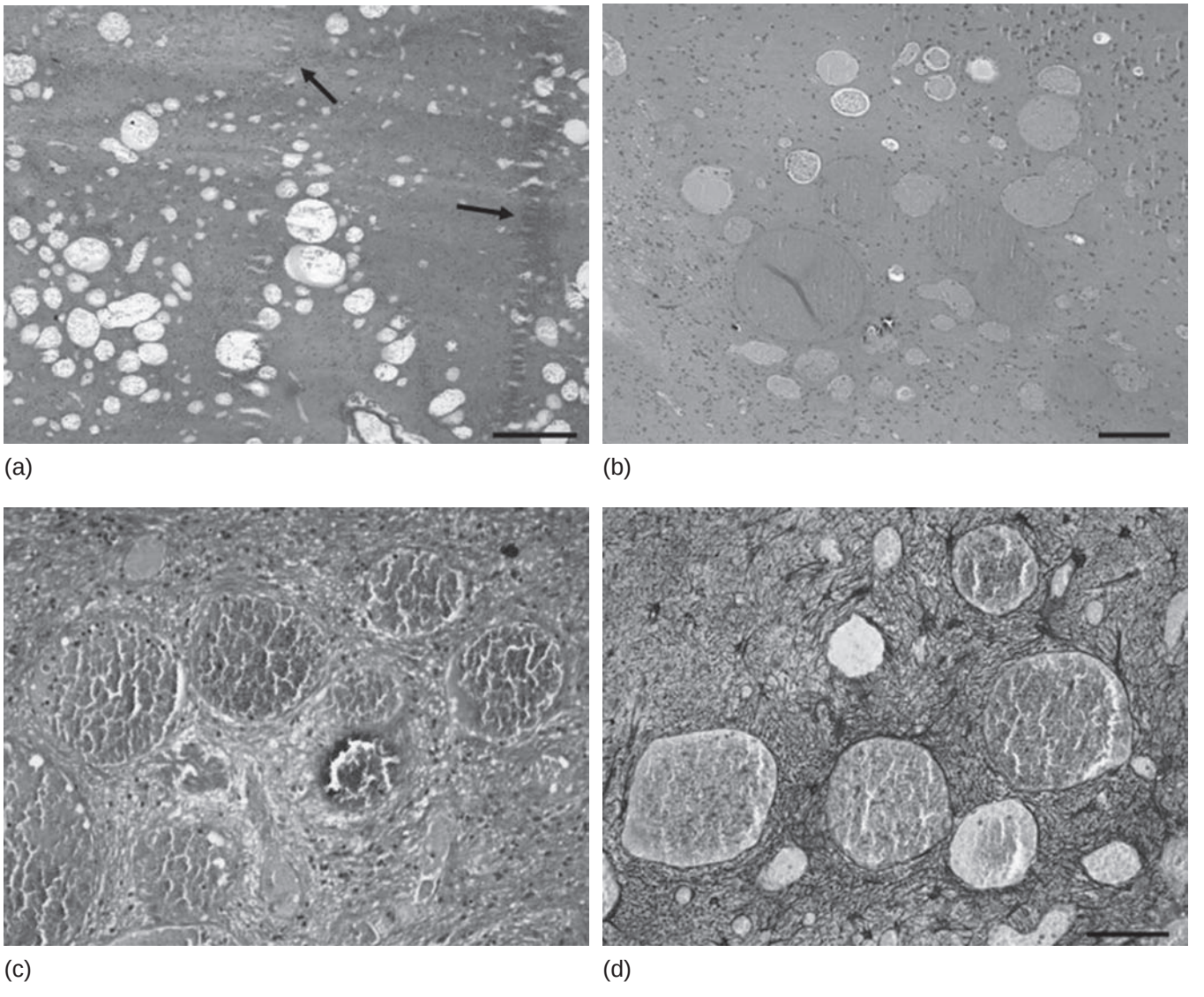

Figure 144.6 a: Ectatic vessels within the hippocampal hilus are identified in this epilepsy patient, the arrows indicate the dentate gyrus, frozen section (HE, scale bar = 500 µm). b: Ectatic vessels in the same specimen following paraffin embedding (HE, scale bar = 200 µm), c: Elastica van Gieson (EVG). d: Gliotic intervening brain parenchyma (GFAP), scale bar =100 µm, refers also to c).

aseptic meningitis. However, likelihood is fivefold increased in patients with bacterial meningitis. The highest risk comes along with viral encephalitis, especially if viral encephalitis is associated with early seizures.

Brain abscess

Brain abscesses may occur per continuitatem from neighboring foci in the paranasal sinus, middle ear or mastoid sinus or via hematogenous dissemination in the context of sepsis. The latter is advantaged by congenital heart disease with septal defect. Most common organisms are *Staphylococcus aureus*, hemolytic streptococci, *Streptococcus viridans*, and various aerobic gram negative rods.

MRI usually reveals a round lesion presenting with a thin capsule and a circumscribed contrast enhancing ring. Due to collagen the abscess capsule is characteristically dark on T_2-weighted MRI scans. A broad perilesional edema reflects the suppurative nature of the lesion. Histologically early stages present with granulocyte infiltrates, necrotic blood vessels, extravasated erythrocytes, and numerous bacteria. Subsequently microvascular proliferates and fibroblast migration from the blood vessel walls occurs as a response to hemorrhage and local infarction. With advanced abscess formation a firm fibrous, partly collagenous capsule encloses a saccular mass filled with purulent material surrounded by lipid-laden macrophages and aggregates of inflammatory cells (neutrophilic granulocytes).

Meningoencephalitis

The agent of bacterial meningitis varies with age. In newborns, *Escherichia coli* and group B streptococcus are the most frequent causes of bacterial meningitis. In children up to 12 years *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitides* are most common. The latter two are also frequent in adults, whereas older age comes along with a higher incidence of *Haemophilus influenzae*.[32]

Acute bacterial meningitis proceeds in two phases. The inital phase is characterized by bacterial proliferation from the primary respiratory focus, leading to bacteraemia. It is assumed that release of toxic molecules by bacterial lysis leads to disruption of the blood brain barrier. CSF has only a slight possibility to counteract infection. Meningeal inflammation is caused

by bacterial cell-wall components, activation of alternative complement pathway, and induction of inflammatory cytokines such as IL-1, IL-6, IL-8, and TNFα. Brain edema is a complication caused by disturbed blood-brain barrier, inflammatory mediators, and vascular changes. Edema and cerebral hypoxemia may lead to tissue damage and consecutive seizures. Moreover, neutrophilic granulocytes and bacterial products may exert a direct cytopathic effect on neurons or glia.[39]

In the early stages of purulent meningitis, neuroimaging often fails to identify the inflammatory foci. In later stages, contrast enhancing of meninges may occur. However, radiology is useful to detect complications such as edema, hemorrhages, or intracerebral abscesses. Histologically, acute phase is characterized by sparse exudation with numerous bacteria and margination of polymorphs in the leptomeningeal arterioles. If the patient survives for more than 2 days, migration of leucocytes leads to development of pus. At this stage cellular exudat composed of polymorphonuclear neutrophilic granulocytes is visible in the subarachnoidal space. Wisps of fibrin and bacteria occur intra- and extracellularly. Underlying cortex is not infiltrated, but it shows edema and beginning ischemic neuronal damage.

Parasitic infections

Within parasitic infections of the brain, neurocysticercosis is the most commonly associated with epilepsy. The cerebral lesion is caused by larvae of the pork tapeworm Taenia solium. Under physiological conditions, humans harboring the intestinal tapeworm are the definitive hosts, whereas pigs infected by eggs from the human stool are the intermediate hosts. The pig contains disseminated larvae. Ingestion of larvae due to inadequately cooked pork infects the human gastrointestinal tract to form mature worms. In contrast, in cysticercosis eggs are ingested by humans, and larvae infect primarily skeletal muscle and the brain. Here the organisms grow within the parenchyma, usually confined to the gray matter or within meninges. Solid or multiple lesions may occur. MRI shows solid, often calcified cystic lesions with a contrast enhancing rim and an internal point of enhancement that represents the scolex. After en bloc resection the organism presents with a surrounded rim of gliotic indurated parenchyma. Microscopically, cysts are composed of an outer eosinophilic lamina and a marginal cell layer containing scant nuclei. Internal parts contain loose connective tissue. The organism is armed with suckers and intimidating hooklets. The surrounding brain shows acute and chronic inflammation. Necrosis with peripheral palisading of monocytes may be seen, but giant cells are not common. Degeneration of the cysts leads to calcification and fibrosis of the lesion, often resulting into chronic seizures.

CNS infections with Taenia echinococcus or Schistosomas rarely cause epilepsy. Protozoa producing cerebral lesions may come along with seizures, namely Toxoplasma gondii and Plasmodium falciparum. In malaria, seizures are major clinical findings.[32]

Viral infections and immunological findings associated with enhanced epileptogenesis

Rasmussen's encephalitis

Rasmussen encephalitis (RE) was first described in 1958 in three patients with focal seizures due to chronic and focally localized encephalitis.[40] RE occurs sporadic, since there is no evidence for a genetic component.[41] A viral etiology was already suggested by Rasmussen due to immune reaction in the brain with lymphocyte infiltration and microglial nodules. The similarities of RE and Russian spring summer meningoencephalitis, caused by flavi virus support this hypothesis.[42] However, a viral agent has not been identified so far. Recent data suggest an immune basis to the pathogenesis of RE, including humoral factors, i.e., autoantibodies as well as cytotoxic T cells.[41] There exist two different hypotheses how autoantibodies lead to brain tissue destruction and seizure activity. First GluR3 autoantibodies have been identified, mediating a cytotoxic activation of the glutamate receptor.[42] Other investigators found signs of induced complement activation by GluR3 autoantibodies, primarily affecting glial cells.[43] However, GluR3 autoantibodies are not present in all RE patients. Moreover, GluR3 autoantibodies were found in other forms of epilepsy and may result rather from neuronal cell degeneration.

In RE the majority of inflammatory round cells are T lymphocytes.[44] Immunohistochemical studies provide evidence for Granzyme B (GrB) mediated cytotoxic T lymphocyte attack against neurons.[41] RE usually occurs unilateral in a progressive way. It is assumed, that seizures disturb the blood-brain barrier (BBB) allowing autoantibodies which in contrast to activated T cells cannot cross an intact BBB to reach the brain tissue. The interplay between immunopathology and seizures seems to provide progressive course of RE. However, the precise nature and sequence of the pathogenetically relevant processes is not clear.

At disease onset, RE becomes manifest with unilateral enlargement of inner and outer CSF compartments which are accompanied by an increased cortical or subcortical T_2 or FLAIR signal. Transient focal swelling may occur. Subsequently, a spread of signal changes and atrophy arises within the affected hemisphere.[45] Usually the uppermost amount of tissue loss happens during the first 12 months after onset of the acute disease state.[46] The histopathological changes in RE are those of a chronic inflammatory process with subsequent neuronal loss and gliosis. Pathological changes have been classified in four stages.[47] The active phase is characterized by numerous microglial nodules with facultative neuronophagia, perivascular cuffing, and reactive gliosis (Figure 144.7). During the active and remote state, these changes are accompanied by necrosis and cavitation of the cortex. Within the remote state neuronal loss and gliosis becomes prominent whereas microglial nodules occur to a lesser extent. At least inflammatory changes run short leading to a residual state with outstanding neuronal cell loss and gliosis. Inflammatory changes are confirmed by immunohistochemistry, indicating activated T lymphocytes with CD3 (Figure 144.7) and macrophages by CD68. Gliosis can be demonstrated by antibodies against glial fibrillary acidic protein (GFAP).

Limbic encephalitis

Patients suffering from tumors can develop an encephalopathy due to limbic encephalitis. Most common neoplasms associated with limbic encephalitis are small cell carcinomas of the lung, ovarian and breast cancers, seminomas, or Morbus Hodgkin.[32] However, limbic encephalitis is not necessarily associated with tumors. Recently, cases with spontaneously occuring non-paraneoplastic limbic encephalitis (NPLE) have

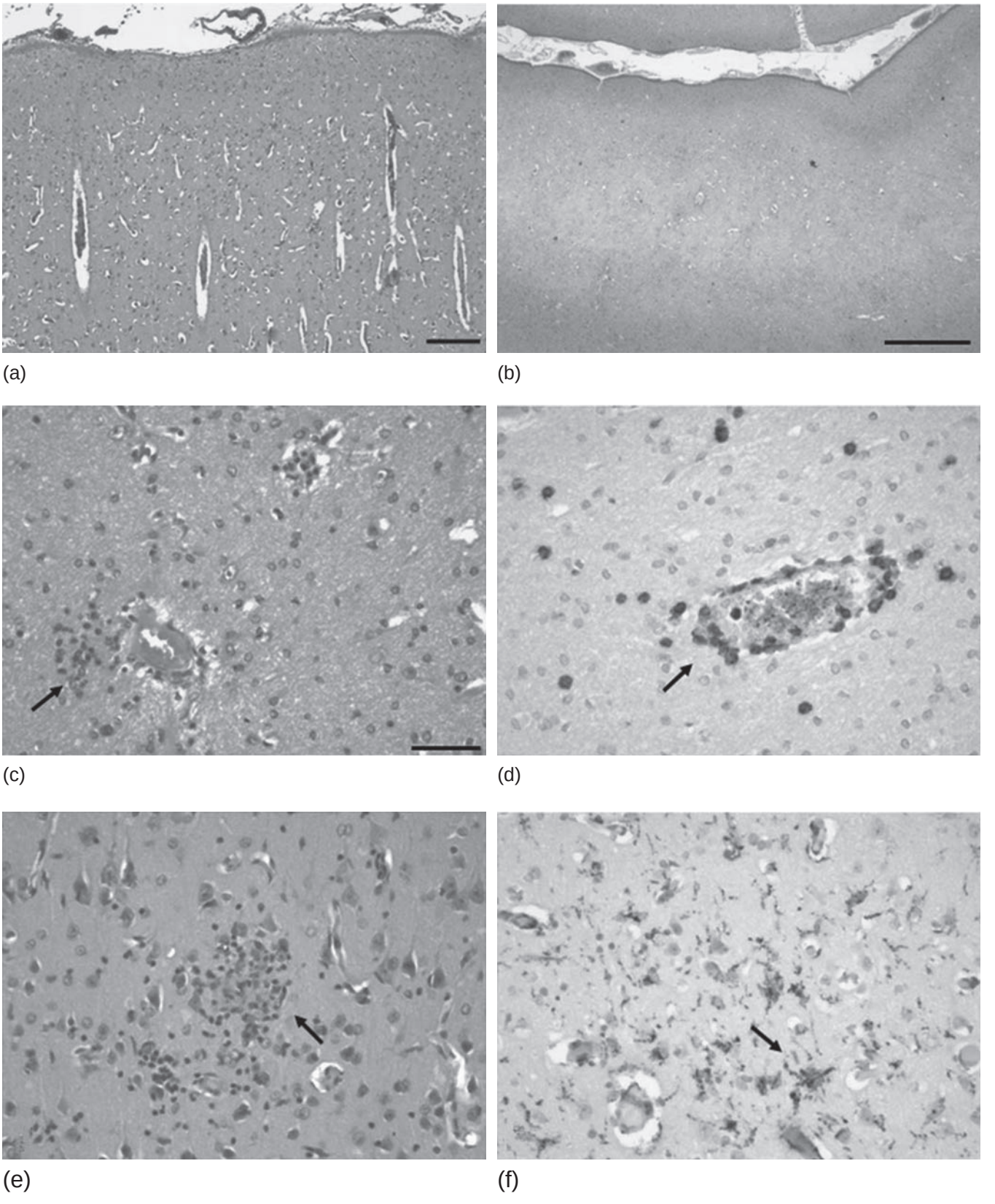

Figure 144.7 Rasmussen encephalitis presenting with cortical edema and atrophy (a). HE staining, scale bar = 500 μm). Cortical gliosis is visualized by GFAP immunohistochemistry (b). Scale bar = 1000 μm. Additional hallmarks of RE include perivascular T lymphocytes (arrows in c) and d (CD3), microglial nodules (arrow in e) and neuronophagia (arrow in f, CD68).

been described.[48] Both entities come along with similar MRI and histological findings. The course of the disease is characterised by subacute development. MRI shows increased T_2 signal in variable areas, mainly confined to limbic structures. It may occur unilateral or bilateral. Different stages may be present in the same image: Acute lesions with cortical swelling and increased signal besides recovering lesions with decreased signal intensity. There is no evidence for local tumor growth or viral infection. Histopathologically, NPLE is characterised by parenchymal and perivascular lymphocytic infiltration and microglial activation, partly in the forms of microglial nodules. Separation from Rasmussen's encephalitis (RE) is not always easy. However, whereas Rasmussen's encephalitis usually occurs within early childhood, NPLE starts rather in adulthood. Moreover, RE is usually restricted to one hemisphere and leads to progressive atrophy, while NPLE may affect both hemispheres with the capability to recover.

Herpes simplex encephalitis (HSE)

Among viral encephalitides herpes simplex is the most common cause of chronic epilepsy. In virus encephalitis, most infectious agents reach the brain by the blood stream, while herpes simplex virus reaches the brain by traversing peripheral nerve axons. HSE is the most common form of severe endemic encephalitis. Initial seizures occur in 60% of patients. Despite antiviral treatment mortality is still high. Most survivors present with severe neurological deficits and therapy refractory epilepsy.[49] Polymerase chain reaction amplification of viral DNA in the cerebrospinal fluid confirms the diagnosis. Almost all cases are caused by HSV-1 virus. Infection with HSV-2 virus is rare. The disease principally occurs at any age with a highest incidence in adolescence and in an immune-suppressive state. Radiologically, HSE presents as a unilateral or often bilateral temporal, insular and frontal lobe process with widespread increased T_2 signal. Contrast enhancement is possible.[50] By macroscopic inspection, the acute lesion consists of an expanding mass of necrotic, often hemorrhagic parenchyma. Microscopic findings include large necrotic areas with macrophage infiltration. Inflammation is characterized by lymphocyte perivascular cuffing and focal aggregates of microglial nodules. Appearance of viral intranuclear inclusion bodies, so-called Cowdry A inclusions within neurons or glia confirms the diagnosis. They typically appear as round or irregular, eosinophilic, intranuclear masses surrounded by a chromatine-free zone. Additional findings are homogenous red-wine nuclei.

Subacute sclerosing panencephalitis (SSPE)

SSPE is a rare but severe complication occurring in 1–22/100 000 patients after measles infection. It manifests months up to 10 years after primary infection. Pathogenetically, SSPE is caused by a genome mutation of intracellularly persisting measles virus (MV), causing viral nucleocapsides to accumulate in the brain cells. MV is not present in cerebrospinal fluid (CFS), therefore a negative PCR for measles in CSF does not exclude SSPE. Oligoclonal bands in the CSF and MV-specific IgG support the diagnosis. Rare SSPE manifestation after measles infection and occurrence of SSPE in siblings leads to a predisposing immune defect.[51] However, a specific predisposing immune defect is not known. Recent studies lead to a decreased cytotoxic T1 helper cell immune response or a defect in virus-specific production of interferonγ.[52,53]

Pathognomic EEG features are so-called Radermecker complexes, indicating fundamentally disrupted brain function. MRI findings are unspecific. Depending on the stage of the disease localized and diffuse T_2 hyperintensities may occur, indicating inflammatory and gliotic lesions followed by regional or global brain atrophy in later stages. Histological investigation reveals common findings in viral encephalitis with perivascular inflammatory cells, necrosis and nuclear inclusion bodies. The latter are large eosinophilic haloed intranuclear masses occurring within ganglion cells. Subtle intracytoplasmatic inclusions may also occur. Immunohistochemistry identifies measles virus antigen. Ultrastructurally nucleocapsids of SSPE are occasionally seen in neuronal processes.

Head injuries

Pathological findings

Head injuries can be separated in perforating and non-perforating lesions. The former are characterized by impressive skull fractures and bare the risk of severe complications by invasion of bone fragments, contamination with debris and pathogen organisms.

The pathology of non-perforating head injury includes two types, focal and diffuse lesions. Contusions and lacerations are the hallmarks of focal lesions differing in intact or torn pia mater. The latter condition is more likely to be found in fronto-temporal localization as well as in superficial gyri. Head trauma usually results a wedge-shaped defect with hemorrhage and edema, complicated by subdural hematoma due to laceration. At later stages, a V-shaped scar develops at apical gyri which carry yellow-to-brown hemosiderin pigment deposition (to be histologically verified using Berliner-blue reaction). The defect zone is surrounded by gliotic tissue and occasionally focal white matter demyelination. As in hemorrhagic infarction macrophage invasion and microvascular proliferates are common findings.

Contusions are frequently accompanied by contre-coup lesions opposite to the initial trauma. The most precarious complication after head trauma is intracranial hemorrhage. Hematoma and contusion lead to brain swelling which results in secondary brain damage. Imaging and macroscopic investigation reveal flattening of the gyri and, in severe cases, shift of the midline structures towards herniation. Diffuse lesions include ischemic brain damage predominantly involving the hippocampus, brain swelling secondary to vasogenic edema, diffuse vascular injury appearing as multiple petechiae, particularly evident in the white matter of the fronto-temporal lobes and diffuse axonal injury.[32] Hippocampal damage frequently occurs bilaterally and predominantly affects the hippocampal subfield CA1, whereas CA4, CA3, and CA2 are involved during disease progression.

Molecular findings and enhanced epileptogenesis associated with head injuries

Head injuries responsible for post-traumatic epilepsy can be divided into penetrating brain trauma with focal damage and

closed brain trauma due to a generalized insult. Incidence of post-traumatic epilepsy was found to be 7%–39% in patients with undamaged dura, whereas in patients with lacerated dura incidence rose from 20% to 57%. Post-traumatic epilepsy is predicted by the age of affected patients, with a higher incidence in children under 5 years, severity of the injury, localization, especially parietal lesions, duration of post-traumatic amnesia, and presence of intracranial hematoma.[32]

Blood-brain barrier dysfunction, vasogenic oedema, anoxic-ischemic neuronal damage, axonal sprouting, altered excitatory synapses, and synaptic disassembly are assumed to play a pivotal role in post-traumatic epileptogenesis.[54] Earlier studies found evidence for the hypothesis that post-traumatic epilepsy may result from blood extraversion and subsequent iron-mediated peroxidation of brain cell membranes.[55] However, recent findings point to a major impact of BBB disruption. As shown in animal studies, cortical exposure of low levels of serum albumin led to extravasion of serum proteins into the extracellular space and early activation of astrocytes followed by a lasting neuronal hypersynchronization.[56] Albumin may also play a role in microglial activation which is implicated in the neurotoxicity of neurodegenerative diseases.[57] Furthermore, intracerebral bleeding followed by activation of the coagulation cascade triggers brain edema. In addition, thrombin produces brain injury via direct brain cell toxicity.[58] There is further evidence that proinflammatory and anti-inflammatory molecules are synthesized during epileptic activity in glial cells. Various cytokines have been shown to affect neuronal excitability, leading to the hypothesis that they may play a role in altering synaptic transmission in epileptic conditions. Numerous studies indicate a central role of IL-1β for the exacerbation of brain damage after ischemic, traumatic or excitotoxic insults, suggesting that it may also contribute to neuronal cell injury associated with seizures.[59]

Besides reactive astrogliosis there seems to be evidence for disturbed astrocyte function following head trauma. The extracellular homeostasis of glutamate in the brain is maintained by the efficient uptake into astroglial cells. High extracellular glutamate levels seen during seizures probably result from an increased synaptic release and a deranged glutamate uptake. A prior study demonstrated decreased cortical levels of astrocytic glutamate transport protein GLT-1 in a rat model of post-traumatic epilepsy.[60]

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145 Pathology of epileptogenic neoplasms

RA Prayson

Summary

This chapter focuses on the pathology of tumors associated with chronic epilepsy. Topics that will be discussed include:

- The prevalence of various tumor types as reported in the literature.
- Issues and pitfalls that may complicate the diagnosis of tumors in this clinical setting.
- Details regarding specific tumor types including gangliogliomas, dysembryoplastic neuroepithelial tumor, astrocytomas and oligodendrogliomas.

Introduction

Neoplasms have been long recognized as a cause of medically intractable epilepsy. Several series in the literature have reviewed large numbers of patients which have undergone surgical excision of lesions for chronic epilepsy. The frequency of various pathologies are a bit different if one examines temporal lobe epilepsy versus extratemporal lobe epilepsy. Table 145.1 summarizes the pathologic findings in four large series of temporal lobe resections, all of which had greater than 200 cases evaluated. The prevalence of tumors in this setting ranged from 12.6–56.3%.[1–4] In the temporal lobe epilepsy literature, summarized in Table 145.2, the prevalence of tumors is generally less; malformations of cortical development (cortical dysplasia) account for a significantly higher percentage of identified lesions.[5,6] In a subset of tumors arising in this setting, the tumor represents part of a dual pathology, where another lesion is pathologically identified which may itself be epileptogenic.[7–11] Most commonly, this second pathology is a form of cortical dysplasia. Several of the tumors which will be later discussed in this chapter are well known to be associated with cortical dysplasia.

Tumors that are associated with chronic, medically intractable epilepsy, tend to present earlier in life, frequently in childhood, and are generally low-grade lesions. Table 145.3 summarizes the prevalence of tumors in various reported series arising in the setting of medically intractable, chronic epilepsy.[12–17] In most series, either low grade glioneuronal tumors, such as gangliogliomas or dysembryoplastic neuroepithelial tumors, or low-grade gliomas, most commonly diffuse or fibrillary type astrocytomas, are the most commonly encountered tumors.

There are obviously a number of differences between results observed in various surgical series and there are several explanations for why these differences exist. The most recent version of the World Health Organization (WHO) Classification of *Tumours of the Nervous System* includes definitions of many of the lesions that will be subsequently discussed in this chapter.[18] Despite this, there are unavoidable differences between pathologists with regard to interpretation of these definitions. For example, exactly how much atypia one needs to see in a lesion to determine that it represents a low grade astrocytoma as opposed to gliosis or hamartomatous lesion can be difficult to decide, and to some degree be in the eye of the beholder. Other lesions, such as the dysembryoplastic neuroepithelial tumor, although fairly strictly defined by the WHO, has been variously interpreted by different pathologists. In contast, the WHO definition of oligoastrocytoma

Table 145.1 Pathologic findings in temporal lobe epilepsy

Pathology	Wolf *et al.* (1993)[4] *N*=216	Plate *et al.* (1993)[3] *N*=224	Bruton (1988)[2] *N*=249	Mathieson (1975)[1] *N*=301
Tumors	34.7%	56.3%	Not specified	12.6%
Cortical dysplasia	18.1%	6.3%	Not specified	1.3%
Vascular malformation	6.0%	8.9%	1.6%	2.3%
Hippocampal sclerosis	71.8% of cases that were available	21.9%	42.9%	20.6%
Normal	Not specified	1.8%	16.2%	26.2%
Other pathology	6.5%	4.9%	8.4%	25.2%

Table 145.2 Pathologic findings in extratemporal lobe epilepsy

Pathology	Wolf *et al.* (1993)[5] √*N*=63	Frater *et al.* (2000)[6] *N*=133*
Tumor	19.0%	27.8%
Cortical dyslasia/ malformative lesion	33.3%	37.6%
Infarct/ischemic lesion	25.4%	18.0%
No pathology	14.3%	17.2%
Vascular malformations	3.2%	2.3%

*Some cases with dual pathology.

(mixed glioma) is somewhat more vague; precise guidelines as to what percent of a minor component needs to be present in a given lesion in order to make the diagnosis has not been agreed upon. Although most pathologists would agree that tumors with geographically distinct areas of oligodendroglioma and astrocytoma qualify as a mixed glioma, lesions in which the two patterns are intermixed are more problematic, and subsequently, the reproducibility of diagnosis is less than optimal. Some series reported in the literature have not separated out or enumerated various subtypes of astrocytoma e.g., pilocytic astrocytoma, from the larger diffuse fibrillary astrocytoma group. There are also differences in terms of how one defines medically intractable or chronic epilepsy that has allowed for the inclusion of certain high grade tumors such as glioblastoma multiforme in some series. However, it is hard to conceive of a glioblastoma multiforme, which has such a poor prognosis, being a cause of 'chronic epilepsy', unless it is the end point of a malignant progression or degeneration from a prior low-grade astrocytoma that has been around for a long period of time.

Tissue sampling is an important consideration in rendering an accurate diagnosis in many of these cases. Gangliogliomas, for example, are tumors marked by an atypical ganglion cell component and a glioma component. Both components of the tumor are generally not evenly distributed throughout the entire neoplasm. In fact, in some gangliogliomas, the ganglion cell component may be present in only a small part of the tumor; obviously, if this region of the tumor is not sampled, a correct diagnosis will not be made. The classic dysembryoplastic neuroepithelial tumor is a multinodular, cortical based microcystic tumor. Small biopsies make it quite difficult or impossible to recognize the architectural pattern which is a salient and useful diagnostic feature of this tumor. In such cases, the differential diagnosis expands to include other low-grade tumors which can have a microcystic appearance and are comprised primarily of cells with rounded nuclei (such as microcystic oligodendroglioma and protoplasmic astrocytoma). Pilocytic astrocytomas classically have a biphasic appearance, which may not be readily apparent if a limited tissue sampling is obtained. Rosenthal fibers and granular bodies, which are useful diagnostic clues to a diagnosis of pilocytic astrocytoma, are not present in all cases, and their absence may also cause diagnostic confusion. To further complicate matters, occasional pilocytic astrocytomas can contain areas with small rounded cells marked by pericellular clearing, mimicking an oligodendroglioma.

More recently, many have come to recognize that there are certain lesions that are not easily classifiable. Over the last several years, there has also been a slowly growing literature describing lesions that seem to have mixed features of more than one tumor type.

The rest of this chapter will address specific details on the pathology of some of the more commonly encountered tumors associated with chronic epilepsy.

Ganglioglioma

Gangliogliomas are tumors which are defined as well differentiated, slow growing, neuroepithelial neoplasms comprised of an atypical ganglion cell component in combination with a glioma component.[19–24] The majority of gangliogliomas are designated as grade I or II tumors in the WHO classification.[18]

Table 145.3 Tumor types encountered in medically intractable epilepsy

Tumor type	Zentner *et al.* (1997)[12] *N*=146	Pasquier *et al.* (1996)[13] *N*=63	Morris *et al.* (1996)[14] *N*=124	Britton *et al.* (1994)[15] *N*=51	Wolf *et al.* (1993)[16] *N*=87	Bourgeois *et al.* (1999)[17] *N*=98
Ganglioglioma	65	17	49	4	4	11
Pilocytic astrocytoma	21	0	2	6	17	Not specified
Fibrillary astrocytoma	15	3	29	12	10	21*
Oligodendroglioma	14	1	10	15	10	24
Oligoastrocytoma	10	0	6	6	2	15
Dysembryoplastic neuroepithelial tumor	19	30	15	4	6	23
Pleomorphic xanthoastrocytoma	1	4	1	1	1	0
Other	1	8	12	3	0	4

*Designated as 'astrocytoma' without any further specification.

Rare anaplastic gangliogliomas (grade III tumors) are recognized as well.[19,25–27] Gangliogliomas may present at any age, but are most commonly encountered in the first two decades of life. They arise anywhere throughout the neuroaxis, but are most commonly observed in the temporal lobe.

Grossly, the tumor may be solid or cystic and is generally not marked by mass effect. Calcification may be present. Necrosis and hemorrhage are unusual findings, the former being observed more commonly in anaplastic forms.

Microscopically, gangliogliomas are marked by an atypical ganglion cell or neuronal cell component (Figure 145.1). This component is not necessarily distributed evenly throughout the neoplasm, and therefore, sampling is sometimes required to discover it. A neuronal cell component may be marked by increased numbers of abnormally distributed or clustered ganglion cells. Many times, there are morphologic alterations to these cells including binucleation, abnormal distribution of Nissl substance, and rarely the presence of neurofibrillary tangles. Binucleate neuronal forms may be observed in up to 60% of these tumors. Immunohistochemical staining with markers of neuronal differentiation, such as synaptophysin, may be helpful in highlighting this component of the tumor. The typical neuronal cell component is often intermixed with a gliomatous component. The glioma component most commonly resembles a low-grade astrocytoma (Figure 145.2). The degree of cellularity may be focally prominent. Mild vascular proliferative changes may also be evident. Prominent mitotic activity and necrosis are generally not features of lower grade tumors and are used to differentiate the rare anaplastic variant. Occasionally, the glioma component may show features resembling a pilocytic astrocytoma or oligodendroglioma. Focal extension to involve the leptomeninges may be evident (Figure 145.3) Perivascular chronic inflammation, consisting primarily of lymphocytes, is not commonly encountered. Eosinophilic granular bodies and microcalcifications may also be focally present (Figure 145.4). Microcystic degenerative changes are also a feature of a subset of these tumors. Care should be taken not to overinterpret synaptophysin positive staining in normal resident neurons as the ganglion cell component of a tumor.[28]

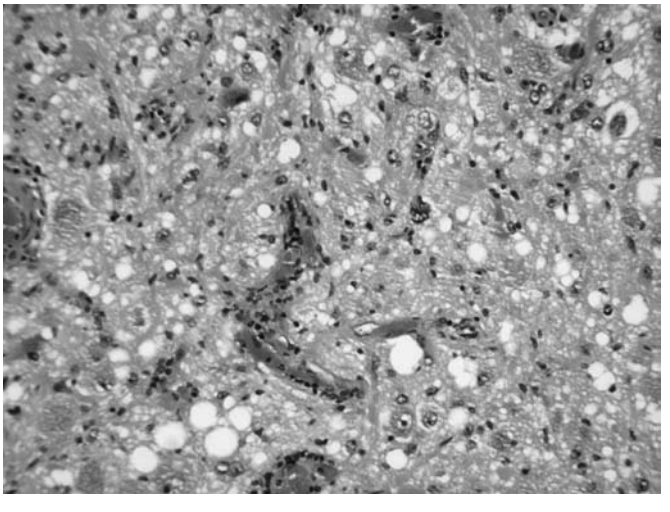

Figure 145.1 A ganglioglioma marked by predominantly ganglionic cells and blood vessels with mild perivascular chronic inflammation.

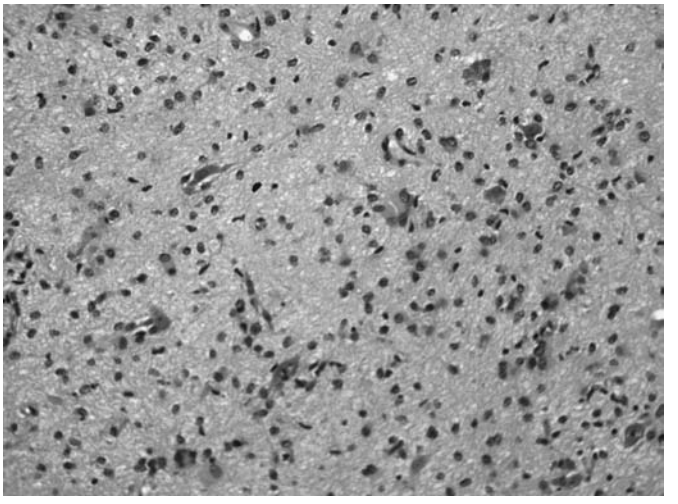

Figure 145.2 A ganglioglioma with intermixed large ganglionic cells and smaller glial cells.

Studies which have examined cell proliferation markers in these tumors found low rates of proliferation in the majority of neoplasms.[19,20] The two largest series to date that have examined this issue have observed Ki-67 or MIB-1 labeling indices of approximately 1%.[19,20] The rare anaplastic variant shows high rates of cell proliferation.

Information regarding genetics on these tumors is limited. These tumors demonstrate multiple chromosomal abnormalities.[29] P53 expression by immunohistochemistry has not been observed; however, increased immunoexpression in a subset of tumors with antiapoptotic proteins bcl-2 and bcl-X_L have been reported.[20,30] Fairly recent work has noted a splice-type-associated polymorphism in the tuberous sclerosis 2 gene that may predispose one to the development of sporadic ganglioglioma.[31]. Polymorphisms have also been noted in the tuberous sclerosis 1 gene.[32]

Gangliogliomas generally have an excellent prognosis and are quite amenable to surgical resection. There is little role for the use of adjuvant radiation therapy or chemotherapy in the routine management of these tumors. Such adjuvant therapies may be utilized in the management of the rare anaplastic variant.

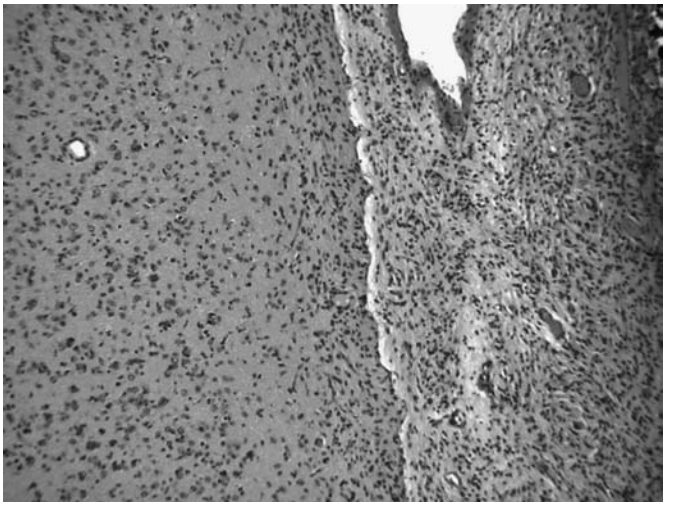

Figure 145.3 Extension of a ganglioglioma to involve the leptomeninges (right).

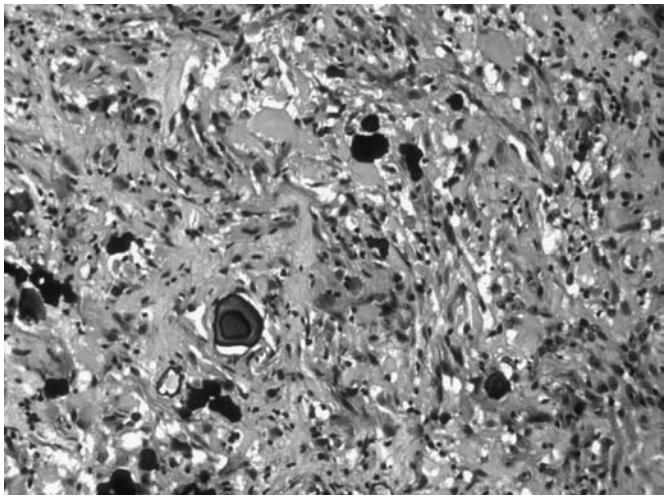

Figure 145.4 Foci of dystrophic calcification in a ganglioglioma.

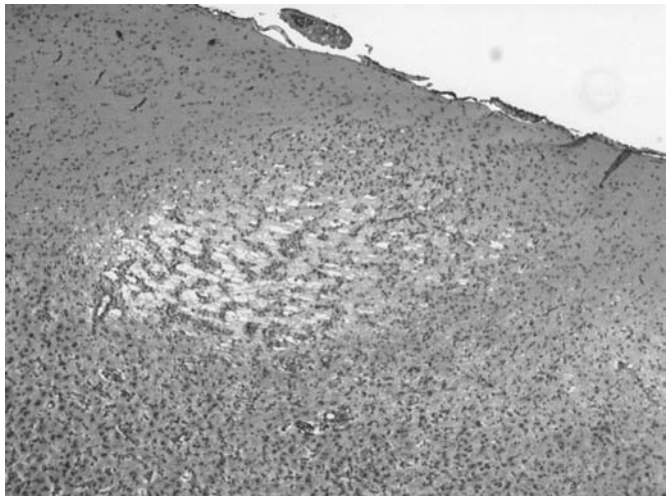

Figure 145.5 Low magnification appearance of a portion of a dysembryoplastic neuroepithelial tumor depicting the superficial, cortical basal location of the tumor.

The origin of ganglioglioma is still not known. As previously discussed, there may be a genetic component to the development of a subset of these tumors. A number of studies have also established an association of ganglioglioma with malformations of cortical development (cortical dysplasia).[19,20,33,34] The coincidence of cortical dysplasia with ganglioglioma appears to be more than just chance. Similar to cortical dysplasia, gangliogliomas may have a maldevelopmental basis to their origin. Some forms of cortical dysplasia are morphologically quite similar to ganglioglioma and distinction of one from the other may be difficult without the proper clinical or radiographic context.

Dysembryoplastic neuroepithelial tumor

Dysembryoplastic neuroepithelial tumors were first recognized as a distinct pathologic entity in 1988 by Daumas-Duport *et al.*[35] Prior to this time, many of these lesions were likely diagnosed as oligodendroglioma or perhaps even ganglioglioma. Subsequent literature on the entity has established it as a distinct lesion, which is commonly encountered in the setting of chronic epilepsy.[36–41] These tumors are generally thought of as glioneuronal neoplasms, marked by a multinodular architectural pattern and predominant cortical location. They are regarded by the WHO as grade I. Similar to gangliogliomas, they may arise at any age; however, they show a predominance in the pediatric population. Origin of these tumors in a variety of locations throughout the central nervous system have been reported, although the majority of them arise in the temporal or frontal lobes.

Grossly and on imaging studies, they are predominantly intracortical in location and multinodular (Figure 145.5). Peritumoral edema is usually absent. Foci of microcystic change are frequently present. The involved surface cortex may show a bubble-like or blustered appearance, secondary to this microcystic change.

Microscopically, the tumor is marked by a proliferation of cells with generally rounded nuclei, scant cytoplasm, and frequent pericellular clearing, very similar to oligodendroglial cells (Figures 145.6 and 145.7). These cells are often arranged against a microcystic background. Floating in the cystic pools are benign, normal appearing neuronal cells. Small numbers of astrocytic cells are interspersed among the other cells present. The tumor demonstrates minimal cytologic atypia. A chickenwire or arcuate capillary vascular pattern is often prominently noted. Mitotic activity is frequently absent. Necrosis and vascular proliferative changes are not seen. Occasional tumors may demonstrate evidence of focal calcification. By immunohistochemistry and ultrastructural studies, a subpopulation of the oligodendroglial-like cells may also demonstrate evidence of neuronal differentiation, but the majority of cells do not.[40,42]

Similar to ganglioglioma, an association of the dysembryoplastic neuroepithelial tumor with adjacent malformations of cortical development has also been described.[34–39,43] It has been suggested that these tumors might arise from subpial granular cells layer, their specific derivation has not been universally

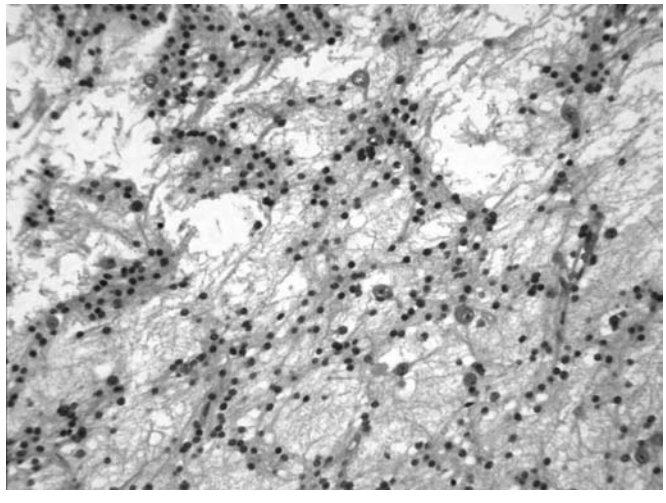

Figure 145.6 Typical microcystic appearance of a dysembryoplastic neuroepithelial tumor. Most of the tumor's cells resemble rounded oligodendroglial cells with an occasonal normal appearing neuron.

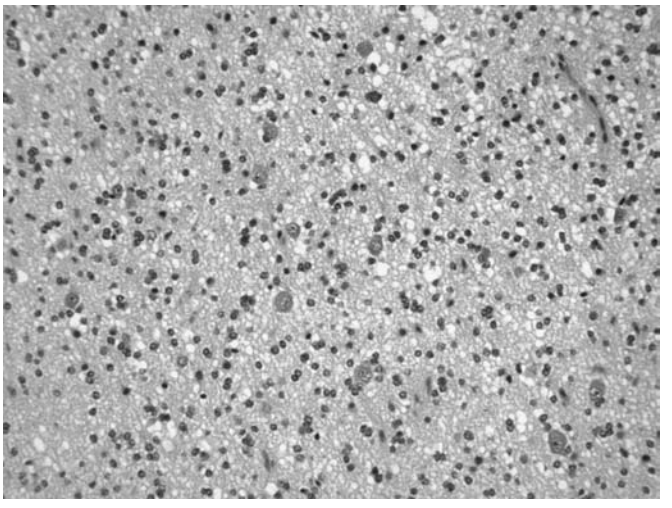

Figure 145.7 A more solid region of a dysembryoplastic neuroepithelial tumor showing both oligodendroglial-like cells and neuronal cells.

agreed upon. Again, the coexistence of this lesion with cortical dysplasia suggests a malformative basis for the tumor.

Studies which have examined cell proliferation markers in these tumors have demonstrated low labeling indices, typically on the order of 1% or less.[38,39,43,44] Because of the morphologic resemblance to neurocytomas and oligodendrogliomas, a few studies have explored genetic markers that are more commonly associated with these tumor types. Allelic loss on chromosomes 1p and 19q have not been observed in dysembryoplastic neuroepithelial tumors, in contrast to oligodendrogliomas, where approximately 60% of tumors demonstrate these allelic losses.[45,46]

Similar to gangliogliomas, dysembryoplastic neuroepithelial tumors are amenable to surgical resection and are potentially curable with a gross total resection. There is currently no role for adjuvant chemotherapy or radiation therapy in the management of these tumors. Rarely, cases of supposed malignant transformation or progression of these tumors to high-grade lesions have been reported; however, careful examination of these cases often shows atypical features making the diagnosis suspect. If one maintains strict criteria for the diagnosis, these tumors almost invariably have a benign clinical course.

Because the diagnosis requires assessment of architectural pattern, small biopsies may be inadequate and inappropriate for purposes of definitive diagnosis. The strong resemblance of this tumor to a low-grade microcystic oligodendroglioma or protoplasmic astrocytoma may cause differential diagnostic problems in the setting of a limited biopsy, where the location of the tumor, multinodularity of the lesion, or adjacent cortical dysplasia may not be appreciated.

Diffuse or fibrillary astrocytomas

Diffuse or fibrillary astrocytomas comprise the most common primary neoplasms of the central nervous system.[18] They arise anywhere in the neuroaxis and have peak incidence in young adults between the ages of 30–40 years; although, they may arise at any age. Seizures are a fairly common presentation for these tumors. The clinical course of higher-grade lesions (glioblastoma multiforme) often culminates in the death of the patient within a relatively short period of time. Therefore, these patients typically do not present with a medically intractable epilepsy. The World Health Organization stratifies the fibrillary astrocytomas into three grades. The low-grade lesions are generally designated as grade II neoplasms and are the lesion of primary interest in the chronic epilepsy venue. Higher-grade tumors are designated as anaplastic astrocytoma (grade III) and glioblastoma multiforme (grade IV).

Typically, the low-grade astrocytomas arise in the white matter and have an infiltrative growth pattern. As tumor cells infiltrate into the overlying cortex, they frequently obscure the gray-white interface. Microcystic or grossly cystic areas may be evident. Microcalcifications may be observed in approximately 15% of tumors.

Histologically, low-grade fibrillary astrocytomas are marked by increased cellularity due to a proliferation of atypical appearing astrocytes (Figure 145.8). The atypia is marked by nuclear enlargement, nuclear hyperchromasia associated with a coarse chromatin pattern, and nuclear irregularity or pleomorphism. Rarely, mitotic figures may be observed; they are more readily discernible in the higher-grade tumors. Vascular proliferative changes and necrosis, which are features more commonly associated with glioblastoma multiforme, are absent in low-grade tumors. Occasional tumors may show a prominent gemistocytic component. These gemistocytic cells are characterized by prominent eosinophilic cytoplasm and a laterally displaced, slightly enlarged nucleus with small nucleolus.[47,48] Tumors with a significant gemistocytic component tend to behave in a more aggressive fashion.

Rates of cell proliferation utilizing cell proliferation markers are generally low in the grade II fibrillary astrocytomas.[49–51] In general, the mean labeling index of the low grade fibrillary astrocytoma group is a bit higher than the gangliogliomas and dysembryoplastic neuroepithelial tumors. Tumor cells are generally (GFAP) positive. As previously mentioned, distinction of this lesion from ganglioglioma may sometimes be dependent on the extent of sampling of the

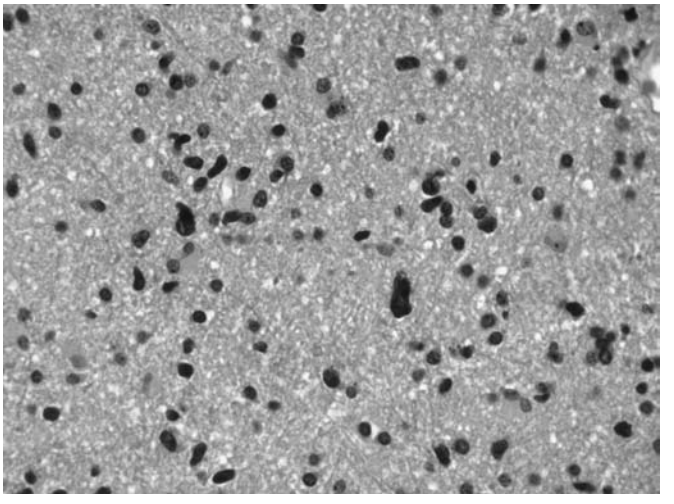

Figure 145.8 A low-grade fibrillary astrocytoma marked by atypical astrocytic cells with enlarged nuclei and irregular nuclear contours.

lesion in that the gliomatous component of ganglioglioma may resemble a diffuse or fibrillary type astrocytoma.

In contrast to most gangliogliomas and dysembryoplastic neuroepithelial tumors, fibrillary astrocytomas are well known to evolve over time into higher-grade lesions. This underscores the importance of distinguishing this entity from ganglioglioma. There is some recent suggestion in the literature that among the grade II fibrillary astrocytomas, a subgroup of these tumors arising in patients with long term epilepsy may have a more benign clinical course with a lower rate of occurrence and higher percentage of survival at 10 years.[50] Although differences were observed in this study based on clinical parameters, the morphologic distinction of this subset of tumors from other fibrillary astrocytomas is not possible. In contrast to gangliogliomas and dysembryoplastic neuroepithelial tumors, it appears that a significant subset of low-grade fibrillary astrocytomas demonstrate p53 mutations or alterations.[18] Treatment is generally determined by a variety of parameters including grade of tumor at time of presentation, location, age, and time course of the neoplasm. Low-grade lesions may be amenable to surgical excision and followed by observation. Adjuvant therapies are often reserved for tumors which demonstrate progression or are higher-grade lesions.

Protoplasmic astrocytoma

The protoplasmic astrocytoma is a rare low-grade astrocytic neoplasm (WHO grade II) that also has been linked to chronic epilepsy.[18] Many of these tumors arise in the first few decades of life and present with a long history of epilepsy. Temporal and frontal lobes are the most common sites of origin.[52] Many of these tumors appear to be cortical based.

Microscopically, these tumors are marked by a proliferation of astrocytic cells with round or slightly oval nuclear contours and scant amount of cytoplasm (Figure 145.9). Cells are arranged against a microcystic background. Prominent mitotic activity, vascular proliferative changes, and necrosis are not seen. Eosinophilic granular bodies or Rosenthal fibers, features that are fairly typical of pilocytic astrocytoma, are not observed in these tumors. In contrast to dysembryoplastic neuroepithelial tumors, which protoplasmic astrocytomas may also resemble, the protoplasmic astrocytoma lacks adjacent cortical dysplasia and usually presents as a unifocal mass.

The rate of cell proliferation in these tumors is rather low, with a mean MIB1 labeling index in one series of 0.7.[53] P53 immunoreactivity is present in a minority of tumors.[53] In contrast to oligodendrogliomas, 1p chromosomal deletions are not observed in these tumors.[54]

Clinically, most of these tumors behave like low-grade lesions. Their superficial location may make them somewhat more amenable to surgical excision.

Pilocytic astrocytoma

Pilocytic astrocytomas are the most common of the astrocytoma variant tumors. These neoplasms most commonly arise in the cerebellum, region adjacent to the third ventricle, brainstem, and optic nerve/chiasm. A subset of these tumors may present in the clinical setting of medically intractable epilepsy. Recognized by the World Health Organization as a grade I lesion, these tumors have a much better prognosis than the fibrillary type astrocytomas, and are important to distinguish from these tumors for that reason.[18] The majority of pilocytic astrocytomas arise in the pediatric age group.

Grossly, the classic pilocytic astrocytoma is a cystic tumor that has a mural nodule or nodules. Radiographically, these nodules enhance because of the increased vascularity of these neoplasms.

Microscopically, the classic pilocytic astrocytomas are biphasic neoplasms (Figure 145.10). Areas of the tumor consist of a dense fibrillary background and spindled cells. Often in these more compact areas, brightly eosinophilic Rosenthal fibers may be evident (Figure 145.11). These dense fibrillary areas are frequently juxtaposed to other regions of the tumor which may have a looser, more microcystic appearance. Often in these more microcystic areas, eosinophilic granular bodies may be evident. Foci of perivascular chronic inflammation

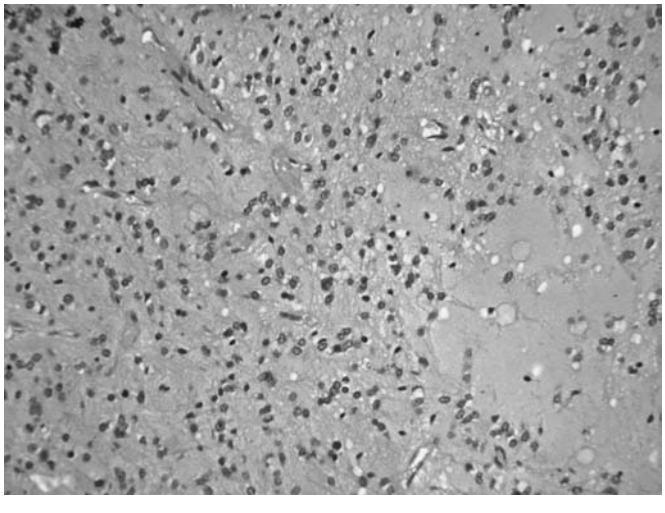

Figure 145.9 A protoplasmic astrocytoma composed of astrocytic cells with generally rounded nuclei arranged against a cystic or loose background.

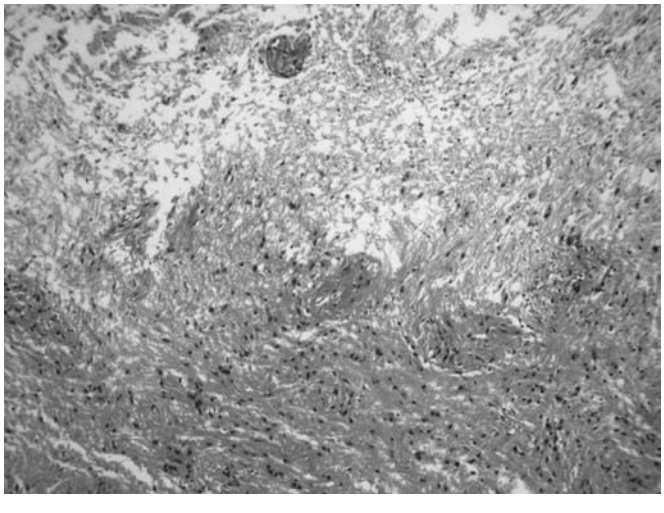

Figure 145.10 Compact fibrillary and loose patterns characterize the biphasic appearing pilocytic astrocytoma.

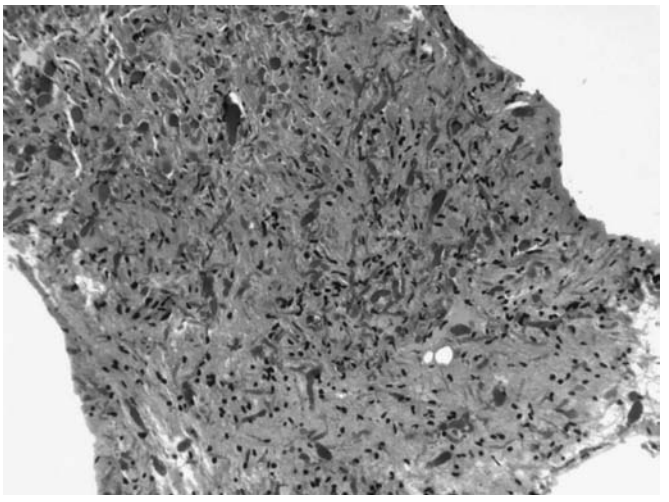

Figure 145.11 Numerous eosinophilic Rosenthal fibers in a compact area of a pilocytic astrocytoma.

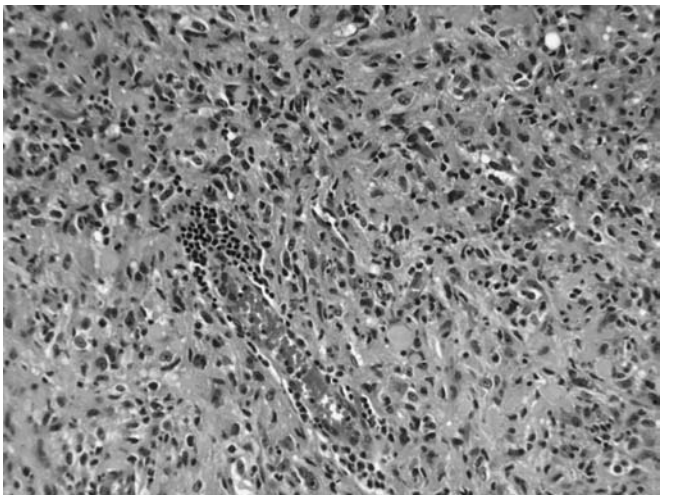

Figure 145.12 A markedly cellular pleomorphic xanthoastrocytoma with perivascular chronic inflammation.

consisting primarily of lymphocytes are frequently present. Vascular sclerotic changes may also be evident. Nuclear pleomorphism may prominent. Misinterpretation of the vascular proliferative changes and pleomorphism as representing features of a fibrillary type astrocytoma may result in an erroneous diagnosis of anaplastic astrocytoma or glioblastoma multiforme. Prominent mitotic activity and necrosis are generally not viewed as features of the pilocytic astrocytoma.

Being astrocytic in derivation, these tumors demonstrate GFAP immunoreactivity. Distinction of these tumors from ganglioglioma must be considered, given that the gliomatous component of the ganglioglioma may on occasion resemble a pilocytic astrocytoma. Rates of cell proliferation are generally low in keeping with the low grade of these neoplasms.[55–58] Many of the genetic alterations that have been previously attributed to diffuse or fibrillary type astrocytomas are generally not observed in pilocytic astrocytomas. The literature seems divided over the frequency of p53 mutations in these tumors.[59–61]

The vast majority of these tumors behave in a benign fashion and are amenable to surgical excision. Only rare cases of malignant degeneration or progression have been documented.[62] There is generally no role for adjuvant therapy in the treatment of most pilocytic astrocytomas.

Pleomorphic xanthoastrocytoma

Pleomorphic xanthoastrocytomas are low-grade tumors (WHO grade II) that account for less than 1% of all astrocytic neoplasms.[18,63–65] The majority of patients are in the pediatric age group. Tumors are typically located in the temporal or parietal lobes. On imaging studies, these tumors often have a cystic component with enhancing mural nodule or nodules. Focal areas of dystrophic mineralization may be evident. They are usually superficial and often attached to the meninges. Leptomeningeal spread of tumor may occasionally be observed.

The neoplasm is marked by prominent hypercellularity, comprised of cells which demonstrate considerable nuclear pleomorphism (Figure 145.12). In some cases, vacuolated or xanthomatous changes in the cytoplasm of astrocytic cells may evident (Figure 145.13). Multinucleated, giant astrocytes may also be present. On casual inspection, these tumors resemble high-grade fibrillary astrocytoma in terms of cellularity and pleomorphism. Vascular proliferative changes, which may be quite prominent in these tumors and account for the enhancement seen radiographically, may cause further confusion with high grade fibrillary astrocytoma. In contrast to high grade fibrillary astrocytomas, however, pleomorphic xanthoastrocytomas generally lack significant mitotic activity or evidence of necrosis. Eosinophilic granular bodies are frequently present as are perivascular collars of lymphocytes. In contrast to the usual fibrillary type astrocytoma, pleomorphic xanthoastrocytoma shows increased reticulin deposition between individual cells and small groups of tumor cells. In the usual fibrillary astrocytoma, reticulin deposition is confined to blood vessels and vascular proliferative changes. Rare examples of more aggressive pleomorphic xanthoastrocytomas, so-called anaplastic pleomorphic xanthoastrocytoma

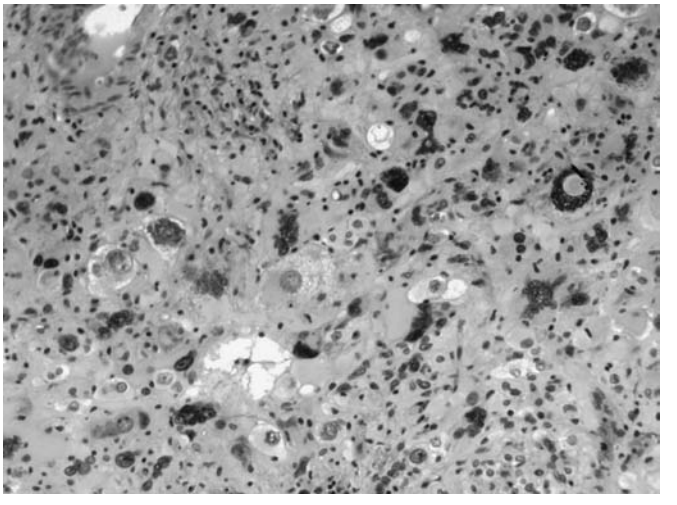

Figure 145.13 Scattered pleomorphic tumor cells and occasional vacuolated or lipidized appearing tumor cells in a pleomorphic xanthoastrocytoma.

(WHO grade III), have been recognized and are marked by increased mitotic activity and/or necrosis.[66–68]

GFAP immunoreactivity in these tumors is evidence for their astrocytic differentiation. Of interest in pleomorphic xanthoastrocytomas is that a small subpopulation of cells demonstrate evidence of neuronal differentiation by immunostaining, suggesting that perhaps these tumors may be glioneuronal in nature rather than purely astrocytic.[69] Furthermore, the presence of associated cortical dysplasia in a subset of these tumors and existence of cases of ganglioglioma/pleomorphic xanthoastrocytoma mixed tumors raise further questions with regard to the exact nature of this neoplasm.[70–72] In one series in which 29 tumors were evaluated with MIB1 antibody, a mean labeling index of 1.9 ± –3.1% was observed.[65]

As a group, pleomorphic xanthoastrocytomas generally do well with surgical excision. As previously indicated, a subset of tumors have demonstrated more aggressive behavior and may require additional adjuvant therapy

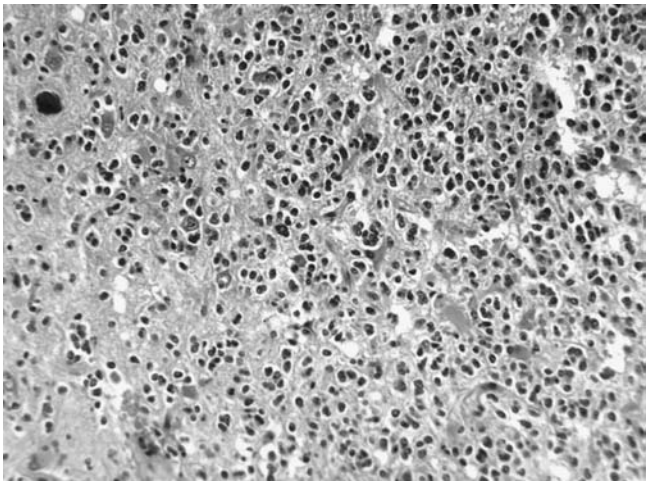

Figure 145.14 A low grade oligodendroglioma characterized by a proliferation of rounded cells with pericellular clearing or halos (fried egg appearance) and focal calcification.

Oligodendrogliomas and mixed gliomas (oligoastrocytomas)

Oligodendrogliomas comprise between 5–18% of intracranial gliomas.[18] Similar to astrocytomas, the majority of cases arise in adults, with the peak incidence in the 5th and 6th decades of life. They are relatively uncommon in the pediatric population. Many pediatric lesions, which were historically diagnosed as oligodendrogliomas, have turned out to be dysembryoplastic neuroepithelial tumors. Several large series that have been published on these tumors show that oligodendrogliomas arise in the white matter, with frontal lobe being the most common location, and often present with a long preoperative history of neurologic signs and symptoms.[73–78]

Like their fibrillary astrocytoma counterparts, these tumors frequently are infiltrative and cause obscuring of the gray matter/white matter interface. The majority of tumors demonstrate calcification. Cystic degenerative changes and evidence of hemorrhage may be seen.

Microscopically, these tumors are marked by a proliferation of cells with rounded nuclei and scant cytoplasm (Figure 145.14). An artefact of delayed formalin fixation results in the classic 'fried egg' or perinuclear halo that may be seen morphologically. A delicate capillary vascular pattern is evident in these tumors. Microcalcifications are also fairly frequent findings (in up to 80% of tumors). Occasional tumors may be marked by a population of cells with increased eosinophilic cytoplasm, so-called mini gemistocytes; there is no prognostic significance attached to these cytologic changes. The WHO recognizes two grades of oligodendroglioma (grades II and III).[18] Grade III or anaplastic oligodendrogliomas are marked by increased cellularity and nuclear pleomorphism, readily identifiable mitotic activity, vascular proliferative changes, and/or necrosis.

To date, there are no reliable immunohistochemical markers for the identification of oligodendroglial cells. Studies looking at cell proliferation indices in these tumors have shown correlation of grade with labeling indices. Of particular note is the presence of deletions on chromosome 1p and 19q in the majority of these tumors.[78–82] Interestingly, these deletions have been associated with better prognosis and chemoresponsiveness in the anaplastic oligodendroglioma group.[78–82] This has prompted some institutions to routinely screen their oligodendrogliomas for these molecular markers. In addition, the markers may also be useful in selected situations from a diagnostic standpoint. A limited biopsy of a microcystic tumor in the temporal lobe consisting of rounded cells with interspersed neurons raises a differential diagnosis of infiltrating oligodendroglioma involving gray matter versus dysembryoplastic neuroepithelial tumor. Evidence of deletions on chromosomes 1p and 19q in this setting would favor oligodendroglioma.[46] In a tumor that does not demonstrate deletions on these chromosomes, the differentiation between the two entities may still be uncertain.

In contrast to diffuse fibrillary astrocytomas, oligodendrogliomas are often (although not invariably) chemoresponsive. As previously noted, chemoresponsiveness appears to be associated with certain chromosomal deletions. High-grade tumors may also be treated with adjuvant radiation therapy.

There clearly are a subset of low-grade gliomas that appear to demonstrate mixed features of oligodendroglioma and fibrillary astrocytoma. In some cases, these two patterns of cell types are intermixed, and in other instances, there appears to be geographically distinct areas of each tumor type. The designations of mixed glioma or oligoastrocytoma have been used in reference to this subset of gliomas.[83–85] A universally agreed upon precise definition as to what constitutes a mixed glioma has not been well defined in the literature. Arbitrary cutoff points between 20–35% of a minor component have been variously used. Due to the lack of uniformity with regard to definition and diagnosis of this entity, it has been difficult to come to an understanding of the significance or the characteristics of this group of tumors. Similar to oligodendrogliomas, the World Health Organization stratifies these lesions into low grade (grade II) and high grade anaplastic (grade III) lesions.[18] There is some data to suggest that a subset of mixed gliomas demonstrates deletions on chromosomes 1p and 19q, and this subset may be more amenable to chemotherapy.[80]

Composite lesions

A number of cases reports and small series have been published describing tumors which demonstrate features of more than one tumor type, i.e., composite tumors. Cases of composite pleomorphic xanthoastrocytoma and ganglioglioma[70,71,86,87] as well as reports of tumors demonstrating areas of dysembryoplastic neuroepithelial tumor and ganglioglioma,[88–90] have been reported. Coexistence of these lesions raises interesting questions regarding the pathogenesis of these entities and possible malformative nature of this group of tumors. Interestingly, these are also tumors that have been described arising in association with cortical dysplasia.

Hamartoma

Hamartomatous lesions may rarely account for chronic epilepsy. Hamartomas in this context are defined as tumoral lesions composed of disorganized, but mature cellular elements.[91] These lesions may consist of admixtures of both glioneuronal elements, but in contrast to gangliogliomas, they lack appreciable cytologic atypia (Figure 145.15). Occasional granular bodies and microcalcifications may be present. Adjacent cortical dysplasia may also be noted. Cell proliferation markers show negligible evidence of cell proliferation. Because of the benignity of these lesions and their circumscribed nature, they are amenable to surgical excision and have a good postoperative outcome.

Meningioangiomatosis

Meningioangiomatosis is a rare benign lesion that probably has a maldevelopmental basis to its origin that may arise as a mass lesion in the setting of chronic epilepsy.[92–95] This lesion has been variously associated with a neurofibromatosis. The entity is marked by a benign proliferation of blood vessels collared by meningothelial cells which extends into the cortex and white matter (Figure 145.16). The intervening neural parenchyma shows gliosis and may show dystrophic mineralization. Gross total resection of the lesion appears to be curative.

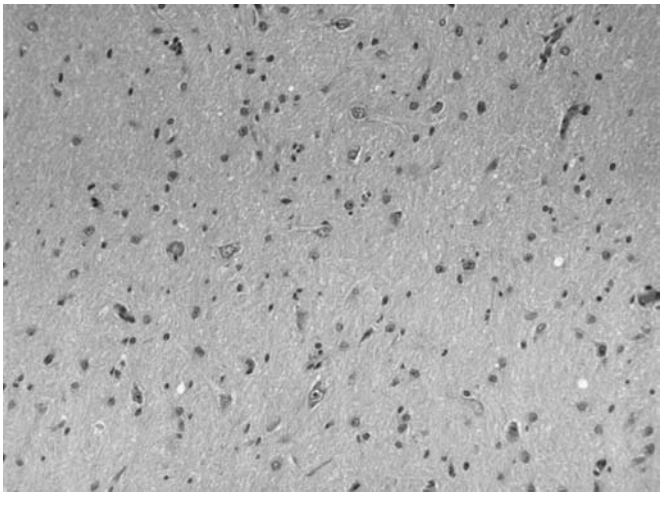

Figure 145.15 Glioneuronal hamartoma characterized by a disordered admixture of relatively benign appearing glial and neuronal cells.

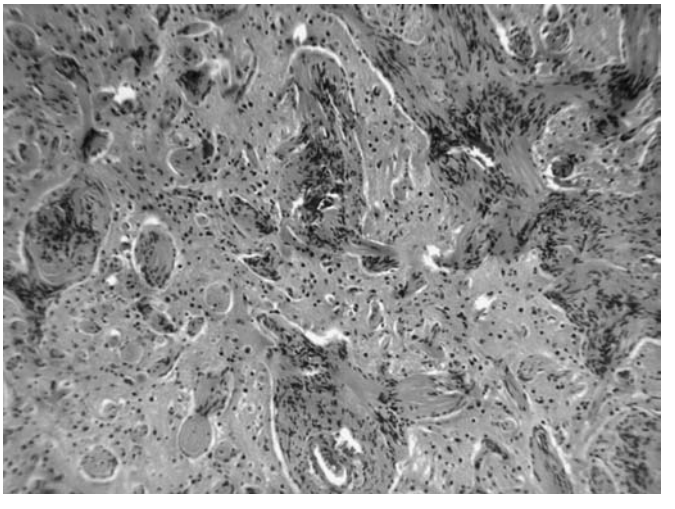

Figure 145.16 Meningoangiomatosis marked by a prolifertion of blood vessels collared by benign meningothelial cells.

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146 In vitro neurophysiological studies

GL Möddel and IM Najm

Introduction

For the past 50 years researchers have developed powerful methods in order to study the mechanisms which are involved in the generation of epileptic activity in neuronal tissues. In general, experiments can be performed using either living laboratory animals ('in vivo'), or tissue preparations (e.g., brain slices or separated single neurons) derived from such subjects ('in vitro'). In vivo experiments enable the researcher to study epileptic phenomena in an intact brain with all its neuronal structures and white matter connections preserved. Accordingly, those experiments constitute a rather valid model mimicking the processes that generate seizures in an epilepsy patient. However, many questions arising in regard to the basic mechanisms of epileptogenesis require more reduced, simplified models that enable the researcher to control for as many experimental parameters as possible and to manipulate others.

In vitro neurophysiological methods in experimental epilepsy research – an overview

The 'brain slice in vitro' preparation constitutes such a powerful experimental model. In short, axial sections of the hippocampus or neocortex of about 400–500 μm thickness are prepared from the brains of experimental animals (i.e., mostly, rats, mice, or guinea pigs). Additionally, human brain tissue samples resected from epilepsy patients for the treatment of intractable epilepsy have been studied using the in vitro slice model since resective surgery became a widely accepted treatment for intractable focal epilepsy in the late 1970s.[1–4]

Brain slices contain a limited, relatively simple, virtually two-dimensional neuronal network that is anatomically and physiologically well-described.[5] Following preparation, brain slices are incubated and stored in artificial cerebrospinal fluid (ACSF, i.e., saline mimicking the ional and glucose concetrations of CSF).[6] For electrophysiological recordings, individual brain slices are placed in a recording chamber and constantly superfused with oxygenated ACSF. Flow velocity, temperature, and pH are monitored and held constant throughout the experiment (Figure 146.1). This setup allows experimental manipulations such as changing the ionic composition of the extracellular medium, application of convulsant or anticonvulsant substances in exact, graded concentrations and without interference by the blood–brain barrier, transsection of defined axonal connections, or electrical stimulation of gray or white matter structures. Extracellular recording electrodes ('field potential electrodes') can be used to assess spontaneous or electrically induced synchronized discharges of the surrounding neuronal population ('epileptiform field potentials', EFP) or the extracellular correlate of synchronized action potential generation ('population spike'). Positioned within the dendritic layers of the neocortex or hippocampus, the extracellular correlate of excitatory or inhibitory synaptic potentials (eEPSPs, eIPSPs) can be recorded. Sharp electrodes which penetrate neuronal membranes are used to record membrane potential fluctuations of individual neurons as well as to inject positive or negative current pulses into neurons. These intracellular recordings can be maintained for many hours, and the effects of changes in the perfusion medium can be assessed. Parameters of interest are, for example,

- the resting membrane potential,
- input resistance (i.e., change of membrane potential in relation to amplitude of injected current),
- EPSPs and IPSPs (spontaneous, electrically induced, pharmacologically induced),
- spontaneous and electrically induced firing pattern (i.e., regular action potential firing with slow adaptation, fast adaptation, or intrinsically bursting firing mode; see Figure 146.2).

The patch-clamp technique[7] allows single-cell recordings using low-resistance electrodes in conjuction with special software to keep either the membrane potential or the current across a membrane patch constant over time (i.e., 'voltage-clamp' or 'current-clamp') while measuring the respective other parameter. By using suitable ion channel agonists and antagonists, the voltage-clamp technique can be employed to 'filter out' individual channel species and thus assess, for example, the time course of fast sodium currents or slow calcium currents directly. Besides, patch-clamp electrodes in situ can be used to inject neurons with dyes, so that individual recorded neurons can later be identified in histologically or immunocytochemically stained sections. Ion-selective electrodes are sensitive to concentration changes of defined ion species in the extracellular medium, so that localized activity-dependent changes in extracellular ion concentrations (e.g., potassium or chloride) can be assessed. Comb-like arrays of up to eight or ten extracellular electrodes provide field potential profiles, e.g., across neocortical layers. Recently, optical imaging techniques

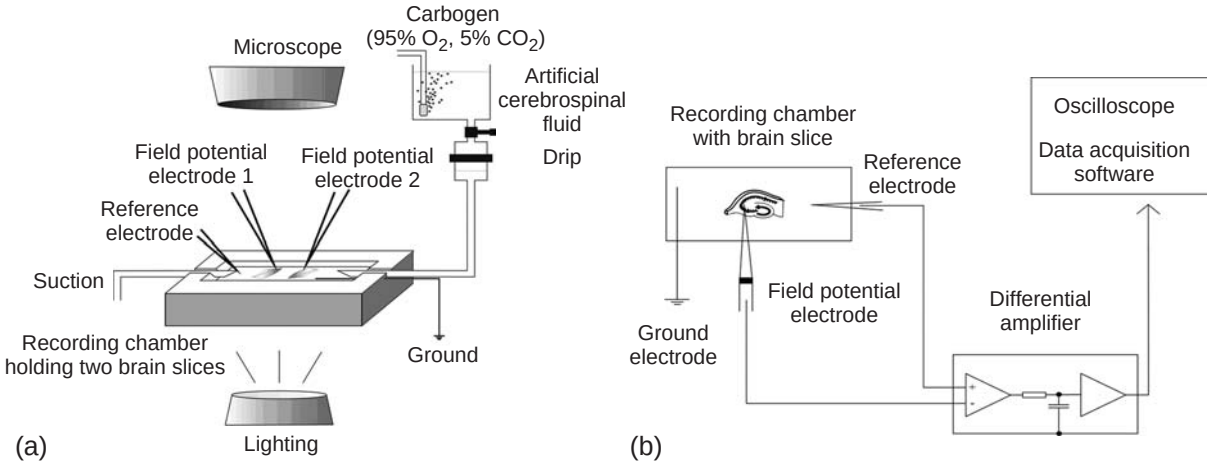

Figure 146.1 Experimental setup used for in vitro neurophysiological experiments. a, Mechanical setup; b, electrical setup.

have been developed which employ voltage-sensitive dyes and two-dimensional diode arrays instead of electrodes in order to assess the spread of neuronal activity across a brain slice and along pathways with high time and space resolution.[8]

When recording from a brain slice bathed in normal ACSF, spontaneous synchronized network activity is only rarely present. This is the case, for example, in cortical samples derived from surgically excised seizure foci of patients with medically intractable epilepsy,[9] or in slices prepared from animals with exprerimentally induced epileptogenic lesion or a genetic epileptic predisposition. In most cases, however, additional manipulations are necessary to induce epileptiform activity in brain slices. These 'in vitro seizure models' include:

- Electrical stimulation of afferent or efferent axonal pathways
- Application of substances which block GABAergic inhibition, such as penicillin,[10–12] bicucullin or picrotoxin.[13,14]
- Application of agents which block repolarizing voltage-gated potassium channels, such as 4-aminopyridine or barium.[15]
- Changes of the ionic composition of the bathing medium, such as
  – lowering of $[Cl^-]_o$, $[Ca^{2+}]_o$, $[Mg^{2+}]_o$, or $[K^+]_o$
  – elevating $[K^+]_o$.

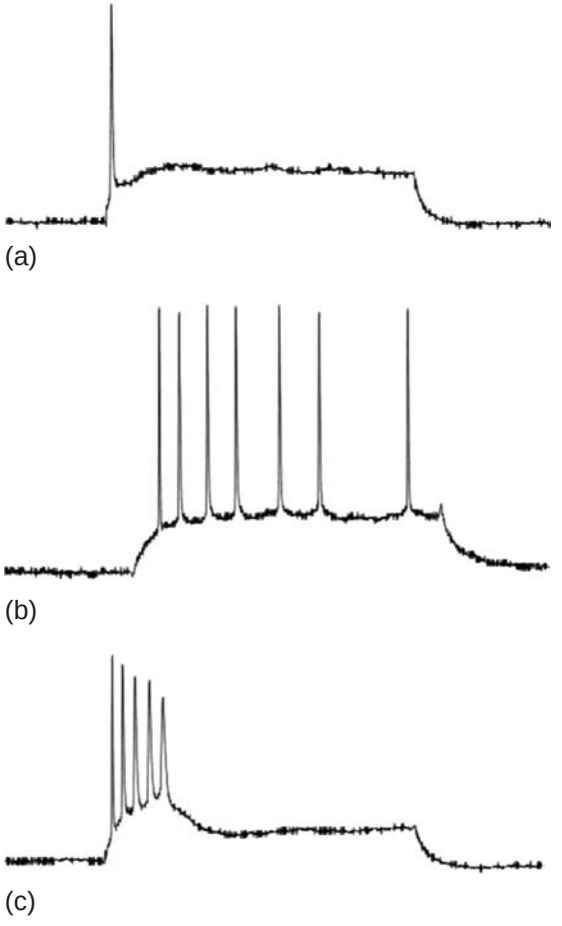

Figure 146.2 Typical neuronal discharge patterns, elicited by intracellular injection of positive current pulses (400 nA, 200 msec). a: Fast adaptation. b: Regular spiking with slow adaptation. c: Intrinsically bursting neuron. (guinea pig, hippocampus, CA3 pyramidal cells).

Among these models, the lowering of $[Mg^{2+}]_o$ ('low-magnesium model' or 'zero-magnesium model') has been proven to be especially useful because it reliably induces robust periodic spontaneous network bursts in both hippocampal and neocortical slices without requiring external stimulation. These 'epileptiform field potentials' (EFP) of 10–200 ms duration resemble interictal spikes in the EEG and were therefore termed 'interical bursts'. The epileptogenic effect of low $[Mg^{2+}]_o$ is mainly mediated by increasing sodium and calcium influx through N-methyl-D-aspartate (NMDA)-receptor associated ion channels.[16–21] At normal resting membrane potential of around –60 mV, magnesium ions block the NMDA-receptor channel pore, so that the channel remains inactive despite binding of the agonist glutamate to the receptor. Depolarization of the postsynaptic membrane (e.g., by concomitant activation via AMPA receptors) reduces the electrochemical gradient and causes magnesium ions to exit the channel pore, thereby removing the block. (Figure 146.3) Calcium ions entering the neuron cause further depolarization and serve as second messengers, inducing processes that are the basis for activity-dependent neuronal plasticity, such as induction of long-term potentiation (LTP),[22,23] or changes in

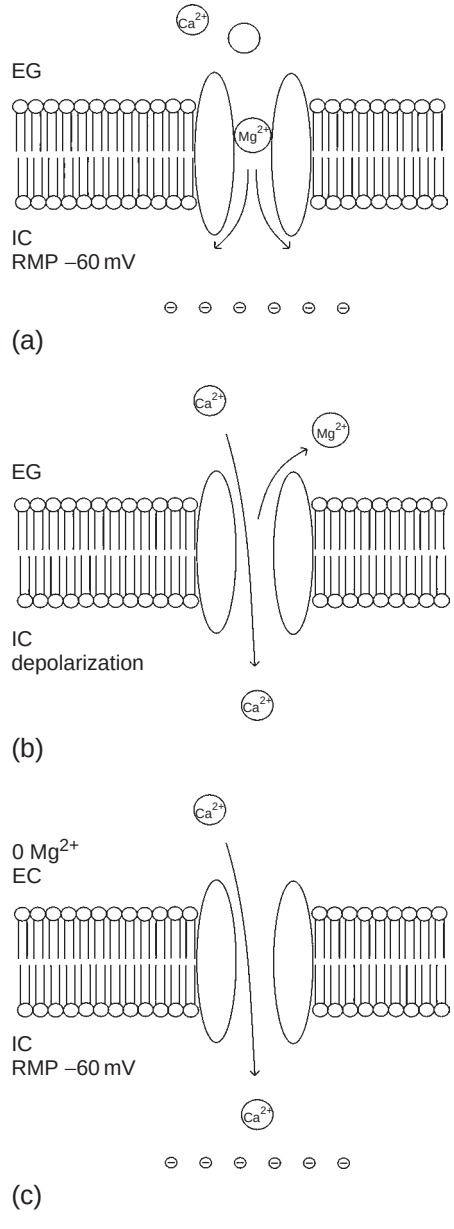

Figure 146.3 Gating of the NMDA receptor associated channel by extracellular magnesium ions. a: At normal resting membrane potential (–60 mV), the NMDA receptor channel pore is blocked by a magnesium ion, preventing cation influx into the postsynaptic neuron despite NMDA binding. b: Depolarization of the postsynaptic membrane releases the magnesium block. NMDA binding consecutively leads to sodium and calcium influx. c: When extracelluar magnesium concentration is markedly reduced, NMDA receptor activation leads to cation influx into the postsynaptic neuron without previous depolarization of the postsynaptic neuron. (0 Mg^{2+}: virtually magnesium-free extracellular solution; RMP: resting membrane potential; EC: extracellular; IC: intracellular).

gene expression patterns. When $[Mg^{2+}]_o$ is reduced by using nominally magnesium-free ACSF, NMDA-receptor associated ion channels can be activated at resting membrane potential without requiring prior depolarization, resulting in increased glutamatergic excitation. Secondarily, increased intracellular calcium, via calcium-calmodulin dependent enzymes, induces dephosphorylation of GABA-A receptors[24] which impairs GABA-ergic inhibition by reducing the receptor affinity for GABA.[25–27] NMDA-receptor independent effects of low-$[Mg^{2+}]_o$ include: direct membrane depolarization, as the 'screening' of negative phospholipid surface charges by the divalent cations magnesium and calcium is impaired,[28] and reduced presynaptic adenosin-receptor mediated inhibition.[29]

In vitro correlates of epileptiform activity

Simultaneous extracellular and intracellular recordings in the hippocampus demonstrated that synchronized epileptiform field potentials are correlated intracellularly by bursts of action potentials riding on a slow depolarizing wave-like potential fluctuation see Figure 146.4a).[21,30] Similar bursts had first been recorded by Spencer and Kandel[31] from the CA3-region of the hippocampus in cats in vivo. Plateau-like epileptiform bursts beginning with a steep initial depolarization are also termed 'parosysmal depolarizing shifts' (PDS).[32,33] Alongside epileptiform bursts resembling interictal spikes, prolonged seizure-like discharges have been described in brain slices in vitro.[4,6,9,15,34–36] Intracellular recordings show a steep initial depolarization with occasional superimposed action potentials, followed by a plateau and prolonged, slow repolarization with multiple superimposed after discharges (Figure 146.4b).

'Interictal-like' epileptiform bursts and epileptiform field potentials (EFP)

The majority of hippocampal pyramidal cells respond to supra-threshold depolarizing stimulation (i.e., injection of square current pulses via intracellular electrodes) with trains of action potentials showing slow or fast frequency adaptation. A subpopulation, however, generates intrinsic bursts of action potentials riding on a slow wave-like depolarizing envelope ('intrinsically bursting neurons', Figure 146.2). Intrinsic bursters serve as putative amplifying elements within neuronal networks and are thought to initiate synchronous activity in the hippocampus.[31,37,38] Dichter and Spencer[39] and Ayala *et al.*[40] have postulated that the process of synchronization is mainly facilitated by recurrent excitatory synaptic connections. Using computer simulations of hippocampal networks, Traub and Wong[41–43] and Traub and Dingledine[44] developed the following model scenario for the generation and spread of synchronous burst activity in the CA3 region of the hippocampus: postsynaptic membranes generate occasional 'spontaneous excitatory postsynaptic potentials' (EPSPs), e.g., by 'random' transmitter release from presynaptic terminals. If two or more of these spontaneous EPSPs occur virtually simultanously in an 'intrinsically bursting' neuron, the cell will generate an epileptiform burst. Given that (a) the excitatory interconnectivity is strong enough and (b) recurrent and lateral inhibition are weak enough to evoke consecutive epileptiform bursts in more than one neighboring neuron, a chain reaction will result: as soon as the number of simultaneously bursting neurons within the population exceeds a critical value, the number of firing cells will first rise explosively and then suddenly drop as the majority of neurons will almost simultaneously be hyperpolarized by recurrent inhibitory interneurons. The electrical correlates of this event as recorded by extracellular electrodes will be an 'epileptiform

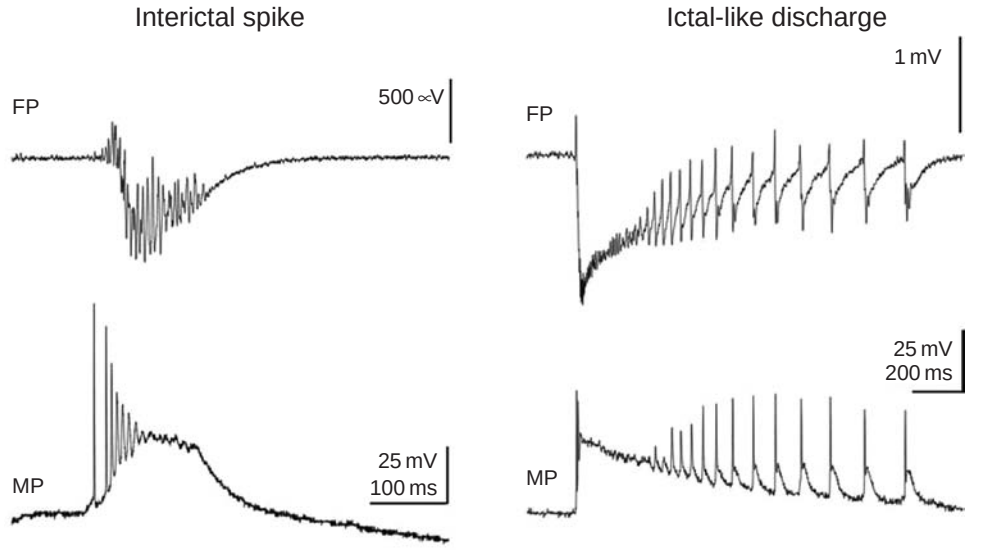

Figure 146.4 Spontaneous interictal and ictal-like epileptiform discharges recorded in vitro. Simultaneous extracellular field potential (FP) and intracellular membrane potential (MP) recordings, guinea pig, hippocampus, CA 3 region, pyramidal cell layer. Epileptiform activity was induced by reduction of the extracellular magnesium concentration (0 Mg^{2+}).

field potential' (EFP) in vitro, or an epileptiform spike or sharp wave in vivo. According to this model, the propensity of a neuronal network to generate EFPs is directly dependent on the proportion of intrinsic bursters within the neuron population, the degree of excitatory connectivity, and on active inhibition.

Seizure-like discharges

Alongside epileptiform bursts resembling interictal spikes, prolonged seizure-like discharges have been described in brain slices in vitro. Intracellular reocordings show a steep initial depolarization with occasional superimposed action potentials, followed by a plateau and prolonged, slow repolarization with multiple superimposed after discharges (Figure 146.4b). Extracellularly, an initial negative spike is followed by a sustained negative potential shift and multiple afterdischarges towards the end of the event. The occurrence of seizure-like discharges suggests that the mechanisms involved in epileptiform burst repolarization are impaired. This includes increased excitatory neurotransmission, reduced inhibition, or impaired intrinsic membrane repolarizing mechanisms:

- low $[Cl^-]_o$ which reduces GABA-A-mediated chloride currents[6,34]
- penicillin and bicuculline that block GABA-A-ergic inhibition[35]
- 4-aminopyridine which blocks repolarizing K^+ channels[15]
- low $[Mg^{2+}]_o$ which leads to increased NMDA-receptor activation,[4,9]
- low $[K^+]_o$ (unknown mechanism, probably increased AMPA/kainate receptor activation[36]

As the transition of epileptiform bursts into prolonged seizure-like discharges serves as a model for interictal to ictal transition in vivo, the involved mechanisms are of special clinical relevance.

Mechanisms of epileptogenesis revealed by in vitro neurophysiological studies

The following processes have been postulated to underly the generation of synchronized network dicharges:

- Intrinsic burst activity. Membrane excitability is regulated by
  – 'active membrane properties' such as voltage-gated ion channels or ligand-gated ion channels, and
  – 'passive membrane properties' such as the resting membrane potential, membrane resistance and capacitance, neuron geometry, leak channels, etc.
- Excitatory coupling between neurons, which can hypothetically be mediated by
  – excitatory synaptic connections,
  – electrical coupling via gap junctions,
  – direct electrical ('ephaptic') interactions between neighbouring neurons, and
  – changes in the concentrations of extracellular K^+ concentration.
- Reduced or impaired inhibition.
- Membrane properties, excitatory neurotransmission, and inhibition are further regulated by
  – Extra- and intracellular ion concentrations,
  – Neuromodulators, and
  – Second-messenger mechanisms.

Mechanisms regulating neuronal membrane excitability

Active membrane properties: voltage gated channels, ion-gated channels

The wave-like depolarization underlying an epileptiform burst has been shown to be caused by a slow cation influx. For hippocampal CA3 pyramidal cells and dentate gyrus granule

cells, slow voltage-activated sodium *and* calcium currents have been identified.[45–48] In CA1-neurons, a persistent sodium current ($I_{Na,p}$) is of major relevance.[49,50] Superimposed somatic action potentials are generated by an interplay between fast voltage-activated sodium currents and subsequent 'delayed rectifying' potassium efflux. Pyramidal cell dendrites generate slow calcium-dependent action potentials ('calcium spikes') which may coincide with somatic sodium spikes, producing the after-depolarization (ADP) that is often seen following action potentials recorded from the cell soma. The epileptiform burst ends with a repolarization, followed by an after-hyperpolarization (AHP) of up to 2 seconds duration. The initial burst repolarization is mainly facilitated by slow voltage-activated potassium channels and GABA-A-receptor mediated recurrent inhibition leading to chloride influx.[51] The same GABA-A-induced chloride influx contributes to the early phase of the AHP. The late phase of the AHP, which also determines the duration of the AHP, is generated by two potassium-dependent mechanisms: GABA-B mediated inhibition and slow Ca^{2+}-acitvated potassium currents.[14,52–54] Chamberlin and Dingledine[55] found that the duration of the AHP correlates positively with the inverval between two subsequent epileptiform bursts ('inter-burst interval') and negatively with the repeptition rate of EFP. Therefore, burst repetition rate in the hippocampus is regulated by GABA-B mediated inhibition and by the extracellular potassium concentration.

These data on burst generation mechanisms have facilitated research investigating the efficacy of voltage-gated ion channel blockers as anticonvulsant drugs. Blockade of slow voltage-activated calcium channels by application of the organic calcium antagonist verapamil exerts strong suppressant effect on bicuculline-induced and low-Mg^{2+}-induced epileptiform burst dicharges in the hippcampus and in the neocortex.[56–58] Similar results have demonstrated the efficacy of flunarizine in vitro. Severe cardiac side-effects in vivo have so far precluded these drugs from clinical use as anticonvulsants. Inhibitors of voltage-gated sodium channels, such as lidocaine, are widely used clinically as local anesthetics and antiarrhythmic drugs. However, their anticonvulsant properties are also well described (e.g., Schurr *et al.* 1986).[59] Lidocaine has been proposed as a drug of third choice for the treatment of refractory status epilepticus. Moreover, blockade of sodium channels is thought to be the major mechanisms of action of the anticonvulsant drug phenytoin.

Passive membrane properties

The excitability of neurons is crucially dependent on intrinsic properties of neuronal membranes. The resting membrane potential (RMP), described mathematically by the Goldman equation,[60] is determined by concentration gradients of ions in the extra- and intracellular compartments and by the membrane permeabilities of the respective ions. At resting conditions, the membrane permeability for potassium ions by far exceeds the permeability for all other ions, so that the RMP is basically a function of the relation between intracellular and extracellular potassium concentration. Potassium permeability is mainly dependent on potassium leak channels ($I_{K,leak}$), whereas ion concentration gradients are maintained by active transport through ATP-dependent pumps (e.g., Na-K-ATPase). Although, to the authors' knowledge, no experimental data exists so far that links changes of $I_{K,leak}$ to epileptogenesis, the block of this current can result in sustained changes in RMP and thereby change the probability of action potential generation. Inhibition of the Na-K-ATPase by the cardiac glycoside dihydroouabaine (DHO) has been shown to induce synchronized burst discharges in the CA1 area of rat hippocampus.[61] Hypoxia-induced epileptiform discharges[62] are, at least in part, mediated by ATP depletion and resulting impairment of ion pumps. Neuronal geometry is another, commonly underestimated determinant of excitability: The capacitance of neuronal membranes, i.e., the amount of electrical charge (e.g., number of ions) necessary to produce a given change in membrane potential, is a function of membrane surface area. The length constant of dendritic processes determines the probability of distal dendritic input to depolarize the soma and is the greater the larger the diameter of the dendrite. Cepeda *et al.*[63] have shown that these passive membrane properties are altered in dysmorphic neurons in cortical dysplastic lesions resected from pediatric epilepsy patients. Dysplastic neurons are characterized by thickened dendritic shafts and a loss or enlargement of dendritic spines.[64] Dendritic spines control excitability by compartmentalization of postsynaptic calcium influx, by enlarging total membrane area, and by attenuating electrotonic propagation of EPSPs: The spine neck accounts for approximately one half of the electric resistance between a given synapse and the cell soma. Hence, loss of spines in cortical dysplasia may be one factor responsible for hyperexcitability.

Mechanisms regulating network connectivity

Excitatory synaptic neurotransmission

Induction of epileptiform activity in hippopcampal slices by disinhibition (bicuculline, penicillin) or reduction of extracellular magnesium concentration gives rise to paroxysmal depolarization shifts (PDS), which behave like giant synaptic potentials: Their amplitude is dependent on the membrane potential, with hyperpolarization increasing and depolarization decreasing PDS amplitude.[36,65] Therefore, excitatory synaptic transmission plays an important role in synchronization of neuronal networks, at least during 'interictal' conditions. Excitatory neurotransmission in the mammalian brain mainly depends on the amino acid transmitter glutamate. Two classes of ionotropic glutamate receptors have been described: (1) those that respond to alpha-amino-3-hydroxyl-5-methyl-4-isoxazole propionic acid (AMPA) or kainic acid, and (2) those that respond to N-methyl-D-aspartate (NMDA).

AMPA/kainate receptors

AMPA/kainate receptors are tetramers or pentamers of subunits (termed GluR1-GluR7, KA-1, and KA-2) derived from three gene families and constitute the major vehicles for fast excitatory synaptic transmission. Their activation gives rise to excitatory post-synaptic potentials (EPSPs) which are mainly mediated by sodium influx and characterized by a short latency, rapid rise time, and short duration of several milliseconds. A subgroup of AMPA/kainate receptors that lack the GluR2 subunit are also permeable to Ca^{2+} ions.[66,67] In most in vitro preparations, interictal epileptiform burst discharges are dependent on AMPA/Kainate receptor activation: Sponaneous,[9] electrically induced,[68] and low-Mg^{2+}-induced[69] epileptiform burst discharges in human neocortical neurons are completely abolished by the AMPA/Kainate-receptor

specific antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). In contrast, blocking AMPA receptors with 1-(aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466) in rat neocortex only gradually reduces low-Mg^{2+} and 4-aminopyridine (4-AP) induced epileptiform discharges, while still abolishing spontaneous discharges induced by bicuculline.[70] This might reflect species differences between rodent and human neocortex. The horizontal propagagion of epileptiform discharges in normal rat somatosensory cortex[71] as well as in an animal model of focal cortical dysplasia induced by cortical freeze lesions[72] is dependent on AMPA-repeptor activation.

In the hippocampus (CA1) of rats, the ampltitude of epileptiform discharges is reduced by application of CNQX, but block of both AMPA/kainate and NMDA receptors is necessary to completely abolish spontaneous bursts in the bicuculline model.[73] Excessive hippocampal activation by repetitive seizures has been shown to increase the number of functional AMPA receptors at Schaffer collateral synapses, indicating their potential role in activity-dependent plasticity and kindling-induced epileptogenesis.[74] In rat hippocampal slices made chronically epileptic by perinatal hypoxia, the expression of GluR2 subunits is markedly reduced, resulting in increased calcium influx through AMPA receptors.[75] Hence, intracellular calcium is likely to play an important role in the development of chronic epileptogenesis.

NMDA-receptors

Numerous studies, using different in vitro seizure models, demonstrate the blocking effect of NMDA receptor antagonists on epileptiform activity, implying that NMDA receptors play a pivotal role in the generation of synchronized discharges. Avoli and Olivier[4] showed that the the nonspecific NMDA receptor antagonist D-2-amino-5-phosphonovalerate (APV) blocks electrically-induced epileptiform bursts in human neocortical slices resected from epilepsy patients. In rodent hippocampus, the durations of bicuculline- or pentylenetetrazol-induced epileptiform depolarizations is reduced by APV.[76] Several features make NMDA receptors particularly interesting for the pathophysiology of epilepsy: (a) the NMDA receptor is activated in a voltage-dependent manner, i.e., depolarization of the membrane is necessary for relieving the block by Mg^{2+} of the ion channel pore; (b) the NMDA receptor interacts with numerous intracellular scaffolding, anchoring and signalling molecules associated with the postsynaptic density, such as the tyrosine kinase Fyn or neuronal nitric oxide synthase (nNOS);[77–79] (c) Ca^{2+}-permeability of NMDA receptor associated channel by one to two orders of magnitude larger than Ca^{2+}-permeability of AMPA/kainate receptors, depending on the subunit composition of receptors.[66,67,80–83] Intracellular calcium acts as a second messenger with short-term (e.g., activation of protein kinases and nNOS) and long-term (alteration of the gene expression pattern) effects, thus NMDA receptors constitute an important substrate for synaptic plasticity;[84–86] (d) NMDA receptors display slow kinetics with an inactivation time constant one to two orders of magnitude longer than that of AMPA receptor channels. NMDA receptors are likely to play an important role in the generation of seizure-like discharges. Upon activation, NMDA receptors generate prolonged excitatory postsynaptic currents (EPSCs). These prolonged NMDA-receptor mediated depolarizations are normally masked by recurrent inhibition via GABAergig interneurons. Luhmann and Prince[87] showed that minimal disinhibition by application of low doses of bicuculline in adult rat neocortex can 'unmask' the NMDA receptor mediated depolarizations and give rise to synchronized afterdischarges which are senstitive to APV. In juvenile rat neocortex, the same investigators demonstrated long-lasting oscillatory NMDA-dependent field potential responses upon layer VI electrical stimulation without experimental disinhibition, indicating an imbalance between NMDA-mediated excitation and GABA-mediated inhibition in immature cortex. Additionnally, excessive NMDA receptor activation is known to reduce GABA efficacy by Ca^{2+}-mediated dephosphorylation of the $GABA_A$ receptor.[24,87,88] Repetitive tetanic electrical stimulation of hippocampal stratum radiatum induces increased NMDA-receptor activity. Hence, changes in NMDA and, consecutively, GABA receptor efficacy are probably the molecular basis for kindling-induced hyperexcitability.[87]

Three families of NMDA receptor subunits have been identified, termed NR1, NR2, and NR3. The NR 1 subunit is a single-gene product with eight different mRNA splice variants.[89] The four different NR2 subunits (termed NR2A-D) and two NR3 subunits (NR3A-B) are encoded by separate genes. Native NMDA receptors are heterotetramers or pentamers[90,91,92] consisting of multiple NR1 subunits and at least one NR2 subunit. NR2 subunits alone cannot form functional receptors, but have to co-assemble with NR1. Heteromeric NR1-NR2A NMDA receptors dominate in the mature neocortex. In contrast, NR1-NR2B receptors are physiologically expressed during fetal and early postnatal development and display higher peak ionic currents and a six times slower inactivation time constant,[93–95] resulting in an increased Ca^{2+} influx upon activation. Several reports have demonstrated the association of increased NR2B expression with human epilepsy.[69,96–98] Crino *et al.*[96] reported increased NR2B and NR2C, along with decreased NR2A mRNA levels in dysplastic compared with pyramidal neocortical neurons in surgical specimen from epilepsy patients with focal cortical dysplasia. Ying *et al.*[97] and Najm *et al.*[98] have demonstrated differential NR2B expression in areas of cortical dysplasia resected from patients with intractable epilepsy and correlated the density of immunocytochemical staining for NR2B with in situ epileptic activity assessed by subdural grid recordings. Epileptiform field potentials recorded from NR2B-overxpressing dysplastic human neocortex are differentially blocked by the NR2B-specific NMDA receptor antagonist ifenprodil.[69]

Electrical synapses: gap junctions and the influence of pH

Gap junctions are connections between neighbouring neurons made up by large transmembranous proteins that extend through the membranes of both cells, forming ion permeable pores that result in direct electrical coupling of neurons. At least in some brain regions, the conducting properties of gap juctions can additionally be altered by neurotransmitters or modulators. Traditionally, gap junctions have been thought to be of minor importance for neurotransmission in the mammalian brain. However, Somjen *et al.*[99] found that action potentials in dentate gyrus granule cells and CA3 pyramidal cells of the rat hippocampus are highly synchronized without detectable preceding synaptic potential, indicating that direct

electric interactions exist between these neurons. Some recent publications suggest that gap junctions might be involved in the pathophysiology of epilepsy. Naus *et al.*[100] and Elisevich *et al.*[101] found that mRNA and protein levels of the heart-type gap junction protein connexin 43 are increased in temporal lobe neocortex and hippocampus, respectively, of patients with intractable seizures. The patency of gap junctions is regulated by intracellular pH, with intracellular acidosis reducing, and intracellular alkalinization increasing their ion permeability. Additionally, gap junctions are blocked by heptanol, octanol, or carbenoxolone. Intracellular acidification or addition of octanol, heptanol, or carbenoxolone has been shown to reduce epileptiform activity in rat hippocampus,[102–105] whereas alkaline perfusion with ammonium chloride induced spontaneous ictal-like epileptiform discharges in piriform cortex,[106] suggesting that gap junctions indeed play a role in epileptic synchronization. Köhling *et al.*[107] demonstrated that hippocampal gap junctions are involved in the transition from interictal to ictal-like activity in the low-Mg^{2+} model. Gap junction blockers reversibly block low-Mg^{2+}-induced ictal-like activity without abolishing interictal bursts. Intrinsic membrane properties and chemical synaptic transmission are not altered by gap junction blockers.[107] As spontaneous and evoked epileptiform discharges in hippocampal slice cultures chronically exposed to bicuculline are correlated with an increased expression of connexin 43 and connexin 32,[108] activity dependent gap junction protein upregulation may be involved in the epileptogenic process. Finally, besides neuronal electrical coupling, gap junctions connecting glial cells may play a role in hypersynchronously active cortex. Lee *et al.*[109] found increased gap junctional coupling between astrocytes in human epileptic cortex specimen, compared to extrafocal cortex. As glial cells are involved in clearing and buffering extracellular potassium following intense neuronal activity, syncytial coupling of glia may facilitate the spread of 'potassium waves' that lead to increased neuronal synchronization.[110]

Ephaptic interactions and the role of extracellular osmolarity

Ephaptic interactions refer to interaction between neighboring neurons caused by direct electrical field effects. Neuronal activation induces extracellular electrical potential and ion concentration gradients. These result in extracellular currents which direcly influence surrounding cells. The degree of ephaptic electrical interactions between neurons is dependent on the spacial proximity of the cells and is therefore increased when the extracellular space shrinks. Ephaptic interactions are involved in synchronizing neuronal networks and can also influence firing patterns of single neurons.[111] Ephaptic coupling is increased by conditions that induce cell swelling, such as intense neuronal activity, or hypoosmolar extracellular medium: high-$[K^+]_o$-induced seizure-like events in the hippocampal CA1-subfield increase the electrical resistance of the tissue by 10–20%, indicating a reduction of extracellular volume.[112] Hypoosmotic bath solutions increase synchronized burst firing in hippocampal slices. Conversely, media made hyperosmotic by addition of agents that remain restriced to the extracellular space (such as mannitol, sucrose, or dextran) abolish high-$[K^+]_o$-induced seizure-like events in the hippocampal CA1-region and reduce the duration of interictal bursts in CA3, while simultaneously decreasing the electrical resistance of the tissue.[112] The epileptogenic effect of hypoosmolarity (e.g., hyponatremia-induced seizures) and the depressant effect of extracellular hyperosmolarity on neuronal excitability (e.g., hyperosmolar coma diabeticum) are in line with common clinical observations.

The role of extracellular potassium in network synchronization

Increased extracellular potassium concentration. There is good evidence for the crucial involvement of synaptic transmission in interictal burst discharges. However, seizure-like events in vitro are seen under experimental conditions that preclude neuronal communication via chemical synapses, suggesting that interictal spikes and focal seizures are triggered by different mechanisms. Blockers of synaptic transmission abolish high-$[K^+]_o$-induced interictal-like bursts in hippocampal slices, but do not inhibit the initiation of seizure-like events in the CA1-subfield.[113] Lowering of extracellular calcium concentration ($[Ca^{2+}]_o$) to values less than 0.2 mM blocks synaptic transmission, because calcium influx into the presynaptic terminal is the triggering stimulus for the release of synaptic vesicles. Despite this block, low-$[Ca^{2+}]_o$ induces spontaneous seizure-like events in CA1, suggesting that mechanisms other than synaptic transmission are sufficient to synchronize a neuronal network.[114] Yaari *et al.*[115] showed that washout of $[Ca^{2+}]_o$, as well as transient hypoxia, are accompanied by a rise in extracellular potassium concentration ($[K^+]_o$) that precedes the onset of seizure-like events. Lian *et al.*,[116] using the same model, demonstrated that this nonsynaptic synchronization between CA3 and CA1 region, mediated by a slowly diffusing 'wave' of increased extracellular potassium, persists even when the axonal connections between CA3 and CA1 subfields are physically transected. Insertion of a thin water-impermeable film into the transsection site abolished synchronization. In another study, Voskuyl *et al.*[117] demonstrated that one type of 4-aminopyridine-induced spontaneous discharges in hippocampal slices slowly propagates from CA3 to CA1 and cannot be suppressed by blockade of synaptic transmission. Even transsection of the Schaffer axon collaterals that connnect CA3 and CA1 pyramidal neurons, does not block propagation of these discharges as long as stratum moleculare is preserved.[117] These data indicate that potassium homeostatis is likely to play a crucial role in seizure initiation. The amplitude of a potassium current with given membrane potential and membrane conductance is dependent on the potassium equilibrium potential ('Nernst potential'), which is determined by the relation between extracellular ($[K^+]_o$) and intracellular potassium concentration ($[K^+]_i$). The electrochemical gradient for repolarizing potassium currents is increased by low $[K^+]_o$ and decreased by high $[K^+]_o$. Accordingly, changes of $[K^+]_o$ effectively change both the excitability of single cells and the behaviour of neuronal networks. There is extensive evidence that elevated $[K^+]_o$ induces epileptiform activity[118–120] and increases the repetition rate of EFP.[121,122] Jensen *et al.*[123] found an increased proportion of intrinsically bursting neurons in the hippocampal CA1-region with elevated $[K^+]_o$. Besides reducing the amplitude of repolarizing potassium currents, elevated $[K^+]_o$ leads to direct neuron depolarization.[124] Korn *et al.*[118] showed that increased $[K^+]_o$ is accompanied by increased intracellular

chloride concentration ($[Cl^-]_i$), probably by activation of a K-Cl co-transporter, with consecutive reduction in the amplitude of inhibitory GABA-A mediated chloride currents. Extracellular potassium ions released from the intracellular compartment during neuronal activity are normally cleared by neuronal and glial K^+ reuptake. Excessive elevation of $[K^+]_o$ leads to osmotic glial swelling[119,120] with reduction of the extracellular volume and increased ephaptic interactions between neighbouring neurons (see above). These findings have major implications for the pathophysiology of epileptic seizures: during excessive neuronal activity, $[Ca^{2+}]_o$ decreases to values incompatible with synaptic transmission.[110] Maintenance of long-lasting epilepitc acitvity as it occurs, for example, during status epilepticus, is therefore very unlikely to be dependent on synaptic mechanisms. As extracellular potassium concentration increases to values above 10 mM during seizures, impaired potassium homeostasis may be one of the key mechanisms leading to prolonged ictal discharges.

Reduced extracellular potassium concentration

Elevation of $[K^+]_o$ during neuronal activity is normally followed by a transient reduction of $[K^+]_o$ below the physiological baseline ('K^+ undershoot',[121,122] possibly by excessive Na^+-K^+-ATPase activation. The effect of reduced $[K^+]_o$ on epilptiform activity is not yet well characterized, but several studies report an epileptogenic effect of low extracellular potassium.[36,123] The epileptogenic effect of low $[K^+]_o$ may be related to increased GABA-B mediated potassium outward currents leading to recruitment of low-threshold calcium channels which are inactivated at normal resting potential.

Inhibition

Gamma-amino butyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian brain. Two major types of GABA receptors play a role in the neocortex and hippocampus, termed GABA-A and GABA-B receptors. (GABA-C receptors are encountered in the retina and are not further discussed here).

GABA-A mediated inhibition

The cortical glutamatergic principal neurons innervate GABA-ergic interneurons, which in turn inhibit the original pyramidal cell ('recurrent inhibition'), and surrounding excitatory neurons ('lateral inhibition'), thus restricting neuronal activity temporally and spacially. GABA binding to postsynaptic GABA-A receptors opens chloride (Cl^-) selective ion channels. As the chloride equilibrium potential ('Nernst potential') at baseline conditions is negative to the resting membrane potential (RMP), chloride ions will enter the cell and cause a hyperpolarizing, inhibitory postsynaptic potential (IPSP). In rodent hippocampus, as well as in human and rodent neocortex, application of substances that block GABA-A-ergic inhibition, such as bicuculline or penicillin, leads to synchronized epileptiform bursts driven by large and long-lasting inhibitory synaptic conductances.[10–13,35,124–126] In the neocortex, these bursts are initiated within small, spatially discrete subpopulations of cells[127] and then spread to the disinhibited surrounding cortex. The role of lateral inhibition in confining neuronal activity to a limited portion of cortex has been demonstrated by Chagnac-Amitai and Connors:[128] using horizontal arrays of extracellular electrodes, they showed that neuronal activity evoked by focal electrical stimulation remained restriced to a narrow strip of cortex at control conditions, whereas disinhibition by application of graded concentrations of bicuculline first increases the spatial spread of acitvity and finally gives rise to synchronized evoked epileptiform activity. Interestingly, epileptiform activity occurred at bicuculline concentrations that were still insufficient to completely abolish IPSPs. This finding suggests that minimal disinhibition can already induce epileptiform activity. Although these findings derived from in vitro models are dependent on pharmacological manipulations, they are of major relevance for the initiation and spread of epileptic acitivity under clinical conditions: Strowbridge *et al.*[129] showed that inhibitory synaptic potentials are reduced in the vicinity of cortical lesions resected from patients for treatment of intractable epilepsy, indicating that loss of inhibition is involved in the pathophysiology of epileptogenic foci. It remains unclear, however, whether disinhibition constitutes an underlying cause for epileptiform activity, or merely one step in a pathophysiological sequence that finally leads to seizures: repetitive GABA-A-receptor activation during long-lasting neuronal firing is associated with chloride influx into neurons. As extracellular chloride concentration is reduced, the chloride equilibrium potential ('Nernst potential') is shifted to more positive values, with IPSPs decreasing in amplitude. As soon as the chloride equilibrium potential becomes more positive than the resting membrane potential, GABA-activated chloride currents become excitatory, leading to a breakdown of GABA-A-receptor mediated inhibition. Impaired recurrent inhibition interferes with the termination of burst discharges, facilitating ictal transition, whereas impaired lateral inhibition allows spread of seizure activity. The epileptogenic effect of reduced extracellular chloride concentration ($[Cl^-]_o$) has been demonstrated by Chamberlin and Dingledine:[130] reduction of $[Cl^-]_o$ from the physiological 136 mM to 53 mM induced spontaneous interical bursts in hippocampal slices, which was associated with a +10 mV positive shift in the chloride reversal potential. Recent experiments using intraoperative microdialysis in epileptogenic foci of patients undergoing epilepsy surgery have indeed demonstrated extracellular chloride concentrations which are incompatible with intact inhibition (Speckmann, unpublished observations).

GABA-A mediated inhibition is also related to the anticonvulsant action of benzodiazepines. Benzodiazepine binding to its binding site on the extracellular domain of GABA-A receptors facilitates GABA-ergic inhibition by increasing chloride influx. Long-term exposure to benzodiazepines, however, induces secondary changes in the efficacy of the GABAergic system that have epileptogenic effects. Davies *et al.*,[131] for example, showed that long-term incubation of rat hippocampal slices with clonazepam induces spontaneous epileptiform bursts, which are associated with a reduced duration of the post-spike-train afterhyperpolarization. This is the putative basis for benzodiazepine withdrawal seizures.

GABA-B mediated inhibition

GABA-B receptors are located pre- and postsynaptically and induce G-protein mediated opening of potassium channels.[132,133] The hyperpolarization caused by GABA-B receptor activation has a slower onset and longer duration than the 'fast' GABA-A inhibition. GABA-B mediated IPSPs therefore contribute to the late phase of the afterhyperpolarization (AHP)

following epileptiform bursts and determine its duration. Presynaptic GABA-B receptors inhibit synaptic neurotransmitter release.

Data about the involvement of GABA-B receptors in epileptogenesis are ambiguous: Asprodini *et al.*[134] report that in vivo kindling of rats reduces the sensitivity of presynaptic GABA-B receptors as assessed by the EC50 of the GABA-B receptor agonist baclofen needed to depress EPSPs, suggesting a protective role of GABA-B receptors against excessive excitatory activity. On the other hand, presynaptic GABA-B receptors can enhance epileptiform activity by reducing synaptic GABA release by interneurons.[135] Sutor *et al.*[136] report a concentration-dependent differential effect of GABA-B receptor antagonists on bicuculline-induced epileptiform activity in rat neocortex, with low concentrations enhancing, but higher concentrations suppressing stimulus-evoked epileptiform discharges. GABA-B receptor activation by baclofen has been shown to induce a long-lasting potentiation of evoked population spikes and spontaneous epilepitform discharges.[137] Low-Mg^{2+} and 4-aminopyridine induced interictal-like epileptiform activity in the hippocampus is reversibly transformed to ictal activity by application of baclofen.[138,39] These findings suggest that interictal discharges may be to some degree protective against ictal transition. Reducing the repetition rate of interictal discharges by enhancing the GABA-B-mediated late phase of the burst afterhyperpolarization might be a mechanism involved in seizure generation, possibly by synchronizing large cell populations and/or by recruiting cation conductances that are otherwise incativated at resting membrane potential, such as the hyperpolarization-activated inward current (I_h) or low-threshold Ca^{2+} channels.[140] A similar interaction between GABA mediated inhibition and slow conductances activated by hyperpolarization has been proposed as the underlying mechanism for the generation of generalized spike-wave seizures through thalamocortical loops.[141]

Neuromodulators and second messenger mechanisms

Metabotropic glutamate receptors

Metabotropic glutamate receptors (mGLU) are second-messenger coupled receptors that have diverse effect on neuronal excitability and are likely to be involved in neuronal plasticity. Some evidence suggests a role of mGLU receptors in epileptogenesis.[142,143] Pasti *et al.*[144] have demonstrated that mGLU receptors mediate glutamate release from astrocytes, which might play a role in seizure propagation. However, several studies have shown that some mGLU subtypes have anticonvulsant effects as well. For example, mGLU types I and II reduce the ampltidute of AMPA- and NMDA-receptor mediated EPSPs by a presynaptic mechanism.[145,146] This may be a means of regulating excitatory transmission during massive excitation. The relevance of these various data for human epilepsy is still unknown and requires further investigation.

Adenosine receptors

Adenosine is an endogenous neuromodulator that is released following excessive metabolic activity and exerts inhibitory effects on neurons. As extracellular adenosine concentration rises markedly during seizures, its depressant effects on excitability and extitatory transmission may be involved in seizure termination. Adenosine and other purinoreceptor agonists suppress epileptiform activity in the CA3 region of the hippocampus by a presynaptic mechanism.[147] Blockers of the adenosine receptor, such as caffeine and other methylxanthines, have well-known stimulating effects on cortical activity. In the guinea pig hippocampus in vitro, caffeine induces epileptiform discarges.[148] Moreover, blocking effects on adenosine receptors have been shown to be involved in the epileptogenic effect of reduced extracellular magnesium concentration.[29]

Acetylcholine (ACh) receptors

Muscarinic ACh receptors

Slow excitatory postsynaptic potentials (EPSPs) have been identified in rat neocortical slices which are antagonized by muscarinic acetylcholine receptor antagonists and enhanced by cholinesterase inhibitor,[149] suggesting a role of muscarinic acetylcholine receptors in regulating excitability. In cat visual cortex, acetylcholine induces depolarization by reducing the conductance of potassium channels.[150] Application of muscarinergic substances such as pilocarpin causes severe seizures in rodents.

Nicotinic ACh receptors

Activation of the nicotinic ACh receptor–ion channel complex by ACh leads to fast unspecific ion influx through a nonselective cation channel. The pharmacological properties of nicotinic ACh receptors are dependent on their subunit composition which is differentially distributed throughout the brain. The role for the pathophysiology of epilepsy is still unclear from a mechanistic standpoint. Genetic studies, however, revealed that a missense mutation in one nicotinic ACh receptor subunit is associated with nocturnal frontal lobe epilepsy in an Australian family.[151]

Noradrenergic receptors

Noradrenaline (norepinephrine) (NA) exhibits differential modulatory effects on epileptiform activity. Via alpha-1 receptors, NA blocks low-Mg^{2+}-induced epileptiform activity in the entorhinal cortex.[152] In rodent dentate gyrus and neocortex, in contrast, NA exerts proconvulsant effects mediated by beta receptors.[149,152] Beta receptor activation induces prolongation of low-Mg^{2+}-induced ictal discharges, probably by activation of a slow synaptic cation current.

Dopamine receptors

Co-application of dopamine (DA) and NMDA enhances NMDA-induced membrane depolarization and action potential firing. Co-application of DA and glutamate, however, decreases fast synaptic potentials mediated by non-NMDA glutamate receptors.[153] From a neurocognitive perspective, this might represent the underlying mechanism of dopamine as regulator of the 'signal-to-noise ratio' in the neocortex. The proconvulsant properties of dopamine antagonists, such as neuroleptic drugs, may be related to enhancement of AMPA/kainate receptor mediated lateral spread of epileptiform activity.

Neuropeptide Y

Neuropeptide Y (NPY) and two neuropeptide Y agonists ((P)YY(3-36) and 1-4-(6-aminohexanoic acid)-25-36-([ahx(5-24)])-NPY) inhibit low-$Mg2^{+}$- and picrotoxin-induced interictal epileptiform discharges in rat hippocampal slices in vitro by inhibiting glutamatergic synaptic transmission, suggesting a protective role of NPY against epileptogenic hyperactivity.[154]

Nitric oxide

Nitric oxide (NO) is synthetized by nitric oxide synthase (NOS) from L-arginine.[155] The neuronal form of NOS (nNOS) is linked to the postsynaptic density protein complex[156] and is activated by increase of intracellular free Ca^{2+}, mediated by Ca^{2+}-calmodulin, which enters the cell through NMDA-receptor channels and voltage-gated Ca^{2+}-channels.[157–160] NO affects neuronal excitability via a multitude of actions that are mediated by guanylate cyclase activation[161–163] and S-nitrosylation of target proteins.[164,165] Most effects of NO are excitatory: As a 'retrograde transmitter', NO increases presynaptic glutamate release after crossing the synaptic cleft by diffusion.[157,167] Besides, it facilitates voltage-gated Na^{+} channels,[168] and decreases $GABA_A$ repeptor mediated currents.[169] On the other hand, NO also exerts some depressant actions on excitability: it dampens excitatory post-synaptic potentials (EPSPs) by decreasing AMPA-receptor[170,171] and NMDA-receptor[172–174] mediated currents, thus providing a 'negative feedback' following synaptic activation. It may also decrease membrane excitability by inducing tonic activation of K^{+} channels.[175]

Other neuromodulatory effects on epielptiform activity

Activation of mu opioid receptors in the ventral, but not in the dorsal hippocampus induces triggered and spontaneous epileptiform bursting.[176] Pregnanolone, a metabolite of progesterone, depresses the amplitude of population spikes in the CA1 region of the hippocampus, probably by enhancing GABA-A receptor function.[177] This might have implications in regard to catamenial epilepsy. Ethanol reversibly suppresses the duration of NMDA-receptor mediated synaptic responses, implying that it exerts anticonvulsant properties when acutely applied.[178] Long-term exposure to ethanol, in contrast, leads to up-regulation of NMDA-receptor NR2B subunits, thereby increasing the potency of NMDA receptors.[179] This may be the mechanism underlying epilepsy induced by chronic alcohol intake.

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147 In vitro cytochemical studies in epilepsy

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Introduction

Initially, data about the histology of epileptic tissue started with histochemical descriptions in tissue processed by relatively simple techniques such as cresyl-violet, Nissl, hematoxylin-eosin and Golgi stainings.[1–3] The current epileptic tissue research includes not only these studies, but also single-cell injection of markers that fill all the projections of the cell,[4,5] immunohistochemistry of many proteins[6–8] and *in situ* hybridization that shows expression of mRNA.[9,10] Those techniques provide not only morphological data, but also elucidate cell morphology, type, functionality, chemistry and role in the epileptic brain.[11]

In this chapter, we will review the general findings in cytochemical studies in epilepsy research and their contribution in the understanding of pathophysiological mechanisms of epileptogenicity.

In vitro cytochemical studies in temporal lobe epilepsy

More than a century after the first histological description of sclerotic hippocampus associated with temporal lobe epilepsy (TLE),[3] much has been added to the description of the tissue, but the mechanisms by which hippocampal sclerosis (HS) occurs and its specific role in seizure initiation and propagation is still uncertain.

Hippocampal sclerosis

Hippocampal sclerosis (HS) is characterized by extensive loss of pyramidal neurons from areas 1, 3, and 4 of the Ammon's horn (CA1, CA3, and CA4, respectively), as well as neurons in granular, polymorphic and molecular layers of dentate gyrus (DG).[3,12] Granular cells of DG suffer dispersion and marked plasticity, which includes primarily a simplification of its dendritic arbor, loss of dendritic spines and nodulation of dendrites.[2,13,14] Cytochemical studies showed the loss of dentate gyrus (DG) interneurons, supposedly GABAergic, with plasticity of the remaining ones.[15–17] In addition, synaptic terminals coming from granular cells of DG and probably also from the supramammilary tract sprout their connections through the inner third of DG molecular layer.[18]

Hippocampal-related areas such as amygdala and temporal lobe cortices can also have cell loss in different magnitudes, and although this is frequently found in association with HS, it can also be independent.[19] Indeed, amygdala damage may contribute to seizure propagation, as this structure receives monosynaptic inputs from large areas (frontal and temporal cortices), and spreads the signals to its outputs by activating dense intradivisional connections (extrapyramidal system, cortex and hippocampal formation).[18] Hystological studies revealed that the volume of amygdala reduces as a function of lifetime seizure number, and also argue that the presence of fear in seizures may be an indication of amygdala participation.[18]

Hippocampal sclerosis and mossy fiber sprouting

One of the most striking findings from cytochemical studies in HS tissue is the mossy fiber sprouting (MFS), which was first described in animal models of epilepsy and later confirmed in human specimens by in vitro cytochemical studies.[7,20] This intense reorganization of excitatory connections in the hippocampal circuitry can be easily visualized by TIMM's staining, a cytochemical technique that enhances zinc-containing synaptic terminals,[21] which are supposedly linked to excitatory neurotransmission. The dentate gyrus (DG) of sclerotic hippocampus presents a zinc-positive region in the inner third of molecular layer, which is completely absent in the normal hippocampus.[20]

Hippocampal neuroanatomy is very well characterized, and the MFS findings with HS attracted so much attention to hippocampus as a probable seizure-causative structure in epilepsy that for decades the study of other related structures was put aside. Interestingly, the first theories that considered MFS in HS and its relation to seizure initiation and propagation claimed that loss of inhibitory interneurons and/or the recurrent excitatory pathway in the DG would contribute to the hyperexcitation of the hippocampus.[22,23] Later, evidence both in animal models and human studies showed that the DG, in spite of hyperexcitation, presented a tonic hyperinhibition, and that the collapse of such inhibition would be responsible for seizure initiation.[19]

Much work remains to further illustrate how such circuitry alterations contribute to seizures in epileptic patients. There is evidence suggesting that modifications occurring in HS are an acute process, and seizures do not contribute to damage of remaining neurons.[24,25] Mathern *et al.*[24] based this assumption on results from children's HS compared to autopsy cases, where they confirmed hippocampal sclerosis and found no evidence of increased dead neurons (using TUNEL staining, a technique that marks neuronal apoptosis). Additionally, some studies utilizing immunocytochemistry to PSA-NCAM and GAP-43 (developmental related molecules) suggested that

sprouting is an ongoing event in sclerotic hippocampus from TLE patients, as both molecules are increased in the molecular layer of the DG in this tissue.[26,27]

Neurotransmitters and receptors

Characterization of neurotransmitters and receptors in the epileptic area can indicate the relation between excitation and inhibition in the tissue. The differential expression of many excitatory receptors is already described in HS.[9] Ying *et al.* found NMDA-R1 receptor (NR1) upregulated in both granular cells and molecular layer of DG in sclerotic hippocampus as compared to nonsclerotic hippocampus of epileptic patients with TLE.[28] In contrast, Mathern *et al.* did not find NR1 protein expression increased in HS, but its mRNA. In addition, they also found that other subunits of glutamate receptors of AMPA and NMDA families were increased, both mRNA and proteins (GluR1-3 and NR2b).[9] They discuss the fact that other works found decreased expression in the same proteins/mRNAs, and point to the possibility that these differences can be a result of presence or absence of correction of the quantification per neuron in HS, as there are much less neurons in sclerotic hippocampus that survive and are able to express proteins as compared to a normal, nonsclerotic hippocampus.

Different receptor compositions can result in different patterns of channel activation and inactivation, what could directly impact on neurotransmitter-mediated neuronal response. Indeed, heteromeric combinations of NMDA receptors (NR1 plus NR2B) result in higher and slower decay currents when compared to a channel composed exclusively by NR1.[29,30]

There is a 100% increase in AMPA receptors binding and a 50% decrease in NMDA receptors binding in DG of human HS.[31] This could indicate a differential expression of receptors or a different affinity of the receptors to its binding molecules. In contrast, studies in a rat model of TLE show a reduction of AMPA binding in hippocampus.[31] In a study of MTLE granular cells of DG, glutamate currents were found prolonged and this phenomenon would be related to NMDA receptors activation.[5] They suggest that the dendritic alterations usually seem in DG granular cells may have a role in this excitatory facilitation, based on the fact that cells growing in a medium containing bicuculline develop epileptic tissue-like characteristics.[5]

According to in vitro cytochemical studies, inhibitory neurons can be extensively affected and modified in epileptic tissue. Parvalbumin (PV)-positive cells are reduced in MTLE patients, compared to autopsy hippocampi.[15] The surviving cells in HS receive the majority of inputs probably excitatory (asymmetric synapses as seen by electron microscopy) and send inhibitory (symmetric synapses) connections to pyramidal neurons of the Hippocampus.[15] In addition to PV-positive, the number of calbindin (CB)-positive neurons is also reduced in HS.[16] These interneurons are dispersed in the DG granular layer and this dispersion is accompanied by proliferation of PV- and CB-positive terminals, as well as in GABA transporter 1-positive terminals, mainly in hippocampi presenting stronger sclerosis.[16] Additionally, there are chandelier terminals in the granular cells layer of DG, which are absent or less complex in nonsclerotic hippocampi. Chandelier terminals are synaptic buttons complexes localized in the axon of pyramidal cells, proximal to cell body, and have strong inhibitory action.[17] The same increased complexity of synaptic terminals is found in PV-positive basket formations around surviving neurons at the border between CA1 and subicullum areas.[16] Interestingly, cytochemical studies revealed that microregions of the DG maintained cellular density but lacked inhibitory terminals, maybe resulting in hyperexcitatory microregions. Additionally, there are evidence that $GABA_B$ receptor histology in non-sclerotic hippocampi closely matches hippocampal cytoarchitecture, but it is down regulated in HS.[32]

Maglóczky *et al.* also report loss of CB-positive neurons in TLE, but additionally describe that the remaining cells have larger soma, acquire somatic spines and present invaginated nuclei (indicative of been metabolically very active). On the other hand, those cells are extensively surrounded by glia, what can bock the formation of synapses.[33] In the same work, they report that calretinin (CR)-positive neurons are also lost, and the remaining ones also present nucleus invagination and are surrounded by glial processes.[33] CR-positive terminals distribution is expanded in the DG, and the authors suggested that these terminals are probably coming from the supramammillary tract, indicating a second source of excess excitation of DG cells in addition to de MFS.[33] Maybe even more interestingly then the compensatory sprouting described above, substance P receptor (SPR)-positive neurons change their position, migrating from inside the hilus of DG to the molecular layer.[33] These neurons also present a deeply invaginated nucleus and a cell body partially covered by glial processes.[33] Substance P containing neurons in MTLE have also been described by de Lanerolle *et al.* (2003),[34] with concomitant sprouting of substance P-containing fibers to the DG.

In vitro studies in neocortical epilepsy and malformations of cortical development

Malformations of cortical development (MCD) are one of the main causes of epilepsy in humans.[35–37] They include many pathologies, among them polymicrogyria, paquigyria, hemimegalencephaly, tuberous sclerosis, and focal cortical dysplasia (FCD).[38,39] In this review, we will focus our discussion in in vitro cytochemical findings in human FCD.

FCD are characterized by a disruption of the normal lamination of the cortex that can vary in intensity, ranging from a light disruption of lamination with normal-appearing neurons to a strong loss of lamination, usually accompanied by the appearance of dysmorphic and misoriented neurons, neuronal clustering, giant neurons and balloon cells (BC).[1,40,41] In addition, heterotopic neurons and gliosis are observed in the white matter,[1,40,41] sometimes concomitant with a lack of myelin in that region.[42] Giant neurons in FCD apparently have a normal content of cytoplasmatic organelles[43] and, as normal pyramidal cells, receive numerous symmetric synapses in cell body and proximal dendrites.[43] There is evidence for morphological alteration of both excitatory and inhibitory neurons in FCD.[6,44,45]

FCD may be a consequence of erroneous migration of stem cells, or their maturation, programmed cell death that also

occurs in ontogenesis, or maybe even a combination of various factors.[46–48] Based on morphological studies using antibodies against NeuN, a specific marker for neurons, Andres *et al.*[40] suggested that some characteristics of the dysplastic cortex resemble prenatal cortex of primates and humans and propose that FCD would be a defect occurred in late phases of development. This data is partially in agreement with Mischel *et al.*[49] who proposed a classification of the MCD with a grading system, based on the probable time-frame when the abnormality of development takes place, suggesting that mild FCD (or FCD type I) would be in late development and FCD with BCs would be severe (or FCD type IIb), happening in early developmental phases.[36]

The study of protein expression in FCD is very useful in order to help to highlight dysmorphisms in the disrupted cortex.[6] Using immunocytochemical studies (with primary antibodies for MAP2, neurofilaments, GFAP, PV, CB, and CR), Spreafico *et al.*[48] suggested that the lesion observed in MRI does not correspond exactly to the area of dysplasia, but is included in it. Additionally, an abnormally increased expression of neurofilaments can be observed in the areas where FCD is more evident on MRI. MAP1B is increased in dysmorphic neurons from FCD, and it is abundant in immature brain, declining with maturation in the normal brain, thus indicating that morphological remodeling may be an ongoing process in FCD.[6,50] Other proteins that are usually expressed during brain development and are downregulated in mature neurons such as vimentin, nestin, and SMI311 (marker for nonphosphorilated filaments), are expressed in BCs from FCD, tuberous sclerosis and hemimegalencephaly.[6,47] mRNA of vimentin, nestin, neurofilament, peripherin, and α-internexin are also suggestive of neuron immaturity and are detected in a subset of neurons in FCD tissue.[37]

In malformations of cortical development, the histological appearance and the location of balloon cells suggest that they are developmentally immature. By using silver impregnation technique, Derosa *et al.*[51] had shown the presence of nucleolar organizer regions that were believed to be involved in cell proliferation. Additionally, transcription of genes for nestin and vimentin were enhanced in the balloon cells.[37] Over the past several years, much more attention has been focused on nestin, a marker for neuronal progenitor cells.[52–55] Recently, human hematopoietic stem cell antigen AC133, also called CD133, was shown to be expressed in both hematopoietic and neuropoietic cells.[56] CD133 positive cells are capable of neurosphere initiation, self renewal, and multilineage differentiation at the single cell level.[56] Therefore, CD133 has been used to identify neural stem cells in the human brain.[56–58]

Balloon cells were found to be immunoreactive to CD133, nestin, Bcl-2, Tuj1, vimentin, and GFAP. Confocal double labeling analyses also showed that balloon cells were dual immunopositive for CD133/nestin; CD133/GFAP; CD133/Bcl-2, and nestin/GFAP (Figure 147.1).

The expression of CD133 protein in BCs may suggest that these cells fail to mature fully and therefore continue to express embryonic genes. Subsequently, these immature cells may lack some of the cellular machinery for migration. This may explain at least in part the localization of the BC in the white matter and gray/white matter junction.

Using organotypic slice preparation, our group identified the presence of BrdU uptake in neocortex of patients with epileptic cortical dysplasia, suggesting increase cell proliferation in epileptic cortical dysplastic samples. It is unknown if the increment in BrdU uptake observed in the epileptic samples corresponded to neurogenesis (Figure 147.2).

We also found the presence of Tuj1 expressing cells (a marker for immature neurons) in the subventicular zone of dysplastic epileptic patients (Figure 147.3a). The immature neurons were organized in chains, suggesting the presence of migration. Additionally, in the same tissue samples, BrdU positive cells double-labeled with nestin were presented, suggesting stem cell proliferation and probably differentiation (Figure 147.3b).

There is an extensive modification of neurotransmitters receptors in FCD.[28,59] For example, NR2A/B and NR1-1a, 1b, 2a, and 2b are over-expressed in FCD tissue, more specifically in dysplastic neurons.[60] Other glutamate receptor subunits are distributed equally in both FCD and normal cortex, such as NR1-3a, 3b, and 4a.[28] This abnormal expression of glutamate receptors in FCD may be part of the mechanism of epileptogenesis in this tissue. In microdissected cells of FCD tissue, where RT-PCR was used in order to identify mRNA differential expression, there is a reduction in glutamate receptors subunits Glu R1 and NMDA-R2A, and GABA receptor subunits GABA α1, α2, β1, and β2.[59] Increased expression was described for Glu R4, NR2B, and NR2C glutamate subunit receptors.[59]

In vitro cytochemical studies also indicated differential expression and interaction between glutamate receptor subunits and related proteins. Ying *et al.*[61,62] found an increased expression and co-assembly of NR1, NR2B, and PSD-95 in epileptic versus nonepileptic cortical samples from patients with cortical dysplasia and epilepsy who underwent resective surgery. Interestingly, in another set of experiments using ICC, the same group found no change in NR1 quantity in epileptic cortex from FCD, but increased expression of NR2A/B in dysplastic area.[44,63] These results suggested that these alterations and apparent differential interaction between NR1 and NR2A/B may be an important mechanism of epileptogenesis in FCD.[61] Electrophysiology of FCD tissue showed that normal appearing neurons have characteristics of neurons from control cortex, but dysmorphic neurons have lower capacitance, increased resistance and decreased time constant.[64] On the other hand, giant neurons are more excitable, as they present increased capacitance, decreased resistance and longer time constant,[4,8] and need prolonged time to recovery from desensitization to NMDA.[8] Cepeda *et al.*[8] found that BCs are not excitable at all, and suggested that their presence could lead to modification of the structure of surrounding cortex, thus collaborating to the net excitability of the tissue.

Advanced molecular techniques such as proteomics and cDNA arrays are becoming important tools in the investigation of FCD and other types of epilepsy. Nonetheless, although some first works in this area have been successful in finding variation in various molecules in FCD as compared to normal cortex, they are not able to discuss in details their findings, probably because of the quantity of molecules with altered expression as well as the fact that many of those molecules have their role in nervous system poorly understood or apparently not related to mechanisms that could lead to epileptogenicity. Kim *et al.*[65] found seven genes that had modified regulation in FCD compared to normal cortex, three of them up-regulated and 4 down-regulated, showing that those

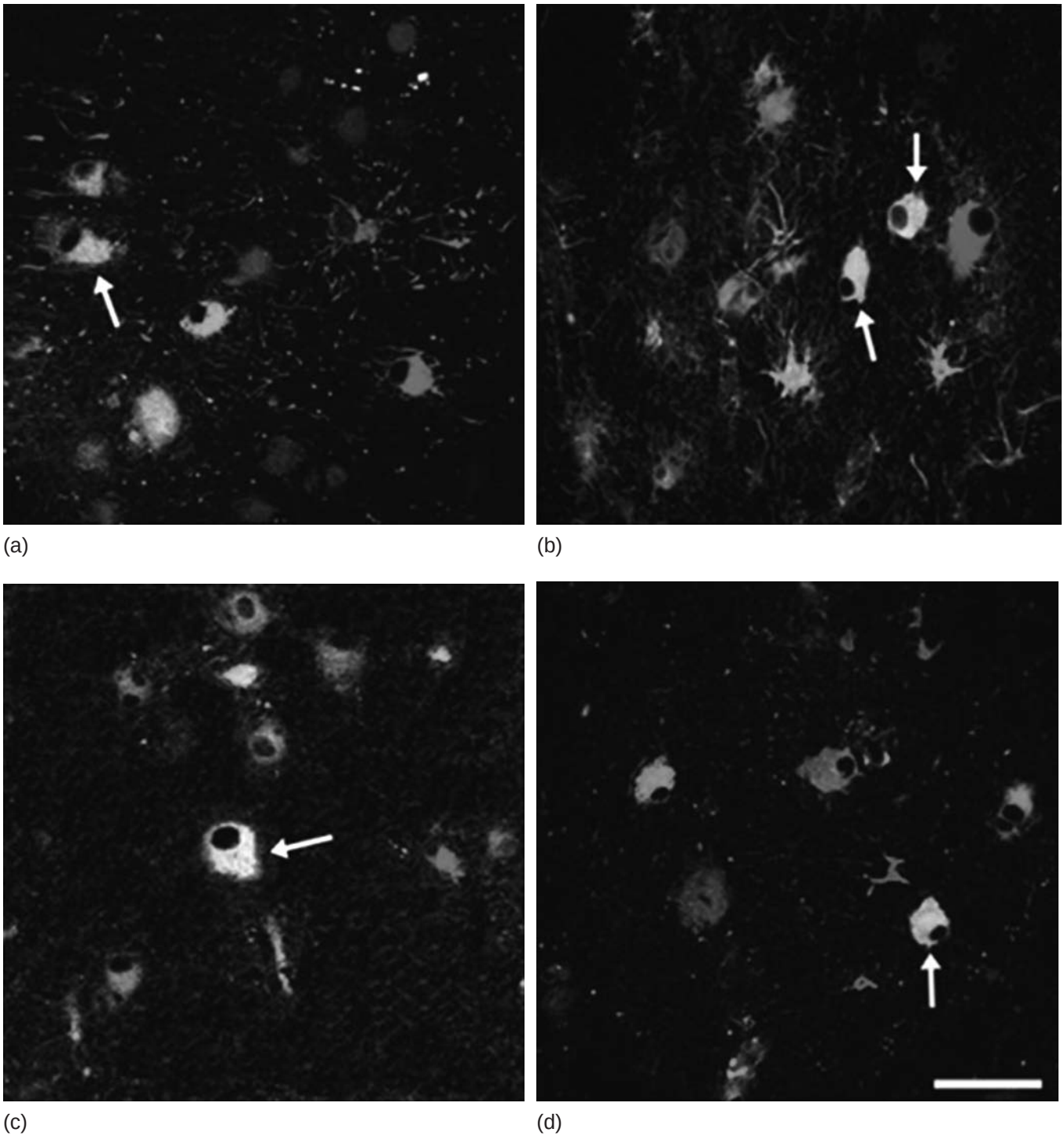


Figure 147.1 Colocalization of antibodies against CD133 with antibodies to intermediate filament proteins (nestin and GFAP) in balloon cells by confocal microscopy. Co-expression of CD133 with either nestin or GFAP was clearly detected in the balloon cells (a and d). The presence of singly-labeled CD133, nestin, or GFAP were also observed. Co-expression CD133 and Bcl-2 in a subset of balloon cells is shown in c. A population of balloon cells is shown to be immunoreative to both nestin (red) and GFAP (green) (b). Double staining for CD133 and MAP2 failed to reveal any co-locolization of these proteins in the balloon cells. (See Color plates.)

molecules may have a potential role in cascades that are related to epileptogenesis, as they participate in neurogenesis, apoptosis and migration-regulation processes. Another study using proteomics showed nine molecules differentially regulated in dysplasic temporal lobe neocortex.[66] Among them, the authors selected two to be discussed, the mitochondrial type Mn-superoxide dismutase, that takes place in antioxidant processes, and the glycerol phosphate dehydrogenase, which is a multifunctional protein involved in triglycerides metabolism.[66]

The comparison between FCD with other types of MCD may give hints of the underlying mechanisms of epileptogenicity in those pathologies. For example, hamartin- and tuberin-expressing genes TSC1 and TSC2, respectively, are found altered in tuberous sclerosis pathology.[67] These proteins are part of a tumor-suppression mechanism, related to cell

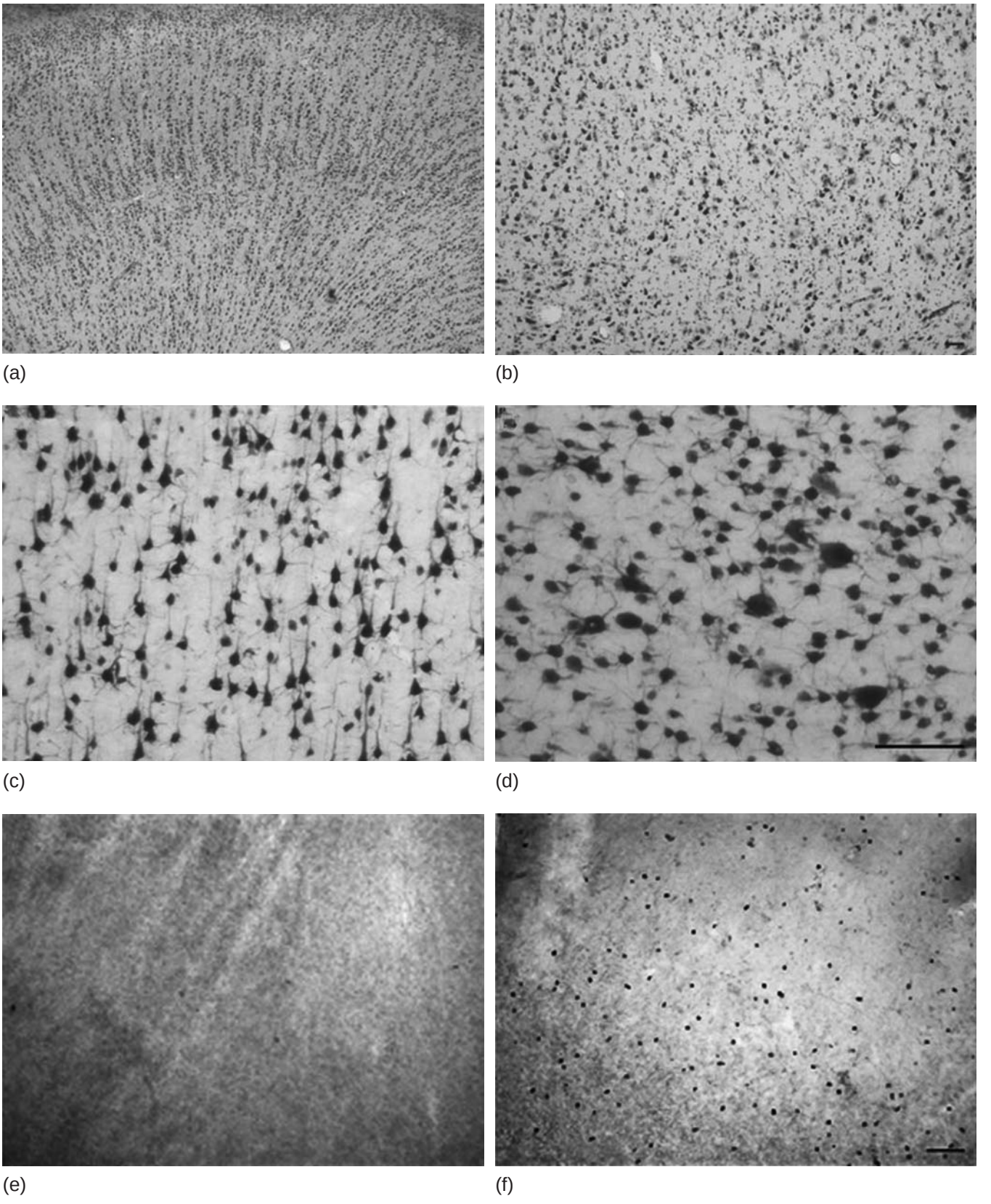
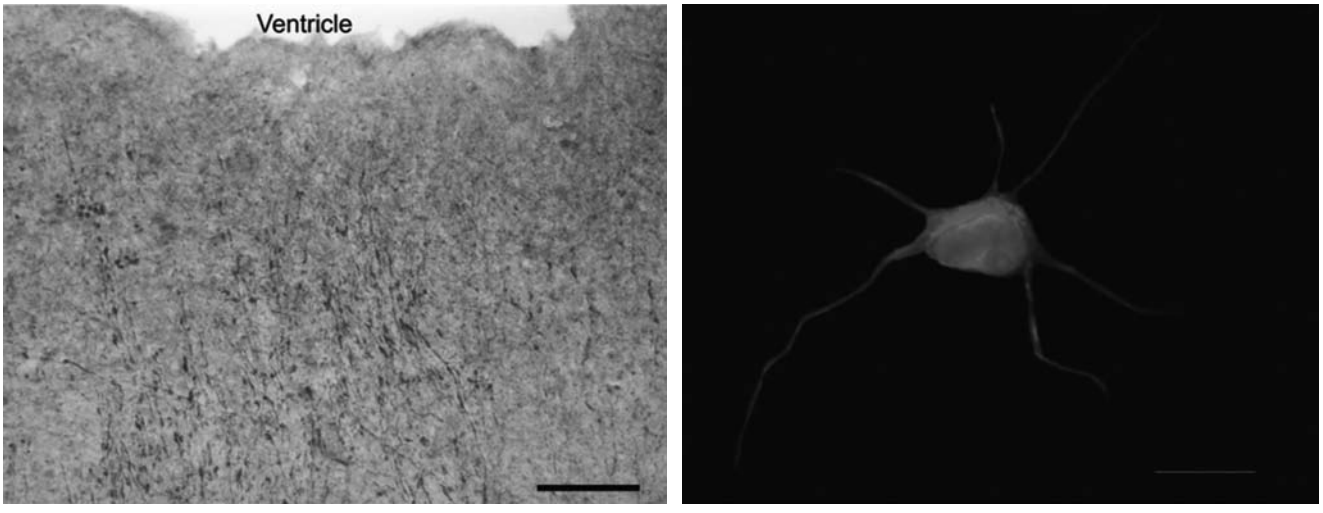


Figure 147.2 Difference in BrdU-labelling in normal versus epileptic dysplastic neocortex and adjacent white matter. a, Cresyl-violet (CV) staining from lateral temporal cortex showing normal cytoarchitetonic columnar organization. b, CV staining from dysplastic lateral temporal lobe showing loss of columnar organization and the presence of cytomegalic cells. c, Similar sample depicted in a showing NeuN expression, demonstrating the normal columnar organization of neocortical neurons. d, Similar sample depicted in b showing NeuN expression, demonstrating the loss of the columnar organization and the presence of cytomegalic neurons (arrow). e, Adjacent white matter (intermediate zone [IZ]) related to the cortical samples depicted in a and c showing the absence of BrdU staining. f, IZ related to the cortical samples depicted in b and d, demonstrating intense BrdU staining. (See Color plates.)



(a) (b)

Figure 147.3 ICC for Tuj1 in the SVZ from epileptic dysplastic sample. Bar: 40 µm. (3b) Double-labeled immunoflorescence (Nestin-red, BrdU-green) in the SVZ from epileptic dysplastic sample. (See Color plates.)

growth and proliferation regulation.[68,69] Both TSC1 and TSC2 genes role were investigated in FCD, and indicate that FCD with BCs is characterized by a high incidence of TSC1, but not TSC2.[68,69] Interestingly, TSC2 is more frequently found altered in familial tuberous sclerosis pathology, while TSC1 alterations are found related to sporadic incidence.[69] When comparing immunocytochemistry in FCD type IIb, hemimegalencephaly and tuberous sclerosis tissue, Fauser *et al*. described similarities in CD34 (neural development marker), GFAP (glia marker), and neurofilament (neural marker) expressions in all groups.[70] Based on similarities between TS and FCD, Mackay *et al*.[71] suggested genetic counseling to patients presenting FCD with balloon cells. Crino *et al*.[6] suggested that extensive histological similarities can be found when comparing hemimegalencephay and FCD, with disorganized cortical lamination and presence of white matter heterotopias and BCs, the main difference been the area committed in the pathology.

Glia in epilepsy

Studies that analyzed the role of glial cells in epileptic tissue point to an important role of those cells in seizure initiation and maintenance.[72–74] Gliosis is frequently found in epileptic tissue.[2,11,73] There is evidence that glia in epileptic tissue is not able to maintain K^+ and Ca^{++} homeostasis.[72,75,76] In MTLE tissue, glial cells from DG hilus have a reduction in the number of K^+ channels, what could contribute for the decreased K^+ conductance in specific regions in the epileptic brain.[76–78] Glial cells from FCD may also have their electrophysiological characteristics modified, suggesting inability to maintain ionic balance in epileptic tissue, thus maybe contributing to its hyperexcitability.[76] Potassium homeostasis may be important in neurons excitability, as its increased concentration in the extracellular medium may result in cell depolarization.[72–74] There is an upregulation of Na^+ channels inHS astrocytes, possibly leading to an enhancement of intracellular sodium, and consequently increasing glial intracellular calcium. Increased intracellular calcium would promote the release of transmitters, cytokines and growth factor in the epileptic tissue.[72]

Conclusions

The availability of resected focal epileptic tissue from patients with medically intractable focal epilepsy and the development and characterization of animal models for various types of epilepsies have provided a better understanding of some of the cellular and electrophysiologic mechanisms of epileptogenesis. At the single-cell or local circuitry level, in vitro models of hyperexcitability or synchronization have provided additional insights about the various mechanisms of epileptogenicity. Synaptic and nonsynaptic mechanisms have been proposed as having critical role in seizure generation and spread. Using in vitro cytochemical studies, changes in excitatory and inhibitory receptors, imbalance between excitation and inhibition and the evidence for plasticity and neurogenesis are being investigated, constituting important mechanisms involved in the generation and maintenance of intrinsic epileptogenicity.

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148 Animal models of epilepsy with special reference to models relevant for transitional research

S Chabardès, I Najm, and HO Lüders

Animals models of epilepsy have been used extensively for the study of mechanisms underlying the epilepsies in general, but also to test new antiepileptic drugs and clarify their mode of action. To face the diversity of epilepsies encountered in human pathology, a large variety of animal epilepsy models have been developed and characterised at a behavioral, electrical, histopathological, and sometimes genetic level. Development of neurosurgical strategies will require also the development of relevant animal models mimicking intractable epilepsies in humans. Epilepsy models in animals are frequently severe, leading to the death of the animal. This is not what is usually seen in humans. New treatment strategies such as electrical brain stimulation (DBS, VNS, cortical stimulation) or local drug delivery, require chronic models to assess the efficacy of the procedures. Besides, excessive severity of seizures may obscure potential efficacy of these therapies.

This chapter will review the main characteristics of animal models of epilepsy and the possible usefulness of these models to evaluate clinical problems.

In this review, we have classified the animal models in a clinical way trying to mimic as much as possible the clinical situations usually encountered in humans.

Focal or regional seizures

Focal epilepsy is the most common type of human intractable epilepsy. The most frequent involves the temporal lobe but can also involve extratemporal cortex.

Limbic seizures

Acute

In rats, limbic status is easily produced by a single intraperitoneal (ip) injection of KA (10 mg/kg). Hippocampal seizures usually occur 5–10 minutes after KA injection and last 50–100 sec. These seizures eventually spread to the neocortex within minutes and sometimes generalise (See Figure 148.1–2). The status usually last 8–12 h. Clinical behaviour is generally well stereotyped with arrest phases, wiping nose, head nodding, and motor manifestation. Histopathological findings show neuronal loss in the amygdala, the hippocampus (mainly CA1, subiculum, and CA1), the entorhinal, and piriform cortex, and also widespread cortical lesions.[1,2] This model is very easy to use, reproducible, with limited interindividual variability, and the seizures tend to be pharmacoresistant. The disadvantage of this model is that usually even the first injection produces inner cell bodies damage created by the KA itself. These structural lesions together with the severity of the seizures do not allow chronic experiments and introduce some bias in case-control studies.

Chronic

Chronic models of limbic seizures can be produced by local injection of small amounts of drugs like KA in the hippocampus and the amygdala, or by single/repetitive (kindling) stimulation of these structures.

Small doses of KA (0.8–2.0 μg) injected in the hippocampus or the amygdala create limbic status[1,3] followed by intermittent limbic seizure 2–4 weeks later. Electrical and clinical manifestations of these seizures have been classified by Racine *et al.*[4–6] into five reproducible steps which allow comparison of the severity of seizure from one situation to another.

Repetitive electrical stimulation of the hippocampus or the amygdala (kindling) in cats has been described by Alonso-De Florida and Delgado in 1958[7] and has since been applied in most species used in experimental conditions. In rats, this technique has been described in details.[8–13] Briefly, the amygdala or the ventral hippocampus is stimulated through bipolar electrodes using trains of 400 μA in intensity, 50 Hz in frequency, and 2–5 sec in duration, for a period of 90 min. The first seizure appears after 8–38 days in 70% of the stimulated rats.[12]

Recently, Nissinen *et al.*[14] have proposed a new kindling paradigm that shortens the stimulation period and produces a temporal seizure that closely mimics temporal lobe epilepsy (TLE) encountered in human pathology. The parameters used are as following: 60 hz bipolar pulse, pulse width 1 ms, 400 μA applied in trains of 100 ms every 0.5 ms for 20–30 min. Using these parameters, 85% of rats developed limbic seizures 6–85 days after the stimulation. Histopathologically, observation indicated neuronal loss in the hippocampus, the amygdala, and surrounding cortex with mossy fiber sprouting in the dentate gyrus. Interestingly, these rats eventually developed memory impairment as assessed in the Morris water-maze. This model is very useful in preclinical studies as it is well characterized, standardized, easy to produce in the lab, and lesions appear to be the result of the seizures and not the result of KA damage.

Figure 148.1 Example of seizures recorded in rats after ip injection of kainic acid. aLH, aRH: left, right hippocampus electrode; RF,LF: right, left frontal electrode. Status involves both hippocampi while bilateral seizures are also recorded at the frontal neocortical level and occur chronically every 10 to 20 seconds.

Neocortical / motor seizures

Focal neocortical seizures are difficult to produce in rats or mice but can be produced more easily in bigger mammals such as cats or monkeys. In rats, partial seizures tend to involve extensive areas of the brain rather than strictly focal areas.

Acute

After discharge model

Acute focal seizures (see Figure 148.3, personal observations) can be obtained using electrical bipolar stimulation of the surface of the cortex.[15] In this model recently revisited by Shigeto *et al.*[16] at the CCF, focal seizure lasting 5–30 sec can be elicited by electrical stimulation. In this model, seizures are obtained using a bipolar, biphasic square pulse of current with pulse width set at 1 ms, frequency at 50 Hz, duration at 5 sec, and intensity varying from 0.5–2 mA. This model, could be relevant for testing the epileptogenicity threshold. However, the electrical stimulation creates an artefact electrical noise which can hide the beginning of seizures.

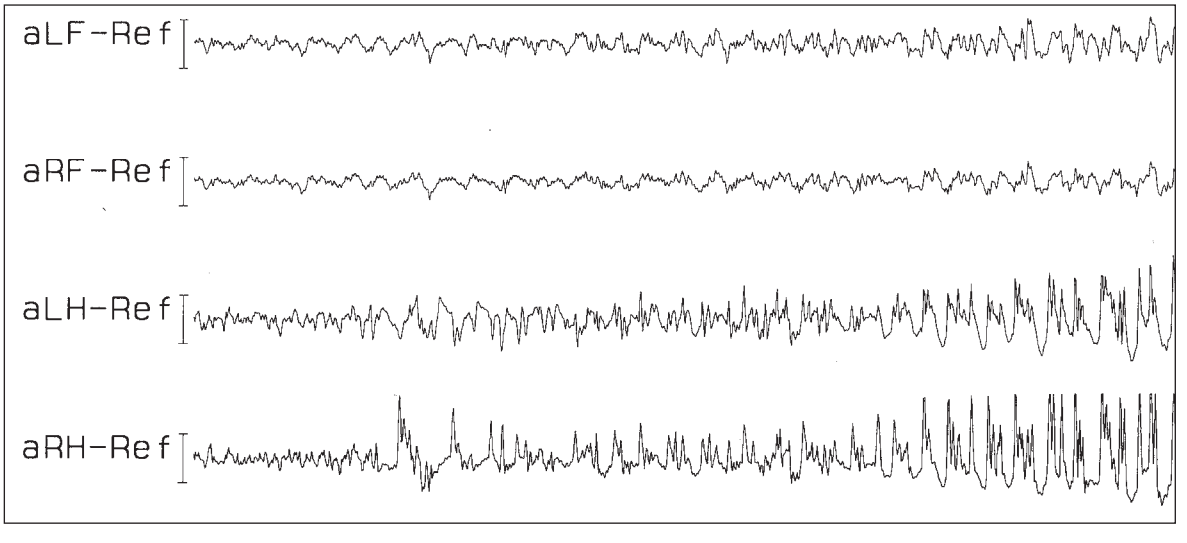

Figure 148.2 Example of seizures recorded in rats after intraperitoneal injection of kainic acid. aLH, aRH: left, right hippocampus electrode; RF,LF: right, left frontal electrode. Referential montage. Seizures start in the hippocampus bilaterally. Seizure activity secondary spreads to the frontal neocortex.

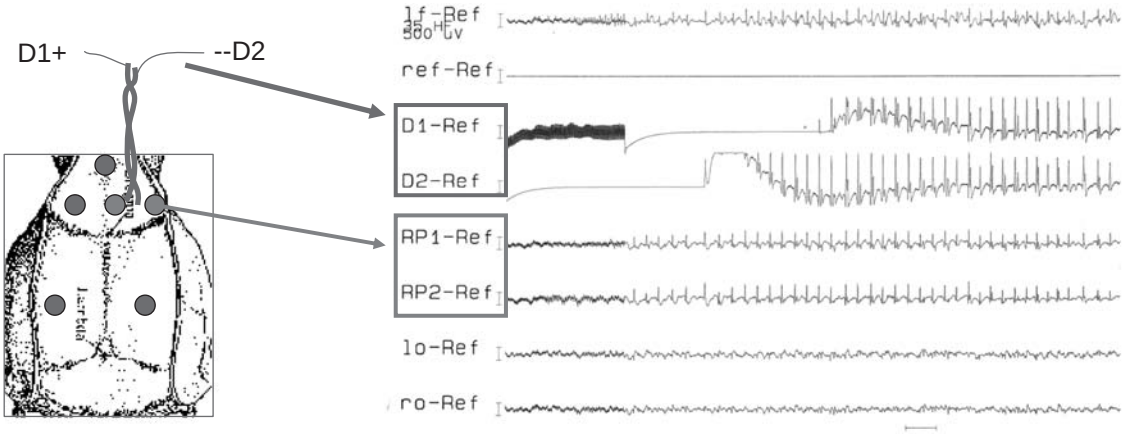

Figure 148.3 After discharges elicited by bipolar stimulation of the neocortex in rats. The seizure is mainly observed in the stimulating electrodes (D1 and D2) and on recording electrodes (RP1 and RP2) located at the vicinity of vicinity of the stimulating contacts (D1 and D2).

Focal chemical agents: penicillin model

Topical application of GABA antagonists agents can produce acute focal or regional spikes. This includes penicillin (PG),[17–24] bicuculline[25–28] and 4-aminopyridine (4AP).[29,30] Topical use of other agents such as KA (glutamatergic agonist) can also produce focal spikes.[31,32] However, seizures produced by topical applications of convulsivant agents (unpublished data) are more difficult to standardize and are less reproducible, leading to frequent rapid generalisation. GABA withdrawal has also been used to elicit focal seizure which starts immediately after having injected GABA in the cortex.

In our experience,[33] intra cortical injection of small amounts of Penicillin G produces very focal, long lasting, reproducible seizures. For preclinical studies, we developed an acute model of focal neocortical status epilepticus, using intracortical injection of PG in the motor cortex of rats. This model of motor seizure mimics seizures that are usually seen in patients suffering from epilepsia partialis continua. Briefly, the right motor cortex was implanted with an intracortical injection-recording cannula, and epidural screws were used for EEG recordings. PG was injected through the cannula using a Hamilton syringe at a dose of 1125–2250 IU per min for 5 min. All the rats developed focal epileptic status (see Figure 148.4 a,b,c,d) in the ipsilateral frontal cortex that lasted up to 36 hours and was always associated with contralateral forelimb clonic movements. Secondary generalisation was very rare and only occurred once when a higher amount of PG was used. In this model, EEG and behavioral patterns are both reproducible in their occurrence and predictable in their evolution. An in-house program for offline analysis was developed in order to automatically detect and characterize the number and amplitude of all spikes (Figures 148.5a and 148.5b). Histopathological examination of the focus revealed no lesions. This model has the advantage to be simple to produce; it is reproducible, well standardized and can be quantified because of the properties of spikes which are well identified. PG injections can be repeated several times in a single animal without any damage.

Chronic/semi chronic

Metal deposits at the surface of the cortex

Different metals introduced in the cortex produce neocortical, focal or regional seizures. One of the most convenient models for transitional research is probably the one obtained after local insertion of cobalt. This model originally developed in the 1970th[34–37] has been recently revisited by Chan *et al.*[38] It consists in inserting a small piece of cobalt wire in the cortex and, approximately 10 days later, focal seizures can be recorded in electrodes surrounding the placement of the cobalt (see Figure 148.6a; 148.6b, personal observations). Seizures are usually stereotyped, focal or regional. The number of seizures increases progressively for 2 or 3 weeks and then stops.

Iron, zinc, and aluminum were also used to create focal neocortical seizures.[39–43] In big mammals like rabbits, cats, dogs, and monkeys, the alumina cream model of focal neocortical seizures has been described extensively.[44–51] Focal neocortical seizures are produced by subpial injection of 0.2–0.4 ml of alumina. Two to four months later, focal seizures can usually be recorded, and these can continue for several years. This model has the advantage of producing neocortical seizures that mimic those usually seen in humans for whom the seizures persist for several years. On the other hand, the seizure focus requires several weeks or months to be established and the severity of the focus tends to vary between animals.

dysplasic related seizures

Models of epilepsy related to cortical dysplasia are of major importance since cortical dysplasia is a frequent cause of intractable epilepsy affecting children and adolescents. Unfortunately, models of epilepsy produced by cortical dysplasia are very rare.[52,53]

Cortical malformations can be obtained by utero insults produced by X irradiation or by exposure to methyl-azoxymethanol (MAM) which is a DNA alkylating agent. To be effective, the exposure must occur between embryonic days 14–17. These methods create a neuronal migration disorder. Experiments conducted at CCF recently showed that low (100 cGy) or mild irradiation (145 cGy), were more effective to create seizures

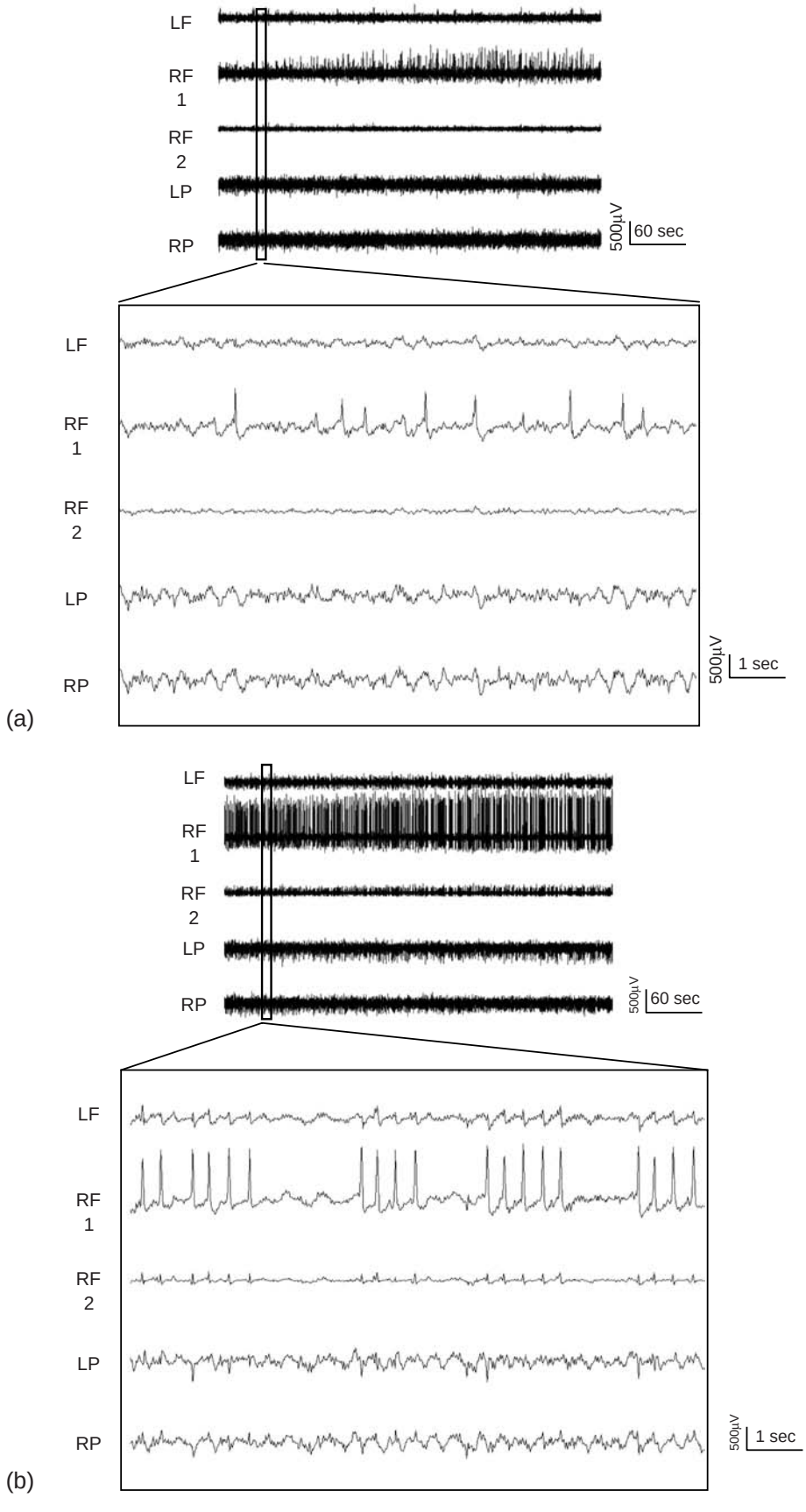

Figure 148.4 a. EEG pattern of a focal neocortical seizure occurring 3 to 8 minutes after penicillin injection in the right motor cortex in rat. For a duration of 1 to 3 min, irregular low amplitude spikes (200–800 V) are restricted to the right frontal electrode (RF1) located at the side of the PG injection. b. EEG pattern of a focal neocortical seizure occurring 4 to 11 min after penicillin injection in the right motor cortex in rats. Bursts of rhythmic focal spiking (800 to 1200 µV in amplitude, 2 to 4 Hz in frequency), are recorded for a duration of 3 to 20 min. These focal spikes are mainly recorded from the right frontal (RF1, RF2) and at times from the right parietal (RP) electrodes. They are always associated with contralateral forelimb clonic movements.

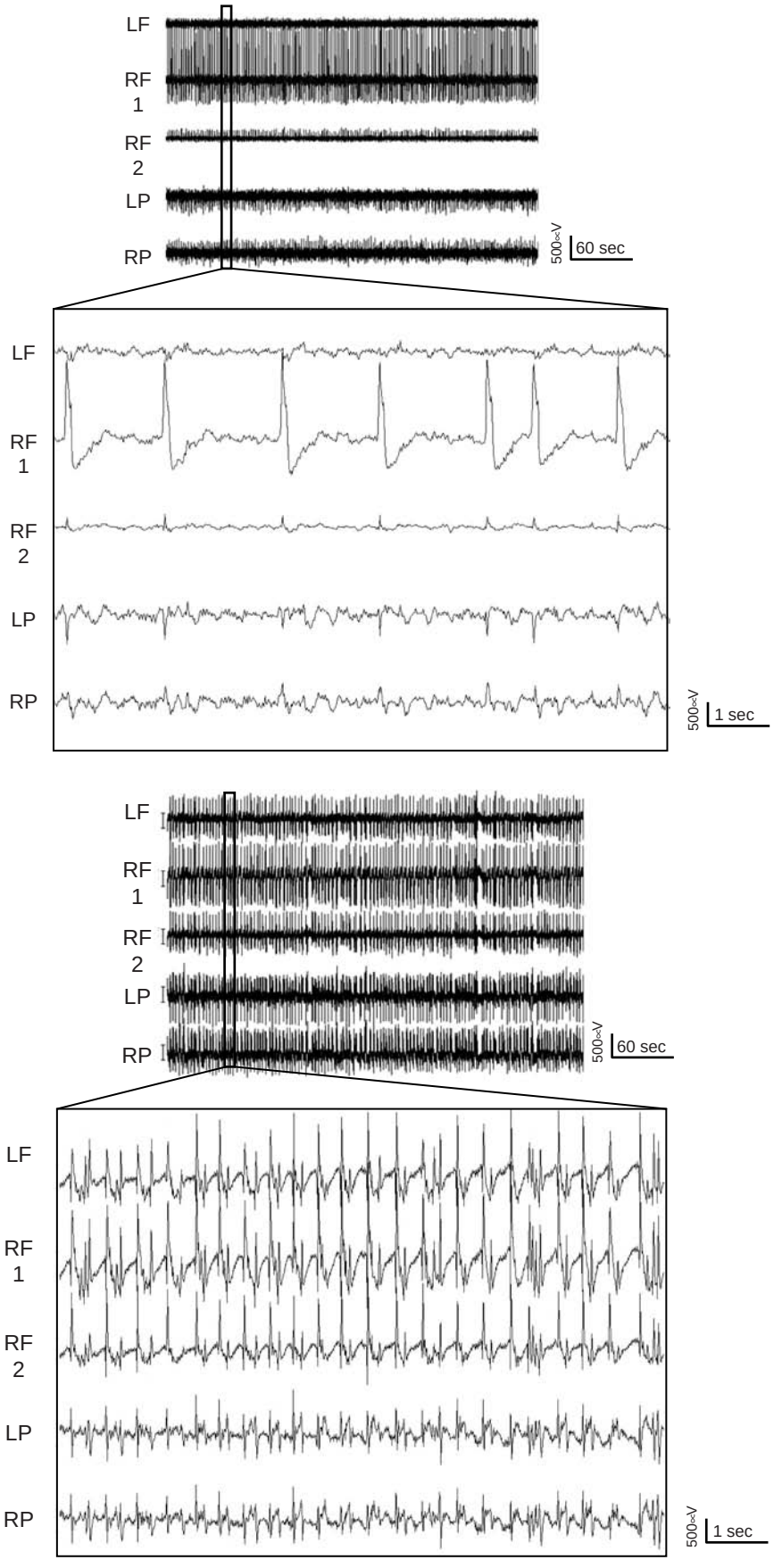

Figure 148.4 c. EEG pattern of a focal neocortical seizure occurring 7 to 31 min after penicillin injection in the right motor cortex in rats. It consists of continuous rhythmic focal (frontal electrodes) or lateralized (ipsilateral parietal area) high amplitude spikes or polyspikes (1200 to 3000 μV in amplitude, 0.5 to 2 hz in frequency) that last between 2 and 8 hours. Each spike is associated with contralateral forelimb and or facial clonic movement. d. EEG pattern of generalised seizure occurring after penicillin injection in the right motor cortex in rats. This is a late seizure evolution pattern consisting of generalized spiking intermixed with low amplitude fast spiking (10–20 Hz). This pattern occurred only once in one rat and apparently is produced by injecting a higher dose of PNG relatively fast.

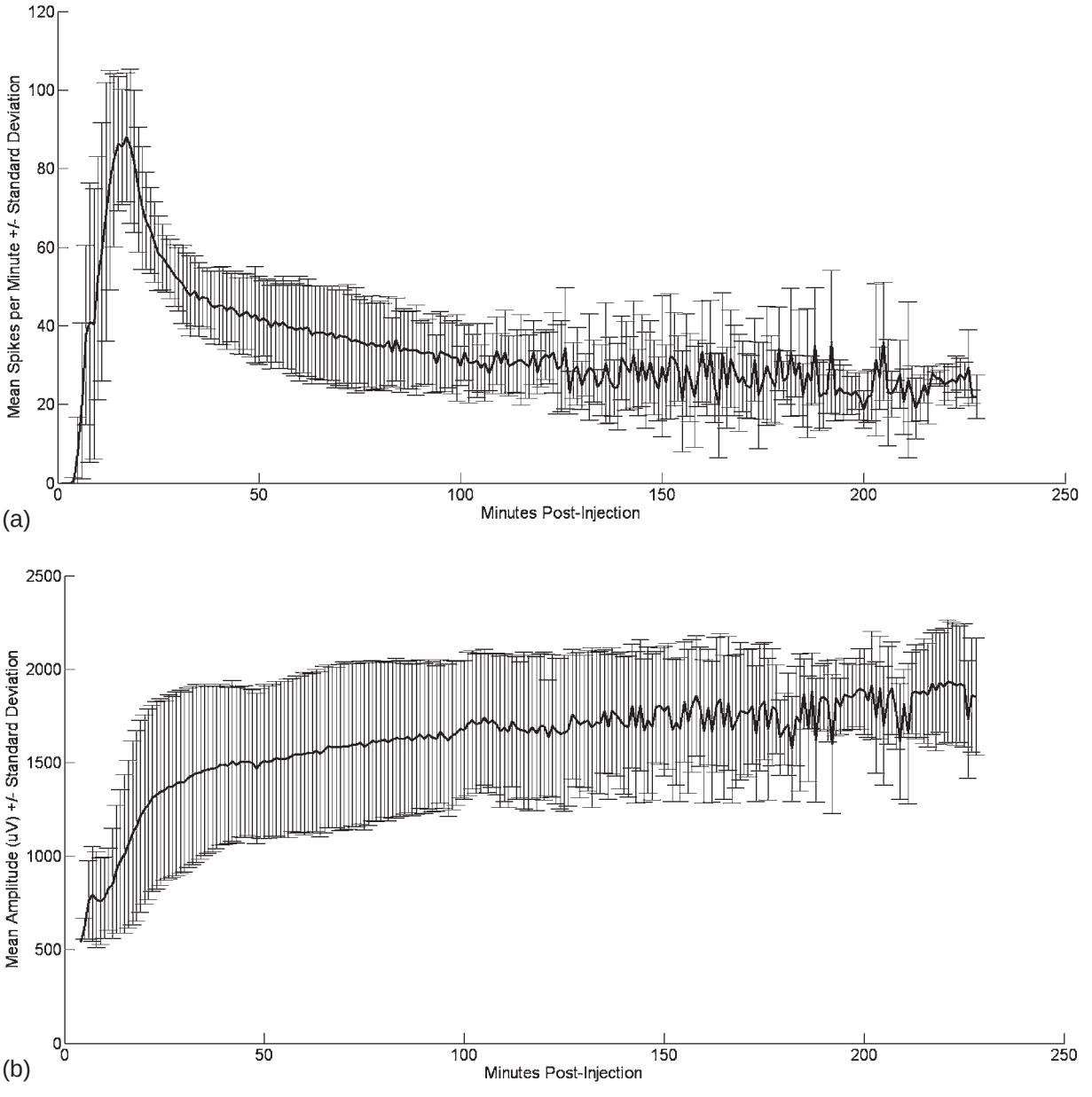

Figure 148.5 a.Time course (± SD) of spikes after one single injection of penicillin in the right motor cortex in rats (*n*=7). Each point represents the mean number of spikes ± SD occurring during 1 mn. Spikes started within 5 min of PG injection, increased rapidly to reach a aximum of 88 spikes/min at an average of 11 min after PG injection. Then, the spike numbers decreased progressively for 2–5 hour. b. Time course of spike amplitudes following a single injection of penicillin in the right motor cortex in rat (*n*=7). Each point represents the mean amplitude of spikes (± SD) occurring in one minute. Threshold of spikes detection was set at 500 ∝V. The amplitude increased dramatically within the first 20 min after penicillin injection and reached a plateau that lasted for several hours. A maximum amplitude of 1934 µV (± 327.1) was achieved 223 min after the penicillin injection.

compared to high dose (175 cGy) of irradiation.[54,55] The EEG characteristics of these models have also been recently described by the same group.[56]

Freeze lesions have also been used to induce focal cortical malformations. They usually create microgyri with hyper excitable cortical tissue because of an excess of excitatory glutamatergic neurons projecting to the affected gyrus.[57–61]

Generalized seizures

Absence-like seizures

Acute models

Various chemical agents have been used to create absence-like seizures. Penicillin injected intraperitoneally in cats and Gamma OH injected intraveinously in monkeys are examples of such models. Snead *et al.*[62] described that in monkeys

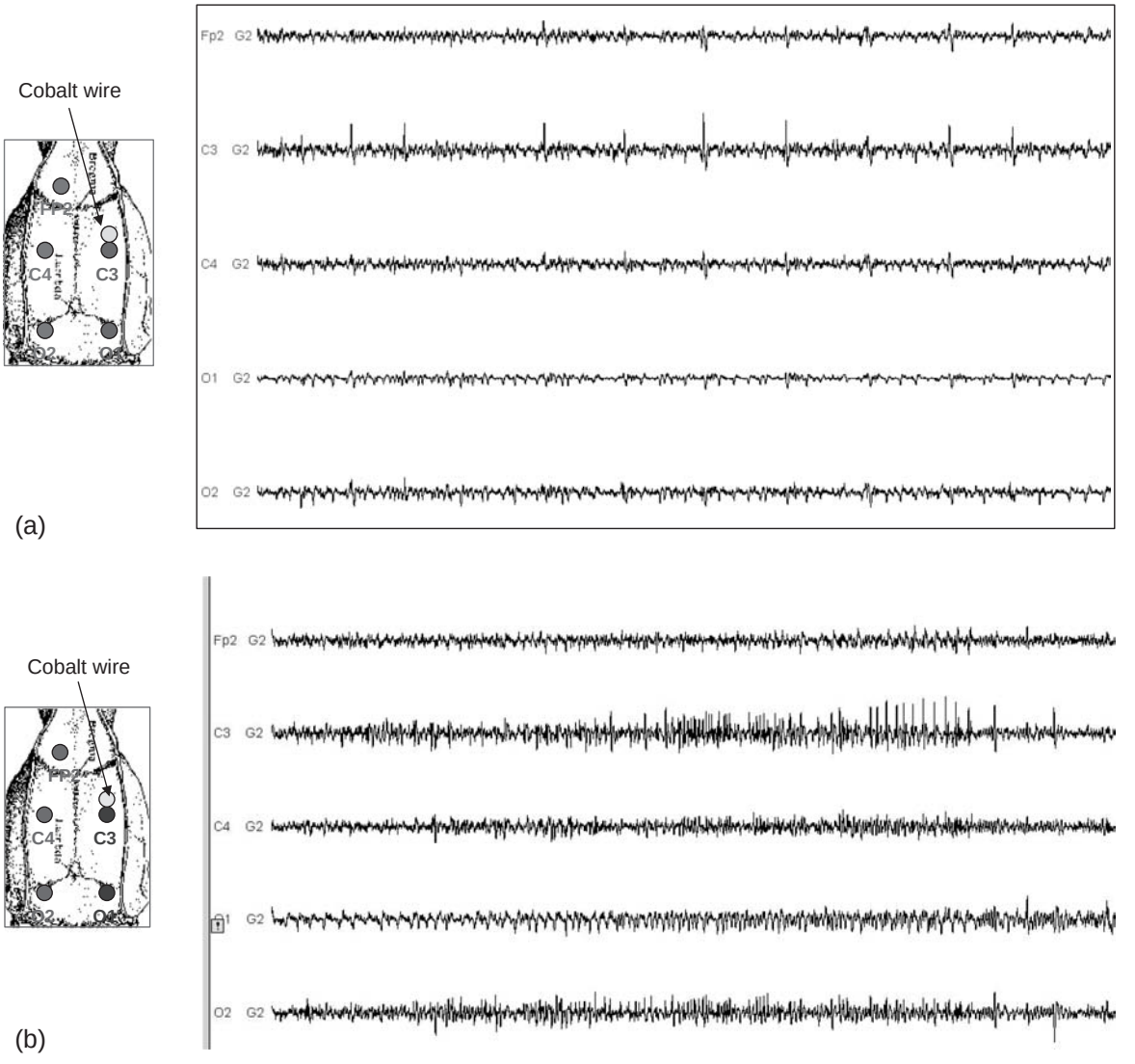

Figure 148.6 (a) Example of interictal spikes recorded on the electrode 'C3' located at the vicinity of the site of the cobalt insertion at the surface of the neocortex. (b) Example of focal seizure recorded 15 to 20 days after the insertion of a small piece of Cobalt at the surface of the motor cortex in a rat. Usually, these seizures can be recorded 2 to 4 weeks after the cobalt insertion at the surface of the cortex and then stopped spontaneously after several weeks.

treated with IV injections of Gamma Hydroxybutirate (200–400 mg/Kg), continuous and hypersynchronous spike-and-wave discharges (SWD) at a frequency of 1–3 Hz occurred 5 min after the injection. Usually, during SWD, the monkeys stared and were immobile, with the eyes closed and without any response stimuli.[65] After injection of ethosuximide (150 mg/Kg), SWD stopped. Snead *et al.* concluded that this was a good model of '*petit mal absence*'. Intraperitoneal injection of pentylenetetrazol (PTZ)[64,65] in rats also induces acute '*petit mal absence*'.

Chronic/genetic

The Genetic Absence Epileptic Rats of Strasbourg (GAERS) and the WAG/Rij strain of rats mimic absence seizures.

GAERS are a strain of Wistar rats in which all animals show spike and wave discharges (SWD) in the cortical electroencephalogram. The seizures occur very often (One up to three per minute) and usually last approximately 20 minutes. They are characterized by generalized spike-and-wave discharges (SWD), and are associated with behavioral arrest. They share many features with human absence epilepsy and generalized epilepsy in human, and the seizure can be suppressed by all antiabsence drugs. These discharges are facilitated by reduction of noradrenergic and dopaminergic neurotransmitters, and increments of Gabaergic transmitters. They are suppressed by ethosuximide and other antiabsence drugs, but are exacerbated by phenytoin and other anticonvulsant drugs. Progress in the understanding of the role of basal ganglia in the control of seizures has strongly benefited from the use of this genetic model of generalized non-convulsive seizures.[66,67] Studies in this model suggest that the cortex, the reticular nucleus, and the ventrobasal relay nuclei of the thalamus play a predominant role in the development of SWD. However, recent evidence[68] seems to indicate a seizure

initiation site within the perioral region of the primary somatosensory cortex (S1po) in the Wag/Rij stain of rats, as another well characterised genetic model of absence seizures.[69–72]

The tottering mouse also, exhibits features of generalized epilepsy (generalized spike-waves on EEG and absence-like clinical seizures).

'EL mice' are the only genetic animal models that express seizure-associated damage to the hippocampus, a region of the brain commonly damaged by epilepsy in humans.

In the past 5 years, the genetic mutations responsible for epilepsy in several different mouse models were identified. Unlike GAERS, the tottering and the stargazer mice have a known genetic mechanism. The stargazer mutation (21), which occurred in a newly discovered calcium channel gamma subunit, interferes with proper functioning of calcium channels, allowing overexcitation of neurons that leads to seizures. A second form of seizure, known as 'slow-wave epilepsy' because of its characteristic pattern of electrical recordings from the brain, is caused by a mutation that inactivates the sodium–hydrogen transporter.

Tonic-clonic seizures

Acute

The Maximal electroshock model (MES) has been extensively used in particular in pharmacological studies to screen AED. Stimulation parameters used are usually as follows: 150 mA, 60 Hz for 0.2 sec delivered via corneal electrodes. Seizures are 'Maximal' when animals show tonic hind-limb extension and flexion followed by clonus.[42]

Chronic /genetic

The genetically epilepsy-prone rats GEPRs have three types of convulsive epilepsy: generalized tonic-clonic seizures, partial seizures, and partial seizures with secondary generalized tonic-clonic seizures. GEPRs have a predisposition to sound-induced seizure assessed by an audiogenic response score (ARS), (0: no response to 9: severe seizure). GEPR rats exhibit a characteristic convulsive response to each ARS. (GEPR 3s: moderate seizures exhibiting clonic convulsions. GEPR 9s: complete tonic extensions). Anticonvulsant treatment can lower the ARS score. GEPRs respond to broad spectrum drugs, and also to those useful in generalized tonic-clonic seizures and partial seizures, but not to baclofen and chlorpromazine.

Conclusions

The existence of many models of epilepsy reflect the vast spectrum of epilepsies that clinicians have to face daily. However, on the other hand, it also reflects the fact that these models have a lot of limitations and unfortunately do not fitful all the clinical, electrical and genetic characteristics of human epilepsies. One must be cognizant of these limitations especially when new preclinical therapeutic strategies are tested in these models.

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SECTION 20

Surgical failures: reoperation

149 Surgical failures: pre-surgical evaluation

CT Skidmore and MR Sperling

Introduction

Epilepsy surgery has been shown to be a reasonably safe and effective therapy for medically refractory localization-related epilepsy. The success of surgery at 1 year ranges from approximately 50–80% depending on the location of the surgery and the underlying pathology.[1–3] However, long-term follow-up reports demonstrate that a substantial proportion of patients, approximately 50%, relapse within 5–10 years of temporal lobectomy.[3–4] Relapse rates are even higher for extratemporal epilepsy, with 70% of patients experiencing a relapse within 5 years of frontal lobe surgery.[1] Therefore, recurrent seizures are a common problem after epilepsy surgery.[1,3,5,6]

It is common practice to consider performing a second operation in selected patients to see if seizures can be stopped, thereby obtaining maximum surgical benefit. This practice is supported by literature reports demonstrating that 48–81% of reoperated patients achieve seizure control or have rare seizures.[5–12] This chapter will focus on the repeat pre-surgical evaluation which needs to be performed prior to subsequent operations.

Before addressing the evaluation process, we should first review which patients are suitable candidates to consider for reoperation. In brief, if the goal of surgery was to abolish seizures, then any patient with persistent seizures after surgery might be a candidate for reoperation. However, deciding to offer additional surgery is not always straightforward. Some patients who relapse after surgery later enter remission, experiencing the 'running down' phenomenon.[13] This observation leads many physicians to adopt a conservative posture, and wait at least a few months, perhaps more, before considering further surgery. Some patients recur after surgery but their seizures are quite rare, so the value of surgery may be uncertain. Lastly, should a physician try additional medications prior to considering reoperation? Whether new medication trials offer a realistic hope of alleviating seizures after unsuccessful epilepsy surgery is uncertain. It seems reasonable to try at least one new medication before proceeding to additional surgery, given the relative risks. Nonetheless, the decision to embark upon the path towards reoperation is a difficult one.

Ultimately, the patient must decide for himself whether he is satisfied with the surgical result, and if not, reoperation should be considered. In our experience, patients who have had as few as two seizures in the year after surgery have asked for additional surgery, since their goal of seizure freedom was not attained, and the secondary benefits of operating a motor vehicle and increased independence were not achieved. Others with more frequent seizures, or seizures that produced injury, have also been interested in reoperation, since the reasons to have surgery the first time remain. Others have elected not to have surgery, because of doubts as to efficacy, or because of satisfaction with the reduction in seizure frequency or severity that might have occurred.

Review of data from the first operation

The first question to be answered is why the initial surgery failed. Possible reasons for surgical failure include inappropriate interpretation of the initial pre-surgical data, incomplete resection of an epileptogenic zone, or the presence of a de novo epileptogenic zone. Unfortunately, there is no single test or method to identify this region precisely prior to epilepsy surgery. One can only know the approximate location of the epileptogenic zone after surgery – if seizures persist, then it was not completely removed. Determining its boundaries relies on the accurate interpretation and application of the pre-operative testing. The surgical plan was employed to address the most logical hypothesis as to the location of the epileptogenic zone based upon this testing. In order to determine why the first surgery failed, a detailed analysis of the initial pre-surgical data and hypothesis needs to be repeated (Table 149.1). If it was known at the time of surgery that complete resection was not possible, then surgical failure might not be a surprise.

This should be easy to accomplish when the patient was operated in the same institution, but there are sometimes challenges in obtaining complete records from other institutions. This barrier is quickly being eliminated by the ability to share electronic records, which allows for the independent reinterpretation of the initial data. Reviewing the initial data and post-operative MRI allows a physician to determine if the initial hypothesis was correct and if the appropriate resection was performed. If it is determined that the localization was incorrect, then alternative hypotheses with regard to location of the epileptogenic zone might be generated to help guide a repeat surgical evaluation. One must reassess all aspects of the evaluation, to determine the concordance of the data and the accuracy of the interpretation.

Table 149.1 Analysis of evaluation prior to first operation

Initial surgery	Questions to consider
Ictal behavior	Was the history correct?
	Was there more then one type of seizure?
	Were all types of seizures captured with video-EEG?
Scalp EEG	Was the interictal focus focal or not?
	In what state did the spikes occur?
	Was the ictal EEG interpreted correctly?
Intracranial EEG	Was the electrode placement adequate?
	Did the EEG onset precede behavioral onset?
	How rapidly did the seizure spread to additional regions or to the contralateral hemisphere?
	Were spread patterns consistent and logical?
	Was the localization concordant with the other information?
MEG	Is there a predominant focus?
	Was it concordant with the resection?
MRI	Were the proper sequences performed?
	Was the image interpreted correctly?
	Was a lesion identified?
	Was there a single lesion or multiple?
Functional imaging	Was focal hypometabolism identified?
	Was an ictal hyperperfusion identified with SPECT?
Data synthesis/Surgical plan	Was the hypothesis correct?
	How concordant was the pre-operative data?
	Was there evidence for multifocal disease?
	Was the localization clearcut?
	Was the surgical plan appropriate?
Surgery	Was the intended resection accomplished?
	Was the desired extent of resection limited by functional or anatomic barriers?

History and semiology

The first step to be performed is to review the epilepsy history and pre-operative seizure semiology. Does the history suggest a particular epilepsy syndrome? Is it consistent with the syndrome that was diagnosed? Is the patient's or family's description of the seizure consistent with the diagnosis? Did the patient have more then one seizure type, and were all types of seizures captured during the video-EEG monitoring session? The assessment of the history provides critical information that aids in identifying the location of the epileptogenic zone.

Neurophysiology

The pre-surgical scalp and intracranial EEG evaluations must be reviewed. If both evaluations were performed they should be reviewed independently to determine if the data are concordant. The EEG evaluation helps determine the irritative and ictal onset zones. Several questions must be addressed. First, were the EEGs correctly interpreted? What was the location of the interictal spikes, and was their more than one location? In what states did they occur? When examining the ictal EEG, were seizures localized and how many ictal patterns were seen? What was the relationship between the timing of the ictal onset, and clinical onset? Was the onset and spread pattern of the seizure consistent with the ultimate localization? If intracranial EEG was performed, did ictal onset precede the clinical onset? Also, if an invasive evaluation was performed, was cortical sampling adequate? Invasive EEG is highly susceptible to sampling error and occasionally too much weight is placed upon the value of intracranial recordings. Therefore, was the intracranial EEG consistent with the rest of the data, or did it contradict the other findings? Lastly, if magnetoencephalography (MEG) was performed, was it correctly interpreted, and where were the interictal spikes located?

Video

The video enables direct observation of the seizure and testing of the patient during seizures. Was the behavior suggestive of a particular type of seizure? Was the behavioral localization reliably seen with several seizures, and was more than one ictal behavior observed? Most importantly, was the behavioral localization consistent with the site of surgery?

Imaging

Perhaps the most important step in the re-evaluation is the review of the pre-operative and post-operative imaging studies, particularly the MRI. The presence of a structural lesion which colocalizes with the other data is perhaps the best prognostic sign for successful surgical treatment. The pre-operative MRI should be re-evaluated to determine if it was correctly interpreted. Was any structural lesions present, if so, how many, and were they within the proposed resection margins? If the extent of resection was limited by the relationship between the presumed epileptogenic zone and eloquent cortex, reassessment of the surgical extent can be performed, and perhaps sub-pial transection considered. Other imaging data, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), must also be reviewed, to ascertain whether they were correctly interpreted and whether relevant imaging abnormalities were included within the resection line.

Synthesis

Since the goal of reassessment is to review all of the available data, one must then determine whether a reasonable hypothesis was generated, and if the appropriate surgery was performed. This assessment requires intellectual honesty and rigor, and a willingness to take a fresh look at the data. After review of the data, one must consider alternative hypotheses, and these will help guide the repeat pre-surgical evaluation. The physician or treatment team may reinterpret the findings of the initial evaluation, perhaps formulating a different hypothesis regarding localization of the epileptogenic zone, or may draw the same conclusions as before. In either circumstance, a rigorous examination of the pre-operative data must be done before embarking on new investigations.

Re-evaluation

The second pre-surgical evaluation has exactly the same goals and objectives of the first, to define the boundaries of an epileptogenic structural lesion. The presence of a structural lesion must be determined, and the limits of the epileptogenic zone established. One must reassess and define the symptomatogenic zone (region producing symptoms), irritative zone (region of EEG or MEG interictal spikes), ictal onset zone (region of EEG ictal onset), and functional deficit zone (regions of abnormal function defined by examination, PET, SPECT and other testing methods) and the extent of an epileptogenic lesion (defined by MRI), though this task is made more complex by the presence of a skull defect and the prior cortical resection. The methods utilized in the repeat evaluation are the same as before the first operation, including performance of a detailed history, neurological examination, scalp video-EEG monitoring, MRI, and a neuropsychological evaluation at a minimum (Table 149.2). Additional tests which may be employed include PET scan with fluorodeoxyglucose (FDG), interictal and ictal SPECT scans, magnetoencephalography (MEG), and functional MRI (fMRI). A full discussion of these technologies is beyond the scope of this chapter and is reviewed elsewhere in this text.

History and semiology

The first order of business is to assess the neurological history, with particular attention to seizures and the psychiatric state of the patient. Have seizures changed in character compared with the pre-operative seizures? Does the patient experience the same aura, and exhibit the same behaviors during seizures? Do family members note a change in the behavior, either during or after a seizure? Is there more than one type of aura? These factors are all important to assess the effects of surgery and determine whence seizures might originate. A change in aura symptoms or behavior might suggest a modification to the pre-existing epileptogenic zone, the development of a new epileptogenic zone, or it might suggest a different ictal propagation pattern. Careful review of the signs and symptoms might lead one to favor one of these possibilities over the others. Do seizures have different implications with regard to risk of injury and ability to function compared with the pre-operative state? Have new psychiatric problems emerged, such as depression, anxiety, or psychosis? These first require treatment, and might affect patient ability to make an informed decision about additional surgery. Changes in the neurological or neuropsychological examination may suggest the existence of new lesions, and offer clues as to the location of these lesions. On the other hand, new deficits in neuropsychological functioning have impact regarding the risks of additional surgery. For example, development of even modest language problems after a first operation may lead a physician to counsel against extending the prior resection, whereas lack of post-operative deficit would not deter further surgery.

Table 149.2 Re-evaluation after failed surgery

Repeat surgical evaluation	Questions to consider
Ictal behavior	Has the seizure semiology changed? Is there more then one type of seizure? Were all types of seizures captured with video-EEG?
Scalp EEG	Is the interictal focus focal or not? Is the ictal EEG localizing? Are there multiple ictal onsets?
MEG	Is there a predominant focus? Does it support the other data?
Intracranial EEG	Is the electrode placement adequate? Does the EEG onset precede behavioral onset? What is the relationship between the prior resection and the ictal onset? Is the localization concordant with the other information?
MRI	Were the proper sequences performed? Was the initial surgery complete? Is there evidence of a new lesion or surgical complication?
Functional imaging	Was an ictal hyperperfusion identified with SPECT?
Data synthesis/Surgical plan	How concordant is the data? Is there evidence for multifocal disease? Is the localization clearcut? Is a safe surgical procedure technically feasible?

Neurophysiology

Next, video-EEG monitoring is usually done. The diagnosis of epileptic seizures should be confirmed, since some have found de novo psychogenic seizures after epilepsy surgery.[14] The seizure description should be confirmed by analyzing ictal behavior with video monitoring. Behavioral analysis may yield valuable clues as to location of the remaining epileptogenic tissue. The interictal and ictal EEG need to be assessed and compared with the pre-operative data. This analysis may help reveal the location of the diseased cortex, defining the relationship between the prior surgery and the current ictal onset zones, and assessing whether new areas may be involved in seizure generation. Hennessy *et al.* presented data on 282 consecutive temporal lobe resections with a failure rate of 18%. On analysis of 44 surgical failures, 70% of the post-operative seizures were noted from the ipsilateral hemisphere in patients with mesial temporal sclerosis and in 64% of patients with non-specific pathology.[15] In the remaining patients, findings suggested either a contralateral focus or were inconclusive. However, EEG analysis is influenced by several factors. First, skull defects have been created which alter the potential field of both interictal and ictal EEG discharges. Second, changes in cerebral anatomy occur as a consequence of surgery. These may alter the field distribution of EEG potentials, so that the source of the discharges might be incorrectly identified. Lastly, removal of a portion of a lobe of the brain often results both in different propagation patterns of seizures and loss in amplitude of the ictal discharge in the region of prior surgery. These can lead to false lateralization or localization of ictal discharges. However, the location of the interictal spike often provides a clue as to whether the seizure localization is genuine, for it is uncommon for seizures to arise from the hemisphere contralateral to a prominent unilateral interictal spike focus.

MEG may serve a useful role when evaluating patients for reoperation.[16,17] MEG can identify interictal spikes, providing further definition to the irritative zone and the source localization is not altered by skull defects. Since MEG detects dipoles that are tangential to the EEG, spikes that are invisible to EEG are readily detected with MEG. Also, MEG can be used to identify sensory and language cortex; knowledge of these regions are helpful when planning surgery.

Imaging

Imaging studies play an important role in the evaluation process. The post-operative MRI scan must be reviewed to determine if the initial surgical plan was carried out successfully (i.e., the entire lesion and perilesional tissue was removed), and to determine if a surgical complication such as an infarct or hemorrhage occurred, or if a previously unidentified epileptogenic lesion was missed. To our knowledge, there is no extant literature defining the expected findings at the resection margin after epilepsy surgery. Therefore, in the absence of new lesions, it is difficult to know whether a small gliotic lesion adjacent to the prior resection constitutes a new epileptogenic lesion, or is benign post-operative gliosis. This might only be defined with electrophysiological techniques at a later time. Functional MRI (fMRI) may at times aid in presurgical investigation. It may be used to identify eloquent cortex, thereby guiding the surgeon and perhaps reducing operative morbidity. While fMRI has been used to study interictal spikes, this use is still investigational and not suited for clinical use.[18] PET-FDG scans are generally not useful after epilepsy surgery, since the resection produces a metabolic defect in the region of resection, and distant areas of diaschisis appear as well.

Synthesis and completion of evaluation

Once the non-invasive evaluation is complete, the data can be synthesized (Figure 149.1). The principles that apply at the time of initial evaluation are still valid when contemplating reoperation. Successful surgery usually relies upon multiple lines of evidence converging on a single location. Hence, one hopes to find that the preponderance of data indicates a single location. Reoperation can be considered provided one can generate a clear hypothesis as to why the first surgery failed and determine where the epileptogenic zone now lies. Often, the non-invasive data does not provide information that is sufficiently precise. In these cases, it is advisable to record seizures with intracranial EEG before performing additional resection. This enables confirmation of the location of proposed area to be excised, and permits mapping of cortical function, so that critical areas can be spared. Both interictal and ictal data are obtained with intracranial video-EEG monitoring; these can help define the boundaries of the resection. However, using intracranial EEG does not guarantee success, since it is but one tool, subject to many limitations and biases.

What strategy should be employed when using intracranial electrodes? Electrodes should be placed in any area that is reasonably suspected to be the source of seizures. A sufficient number of electrodes should be used to accurately define the cortex in which seizures originate and the initial spread patterns. One cannot know where seizures begin unless they can be shown to start focally in one area. Thus, it is mandatory that some electrode contacts not show ictal onset but instead show later ictal spread, and that the observed spread pattern logically derives from known anatomic connections. If there is a suspicion that seizures arise from more than one region of the brain, electrodes should be placed in both regions (Figure 149.2). This aids the physician in establishing whether a single epileptogenic zone exists, or if there are multiple areas that trigger seizures. If surgery is contemplated near eloquent cortex, then electrodes should be placed over relevant areas, so that vital functions can be mapped and the boundaries of resection defined.

Factors affecting outcome

Many of the initial reports[6,11] identified the presence of residual epileptogenic tissue as a favorable prognostic factor with regards to reoperative success. However many of these patients were operated before the widespread availability of MRI and advanced intraoperative navigation. Siegel *et al.*[12] assessed seizure outcome in 64 patients who underwent at least one additional surgery and found duration of epilepsy less then 5 years and focal interictal epileptiform activity as positive predictors. Holmes *et al.*[9] reported that data concordant with the prior resection imparted a good prognosis, while no patient with a CNS infection was rendered seizure free. The location of surgery, whether temporal or extratemporal, did not influence outcome after a second procedure. Salanova *et al.*[10] reported

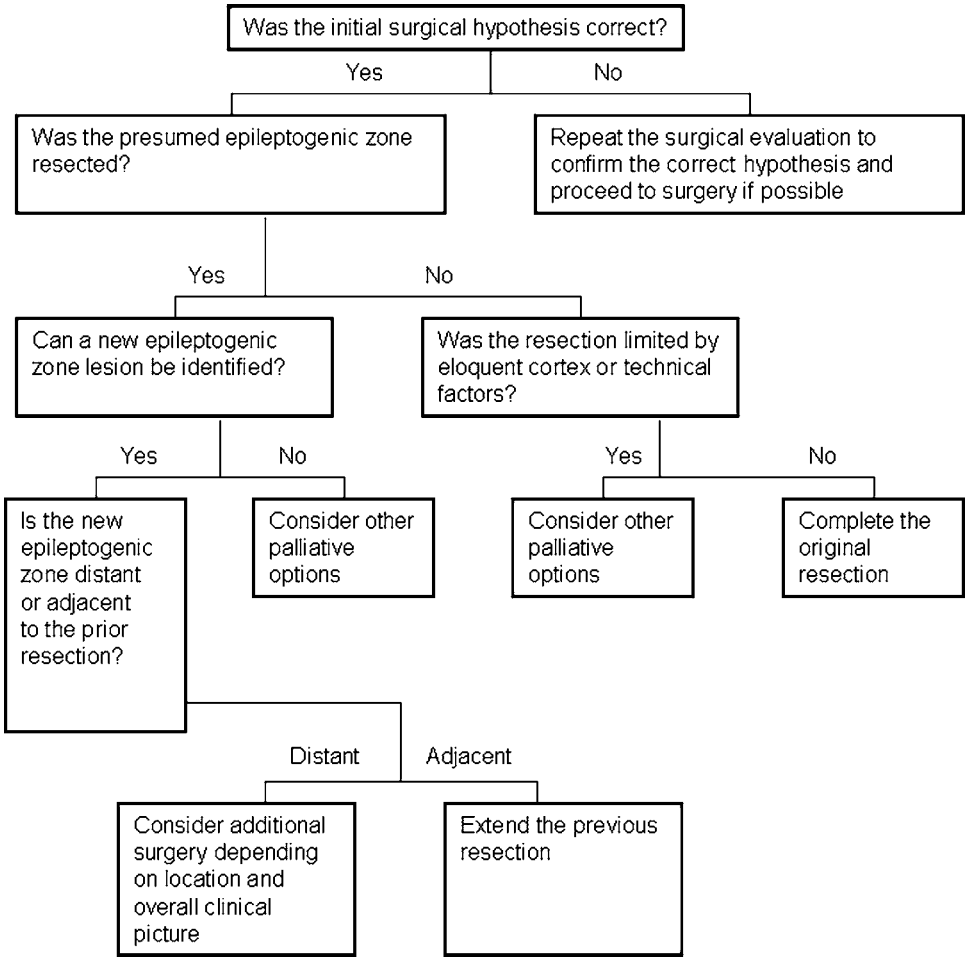


Figure 149.1 Flow chart demonstrating the typical decision algorithm when considering additional epilepsy surgery.

residual interictal epileptiform activity in the postresection electrocorticogram as a poor prognostic sign in patients with frontal lobe epilepsy. González-Martínez *et al.*[5] reported no relation between outcome and history of febrile seizures, CNS infections, seizure semiology, duration of epilepsy, or response to the first surgery. However, patients with tumors or dual pathology at the time of reoperation had a significantly better outcome compared with patients who had cortical dysplasia or mesial temporal sclerosis. Possible reasons for this include the inability to successfully image the entire extent of the cortical dysplasia and the possibility of the development of a contralateral mirror focus in the presumed normal temporal lobe. In an analysis of data from our center, we evaluated 30 patients who underwent reoperation in an attempt to determine if the response to the first surgery could predict the response to the second operation.[19] We found no relationship between response to the first surgery and the outcome of the second surgery. We also found no difference in outcome between temporal versus extratemporal resections or extension of a prior resection compared to resection within a different region.

Illustrative cases

Case 1

A 29-year-old right-handed woman developed complex partial seizures after the birth of her third child. The seizures were described as beginning with an ineffable feeling for several seconds followed by a loss of consciousness. She then had a look of terror on her face, afterward becoming unresponsive with late right-sided clonic activity. She had 4–5 seizures per month despite appropriate medical therapy. Four years after onset of her epilepsy, she had a left anterior temporal lobectomy based on a scalp evaluation. Seizures stopped, and her antiepileptic medication was discontinued 1 year after surgery. Her seizures recurred 6 years after the initial resection, coinciding with the birth of her sixth child. Despite medical therapy she remained refractory and experienced 3–4 complex partial seizures per month.

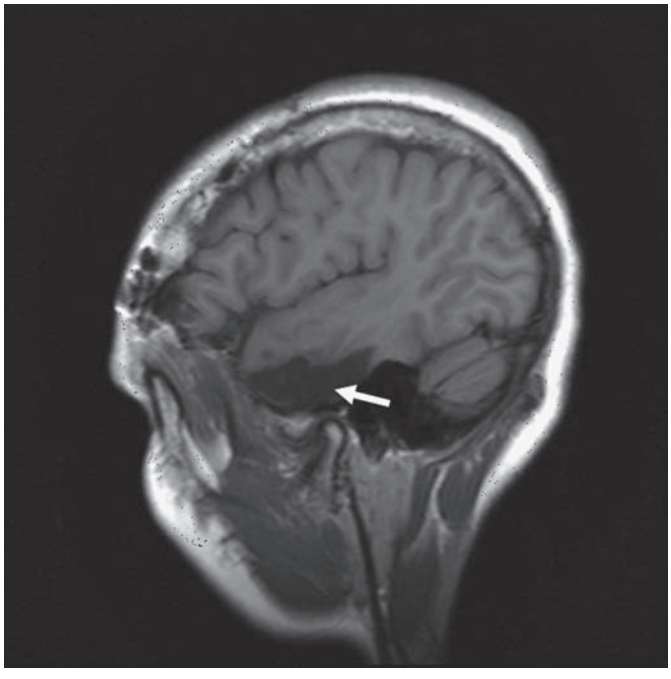
Repeat evaluation

Semiology: She had the same aura as before surgery and loss of consciousness, but the look of terror and right sided clonic activity late in the seizure were not present.

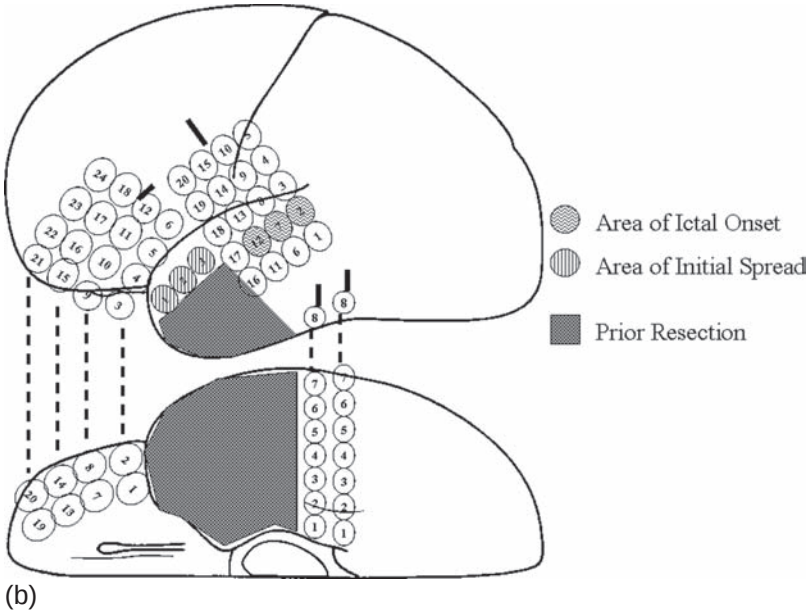
Scalp video-EEG: The interictal EEG showed left temporal continuous theta slowing and rare right sphenoidal sharp waves. The ictal EEG revealed a right sphenoidal ictal onset with rhythmic theta spiking. Semiology was consistent with an automotor seizure with loss of consciousness.

MRI: This showed the prior left temporal resection, with 1 cm hippocampal resection and 4.5 cm lateral temporal resection.

Neuropsychological testing: This showed average visuospatial memory and poor verbal memory.



(a)



(b)

Figure 149.2 (a) Saggital T1-weighted MRI revealing the prior area of resection (white arrow) in a patient with medically refractory aphasic seizures. Note the superior temporal gyrus was spared. (b) Representation of the intracranial implant with inferior frontal, orbitofrontal, lateral temporal and basal temporal subdural electrodes covering the possible epileptogenic regions. Ictal onset was noted behind the resection margin with rapid spread to the anterior superior temporal gyrus. No language function was identified within these regions with electrocortical stimulation. The patient had the superior temporal and middle temporal gyrus resected beyond the ictal onset.

Surgical plan

The patient initially had left temporal lobe epilepsy which had responded to a left temporal resection with a limited mesial resection. However, the re-evaluation EEG data suggested an irritative zone and ictal onset zone within the right anterior temporal lobe. There are two main possible explanations for this. Either she still had left mesial temporal lobe epilepsy with preferential spread to the right temporal lobe due to the prior resection, or developed a new epileptogenic zone in the right temporal lobe. Less likely, an orbitofrontal epileptogenic zone had developed. To address these possibilities the patient was implanted with depth electrodes in the hippocampus and subdural strip electrodes in both left and right temporal lobes. In addition, orbitofrontal subdural strip electrodes were placed bilaterally.

Results

With intracranial video-EEG monitoring, the patient had four complex partial seizures arising from the right anterior hippocampus and six subclinical seizures arising from the left

posterior hippocampus. Due to the bilateral nature of her disease and the predominance of clinical seizures now emanating from the right hippocampus, she was not offered further resection. This case illustrates the potential for progression of disease which can occur in epilepsy and the need to consider the development of de novo epileptogenic zones after failed epilepsy surgery.

Case 2

A 53-year-old right-handed woman developed epilepsy at age 12. She initially had nocturnal generalized tonic-clonic seizures occurring 1–2 times per year despite medical treatment. Then, at the age of 27, she was involved in a motor vehicle accident which resulted in abdominal trauma, but she denied CNS trauma. However, after this accident she developed complex partial (automotor) seizures. Observers now reported a sudden loss of awareness which occurred without a warning. She then looked fearful, having hand and verbal automatisms. Despite medical treatment, she continued to have 2–4 seizures per week while the generalized tonic-clonic seizures continued at 1–2 per year.

First evaluation

Video-EEG: The interictal EEG showed right and left sphenoidal sharp waves, with 10 right-sided sharp waves for every one on the left. The ictal semiology was as described above. Ictal EEG showed bilateral attenuation of background frequencies at onset and then either an independent right or left temporal seizure discharge.

MRI: This showed increased T2 signal in the left temporal-occipital gyrus, located 5 cm from the temporal tip.

Neuropsychological testing: This showed impaired naming and verbal memory.

Wada test: This showed left hemisphere dominance for language.

Initial surgery

The patient had intracranial video-EEG monitoring using bilateral mesial temporal depth electrodes and bilateral temporal lobe subdural strips. The interictal EEG data revealed bilateral hippocampal and amygdala epileptiform activity. Multiple complex partial seizures were recorded with left posterior hippocampal onset followed by spread to the right temporal lobe in 15–30 seconds. She then had a left anterior temporal lobectomy. After surgery, she continued to have 1–2 complex partial seizures per week and the frequency of generalized tonic-clonic seizures increased to once per month.

Repeat evaluation

Neuropsychological testing: This showed significant verbal memory decline and severe anomia compared to the pre-operative data.

MRI: This showed residual left basal temporal T2 signal hyperintensity within the temporo-occipital gyrus.

Video-EEG: This was not performed since the seizure semiology had not changed and the patient had a residual structural lesion.

Surgical plan

The patient was taken back to the operating room approximately 1 year after the first surgery with resection of the residual basal temporal lesion.

Results

The patient had three possible seizures several months after the second operation, and has been seizure free for the next 19 years. Her neuropsychological measures improved after her second surgery, with resolution of the anomia and improvement in verbal memory. Multiple follow-up EEGs have been devoid of epileptiform activity. This case illustrates the need to completely excise an epileptogenic lesion and that extensive basal temporal resection can be performed safely in the dominant hemisphere with improvement in neuropsychological functioning if seizures can be abolished.

Conclusion

Epilepsy surgery is an effective option for many patients with medical refractory epilepsy, but current techniques do not assure a successful outcome. Further surgery may be possible in individuals who fail to fully respond, and approximately half benefit from reoperation. However, better tools and prognostic indicators must be devised to help guide the reoperation and predict which patients are apt to benefit. Until then, an individualized approach must be employed. The evaluation should aim at developing a reasonable hypothesis regarding the location of the remaining epileptogenic cortex, devising a safe strategy for intracranial investigation should this be needed, and planning an effective operation that minimizes the chances of producing a neurological deficit.

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150 Reoperation after failed epilepsy surgery

A Boongird, JA González-Martínez, and WE Bingaman

Introduction

Surgical failure is defined by the inability of surgical intervention to accomplish the surgical goals, whether they are diagnostic or therapeutic in nature. Diagnostic procedures include subdural and/or depth electrode implantations for identification of epileptic tissue, while therapeutic procedures can be subdivided into those which may improve seizures (palliative) and those intended to stop seizures (curative). The seizure freedom rate after a palliative procedure such as vagal nerve stimulator (VNS) implantation is considerably low.[1–3] Residual seizures after VNS implantation therefore would not necessarily be considered a 'surgical failure'. In contrast, resective surgery for a focal epilepsy carries a much greater chance for curing seizures, especially if there is an associated lesion on neuroimaging.[4]

The term 'surgical failure' in resective cases is defined in this chapter as persistent or recurrent seizures after resective epilepsy surgery. Surgical failure rates for common epilepsy surgery procedures such as selective amygdalohippocampectomy or standard anterior temporal lobectomy are well characterized in the literature, with many reports citing widely varying outcomes after resective surgery. These outcomes seem to differ widely from center to center based on underlying substrate, surgical experience and method, outcome grading scheme used, and volume of cases. It is not the aim of this chapter to validate surgical therapy for epilepsy, but rather to explore some common reasons for failure and the potential for improving seizure control with re-operation in selected patients.

Additionally, the time-period for diagnosis of surgical failure needs some consideration. Early versus late recurrenceof seizures is poorly understood. In general, surgical failure should be defined as identification of seizure(s) following the operation, with persistence of habitual seizures perhaps the most important criteria for clinical diagnosis of surgical failure.[5] Prediction of surgical failure differs from patient to patient and should be individualized to the clinical scenario. The 'running down phenomenon' should be kept in mind, especially in patients experiencing major effects on clinical seizures.[6–8] Siegel *et al.* reported 8 of 64 patients that were initially free of seizures after the first surgery for a mean of 4.6 years, followed by late recurrence and reoperation.[9] Other studies also confirm the decreasing success of epilepsy surgery over time.[10] These results underscore the necessity of long-term follow-up after surgery for epilepsy.

Frequency of surgical failure and reoperation

The incidence of surgical failure is different from center to center because of referral bias, criteria for defining surgical success, number of cases, and different surgical experiences and strategies. Munari *et al.* reported 131 of 344 (38%) patients having persistence of seizures immediately after operation. This number might be lower if using different criteria to define outcome.[11] The incidence of surgical failure was also reported in relation to specific locations of surgery. For example, Hennessy reported 51 of 282 patients (18.1%) experiencing persistent or recurrent seizures following temporal resections.[12]

The incidence of reoperation reported varies from 4.3–14%, depending on individual center practices.[9,13,14] Diagnostic procedures are also associated with a chance for failure. Experience at our center from January 1997 through June 2005 included approximately 1440 epilepsy operations, in which 250 procedures were diagnostic, 190 procedures palliative, and about 1000 procedures for curative aims. Among 234 cases of subdural electrode evaluation and 17 cases for bilateral temporal depth electrodes, 30 patients (12%) underwent subdural electrodes removal without surgical resection and ten cases underwent depth electrodes removal without resection.

Surgical failure after resective surgery remains challenging. At our institution, among 1000 resective operations within the same period of study, about 15% of patients still experience persistence of disabling seizures after the first surgery. Ninety-two patients underwent reoperation and within this group, 26 patients (28%) were referred from outside institutions for further evaluation and management. Although these numbers are in line with other published reports on reoperation after failed epilepsy surgery, the true frequency of failure and success after reoperation will remain unknown until the epilepsy community has a standardized method of defining and recording outcomes. In this regard, a national database specific to outcomes after epilepsy surgery is needed.

Possible causes of surgical failure and the surgical approaches for reoperation

For diagnostic procedures, the two main reasons for failure to localize the epileptogenic zone (EZ) are the diffuse nature of specific types of intractable epilepsy syndromes and the anatomical limitations of electrode implantation (insular cortex,

interhemispheric surfaces, posterior basal orbitofrontal region). The first may be considered a failure in the preoperative evaluation and most often occurs due to the clinician's inability to accurately localize the epileptogenic zone. The second is surgical technique related and potentially avoidable. The possibility of combined depth electrode and subdural electrode implantation may be a better method in approaching these difficult anatomical areas. Alternatively, stereoelectroencephalography may be a better method for accessing difficult to access or more widespread cortical regions.[15]

Incorrect localization of the epileptogenic zone

During the presurgical work-up, the epileptologist formulates a hypothesis of the epileptogenic zone by using clinical semiology, neurophysiology, and anatomical and functional neuroimaging. Non-lesional cases and those with discordant data require assumptions based on the interpretation of preoperative data. In most of these cases, further diagnostic invasive recording is necessary prior to establishing surgical resective candidacy. With these particular cases, surgical failure has been reported as higher compared to the more straightforward lesional case.[16] When the preoperative data is discordant and/or there is no lesion present to steer surgical resection, the chances of incorrect localization or perhaps better termed incomplete characterization of the epileptogenic zone is more likely.[16] Additional reasons for incorrect localization of the epileptogenic zone include misinterpretation of preoperative data and presence of dual pathology on imaging.

The following clinical example helps to demonstrate how incorrect characterization of the EZ might occur. In case 1, clinical semiology starts with an aura of 'a scary feeling in my chest' or a hard-to-describe sensation for seconds to a few minutes. This is followed by elevation of both arms and legs with tonic stiffening. Typical seizure duration is 20–30 seconds. Seizures occur mostly out of sleep, about 2–20 times per night. Neurophysiology revealed interictal sharp waves in the right frontotemporal region and non-localizable ictal onset. Magnetic resonance imaging (MRI) of the brain revealed a slightly hyperintense area on fluid-attenuated inversion recovery sequences at the depth of the right inferior frontal sulcus, most likely reflecting a malformation of cortical development. Because of the semiology, lack of electroencephalographic (EEG) ictal onset, and potential for a widespread malformative lesion, invasive mapping was recommended. Two 8×8 subdural electrodes (covering right fronto-parietal convexity area, including the abnormal area) were used for invasive monitoring. The mesial frontal regions were not covered. The EEG onset was characterized by diffuse attenuation of the background activity and was simultaneous to the clinical onset. Focal EEG changes were seen no earlier than 1–2 seconds after the clinical onset when beta-range rhythmic discharges arose from posterior fronto-temporal electrodes and evolved into repetitive spike waves over the adjacent area (Figure 150.1).

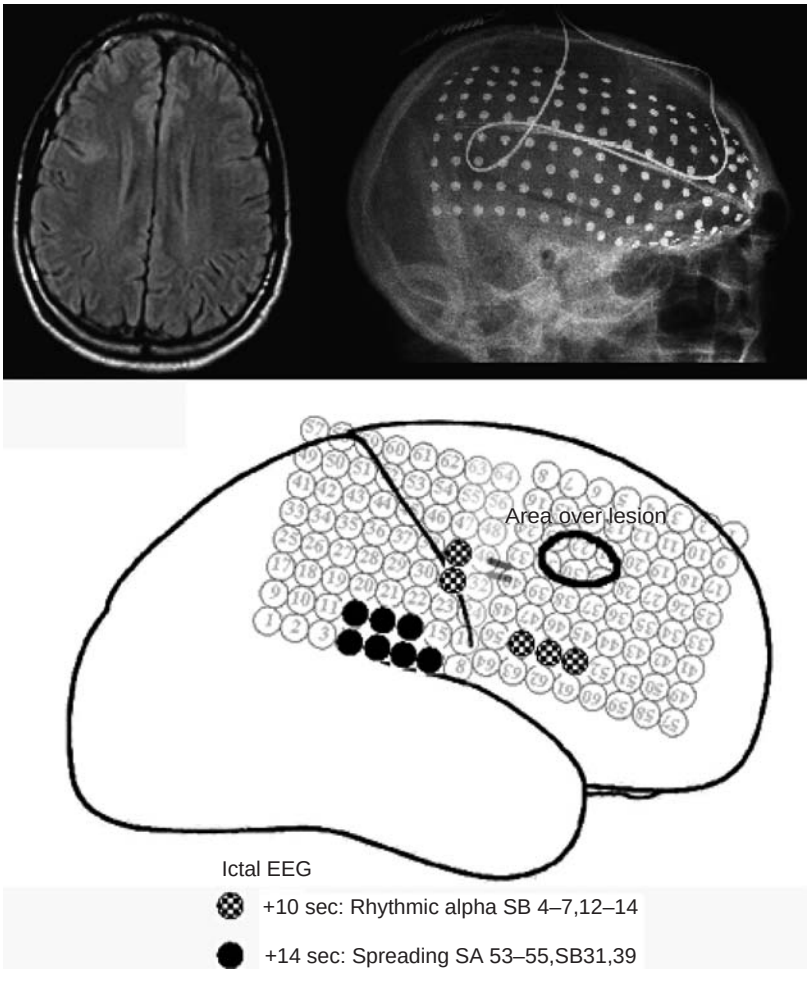

Figure 150.1 Demonstrating the lesional MRI and ictal EEG findings in relation to the area of the overlying lesion.

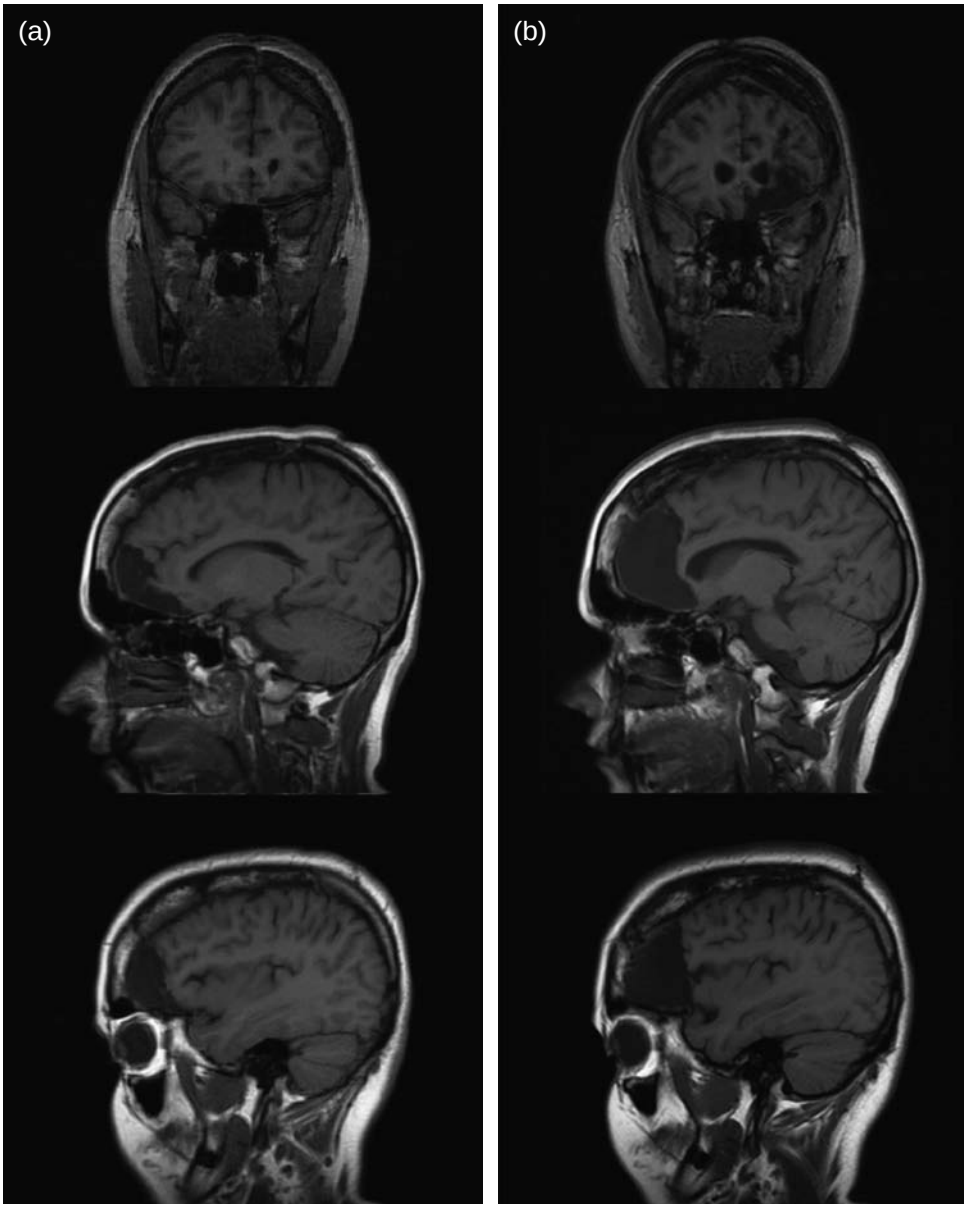

Figure 150.2 Comparison of extent of left orbito-frontal resection between two operations. a. Initial frontal resection based on invasive recording data, b. Second resection of additional cortical tissue in region of initial resection.

The case illustrated demonstrates several salient points that may lead to the incorrect localization of the EZ and thus reduce the chances of a seizure-free outcome. First, the EZ may be more widespread than the lesion, when present. Similarly, the EEG data gathered via scalp or invasive recording may also not correlate with the lesion and/or the EZ. Surgical limitations in the number and location of invasive electrodes implanted may influence the data gathered and the hypotheses from this data. Finally, when a lesion is present (especially cortical malformations) it may or may not coincide with the EZ. In the final synthesis of data and operative plan, the epileptologist and surgeon must decide on the extent of tissue that needs to be removed and it is this human factor where likely most incorrect localizations of the EZ occurs.

As mentioned earlier, surgical accessibility to some cortical regions is limited, especially for surface electrodes (subdural recordings). For example, the mesial frontal and parietal regions, cingulate gyri, orbital frontal, and mesial temporal areas are difficult to access in a comprehensive fashion because of the size and inability to directly visualize the areas of interest. Figure 150.2 is an example of left basal frontal lobe epilepsy with a seizure free outcome achieved after two resections in the same region. This patient experienced a recurrence of habitual hypermotor seizures 3 months after undergoing an initial resection of left orbito-frontal cortex identified by an invasive subdural electrode evaluation. Following seizure recurrence, more extensive resection of the same cortical area under awake conditions led to long-term seizure freedom. Pathology revealed malformation of cortical development from both specimens.

Due to the limitations of subdural electrode evaluation in specific areas of the brain as previously described above, the combination of subdural electrodes and depth electrodes may play a role for improved localization of the epileptogenic zone (Figure 150.3). In this example, the patient had a right posterior frontal seizure onset with a normal MRI. Implantation of

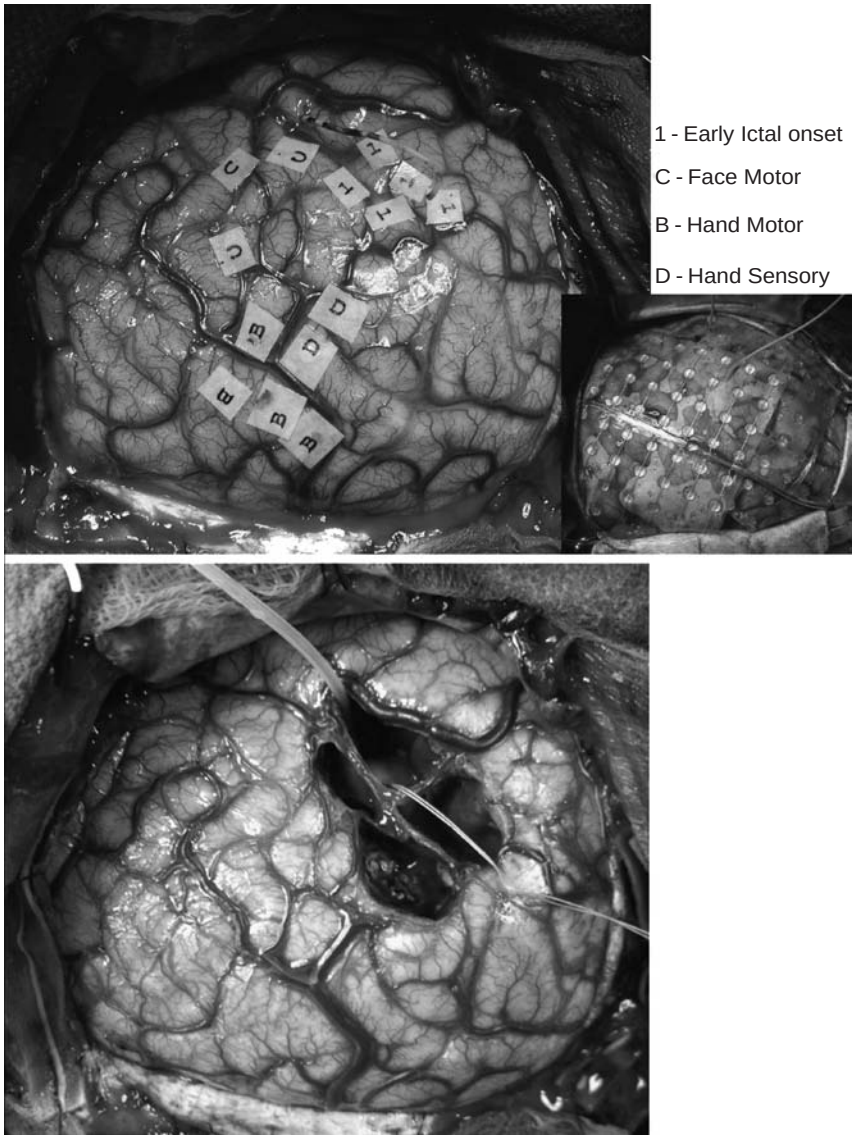

Figure 150.3 Demonstrates the combination of subdural and depth electrodes for an extraoperative brain mapping (upper photo) and intraoperative electrocorticography (ECoG) of the insular lobe (lower photo) during the resection.

a combination of surface electrodes and intra-cortical electrodes in the insular cortex were utilized to document an insular ictal onset with an early spreading pattern to the surface subdural electrodes. The pathology report showed malformation of cortical development (MCD). The patient experienced seizure freedom after surgery.

Limitations in the epileptogenic zone surgical resection

The epileptogenic zone may involve eloquent cortex and resection of such may possibly lead to a permanent neurologic deficit. Invasive monitoring with subdural electrodes can provide information defining epileptic cortex and functional cortex and may lead to potential surgical extirpation of the epileptogenic zone. Despite accurate functional mapping, surgery in and around eloquent cortex carries risks of neurologic decline and this must be adequately discussed with patients and families prior to surgical treatment. Despite these risks, surgery can be performed with minimal deficits in some areas of sensorimotor cortex. For example, if the seizure onset zone arose from the sensorimotor face area, surgery can be performed without significant permanent neurological deficit.[17] Multiple subpial transections (MST) can be performed on the eloquent cortex in selected cases. The Yale group reported a 42% seizure frequency reduction after MST.[18] Other surgical options including vagal nerve stimulation (VNS), responsive cortical stimulation, and deep brain stimulation (DBS) can be considered for palliative aims.

Example 2

Left central lobe intractable epilepsy arose from a malformation of cortical development (MCD) involving motor and language cortex Figure 150.4a. A partial lesionectomy with preservation of hand function after invasive monitoring did not alleviate seizure frequency or severity Figure 150.4b. Other options including vagal nerve stimulation and deep brain stimulation targeting the subthalamic nucleus were performed in an attempt to stop the epilepsia partialis continua that developed after the biopsy procedure. Eventually a

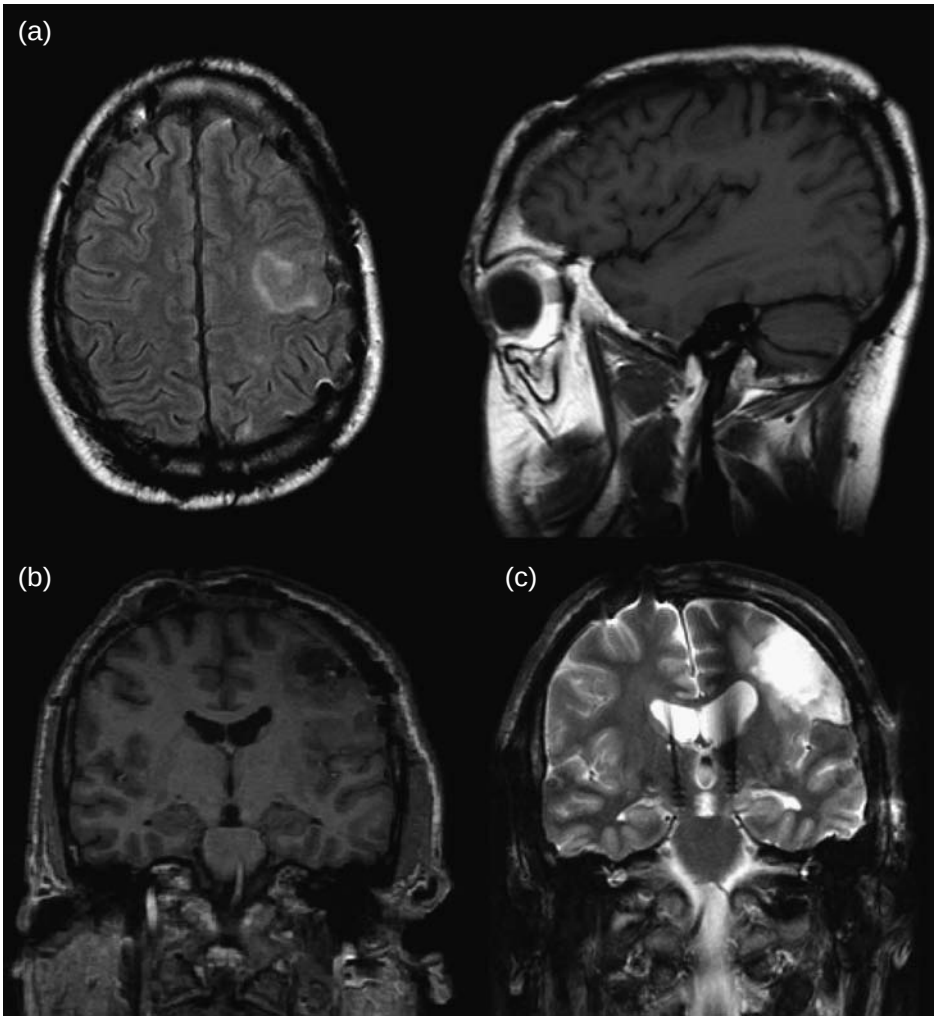

Figure 150.4 a Preoperative MRI of left frontal lobe malformation of cortical development. b. MRI after biopsy procedure, c. final postoperative resection.

lesionectomy completely removing the abnormal cortex was undertaken with successful cessation of the seizures Figure 150.4c. Postoperatively the patient had a significant right hemiplegia and motor aphasia. Recovery of ambulation and language occurred over 12 months. His hand function remains with poor fine motor control.

Postsurgical extension of the epileptogenic zone

Postsurgical processes in the epileptic brain are poorly understood. Cortical re-organization, kindling, and maturation or extension of the epileptogenic zone are processes potentially explaining seizure recurrence. Rasmussen reported the latent period between brain injury and onset of recurring seizures can vary from a few months up to decades.[8] The underlying mechanism of this latent period is still unknown.

Most of the epileptic processes occur in the region of the previous area of pathology such as tumor recurrence, signal changes in MCD, maturation of cortical scarring. However, secondary epileptogenicity can arise from remote areas within the network such as the contralateral hippocampus. For example, Hennessy reported 25% of surgical failures in mesial temporal sclerosis cases had seizure onsets exclusively in the contralateral temporal region.[12]

Weiser reported a patient seizure free for 11 years following stereotactic amygdalotomy who then experienced recurrent complex partial seizure arising from the residual hippocampus. Hippocampectomy regained seizure freedom for at least 9.5 years.[19] This example may indicate a new seizure type arising from a new epileptogenic zone or maturation of the previous epileptogenic zone.

Incomplete resection or disconnection of the epileptogenic zone

Penfield and Jasper first described the role of residual hippocampus resection for the treatment of surgical failure in temporal lobe epilepsy.[20] Rasmussen revealed 45% of 121 patients had remarkable seizure reduction after further cortical excision.[8] Many series confirmed the role of residual epileptogenic lesion removal and long term seizure freedom.[21–23] Surgical resection, if possible, for dual pathology with proof of independent foci should be recommended for long-term seizure freedom.[25] For curative or palliative aims following hemispherectomy, an incomplete disconnection can be the reason for persistence or recurrence of seizures. Postoperative MRI provides useful information for incomplete anatomical disconnection (Figure 150.5). Electroencephalography (EEG) can be difficult to interpret especially following functional

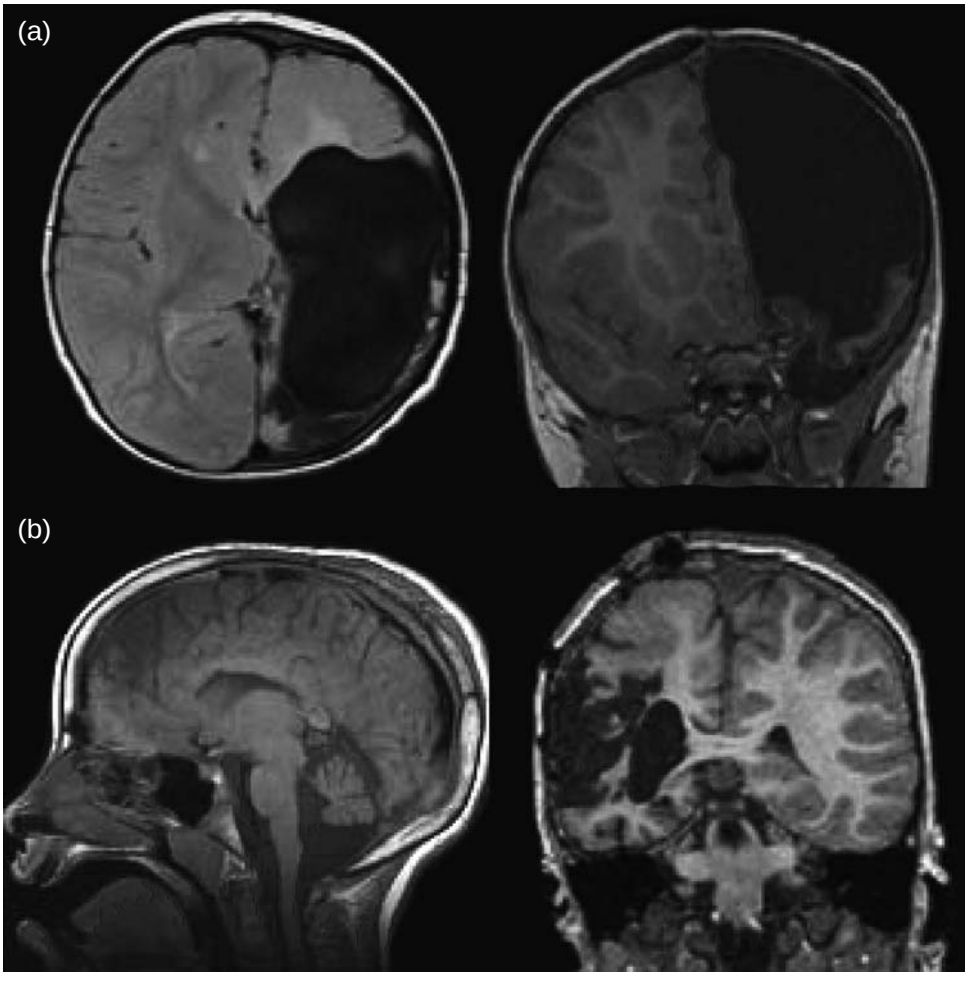

Figure 150.5 Demonstrates two cases of incomplete corpus callosum disconnection causing recurrence of disabling seizures at 6 months and 2 weeks respectively following the first surgery (a – Genu area, b – Splenium area).

hemispherectomy. Clinical semiology is very helpful to determine whether or not the seizure onset is arising from the previously resected hemisphere.

Technical difficulties and complications of using invasive electrodes in reoperation

Foramen ovale electrodes

The electrodes are placed at base of middle fossa (extracranial). Previous intracranial surgery should not be a contraindication for the placement of these electrodes.

Subdural electrodes

The main surgical difficulties for placement of subdural electrodes in previous surgery are dural adhesions with the cortical vessels and distortion of anatomical landmark structures. Careful sharp dissection is necessary, especially when opening adhered dura over major cortical vessels (sylvian fissure). The risk of bone flap infection is also higher in reoperated cases. Watertight dural closure should be accomplished in order to reduce the incidence of CSF leak and postoperative meningitis. Intensive care unit stays during the first 24 hours are routinely recommended for serial neurological examination.

Depth electrodes

Invasive depth electrodes in re-operation cases may carry higher risk of bleeding because of adhesions and anatomical distortion. Depth electrodes should be inserted utilizing stereotactic guidance while observing the precautions of any stereotactic procedure (minimizing crossing of pial planes, avoiding traversing CSF spaces, etc.).

Other technical difficulties

The key to reducing complications during redo-surgery is to find reliable anatomic landmarks in order to orient the surgeon, for example pericallosal artery and corpus callosum. Surgical navigation helps in areas where reliable landmarks are not readily identifiable such as identification of perirolandic cortex and anatomic language areas. Issues that affect stereotactic navigation such as brain shift should be kept in mind as possible technical limitations.

Re-operation in vagal nerve stimulation

The risk of vagal nerve injury may be higher for redo VNS surgery. The main reasons for reoperation are infection and lead failure identified by high lead impedance during device interrogation. Exploration and/or removal or revision of the electrode is often hampered by adhesions and scarring around the

vagus nerve. Redo VNS should be carefully performed under loupe magnification with normal nerve identified above or below the previous operative site. Macdonald recommended using microsurgical dissection for complete removal of the helical electrode from the vagus nerve without apparent physiological consequences.[26]

Outcome of re-operation and its complications

The overall seizure-free outcome for lesionectomy is reported as 70–80%.[23,27] Seizure-free rates after re-operation were described from 20–60%.[9,28–30] The surgical strategies of re-operation for surgical failure vary across individual patients and epilepsy centers. However, two aspects of surgical outcome after re-operation were reviewed. The first aspect is the location of reoperation, which is sub-classified into intralobar resection (same lobe as the first operation), multilobar resection, and distant resection. Shaver reported a 62% seizure-free rate for intralobar resection as compared to 44% seizure-free rate for distant resection or multilobar resection.[29] The second aspect is imaging, which is sub-classified into non-lesional, single lesion, and multiple lesions.

For temporal lobe surgery, residual mesial structures were commonly reported as a cause of surgical failure during the early 1990s. Intralobar resection for residual mesial structures may accomplish a 50–60% seizure-free rate.[21,22,31] Tailored resection based on neurophysiological data and/or functional mapping can be an ideal surgical option for re-operation especially in the dominant hemisphere.[32] Intraoperative hippocampal electrocorticography was also reported for tailored hippocampal resection to maximize seizure-free outcome while leaving a portion of the hippocampus insitu. Hennessy reported 70% of mesial temporal sclerosis had postoperative seizures arising in the same hemisphere of the resection with 85% of those arising from nearby temporal lobe regions. Interestingly, neocortical seizure onset was more frequently found than residual hippocampal seizure onset. Dual pathology was reported in up to 15%, especially in patients with congenital lesions.[33] As our technology improves, the causes of surgical failure may be shifting from technical operative failures to different causes such as large epileptogenic zones, dual pathology, recurrence of tumor, and limited ability for resection to preserve function.[28] Salanova reported the unfavorable factors after reoperation in temporal lobe surgery including a history of head injury or encephalitis and posterior temporal localization. Predictors for favorable outcome after re-operation included anterior temporal localization and abnormal imaging studies.[14]

For frontal lobe epilepsy, Salanova reported 39 of 284 (14%) patients underwent re-operation with a 20% seizure-free rate. The main cause of surgical failure was a large epileptogenic zone, which was demonstrated by residual postresection electrocorticographic spikes.[13]

Re-operation after hemispherectomy had been reported in a few series. Cortical dysplasia is the most common pathological substrate of surgical failure.[34,35] In these cases, a more complete tissue removal operation such as tailored anatomical hemispherectomy may be a better surgical option at the first surgery.[35] In cases of surgical failure after functional hemispherectomy, residual tissue was commonly found at the basal posterior frontal and insular regions. Surgical removal of the residual tissue, especially if it is dysplastic should be considered for maximal seizure-free outcome.[36] The risk of developing postoperative hydrocephalus should be considered for anatomical hemispherectomy.

Acknowledgment

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SECTION 21

Case presentations

151 Lesional mesial temporal epilepsy case discussions

J Mani and IM Najm

Introduction

Lesional mesial temporal epilepsy is by far, the commonest cause of medically intractable partial epilepsy. Mesial temporal sclerosis (MTS) has been identified as the most frequent pathological feature in surgically treatable mesial temporal lobe epilepsy. Mesial temporal epilepsy (mTLE) syndrome is also the epilepsy most frequently associated with drug resistance. It has very good surgical prognosis in suitable candidates.

The establishment of surgical candidacy requires the unambiguous demonstration of the mTLE syndrome associated with MTS, by comprehensive presurgical evaluation.

In this chapter we document the case stories of two patients with mesial temporal sclerosis who had presurgical evaluation followed by surgery, one of the non dominant temporal lobe and the second of the dominant temporal lobe.

Patient 1: clinical details

History

Seizure description and frequency

Ms LN, a 38-year-old, right-handed woman was evaluated for intractable seizures. Her seizure history goes back about 20 years when she developed auras, which she described as a déjà vu sensation occurring about once or twice per month, invariably around her menstrual period. These were brief sensations, lasting 10–15 seconds of familiarity in unfamiliar situations. She took no notice of these events until about a year ago.

Over the 18 months prior to her evaluation, the episodes changed in character. The more recent subjective sensations consisted of a hot flushed feeling in the head with a sensation of *déjà vu* that progressed to loss of awareness. Observers had noted reduced responsiveness with rolling movements of her finger tips, with drooling and chewing. Ms LN had no recollection of this however, and the last event that she remembered of her seizure was the *déjà vu* sensation.

Seizures clustered around her menstrual period, occurring about three to five times a month. There was no history suggestive of a generalized motor seizure, though she did lose control of her urine in one of the episodes.

Between events, Ms LN is in good health. Seizures continued despite two antiepileptic medications in therapeutic doses, Carbamazepine 1200 mg/day and Levetiracetam 2500 mg/day. LN complained of excessive sleepiness on these medications. She had previously been tried on Lamotrigine and Acetazolamide without success.

Medical history and epilepsy risk factors

Perinatal history was notable for neonatal blood transfusion due to Rhesus incompatibility. There was no report of febrile seizures, intracranial infection, or significant head injury. Family history was remarkable in that LN's brother had a single febrile seizure.

Social history

Ms LN had recently lost two jobs in quick succession and was unemployed. She lived with her husband and three children.

Clinical examination

The general physical and neurological examination were unremarkable

Brain imaging

Magnetic resonance imaging (Figure 151.1a, b)

Brain magnetic resonance imaging was performed on a 1.5 Tesla Siemens SP Scanner (Erlangen, Germany). T1-weighted coronal images showed bilaterally small hippocampi with increased signal in the right hippocampal body on FLAIR sequences.

Positron emission tomography (Figure 151.2)

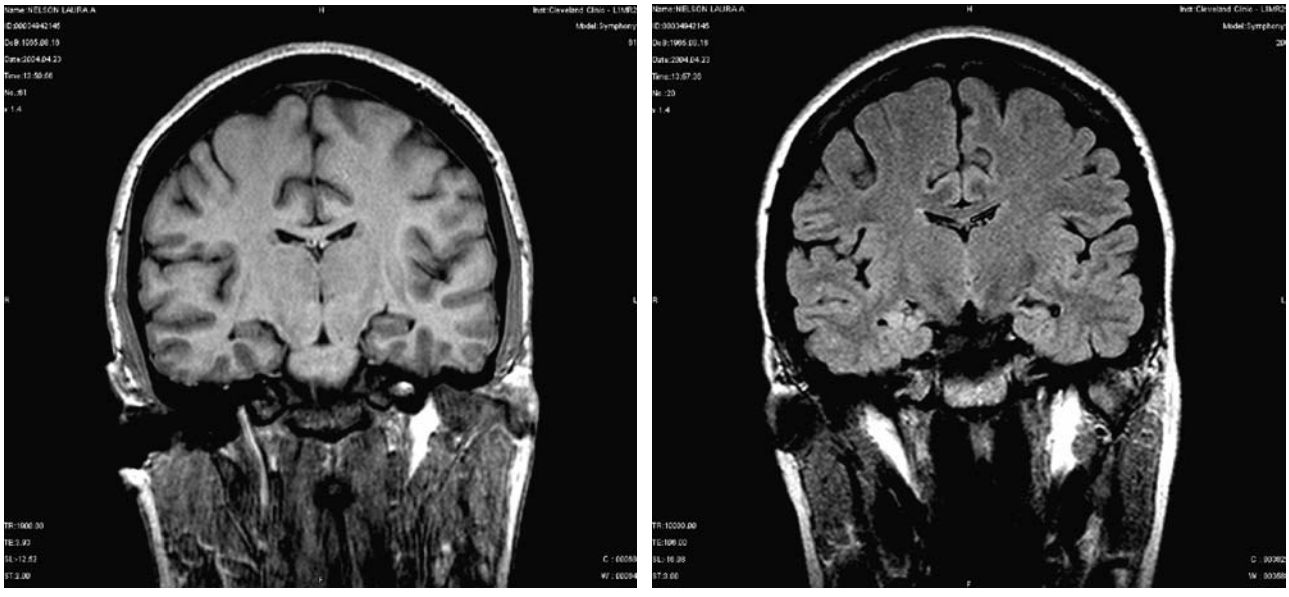
PET study showed reduced Fluorodeoxyglucose uptake in the right mesial temporal structures.

Electrophysiology

A 20 minute scalp EEG did not reveal any epileptiform activity.

Video EEG monitoring

Ms LN underwent video-EEG evaluation after withdrawal of antiepileptic drugs using the 10–20 system of scalp electrode placement with additional 10–10 coverage over the bitemporal regions and with sphenoidal electrodes.



(a) (b)

Figure 151.1 Coronal images through the body of the hippocampi showing biolaterally small hippocampi (T1) with increased signal (FLAIR) in the right hippocampus consistent with predominant right hippocampal sclerosis.

Interictal activity (Figure 151.3a, b)

Runs of intermittent slow activity at 3–4 Hz lasting 3–4 seconds were noted in the right temporal region. These runs were more frequent in drowsiness. Sharp waves were exclusively right temporal with maximum amplitude at the sphenoidal (SP2) electrode.

Ictal activity

Clinical seizure: aura- automotor seizure (loss of awareness)

Five typical seizures were recorded over a period of 24 hours. All the episodes were stereotyped. LN recognized an aura and pushed the button at seizure onset. She was able to declare verbally that she was 'having an aura'. She then had florid mouth and bilateral hand automatisms but continued to follow some verbal and nonverbal commands during the early phase. She was able to appropriately verbalize her name when asked, during the early phase despite the oral automatisms. She subsequently became confused and partially unresponsive during the late phase of the seizure. Immediately after the end of the seizure, LN was able to describe the aura which she called a 'hot flush that spread across her head' with increased salivation. However, she has no recollection of the events after the aura. No postictal tiredness or confusion was noted. The average duration of the clinical event was approximately 1 minute.

This type of seizure would be described under the ILAE system as a *simple partial seizure that evolved into a complex partial seizure*. Under the semiological classification system this would be described as *cephalic aura- automotor seizure*.

The seizure semiology is consistent with temporal lobe involvement, but has no clear lateralizing motor features. However, the preserved awareness and appropriate verbalization during the early phase are consistent with a nondominant temporal lobe origin.

EEG seizure (Figure 151.4a, b)

The ictal pattern on EEG began with rhythmic sharp waves at 1 Hz over the right temporal region, maximum at the sphenoidal electrode. These evolved into rhythmic spikes at 3–4 Hz that then evolved into a sharply contoured theta rhythm (6 Hz) that increased in amplitude but remained localized to the right anterior temporal region without contralateral spread. The clinical and EEG onsets were simultaneous. The duration of the seizure was approximately 60 seconds.

Neuropsychology

Preoperative neuropsychological assessment using the Wechsler Adult Intelligence and Memory Scales III edition revealed a full Scale IQ 118; 116 on the verbal measure, 117 on the visual measure. Verbal memory scores were 111 for the immediate and 99 for the delayed with a delayed recognition score of 90. Visual immediate and delayed scores were 106 and 97, respectively.

Analysis

In summary, data from presurgical evaluation was concordant for a right mesial temporal epileptogenic zone. Seizure semiology was consistent with nondominant temporal lobe origin. Déjà vu sensations that LN reported are commonly associated with epilepsies of the temporal lobes. Isolated auras are reported to be highly specific of mTLE,[1] and in general, are more common in right TLE.[2,3] Oroalimentary and hand automatisms are typical signs in TLE. Preserved ictal consciousness despite involuntary automatisms is a rare finding, but is strongly associated with the primary epileptogenic zone in the nondominant hemisphere.[4] Electrophysiology clearly demonstrated the irritative zone to be in the right temporal lobe, in view of the stable morphology and distribution of the right anterior

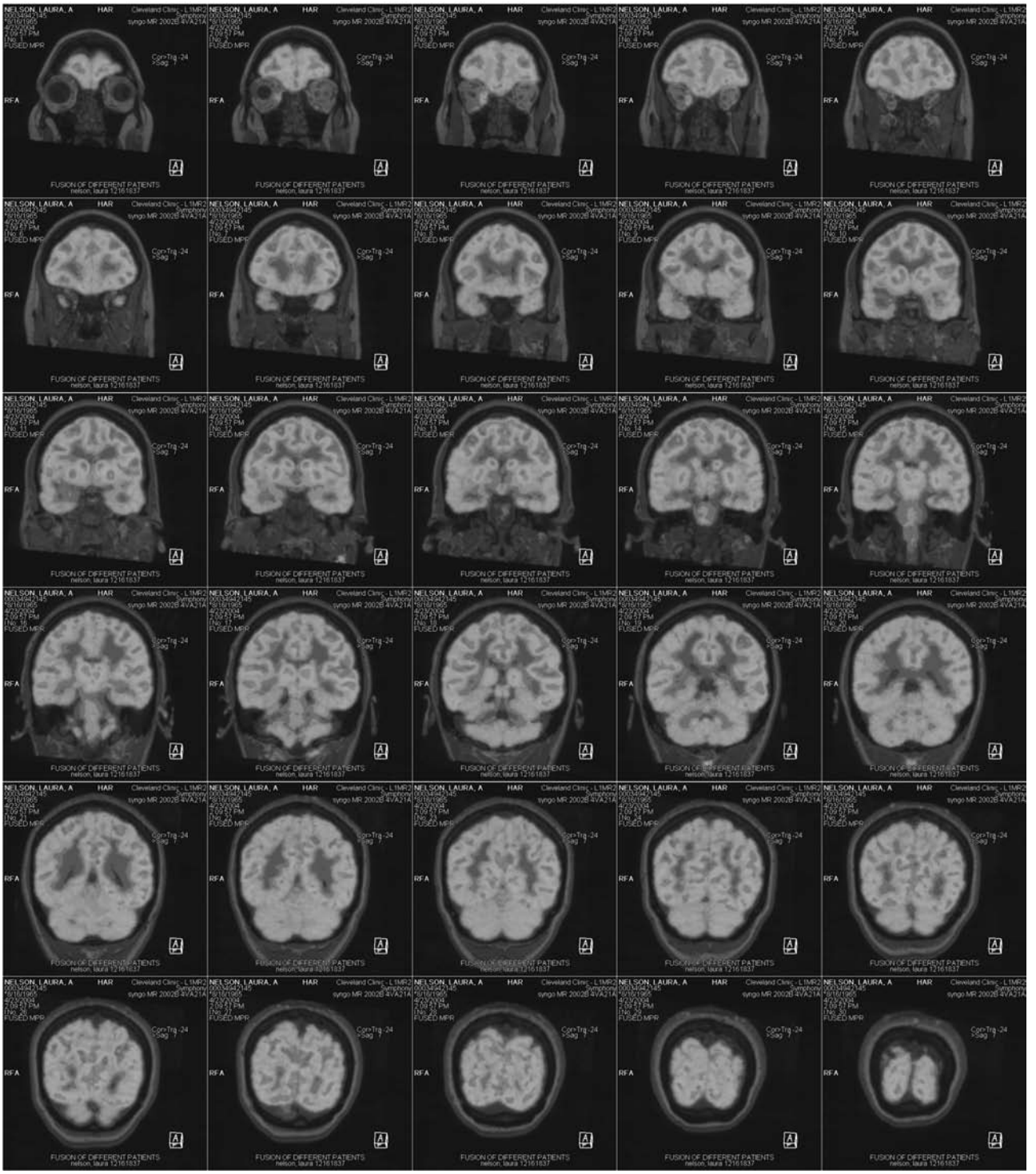


Figure 151.2 Fluorodeoxyglucose PET shows reduced radioactive tracer uptake in the right mesial and basal temporal regions.

temporal spikes. The temporal alpha pattern on the ictal EEG with a maximum in the anterior temporal electrodes confirmed that the seizures (ictal onset zone) were right mesial temporal in origin. This was corroborated by MRI, which revealed right mesial temporal sclerosis. Functional imaging also revealed hypometabolism in the same region. The neuropsychological scores were not strongly lateralized to the right side. Thus the presurgical evaluation was strongly indicative of right mesial temporal lobe epilepsy.

In view of the strong evidence for right mesial temporal lobe epilepsy, the presurgical team was unanimous in its recommendation for right temporal lobectomy. The high preoperative visual memory scores was not considered a deterrent for surgery of the nondominant temporal lobe.

Surgery

Ms LN underwent right temporal lobectomy that included a resection of the lateral temporal lobe extending 5 cm from the temporal pole with removal of the mesial structures. Histopathology was consistent with hippocampal sclerosis.

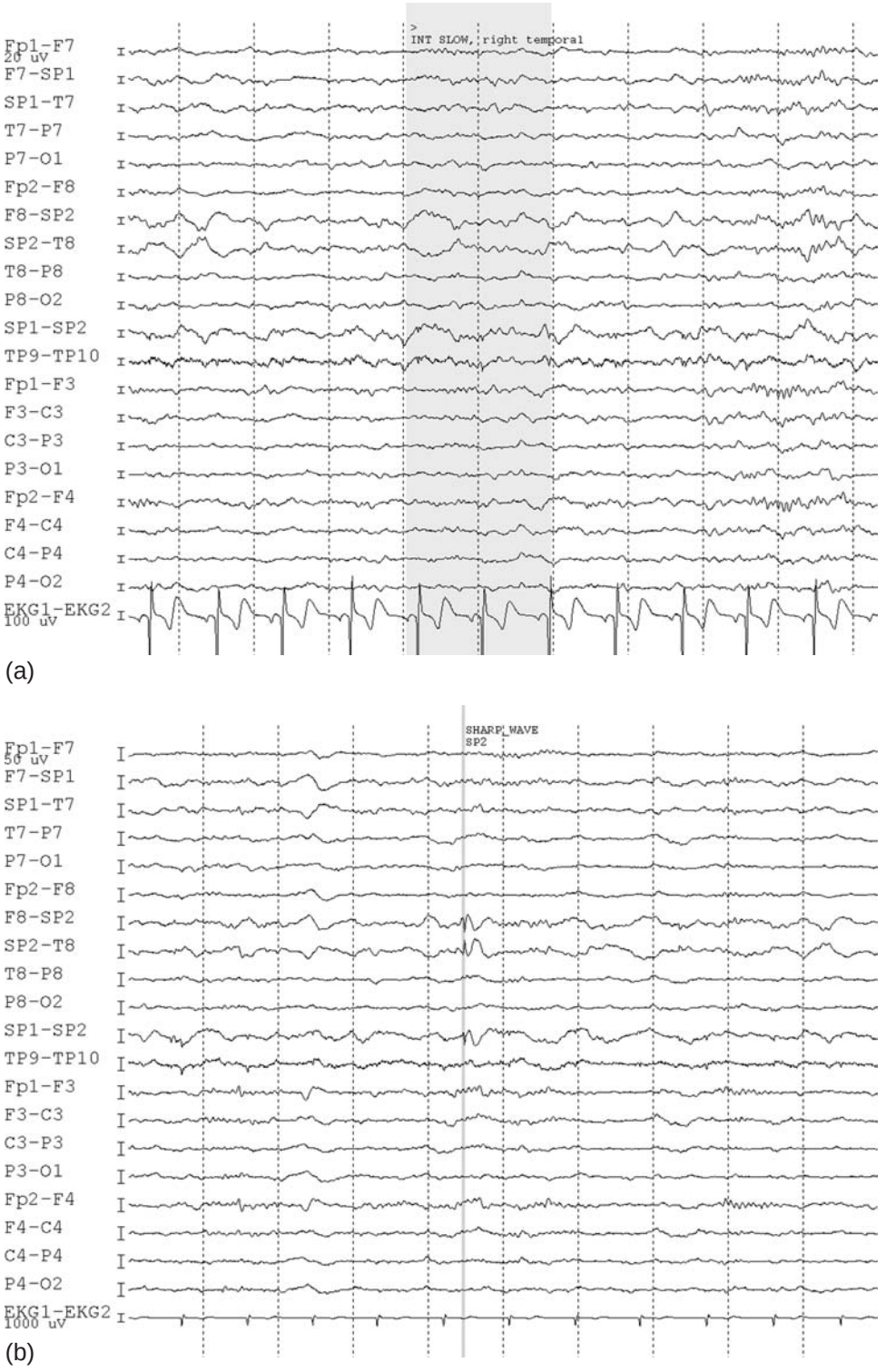
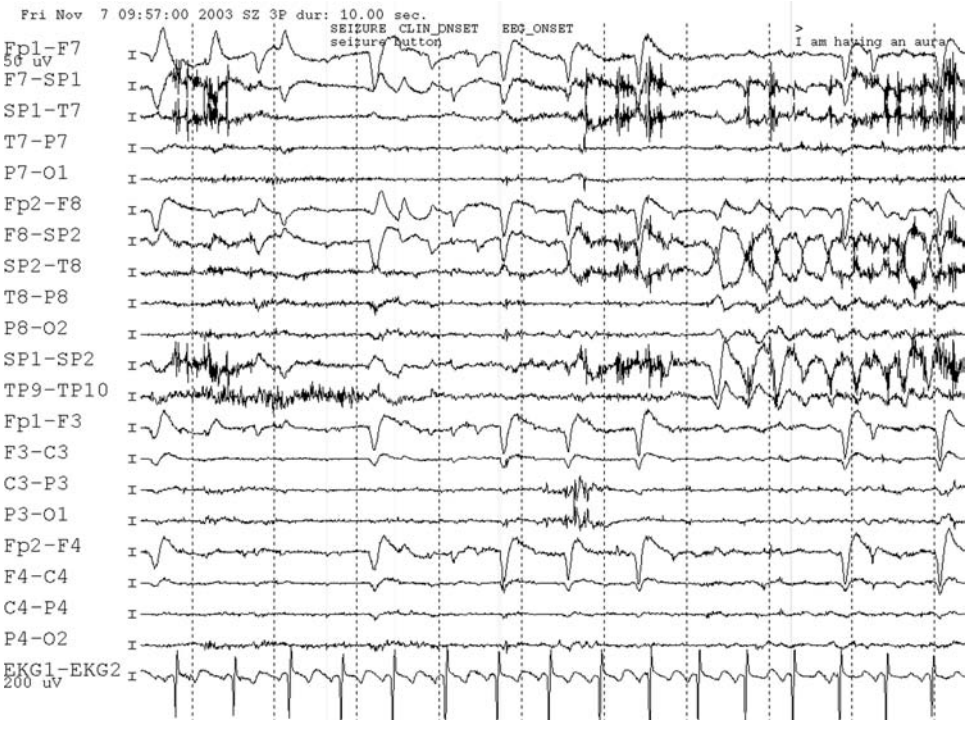


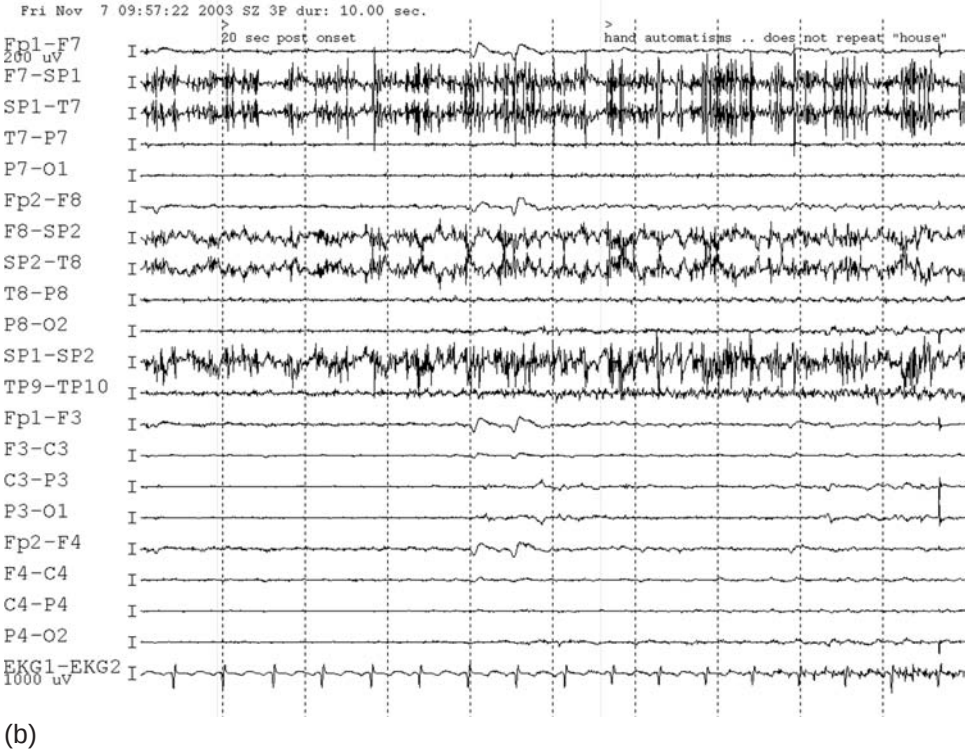
Figure 151.3 (a and b) Interictal scalp EEG tracing on a bipolar montage shows right temporal slowing with sharp waves in the same region having a maximum negativity as SP2.

Post-operative outcome

Ms LN was seizure and aura free at the 6-month follow-up visit. Postoperative MRI revealed resection of the temporal lobe including the mesial structures. Neuropsychological evaluation at 6 months revealed a Full Scale IQ of 121 (superior), a Verbal Comprehension Index of 105 (average), a Perceptual Organization Index of 128 (superior), and a Processing Speed Index of 120 (superior), Auditory Immediate Memory Index of 105, an Auditory Delayed Memory Index of 94, and an Auditory Delayed Recognition Index of 100, Visual Immediate Memory Index of 97 (average) and a Visual Delayed Memory Index of 75 (borderline). These scores were corrected for practice effect and a significant decline was noted in the visual delayed memory scores. In spite of this change, the patient denied having experienced a significant change in her cognitive status or memory as a consequence of her right temporal lobectomy.



(a)



(b)

Figure 151.4 (a and b) Ictal rhythms at seizure onset and after 20 seconds documenting the right temporal seizure rhythm with an SP2 maximum.

Patient 2: clinical details

History:

Seizure description and frequency

Ms DN, a 49-year-old right-handed registered nurse had intractable epilepsy since childhood. Her first seizure occurred at the age of 1 year in the context of high-grade fever secondary to pneumonia. Rare seizures persisted until age 9. These were described as episodes of staring followed by generalized body shaking. She was seizure free on a combination of phenytoin and phenobarbital for many years. Antiepileptic medications were tapered and discontinued at age 28.

Seizures recurred at age 31 during the eighth month of DN's second pregnancy. The seizure frequency increased from one to two per year in the first 3 years of recurrence to two per month in the year prior to the presurgical evaluation.

DN reported an aura which she described as 'a sick feeling in my stomach' and 'a little light headedness,' which lasted for 1–2 min. This was usually followed by loss of awareness. 'All I know is that I do pass out'. Observers reported that she was unresponsive, and then had jerking of her limbs (more marked in the lower limbs) for seizures that lasted more than 30 seconds. She occasionally bit her tongue during seizures but had never been incontinent. There was no significant postictal confusion, but DN had language difficulties. 'When I'm starting to come out of it I know what is happening around me, but I cannot talk'. For example she was able to identify in her mind that she was looking at a computer, but could not 'get the thought related to my speech'. This difficulty in speaking lasted for 30–90 seconds.

There was no history of generalized motor seizures or status epilepticus.

Medical history and epilepsy risk factors

DN had hypertension, depression and chronic back pain. She worked as a part-time registered nurse and continued to drive. Seizures persisted despite a trial of three different antiepileptic drugs (Phenytoin, Phenobarbital, Oxcarbazepine) in the past and the present combination of Lamictal 900 mg/day and Phenytoin 500 mg/day.

Brain imaging

Magnetic resonance imaging (Figure 151.5a, b)

MR imaging of the brain in a 1.5 Tesla Siemens SP scanner (Erlangen, Germany) revealed left mesial temporal sclerosis in the form of a shrunken left hippocampus (head, body, and tail) in T1 coronal images and increased hyperintensity of the left mesial temporal structures on FLAIR imaging.

Positron emission tomography (Figure 151.6)

An interictal PET study of the brain showed reduced fluorodeoxyglucose uptake in the left mesial temporal structures and the anterior temporal neocortex.

Electrophysiology

Routine EEGs documented intermittent slowing and occasional sharp transients in the left temporal region.

Video EEG evaluation

Ms DN underwent video-EEG evaluation with discontinuation of antiepileptic medications over a period of 8 days using 10-10 system of scalp electrodes and additional sphenoidal electrodes.

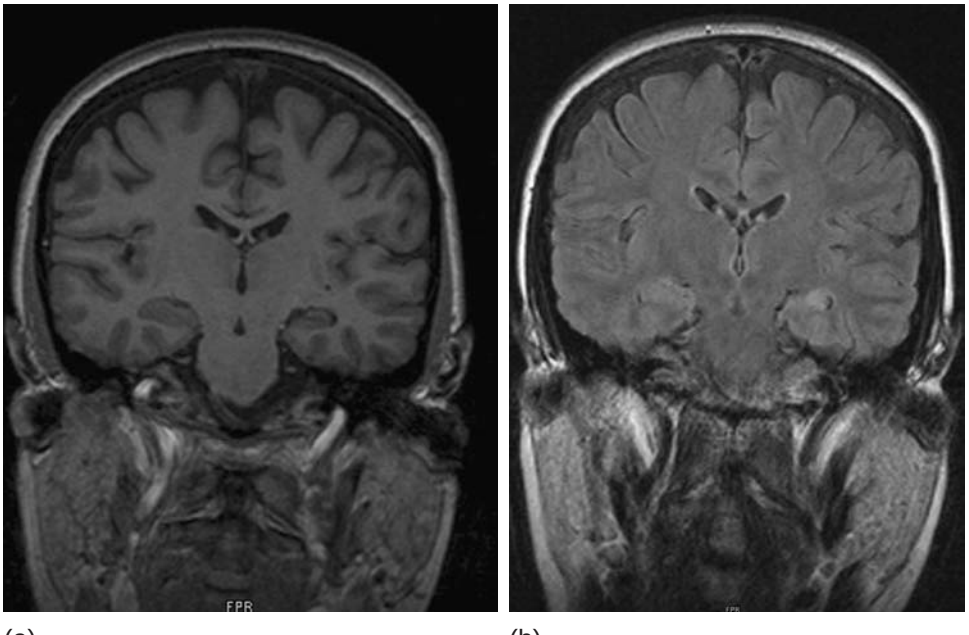
Interictal activity (Figure 151.7)

Interictal recording revealed intermittent left temporal slowing at 5–7 Hz lasting 2–3 seconds in sleep and wakefulness. Rare left temporal spikes were recorded which were maximum at the sphenoidal electrode.

Ictal activity (Figure 151.8a, b)

Clinical seizures: automotor seizure (loss of awareness)

Two of the three typical seizures recorded occurred out of wakefulness. DN did not recognize the onset of her seizures. The seizure began with a prolonged period of staring. She then had chewing and swallowing movements. She was tested towards the end of the clinical seizure and was partially attentive but had difficulty following commands. After the end of the EEG seizure, DN was fully attentive but had difficulty



(a) (b)

Figure 151.5 (a and b) Coronal images through the body of the hippocampi showing a smaller left hippocampal body (T1 image) with increased signal (FLAIR) consistent with left hippocampal sclerosis.

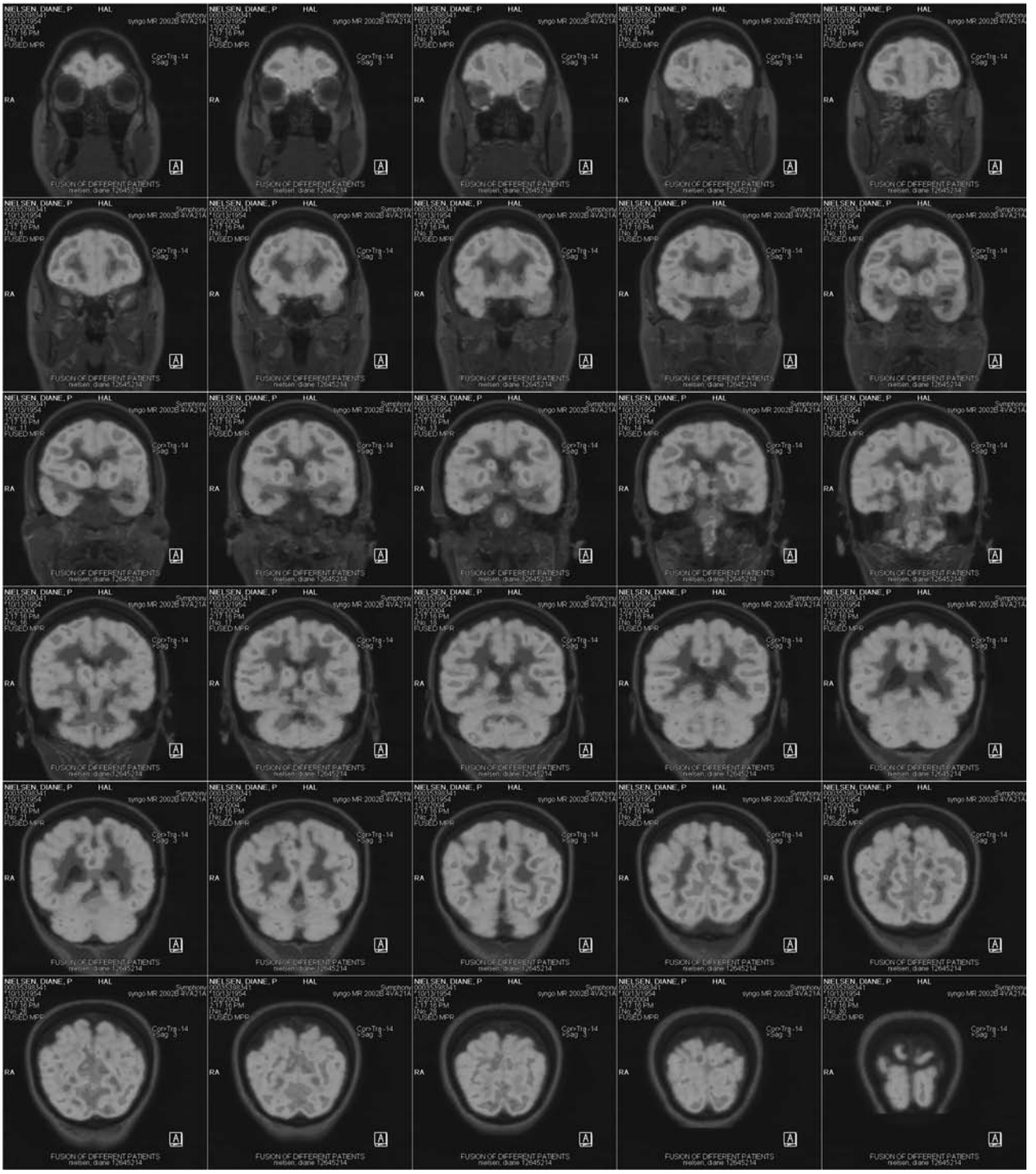


Figure 151.6 Fluorodeoxyglucose PET shows reduced radioactive tracer uptake in the left mesial and basal temporal regions.

saying her name, repeating words and naming a pen. She was however able to stick out her tongue and point to her nose when instructed. This phase lasted for 90 seconds. She later reported being aware of the testing but being unable to speak. This seizure would be labeled a complex partial seizure in the ILAE classification. In the semiological seizure classification this would be an *automotor seizure with loss of awareness*. LN had classical postictal aphasia which lateralized the seizure to the left hemisphere.

EEG seizures

Ictal EEG patterns were stereotyped in all the three seizures.

EEG onset was marked by a rhythmic theta frequency discharge over the left temporal chain, maximal at Sp1. This evolved over 15 seconds to rhythmic spiking over the left hemisphere, that continued for another 25 seconds before slowing to a delta frequency rhythm with sharp components. The delta slowed further, and became smoothly contoured before the end of the EEG seizure. There was no significant involvement of the opposite side in the initial and spiking phase, and modest involvement with a low-amplitude delta-frequency rhythm in the latter part of the seizure. Duration of EEG seizure was 1 min 28 sec.

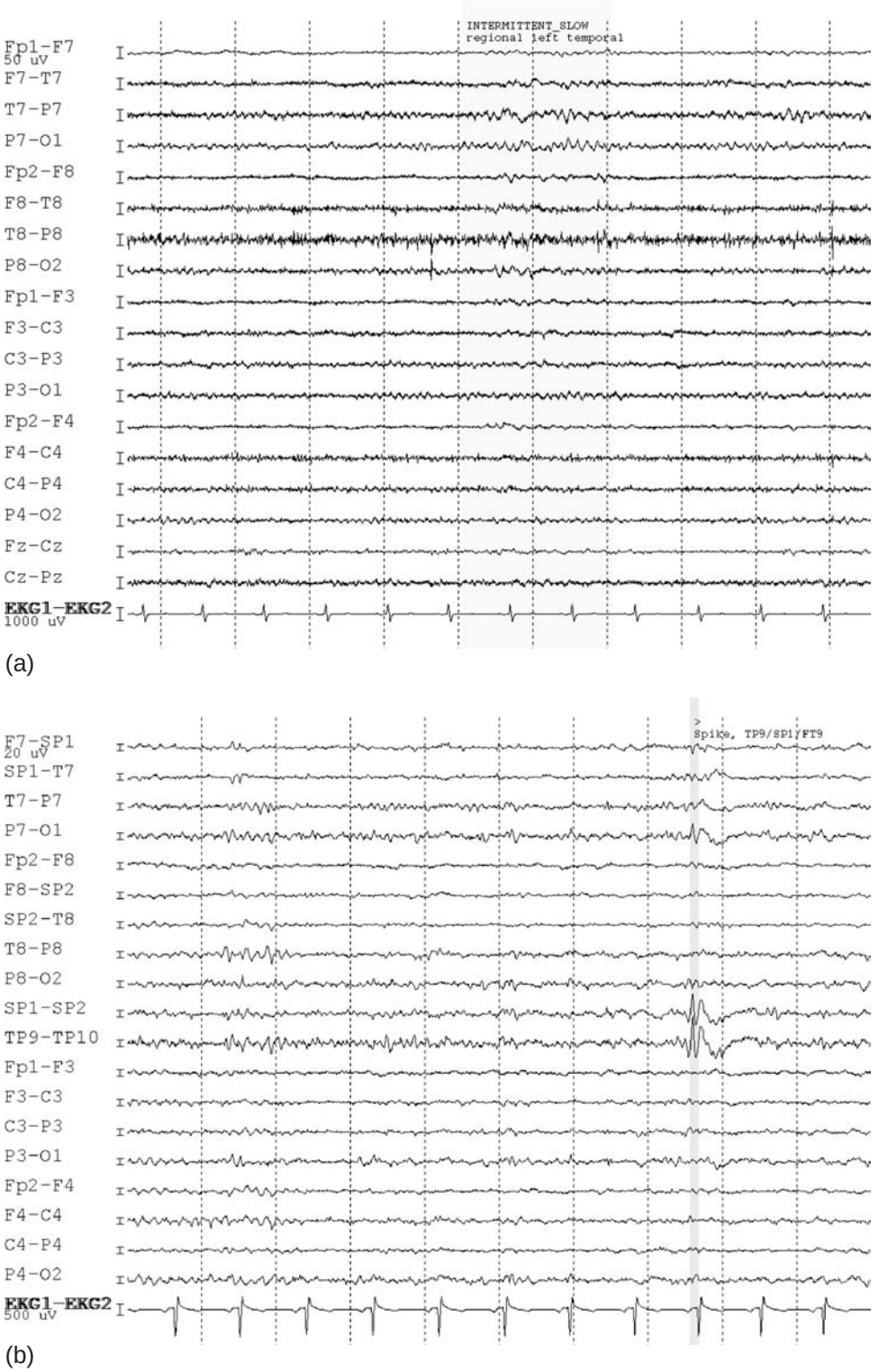


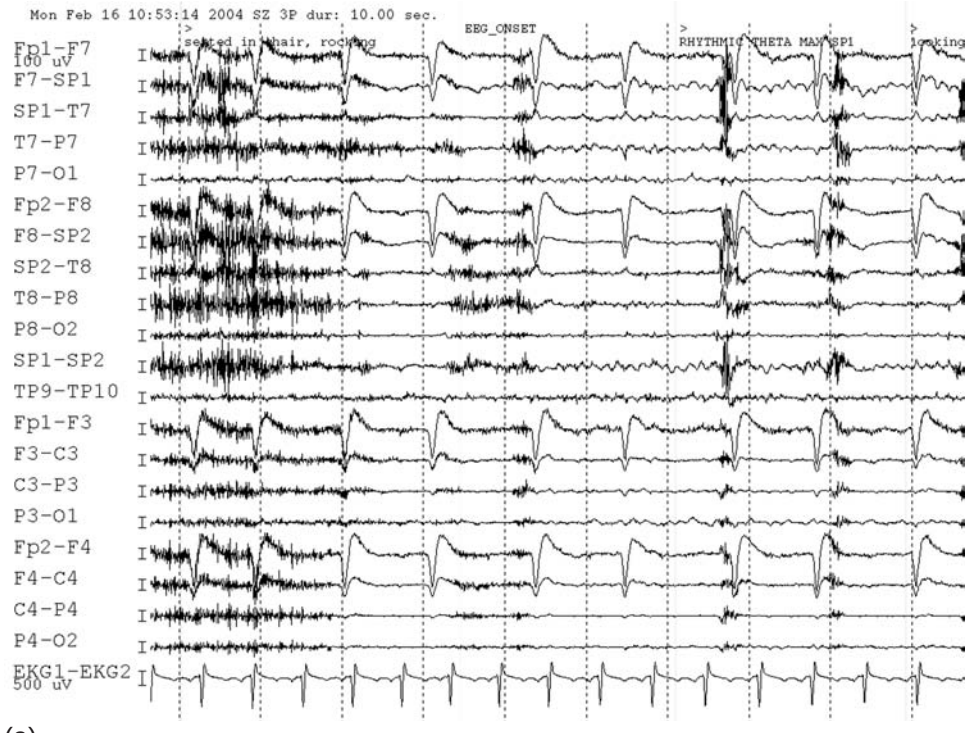
Figure 151.7 Interictal scalp EEG tracing on a bipolar montage shows left temporal slowing with sharp waves in the same region having a maximum negativity as left sphenoidal electrode SP1.

Neuropsychology

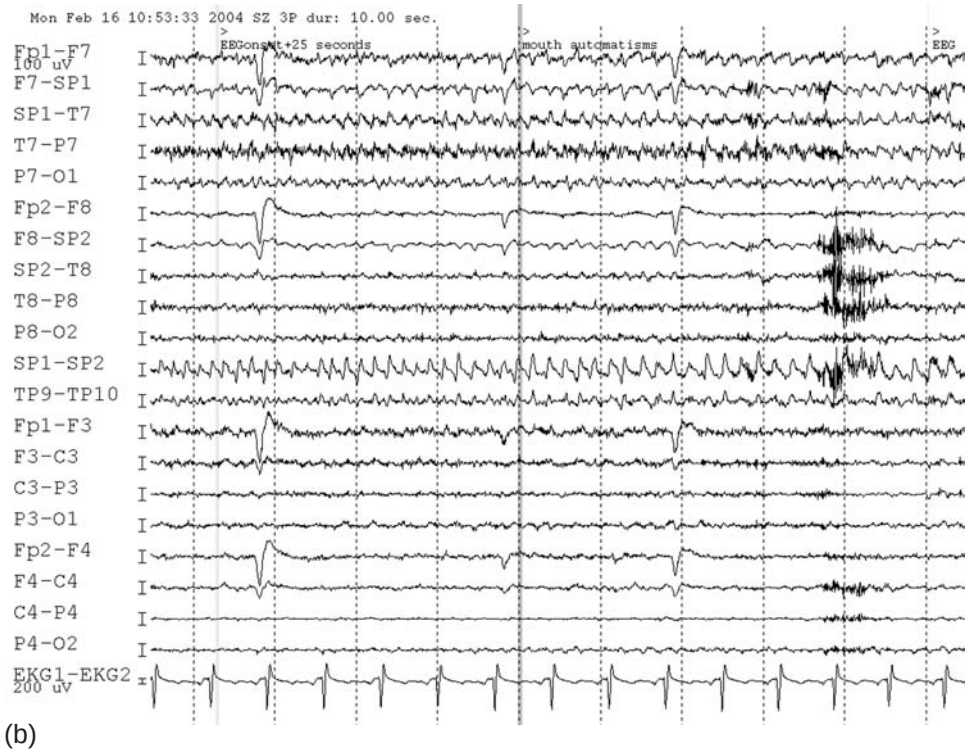
Neuropsychological examination using the Wechsler Adult Intelligence and Memory Scales Version III revealed an average level of preoperative functioning with no asymmetry of verbal and visual scores. The Full Scale Intelligence Quotient (IQ) was 97 with the Verbal IQ at 98 and Performance IQ at 94. Scores for Immediate Memory were 77 and 75 in the verbal and visual spheres, with delayed memory scores of 80 and 78 for verbal and visual material respectively.

Analysis

In summary, the preoperative evaluation provided evidence of left temporal lobe epilepsy, with complete concordance



(a)



(b)

Figure 151.8 (a and b) Ictal rhythms at seizure onset and after 25 seconds documenting the left temporal seizure rhythm with a left sphenoidal (SP1) maximum.

between seizure descriptions by history, interictal EEG, observed clinical semiology, ictal EEG and neuroimaging. Epigastic auras are very common in mTLE but are not specific for mesial temporal seizure origin.[5] Though the seizure semiology in itself was not lateralizing, LN had a striking postictal aphasia. Post ictal aphasia has been consistently associated with seizure onset in the language dominant hemisphere.[3,6–8] The neuropsychological scores did not lateralize memory deficits. In view of the average preoperative verbal memory scores and the presence of significant hippocampal sclerosis on MRI, it was predicted that Ms LN would have only a small risk for memory decline. It was concluded that no Wada test was necessary. DN was offered a left anterior temporal lobectomy.

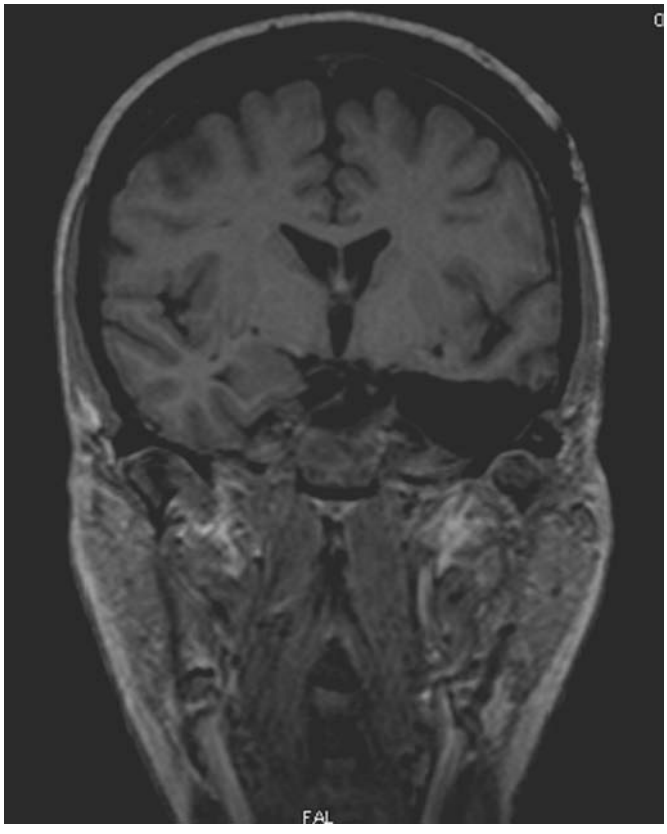


Figure 151.9 Postoperative coronal T1 image showing the resection of the lateral and mesial left temporal structures (6-month postoperative image).

Surgery

A left temporal lobectomy was performed under general anesthesia. Four and a half centimeters of the lateral temporal lobe were removed with resection of the amygdala and the hippocampus. The parahippocampal gyrus was also resected. DN had an uneventful postoperative course. Histopathology revealed hippocampal sclerosis.

Post-operative outcome

Ms DN was seizure free at the 6-month follow-up visit. Phenytoin was discontinued and she was maintained on Lamictal monotherapy. DN continued to do well at the 1-year follow-up visit. She had a single seizure in the 10th month after surgery. Follow-up neuropsychological assessment showed improvement in raw scores for all subsets of performance but these were not considered significant after correction for practice effects.

Discussion

The essential purpose of the presurgical evaluation in lesional mTLE surgery is to demonstrate the overlap between the epileptogenic lesion and the epileptogenic zone.

Seizure semiology in MTLE

Ictal semiology is a reflection of the activation of the symptomatogenic zone(s). The symptomatogenic zone is usually located in the proximity of the epileptogenic zone but very frequently it does not overlap with the epileptogenic zone. It is essential to remember that no single symptom or EEG feature in isolation is diagnostic of mesial temporal cortical activity. It is therefore crucial not to evaluate any symptom in isolation, but to consider the sequence and context of their occurrence.[5]

EEG in mTLE

Interictal discharges in hippocampal sclerosis have a very localized field which may be missed by scalp electrodes.[9] When recorded in the scalp-EEG, they are highly restricted to the anterior temporal electrodes. True anterior temporal electrodes help increase the likelihood of recording temporal interctal epileptiform discharges (IEDs). Sphenoidal electrodes and anterior temporal electrodes help in the differentiation between neocortical temporal epilepsy (spikes have higher amplitude in mid-temporal electrodes) and mesial/anterior temporal epilepsy (spikes have a relatively higher amplitude in sphenoidal and anterior temporal electrodes). Frequent posterior temporal or extratemporal sharp waves may decrease the certainty of the diagnosis of hippocampal sclerosis. *Ictal rhythms* in the form of rhythmic theta (Figure 151.4a) or alpha activity (Figure 151.8a) within the first 30 seconds of the electrographic or clinical seizure onset are observed in approximately 80% of patients with mTLE and have a high lateralizing value.[10,11] However these patterns are significantly more common in patients with moderate to marked hippocampal atrophy rather than those with mild hippocampal atrophy.[12] Neocortical ictal onset patterns may be indistinguishable from those of mesial temporal origin, but some authors have suggested that the 5–9 Hz inferotemporal rhythm is more specific for hippocampal onset seizures.[13]

In patients with history and ictal symptoms suggestive of mTLE, interictal discharges can reliably lateralize the seizure focus if they are consistently unilateral and concordant with the MRI identified unilateral hippocampal atrophy. Concordance of MRI and interictal EEG is more closely associated with good surgical outcome than concordance of MRI and ictal EEG findings with nonlateralized interictal EEG.[14] Studies indicate that noninvasive ictal EEG recordings do not improve seizure localization in patients with suspected TLE in whom MRI and interictal EEG are concordant.[15]

Neuropsychological outcome in mTLE

Cognitive outcome after temporal lobe surgery has been recently evaluated in multivariate analyses.[16,17] Dominant hemisphere surgery, extent of mesial temporal sclerosis on volumetric MRI and good baseline memory scores on neuropsychological testing were associated with a greater risk of memory decline following surgery. IAP memory scores did not contribute to the prediction of memory deficits in one study,[16] but ipsilateral IAP memory score was an independent predictor of outcome in another study.[17]

Conclusion

Lesional mesial temporal lobe epilepsy lends itself to a simple and fairly standardized presurgical work-up and promises an excellent surgical outcome. In patients with intractable focal epilepsy and MTS on MR imaging, it is tempting to assume that the MTS is identical to the epileptic region. However it has been shown that the positive predictive value of MTS alone is not satisfactory.[18] Hence it is essential to establish the overlap of the epileptogenic lesion with the irritative zone, the seizure onset zone and the functional deficit zones, by complementary multimodality testing. Such a demonstration of concordance may permit more selective surgery such as a selective amygdalohippocampectomy. The aim of a limited resection would be to limit postoperative functional deficits especially in cases with dominant temporal lobe epilepsy. The value of selective over more extensive temporal lobe resections in limiting deficits and in relative seizure outcome is still a matter of intense debate.[19,20]

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152 A patient with nonlesional mesial temporal lobe epilepsy

A Ray, G Kalamangalam, and HO Lüders

Clinical history

The patient was a 14-year-old right-handed female whose seizures started at the age of 9 years. Seizures were characterized by a blank stare, followed by repetitive semi-purposeful movements of her hands and lip-smacking (manual and oral automatisms). No preictal aura was reported. Observers reported that she was unable to speak during the seizure; she was amnestic for the seizure afterwards. She would usually fall asleep in the postictal period, though on occasion she would be awake and combative. Seizures lasted approximately 1 minute; seizure frequency varied from weekly to as many as seven seizures per day. There was no history of generalized motor seizures.

There was no past history of febrile seizures, significant head trauma, or intracranial infection. Her health otherwise was excellent. There was no family history of epilepsy or other neurological disease.

The patient had failed combinations of multiple antiepileptic drugs (AEDs) including zonisamide, topiramate, levetiracetam, carbamazepine, and phenobarbital.

Previous EEGs had shown sharp waves at the left anterior temporal electrodes (F7, T7).

General physical, and complete neurologic, examination was normal.

Noninvasive video-EEG monitoring

Recordings were performed with the usual 10–20 scalp electrode coverage with additional sphenoidal electrodes.

Interictal EEG

Spikes, regional left temporal, maximum at the left sphenoidal (Sp1) electrode (Figure 152.1); 100% of discharges.

Ictal EEG

Four seizures were recorded.

Clinical seizures

These were characterized by blank staring, florid oral automatisms, and symmetric automatisms of the upper extremities. The patient could not speak or follow commands during seizures.

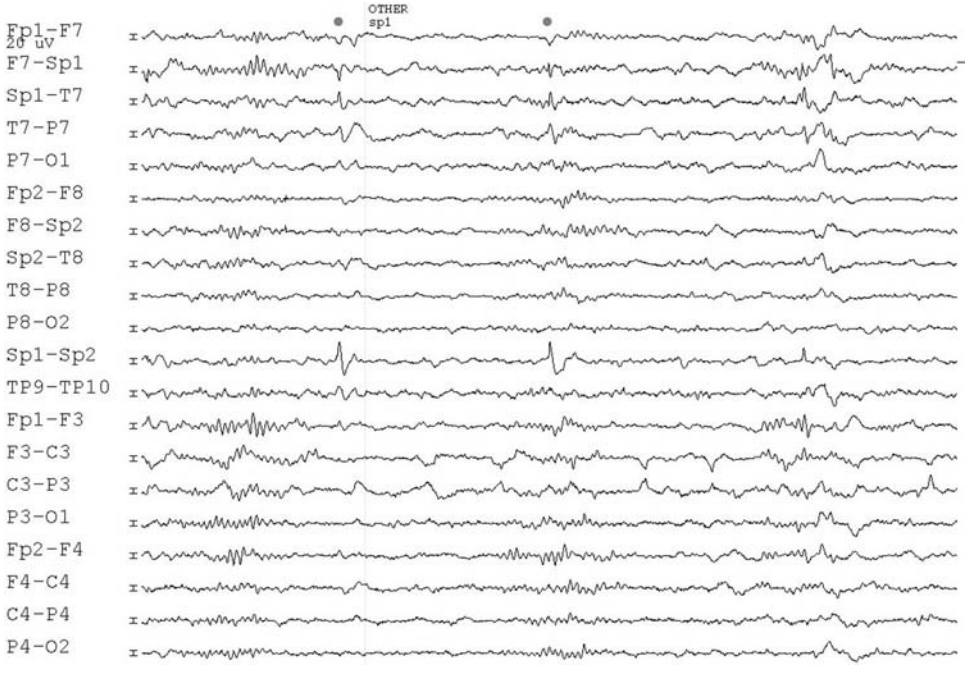

Figure 152.1 Left temporal spikes (location marked by grey dots) on scalp EEG, maximum at the left sphenoidal (Sp1) electrode.

In this phase progressed to clonic movements of the right side of the face. The patient was aphasic in the postictal period and wiped her nose with her left hand. In the ILAE classification system, the patient would be regarded as having complex partial seizures, as there appeared to be an 'alteration of consciousness' during the seizure. However under the semiological classification system[1] followed in the Cleveland Clinic, the patient would be classified as having automotor seizures progressing to right face clonic seizures, with lateralizing signs of postictal aphasia and postictal nose-wipe. The latter two features, and the right face clonic activity, suggested a dominant (left) hemisphere seizure onset.[2,3]

EEG seizures

Regional left temporal. Seizures began with brief electrodecrement over the left temporal region. This was followed (usually within approximately 10 seconds) by rhythmic theta activity over the left temporal region, maximal over the left sphenoidal (Sp1) electrode. Theta activity usually lasted between 30–40 seconds followed by postictal slowing, again maximal over the left temporal region (Figure 152.2).

High-resolution brain MRI

Normal T1-weighted and FLAIR coronal sequences. In particular, there was no evidence of shrinkage or asymmetry of hippocampal volumes, or hippocampal high signal (Figure 152.3).

PET (positron emission tomographic) scan

Left temporal hypometabolism (Figure 152.4).

Ictal SPECT (single photon emission computed tomographic) scan

Injection was performed at 35 seconds after EEG seizure onset. Intense ictal hyperperfusion (20–25%) was observed in the left temporal region (Figure 152.5).

Neuropsychological evaluation

This is detailed in Table 152.3 (left-hand columns). Memory was mildly impaired overall, with low-average impairment of verbal immediate memory (with delayed verbal recall relatively spared), and impairment of both immediate and delayed visual recall. Full-scale and verbal IQ were both in the normal range, with performance IQ scored in the low-average range. Overall, the patient was judged to function in the average range of intellectual ability, with an advantage for verbal, over nonverbal, material. Memory scores also reflected an advantage for verbal over visual tasks. This pattern was considered unusual in view of her right-handedness and putative left temporal lobe epilepsy. She was deemed to be at risk for decline in her verbal memory if subjected to left anterior temporal lobectomy.

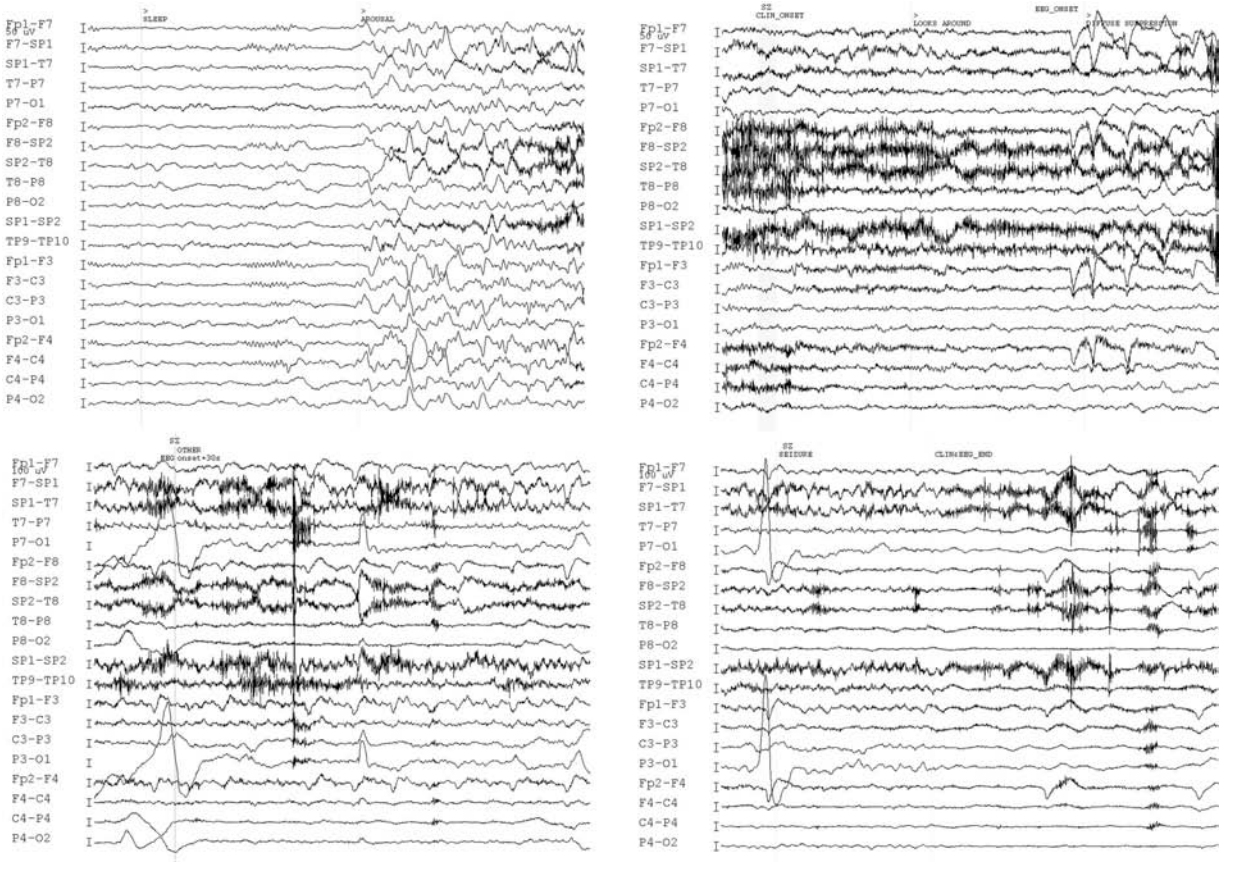

Figure 152.2 EEG seizure on scalp EEG. Top left: Baseline: sleep in the first half of the page followed by arousal. Top right: Clinical onset followed about 8 seconds later by EEG seizure onset characterized by brief electrodecrement. Bottom left: EEG Onset + 30 seconds: theta rhythms are seen over the left temporal region, maximum over the Sp1. Bottom right: Seizure rhythms continue in the first half of the page, terminating in the middle of the page. Postictal slowing follows, again maximal over the left temporal region.

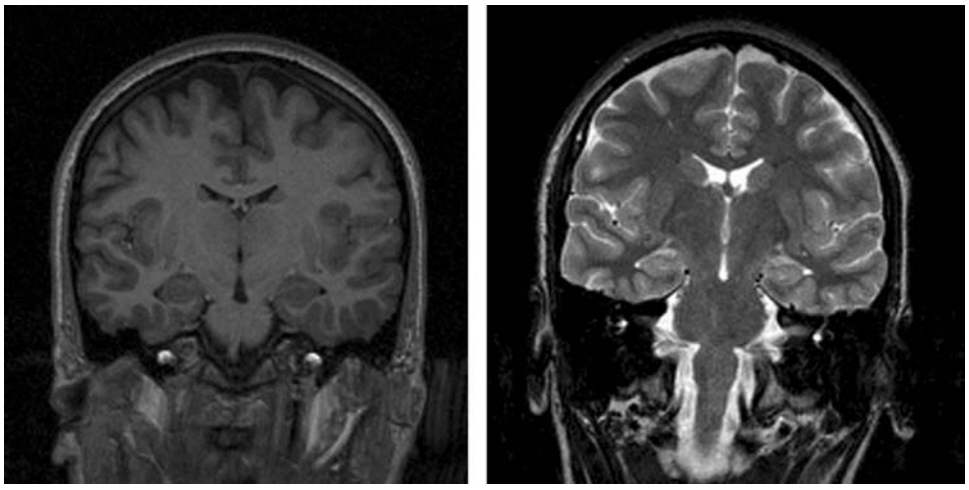

Figure 152.3 Brain MRI. Left image shows T1-weighted volumetric coronal sequences. Right image is a T2-weighted coronal study. Hippocampi are normal in volume and appearance.

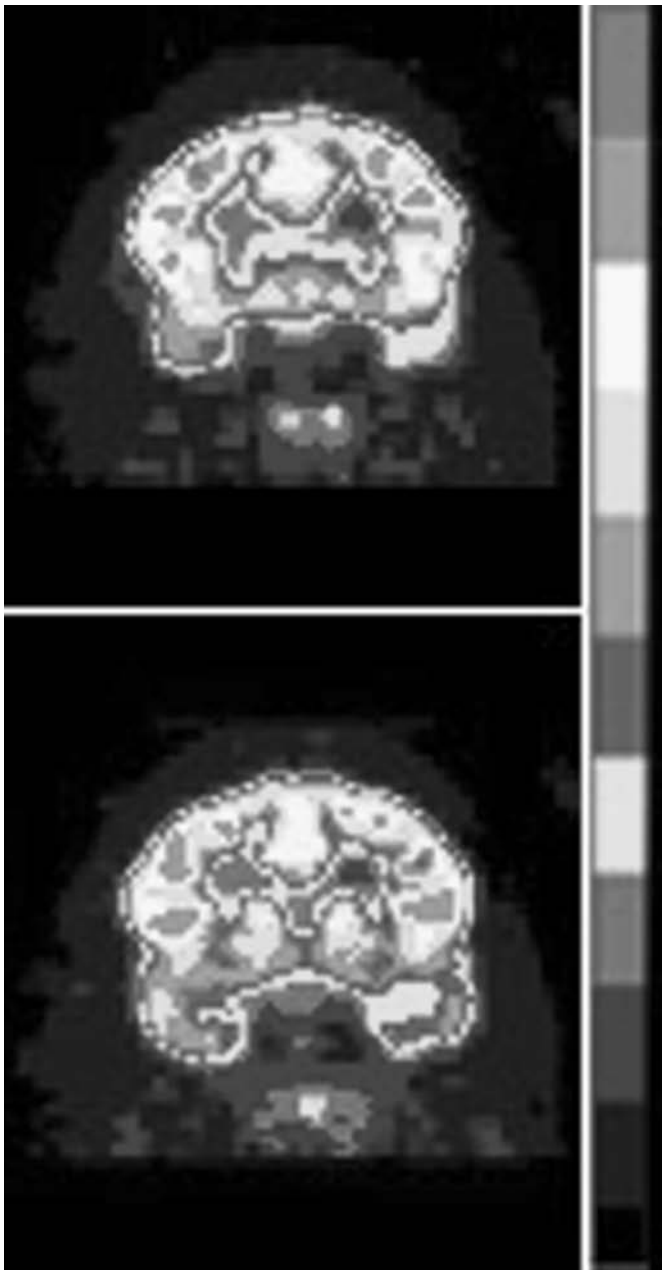

Figure 152.4 (Interictal) PET scan: left temporal hypometabolism.

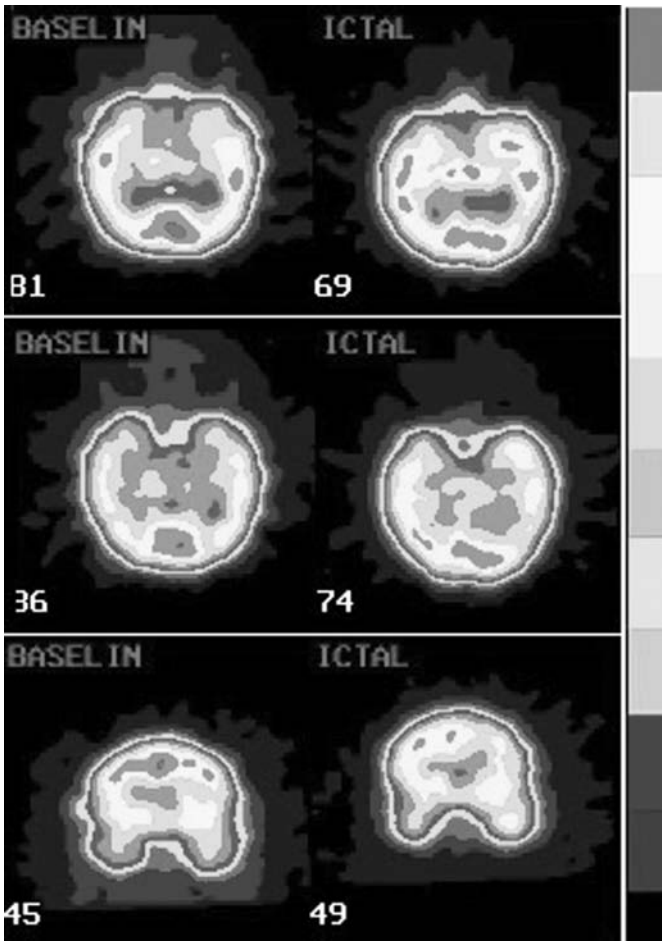

Figure 152.5 Ictal SPECT scan: left temporal ictal hyperperfusion. Axial (top two) and coronal (bottom) images.

Intracarotid amobarbital (Wada) testing

Results are summarized in Table 152.1. There was left hemispheric dominance for language, and bilaterally intact memory representation. Together with the preoperative neuropsychological evaluation, this emphasized the risk for some decline in verbal memory following left temporal lobe resection.

Summary of evaluation and further management

The patient's history and seizure semiology suggested left temporal lobe epilepsy. Interictal EEG showed a single population of epileptiform discharges, maximum over the left sphenoidal electrode; ictal EEG rhythms were best developed over the left sphenoidal electrode (with the earliest changes of electrodecrement also over the left temporal region). The electrographic findings were thus of left mesial temporal lobe epilepsy. Interictal PET and ictal SPECT were concordant. However, the lack of an MRI lesion, the relatively preserved verbal memory scores on the neuropsychological evaluation, and bilateral memory representation on Wada put her at risk for memory decline following a standard left anterior temporal lobectomy.

Following discussion at the epilepsy patient management conference, it was recommended that the patient undergo invasive evaluation with subdural grid electrodes prior to resective surgery. This would allow precise localization of the ictal onset zone, allowing a tailored resection sparing eloquent cortical areas identified by cortical stimulation mapping.

Invasive video-EEG monitoring

Four subdural grids were placed at craniotomy (Figure 152.6). The A-plate (8 × 8) covered the lateral aspect of the inferior left frontal lobe and the adjacent left temporal lobe. The posterior edge of this plate overlapped the central sulcus. The B-plate (4 × 4) covered the left orbitofrontal region as well as the anteroinferior aspect of the left frontal lobe. The C-plate (2 × 6) was placed over the left midbasal temporal region. The D-plate (1 × 6) covered the left basal temporooccipital region. The position of electrodes was confirmed by 3D reconstructed MRI (Figure 152.7).

Interictal EEG

Recordings were reviewed in a referential montage to an electrode on the A-plate (SA59), presumed distant from the irritative zone. Two populations of epileptiform activity were observed.

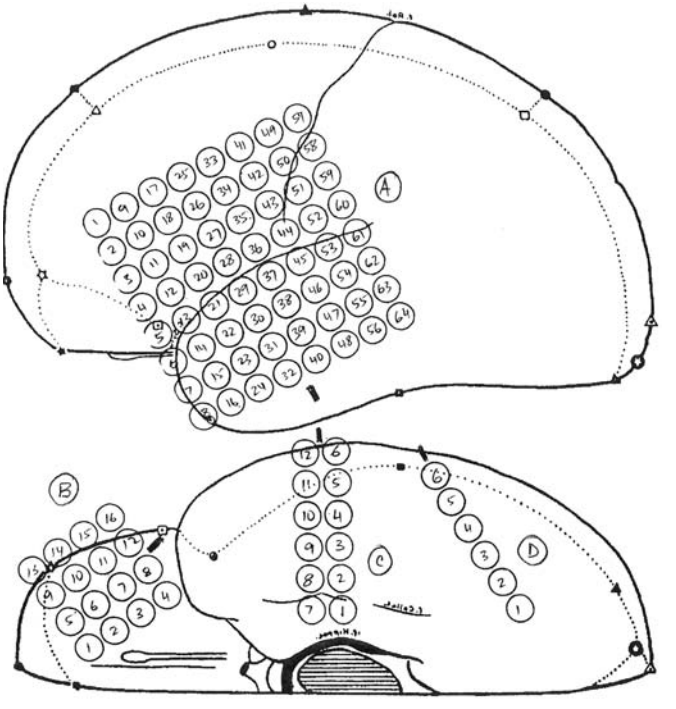

Figure 152.6 Schematic diagram showing A, B, C and D subdural electrode plate positions.

- *Spikes, left mesial temporal:* These were the most frequent (70% of discharges) and present over the C-plate. These were usually maximum over C1 and C7 (Figure 152.8), and occasionally over C10.
- *Spikes, left anterior temporal:* This independent population was present over the A-plate and comprised 30% of all discharges. Spikes were usually maximum over the A8, A16 or A23 electrodes (Figure 152.9).

Ictal EEG

Five seizures were recorded. Semiologically, these seizures were identical to those seen during the noninvasive evaluation, including one that progressed from an automotor phase involving oral and upper extremity automatisms to clonic activity of the right side of the face. Ictal EEG change preceded clinical symptoms by 7–8 seconds but on occasion by up to 30 seconds. The first EEG changes seen were poly-spikes (Figure 152.10) and paroxysmal fast activity over the left mesial temporal electrodes (C1>C2) followed by diffuse suppression over the left frontotemporal region (anteroinferior A-plate and entire C-plate) as well as the left orbitofrontal (B-plate) region. About 20 seconds after

Table 152.1 Wada test

	Left Injection	Right Injection
First verbal response	1 min 18 seconds after injection (followed by perseveration until 1 minute 37 seconds)	12 seconds after injection
Memory retention score	11/12 (92%)	12/12 (100%)

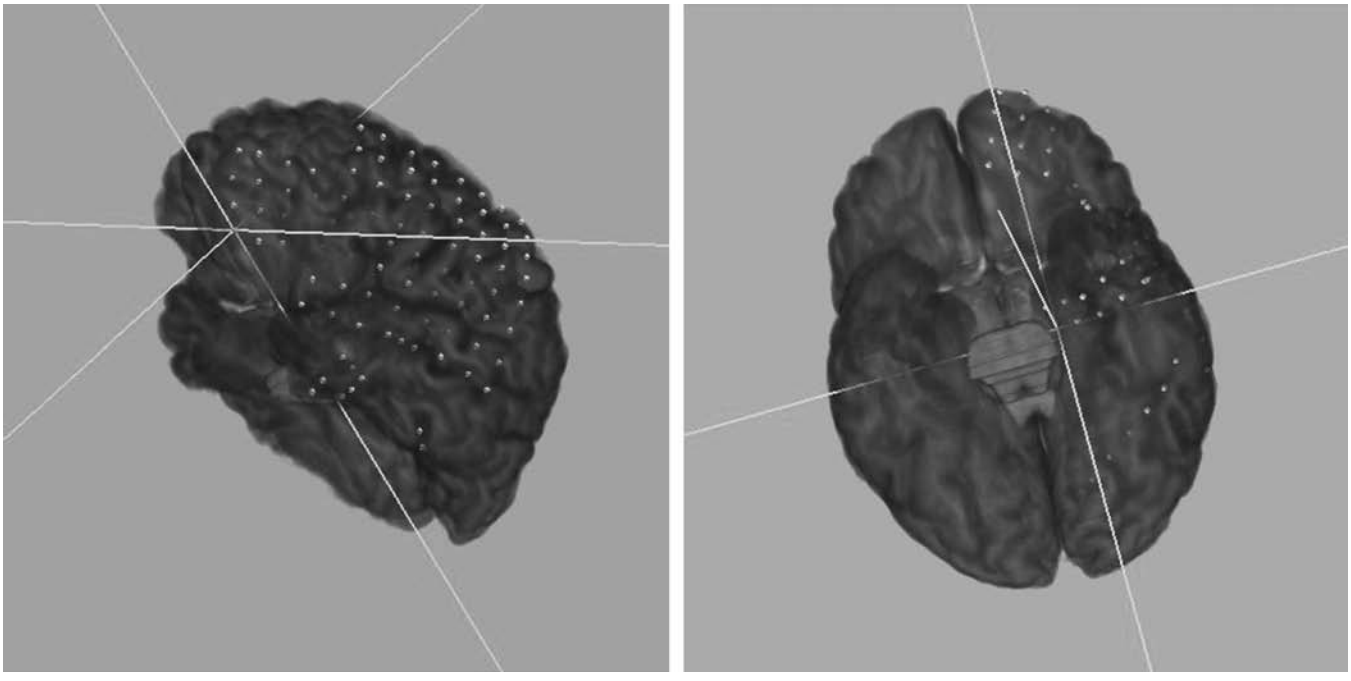

Figure 152.7 3D reconstructed images of electrode locations. These were obtained by superimposing the patient's preoperative brain MRI on a further MRI obtained after subdural electrode placement.

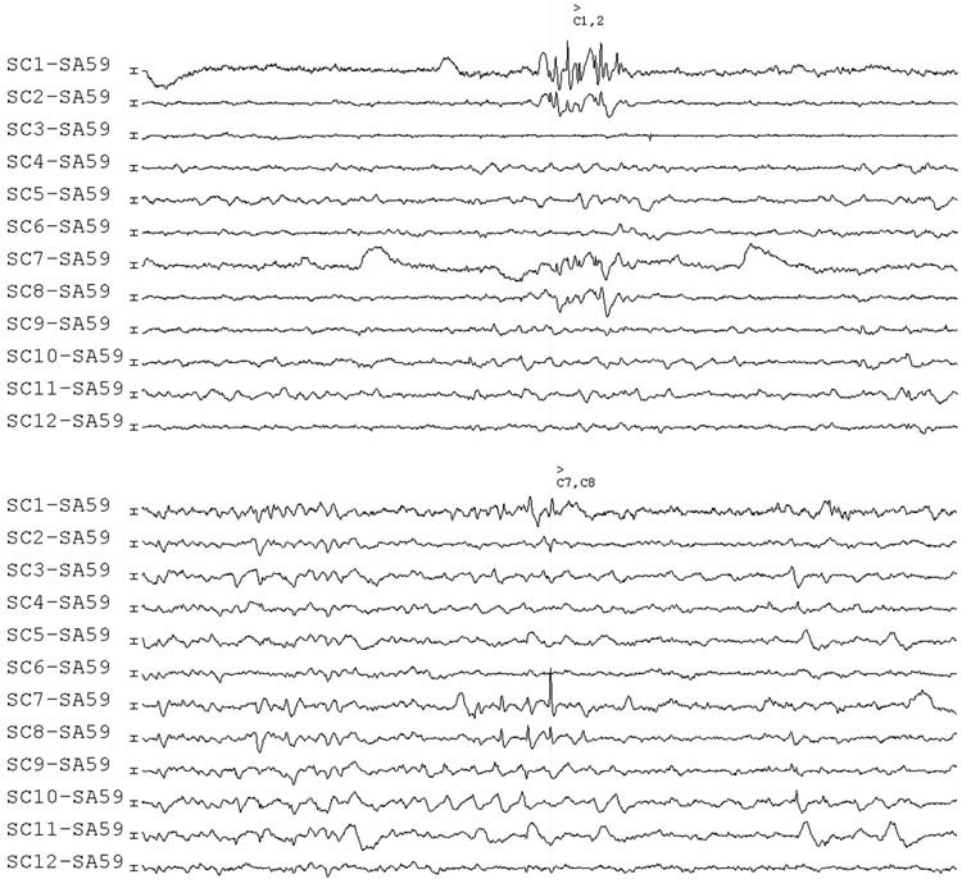

Figure 152.8 Intracranial EEG of spikes on the C-plate (the main spike population). The top figure shows spike-polyspike discharges with maxima over the C1–2 electrodes (also seen at C7–8). The bottom figure shows spikes with maxima over the C7–8 electrodes (also seen at C1–2).

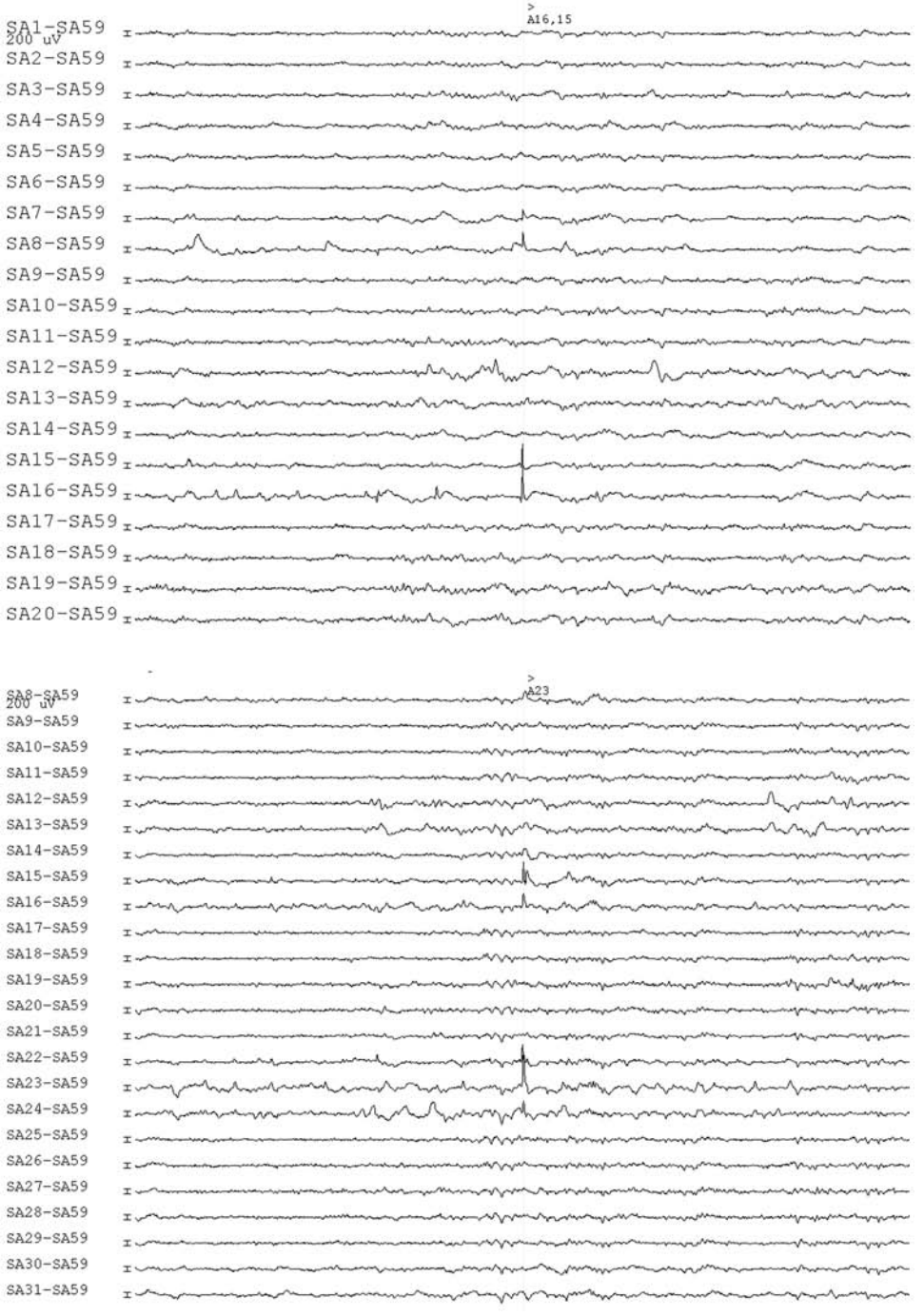

Figure 152.9 Intracranial EEG showing spikes on the A-plate (the other spike population seen in this patient). The top image shows spikes with maxima over A15–16 electrodes (also seen at A7–8). The bottom image shows spikes over A23–24 electrodes (also seen at A15–16).

EEG seizure onset, theta rhythms were seen over the basal temporal region (C-plate), followed by similar rhythms over the lateral temporal neocortex (A-plate). Rhythms slowed down to delta frequency about 40 seconds after EEG seizure onset and finally diffuse suppression was seen (Figure 152.11).

Evoked potential studies

Median nerve SSEPs localized the central sulcus between the A59 and A57 electrodes.

Cortical stimulation mapping

Receptive language function was localized to mid- and posterior temporal regions (A29, A37–39, A62–63), with the patient having difficulty with speech comprehension on stimulation of this area. Face and tongue motor responses were recorded from the A-plate above the sylvian fissure (A45, A53). Visual symptoms were reported on stimulation of the temporoparietal region (A54, A56, A61). A brief (5–8 second) seizure with clonic movements of the right face, was provoked by stimulation of the A36 electrode. Results of cortical stimulation are summarized in Table 152.2.

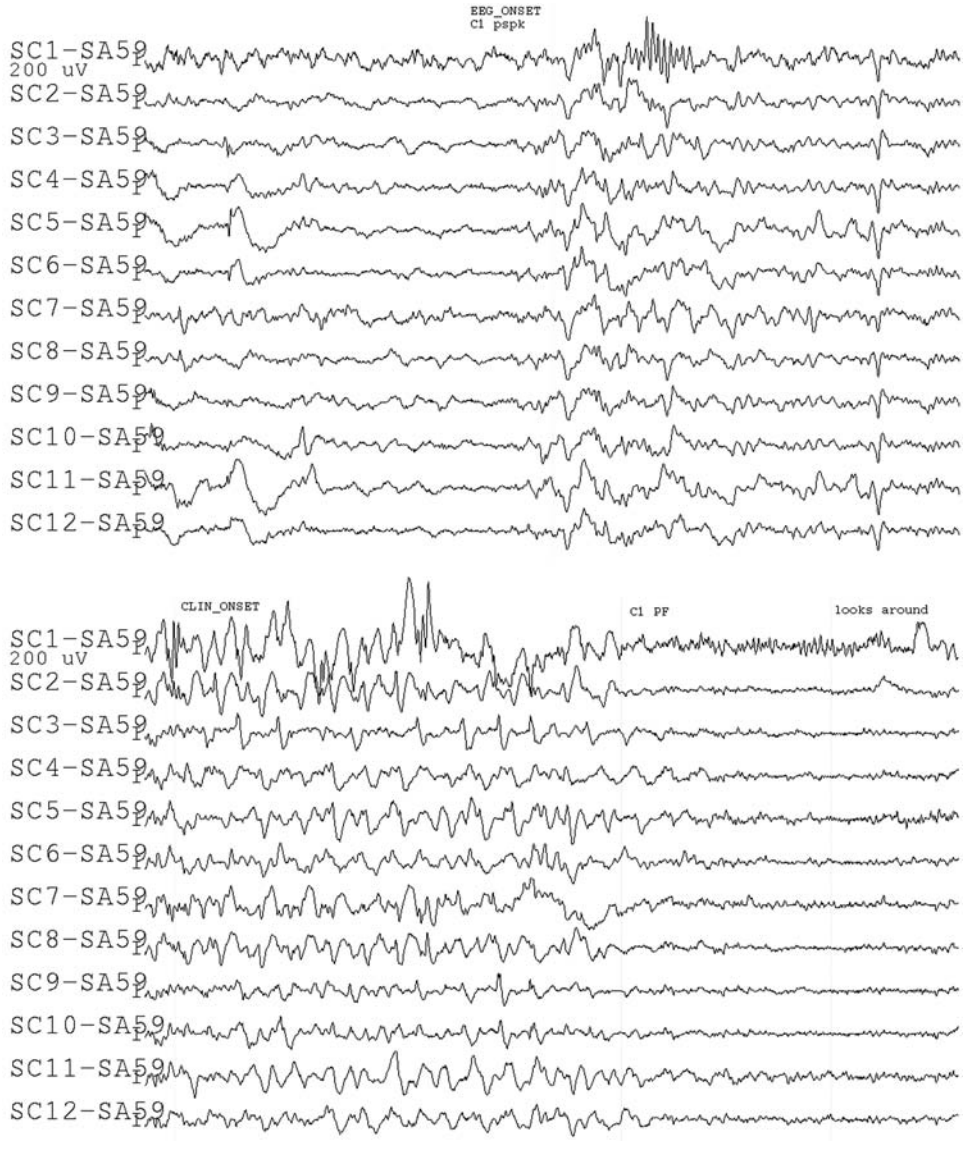

Figure 152.10 Intracranial EEG seizure. The top image demonstrates the EEG seizure onset with a polyspike discharge at the C1 electrode. This is followed by rhythmic spiking (bottom image) at the C-plate, maximally seen over the mesial temporal electrodes (C1–3, C7–8). Also appreciated, in the second half of the bottom image is a diffuse suppression over the entire C-plate along with paroxysmal fast activity, again best appreciated over the C1 electrode.

Summary of invasive evaluation

Left mesial temporal lobe epilepsy was confirmed. The majority of interictal discharges originated from the left mesial temporal region with the remaining discharges from the left anterior temporal lobe. The first EEG changes during seizures were over the left mesial temporal electrodes, confirming the latter as the ictal onset zone. Seizures spread rapidly to the basal temporal, followed by lateral temporal neocortex. Language function was localized to the mid to posterior temporal regions, well away from the ictal onset zone.

Overall summary; surgical strategy

The noninvasive and the invasive video-EEG monitoring were both suggestive of left mesial temporal lobe epilepsy. Concern remained about the relatively high preoperative neuropsychological verbal memory scores as well as the bilateral memory representation on Wada. However, from the point of view of seizure control, a left temporal lobectomy was felt to be the optimal procedure. Informed consent for this procedure was taken after the risks and benefits of the procedure were explained to the patient and her family.

Epilepsy surgery

The patient underwent a 4.5-cm left temporal lobectomy. A standard subpial technique was employed for dissection down to the temporal horn. The lateral temporal lobe was then amputated followed by resection of the left amygdala and the left hippocampus.

Histopathology (Figure 152.12)

Left temporal lobe: mild cortical dysplasia.
Left amygdala: microscopic dysplastic foci.
Left hippocampus: no significant pathology.

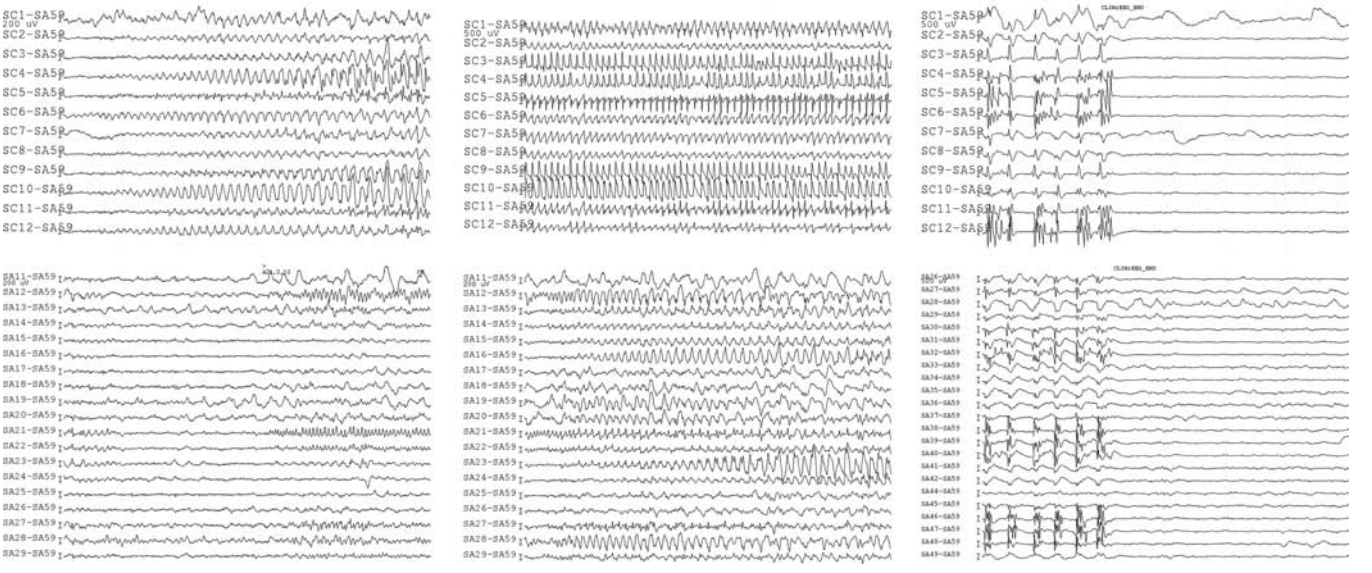

Figure 152.11 Intracranial seizure progression at 20 (left panel), 40 (middle panel) and 60 seconds (right panel) following EEG seizure onset. The top images demonstrate seizure rhythms over the C-plate and the bottom images demonstrate simultaneous seizure rhythms at the A-plate.

Follow-up

No postoperative motor deficits were observed. Seizure outcome was excellent, with no seizures during a 4-year outpatient follow-up period. The patient now has driving privileges. She remains on zonisamide 200 mg daily. Repeat neuropsychological evaluation was performed once, 6 months after surgery. The patient elected against having a further interval evaluation. Details of the former appear in Table 152.3 (right-hand column). Overall memory remained impaired, with a slight postoperative deterioration. However, this was entirely due to a significant (and expected) drop in both immediate and delayed verbal recall. Visual memory, on the other hand improved considerably, for both immediate and delayed items. This pattern carried over to IQ testing, with verbal IQ dropping modestly, but performance and full-scale IQ improving over preoperative scores.

In conclusion, the patient experienced an overall improvement from her epilepsy surgery in terms of physiological distress. Mood and adjustment issues were of some persisting concern when she was last interviewed.

Discussion

The management of a patient with mesial temporal lobe epilepsy associated with hippocampal sclerosis (HS) on brain MRI is now considered relatively straightforward. Most centers report good seizure outcome from anterior temporal lobectomy in a typical case; postoperative neuropsychological deficits are thought to be somewhat mitigated by the presence of HS. Temporal lobe epilepsy in a patient with a normal MRI is more challenging; identification of the ictal onset zone requires further investigation, and postoperative neuropsychological deficits are of more concern. Epilepsy surgery centers vary in their approach to this issue; at the Cleveland Clinic, subdural grid evaluation similar to that performed in this patient is the favored invasive electroencephalographic approach for purposes of localization. Controversies regarding neuropsychological issues are outlined below.

An early report of Penfield and Milner[4] described memory decline in two patients following standard unilateral left temporal resection. Subsequent reports[5,6] have documented

Table 152.2 Cortical stimulation

Symptom elicited	Electrodes stimulated
Difficulty with comprehension	A29, A37–39, A62–63
Tongue and face motor response	A45, A53
Visual symptoms	A54, A56, A61
Right face clonic seizure	A36

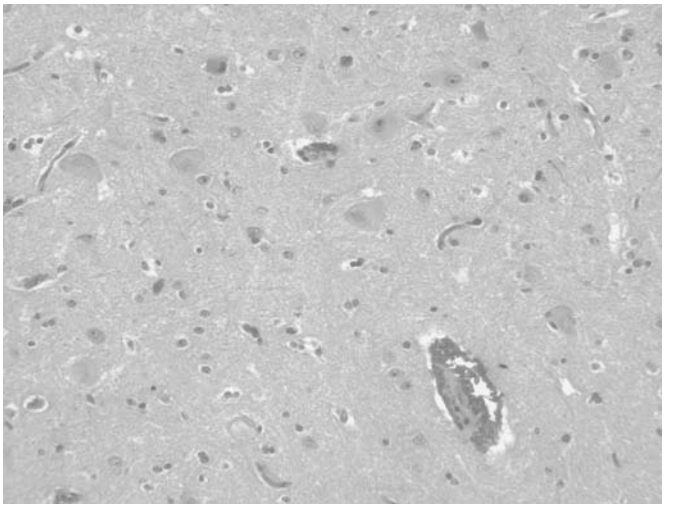

Figure 152.12 Neuronal cytomegaly seen at layer 6 of the temporal neocortex suggestive of cortical dysplasia. No significant pathology was seen in the hippocampus.

Table 152.3 Pre- and postoperative neuropsychological evaluation

Neuropsychological parameter	Presurgical evaluation	6-month postoperative evaluation
Overall memory	74 (4th percentile; mild impairment)	68 (2nd percentile; significant impairment)
Verbal immediate memory	78 (7th percentile; low-average to mildly impaired)	54 (0.1 percentile; significant impairment)
Verbal delayed memory	97 (42nd percentile; average)	54 (0.1 percentile; significant impairment)
Visual immediate memory	69 (2nd percentile; impaired)	100 (50th percentile; average)
Visual delayed memory	85 (16th percentile; low-average)	103 (58th percentile; average)
Full Scale IQ	90 (average)	93 (average)
Verbal IQ	98 (average)	89 (low-average)
Performance IQ	83 (low-average)	99 (average)

similar findings. Prediction of which patients are at particular risk for postoperative memory decline has prompted two explanatory neuropsychological models.[7]

The functional reserve model

This model, now somewhat dated, postulated that memory function in the normal (i.e. contralateral to the epileptic) temporal lobe (the 'functional reserve') was predictive of postoperative memory decline. Thus, poor memory function of the contralateral (normal) temporal lobe on Wada testing predicted postoperative memory decline. This model was based on the observation[8,9] that patients who passed the Wada memory test with ipsilateral injection (i.e. demonstrated adequate contralateral functional reserve), did not have significant postoperative memory complaints. This observation was however contradicted by the study of Wyllie and co-workers,[10] who found no significant differences in postoperative memory outcome in patients who had passed or failed the Wada memory test after ipsilateral injection.

The functional adequacy model

According to this model,[11–13] good ipsilateral memory scores on the Wada test predict poor memory outcomes after temporal lobectomy. This correlates with MRI hippocampal volumetric studies that suggest that patients with larger hippocampi experience more memory decline after left temporal resection.[14] Neuropathologic studies also suggest that higher degrees of hippocampal sclerosis are associated with less postoperative memory decline after dominant temporal resection.[15] However, it has also been demonstrated that patients with unequivocal hippocampal sclerosis on brain MRI and good preoperative verbal memory scores experience memory decline after dominant temporal lobe resection.[18,19] Thus, it appears that good preoperative verbal memory scores and a structurally normal dominant hippocampus are independent predictors of post-operative memory decline.[20,21]

Synthesis

While the functional adequacy model appeared sound in the 1990s, towards the end of that decade and the early years of the current century, the validity of this model was also questioned. Various studies[22–24] demonstrated that good preoperative right side memory scores on the Wada test in fact predicted a favorable memory outcome after dominant temporal lobectomy, if the age of seizure onset was taken into account. It has been postulated that early damage to the dominant temporal lobe possibly results in transfer of memory to the right temporal lobe resulting in a better postoperative memory outcome.

In summary, while there is no clear consensus on which of these above models is correct, it may be that the risk of memory decline in individual patients is along a spectrum between these two extremes. Our patient's outcome was concordant with the functional adequacy model, possibly in view of her relatively late onset of seizures.

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153 Patient with bitemporal lobe epilepsy

AV Alexopoulos and HO Lüders

History of present illness

The patient is a 30-year-old right-handed woman, who presents for evaluation of poorly-controlled seizures. Her birth and development were normal. She reports a history of minor head trauma without associated loss of consciousness at the age of 5 years. Otherwise, she has no identifiable risk factors for epilepsy.

Her history of seizures starts around the age of 20 years. Seizures consist of initial loss of awareness, a fixed stare and hand automatisms (described by her husband as 'rubbing her hands together'). The patient does not report an aura and is amnestic for events during seizures. Average duration is 2 to 3 minutes, followed by a brief period of postictal confusion. Seizure frequency is approximately 1–2/week (predominantly around her menses). Exact seizure frequency has been difficult to estimate, as the patient may remain unaware of her seizures, when no one is with her. On one occasion, a seizure while cooking resulted in first degree burns of both hands. Several years ago the patient used to have episodes of 'smelling something like ammonia'; these spells were not clearly linked to her habitual seizures and have not recurred in recent years.

The patient is a high school graduate, who went on to complete all but three classes for an associate's degree in general studies. According to her account she was forced to stop taking classes because of continued seizures and medication side effects. She then worked for several years as an assistant at a group home for handicapped children, but has been able to do so in the last 4 years.

She is married and lives with her husband and their four children. She reports that seizures have taken away her independence, as she is afraid to go out on her own and '... can't do the things I want to do with the kids'. She has a history of two seizure-related motor vehicle accidents in the past and is not allowed to drive. Her father provides transportation when her husband is at work.

The patient does not smoke and does not consume alcohol. She denies use of any other recreational or illicit drugs. Her general physical and neurological examination is unremarkable. Formal psychological evaluation reveals that the patient has been depressed for several years in response to her ongoing, seizures and the multiple consequences associated with uncontrolled epilepsy including interference with college, employment and driving. She is currently on antidepressant therapy with a selective serotonin and norepinephrine reuptake inhibitor (venlafaxine) and participates in bimonthly counseling. Past medical history is otherwise unremarkable with the exception of a previous cholecystectomy and surgical removal of an ovarian cyst. Chronic anticonvulsant therapy consists of a combination of topiramate (500 mg/d) and valproic acid (1,000 mg/day). She has failed maximum tolerated doses of carbamazepine, levetiracetam, and phenytoin in the past. She is not under treatment for any other active medical condition. The patient is considering epilepsy surgery and expresses motivation to return to college in the future (she states that she would be interested in pursuing a degree in psychology and working to support single mothers and their children).

Presurgical investigations

As seizures proved resistant to multiple antiepileptic medications the patient was admitted to the epilepsy monitoring unit for a noninvasive video-EEG evaluation using a combination of scalp and sphenoidal electrodes. Interictal EEG (Figure 153.1) showed sharp waves arising independently from the left and right anterior temporal regions (maximum at the ipsilateral sphenoidal electrode), with an estimated left (Sp1) to right (Sp2) ratio of approximately 60:40 overall (during one week of recording). No other temporal or extratemporal spike foci were noted.

All recorded seizures had similar electroclinical features and were associated with a stereotyped ictal EEG, characterized by a rhythmic buildup of 5–6 Hz rhythmic theta localized in the left temporal region maximal in the left sphenoidal electrode (Figures 153.2a and b). Ictal patterns remained restricted in the left temporal distribution throughout the seizure without spreading to other brain regions. None of the recorded ictal patterns showed evidence of right hemisphere lateralization. Semiologically all of the patient's recorded episodes were classified as automotor seizures. Her typical seizures were punctuated by an initial motionless stare heralding a period of unresponsiveness. Oral (lip-smacking) and distal hand automatisms were observed with all seizures, starting approximately 15–20 seconds after clinical onset. There were no other motor manifestations. Such seizures are most frequently seen with temporal lobe epilepsies.[1,2]

Detailed semiological analysis of video recordings did not reveal any distinct lateralizing signs. During the noninvasive evaluation a total of nine seizures were recorded, six of which

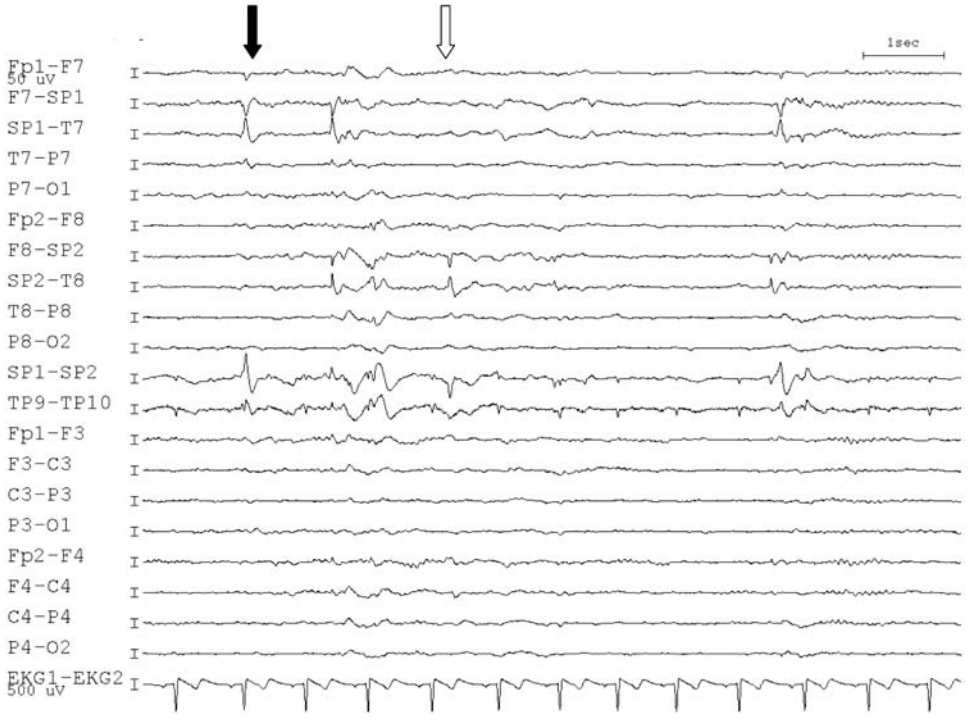


Figure 153.1 Scalp-EEG tracings demonstrating interictal, independent left (dark arrow) and right (white arrow) anterior temporal spikes, maximum at the ipsilateral sphenoidal electrode as seen on a longitudinal bipolar montage (the temporal chains have been extended with the addition of sphenoidal electrodes).

arose from sleep and three from wakefulness. No secondarily generalized seizures were recorded. The patient did not press the seizure button with any of these spells. Seizure duration based on EEG ranged from 30 to 80 seconds. Postictally, she was noted to be confused for a brief period lasting less than a minute. The patient was amnestic of her seizures.

Results of noninvasive video-EEG studies pointed to a left temporal seizure focus, and prompted referral for further presurgical investigation (phase 1.5 testing), which included a high-resolution anatomical MRI with thin cuts through the temporal lobes (temporal lobe epilepsy protocol),[3] an interictal FDG-PET study and formal, standardized neuropsychological evaluation.

Initial qualitative review of the patient's MRI did not reveal clear asymmetries of hippocampal size and/or signal intensity (a subtle decrease in the size of the right hippocampos was questioned). Careful visual inspection of contiguous 3D slices, however, provided no evidence to suggest unilateral atrophy, developmental dysplasia or a subtle mass lesion within the temporal lobes (Figure 153.3). On quantitative analysis the hippocampal formations were found to be volumetrically symmetrical.[3]

Axial and coronal interictal ^{18}FDG-PET images (coregistered to the patient's MRI) demonstrated bilateral hypometabolism involving the left and right mesial temporal regions. In addition, a small area of restricted hypermetabolism was seen within the region of the left amygdala (extending to a lesser degree to the left temporal pole). Otherwise, metabolic activity throughout the cortex and subcortical structures was uniform and symmetric (Figure 153.4).

The presence of bilateral hypometabolism on ^{18}FDG-PET is suggestive of an interictal functional deficit zone involving the left and right temporal regions and has been associated with bitemporal or less commonly diffuse or extratemporal seizure foci.[4–6] The patient's interictal PET study was unusual in that it also showed a distinct hypermetabolic focus in the region of the left amygdala. No electroencephalographic or clinical seizures were recorded during acquisition of these PET images, as confirmed by concurrent scalp EEG recordings (which started approximately 20 minutes before injection of radiotracer and continued for a period of 60 minutes).

Preoperative neuropsychological testing was notable for mild diffuse dysfunction involving multiple cognitive domains (Figure 153.5a). In addition, there were indications of at least mild level of psychological distress characterized by symptoms a verbal and nonverbal memory tests administered. Auditory memory index scores fell in the impaired range, and visual memory index scores ranged from mildly impaired to the lower end of the borderline range (Figures 153.5b and c).

The interpreting neuropsychologist suggested that some of the patient's difficulties on testing may be attributable to her uncontrolled seizures, level of psychological distress and/or medication adverse effects. The results of this extensive preoperative neuropsychological battery did not reveal a lateralized pattern of impairment and were consistent with other preoperative evidence pointing to 'bilateral mesial temporal dysfunction'. Because memory function was significantly impaired it was felt that the patient would be at relatively little risk for decline, if she were to have a left (presumably dominant) temporal lobectomy.

Summary of presurgical evaluation and surgical plan

The patient's noninvasive EEG recordings incriminated the left temporal region. Her structural MRI, however, did not provide lateralizing information in support of a left temporal epileptogenic focus. Furthermore, interictal EEG, interictal PET and preoperative neuropsychological findings indicated a bilateral functional deficit zone involving both mesial

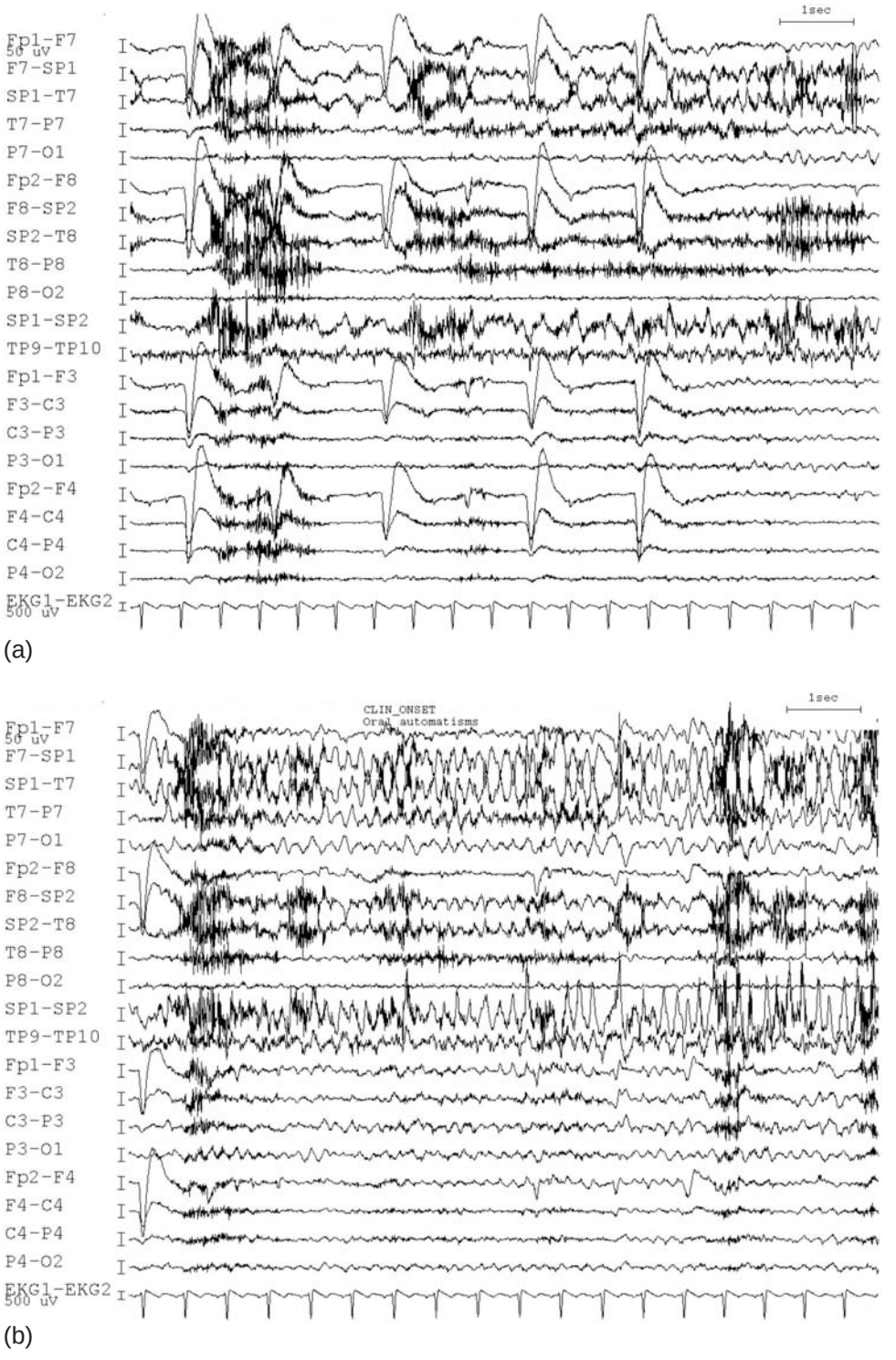


Figure 153.2 Scalp video-EEG evaluation: Two consecutive 10-second scalp-EEG tracings of a typical seizure occurring out of wakefulness, characterized by arrest of activity followed by unresponsiveness and oral automatisms (same montage as seen in Figure 153.1). (a) Electrographic onset with the emergence of initially arrhythmic, sharply contoured delta activity at the left temporal region (left sphenoidal electrode); (b) Evolving ictal pattern: a well-developed left temporal rhythmic discharge (5–6 Hz) is seen within 10 seconds of electrographic onset. As the seizure progresses the left temporal ictal discharge appears to gradually slow down, and ends after a total duration of ~40 seconds (not shown).

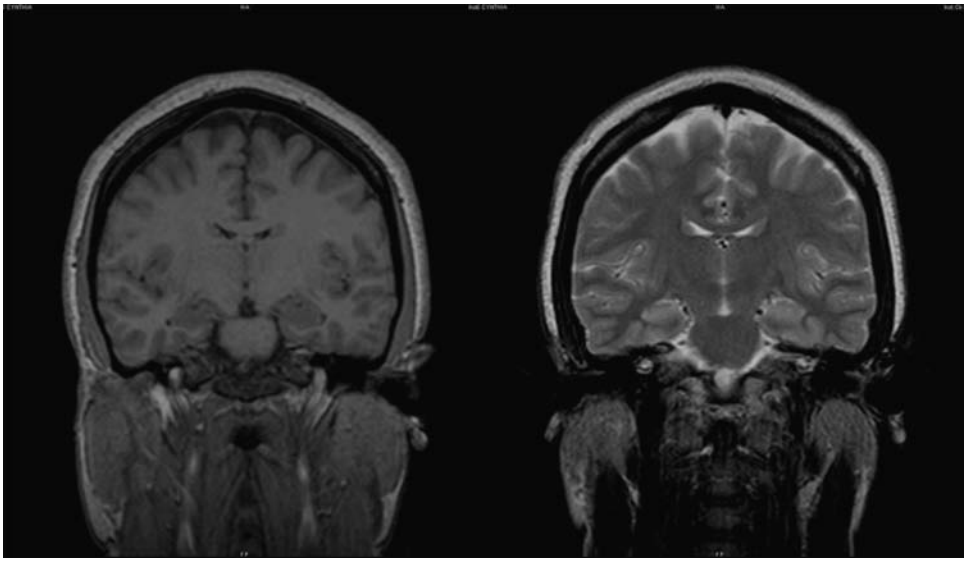


Figure 153.3 Preoperative MRI: Coronal high-resolution T1-weighted and corresponding T2-weighted images at the level of the hippocampal head depicting the normal basal and lateral surface of both temporal lobes along with the hippocampal formations. Qualitative visual analysis of preoperative MRI images did not reveal any clear asymmetries of hippocampal size and/or signal intensity. The neuroradiologist suggested a subtle decrease in the size of the right hippocampal head, but this was not confirmed upon reviewing the reformatted 3D MPRAGE images. The two hippocampi were volumetrically symmetrical on formal quantitative analysis.

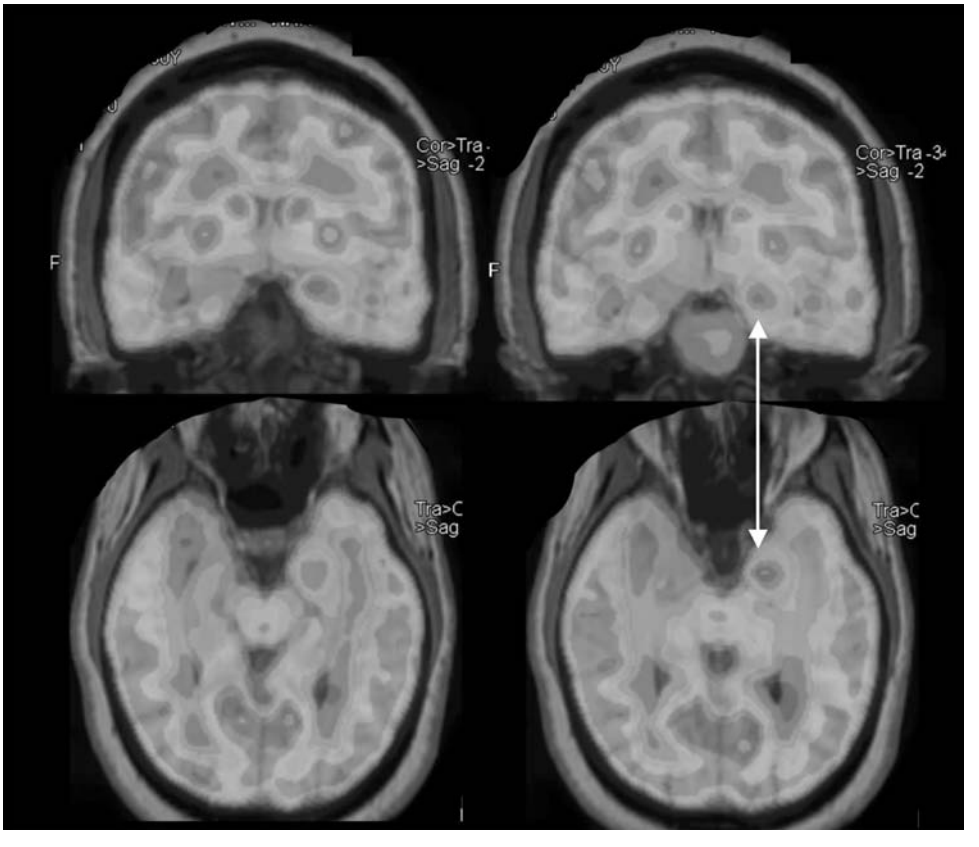
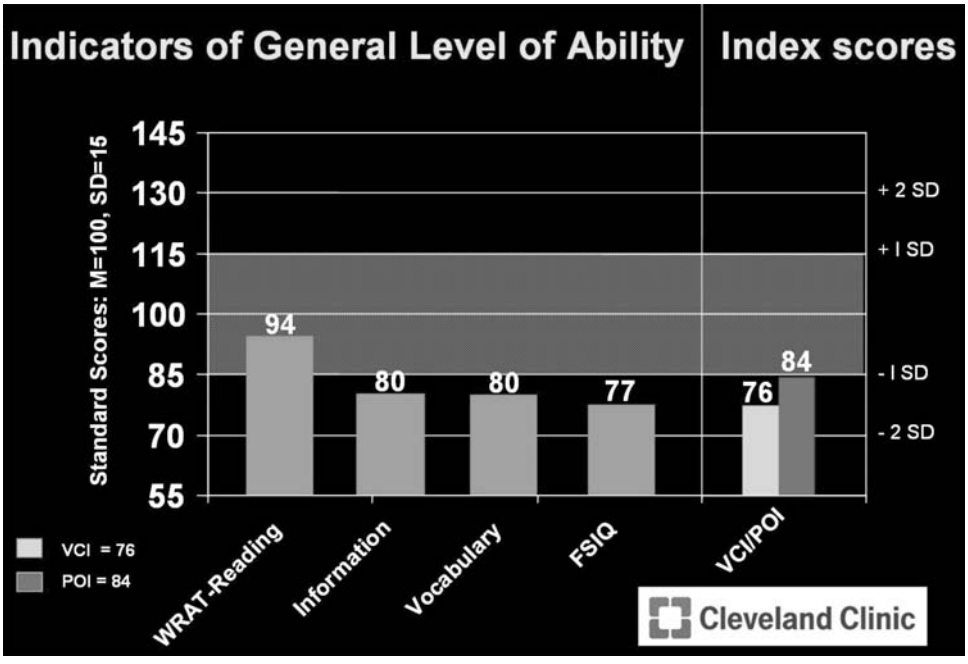
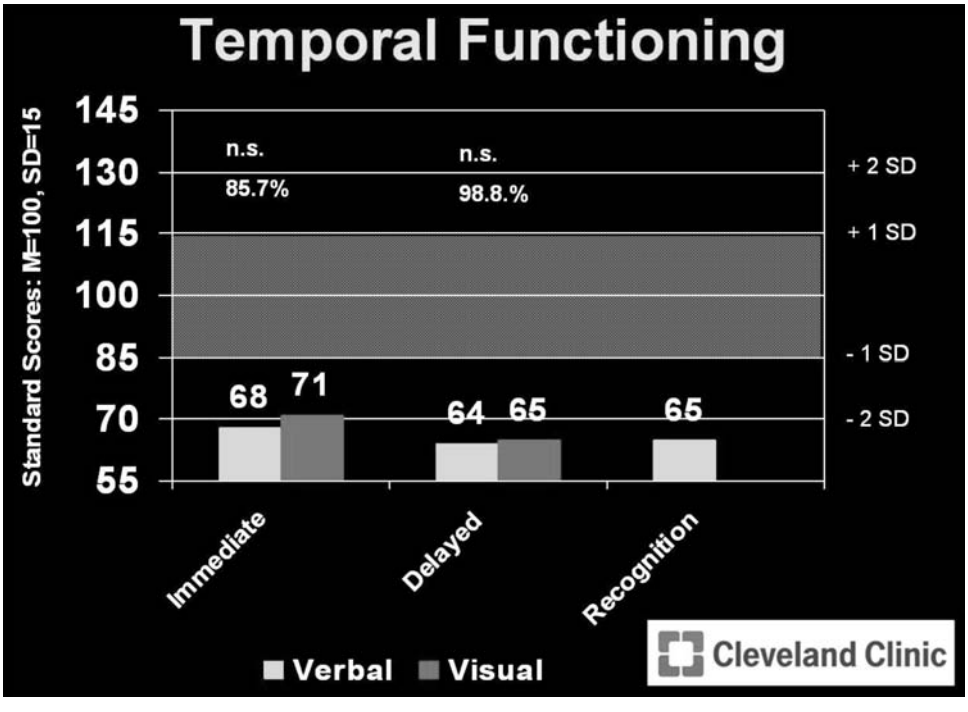


Figure 153.4 Coronal and axial preoperative interictal ^{18}FDG-PET images (coregistered to the patient's MRI) demonstrate bilateral hypometabolism involving the left and right mesial temporal regions. In addition, a small area of restricted hypermetabolism is present within the region of the left amygdala (double arrow). This restricted area of increased uptake overshadows any evidence of lateralized/asymmetric temporal hypometabolism. Otherwise, metabolic activity throughout the cortex and subcortical structures is uniform and symmetric.



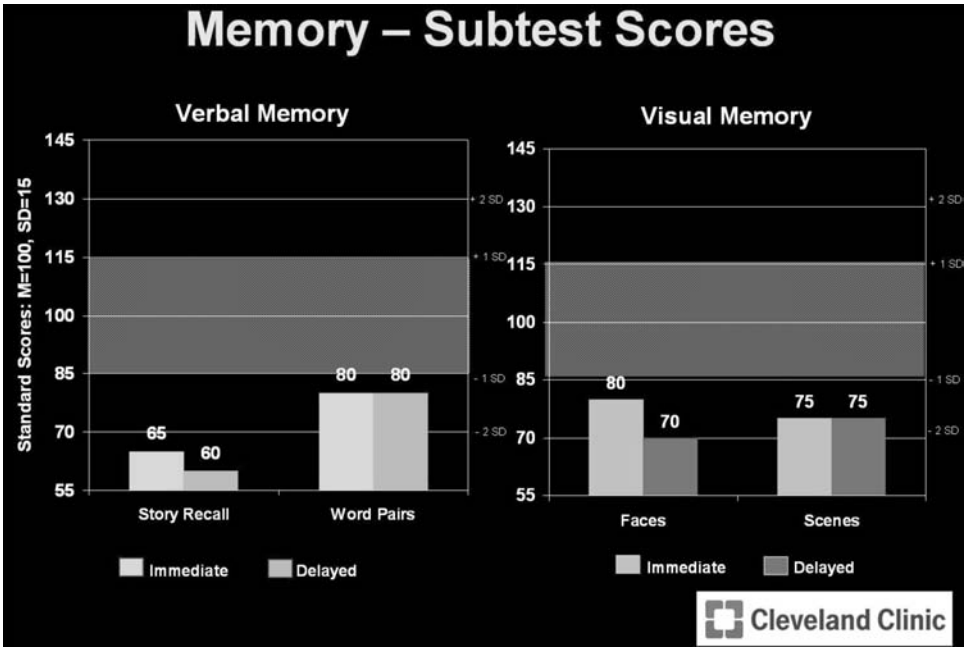
(a)



(b)

Figure 153.5 Preoperative neuropsychological battery results. The shadowed area corresponds to the mean ± 1SD of normative values. (a) Overall, the cognitive data suggest a pattern of a mild, diffuse dysfunction involving multiple-cognitive domains. Indicators of general level of ability, depicted on the left, include: the Reading score based on the WRAT (Wide Range Achievement Test), the Information and Vocabulary subtest scores based on the WAIS-III (Wechsler Adult Intelligence Scale-Third Edition), and the FSIQ (Full Scale IQ) results of the WAIS-III. Two of the factor index scores derived from the WAIS-III, the VCI (Verbal Comprehension Index) and POI (Perceptual Organization Index) are plotted on the right. The WAIS-III yielded a full scale IQ of 77 with a VCI of 76 and a POI of 84; the difference between VCI and POI is not statistically significant; (b) Both verbal and visual memory scores were below normal, without evidence of significant discrepancy between the two sides.

Continued



(c)

Figure 153.5 *cont'd* (c) Material-specific verbal and visual memory subtest scores.

temporal regions. During review of this case in the interdisciplinary patient management conference, participants noted the bitemporal interictal sharp waves and lack of an unequivocal abnormality on MRI. Most noninvasive tests were suggestive of bitemporal dysfunction. It was also noted that aside from the curious left-sided 'hot spot' on the interictal PET, the MRI and semiology of recorded seizures failed to provide any additional lateralizing information.

It was therefore decided to proceed with an invasive evaluation with bitemporal depth electrodes to confirm or refute the hypothesis that all of the patient's habitual seizures arise from the left temporal lobe.[7,8] Concepts and implications related to the presence of unitemporal versus independent bitemporal seizure foci were reviewed with the patient and her family, and the patient's expectations of surgery were clearly discussed.[9,10]

Invasive evaluation

Three pairs of depth electrodes were inserted symmetrically by an orthogonal approach. Each depth electrode consisted of eight platinum contacts (with a contact diameter of 1mm; Ad-Tech, Racine, WI, USA) located 5mm apart.[11] They penetrated the temporal lobe horizontally through the middle temporal gyrus, and their tips (most distal contacts) were aimed at the amygdala, anterior hippocampus and mid/posterior hippocampus (Figure 153.6).

Invasive video-EEG evaluation with bitemporal depth (and 10–20 scalp) electrodes

Interictal depth EEG showed frequent, independent bitemporal abnormalities with spikes arising from the left and right hippocampal contacts (Figures 153.7 and 153.8). In contrast to the noninvasive findings (on sphenoidal electrodes) the majority of the depth-recorded spikes originated from the right hippocampus (with an approximate left-to-right ratio of 25:75).

A total of 30 electrographic seizures were recorded during the period of stereotactic depth investigation. All seizures were characterized by a focal onset[8] involving the left anterior hippocampus (nine seizures, Figure 153.9) or the right anterior hippocampus (17 seizures, Figure 153.10) or the left amygdalar contacts (four seizures). The majority (almost 70%) of the 13 left-sided seizures (Figure 153.9) were reflected

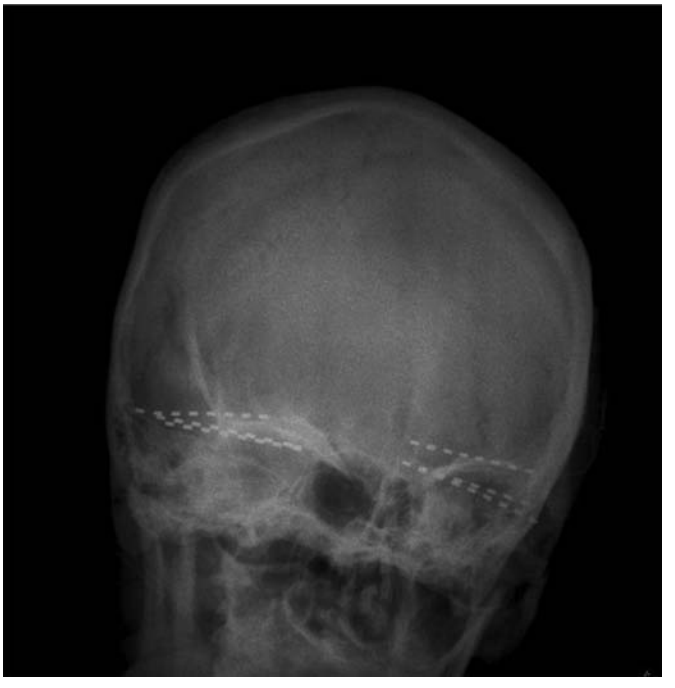


Figure 153.6 Skull X-ray following placement of pairs of temporal depth electrodes targeting bilaterally the amygdala, and the anterior and posterior hippocampus.

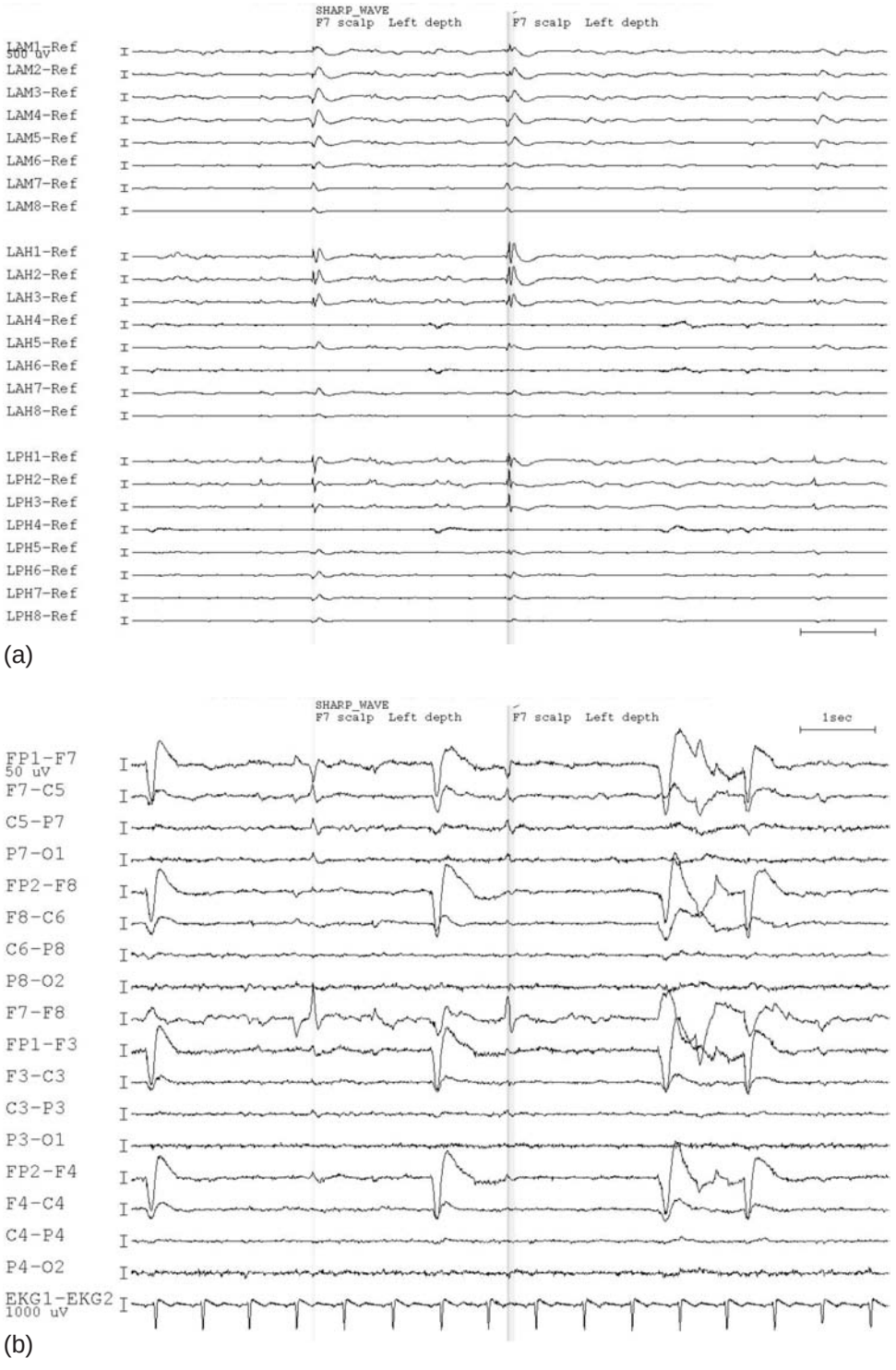


Figure 153.7 Simultaneous scalp and depth electrode recordings depicting interictal epileptiform activity arising from the left anterior temporal region: (a) Depth electrodes in the left mesial temporal structures (LAM = left amygdalar, LAH = left anterior hippocampus and LPH = left posterior hippocampus; contact 1 is the most distal and contact 8 the most proximal electrode). Referential montage using the extracranial vertex (Pz) electrode as reference. Interictal spikes appear to form a dipole with maximum negativity at the most distal left anterior (and posterior) hippocampal contacts and positivity at the left amygdalar electrodes; (b) The same interictal discharges as reflected on the scalp on this longitudinal bipolar montage (note that the standard T7 and T8 electrodes have been replaced by the adjacent C5 and C6 on the international 10–10 system to allow for concurrent depth and surface EEG recordings).

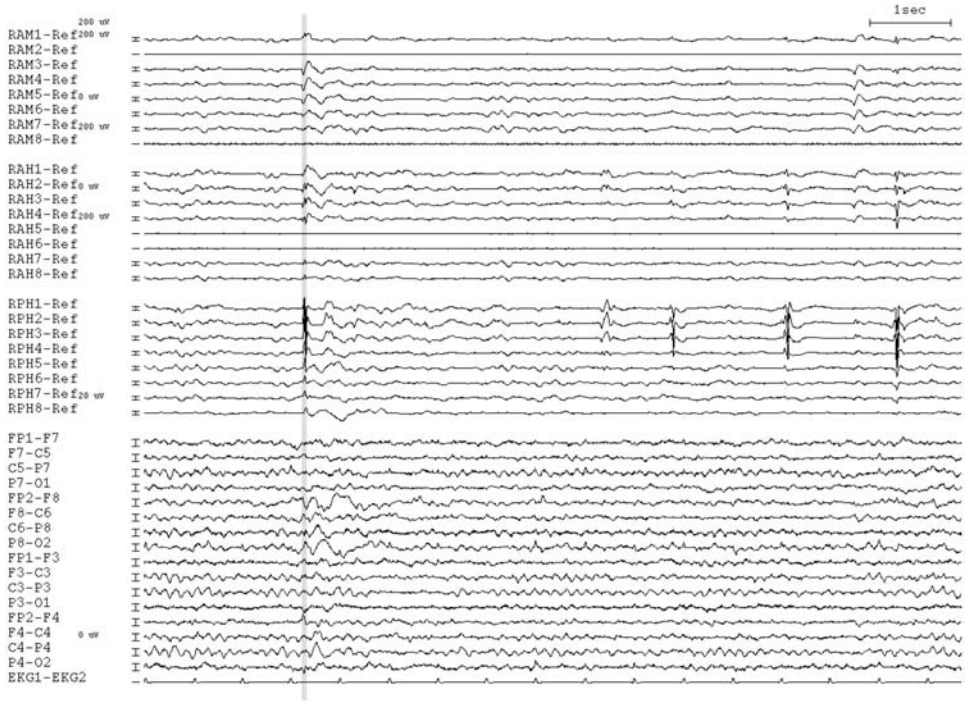


Figure 153.8 Simultaneous scalp and depth electrode recordings depicting independent interictal epileptiform activity arising from the right anterior temporal region (Abbreviations as for Figure 153.7. RAM = right amygdalar, RAH = right anterior hippocampus and RPH = right posterior hippocampus depth electrodes). Interictal spike appears to form a dipole with a maximum negativity at the most distal left posterior hippocampal contacts and positivity at the right amygdalar electrodes. Note that the right-sided anterior temporal epileptiform discharge has a less conspicuous appearance on scalp electrodes, compared to the left-sided abnormalities (compare with Figure 153.7).

on scalp electrodes. Right-sided seizures were typically not reflected on the scalp except for occasional right temporal delta/theta slowing.

A clinical accompaniment was observed with all nine left-sided seizures. Clinically these were similar to the seizures captured during the noninvasive video-EEG study, and lasted for less than 90 seconds. Most right-sided seizures were subclinical except for one clearly dialeptic seizure, which was recognized by the patient's husband as one of her habitual spells. Electrographic seizures lasted for 70–120 seconds except for one seizure, which was sustained for a period of 3.5 minutes. Almost half of these subclinical seizures were identified by the technologist or nursing staff on the basis of EEG changes. When tested, the patient appeared to respond promptly and appropriately to verbal and nonverbal commands. There were no outward manifestations and no evidence to suggest speech or cognitive impairment.

Summary of invasive evaluation and surgical plan

The invasive evaluation lends support to the presumptive noninvasive diagnosis of bitemporal epileptogenicity and demonstrates independent interictal activity and electrographic as well as clinical seizures arising from the left and right mesial temporal structures. Prolonged recordings with bitemporal depth electrodes showed that the vast majority of electrographic seizures from the right temporal contacts occurred in the absence of clinical signs. On the other hand, seizures emanating from the left temporal contacts were almost always associated with alteration of awareness. It was also noted that left temporal onset seizures persisted after resumption of full doses of antiepileptic medications during the latter part of invasive video-EEG recordings. Thus, the left mesial temporal region constitutes the predominant epileptogenic focus responsible for the majority of the patient's habitual seizures. Given the patient's seizure burden and lack of good alternative therapeutic options it was decided to proceed with a left temporal resection.

Pathology and outcome

Rare seizures were noted by the patient and her family at the 6- and 9-month postoperative follow-up intervals – an estimated total of 4 seizure-days corresponding to a class II Engel[12] or class 4 Wieser seizure outcome.[13] No further seizures were reported at 12 months and following adjustment of the patient's antiepileptic medications. Although, the patient has experienced 2–3-month periods of seizure freedom following surgery, she has not been completely seizure free for longer periods of time, and has not been allowed to resume driving.

Neither the patient nor her relatives noticed any significant memory changes following surgery. However at the time of this report the patient has not had a formal postoperative neuropsychological assessment.[14] As she has recently relocated efforts are being made to have her come back for testing at our institution.

Pathology only showed nonspecific changes characterized by a mild degree of gliosis and neuronal loss involving the CA4 (cornus ammonis or Ammon's horn, subfield 4) region of the left hippocampus. The neuropathologist commented that the specimen was 'somewhat fragmented', and that qualitatively there was evidence for a mild degree of neuronal loss.

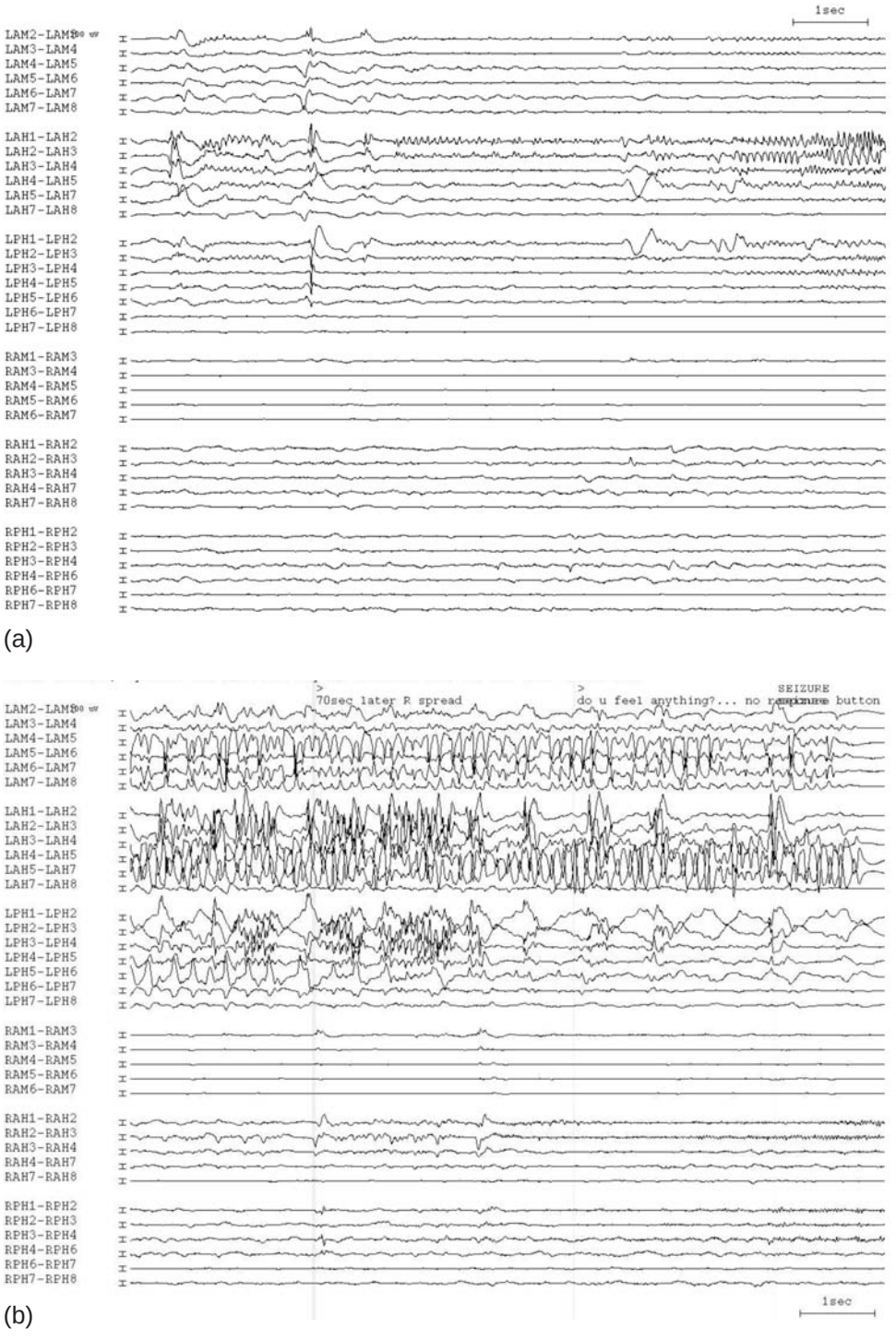
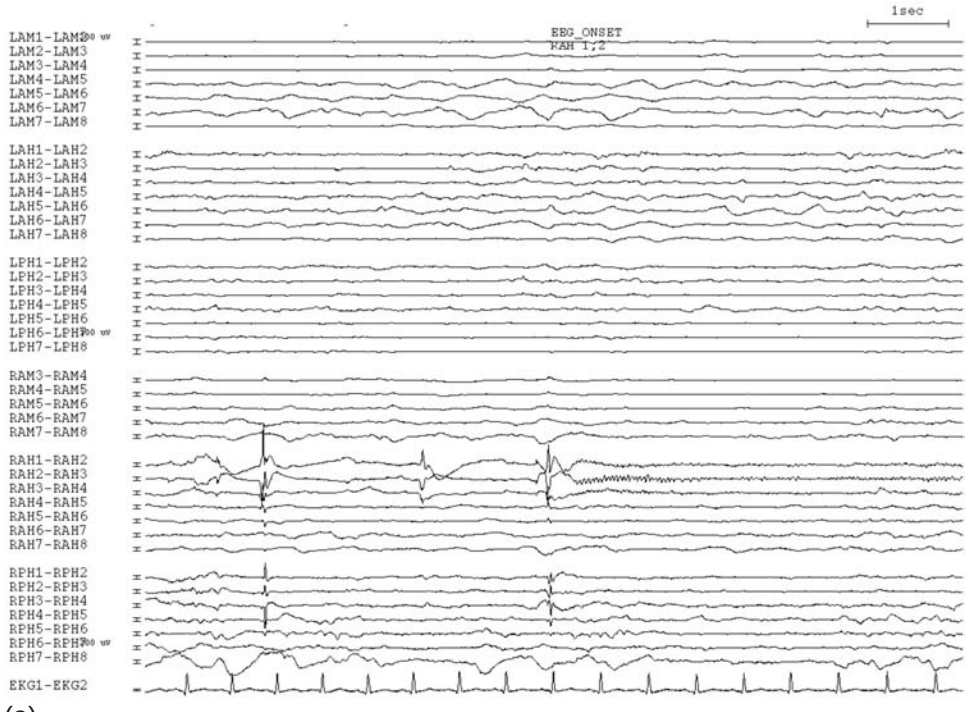
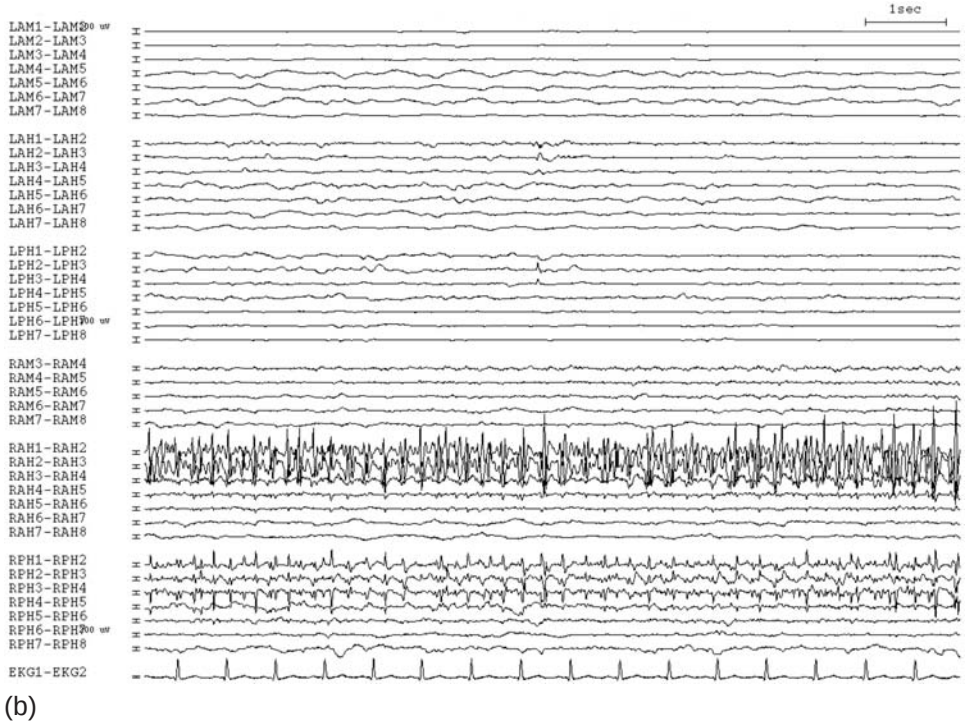


Figure 153.9 Invasive video-EEG evaluation: Bitemporal depth electrode tracings of a typical automotor seizure as displayed on a bipolar montage connecting adjacent depth electrode contacts (10-second epochs). *Note that 'bad' electrode contacts (such as the left-sided LAM1 and LAH6 in this instance and RAM2, RAM8, RAH5, RAH6, and RPH6) have been omitted to facilitate visual analysis*. (a) Electrographic onset with spike discharges – similar to the patient's interictal activity (see Figure 153.7a) – but now accompanied by an emerging low voltage fast (alpha-beta) rhythm. This rhythm is first seen at the most distal left anterior hippocampal contacts (Figure 153.9a). Sustained fast-rhythmic activity involves the most distal left anterior and posterior hippocampal contacts (not shown). At the time, that this activity spreads to involve the left amygdalar leads an ictal pattern becomes apparent on the scalp electrodes, and the seizure follows its stereotyped electroclinical evolution (similar to Figure 153.2); (b) Approximately 70 seconds after the appearance of ictal activity on the left-sided contacts, a fast ictal rhythm is now seen on the right-sided depth electrodes, which persists after the end of the left-sided seizure. Note, that at the end of the left-sided ictal pattern the patient appears to recover clinically and is again responsive and able to follow commands in spite of evolving right-sided ictal activity.



(a)



(b)

Figure 153.10 Bitemporal depth electrode tracings showing a typical subclinical electrographic seizure originating from the right hippocampus (same montage as Figure 153.9). (a) Onset in the latter half of the page punctuated by a spike discharge with superimposed, evolving low voltage fast activity arising from the most distal right anterior hippocampal contacts; (b) Involvement of the right posterior hippocampal contacts and evolution to repetitive high amplitude spiking is seen 20 seconds later. (Total duration of ictal activity: approximately 70seconds).

Detailed histopathological analysis of the amygdala was not feasible because of tissue fragmentation during surgery. It was felt that the amygdala section also showed evidence of mild gliosis and cell loss. Interestingly, a few microglial nodules were seen in the amygdalar area. Such nodules have been likened to 'the tombstones of dying neurons' and are occasionally seen in patients with temporal lobe epilepsy.[15] The resected temporal specimen did not show any other pathological abnormalities outside the mesial temporal area.

Discussion

The patient has bitemporal lobe epilepsy as defined by bitemporal depth EEG recordings, which demonstrate independent

seizure onsets arising from each temporal lobe.[16,17] The clinical history, video-EEG monitoring results, neuroimaging and neuropsychological evaluation support this diagnosis. The observed seizure semiology with arrest of activity, staring and altered responsiveness followed by automatisms is typical of temporal lobe epilepsy.[1,18,19] In this case, neither the patient herself nor other observers provided a history of aura. Such lack of aura experience has been correlated with bitemporal dysfunction in patients with temporal lobe epilepsy.[20–22]

Temporal lobe epilepsy is frequently a bilateral disease.[2,16,23] Up to one-third (or more) of patients with surgically-proven unitemporal epilepsy present evidence of bilateral irritability in the form of bilateral independent interictal epileptiform abnormalities.[7,8,24,25] Temporal lobe seizures can propagate directly to the contralateral temporal region as evidenced by scalp or intracranial recordings.[23,26,27] Moreover, structural and/or functional neuroimaging reveals a spectrum of bitemporal abnormalities.[2,5,28] Bilateral atrophy may be seen in approximately 10% of patients with intractable focal epilepsy and MRI evidence of hippocampal atrophy.[29] Finally, bilateral hippocampal neuropathological abnormalities are a common autopsy finding in patients with a clinical diagnosis of temporal lobe seizures.[24,30,31]

The ictal and interictal electroencephalographic findings suggest that the epileptogenic zone resides within the mesial temporal region. Indeed, hippocampal epilepsy is often accompanied by a highly characteristic epileptiform abnormality with maximal amplitude in the anterior and inferior temporal region.[24] These findings have been described as 'the interictal EEG signature' of epilepsy arising from the mesial temporal limbic structures,[19] and are best seen using basal derivations (such as sphenoidal electrodes; Figure 153.1). Bilateral independent temporal interictal epileptiform discharges (IEDs) are seen in approximately one third of patients with temporal lobe epilepsy.[8,32–34] The majority of patients with bitemporal IEDs have seizures arising exclusively (or with a strong predominance) from a single temporal lobe.[8,35] On that ground, most patients with bitemporal IEDs on surface EEG may be appropriate candidates for surgical treatment with anterior temporal lobectomy.

At the same time, the probability of independent seizure onset from both temporal regions is higher in the presence of bitemporal IEDs.[33,36] The degree of lateralization of independent bitemporal IEDs on scalp EEG may predict the likelihood of unitemporal seizure onset and/or favorable surgical outcome following anterior temporal lobectomy.[37] Chung and colleagues reviewed the operative seizure outcome in the second year after temporal lobectomy in 52 patients with preoperative evidence of bitemporal IEDs (interictal spikes and sharp waves). The authors established that there was a significant and progressive decrease in the number of good operative results that mirrored increasingly lower degrees of lateralization. The risk for poorer operative results was found to be considerably higher in patients with less than 90% lateralization of temporal IEDs, even in cases where subsequent depth electroencephalography indicated that all recorded seizures emerged from a single temporal lobe.[33] It should be noted, however, that such measures of IED lateralization are susceptible to sampling effects and may be affected by a number of other factors, including sleep stage and antiepileptic drug levels.[38–40]

In cases of suspected bitemporal lobe epilepsy or temporal lobe epilepsy with inconclusive lateralization, investigation with bitemporal intracranial depth electrodes may show that the patient's habitual seizures arise exclusively or predominantly from one temporal lobe.[8] Hirsch and colleagues performed a retrospective review of a large cohort of 166 consecutive patients studied with stereotactic depth electroencephalography. In this series 87 patients were found to have seizures arising from a single temporal lobe (unitemporal group), while 23 patients had seizures arising independently from either temporal lobe (bitemporal group). When comparing these two groups the authors did not find any statistically significant differences in terms of age at onset of seizures, duration of epilepsy, localization of scalp EEG abnormalities, surgical results or pathological findings. It was noted, however, that the bitemporal group had significantly fewer patients with a history of febrile seizures.[16] No history of febrile seizures was reported in our patient or her immediate family.

The typical ictal pattern seen with scalp EEG recordings consists of rhythmic theta activity in one sphenoidal electrode evident at the onset of the automotor or dialeptic temporal lobe seizure.[79] When present on scalp-sphenoidal electrode derivations such strictly defined, unilateral temporal ictal patterns can correctly predict the findings of depth electrode investigations in 82 to 94% of patients.[79] However, the reliability of scalp/sphenoidal ictal EEG recordings is considerably reduced in patients with bitemporal IEDs, in whom ictal scalp-sphenoidal EEG is significantly less likely to predict the correct side of surgery (only 64 to 77% of the time in one study).[41]

Patients with suspected temporal lobe epilepsy should undergo detailed MRI studies that consist of multiple coronal T1, T2 and FLAIR (fluid-attenuated inversion recovery) images, sagittal T1 images, and axial T2 and FLAIR images. Coronal three-dimensional T1-weighted MP-RAGE (magnetization-prepared rapid gradient echo) sections with a 2 mm thickness and no interslice gap should be acquired and used for anatomical reconstruction. In the case discussed here, qualitative visual analysis suggested a subtle abnormality involving the right hippocampus (questionable decrease in size). In addition to visual inspection the volumes of the left and right hippocampal formations were measured from the coronal sections following standard anatomic guidelines.[42] Absolute measures of hippocampal volumes were compared to normative data obtained from a sample of healthy volunteers.[43] Although both right and left hippocampal volumes were relatively decreased, this decrease did not exceed two standard deviations, when compared to normative data. Furthermore, the right hippocampus al volume was slightly smaller, but the volumetric asymmetry between the two sides was not significant (volumetrically symmetrical 'normal' hippocampi). Previous studies suggest that temporal epilepsy may exhibit a spectrum of volumetric abnormalities ranging from bilateral asymmetrical or symmetrical hippocampal atrophy, to unilateral atrophy or no atrophy.[44] Our patient belongs to the challenging latter group – i.e., patients 'with marginal MRI abnormalities that approach the limit of normal variation'.[45]

Prognosis following temporal lobectomy in the nonlesional group is regarded as least favorable,[46] but postoperative seizure freedom or worthwhile improvement occurs. In a study of 74 consecutive patients with pharmacoresistant TLE, investigators

performed preoperative bilateral volumetric MRI measurements of the mesial temporal structures. Patients were divided into three groups according to volumetric findings: unilateral atrophy (63.5% of the patients), bilateral atrophy (23%) or no atrophy (13.5%) of the amygdalohippocampal formation. Surgical outcome was assessed at least 1 year after surgery. Excellent results – class I or II outcome using a modified Engel's classification[12] – were observed in 93.6% of patients with unilateral atrophy, 61.7% of those with bilateral atrophy and only 50% of the group with no significant atrophy of the amygdalohippocampal formation.[47]

The presence of bilateral hypometabolism on ^{18}FDG-PET suggests that the 'functional deficit zone' involves both the left and right mesial temporal regions.[4,48] In a study of 15 patients with temporal lobe epilepsy Koutroumanidis and colleagues reported that the finding of symmetric or even asymmetric bitemporal hypometabolism was associated with bilateral independent seizure onset in almost half of these patients – especially when involving the inferior temporal gyrus.[5]

Most human epilepsy studies have utilized ^{18}FDG-PET imaging to examine cerebral metabolic rates for glucose during the interictal state.[49,50] In this case however, the interictal PET study was also notable for the presence of a distinct and unusual, small hypermetabolic focus in the region of the left amygdala (extending to a lesser degree to the left temporal pole) (Figure 153.4). No electroencephalographic or clinical seizures and no repetitive epileptiform discharges were recorded from scalp electrodes during acquisition of these PET images.

It has been suggested that prolonged discharges confined to the amygdala and/or hippocampus may not be reflected on the surface EEG.[2,51] During her invasive evaluation it was estimated that less than 25% of the patient's depth-recorded, left-sided interictal spikes were visible on scalp electrodes. This lack of interictal epileptiform abnormalities on scalp recordings, while concurrent depth recordings show spiking activity, has been attributed to the distance separating scalp electrodes from a putative generator in the amygdalo-hippocampal complex.[51,52] It is also known that the amygdala tends to behave as a closed electrical field,[53–55] a fact that may contribute to discrepant scalp versus invasive recordings.

Neuropsychological testing commonly reveals an asymmetry in memory functions in patients with unilateral mesial temporal lobe epilepsy. Memory deficits are typically material-specific for the temporal lobe primarily involved,[2,19] but patients with mesial temporal lobe epilepsy may manifest a more generalized cognitive impairment.[56] Neuropsychological testing suggestive of bilateral or more diffuse functional deficit zones may identify surgical candidates with a poorer surgical outcome, presumably related to more extensive or diffuse epileptogenic zone(s).[57]

Neuropsychological data in our patient were nondiagnostic in terms of lateralization, and suggested bilaterally decreased memory function. The presence of independent bitemporal seizure foci has been associated with impairments of both verbal and spatial memory.[5,24,58] Patients with bitemporal epilepsy may have increased difficulties recalling personal events and may show a pattern of general memory impairments. Hence, it has been suggested that from a functional standpoint, patients with bitemporal epilepsy may be regarded as partially amnestic.[58]

In surgical decision making it is also important to consider and discuss the concept of *'apparent bitemporal epileptogenicity'*:[59] several authors have reported that seizure onset in a posterior epileptogenic focus can masquerade as bitemporal epilepsy.[16,60,61] In a recent study the Montreal group presented six patients with nonlesional focal epilepsy, who failed anterior temporal lobectomy despite localized EEG findings pointing to the anterior and inferomesial temporal region. It was noted that all six patients reported a soma tosensory aura, a clinical feature suggestive of a more posterior temporoparietal symptomatogenic origin.[62]

Because of their inherently narrow scope, invasive recordings with bitemporal depth electrodes may fail to disclose a posterior or other epileptogenic focus outside the temporal regions.[8] If the apparent bilateral EEG onset in mesial/basal structures results from a posterior epileptogenic region with variable propagation to these structures, then resection targeting the anteromesial temporal lobe (i.e., the site of propagation) is destined to fail.[59] Notwithstanding these limitations, there was no evidence from the noninvasive evaluation to suggest a posterior temporal or extratemporal focus in our case. Preoperative MRI did not reveal any structural abnormalities outside the temporal lobes.

Furthermore, neither the patient's surface EEG nor her interictal PET studies were suggestive of an extratemporal focus. Prolonged interictal scalp EEG recordings did not disclose additional spike foci outside the bilateral inferomesial regions. Ictal scalp EEG recordings were localized early on during seizures to the left (or right) temporal region and no diffuse or nonlocalizing patterns were recorded. Finally, the patient's stereotyped clinical semiology was not suggestive of a temporoparietal or extratemporal origin.[63]

Eccher and colleagues recently reviewed the Cleveland Clinic surgical database from 1990 to 2001 and identified a total of 105 patients, who underwent unilateral temporal lobectomy despite evidence of bitemporal epileptiform abnormalities (bilateral interictal spikes and/or seizures) on the preoperative surface EEG evaluation. In this cohort the majority of patients 48.6% (51/105, group A) had evidence of unilateral scalp EEG seizures and bilateral interictal epileptiform discharges. Another 24.8% (26/105, group C) had evidence of scalp EEG seizures arising independently from the left and right hemispheres. The remaining 26.7% (28/105, group B) presented with bilateral interictal spikes and a mixture of EEG seizures which consisted of strictly unilateral as well as nonlateralizable seizures–in the absence of scalp EEG evidence for strictly contralateral seizures (Eccher MAR *et al.*[64] and personal communication). Roughly one-third of patients in this cohort 32.3% (34/105) underwent an invasive evaluation with bilateral subdural and depth electrodes prior to surgery. Of note, seizure freedom at last follow-up (for duration of follow-up ranging from 2 years to more than 10 years) was found to be similar in the three groups: 58.8% for group A (30/51), 57.1% for group B (16/28), and 65.4% for group C (17/26). Regression analysis suggested that the following four factors were associated with a higher likelihood of postoperative seizure recurrence: a history of secondarily generalized seizures, a positive family history of epilepsy, the absence of a history of febrile convulsions, and a preoperative seizure frequency that exceeded 20 seizures/month. Invasive recordings revealed bilateral independent ictal onsets on depth electrodes in 23.5% of the patients referred for invasive evaluations (8/34). Four of these eight patients remained seizure free at last follow-up.[64]

The patient discussed here did not undergo a Wada test (intracarotid amobarbital procedure, IAP). Whether IAP testing provides meaningful clinical information that aids in predicting postoperative memory changes is controversial, more so in cases of suspected bitemporal epilepsy.[65] The IAP protocol used at our institution was evaluated in a study of 72 consecutive patients with unilateral temporal lobe epilepsy (39 left ATL and 33 right ATL). Neither the contralateral injection IAP memory score (a measure of functional adequacy) nor the ipsilateral injection IAP memory score (a measure of functional reserve) were shown to significantly predict verbal memory outcome, based on a model of backward stepwise regression analysis.[66] This model showed that the only variables predicting postoperative verbal memory were MRI hippocampal volume ratio, baseline verbal memory and side of surgery. A more recent study at our institution examined 12 patients with unilateral left (dominant) TLE who showed neuropsychological evidence of poor presurgical verbal and visual memory scores. None of these patients demonstrated a reliably meaningful decline in delayed verbal memory score following left ATL.[67] As expected, most reports review the value of presurgical studies (including Wada testing) in patients with a unilateral temporal lobe seizure focus. Consequently, very limitedinformation exists about the value of presurgical studies in predicting morbidity in patients with bitemporal epilepsies.

The incidence of TLE without an identifiable pathological substrate is difficult to estimate. Significant bias (sampling and ascertainment bias, for example) confound results of reported surgical series and autopsy studies.[68,69] Wieser points out that in patients without definite/specific histopathological abnormalities one cannot exclude the origin of seizures outside the resected temporal lobe–given that the surgical outcome in this group tends to be worse compared with patients with demonstrable pathological changes in the resected surgical specimen.[70] It has been estimated that approximately 10% of resected temporal specimens in patients with suspected temporal lobe epilepsy (TLE) show no significant histopathological abnormalities.[70] Ongoing surgical experience with TLE suggests that the absence of mesial temporal sclerosis is more common than previously suspected.[69] Such observations have led to the use of the term 'paradoxical TLE' or 'cryptogenic TLE' for these patients, because of the paucity of appreciable neuronal loss.[71] Lastly, hippocampal sclerosis can be so mild that it cannot be identified on structural MRI despite the use of high-resolution imaging, and in some cases it may even not be detectable by routine histopathological examination.[19]

Patients with bitemporal epilepsy without a predominant seizure focus are not considered candidates for resective surgery. Several authors have reported on the use of alternative therapies such as chronic vagus nerve stimulation[72] or experimental deep brain stimulation applied directly to the amygdalohippocampal structures[73,74] or to various modulatory subcortical structures such as the anterior nucleus of the thalamus[75,76] and the subthalamic nucleus.[77] An interesting neurosurgical approach, which may hold promise for patients with bitemporal epilepsy, is under development in Japan. The technique entails transection of the hippocampus in a manner similar to that of multiple subpial transections, performed under intraoperative electrocorticographic guidance. A recent report only included patients with unilateral temporal lobe epilepsy, and intact preoperative material specific memory function in the presence of a structurally normal-appearing hippocampus. The authors express their intent to further explore this technique in bitemporal lobe epilepsy encouraged by their positive, albeit very preliminary, seizure and functional results in patients with unitemporal seizures.[78]

Summary

A 30-year-old patient with a history of poorly-controlled seizures starting at the age of 20 years is presented. Her seizures consist of initial alteration of awareness and staring followed by bimanual and oral automatisms and a brief period of postictal confusion. Seizures have persisted despite multiple trials of appropriately chosen antiepileptic medications resulting in significant psychosocial disability.

A comprehensive noninvasive presurgical evaluation raised concerns for bitemporal epileptogenicity. Subsequent invasive evaluation with bilateral temporal depth electrodes demonstrated electrographic seizures arising from both the left and right temporal lobes. However, the majority of the patient's disabling clinical seizures were shown to originate from the left amygdalohippocampal complex. A left anterior temporal lobectomy was performed. One year later, the patient reports significant benefit in terms of seizure control, although at her last follow-up she has not achieved seizure freedom for a period longer than 6 months.

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154 Patient with lesional neocortical focal epilepsy

B Abou-Khalil

Case presentation

A 42-year-old right-handed man presented for evaluation and treatment of seizures since age 10. He could not remember his initial seizures well. They started with a strange feeling in the head that he could not describe. He would then lose awareness and have picking motions of the hands. After the seizure, he would be very tired. Epilepsy was diagnosed, but seizures were never controlled for more than 1 year, and they changed over time. At the time of last presentation he had a consistent aura which he now described as a feeling like a 'pop' in his head. The aura would last 5–10 seconds, then he would lose awareness and would be noted to stare and to purse and smack his lips. He would repeat 'what' over and over. He fumbled and picked with either hand. He hummed at times. He reported seizure duration as 20 seconds, after which he was confused and had slurred speech for about 1 minute. He did report word finding difficulty postictally for about 5–10 minutes. He tended to have seizures in clusters. For example, 30 seizures had occurred in the previous year, but he had eight seizures in 1 month before presentation. In addition, he averaged about three isolated auras per month. He had had only four secondarily generalized tonic-clonic seizures in his life, all in one year, in 1984. With these, his wife thought that he had head-turning to one side, but she could not remember which side.

At presentation, he was taking lamotrigine, 200 mg three times a day, and carbamazepine, 500 mg in the morning and 600 mg at night. He had failed treatment with phenytoin, valproate, and tiagabine. He thought that his medications were all in combinations never in monotherapy. Past medical history revealed no clear risk factors for epilepsy, with the exception of a positive family history of seizures in one of his two sisters and in one paternal cousin. In both instances, seizures were outgrown. He had been a heavy drinker in the past, but had stopped drinking 20 years previously.

The review of systems was notable for complaints of memory loss, depression, and irritable mood.

Social history indicated that he graduated from high school with average grades. He was self-employed as a farmer. He had been married for 21 years with one 13-year-old daughter.

General and neurological examinations were completely normal, including mental status, cranial nerves, motor system, reflexes and sensory system.

Review of past evaluations indicated that he had had an MRI that was reported normal. No other outside data were available.

The patient was interested in a definitive treatment for his seizures, and had heard about epilepsy surgery. He underwent a complete presurgical evaluation.

MRI revealed a 20-mm lesion that had increased T2 signal in the center and decreased signal in the surround, suggesting old hemorrhage (Figure 154.1). This lesion was abutting the interior aspect of the left petrous pyramid laterally. There was no hippocampal sclerosis.

18F-Fluorodeoxyglucose positron emission tomography (PET) scan revealed a zone of reduced FDG uptake over the inferolateral region of the left temporal lobe, corresponding to the MRI lesion (Figure 154.2).

Inpatient video-EEG monitoring for 4 days in conjunction with medication withdrawal recorded six partial onset seizures, two of which secondarily generalized. Five events began in sleep, and were characterized by arousal with restless movements, glancing around, initial fumbling with the left hand in two events, right arm dystonic posturing or immobility of the right arm in four events, and lip-smacking and chewing in three events. In the two seizures that generalized, there was adversive head and eye deviation to the right in

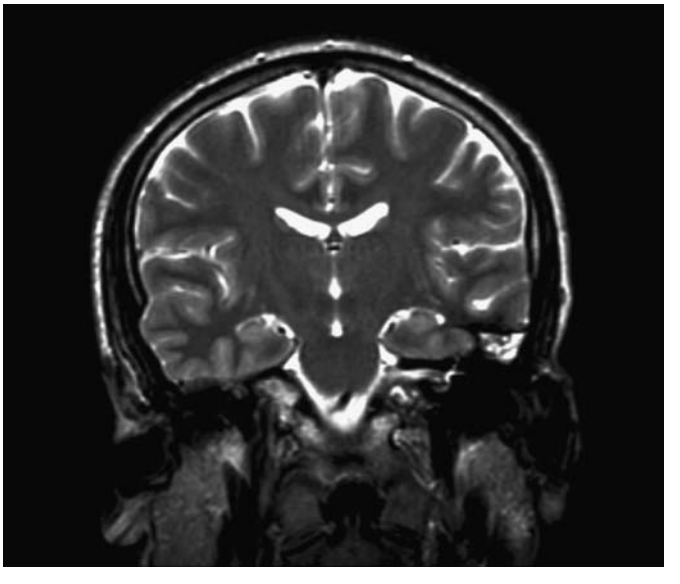

Figure 154.1 MRI shows a probable left inferior-lateral temporal cavernous angioma (arrow).

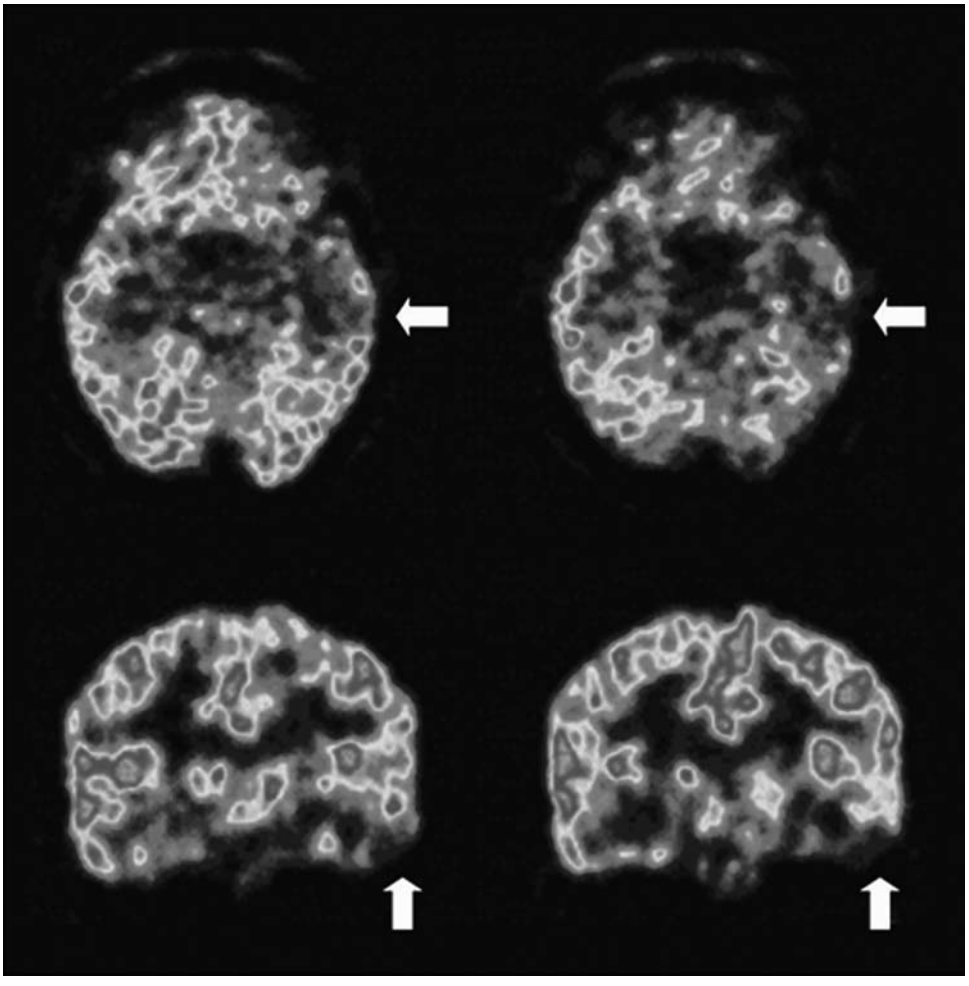

Figure 154.2 FDG PET (axial top row; coronal bottom row) shows a defect in FDG uptake in the left inferior-lateral temporal region, corresponding to the MRI lesion (arrows).

transition to generalization. There was nose-wiping postictally with the left hand in one event.

The associated ictal onset was consistently left temporal, but with predominance in the left sphenoidal electrode (Figure 154.3). Interictally, there were independent epileptiform discharges recorded from the left mesial-basal and lateral anterior-mid temporal region (with mesial-basal predominance), and from the left posterior and mid lateral temporal region with variable involvement of the left posterior quadrant. Finally, there was intermittent irregular left temporal slow activity (Figures 154.4 and 154.5).

Neuropsychological testing (see Table 154.1) revealed borderline abilities, with significantly stronger aptitude for nonverbal skills in comparison to verbal skills. He also had stronger visual memory skills in comparison to verbal recall on the Wechsler Memory Scale WMS-III. He did not do well with either Rey-O Complex Figure. Recall or Buschke Selective Reminding Recall.

The intracarotid sodium amobarbital procedure was performed with 125 mg of sodium amobarbital on each side, with about 30 minutes between injections. The left hemisphere was injected first. The patient developed global aphasia for more than 7 minutes, indicating left hemisphere dominance for language. He had only dysarthria (no language impairment) with right injection. He passed memory testing marginally with both left and right injection.

Summary of presurgical evaluation and surgical plan

The lateralization of the epileptogenic zone was confident to the left hemisphere, based on the combination of MRI and PET findings, seizure semiology (the strongest lateralizing signs were the right arm dystonic posturing and the versive head turning to the right in transition to generalization – the postictal aphasia was also an important features derived from the history), interictal epileptoform discharges, ictal EEG onset, and interictal slow activity. However, there was a discrepancy between the imaging findings which indicated a neocortical temporal structural and functional lesion, and the ictal EEG onset which favored a mesial-basal seizure onset. The EEG interictal epileptiform abnormalities were consistent with independent lateral temporal and mesial-basal temporal irritative zones. The aura of 'pop' in the head can be considered a cephalic aura. It is nonspecific with respect to localization, but may be more common with neocortical seizure foci. The remainder of the seizure semiology was consistent with mesial temporal seizures, but seizures can spread and the predominant seizure semiology may actually reflect involvement of structures after seizure spread. Since cavernous angiomas are highly epiletogenic, it was felt that the left neocortical temporal cavernous angioma was most probably the epileptogenic lesion. It is also not

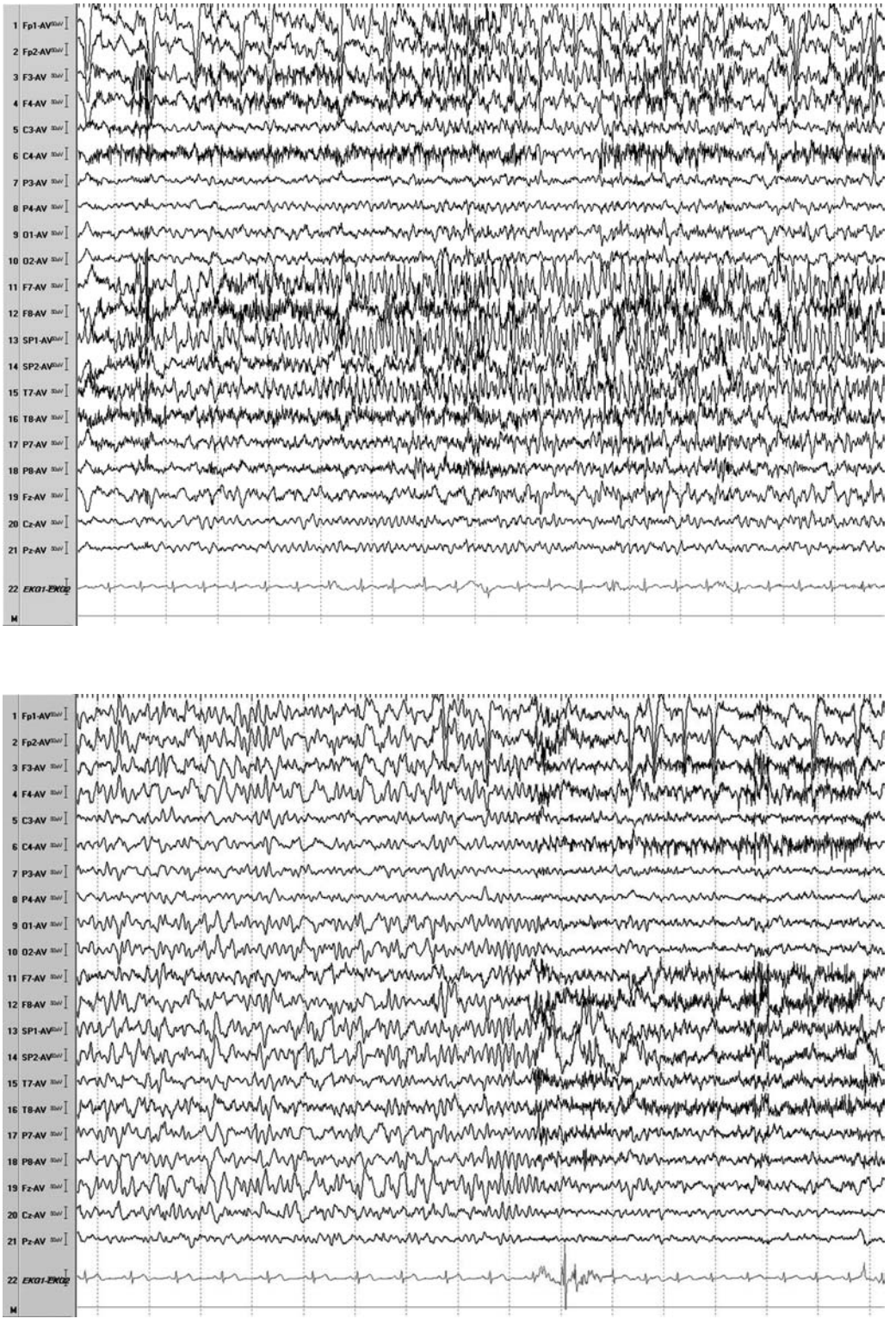

Figure 154.3 Ictal onset on an average referential montage. There was initially a voltage attenuation in conjunction with muscle artifact. The first definite rhythmic ictal activity was in the theta range. It was left temporal, with voltage predominance at Sp1.

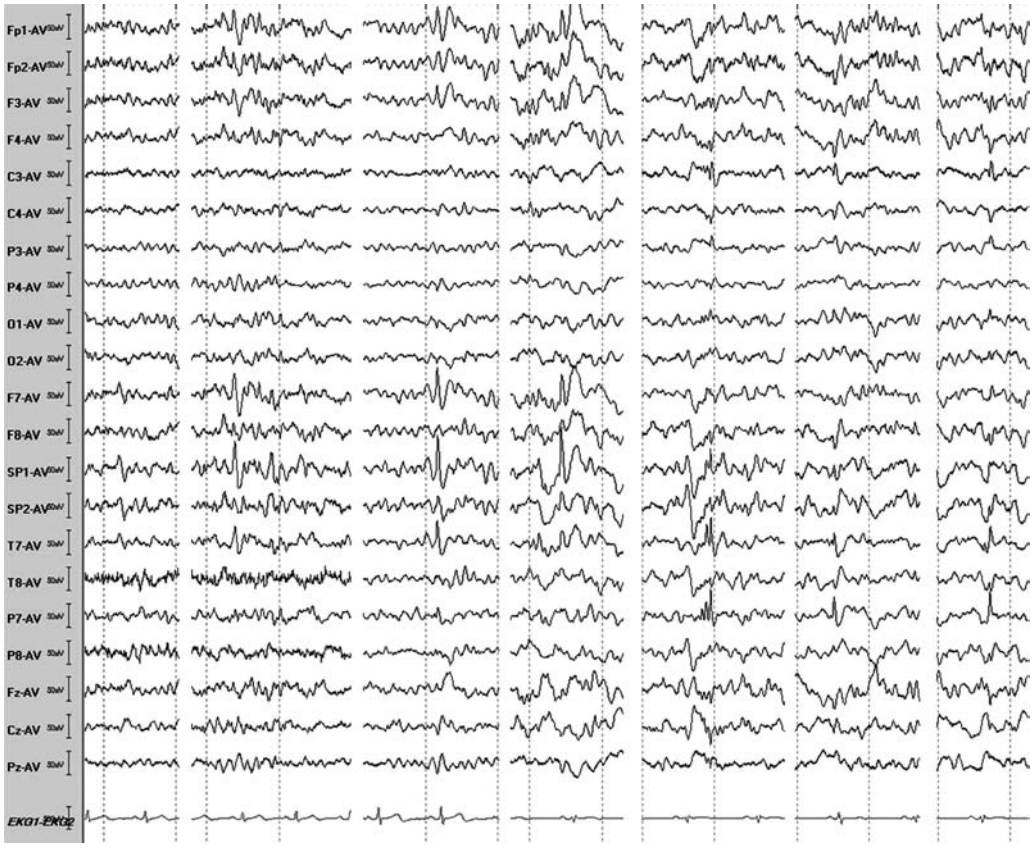

Figure 154.4 Interictal epileptiform activity was recorded independently from the left mesial-basal-anterior temporal and the left posterior-mid-temporal regions (a series of discharges from each field are illustrated).

unusual to see mesial-basal temporal epileptiform discharges with neocortical epilepsy, whether neocortical temporal or extratemporal. The posterior temporal interictal epileptiform discharges may reflect irritative activity from around the lesion itself, while the sphenoidal electrode discharges could represent a form of secondary epileptogenesis. We had the option of either pursuing the presurgical investigation with invasive monitoring, using subdural grid electrodes for recording seizures and localizing language cortex, or proceeding with a lesionectomy since the lesion was surgically accessible. With the latter choice, an invasive evaluation could be pursued if seizures persisted. It was decided to proceed without invasive monitoring. The patient was left hemisphere dominant for language, but since the lesion was in the inferior temporal gyrus, the risk to language was felt to be minimal, and it seemed reasonable to proceed with a lesionectomy, including hemosiderin stained margins of the lesion, without mapping language functions.

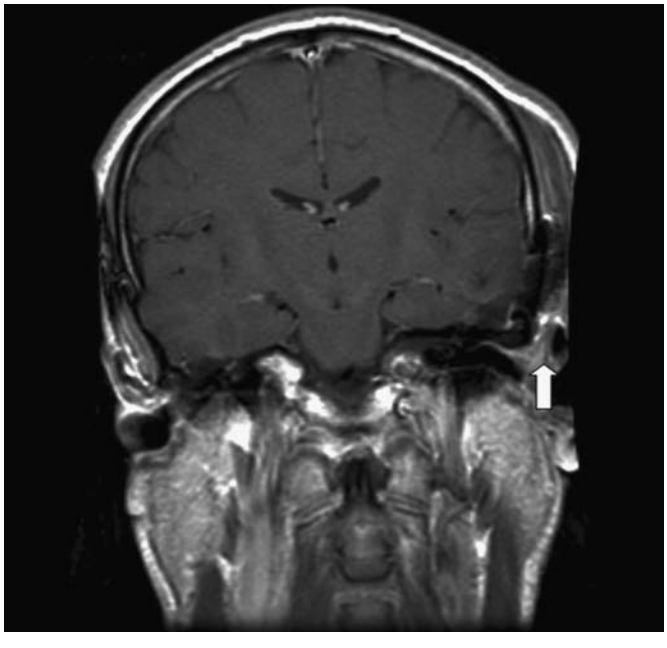

Figure 154.5 Postoperative MRI demonstrating extent of resection (see arrow).

One other decision was whether to extend the resection to remove the hippocampus, in view of the mesial-basal temporal irritative zone by EEG. This case illustrates a frequent dilemma that occurs with lateral temporal neocortical lesions, when the EEG supports a mesial-basal seizure origin and predominant epileptiform activity. When there is associated hippocampal sclerosis by MRI (dual pathology), there is evidence that surgical outcome is better with removal of both the neocortical lesion and the sclerotic hippocampus. In this particular patient, the ipsilateral hippocampus appeared to be structurally normal, even though it may have participated in seizure propagation. Therefore, it was decided to perform a lesionectomy sparing the hippocampus.

Table 154.1 Selected neuropsychological measures

Area/test	Score	Age/education expected
Intelligence – WAIS-III		
Verbal IQ	72	100 ± 15
Performance IQ	87	100 ± 15
Full-scale IQ	77	100 ± 15
Verbal comprehension	68	100 ± 15
Perceptual organization	91	100 ± 15
Working memory	97	100 ± 15
Processing speed	86	100 ± 15
Memory– Wechsler Memory Scale-III		
Immediate auditory	68	100 ± 15
Immediate visual	81	100 ± 15
Delayed auditory	64	100 ± 15
Delayed visual	75	100 ± 15
Rey-O-Complex figure copy	33.5/36	≥32/36
Rey-O-Complex figure immediate recall	6.5/36	≥32/36
Rey-O-Complex figure delayed recall	6.5/36	17/36
Buschke Selective Reminding Task-immediate	7/12 by 8th trial	≥10/12
Buschke Selective Reminding Task-delayed recall	1/12 after 30 min delay	8/12
Language		
Boston naming test	32/60	≥52/60
Reitan Aphasia Screening	3 errors	0 errors

Surgical procedure and surgical outcome

Surgery performed 28 months before this report was a left image-guided craniotomy for resection of the temporal lesion. It was performed under general anesthesia. The skin incision was made from the posterior aspect of the zygoma superiorly over the top of the ear for about 4 centimeters. Dissection was carried down to the squamous portion of the temporal bone. A craniectomy defect was created with a drill, exposing the inferior temporal gyrus and petrous apex area. After opening the dura, hemosiderin stained tissue was seen, along with a rather large vein presumed to be the vein of Labbe. The pia was separated from the inferior aspect of the vein, and the vein was retracted superiorly, then the hemosiderin stained area of the inferior temporal gyrus was slowly removed using bipolar and suction. The lesion measured 2–3 centimeters in diameter. Eventually, the entire nidus around the vascular lesion was delineated with a pedicle arising off the floor of the temporal lobe just over the petrous apex. The lesion was resected. The remaining portion of any hemosiderin stained brain was then aspirated. The wound was then irrigated and closed.

The anatomic pathology was cavernous angioma.

A postoperative MRI showed almost complete resection of the lesion (Figure 154.5).

There were no immediate postoperative seizures. There were no neurological deficits and specifically no difficulties with word finding or naming. On follow-up visit 3 months postoperatively, the patient reported no full-fledged seizures. However, he did report some isolated auras lasting a few seconds, occurring two to three times a month. He was now on lamotrigine, 300 mg twice daily. When he returned 6 months after surgery, he reported only a single possible aura, about 3 weeks before the visit, during the whole 3-month interval. At the 1-year postoperative visit he reported that seizure auras had recurred, sometimes up to three to four times per week. He said that they lasted only a second or so. He remained on lamotrigine, 300 mg twice daily. He continues to be self-employed as a farmer, working full-time. He reports no decline in his function.

The favorable outcome with respect to disappearance of disabling seizures supports the decision to limit the surgery to lesionectomy with removal of hemosiderin-stained margins, sparing the structurally normal hippocampus. However, the residual auras suggest that the epileptogenic zone may not have been fully resected.

Video seizure description

The patient was lying with eyes closed. He suddenly opened his eyes and reached for the event button, but did not push it. He seemed to freeze, staring straight ahead, with his right hand fisted around the event button. He then looked slightly to the left. He pursed his lips and had slight chewing motions, while his right hand continued to hold the event button in a fist, the right elbow flexed and the hand held up in the air, with a rotatory component consistent with a dystonic posture. He then began to have restless fumbling and picking motions with the left hand and restless motions of the legs and trunk. The right hand remained fisted, holding the event button. As he sat on the bed, he began to make rhythmic grunting sounds and had versive eye and head deviation to the right. This was followed by secondary generalization.

155 Patient with nonlesional neocortical epilepsy

L Tassi and GL Russo

Summary

We present the case of a 9-year-old boy, with a negative personal and familial history, who started having seizures at the age of 3 years. From the beginning, seizures have always been characterized by asymmetrical spasms, predominant on the left side. Brain MR was normal. His neurological examination was normal, but the IQ, 78 at the first evaluation (35 months) dropped to 55 three years later.

Interictal EEGs showed since the beginning, a continuous slow wave and spike and wave activity, well localized in the right frontal region.

We performed a stereo-EEG investigation, and on the basis of anatomo-electro-clinical correlation, a frontal corticectomy.

The histological examination showed an architectural dysplasia, and since then the patient is seizure free (more than 1 year).

Clinical data

Clinical history

G.F., when referred to our epilepsy surgery center, was a right-handed 9-year-old boy without any personal or familial antecedent for epilepsy, and normal delivery after a physiologic pregnancy. Psychomotor development was normal until the onset of seizures.

Ictal episodes started at 2 years and 9 months and from the beginning were characterized by a sudden bilateral elevation of the arms, predominant on the left side, sometime associated with a left oculo-cephalic deviation. Fits were very brief (1 second) and tended to present in clusters, lasting about 10 minutes, at the end of which no postictal deficit was present.

Seizure frequency rapidly worsened (1–5 series a day) during the following 2 months, until a pharmacological treatment (GVG) was started and induced a 2-month seizure-free period.

After that, episodes started again, occurring more than once a day only during wakefulness; they were always characterized by a cluster of spasms (abrupt asymmetric arms elevation with a left predominance) lasting 5–15 minutes during which the boy became more and more restless and was slightly pale and polypnoic; speech was preserved all along the cluster.

No more prolonged seizure-free interval has been obtained by drug treatment which, after GVG, included VPA, CBZ, LEV, TPM, Hydrocortison, and CLB, in various associations.

Neurological and neuropsychological investigation

Neurological examination was normal except for cognitive functions.

Serial neuropsychological evaluations documented a progressive decline in global IQ (Griffiths) from the very beginning of the illness (35 months: 78) with a sensible drop at 1 year (72) but namely at 2-year follow-up, when it was 55.

Preoperative evaluation showed a language deficit, and a loss in verbal and non-verbal memory. Furthermore there were a difficulty in visuo-spatial perception and motor ability.

Neuroimaging

MR evaluation, performed following our protocol also included some additional cuts targeting the right frontal lobe. The following sequences were obtained: transverse spin-echo double-echo of the entire brain and axial TSE inversion recovery (Figure 155.1), coronal turbo spin-echo (TSE) T2-weighted (W), coronal TSE fluid-attenuated inversion-recovery (FLAIR) T2W and coronal TSE inversion recovery (IR) T1W (Figure 155.2). Additional FLAIR images in the sagittal plane were acquired.

The MR was totally normal.

Video-EEG recordings

Long-term video-EEG monitoring allowed a further definition of interictal EEG features and, mainly the evaluation of three series of 'asymmetric spasms'.

Interictal EEG was characterized by a mid amplitude posterior background rhythm at 8–9 Hz, symmetric and reactive to eye opening.

Electrical activity was quite peculiar over the right frontal region, where theta-delta waves were almost constantly recorded, without arrest reaction but with the frequent intermixing of spikes and spike-and-waves (Figure 155.3a, b). This actual 'electrical' status epilepticus did not vary during wake and sleep cycle, almost always being present over the right fronto-temporal region.

The three ictal clusters recorded, lasting from 1 minute 16 seconds to 5 minutes 33 seconds, were characterized by a progressive restlessness, then interrupted by sudden, brief, abrupt movements (left arm, left shoulder, a forced inspiration) with different entity, sometimes unperceivable.

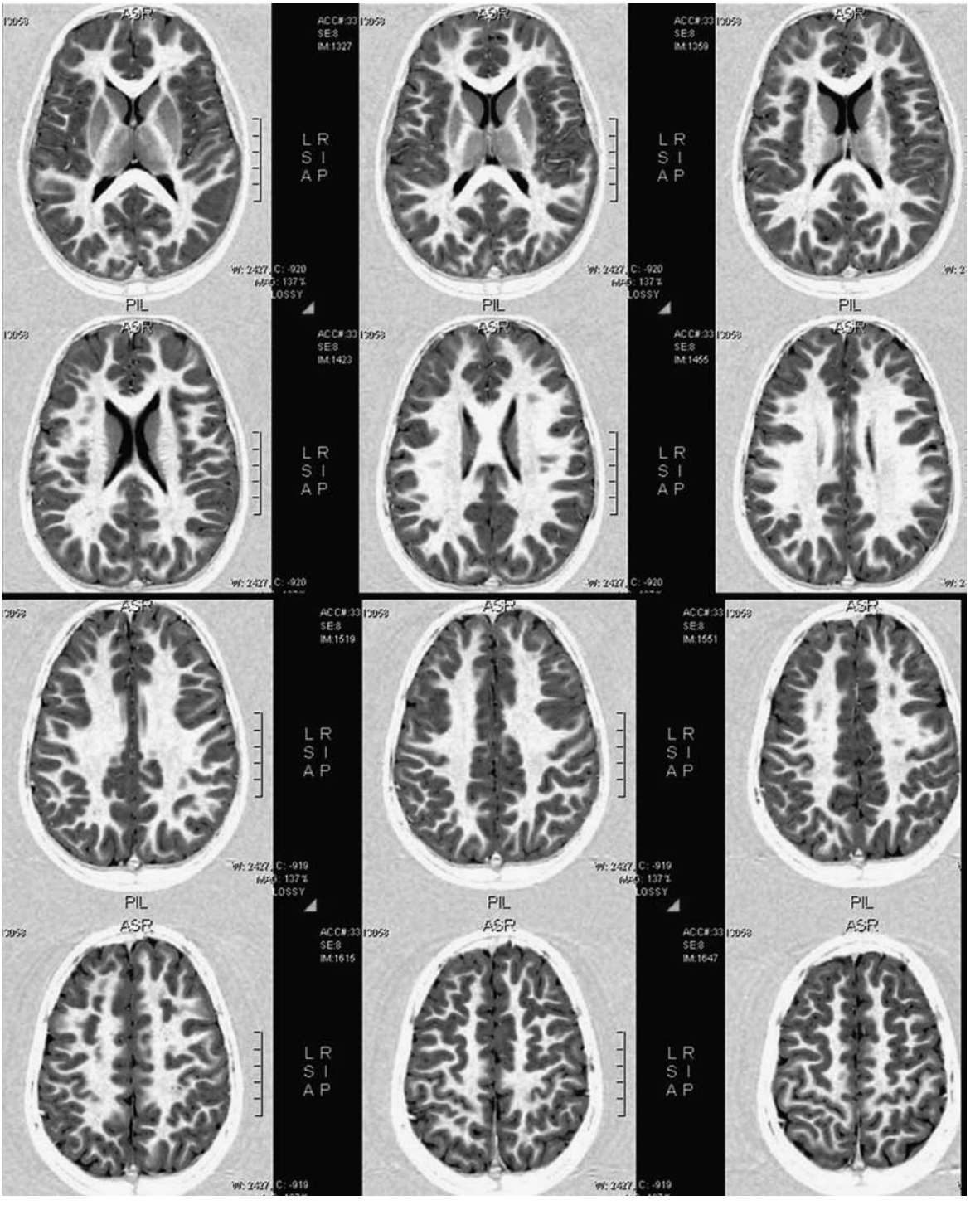

Figure 155.1 Preoperative brain MR showing an axial TSE inversion recovery (3 mm slices). No anatomical abnormalities were noticed.

On the EEG slow activities were gradually replaced by a non-tonic rhythmic activity (Figure 155.4a), localized on the right fronto-temporal region, and by the appearance of rhythmic high-amplitude slow-wave surcharged by a low-voltage fast activity (Figure 155.4b); these last, maintaining a clear right fronto-temporal predominance, represented the electrical correlate of the motor ictal manifestation. A concomitant increase of generalized slow-spike and waves have to also be noticed. At the end of clinical manifestations, EEG recovery was prompt and without postictal slowing.

Summary of presurgical evaluation

The clinical ictal semiology (including the presence of 'asymmetric spasms' predominantly localized on the left side of the body, associated with–or preceded by–an irritability and presenting in cluster with a high daily frequency) suggested a right hemispheric localization of the epileptogenic zone but could not indicate its lobar predominance.

EEG interictal and ictal features, notwithstanding a fast and consistent contralateral spread, demonstrated a constant right fronto-temporal involvement.

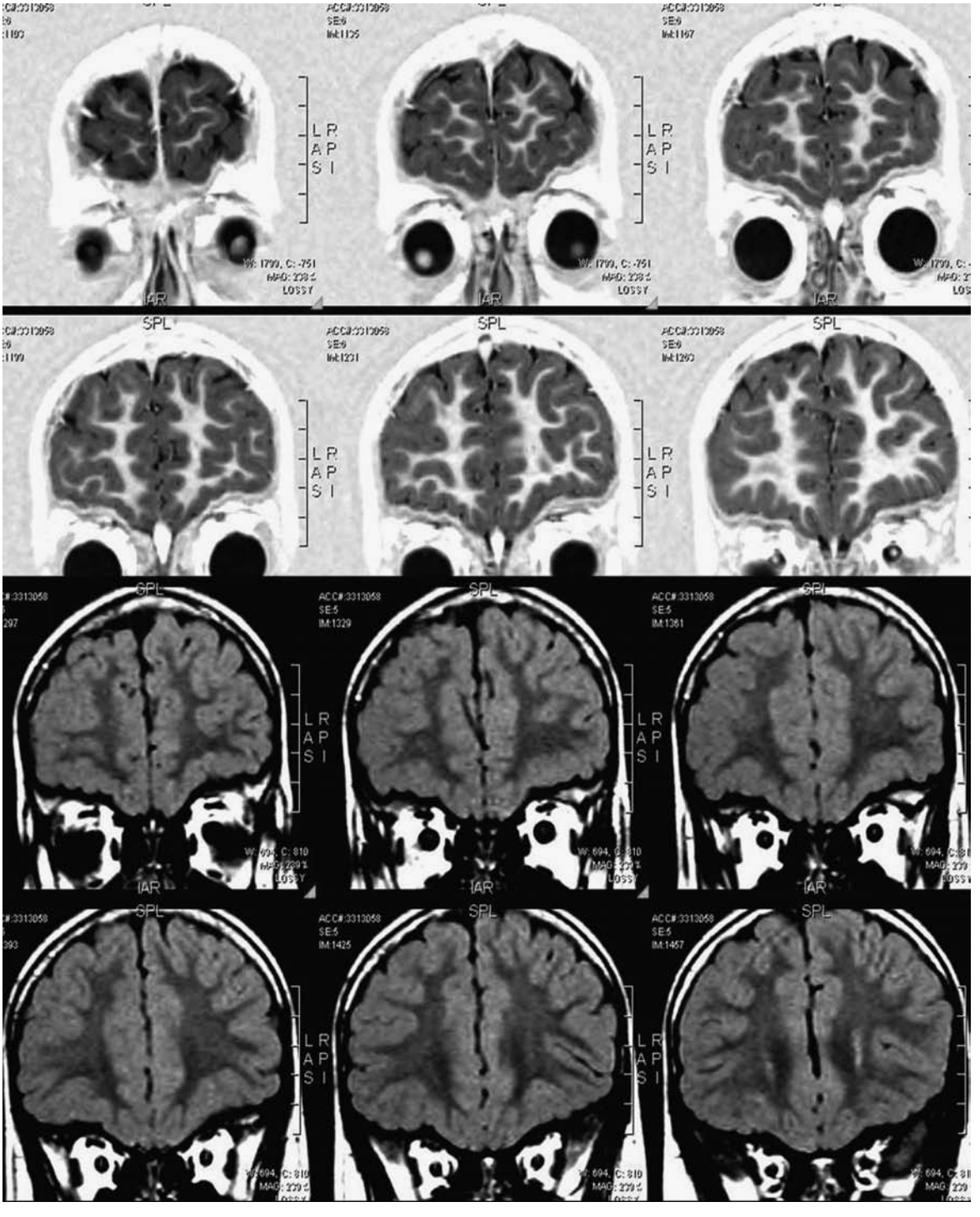

Figure 155.2 Preoperative MR, including coronal inversion recovery (a) and coronal FLAIR (b). The MR was completely normal.

MR was normal.

On these electro-clinical basis, a right frontal (-temporal) epileptogenic zone represented the most likelihood localization hypothesis, and stereo-EEG exploration by mean of stereotactically implanted intracerebral electrodes was judged necessary for verifying this hypothesis and, possibly, define the actual extension of the surgical exeresis.

The implantation strategy – once the lateralisation defined on clear electro-clinical basis – mainly followed the indications coming from EEG, showing a widespread right fronto-temporal origin of ictal discharges.

Stereo-EEG investigation

An unilateral, right fronto-temporal exploration was then realized, after an arteriographic study, by means of 14 multileads electrodes, ranging from five to 18 contacts (Figure 155.5).

Invasive recordings (interictal and ictal)

The patient was monitored for 7 consecutive days, during which seven series of spontaneous 'spasms' have been recorded. No ictal manifestations were induced by electrical stimulations.

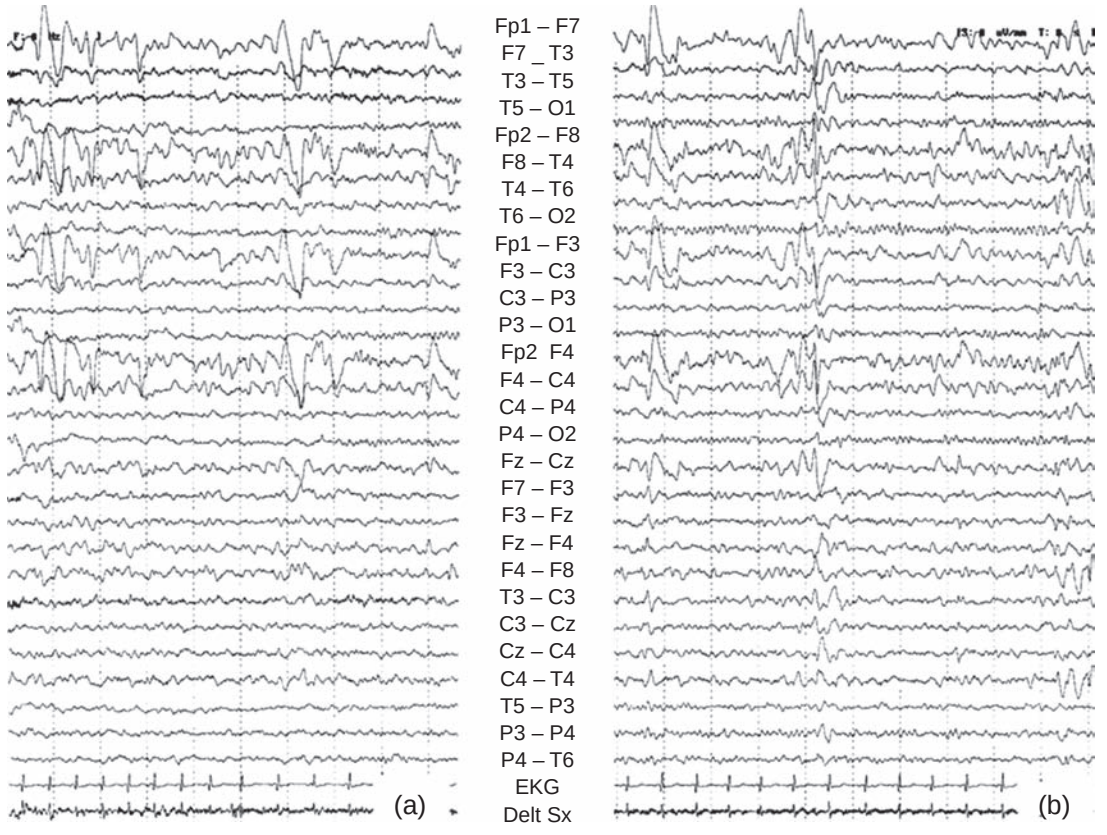

Figure 155.3 Interictal scalp activity: 8 Hz background activity, symmetrical. High-amplitude repetitive slow-waves and slow-spike and waves on the fronto-temporal regions, predominant on the right side (a). Slow-waves on the right fronto-temporal region may assume a rhythmic aspect (b).

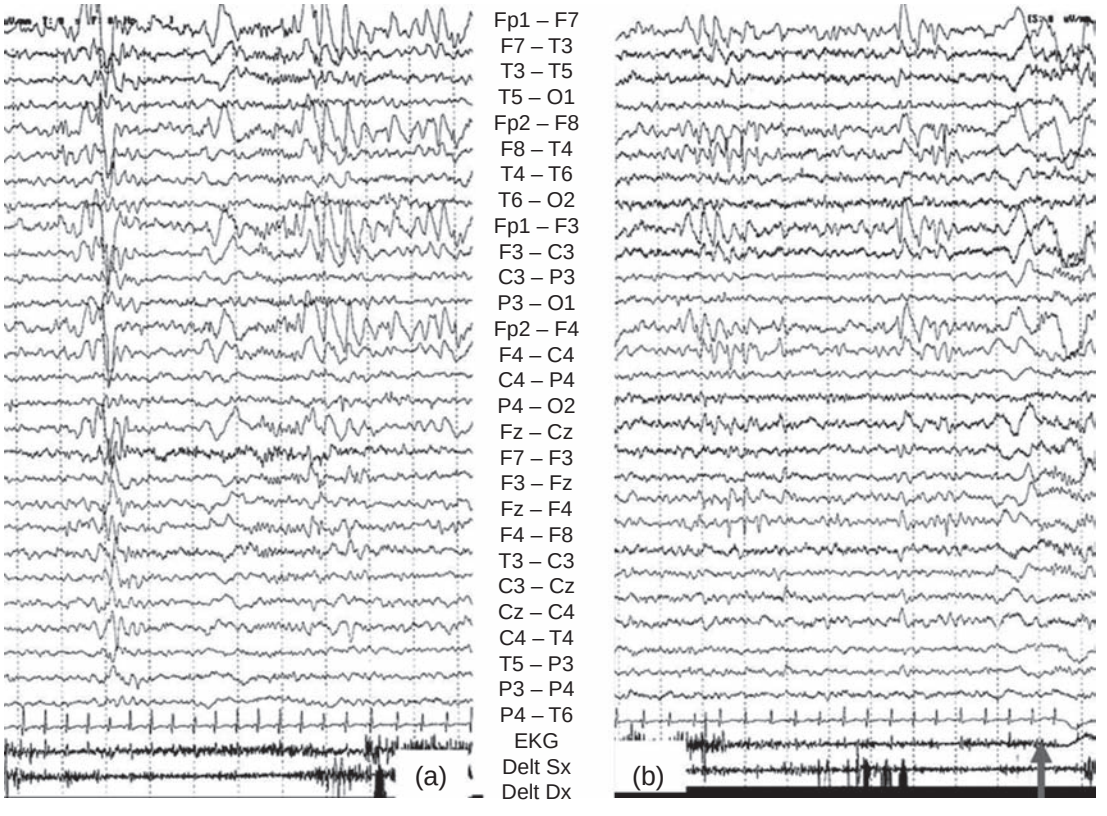

Figure 155.4 In the period immediately preceding ictal manifestation (a), there was a cut-down of slow-waves and a build-up of fast rhythmic activity, clustering in brief sequences. The first 'spasm' (red arrow) corresponds to a high-amplitude slow-wave probably preceded by and mixed with a rhythmic fast activity on the right fronto-temporal region (b). (See Color plates.)

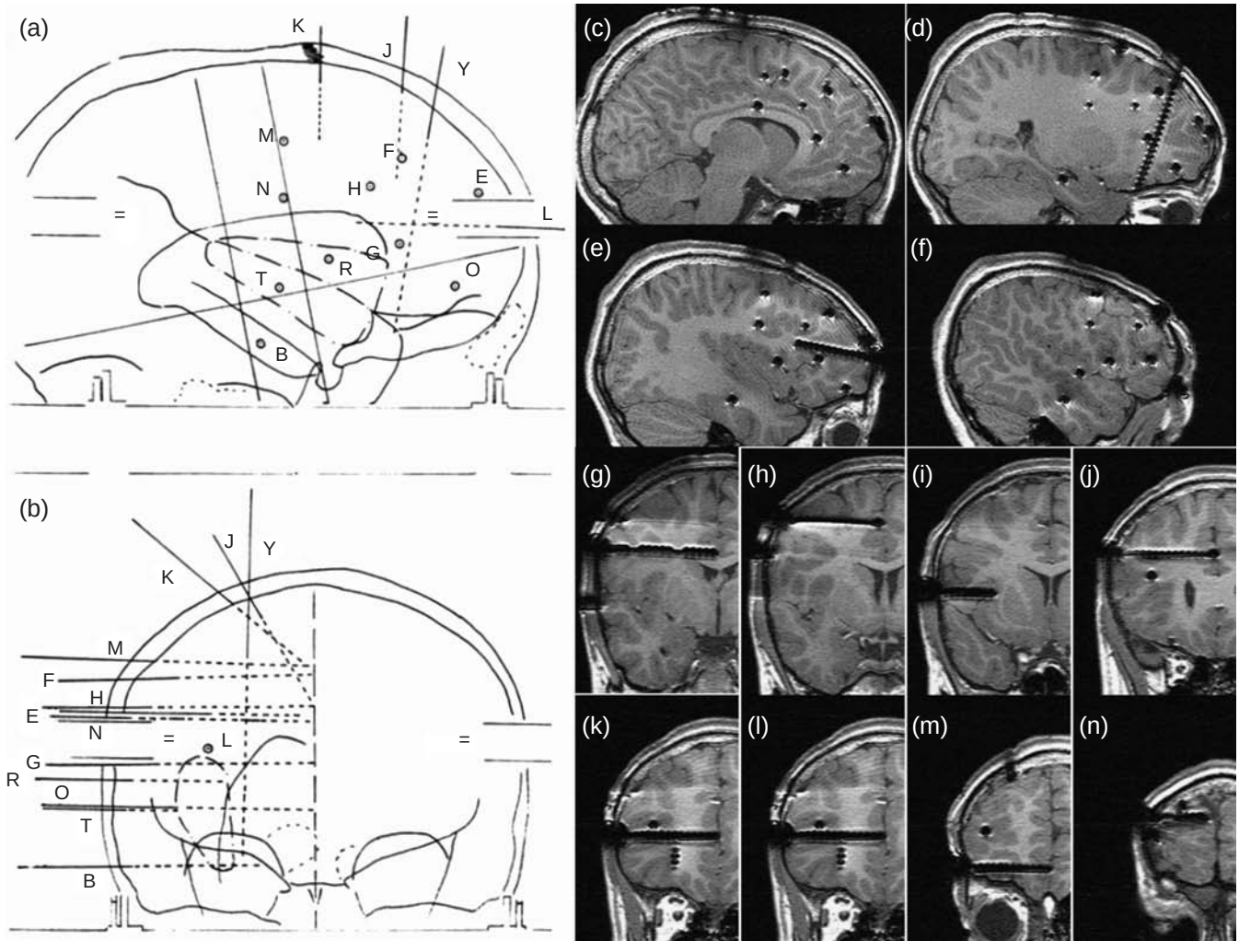

Figure 155.5 Lateral (a) and antero-posterior (b) views of the stereotactic scheme, according to the bicommissural reference system, of the SEEG exploration of this patient. Electrodes are indicated with either circled dots or dashed lines labelled by upper case letters. (c–f) T1-weighted 3D postimplantation MRI, sagittal slices from mesial to lateral. (g–n) same MRI, coronal slices from posterior to anterior. Intracerebral electrodes sample the following structures, from external to internal contacts: B: middle temporal gyrus, hippocampus, parahippocampal gyrus. T: superior temporal gyrus, Heschl's gyri. R: inferior frontal gyrus, insular cortex. G: inferior frontal gyrus, genu of cingulated gyrus. H: inferior frontal sulcus, anterior cingulated gyrus. N: precentral gyrus, central cingulated gyrus. M: middle frontal gyrus, mesial frontal cortex. F: middle frontal gyrus, mesial frontal cortex. O: inferior frontal gyrus, fronto-orbital gyri, mesial frontal cortex. E: frontal pole. L: frontal pole. Y: superior frontal sulcus, fronto-orbital cortex. J: superior frontal gyrus, mesial frontal cortex. K: superior frontal gyrus, mesial frontal cortex.

The interictal activity (Figure 155.6a) is characterized by the presence of very frequent slow waves (theta delta) and slow–spike and waves localized on the orbital region, the frontal pole, the very anterior part of the cingulated gyrus and the anterior part of the first, second and third frontal gyri. HPN doesn't modify the pathological activity and ILS was ineffective.

During sleep (Figure 155.6b) slow–spike and waves become more frequent and intermingled by the presence of some 'flattenings', mostly localized on the orbital region and the frontal pole.

During ictal episodes, as in surface recordings, ictal symptoms are preceded by clear electrical modifications: a dramatic reduction of slow waves, and the appearance of 1–2 seconds rhythmic fusiform discharges (Figure 155.7a), well localized, on the frontal pole and the orbital region.

Progressively these discharges involve the anterior part of F1, F2, and F3 as well as the anterior part of the cingulated gyrus (Figure 155.7b).

Later a low-voltage fast activity appears concomitantly with the fusiform anterior discharges (Figure 155.8a), involving almost all the explored structures, but only when a high-amplitude slow wave emerges, the clinical 'spasm' becomes evident (Figure 155.8b).

Then the EEG becomes slower and slower (Figure 155.9a), and at the end of the episode, no postictal slow–waves were noticed, and it exists an impressive decrease of the previous interictal slow activity (Figure 155.9b).

Video

The boy, seated in the bed, is doing his homework with his father.

Since 13.47.50 (10 seconds after the beginning of the fusiform fast activity in the anterior part of the frontal lobe) he becomes confused, restless, and he speaks with a feeble voice. The first spasm is at 13.49.21, and the last one at 13.52.22.

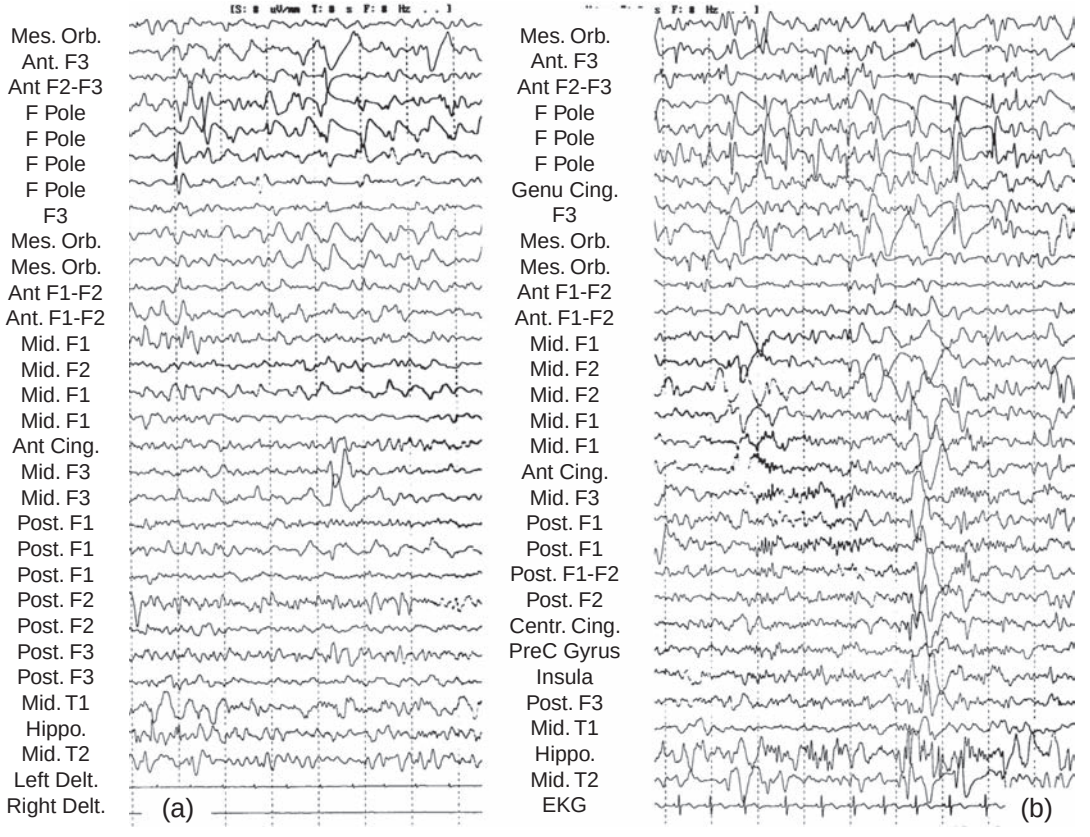

Figure 155.6 Stereo-EEG recording, during wakefulness (a) and sleep (b), demonstrating the presence of persistent slow waves and slow spike and waves in the anterior part of the frontal lobe, worsening during sleep. Mes Orb: mesial orbital region. Ant: anterior. F2: second frontal circumvolution. F3: third frontal circumvolution. F: frontal. Mid: middle. F1: first frontal circumvolution. Ant Cing: anterior part of the cingulated gyrus. Post: posterior. Mid. T1: middle part of the first temporal gyrus. Hippo: hippocampus. Mid. T2: middle part of the second temporal gyrus. Delt: deltoid. Genu Cing: genu of the cingulated gyrus. Centr. Cing: central part of the cingulated gyrus. PreC Gyrus: precentral gyrus.

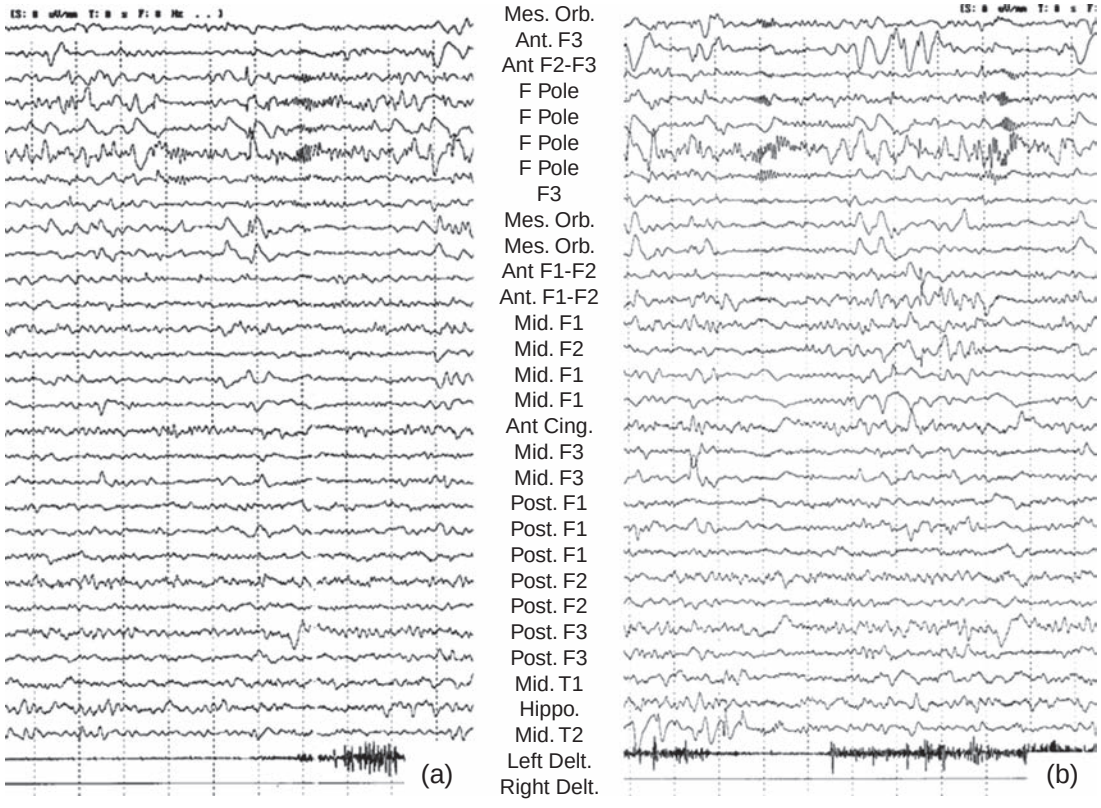

Figure 155.7 Stereo-EEG recordings, showing the onset of fusiform fast activity (a), becoming more and more frequent (b), well localized in the frontal pole and the mesial orbital regions.

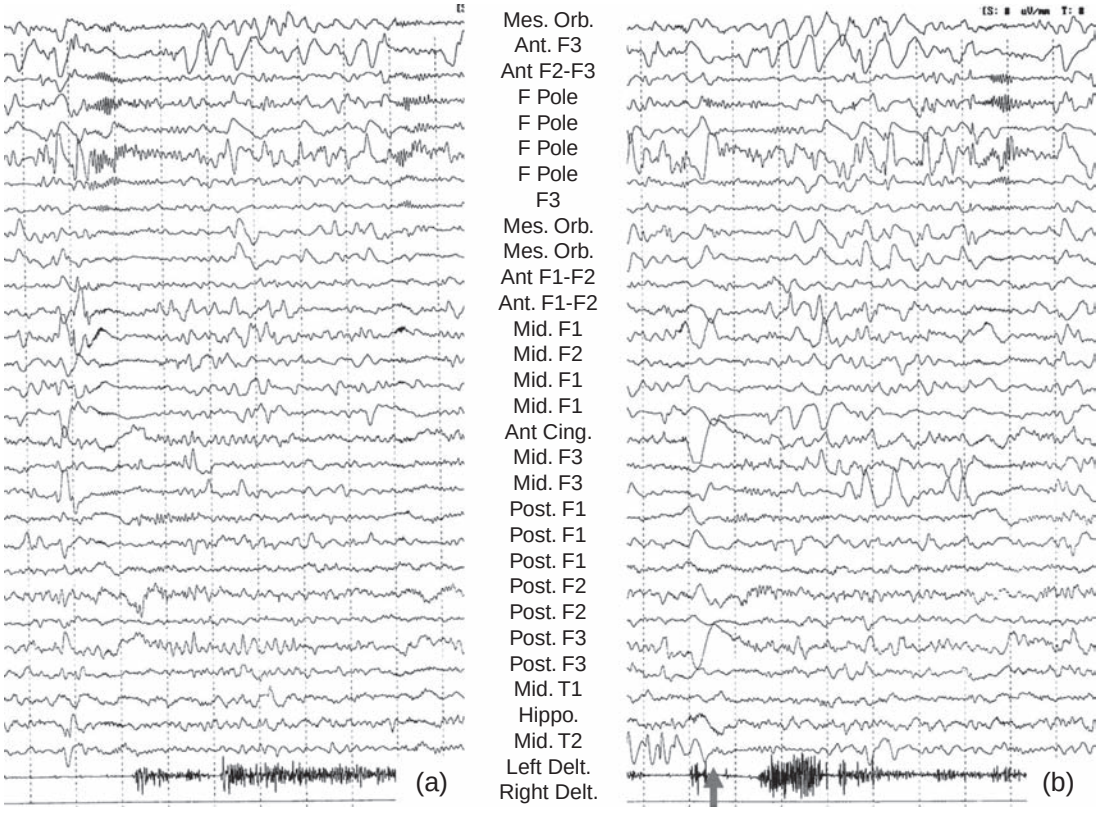

Figure 155.8 Stereo-EEG recordings: the fusiform activities are associated with a faster activity, spreading to the posterior part of the frontal lobe, as well as to the temporal structures, with no symptoms, except for the irritability (a). The first spasm (red arrow) coincide with a high-amplitude slow wave. (See Color plates.)

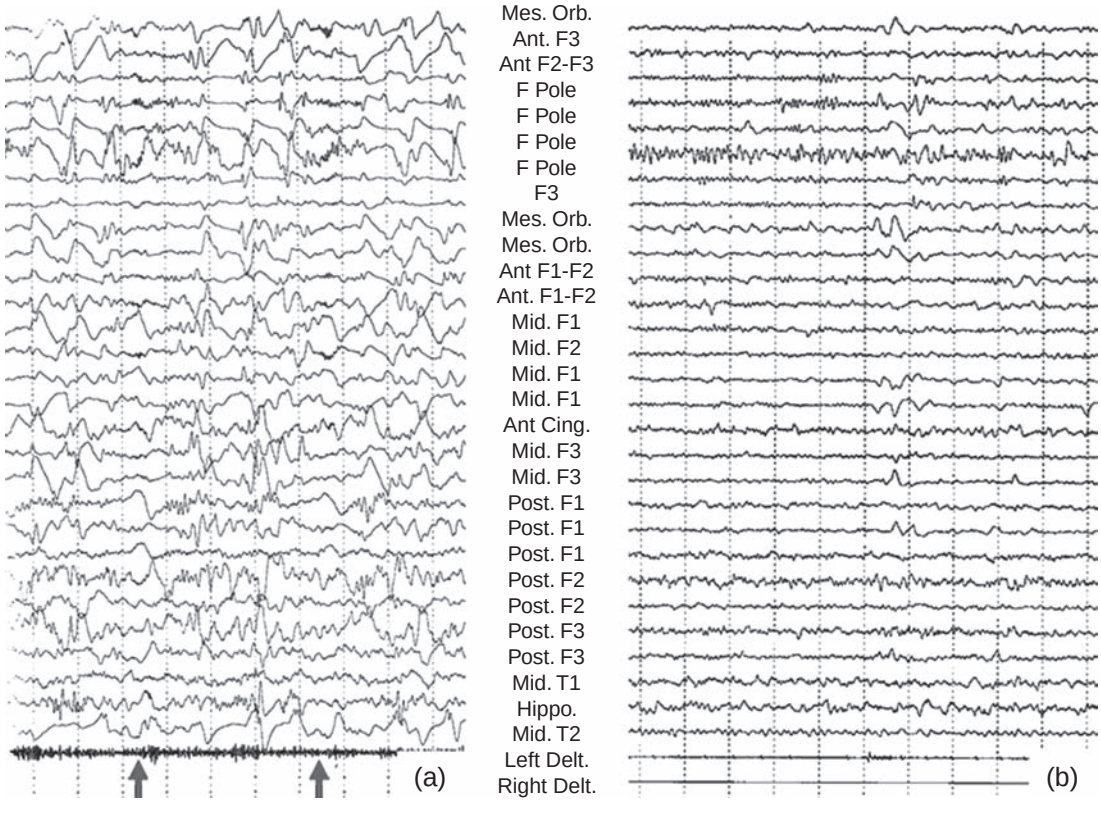

Figure 155.9 Stereo-EEG recordings: slow waves grow up and the spasms are repetitive (red arrows) (a). At the end of the cluster, the total and abrupt disappearance of the slow activities is the main electrical feature. (See Color plates.)

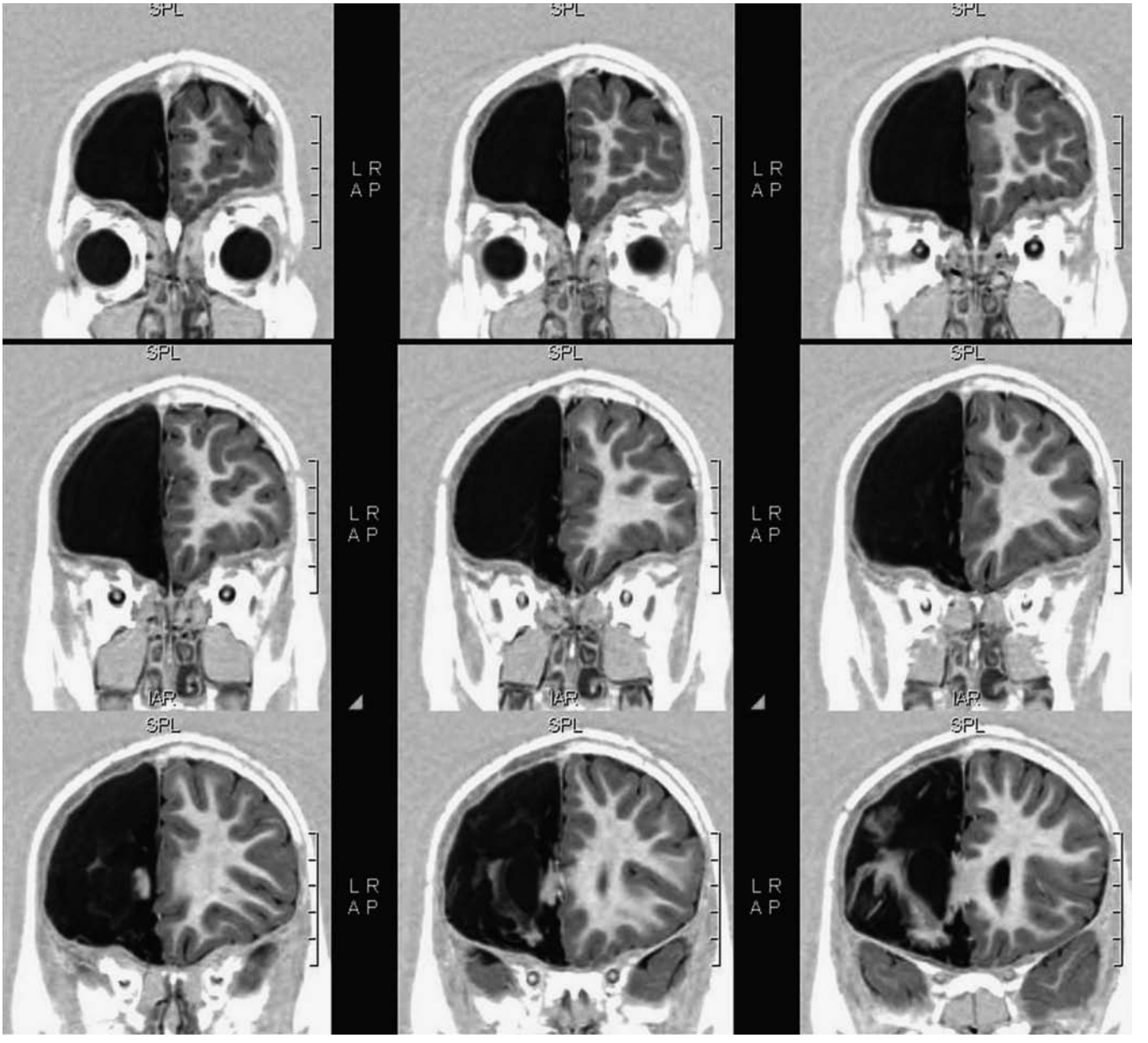

Figure 155.10 Postoperative MR, coronal TSE inversion recovery (3 mm slices), demonstrating the right frontal corticetomy.

Electrical intracerebral stimulations

The neurophysiological mapping obtained by electrical stimulations, pointed out clonic jerks (hand motor area) in the right hand, only in contact R6–7 (posterior F3).

No other clinical or electrical effect has been induced.

Definition of epileptogenic zone and surgical plan

According to the electro-clinical data obtained during the stereo-EEG, the definition of the epileptogenic zone was mainly based on the following electrical features:

- slow waves and spike and waves were prevalently localized on the frontal pole, the orbital region, the anterior part of the cingulated gyrus and the anterior third of F1, F2, and F3;
- during sleep, on the same regions, we noticed spike and waves intermingled with brief periods of flattening;
- ictal symptomatology was preceded (in some cases 2–3 minutes before) by the appearance of rhythmic fusiform discharges, always localized on the frontal pole and the orbital region, and then involving the anterior part of F1, F2, and F3, and the anterior part of the cingulated gyrus; these localized electrical modifications have always been the prelude for a widespread (almost all the explored structures) electrical change, characterized by an high-amplitude slow wave associated with the motor ictal phenomena.

Therefore we proposed a right frontal corticectomy, including the frontal pole, the orbital cortex, the cingulated gyrus and the superior, middle and inferior frontal circumvolutions, up to the projection of the electrode H, expecting a good outcome concerning seizure freedom. On the other hand, the evolution of cognitive functions could be hardly anticipated in

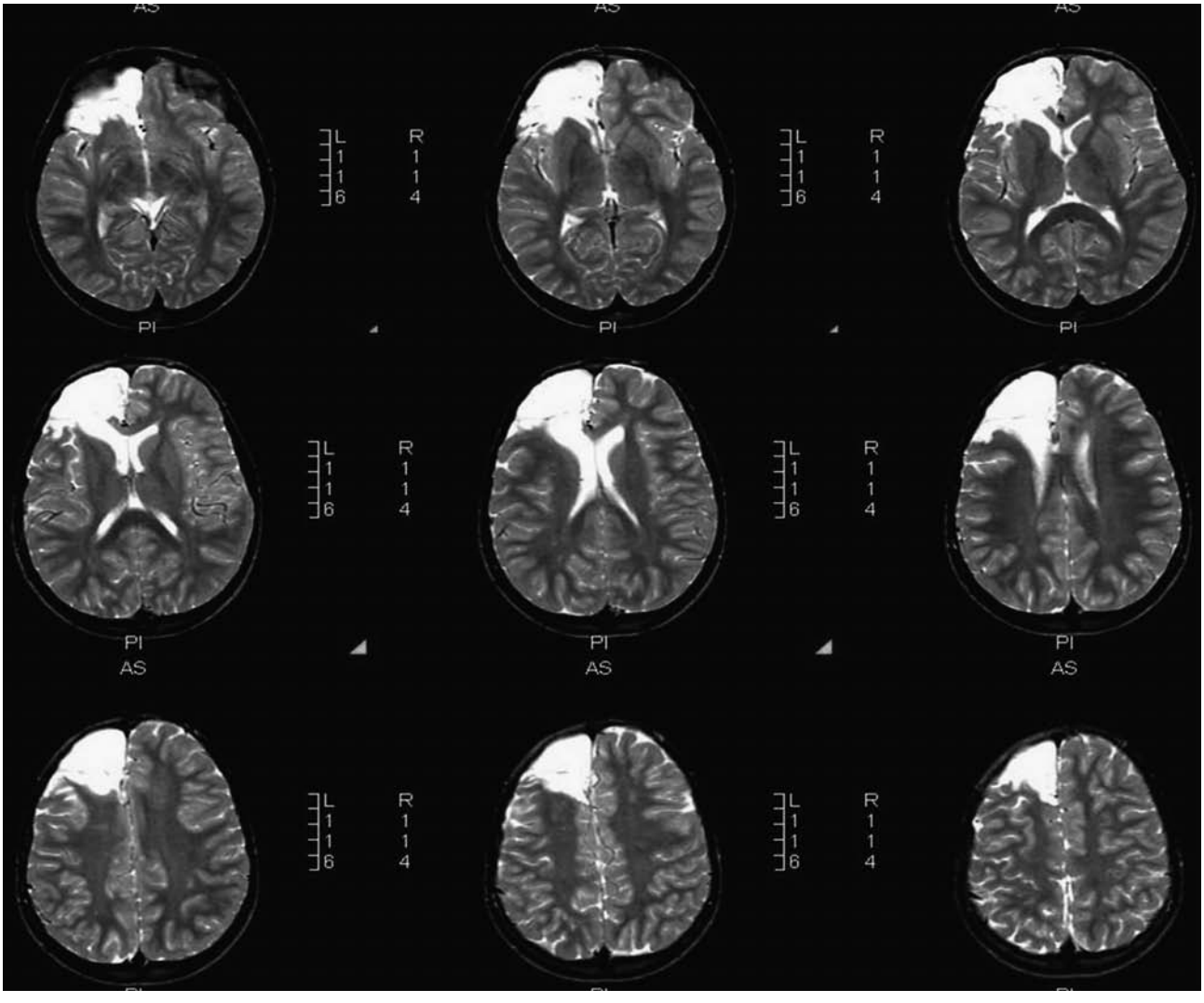

Figure 155.11 Postoperative MR, transverse turbo spin-echo (TSE) T2-weighted.

view of the electrical 'status epilepticus' persistent from the beginning of the epilepsy.

Surgical procedure

Anatomo-pathological results

The histological examination showed a laminar cortical disruption, configuring an architectural focal cortical dysplasia (Type Ia), well localized in the gyrus rectus and in the very anterior part of the second and third frontal circumvolutions.

A gliosis was also present in all the surgical specimens.

Postoperative MR

The postoperative MR (Figures 155.10 and 155.11) illustrates the frontal corticectomy, complying with the presurgical plan.

Outcome

Since the intervention the patient is seizure free (18 months). The pharmacological treatment is unchanged.

Follow-up

The postoperative EEG shows the disappearance of the continuous slow-waves and slow-spike and waves which characterized the two fronto-temporal regions with a right side predominance.

The first neuropsychological (6 months of follow-up) fails in putting in evidence a remarkable variation concerning the IQ, which is now assessed at 58; however the boy is more attentive and concerned with the proposed tests. A further evaluation is scheduled two years after the intervention.

156 Patient with extensive malformation of cortical development

DK Lachhwani

Case history

DC was 8 weeks old when he presented to our practice with medically refractory epilepsy. Seizures had started on day 3 of life and were increasing in frequency and intensity despite use of multiple antiepileptic medications.

His current seizures were occurring daily in clusters, with 10–30 seizures per cluster and five seizure clusters every day. Mother described the individual seizures as facial grimacing and tonic stiffening of all four extremities, followed by rapid eye blinking lasting up to 30 seconds. During some seizures, the eye blinking was more noticeable on the right side. After the cluster of seizures, DC was tired and exhausted for 2–3 hours with very few spontaneous movements.

Initial seizures were very brief and involved a subtle flexion of trunk and facial grimacing, lasting < 3–5 seconds. These occurred sporadically, a few times per day. By the second week of life, episodes had picked up in intensity and DC had lost the sparkle in his eyes. A diagnosis of infantile spasms was made when a stronger episode was witnessed in the pediatrician's office. DC suffered a cardiac arrest while being transported to the nearest hospital from the pediatrician's office, however he was successfully resuscitated. Since then, he had mostly remained in the hospital for management of refractory epilepsy, before being transferred to our epilepsy service. Attempts to discharge him home had failed, and he would inadvertently present to the emergency room within 24 hours of discharge with an intense seizure cluster or an acute life-threatening emergency due to cyanosis, respiratory depression, and bradycardia.

Antenatal and perinatal course

Mother had received adequate perinatal care with close follow-up due to polyhydramnios. DC was born at 36 weeks of gestation, with a birth weight of 6 lbs 3 oz. His postnatal course was unremarkable and he was discharged home on day 2 with no concerns.

Neurodevelopment

His development had been delayed. At 8 weeks of age, he made eye contact and registered his mother's presence; however he did not have a social smile and had little head control. Mother felt that this was largely due to heavy doses of medications and frequent seizures. She noted that on days with fewer or less intense seizures, he looked brighter and attempted to hold his head better.

Epilepsy risk factors

No history of head trauma or meningitis.

Medications

He was on therapeutic doses of four antiepileptic medications – lamotrigine, leviteracetam, oxcarbazepine, and phenobarbital. He had previously failed a trial of phenytoin and intravenous pyridoxine.

Family history

DC's mother had a history of cerebral vascular malformation and had experienced two generalized motor seizures. She remained seizure free on oxcarbazepine. Two maternal first cousins had history of seizures; one with febrile seizures and the other with epilepsy of unknown etiology.

Pertinent positive findings on physical exam

Length and head circumference were appropriate for age. (Weight 4.7 kilograms.) Airway conducted sounds suggestive of moderate to severe resistance in the upper airways.

Subtle decrease in spontaneous movements and mild hypotonia of the right upper extremity was noted. He also showed an intermittent fisting with flexion of thumb across the palm in the right hand. Strength and reflex testing did not demonstrate any obvious asymmetry.

Non-invasive epilepsy evaluation

Interictal abnormalities

Modified hypsarrhythmia, lateralized left hemisphere. This was characterized by high amplitude (50–200 uV) bursts of multiregional (F7, P3, F3) spikes, and spikes lateralized to the left hemisphere which occupied 40–50% of the record. In between the bursts, there was a generalized, continuous slowing (20–40 μV). Rarely (<2%) the spikes were seen over the right temporal region.

Ictal abnormalities

First clinical seizure

Epileptic spasms (>20–30 recorded per day) characterized by clusters of sudden forward head flexion associated with bilateral arm and leg flexion, lasting for 1–5 seconds at a time were seen.

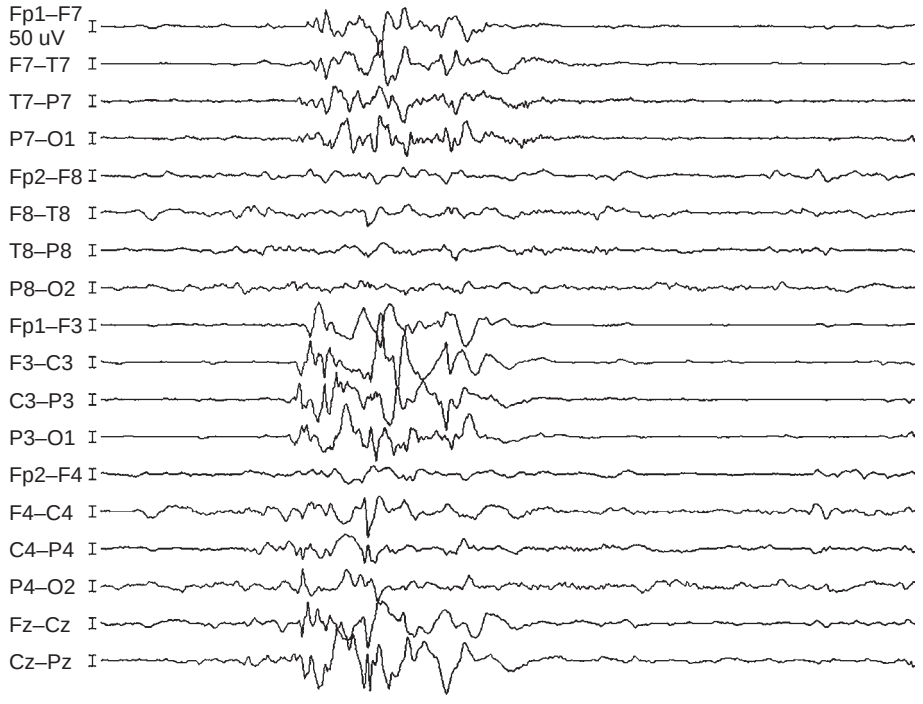

Figure 156.1 Interictal EEG showing modified hyppsarrhythmia involving left hemisphere.

Clusters lasted 2–30 minutes each, and consisted of a spasm every 10–20 seconds.

EEG seizure

Generalized (20–30 per day recorded) ictal pattern, characterized by diffuse electrodecrement followed by superimposed low-amplitude (10–50 μV) paroxysmal fast (20–40 Hz) activity, lasting 2–5 seconds.

Second clinical seizure

Right face clonic followed by generalized clonic seizure (20–30 recorded per day): Intermixed with the spasms described above, DC would have episodes of arrest of activity, bilateral eye blinking, right face pulling followed by right arm extension prior to a more generalized clonic pattern.

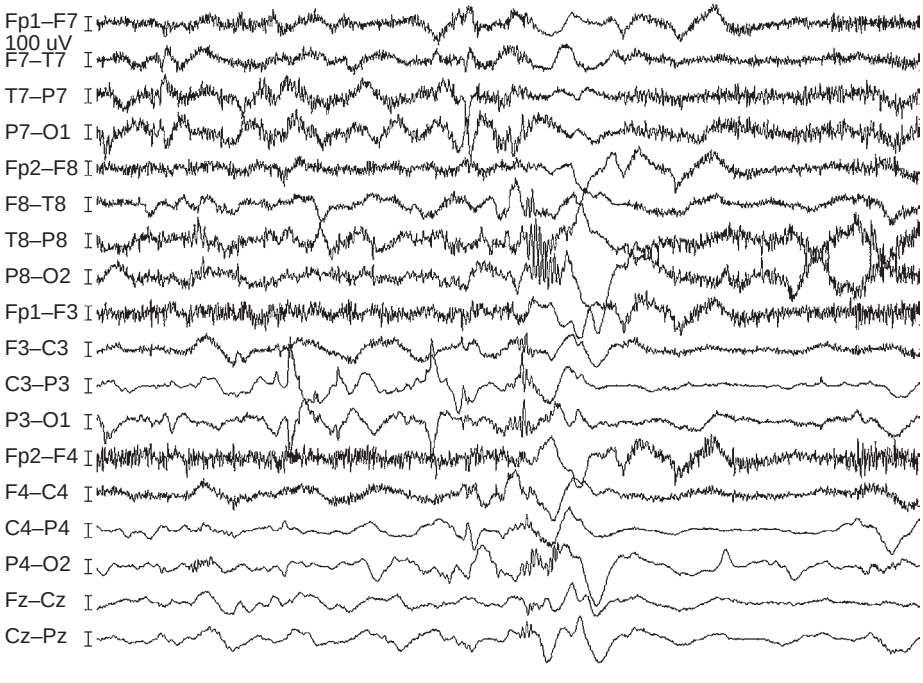

Figure 156.2 Ictal EEG showing diffuse electrodecrement during epileptic spasm.

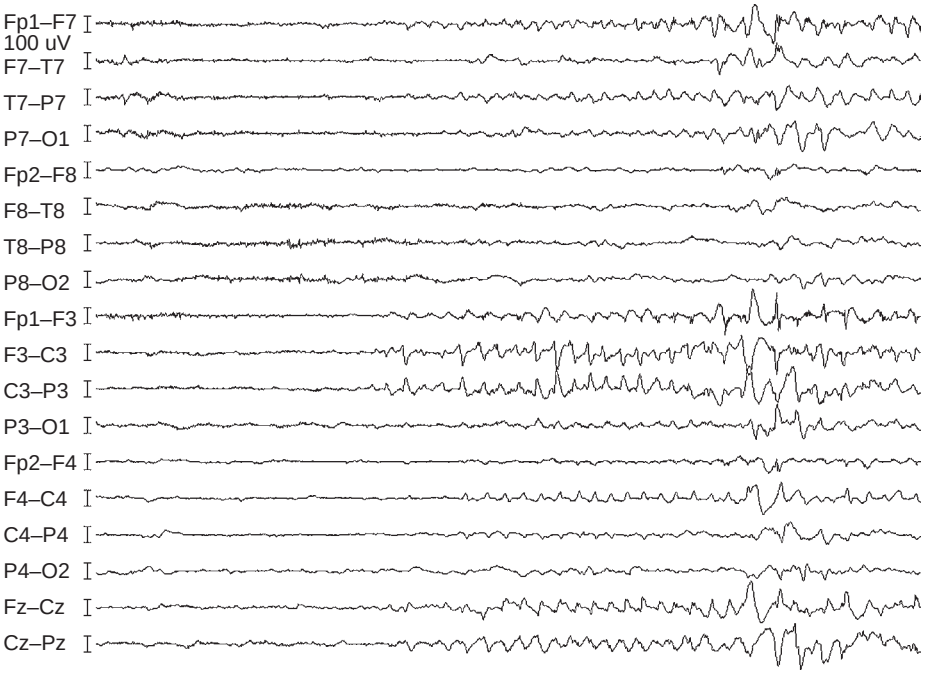

Figure 156.3 Ictal EEG showing evolution of the ictal rhythms over left hemisphere coinciding with bilateral (right>left) eyelid myoclonia.

EEG seizure

Ictal pattern was lateralized to the left hemisphere and showed rhythmic (3–4 Hz) high amplitude(50–300 μV) spike- and slow-wave complexes starting at C3 or P3 before becoming diffuse and evolving within the left hemisphere or both hemispheres.

MRI brain

Extensive malformation of cortical development involving the left cerebral hemisphere.

FDG PET scan

Moderately increased FDG uptake in the dysmorphic left hemisphere.

Neuropsychological assessment

Due to the young age, and the frequency of seizures, the Bayley Scales of Infant Development were not attempted. Mother's responses to The Vineland Adaptive Behavior Scales suggested that the motor and cognitive skills were within the adequate adaptive level range for a two-month infant.

Pediatric ENT consultation

Congenital Pyriform aperture stenosis, resulting in severe compromise of air exchange through nasal passages. This was felt to have contributed to previously observed life threatening apnea and bradycardia episodes during seizures.

Summary of epilepsy evaluation and plan

The discussion at patient management conference included experts in pediatric and adult epilepsy, neurosurgical team, neuropsychologists, neuroradiologists, bioethicists, and other support staff. The group unanimously appreciated that DC had left hemispheric epilepsy due to an underlying cerebral malformation, since 3 days of age, with medically refractory clinical and EEG status epilepticus. At presentation he had a subtle left hemiparesis, but no other fixed neurological deficits.

Experts were unanimous that continued medication trials were likely to be futile and would expose him to a significant risk of morbidity and mortality due to refractory status epilepticus. His risks were further compounded due to his very young age and a comorbid congenital upper airway stenosis (predisposing to airway obstruction and bradycardia during seizures).

Therefore, surgical correction of the airway malformation followed by surgical removal of the brain malformation (left hemispherectomy), was felt to be the preferred treatment option. His young age (2 months, 4.7 kg weight) was a significant mitigating factor, and it was appreciated that this would add to the risk inherent to brain surgery involving a large resection. It was also realized that epilepsy surgery would result in worsening of the pre-existing subtle hemiparesis and a new fixed homonymous visual field deficit.

Overall, it was felt that the risk of continued refractory status epilepticus would outweigh the surgical risks and therefore epilepsy surgery should be pursued imminently. Bioethics team was urged to meet the family to highlight the complicating features of the case before pursuing any treatment options. The family elected surgery.

Further management considerations

Identification of surgical candidates

Careful attention to clinical details is impertinent when evaluating and treating patients with epilepsy. It is well known that infantile spasms may be the presenting feature of focal epileptogenic substrates.[1] Careful investigation for the underlying cause and an accurate diagnosis of the epilepsy syndrome

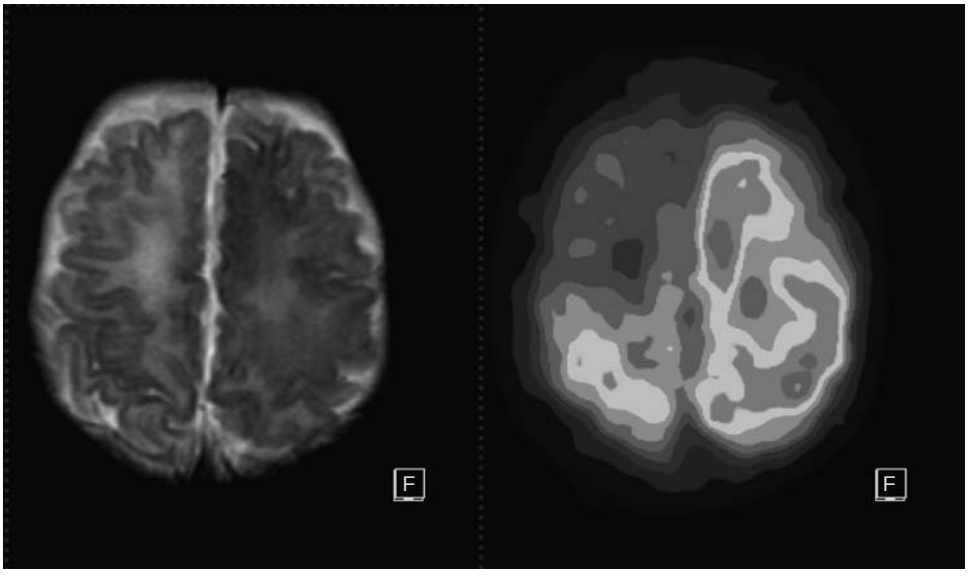

Figure 156.4 Axial MRI T2-weighted image showing diffuse left hemispheric malformation of cortical development and corresponding FDG-PET scan showing increased FDG. uptake in the dysplastic hemisphere.

(focal vs multifocal or generalized) is very important for the planning of treatment strategy. Indicators of focal epilepsy in our case include the asymmetric features in motor manifestation of the seizures as well as a subtle hemiparesis on neurological exam. Such clinical details indicating possible focal epilepsy syndrome may not always be evident in very young patients and therefore, a video-EEG evaluation, MRI brain and other adjunctive neuroimaging tests are important investigative tools that must be considered early in the course of investigation of infants with epilepsy.

Refractory status epilepticus

Medically refractory status epilepticus has significant morbidity and mortality risks associated with it. Currently accepted line of treatment involves high dose suppressive therapy with intravenous medications.[2,3] The improvement in our capability to offer multidisciplinary symptomatic and supportive care for very young patients in an intensive care unit enables us to prolong medical management form several days to several weeks. However this approach is not without a heavy price. In one study[2] authors found universal morbidity at follow-up in children who survived prolonged high-dose suppressive therapy. None of the children in this series returned to baseline neurological function and all of them continued to have epilepsy.[2] Just as morbidity rates are very high, the risk to life is also substantial during the course of aggressive and prolonged pharmacotherapy for unremitting seizures. Mortality rates as a result of refractory status epilepticus may range from 16–43.5%.[4–6]

Unfortunately, the paradigm of aggressive and prolonged medical management with intravenous agents may be the only recourse for patients with non-existent surgical options. However, symptomatic refractory status epilepticus with available surgical options need not be subject to a similar stratagem. In favorable surgical candidates, resective surgery may offer an immediate cure from status epilepticus as well as future epilepsy.[7,8] This approach is not commonly utilized. Until recently, the literature referring to such surgical experience was limited to rare case reports or very small case series.[9–13] Lately, experienced pediatric epilepsy centers have published more data supporting the role of resective approach to symptomatic refractory status epilepticus. In one series, status was stopped in all patients after surgery, 67% patients continued to be seizure free at follow-up and 33% had a significant improvement in their seizures.[7] Another surgical series found seizure control in >71% patients at most recent follow-up.[8]

Status epilepticus is an acute medical emergency and surgical removal of epileptogenic cortex during such a crisis is a delicate decision, fraught with potential for complications. The hesitancy to pursue surgery is valid, and only centers with adequate medical and surgical experience with complicated cases may be suited to offer such expertise. Authors of the above mentioned study reported that the morbidity related to the surgical intervention was seen in a third of the patients, and none of the patients died.[7] This rate of morbidity due to epilepsy surgery in refractory status epilepticus is certainly not any worse than the frequency of complications related to prolonged medical therapy, and further underscores that only comprehensive epilepsy centers with expertise may be well suited for exploring surgical options in this patient subpopulation.[2,5]

Upper airway disease

The objective influence of additional comorbid medical conditions on the overall risk of status epilepticus per se is not quantifiable due to lack of specific data. It may be reasonable to assume that the odds would favor an increased risk of complications when there are other concomitant medical problems. The presence of a congenital stenosis of the pyriform aperture predisposed this young infant to acute life threatening apnea and bradycardia episodes during seizure clusters. Indeed, these resulted in at least one episode of cardiopulmonary arrest needing resuscitation and several other emergency room visits culminating in endotracheal intubation to

stabilize respiration. Risk of hypoxemic ischemic cerebral insult seemed cumulative and compounded the pre-existing morbidity risks related to status epilepticus itself.

Body weight

Very young patients have a relatively small blood volume and are less well adapted to withstand major surgical stress. Traditionally, surgical teams are inclined to defer major surgical procedures until the age of one year or a body weight of 10 kilograms is achieved, to offset some of the increased surgical risks noted at a lower body weight and younger age. Estimated blood volume of less than 400 cc in our patient (average blood volume 80 cc/kg, operative body weight 4.7 kg) immature and delicate intracranial tissues of an 8-week-old; are factors that elevate the surgical of bleeding, DIC, or shock associated with large resections such as hemispherectomy. Surgical interventions in younger infants carry immense gravity and these are best relegated to the judgment of only the most experienced surgical teams. Under extreme circumstances, when the risks of not doing surgery (i.e., continued medical management) outweigh the operative risks, resective surgery may become a consideration in the hands of experienced personnel.

Developmental plasticity

Early intervention to control seizures is especially relevant in infancy for reasons of neuronal plasticity – a virtue which rapidly declines during early childhood.[14] One of the factors determining good neurocognitive outcome in infants with epileptic spasms, is the ability to rapidly control seizures after onset of epilepsy.[15] On the other hand infants with poorly controlled seizures are more likely to have an irreversible epileptic encephalopathy.[16]

It is also recognized that if an immature brain suffers a regional insult, it stands a better chance to compensate for this insult and transfer the impairment in function to preserved areas. For instance, transfer of language to the non-dominant hemisphere is more likely if the injury to the language dominant hemisphere is incurred in early childhood rather than later in life.

The plasticity of a young brain offers this unique and somewhat narrow window of opportunity to improve upon development, if an intervention to halt seizures is made early. It also offers the best chance to recover function by recruiting the adaptive potential of preserved areas.

Early identification of medically refractory epilepsy should therefore, prompt a diligent evaluation for surgical options. Compelling data suggest that failure of two antiepileptic drugs implicates medical refractoriness and while this cautions against the futility of further AED trials, it also provides an opportunity to consider alternate options early in the course of epilepsy.

Neurological deficits

Expected neurological deficits as a result of surgery in this young infant included worsening of a subtle pre-existing hemiparesis and a homonymous hemianopia. The prospect of continued status with no clear endpoint with medical management, exposure to mortality risk of acute life-threatening events and imminent neurocognitive morbidity were unique features urging towards surgical intervention. Even though these may seem exceedingly pressing reasons, the sensitivity and perceptions regarding fixed neurological deficits are unique to each clinical challenge and must be adequately addressed with aid of medical ethics and other appropriate team members.

Surgical procedures

Congenital pyriform stenosis

Prior to the epilepsy surgery, a midfacial degloving procedure involving bilateral medial maxillectomies was performed with an uneventful recovery. This was done with the goal to achieve physiological upper airway patency and relieve the underlying congenital stenosis.

Anatomic vs functional hemispherectomy

Anatomic hemispherectomy was preferred over a functional disconnection in our patient. Experience at our and other specialized epilepsy centers suggests that patients with large, hemispheric cortical malformations may not achieve complete seizure freedom after functional hemispherectomy.[19,20] In our series authors reported that an incomplete disconnection after functional hemispherectomy was the single statistically significant variable associated with persistent seizures postoperatively.[19] Revision to an anatomic hemispherectomy resulted in improved outcome in previously failed patients and authors advocate an anatomic removal of the malformed hemisphere as the preferred procedure of choice.[19]

Brain histopathology

This showed a severe cortical dysplasia with microcalcifications and gliosis.

Outcome

Immediate post operative

Status epilepticus was stopped immediately following surgery. After acute convalescence, DC was discharged home on antiepileptic medications with no further seizures and a stable respiratory status.

Eighteen months later

At most recent follow-up, DC remains seizure free with reduction of his seizure medications. Neuropsychological testing was performed at 10-months' age. He had a normal cognitive development for age and was noted to have a strong propensity for language development. His motor development lagged on account of the hemiparesis. His family shares that he has a very bright and cheerful disposition and that he continues to make developmental progress.

Summary and conclusion

Infantile spasms may result from a focal epileptogenic substrate and careful evaluation including attention to clinical detail, neurophysiological and neuroimaging data is important. If a focal epileptogenic substrate is appreciated and

seizures are medically refractory, an early intervention may offer the best chance for seizure relief and neurodevelepmental rehabilitation due to the plasticity of an immature brain. Undertaking a major neurosurgical procedure in the midst of a medical emergency such as status epilepticus needs careful consideration due to several compounding factors and may be offered at centers with multispeciality state of the art expertise. In the hands of an experienced team, status epilepticus need not delay epilepsy surgery for carefully selected candidates and may even be life saving.

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157 Hemispherectomy in a patient with catastrophic epilepsy

A Gupta

Introduction

Hemispherectomy is a not uncommon surgery that is performed usually in infants and children for the treatment of intractable epilepsy. This procedure, often quoted as being radical in the media and journal articles, is obviously reserved for catastrophic epilepsies that usually present with daily and some times life-threatening seizures or status epilepticus, progressive or malignant course, rapid cognitive decline, neurological deficits, lack of seizure response and toxicity from multiple antiepileptic medications, poor prediction for prognosis and mortality risk (unless surgery is imminently considered), and parental anxiety and stress. Common indications for hemispherectomy are congenital hemispheric malformations such as hemimegalencephaly or extensive cortical dysplasias, perinatal ischemic stroke, Rassmussen's encephalitis, and Sturge-Weber syndrome.[1] The goal of this chapter is to present an instructive case to illustrate important presurgical findings, decision-making steps, and surgical planning in an infant who underwent hemispherectomy. This case also exemplifies some of the unique aspects of evaluating infants who are candidates for surgery (also see Chapter 46). Hemispherectomy procedure and techniques are discussed elsewhere in this book (see Chapter 121).

Case history and examination

A 6-month-old female baby presented with daily seizures that began soon after her birth. This was mother's first and twin pregnancy induced by in vitro fertilization. She was on ovulation stimulation agents before pregnancy. Pregnancy was uneventful except for mild gestational diabetes managed by dietary modifications. Around 36 weeks period of gestation, mother went into spontaneous labor. However, the labor failed to progress, and twins were delivered by cesarean section. The first twin, our patient, was 2 kg birth weight and required supplemental blow-by oxygen for a few minutes after birth. The second twin was noted to be pink and active at birth with no subsequent medical concerns after delivery.

In the nursery, on the second day after birth, it became clear from repeated observations that the infant was having seizures. Initially, her seizures were behavior arrest, rapid eye fluttering, facial twitching, and multifocal clonic movements (all extremities) occurring for 20–45 seconds 5–6 times a day. Medication management failed to control her seizures while parents went through many frightening procedures, hospital admissions, emergency room visits, nutritional and feeding difficulties, and researching on their daughter's condition. Around the age of 6 weeks, she developed typical infantile (epileptic) spasms and her epilepsy took a course for the worse. Her seizures (described above) were now mixed with infantile spasms in clusters of 5–10 seizures every few seconds lasting for 2–5 minutes. She was having 30–60 clusters daily by the time she was referred for surgery. During this time, she attained no developmental milestones, did not smile or even make eye contact with the parents, became hypotonic laying in bed sleepy and encephalopathic, was supplemented by nasogastric tube for failure to thrive, and was taking Valproate, Phenobarb, and Levetiracetam in toxic doses along with a ketogenic diet. She had previously failed to respond to Topiramate and Clonazepam. Parents also noted decreased spontaneous movements in the right arm and leg. It was now clear to the treating physicians and the parents that the child's condition demanded some critical decisions. At this point, the child was referred for surgical options.

At the time of our first examination at 6 months of age, she was an encephalopathic infant with severe developmental delay and generalized hypotonia. Her weight was 7 kg. Her scalp examination and head circumference were normal. She had one or more seizure clusters every hour. Repeated observations and careful examinations revealed right hemiparesis with extreme paucity of right hand and finger movements, but without any asymmetry in the deep tendon reflexes, tone or plantar responses (generalized hyptonia and hyporeflexia). Skin examination revealed a linear nevus on the bridge of the nose and small overgrowth over the left lip (Figure 157.1) suggesting a diagnosis of Epidermal Nevus Syndrome. Dilated eye examination was normal. Visual tracking or field deficits were untestable.

Presurgical evaluation

Video-EEG evaluation at 6 months of age showed absence of normal awake rhythms and physiological sleep elements. The interictal EEG showed high-voltage, almost continuous sharp waves (1–2 per second) in the bioccipital regions with maximum in the left occipital region (Figures 157.2 and 157.3). Many clusters of seizures were recorded with behavior arrest, whole-body stiffening, rapid eye fluttering, and multifocal clonic jerking. Ictal onset (Figure 157.4) was again noted in

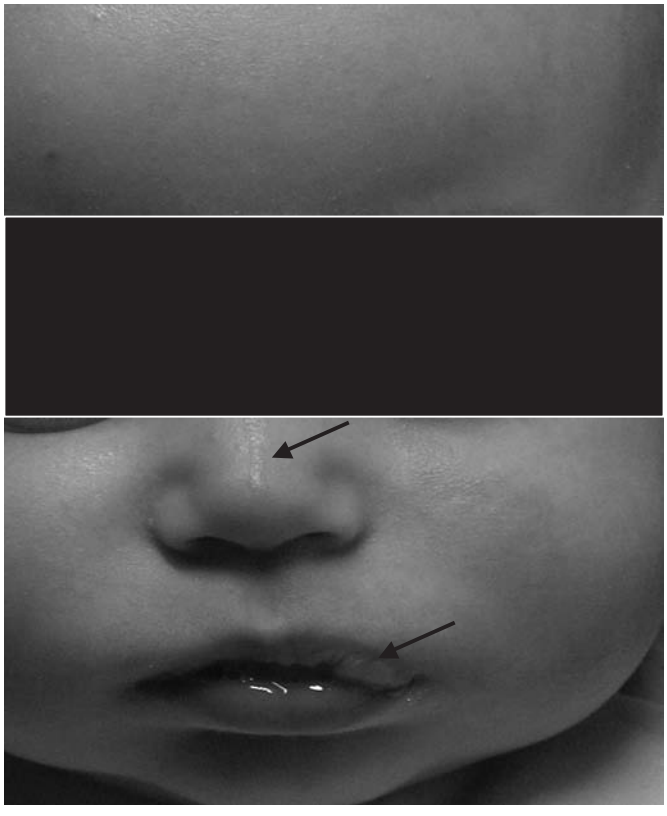

Figure 157.1 Facial photograph of the infant with arrows showing linear nevus in the midline over the bridge of the nose and overgrowth of the left lip ipsilateral to the hemimegalencephaly.

the bioccipital regions, however, maximum distribution was in the left occipito-parietal and mesial parietal channels. A brain MRI (Figure 157.5) revealed left hemimegalencephaly, agenesis of corpus callosum, and midline lipoma confirming the diagnosis of Epidermal Nevus Syndrome. No abnormalities were noted in the right cerebral hemisphere. Brain FDG-PET showed marked left cerebral hypometabolism concordant with the MRI and EEG findings. Only limited neuropsychological evaluation was possible by parental report, and it revealed profound developmental delay.

Epilepsy management conference and decision making

The case was presented and discussed in the Epilepsy Management Conference. It was the consensus that the infant had catastrophic left hemispheric epilepsy and surgery could have been considered even earlier given the diagnosis and expected intractability of her epilepsy. The burden of seizures, degree of encephalopathy and developmental delay, toxic doses of multiple antiepileptic medications, pre-existing right motor deficit, and the etiology argue favorably in considering urgent left hemispherectomy.[2] No further studies such as invasive recordings were needed to refine surgical strategy. Extensive resective surgery in the face of small size (weight 7 kg) and encephalopathic state would entail higher perioperative risks of mortality and morbidity. However, the risk of mortality from surgery compares favorably to nonsurgical options, and is likely to be only higher if surgery is further delayed or not performed. The literature suggests 50% chance of seizure freedom with additional 20–30% chances of >75% seizure improvement on lesser medications.[2,3] It is likely that the patient will remain developmentally delayed, however, significant gains in global development and affect are expected. All this information was presented to the parents who were already on the verge of giving up on their child. After considering benefits, risks and no promising nonsurgical alternatives in the future, they agreed to proceed with hemispherectomy, the thought of which they had so far resisted.

Surgery and outcome

A modified left anatomic hemispherectomy was performed (Figure 157.6). Perioperative course was unremarkable for any acute complication. The child did not have any seizure in the acute postoperative period. She was discharged from the hospital with intensive motor rehab and intervention for cognitive development. Two years since surgery, the child remains seizure free. She was on one medication in low doses at the 2-year follow-up visit. At two and a half years of age, she made significant motor and cognitive gains. She was learning to stand and did not yet have any clear words with meaning. Surgical pathology showed increase bulkiness of the resected left hemispheric tissue with thick and smooth gray matter in the left occipital, parietal and temporal lobes. Predominant microscopic findings included lack of cortical organization, dysmorphic neurons, regions of polymicrogyric cortex, and areas of nodular neuronal heterotopia. Numerous islands of microcalcifications were noted in the subcortical white matter. These findings confirmed the diagnosis of hemimegalencephaly.

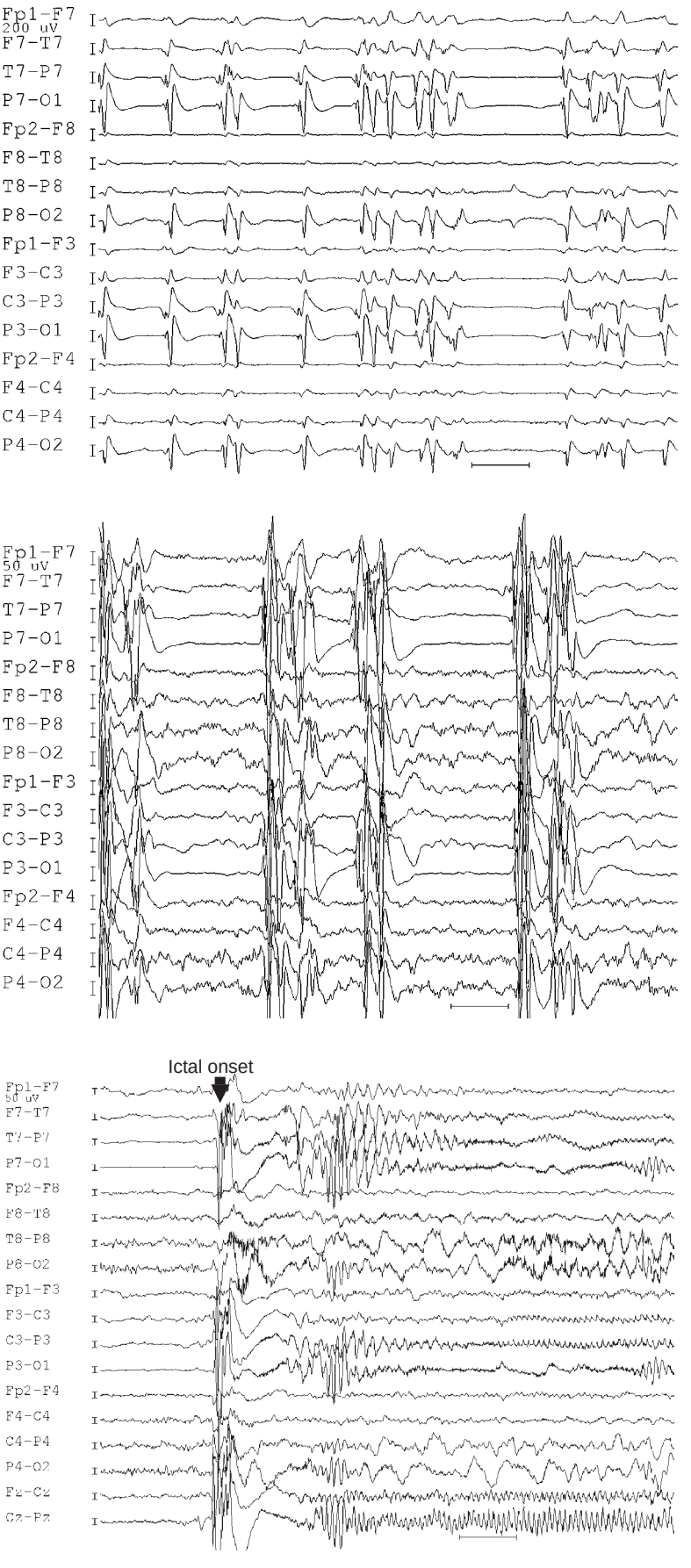

Figure 157.2–4 Interictal EEG showing high voltage repetitive generalized (maximum bioccipital) sharp waves every 1–2 seconds (Figure 157.2) maximum in the left and mesial occipital (O1 and Pz) regions. On increasing the voltage gain, left hemispheric burst suppression pattern (modified hypsarrhythmia) is seen with relative preservation of the faster frequencies over the right hemisphere. Ictal onset (Figure 157.3) showed a burst of high voltage generalized sharp waves maximum in the left occipital and mesial parietal electrodes followed by emergence of sharp alpha in the same region. Note that due to hemimegalencephaly and protrusion of left parieto-occipital region across the midline, the mesial parietal (Pz) electrode is most likely over the left parieto-occipital lobe (Figure 157.4).

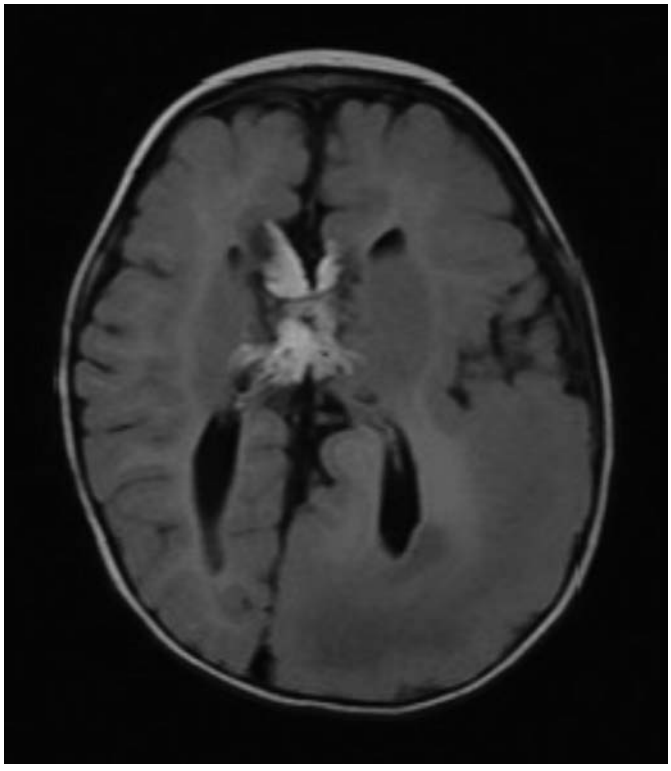

Figure 157.5 T1 weighted brain MRI of the infant showing left hemimegalencephaly with left hemispheric enlargement, thickened cortex, poor gray-white differentiation, and a midline lipoma with hypoplastic corpus callosum. Right hemisphere appeared normal on MRI.

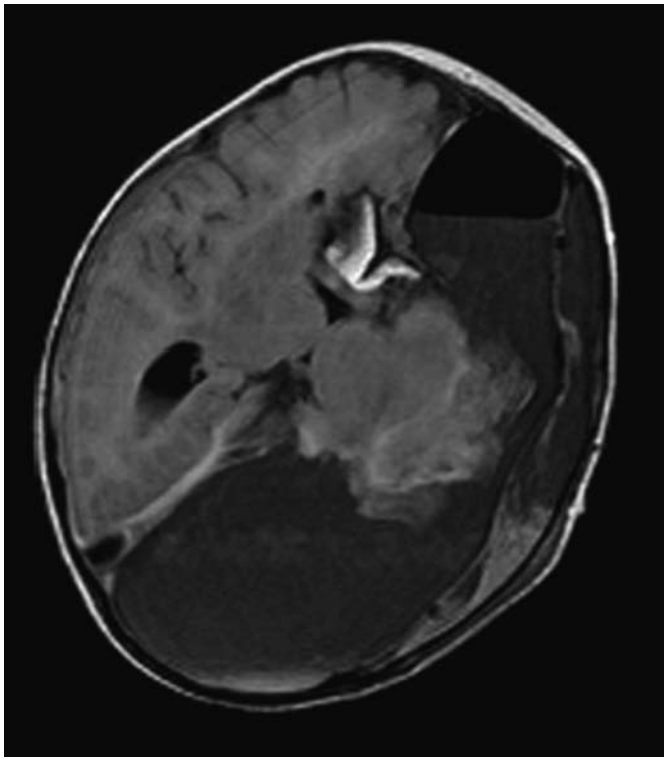

Figure 157.6 Postoperative brain MRI showing modified anatomic hemispherectomy with resection and disconnection of the brain except for insular region and deep gray nuclei.

Discussion

Our case illustrates several unique age-related aspects of infants who are candidates for epilepsy surgery (discussed in Chapter 49). First, the clinical course was catastrophic from the onset to the time of surgery. Beginning life with daily seizures due to extensive brain malformation (hemimegalencephaly) was further complicated by the toxic doses of antiepileptic medications, stupor state with encephalopathy, feeding difficulties and failure to thrive. This rendered accurate assessment of motor function, visual function, and neuropsychological assessment difficult, if not impossible. In addition, the stress of taking care of such an infant for new parents, especially so in the presence of a normal twin sibling, can not be underestimated. There usually is tremendous grief, guilt, anger, with psychosocial and economic impact on the family, and the family may be averse to making decisions for surgery (often considered more risky) early on in the course. Second, the intractability of seizures in infants such as our case is not just a function of time and trial of medications, but also, the evaluation of underlying etiology. Daily seizures that begin at birth due to hemimegalencephaly are most unlikely to respond to medical management, and surgical planning should start at the time of diagnosis. Surgical timing is crucial, and recent studies suggest that consideration for early surgery reduces the impact of daily seizures and encephalopathy on cognition and developmental outcome.[4] With advances in pediatric anesthesia, critical care, neurosurgery, and epilepsy management, tertiary care centers with experience in pediatric epilepsy are able to operate with low mortality and morbidity even in infants weighing <10 kg.[1] Therefore, age is no bar for hemispherectomy, if the situation so demands. However, parental lack of understanding and fear of radical surgery coupled with physician's persistence to try more medical treatment often delays consideration for surgery. Third, our case points out challenges in pediatric epilepsy for evaluating an infant who despite focal (hemispheric) epilepsy manifested with generalized seizure phenotype and poorly localizing scalp-EEG. Brain MRI is the most important element in infants being considered for epilepsy surgery. Ictal SPECT, PET or other invasive studies and brain mapping are often impractical or difficult to interpret alone (in the absence of MRI lesion) or not contributory. Fourth, brain malformations such as hemimegalencephaly[2] have important implications for making the correct genetic diagnosis. Our patient had Epidermal Nevus Syndrome, a sporadic condition that may involve other organ and systems (eyes, bones, etc.), required further evaluation and management for co-morbid conditions. Genetic counseling is also important, as certain autosomal dominant diseases like tuberosis sclerosis complex may be associated with hemimegalencephaly with high risk of recurrence in subsequent pregnancy, if one of the parents have subtle unrecognized disease. Fifth, psychosocial support to the parents and the family, assessing parental understanding and level of education, repeated hospital admissions and procedures, need for prolonged intensive rehabilitation after surgery, life-long cognitive and behavior interventions, and long-term special multidisciplinary needs of such a child are often underestimated by most physicians, and therefore, require emphasis and attention to provide the best overall outcome to infants such as the one illustrated in this chapter.

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158 Case studies: Landau–Kleffner syndrome

AM Kanner, MA Rossi, and MC Smith

Introduction

Landau–Kleffner syndrome (LKS) or acquired epileptic aphasia of childhood is a rare disorder characterized by the development of expressive and receptive language disturbances following a normal development of language functions, that results from an epileptogenic lesion in speech cortex (or that impacts speech cortex) during a critical period of language development.[1,2] At the height of receptive aphasia, the child may display an auditory agnosia consisting of an inability of recognizing common sounds.[3,4] In addition to the language disturbances, children exhibit psychiatric problems consisting of motor hyperactivity, impulsive behavior, poor frustration tolerance that may even reach to overt aggression, or withdrawn behavior. While the epileptic seizures may be absent in up to 30% of children, EEG recordings of children with LKS present a characteristic pattern of continuous spike and wave during slow wave sleep (CSWS), which consists of bisynchronous discharges originating from intra- and peri-sylvian cortex unilaterally with a rapid propagation to homologous regions contralaterally. A certain percentage (unknown as of yet) of children with LKS experiences a spontaneous remission of their language disturbances.[3,4] In others, trials with steroid therapy may result in symptom remission, while the success of antiepileptic drugs (AED) in LKS has been rather disappointing. Epilepsy surgery has been advocated in children with a classic presentation of LKS who failed to regained functional language for a period of at least one year either spontaneously or in the absence of response to pharmacologic interventions (including an inability to tolerate steroid therapy because of serious adverse events) as these children are at a very significant risk of not having any functional language by the time they reach adulthood.[5–7]

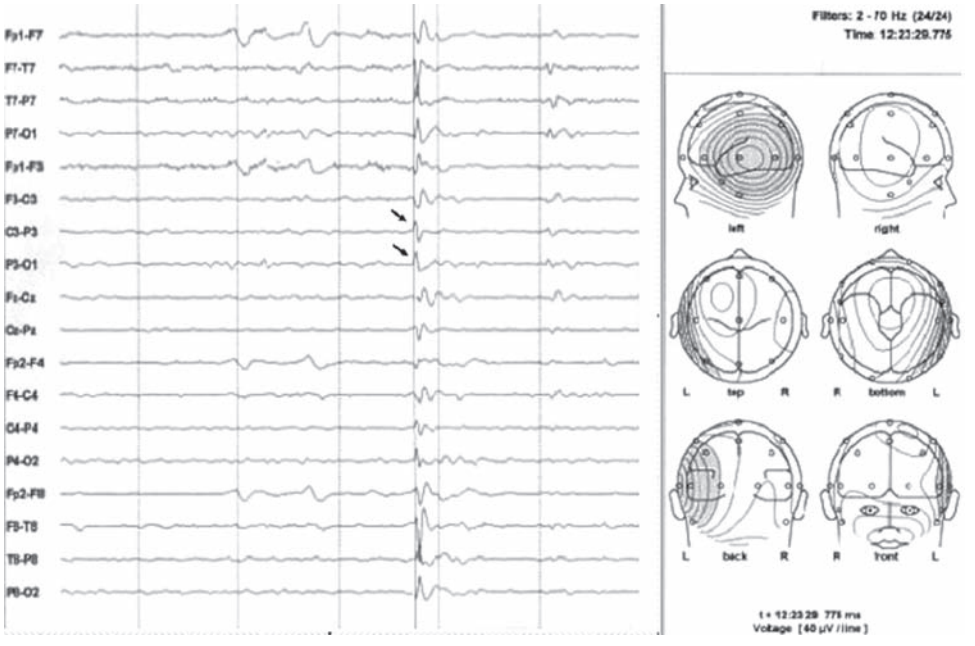
The clinical, neurophysiologic and neuropsychological characteristics of LKS have been reviewed in great detail in Chapter 45. The diagnostic evaluations including pre-surgical work-up and treatment strategies have also been reviewed in that chapter. The aim of this chapter is to present three representative cases that help illustrate various aspects of the pre-surgical evaluation and surgical treatment in LKS.

Case 1: SF

SF was born at 36 weeks gestation with APGAR scores of 8 and 9. He met normal motor developmental milestones, sitting up at 6 months and walking at 12 months. Since an early age, he suffered from recurrent middle ear infections requiring the placement of myringotomy tubes at 7 months of age and at 4.5 years a tonsillectomy with adenoidectomy was performed. Compared to his male sibling, speech and language were slow to develop. At 2 years 4 months, SF was diagnosed with verbal dyspraxia, but he was able to learn American sign language without difficulty. Language continued to develop until five years of age at which time his expressive language consisted of sentences of 10–14 words in length. At that age, however, his parents began noticing 'periods of inattentiveness' and an EEG at this time revealed a CSWS pattern. Carbamazepine (CBZ) was started which was followed by the immediate occurrence of overt clinical seizures consisting of myoclonic jerking associated with staring. Soon after the start of CBZ, language functions deteriorated rapidly with greater involvement of expressive than receptive language. Within two months he stopped responding to directives and his receptive speech began to noticeably worsen. At that time he was diagnosed with LKS and was started on valproic acid (VPA) and clonazepam (CZP) followed by a pulse-dose course of prednisone. Steroid treatment was associated with severe behavioral disturbances that included marked agitation diagnosed as steroid psychosis. Steroids were stopped; his receptive and expressive language functions continued to worsen and one month later he became totally mute. Topiramate (TPM) and phenytoin (PHT) were started. His behavior improved but his language did not. Following sedation with propofol for a lumbar puncture he transiently produced words and simple sentences.

Since the patient had failed to regain any functional language for more than 12 months, he was admitted to the Rush Epilepsy Center where he underwent a pre-surgical evaluation that consisted of the following tests:

a) A scalp video-EEG monitoring study: *Interictal recordings* revealed during awake states abundant epileptiform activity consisting of bifocal independent sharp wave activity of left frontal and left mid-posterior temporal origin, with a predominance of the latter.
   Sleep recordings revealed a CSWS pattern. Mapping of epileptiform discharges revealed a bisynchronous posterior temporal lateral source.
b) *Methohexital suppression test* had to be carried out to lateralize the source of the epileptiform activity. It revealed a left posterior temporal source with frequent propagation to the left frontal region. Of note, no independent frontal source was identified (see Figure 159.1A).



(a)

Figure 158.1a The last epileptiform discharge is seen during methohexital suppression testing using scalp electrodes. Left focal posterior quadrant epileptiform activity is seen with rapid propagation frontally. A voltage map generated in BESA represents the negative polarity onset (shaded contours).

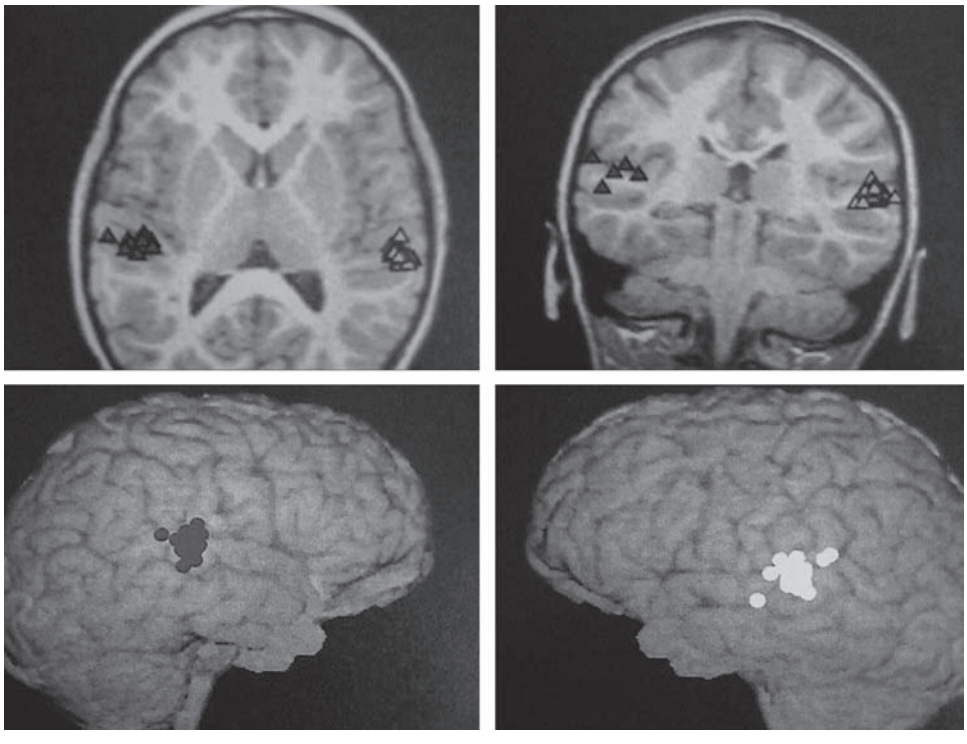
c) *A speech evaluation* was carried out using the Expressive One Word Picture Vocabulary Test-Revised (EOWPVT-R) (expressed as age equivalent in months old) and the Peabody Picture Vocabulary Test-Revised (PPVT-R) for evaluation of expressive and receptive language functions, respectively. A severe expressive and receptive language disturbance was demonstrated with a severe verbal auditory agnosia, the latter evidenced by not responding to any verbal commands given verbally with the exception of his name. SF was only able to identify simple pictures (i.e., fish, bathroom, eat, color, and turtle). He verbalized 'you', 'me', 'mom', 'da', and imitated a dog. SF was presented with letters and did not demonstrate any understanding of them or their sound symbol relationships.
d) *A neuropsychological evaluation* to assess non-verbal cognitive functions was complicated by repeated refusals by SF to participate in testing. No inappropriate or unusual behaviors were noted. SF completed the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R). Perceptual and constructional skills measured by Object Assembly and Block Design were at the 63rd and 2nd percentiles, respectively. His copying and drawing skills (Mazes, VMI) were measured at the 6th percentile. SF did not complete the Picture Completion or Coding subtests.
e) *A positron emission test (PET)* with 18-fluoro-deoxyglucose (18-FDG-PET) revealed an asymmetry in the posterior temporal cortices bilaterally with lower activity on the left.
f) *A magentoencephalogram study (MEG)* revealed focal left posterior sylvian interictal activity with rapid propagation to the contralateral homotopic region (see Figure 159.1B).

Eighteen months after the onset of symptoms. SF underwent surgical treatment consisting of MST of the epileptogenic zone. Specifically, an exquisitely focal MST was performed limited to the left posterior infrasylvian fissure. Intraoperative monitoring at the site of MST did not reveal any epileptiform activity post-transection. SF was started on PHT and phenobarbital (PB) postoperatively, which was then replaced by levetiracetam (LEV).

Postsurgical course: SF had an uneventful immediate and delayed post-surgical course. However, return of language functions was first identified approximately 6 months after surgery, when his parents noticed the return of receptive language and the use of sign language more frequently to communicate. Previously, SF would attend to signs but rarely use them spontaneously or in imitation. Expressive speech similarly improved at about the same time, but to a lesser extent. SF was observed to spontaneously, meaningfully and intelligibly say, 'you', 'mine', 'no', 'ya ma', 'I do'. Nonverbal abilities were similar to what was seen prior to surgery. One exception was noted on Block Design, where his score improved from the 2nd percentile to the 50th percentile.

His expressive and verbal receptive language markedly improved over a 15–18 month period after resection when he was able to use five to ten word sentences to communicate. His speech remained mildly dysarthric but fluent. He demonstrated an inability to pronounce consonants at the beginning of the sentences. His last formal speech evaluation was carried out four years after surgery. The EOWPVT-R and PPVT-R revealed age equivalent of 78 months each.

The child was kept on LEV at daily doses of 750 mg/day. Repeat EEG studies revealed rare left frontal epileptiform discharges that persisted for three years and was recorded as well on an overnight video-EEG monitoring study. CSWS, however, was no longer observed. No further seizures were witnessed since his surgery and behavioral problems had also remitted.



(b)

Figure 158.1b Magnetoencephalography demonstrates localization of interictal activity in the inferior bank of posterior sylvian fissure. Rapid propagation occurred from left to right homotopic cortex (not shown).

Case 2: NB

NB was an eight-year-old, right-handed boy at the time that he was first evaluated at the Rush Epilepsy Center. He was born following a full-term, uneventful pregnancy and had a normal motor and cognitive developmental history. According to his parents, he started to use single words at the age of ten months, and was speaking in full sentences by three years of age. The first evidence of this child's LKS was identified at the age of five by his kindergarten teacher and consisted of psychiatric rather than cognitive and/or epileptic symptomatology, as he was noticed to have become very hyperactive and impulsive displaying short attention span during his classroom activities. He was started on a regimen of methylphenidate at a dose of 10 mg/day without any significant improvement. Four months later, his parents identified the first disturbance in language functions consisting of problems in comprehensive language which was initially interpreted by the parents as difficulty hearing, which prompted them to request an auditory evaluation. This evaluation identified minor hearing loss which involved high and low frequency ranges bilaterally. However, receptive problems continued to progress, and three months later he started to display clear difficulty in expressing himself. He was unable to use words that he had already learned; his sentences tended to become increasingly shorter, and his speech acquired a strong, dysarthric quality. His expressive language deteriorated progressively, but obvious comprehensive difficulties started to deteriorate at only three months after overt expressive language problems became apparent. Once the comprehensive language had deteriorated, it only took two months before the child was unable to express himself and understand what was said to him and soon after he became mute. At the same time that his expressive and receptive language deteriorated, his behavior worsened significantly with further deterioration of motor hyperactivity, impulsivity and marked difficulty with concentration in any activity. The dose of methylphenidate was increased to a total of 35 mg/day without any improvement.

Approximately one year after the first behavioral disturbances were reported by his kindergarten teacher, a diagnosis of LKS was established with EEG recordings which revealed a CSWS pattern. During that evaluation, the patient was witnessed to display subtle seizures consisting of brief periods of unresponsiveness during which he was also noticed to have eye fluttering for periods of as long as 30–45 seconds. One of these seizures was captured during the EEG recordings. At that point, he was started on a regimen of valproic acid with doses of up to 500 mg/day without any significant change. He was then started on a regimen of prednisone at a dose of 2 mg/k/day, which resulted in gradual improvement of expressive and receptive language functions over the course of four to six weeks with a final return of comprehensive and expressive language equivalent to 85% of baseline. The trial with prednisone, however, was complicated by a weight gain of 30 lb. and worsening of behavior consisting of aggressive outbursts and further deterioration in his impulsive behavior. The combination of these adverse events prompted the discontinuation of the prednisone over the course of a three-month period. During the trial with prednisone, subtle seizures that had been identified were not witnessed any longer. However, after the prednisone was stopped, seizure activity recurred, associated with a loss of language gains noted during the trial with prednisone. Four months later, he was restarted on prednisone at doses of up to 30 mg/day which resulted in regaining of both expressive and receptive

language functions. This trial, however, was complicated again with the development of significant Cushingoid features. During his trial with prednisone, he was able to attend school, although he needed to get additional help from a special education teacher, and he required daily speech therapy. The severity of the adverse events of prednisone prompted the discontinuation of this drug again, which was again followed four weeks later by the recurrence of severe receptive and expressive language dysfunction and the recurrence of seizure activity.

At the time that he was seen at the Rush Epilepsy Center, he underwent a pre-surgical evaluation to see if he could be a candidate for epilepsy surgery. The evaluation consisted of the following:

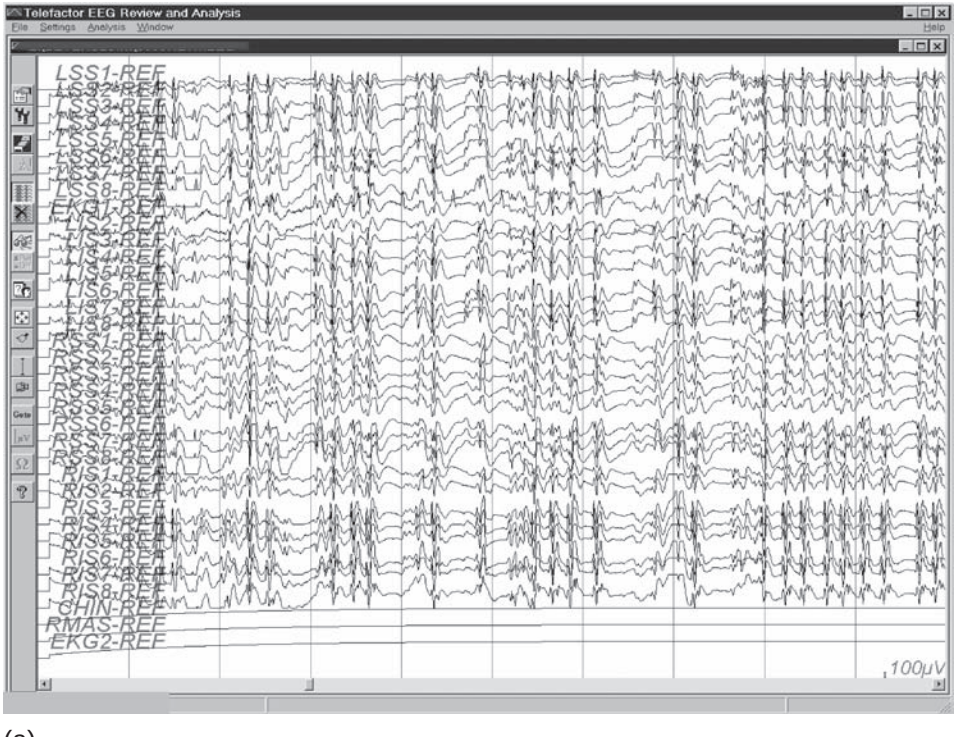
a) *A high resolution MRI* of the brain was unremarkable.
b) *A prolonged video-EEG monitoring study* revealed the presence of a CSWS pattern with bisynchronous discharges originating from posterior temporal lateral regions.
c) *Methohexital suppression test* carried out with scalp recordings could not lateralize the source of the epileptic activity, however.
d) *Speech evaluation* revealed a severe auditory-verbal agnosia with an expressive language function equivalent to an age of less than 12 months of age. The child was identified using gestures to communicate.
e) *A neuropsychological evaluation* revealed that NB performed according to the expected level for his chronological age in nonverbal cognitive functions.

Given that the epileptic source could not be lateralized on scalp electrodes with a methohexital suppression test, the patient underwent a prolonged video-EEG monitoring study with intracranial recordings which consisted of a pair of epidural strips of eight contacts each, positioned superior and inferior to the Sylvian fissure. Figure 159.2A shows a CSWS pattern recorded with these intracranial electrodes.

A methohexital suppression test done with these electrodes revealed the source of epileptic activity in the right intrasylvian cortex (see Figures 159.2B and 159.2C). NB underwent a topectomy of the planum temporale on the right side, given that he was strong right-handed at the time of the onset of his symptomatology and throughout the duration of his illness, indicating that the right hemisphere was non-dominant for speech.

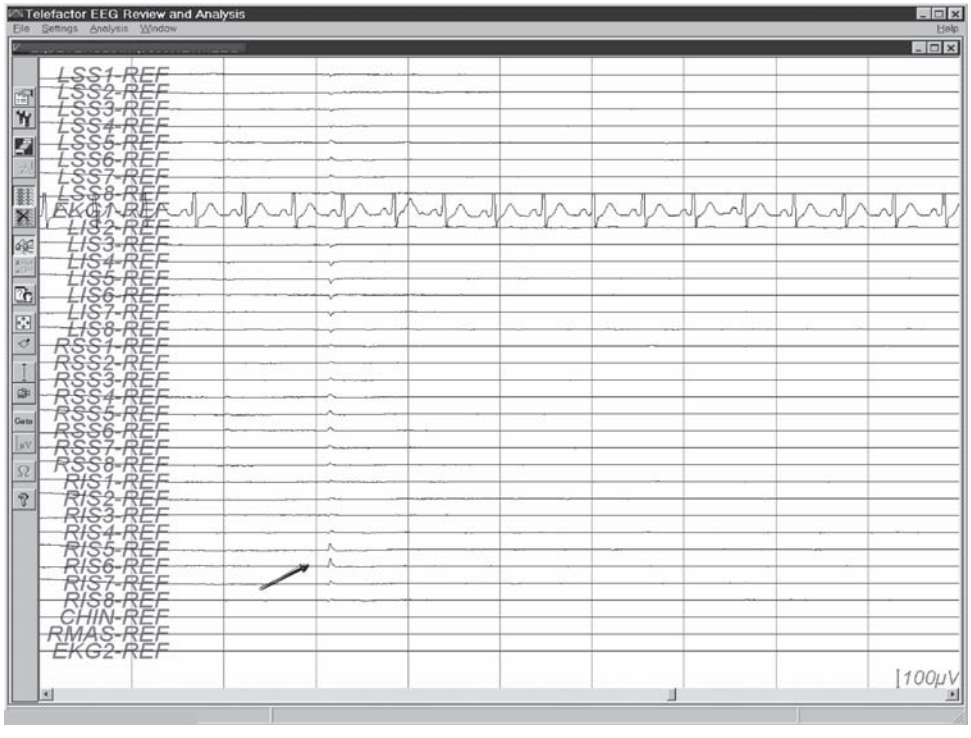
Postsurgical course: The patient had an uneventful, immediate postoperative course. He was discharged home five days after surgery on a regimen of valproic acid and clonazepam and instructions to resume speech therapy. He started to display expressive language one week after surgery, and his ability to understand was also noted by his parents by that time. Since the child was placed on prednisone for two weeks after surgery, this improvement was attributed to the trial with dexamethasone. However, discontinuation of the dexamethasone was not followed by loss of the gains noticed. On the contrary, NB continued to display steady improvement in both receptive and expressive language functions, and by three weeks after surgery he was using three and four word sentences. An EEG study done two months after surgery revealed no epileptiform activity (see Figure 159.2D).

EEG recordings done six months after surgery revealed the presence of the recurrence of epileptiform activity in the temporal lateral region in electrodes T4 and T6 (see Figure 159.2E). This activity, however, did not propagate to the contralateral side or to suprasylvian regions and was not



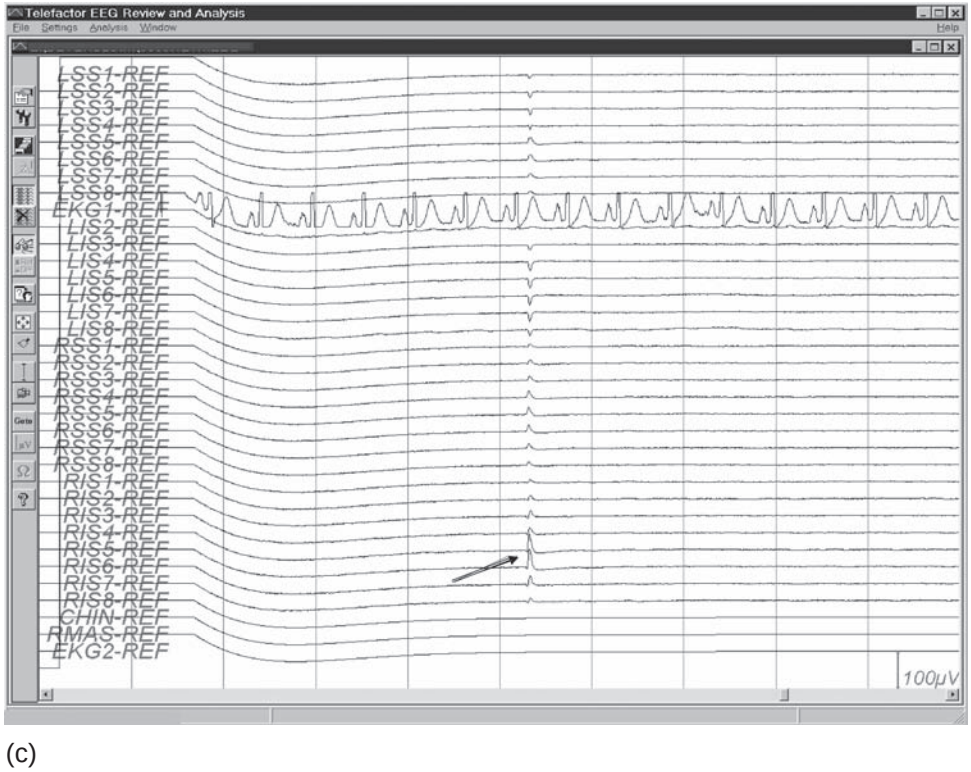
(a)

Figure 158.2a CSWS pattern of patient NB recorded with two pairs of epidural electrodes consisting of eight contact strips positioned parallel to the sylvian fissure 1 cm above (suprasylvian strips (LSS1-8 and RSS1-8)) and 1 cm below (Infrasylvian strips (LIS1-8 and RIS1-8)).



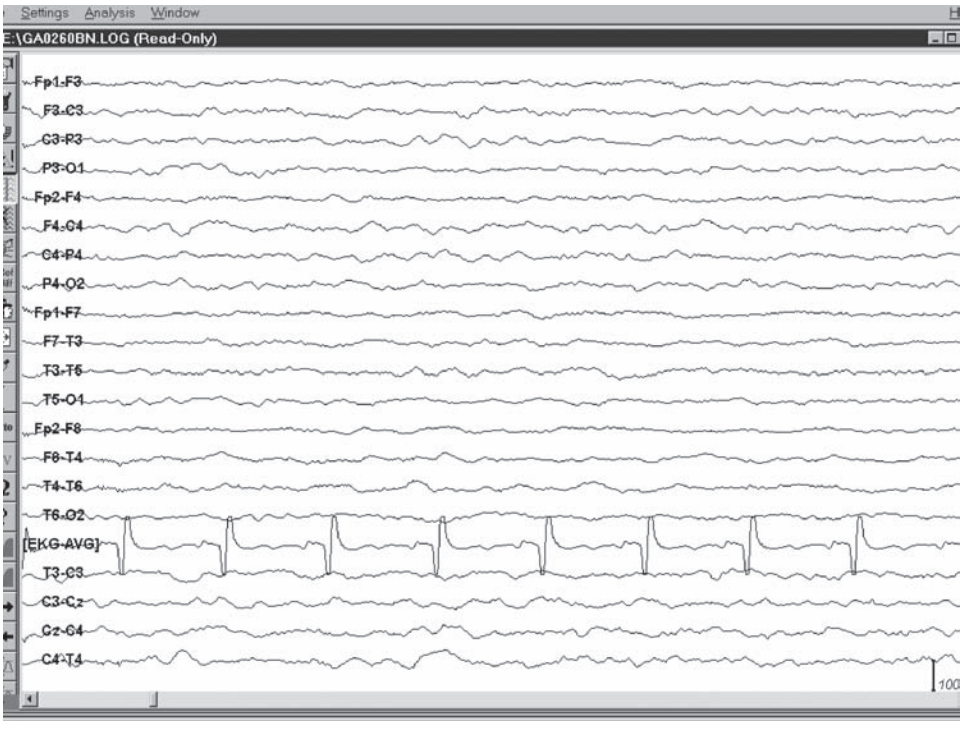
(b)

Figure 158.2b Methohexital suppression test. The arrow shows the last discharge in the right strips to be identified before complete suppression of the electrical activity. There is a rapid propagation to the contralateral side.



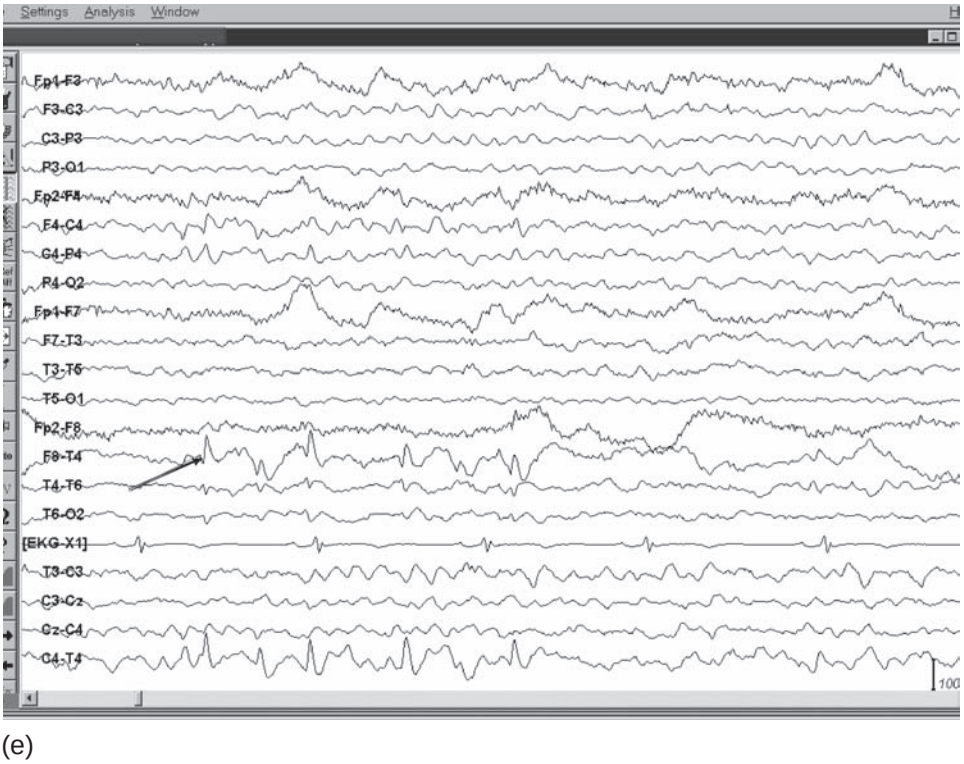
(c)

Figure 158.2c Methohexital suppression test: the arrow shows the first discharge in the right infrasylvian strip to be identified following a complete suppression of the electrical activity. This discharge rapidly propagates to the contralateral side (25 ms).



(d)

Figure 158.2d Stage 1 sleep recording 2 months after surgery.



(e)

Figure 158.2e Awake recordings obtained six months after surgery reveal recurrence of epileptiform discharges in right temporal regions (ipsilateral to the side of the topectomy).

associated with recurrence of seizures or any loss of gains made in the language domain. Since that time, he has had an EEG study done at six month intervals which have continued to show long runs of epileptiform activity in the temporal lateral neocortical region involving electrodes T4 and T6 with a field of distribution at times, including electrodes F8 and occasionally spreading to suprasylvian regions (see Figure 159.2F). Despite the widening of the electric field of this epileptiform activity, no deterioration in receptive or expressive language functions was identified, and he continued to improve steadily and attend school in regular classes, but with additional help from a special education teacher. He continued to receive speech therapy several times a week. He has been maintained on valproic acid monotherapy and has remained seizure-free since surgery.

Speech evaluation done two years and six months after surgery (when he was 11 years old) revealed that his expressive language was equivalent to an eight-year-old boy, while the receptive language functions were equivalent to that of a nine-year-old boy. The patient at that time was reading at a third grade level.

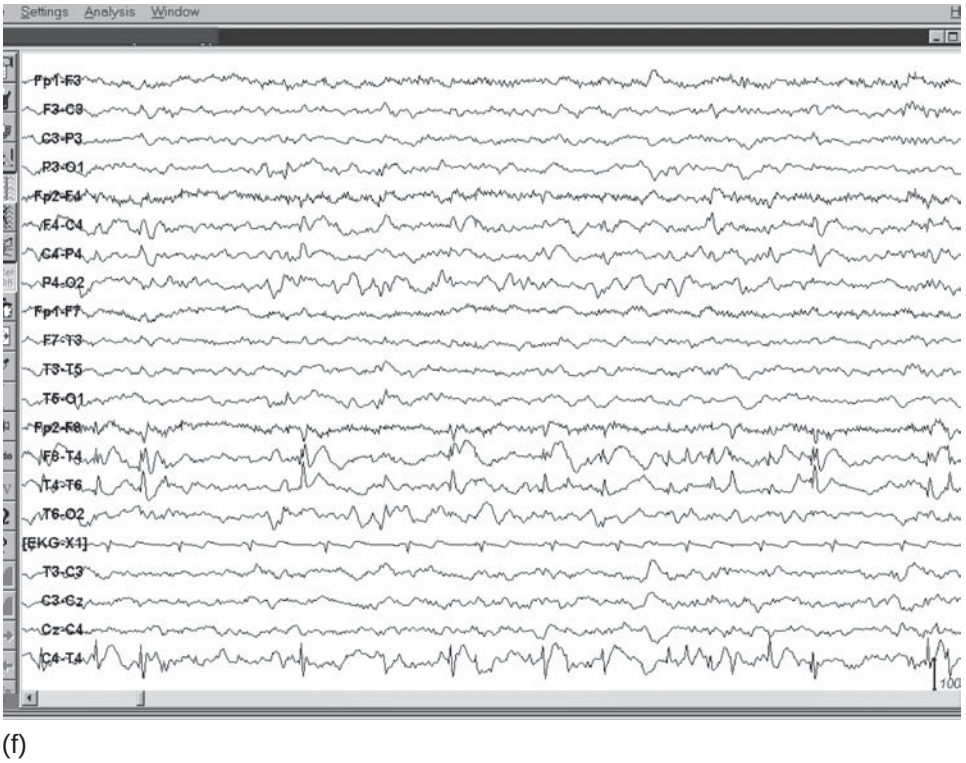
His last follow-up was six years after his surgery, and at that time he was attending regular classes with some remedial help in reading and writing. The parents reported however persistent problems with behavior, particularly, impulsivity and poor frustration tolerance.

Case 3: MP

MP was a six-year-old, right-handed girl at the time that she was evaluated at the Rush Epilepsy Center for epilepsy surgery for the treatment of LKS, which was diagnosed at the age of four years and six months. MP was born following a full-term pregnancy and had an uneventful growth and development. She was one year of age when she started to use single words and was speaking in full sentences by three years of age. The first manifestation of her LKS was at the age of four years, eleven months when she began having difficulty with expressive language. She could not repeat certain sounds and had difficulty saying the name of her favorite cartoon and she could not repeat a sentence without leaving words out. At that time, she underwent an evaluation by a local pediatric neurologist who, on an EEG study, identified the presence of CSWS pattern with a source in the left temporal region.

At the time that MP started to display expressive language, she began experiencing epileptic seizures consisting of motionless staring episodes of 10–20 seconds duration on an almost daily basis. A few weeks later, she was noticed to have difficulty understanding what was being said to her. Expressive and receptive language disturbances worsened over the course of the following two months. She was initially treated with VPA, and then underwent trials with TPM and LEV, but it was not until she was placed on prednisone that she experienced a significant improvement in both receptive and expressive language function. After three months of being on prednisone, a repeat EEG study revealed the disappearance of epileptiform activity after which the prednisone was tapered down and discontinued, but one month later she had a recurrence of expressive language disturbances, which rapidly deteriorated, and she was left with only ten words in her vocabulary. Receptive language functions were also reported to deteriorate, but at a slower pace than expressive language.

Concurrent with the deterioration in language functions, there was deterioration in her behavior. She was noted to become prone to outbursts of anger and poor frustration tolerance, though no motor hyperactivity or problems with



(f)

Figure 158.2f Recordings obtained two years after surgery reveal runs of epileptiform discharges in right temporal regions with a filed of distribution involving fronto-central electrode as well.

attention span were identified. She was able to continue playing with her friends throughout this time. MP underwent a second trial of steroids, but this time they were not associated with any improvement in language function. She was then tried on three trials of IVIG without any improvement. Under these conditions, MP underwent a pre-surgical evaluation at a local University hospital, which consisted of the following:

(a) *High-resolution MRI of the brain* which was normal.
(b) *Video-EEG monitoring study* with scalp electrodes revealed the presence of a CSWS pattern with a source in the left temporal region.
(c) *A MEG* revealed dipoles in the left intrasylvian region.
(d) *Speech evaluation* revealed the presence of a severe auditory agnosia. Her expressive language was at a 2 year-old, age-equivalent level and her receptive language was at a 2.3 year age-equivalent level.
(e) *A neuropsychological evaluation* placed the nonverbal cognitive functions at the 50th percentile,

Under these conditions, she underwent MST on a small area along the margin of the superior temporal gyrus where the MEG study had identified the epileptiform activity. Intraoperative electrocorticography confirmed the MEG data. No epileptiform activity was identified at the completion of the MST and she was discharged off antiepileptic medication.

The immediate postoperative period was unremarkable and parents reported noticing improvement in expressive and receptive language functions within the first four weeks, consisting of understanding complex commands and using one and two words. Two months after the surgery, however, she had a recurrence of epileptic seizures followed by rapid loss of any gains in expressive and receptive language functions. MP was restarted on VPA and prednisone without any improvement in language functions. She was then placed on lamotrigine (LTG) without any benefit, after which she was evaluated at the Rush Epilepsy Center and a repeat pre-surgical evaluation revealed the following:

(a) *The video-EEG monitoring study:* CSWS with bisynchronous spike and slow wave activity during slow wave sleep that revealed a left-sided onset during which sustained, occasional isolated bisynchronous spike and slow-wave activity was seen superimposed. No clinical seizures were recorded.
(b) *A methohexital suppression test*: the source of the epileptiform activity was identified in the left intrasylvian region.
(c) *Speech evaluation:* Receptive language functions were estimated to be at a two years three months of age equivalent on the EOWPVT-R and her expressive language at fourteen months of age on the PPVT-R.

Under these conditions, MP underwent a MST of the entire superior and inferior bank of the Sylvian fissure. Figures 159.3A shows a CSWS pattern recorded during intraoperative electrocorticography and Figure 159.3B a sylvian dipole also recorded during electrocorticography.

Following surgery, MP was placed on a regimen of VPA and LTG and discharged home with instructions to resume speech therapy.

Postoperative course was uneventful and she was noticed to start regaining language functions during the following eight weeks. Four months after her surgery, she was noticed to talk in three to four word sentences as she was attending kindergarten and was receiving speech therapy five times a week. The parents reported that MP could understand most of what was said to her, especially when instructions were given to her in one step commands. From the standpoint of behavior, they reported that she continued to display poor frustration tolerance. No further seizures were identified since her surgery.

Two years after her surgery, MP remained seizure-free. A repeat speech evaluation done at the last visit placed her receptive language function at an age-equivalent level of 5.8 years (she was 9 years old). Improvement in expressive language function was also impressive, but was marked by errors in syntax and grammar which lowered her scores. However, she was able to complete sentences when communicating with others. Repeat EEG studies at that time failed to reveal any epileptiform activity. On a recent telephone contact, MP's parents reported that she was attending a regular third-grade class with remedial help in reading and grammar. She was at age level for reading and six months behind in writing and behavioral problems had remitted.

Discussion

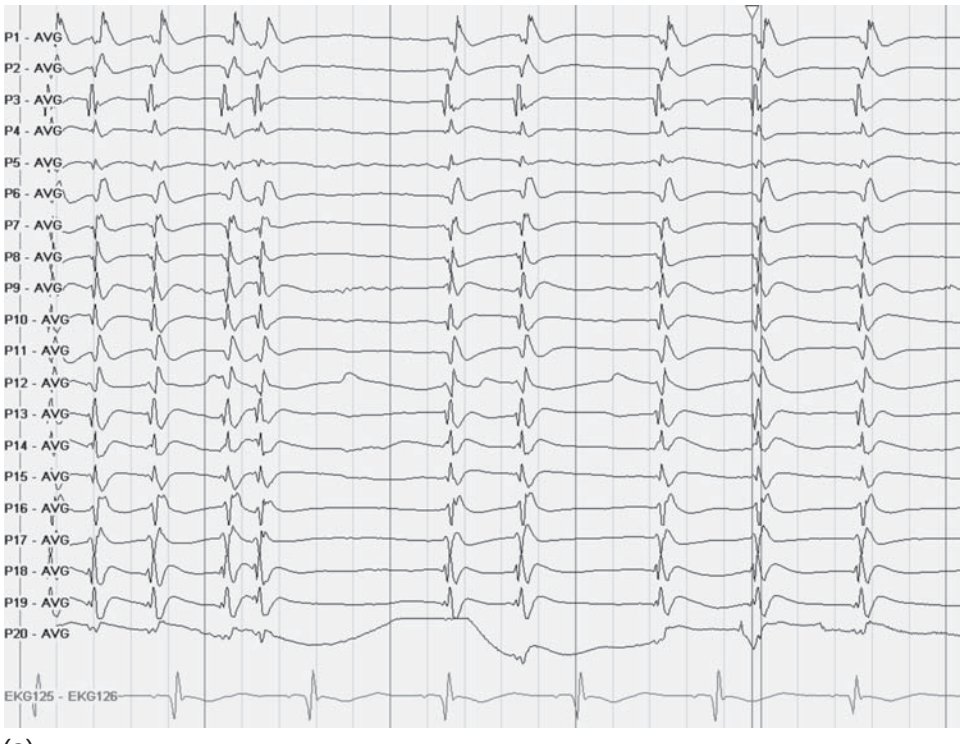
The three children with LKS included in this chapter illustrate unique and representative findings of pre-surgical evaluations, surgical techniques and post-surgical outcome with respect to seizure control, recovery of language functions and remission of psychiatric complications.

Some AEDs may actually worsen the course of LKS

The use of AEDs constitutes the initial treatment of LKS. Yet, as illustrated by Case 1, the use of CBZ can worsen the severity of the language disturbances and epileptic seizures. This has been our own experience and that of other authors, but no controlled study is available to support these observations. By the same token, there are anecdotal data on the efficacy of various AEDs, but no controlled studies, primarily due to the small number of patients afflicted by this disorder (see Chapter 45). Our preference is to consider trials with VPA and a benzodiazepine, particularly in children whose language and behavior disturbances improve or remit following a rectal diazepam protocol (see Chapter 45).

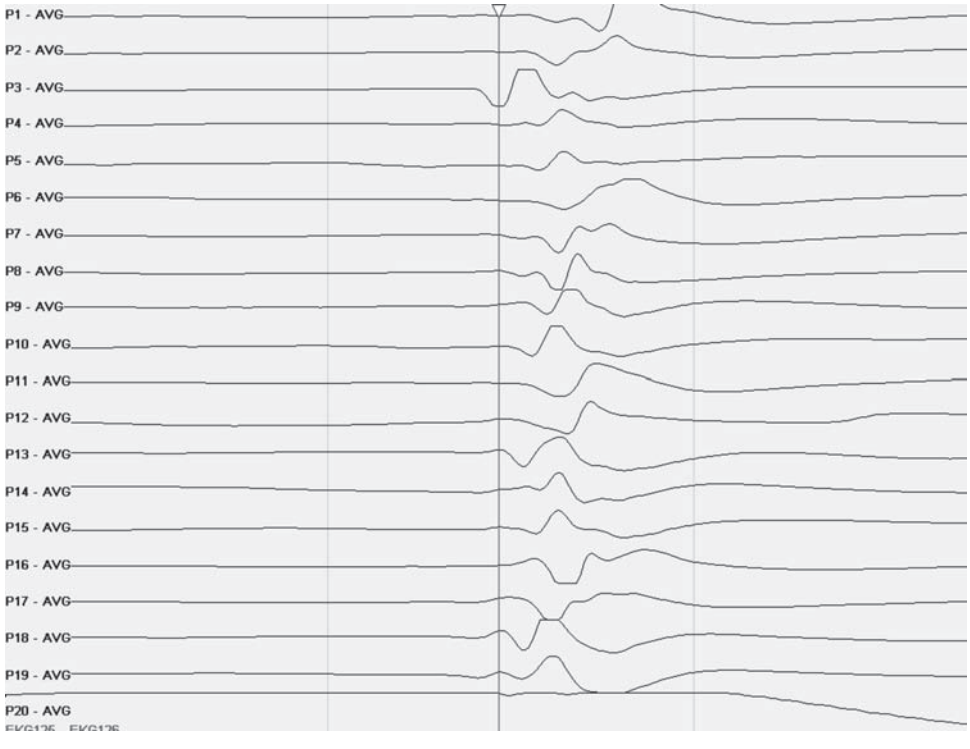
Is MST the only surgical option?

When it comes to the choice of a surgical technique in the treatment of LKS, MST has been the one always considered. The rationale behind using MST is based on the premise that epilepsy surgery is performed on 'eloquent language cortex'. Two of the children (Cases 1 and 3) underwent MST of the intrasylvian region in the (left) hemisphere 'suspected' to be dominant, as these children were right-handed at the time of the onset of the symptomatology. Yet, in Case 2 the epileptogenic was localized in the non-dominant hemisphere (right hemisphere in a (strong) right-handed child) which allowed the surgeon to consider the option of topectomy of the right planum temporale



(a)

Figure 158.3a Intraoperative electrocorticography recording revealing a CSWS pattern. The 20 electrode pad was position over the lateral convexity of the left hemisphere with contact 1 in a most anterior and superior position. Contacts 1–10 covered suprasylvian and contacts 11–20 infrasylvian cortex. Contacts 6–10 and 11–15 were adjacent to the sylvian fissure, the former above and the latter below the fissure.



(b)

Figure 158.3b Epileptiform discharge recorded during Intraoperative electrocorticography reveals a sylvian dipole in the posterior segment of the sylvian fissure. Contact P3 positioned in suprasylvian cortex shows an initial positivity and the infrasylvian contacts P13 and P18 reveal a simultaneous negativity.

over MST. Since the potential to abolish epileptic activity is greater with a resection than transection, it is worth highlighting the option of a topectomy of the planum temporale instead of MST in a child in whom the source of epileptic activity is clearly established in the non-dominant hemisphere.

Post-surgical recovery of language functions

There are significant differences in the rate of language recovery among the three children which merit to be reviewed. The rapid recovery during the two first post-surgical weeks in Case 2, contrasts with the slower recovery rates in Cases 1 and 3. Initial gains were made of lesser magnitude in Case 3, while no meaningful changes were identified until the sixth month. Location of the epileptogenic source in the dominant vs. non-dominant hemisphere probably accounts for the observed differences in the rate of language recovery. Indeed, interference of language cortex by propagated 'bombardment' of epileptic activity from the contralateral hemisphere may play a less serious impact on the pathogenic mechanisms mediating language regression than having the epileptogenic zone within language cortex. Morrell hypothesized a lesser disruption of the synaptic 'anlage' in the former circumstances than in the latter, despite abolition of epileptiform activity and clinical seizures (as illustrated by Case 1) is not unusual after MST (see also Chapter 45).

This supposition is supported by a more likely response to steroid challenges in children with epileptogenic zones in 'presumed' non-dominant hemisphere, as displayed by Case 2.[8] Case 3 started to show signs of recovery within the first month but it was of lesser magnitude and significantly slower than Case 2. In Case 3, the epileptogenic zone was in a presumed dominant hemisphere and recovery of language was observed after the first but not a second steroid challenge. Finally, Case 1 had the slowest rate of language recovery. This may be accounted by having an epileptogenic zone in a presumed dominant hemisphere, having a history of verbal dyspraxia and not having shown any language improvement during a short challenge with steroids.

Significance of post-surgical epileptiform activity on EEG

The post-surgical EEG studies of the two children with a seizure focus in a presumed dominant hemisphere continued to show sparse interictal epileptiform activity, while the EEG recordings of Case 2 revealed recurrence of epileptiform activity in runs in the temporal-lateral neocortical regions of the operated hemisphere. Yet, recurrence of language disturbance only occurred with recurrence of a CSWS pattern that involved both hemispheres, as illustrated in Case 3. Hence the prognostic significance of isolated epileptiform discharges on post-surgical EEG studies does not appear to bear great significance in the long-term recovery of language function (see also Chapter 45).

The uninterrupted recovery of language functions observed in Case 2, despite recurrence of 'abundant' epileptiform activity six months postsurgically in the ipsilateral temporal lateral neocortical region to the epileptogenic area further supports the hypothesis cited above. Indeed, the findings of the serial EEG recordings done postsurgically were remarkable for a failure of the epileptiform activity to propagate to the contralateral (dominant) hemisphere. Clearly, this case may be important in understanding the pathophysiology of LKS, suggesting that a unilateral involvement of epileptiform activity may not be sufficient to compromise language function when it originates in the non-dominant hemisphere, in which case it is necessary to engage both sides of the brain, i.e., language cortex, to elicit language disturbances.

Psychiatric complications of LKS

Behavioral and other psychiatric disturbances are the third clinical expression of LKS. This is clearly illustrated in all three cases presented in this chapter. Of note, a clinical picture consistent with an ADHD was the initial clinical manifestation of LKS in Case 2 and these have persisted despite the marked improvement of language functions. On the other hand, in Cases 1 and 3, the pre-surgical behavioral disturbances improved significantly postsurgically. We can hypothesize that the persistence of behavioral disturbances postsurgically in Case 2 may be associated with the persistent epileptiform activity in the right hemisphere, akin to the findings with epileptic encephalopathies. Likewise, improvement of behavioral problems in Cases 1 and 3 are associated with sparse or no epileptiform activity on post-surgical EEG recordings. This hypothesis, while attractive, needs to be proven in controlled studies.

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159 Deep brain stimulation in a patient with medically intractable generalized seizures

M Hodaie, C Hamani, D Zumsteg, DM Andrade, R Wennberg, and AM Lozano

Introduction

There is a significant subset of epilepsy patients for which there is currently no adequate form of surgical treatment available. Patients with diffuse, non-localized, or multifocal epilepsy currently have very limited surgical options, if medications alone cannot result in adequate seizure control. Neuromodulation is gaining increasing interest as a possible new surgical modality for treatment, particularly in these type of patients.[1–3] Deep brain stimulation (DBS) for epilepsy aims to influence key 'pacemaker' areas in the brain that are thought to be important in seizure genesis or propagation, thereby decreasing seizure severity and frequency. This rationale is based on both animal experiments and human studies.[2,4] A number of lines of evidence point to the thalamus, and particularly to the anterior nucleus of the thalamus, as having an important role in this regard. Initial animal experiments showed evidence of increased metabolic activity in the anterior thalamic nucleus with seizures.[5] High frequency stimulation and lesioning, whether in the AN or its connections also resulted in decreased seizure activity in the pentylenetetrazol model of seizures.[6–8]

In 2002, we published a study of five patients with intractable epilepsy who underwent bilateral DBS of the anterior nucleus of the thalamus.[2] Our initial results were reported with a mean follow-up of 15 months. There was a marked reduction in the number of seizures, with a mean reduction of 54%. Two patients showed a reduction of 75% or more. We recently reported the long-term benefit of this treatment, with a 60 month average follow-up, and it appears that the beneficial results have been sustained in the long-term.[9]

In this chapter, we illustrate the details of one of these patients, who was part of the study reported in 2002. Seizure history, surgical treatment and outcome are presented.

Case report

The patient is a 25-year-old male initially seen at the Toronto Western Hospital at the age of 18. His seizures started when he was seven months of age and he was assessed by multiple pediatric neurologists. There were no reported problems during gestation and he was the product of an unremarkable natural birth. Associated with the seizure history is a history of mental retardation and developmental delay. Family history was positive for at least one more male member in the extended family who had mental retardation. Testing for fragile X syndrome was negative. Examination of the neurological system was remarkable for microcephaly, elevated tone in his upper and lower extremities, and mental retardation.

The patient had been managed with multiple anticonvulsant medications, including carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin, phenytoin, and different forms of benzodiazepines. A trial of the ketogenic diet did not result in any significant benefit.

Seizures typically included abrupt stiffening of the limbs, usually beginning on the left side, tonic clonic movements, unresponsiveness and visual staring, generally lasting about 45 seconds. As a child these occurred approximately 3–5 times per week and eventually became progressively more frequent, increasing to multiple seizures per day.

MRI of the brain revealed atrophy out of keeping with the age of the patient. No hemispheric abnormality and no mass lesions could be visualized.

Interictal scalp EEG recordings showed the presence of multifocal epileptiform discharges recorded independently over both hemispheres, maximal over the frontal lobe structures with a right-sided predominance. Less frequently, bursts of generalized, frontally predominant, bilaterally synchronous spike-and-wave discharges were recorded. The background activity was abnormal and compatible with a diffuse encephalopathy of moderate severity.

Ictal scalp video-EEG recordings documented several motor seizures with a clinical pattern at onset consisting of a left-sided fencing posture indicative of right hemispheric lateralization, however, the concomitant ictal EEG recordings were always apparent bilaterally, contaminated by muscle artifact, and did not favor a discrete localization.

Neuropsychological testing was limited secondary to global delay. Tests of higher cognition and expressive language could not be carried out. Responses were limited to an auditory vocabulary task and matching spoken words. It was estimated that the patient functions at approximately a 2-year-old level. Overall performance was rated below the first percentile.

Based on the severity of the patient's seizures and lack of benefit from other means of treatment, as well as the results of video-EEG recordings indicating the patient to not be a candidate for resective epilepsy surgery, bilateral DBS of the anterior thalamic nucleus was offered as part of a pilot study at the Toronto Western Hospital. The study had been previously reviewed and accepted by the hospital's research ethics board.

As part of the study protocol, the patient's caregivers were asked to keep a daily diary of the number of seizures. Seizure count during a 3 month baseline preoperative period averaged approximately 60 seizures per month. Pre- and postoperative seizure frequencies are detailed in Table 159.1. As per the study protocol, antiepileptic medications were not changed during the baseline preoperative period nor during the first year postimplantation of DBS electrodes.

Surgical procedure

The surgical procedure can be categorized in the following stages:

1. Frame placement: Under local anesthesia, the patient undergoes placement of a Leksell frame. The frame attaches firmly to the skull with four pins. The anterior pins are placed approximately one inch above the eyebrows, and we typically carry out a local block of the supraoptic nerve. The desired orientation of the frame is parallel to a line between the lateral canthus and the tragus of the ear, thereby aligning as much as possible the anterior and posterior commissures. We routinely place these frames under local anesthesia only, and we find that patients do not require further sedation.
2. After placement of the frame, the patient is taken to the MRI suite. A 1.5 T MR with T1, T2 sequences are carried out. The MR localized box for the Leksell frame contains cupper sulfate solution, which results in an MR signal. This signal is used as a fiducial marker for calculation of stereotactic coordinates.
3. The coordinates for the anterior and posterior commissures are calculated on the MRI images, together with the midcommissural point. The coordinates for the anterior nucleus are determined as follows: 6 mm lateral to the midcommissural point, 8 mm anterior to the posterior commissure, and 12 mm above the AC/PC line. The angle trajectory is approximately 60 degrees in the anterior superior to posterior inferior direction.
4. In the operating room and with the Leksell frame attached to the surgical bed, the head is shaved and the area of the coronal suture widely prepped and draped. Two parasagittal incisions centered at the coronal suture are performed and burr holes drilled. The dura is opened and the pia is coagulated. Tisseal is applied to the burr hole to minimize CSF loss, which may result in shifting of brain structures with resultant change in the relative position of the calculated coordinates.
5. Intraoperative microelectrode recordings are carried out. Given the location of the anterior nucleus, the trajectory is invariably through the lateral ventricle. Once the border of the ventricle is crossed, we find action potentials, corresponding to cells of the thalamus. Our recordings typically start 10 mm above the intended target and extend between 5–10 mm beyond intended target. A sample digitized Schaltenbrand–Wahren atlas map of the area of the anterior nucleus is represented in Figure 159.1.
6. After the microelectrode recordings and under fluoroscopic guidance quadripolar DBS electrodes (Medtronic model 3387, Medtronic, Minneapolis, MN, USA) are placed in the intended target. The electrodes are inserted with the bottom contact being typically in the dorsomedian nucleus, because of the size discrepancy between the anterior nucleus and the electrode. The anterior nucleus spans approximately 6 mm, while the contacts of the electrode used span 10.5 mm. Therefore at least one electrode must be either deep to the anterior nucleus or in the ventricle.
7. After placement of the DBS electrodes, the wires are connected to extension cables and externalized through the skin through a separate incision. The wound is then appropriately irrigated and closed. The externalized wires are marked for identification of the appropriate side and the patient is discharged to the epilepsy monitoring unit (EMU). The patient is continued on the same antiepileptic medications as in the preoperative period.
8. After 3–4 days in the EMU, allowing for video-EEG recordings with scalp and thalamic depth electrodes, the patient is returned to the operating room for internalization of the DBS electrodes and connection to a pulse generator. In this case, a Medtronic model Itrel II (Medtronic, Minneapolis, MN, USA). This procedure is performed under general anesthesia. The subclavicular and neck areas are prepped and draped. After adequate identification of the DBS electrode, a connector is passed between the intracranial compartment and a subclavicular incision at either side of the chest. The system is connected and the wounds closed. The left DBS electrode is connected to the left pulse generator and the right DBS electrode to the right. Each Itrel II pulse generator is therefore programmed separately.

Postoperative course

The patient spent three days in the EMU, during which time he underwent combined scalp EEG and thalamic depth

Table 159.1 Pre- and post-operative seizure frequency at 1 year follow-up

Pre-operative seizure frequency per month	60 ± 7.75
Seizure frequency in early (first month) post-operative period (stimulation OFF)	9
Post-operative seizure frequency per month after stimulation	15.9 ± 1.23
Mean seizure reduction	75%

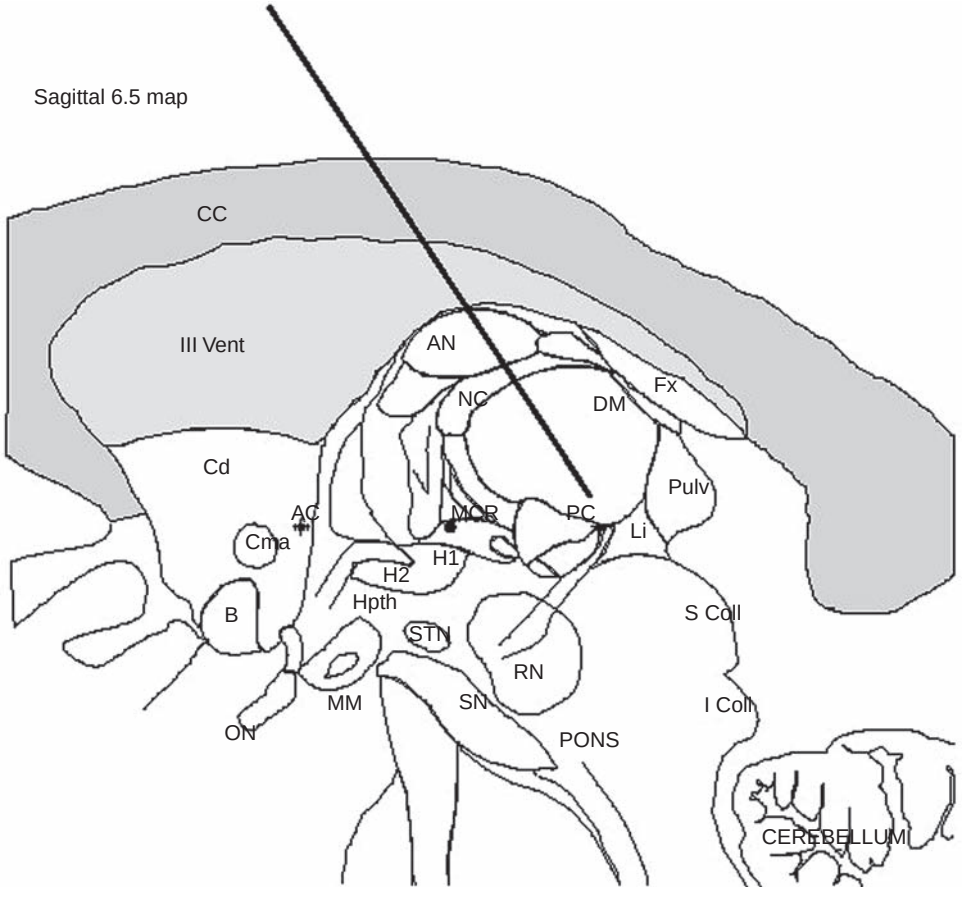

Figure 159.1 Digitized Schaltenbrand–Wahren atlas map of the area of the anterior thalamic nucleus, 6.5 mm from midline. Relationship of the anterior nucleus (AN) and dorsomedian nucleus (DM) can be observed, as well as a typical trajectory of microelectrode recording tract.

electrode recordings via the implanted DBS electrodes. He had a total of 31 focal motor seizures with secondary generalization during this period. A generalized alteration in scalp EEG background activity and the appearance of low amplitude muscle artifact preceded by many seconds the first rhythmic ictal activity. This rhythmic ictal activity was invariably recorded from the right thalamic DBS electrode, initially appearing as an indistinct 5–6 Hz sharp theta activity maximal at the deepest contact of the right thalamic electrode approximately 2 s prior to the clinical onset of the tonic-clonic motor manifestations. This was not accompanied by an identifiable rhythmic ictal correlate on the scalp recording before the appearance of widespread muscle artifact in the scalp recordings. At this point a low amplitude rhythmic ictal discharge was evident in the thalamic electrodes on the right side in the low beta and upper alpha frequency bands, best seen in the deepest contact of the DBS electrode (Figure 159.2). With diminution of the scalp muscle artifact, synchronous rhythmic ictal activity could ultimately be appreciated over the right fronto-parietal region (Figure 159.2) prior to bilateral scalp and thalamic involvement during seizure generalization. Coherence analysis (Rhythm 10.0, Stellate Systems, Montreal, QC, Canada) between the phase locked scalp and thalamic right hemispheric ictal activity before generalization showed a cortical lead on the order of 24 ms with 98% coherence.[10]

Interictally, the high amplitude spikes evident on the scalp EEG were recorded synchronously, and with opposite polarity, from the thalamic DBS electrodes, of slightly higher intracranial amplitude ipsilateral to the maximal scalp potential (Figure 159.3), with a field of distribution indicative of subcortical volume conduction from the superficial cortical spike source.[11]

To assess the influence of thalamic DBS on cortical activity in the early postoperative period, we carried out brief trials of bipolar low frequency stimulation (2–10 Hz, 0.5–10 V, 330–450 μs pulse duration) using various electrode contact combinations while recording the scalp EEG. We were able to elicit a mild recruiting rhythm recorded maximally over the ipsilateral frontal lobe region using bipolar stimulation through contacts 1+3− in this patient. We have since carried out extensive source localization studies of the cerebral responses evoked by low frequency thalamic DBS, as reported elsewhere.[12]

Effect on seizure frequency

A decrease in seizure frequency was observed in the first month after implantation of the DBS electrodes, which continued after the stimulators were turned On. Stimulation was started with the following parameters: 1+/3−, 90 μs pulsewidth, 10 V, 100 Hz, cycling 1 min on/4 min off. At month 3, stimulation contacts were changed to 1−2+ and at month 5 changed back again to 1+3−. At month 6, the stimulation parameters were changed to monopolar stimulation through contacts 0-1− (with the pulse generator case as the

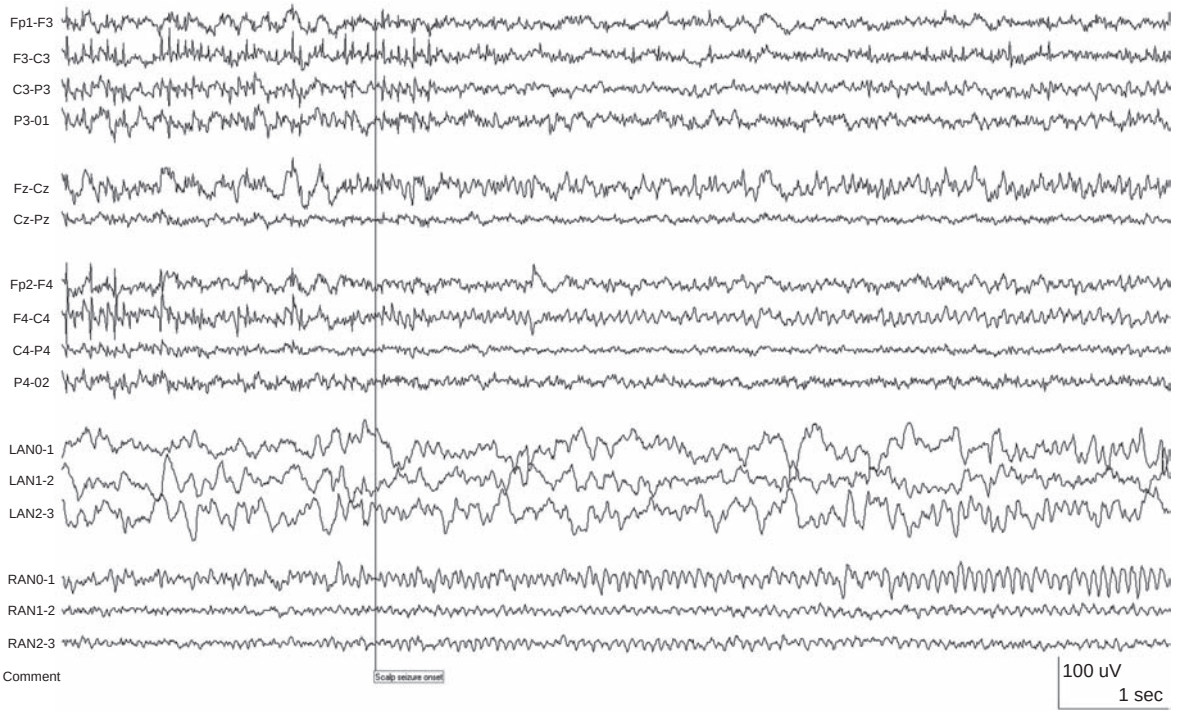

Figure 159.2 Combined scalp-thalamic ictal EEG recording, bipolar montage, left focal motor seizure stage. The clinical seizure commenced before the segment of EEG shown. Rhythmic ictal activity can be appreciated in the right thalamic DBS electrode contacts from the beginning of the sample, increasing in amplitude over time. The first identifiable rhythmic ictal changes in the scalp EEG can be appreciated along with disappearance of the muscle artifact over the right fronto-parietal region, marked by the vertical line. The ictal activity subsequently spread to the left DBS electrode contacts and left scalp electrodes prior to clinical generalization (not shown). LAN = left anterior nucleus DBS electrode; RAN = right anterior nucleus depth electrode; contact 0 = deepest, contact 3 = most superficial. Time constant = 0.3 s; high frequency filter = 70 Hz.

anode). None of these changes, nor any of a number of other alterations in stimulation parameters made over the subsequent 4 years of follow-up, was associated a significant difference in the postimplantation seizure frequency. The benefit has been sustained over 5 years of follow-up, with a 90% seizure reduction compared to preimplantation baseline at last follow-up. The only change to the anticonvulsant regime took place in year 4 post surgery, with the addition of levetiracetam. The patient has been described by his caregivers to be more alert, cooperative and participatory in daily activities such as feeding with DBS, though this could not be quantified.

Discussion

This patient showed a marked and sustained improvement in seizure control associated with DBS of the anterior thalamic nucleus. There are several issues of interest with respect to the surgical intervention that merit further mention. Firstly, the acute benefit observed without stimulation is reminiscent of the microthalamotomy-like effect described with similar procedures for movement disorders.[13] The relative effects of electrode insertion versus active stimulation need to be further studied, something that is currently being investigated in a multi-center clinical trial.[14] Secondly, the possibility of a surgical placebo effect cannot be ignored in open trials such as this, however, it seems unlikely that such a long-lasting benefit would be based on placebo effect alone. Also, the possibility of a regression-to-the-mean phenomenon cannot be entirely ignored as a contributor to the measured decrease in seizure frequency.

We were able to elicit a recruiting rhythm with stimulation of the thalamic depth electrodes during the externalization phase in the immediate postoperative period. We have observed that of the three patients who responded best to stimulation in our initial published study, all showed evidence of a recruiting rhythm, whereas the two patients that failed to a similar benefit from stimulation during the first postoperative year did not show evidence of a recruiting rhythm on EEG. Although we cannot draw any definitive conclusions from the small sample of patients in our pilot study, it appears that the ability to record a recruiting rhythm on EEG might be predictive of benefit from stimulation.

The combined scalp-thalamic ictal EEG recordings in this patient are of some interest in that they demonstrate the potential for early ictal recruitment of the anterior thalamic structures even in patients with extratemporal, suprasylvian neocortical partial epilepsy. This is of interest given the remoteness of seizure onset from the temporolimbic-thalamic circuit of Papez structures, in which the anterior thalamic nucleus might be expected to have its most pronounced involvement.

A further matter to consider is the stimulation parameters used. The selected high frequency stimulation parameters are largely drawn from our experience with DBS in movement disorders. To date, we have been unable to associate changes in seizure frequency with alterations in stimulation parameters. Adequate investigation needs to be carried out in this regard to determine if optimal stimulation parameters can be identified.

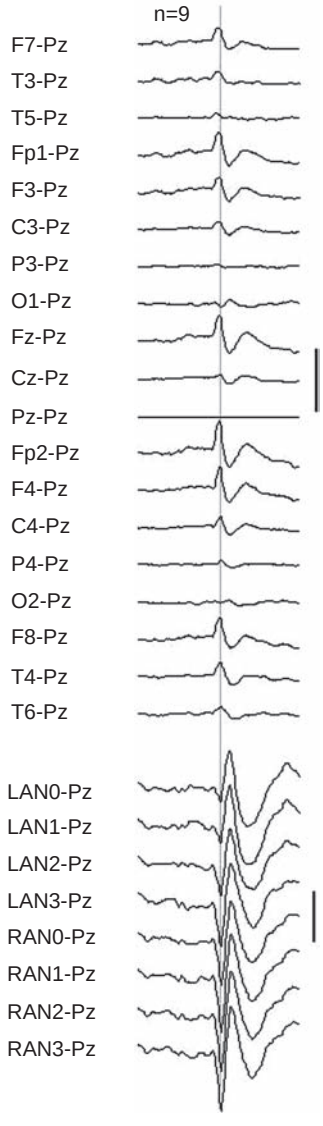

Figure 159.3 Combined scalp-thalamic interictal EEG, Pz reference montage. Shown is an average of nine interictal spikes with a right anterior frontal predominance. Vertical amplitude scale bars for scalp and thalamic intracranial EEG = 100 μV.

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160 Successful transcranial magnetic stimulation in a patient with medically intractable focal epilepsy

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Introduction: applications of TMS in epilepsy

Transcranial magnetic stimulation (TMS) is a noninvasive technique that can be used to transiently induce, modulate or interfere with neuronal activity in relatively circumscribed brain regions. In epilepsy research, it was initially proposed that single pulse TMS could be helpful for seizure focus localization by activation of epileptic activity or seizure induction through TMS over the epileptogenic zone. However, initially promising results could not be confirmed.[1,2] Indeed, the risk of observing a TMS-associated seizure in patients with epilepsy has been estimated to be small in a recent meta-analysis of 49 publications, and doubt has been expressed whether such seizures were induced by TMS or merely coincidental.[3] Instead, TMS today is under evaluation for its possible antiepileptic potential when multiple consecutive TMS pulses, referred to as repetitive TMS (rTMS), are applied in trains at low frequency (around 1 Hz). Such clinical trials in epilepsy with a therapeutic prospect are motivated by the finding that low-frequency rTMS leads to a reduction of cortical excitability that outlasts the duration of stimulation, frequently replicated in studies on motor physiology in healthy controls[4–7] and also confirmed through TMS-studies on non-motor functions.[8,9] Accordingly, it has been argued that low-frequency rTMS might be of potential therapeutic value in epilepsy patients by increasing seizure threshold through reduction of cortical excitability. The clinical trials performed so far have provided overall encouraging results revealing antiepileptic effects of low-frequency cortical stimulation in patients with medically uncontrolled epilepsy. Antiepileptic effects have been reported following 1 day to 4 weeks of rTMS treatment with a significant improvement of number and/or severity of seizures,[10–12] interictal spikes[11,12] or EEG activity associated with epilepsy partialis continua.[13] Others, however, have observed only a trend toward a short-term decrease in seizures following a 1-week treatment.[14,15] Clearly, further studies are needed to contrast different stimulation protocols, and to study prognostic factors and interactions with medications. In the present chapter we aim to provide illustrative examples of the potential utility of TMS in pharmaco-resistant epilepsy. The chapter is structured in three parts. First, a clinical case report is discussed to illustrate the potential of rTMS in humans. Next, the technical challenges faced when combining TMS with EEG recording, critical for properly-guided therapeutic applications of TMS are addressed in a 'technical case report'. Finally, an 'experimental case report' serves to illustrate ongoing research on underlying mechanisms of action and approaches to optimize translational applications of TMS for treatment of epilpetic patients.

Clinical case reports: TMS for treatment of pharmacoresistant epilepsy

Malformations of cortical development (MCD) represent an important etiology of refractory epilepsy and, therefore, a common cause of referrals for epilepsy surgery. However, a large proportion of patients with diffuse MCD and those with lesion in the eloquent cortex are poor surgical candidates. Such patients represent a challenge for treatment and a focus of continuous interest for alternative therapeutic approaches.

A few human studies[11,16] have shown that low-frequency repetitive transcranial magnetic stimulation (rTMS) might be clinically effective in seizure control in patients with MCD and refractory epilepsy. The rationale for the use of rTMS in patients with epilepsy is that this technique modulates brain excitability in a noninvasive and painless way and thus inhibitory effects are possible if low-frequency rTMS is employed[4,7] We describe the outcome of this approach in two patients with MCD, one with focal epileptic activity and the other with multifocal epileptic activity. In addition we discuss the longer follow-up and treatment of these two patients initially after a single session and then for five consecutive TMS sessions.

Clinical case 1: rTMS in a case of focal epileptic activity

A 16-year-old boy with bilateral posterior quadrant polymicrogyria received two different rTMS treatments for epilepsy. Although this patient had received several antiepileptic drugs, he continued to have very frequent complex partial seizures (15 episodes per day, on average) and sporadic secondarily generalized tonic clonic seizures (one episode per month). The complex partial seizures were characterized by episodes of fixed gaze that lasted less than 1 minute. The patient was taking lamotrigine (25 mg/day), valproate (1500 mg/day), carbamazepine (1800 mg/day) and nitrazepam (10 mg/day). His baseline electroencephalogram was characterized by frequent epileptiform discharges (ED) that were predominant in the posterior areas, especially in O1 and O2 (10/10 international EEG system). This patient underwent two different rTMS treatments as follows.

Treatment 1: single session of 1 Hz rTMS

Initially this patient received rTMS over the epileptogenic focus with the following parameters: a continuous train of 10 minutes with a frequency of 1 Hz and an intensity of 60% of the maximum stimulator device. This type of rTMS is expected to increase intracortical inhibition in the targeted brain region, and would thus be expected to suppress epileptic activity in the epileptic focus. Because this patient had two epileptogenic foci, we decided to stimulate O1 for 10 minutes and O2 for 10 minutes (therefore a total of 1,200 pulses). There were no adverse events related to this treatment. At baseline this patient had an average of 15 complex partial seizures per day. Following the rTMS this number decreased to six seizures per day and 1 month after to eight episodes per day. His EEG at baseline showed 313 epileptiform discharges that decreased to 191 immediately after treatment. Remarkably, he had only one epileptiform discharge in the standard clinical EEG performed at day 15. At day 30, there was an increase to 194 epileptiform discharges.

Treatment 2: five consecutive sessions of 1 Hz rTMS

One year after the first rTMS session, this patient received five consecutive sessions of 'inhibitory' rTMS over the epileptogenic focus with the following parameters: a continuous train of 20 minutes with a frequency of 1 Hz and an intensity of 70% of the maximum stimulator output – 1,200 pulses were then applied per day (total of 6,000 pulses). Because the epileptogenic focus of this patient extended to the left and right hemisphere, we decided to stimulate O1 for 10 minutes and O2 for 10 minutes. There were no adverse events related to this treatment. At baseline the patient was again having on average 15 complex partial seizures per day. Following the 5-day course of rTMS the number decreased to three episodes per day as average for the 15 subsequent days and, 1 month after treatment, he maintained the improvement and was having three to four episodes per day. His EEG at baseline disclosed 354 epileptiform discharges that decreased to 252 immediately after treatment and continued to decrease to 120 and 100 ED after 30 and 60 days, respectively.

Clinical case 2: rTMS in a case of multifocal epileptic activity

A 14-year-old girl with band heterotopia received two different rTMS treatments for epilepsy. This patient had also tried several antiepileptic drugs regimen and none of them was able to control her seizures. At the moment of the treatment, she was taking lamotrigine (275 mg/day) and valproate (1250 mg/day). She was having frequent simple partial seizures (one episode per day, on average) and rare secondarily generalized tonic clonic seizures (one episode in the past 3 months). The simple partial seizures were characterized by myoclonic jerks of predominantly the upper extremities and trunk in which she had to be assisted to avoid a fall. Her baseline electroencephalogram (EEG) was characterized by frequent multifocal epileptiform discharges. Similar to case report 1, this patient underwent two different rTMS treatments as detailed below.

Treatment 1: single session of 1 Hz rTMS

Initially this patient received inhibitory rTMS over the vertex (Cz) using a nonfocal circular stimulation coil – as she had multifocal epileptic activity – with the following parameters: a continuous train of 10 minutes with a frequency of 1 Hz and an intensity of 60% of the maximum stimulator device – 600 pulses were then applied. There were no adverse events related to this treatment. At baseline this patient had an average of one simple partial seizure per day and 15 days after the treatment, this number decreased to one simple partial seizure every 4 days. The benefit continued 1 month after the rTMS, when she was having an average of one seizure every other day. Her EEG at baseline showed 106 epileptiform discharges that decreased to 67 immediately after treatment, and then varied between 96 and 27 ED after 15 and 30 days of treatment, respectively.

Treatment 2: five consecutive sessions of 1 Hz rTMS

A year later, this patient received five consecutive daily sessions of inhibitory rTMS over the vertex (Cz) using a circular stimulation coil (thus targeting diffusely both hemispheres) with the following parameters: a continuous train of 20 minutes with a frequency of 1 Hz and an intensity of 70% of the maximum stimulator device – 1,200 pulses were then applied per day (total of 6,000 pulses). There were no adverse events related to this treatment. At baseline this patient had an average of four simple partial seizures per day and 15 days later, this number decreased to an average of only one seizure every 3 days and, 1 month after the treatment, she remained having the same frequency of seizures. Her EEG at baseline disclosed 70 epileptiform discharges that decreased to 38 immediately after treatment and remained decreased when compared to baseline (50 and 46 ED, after 30 and 60 days, respectively).

Discussion

These two cases illustrate that low-frequency rTMS, which is thought to induce an increase in intracortical inhibition in the targeted brain region, can reduce the number of seizures and epileptiform discharges in patients with refractory epilepsy due to malformations of cortical development. In addition, the effects of five sessions of rTMS appear to have a greater magnitude and longer duration when compared to a single session of rTMS. Finally there were no adverse effects associated with this treatment in any of these two patient, nor in others similarly treated.

The first important point that should be discussed is the site of stimulation. For patients with focal lesions and epileptogenic

activity, the first, logical approach would be the stimulation of the dysfunctional brain area. This approach was successful in the case 1, in which the patient had a focal lesion and epileptic activity. This is in accordance with the presumed rTMS mechanism of action: a focal modulation of the stimulated area.[17] For patients with discordant lesion location and epileptiform focus (as indexed by EEG), we speculate that the functional (EEG) focus might be the one that should be targeted. Finally, for patients with multifocal epileptic activity (case 2), the stimulation of a central area, such as the vertex (Cz), using a large circular coil might be the best approach (as we showed in case 2). We showed that the patient in case 2 also had a clinical and electroencephalographic improvement, however it was less pronounced than the patient in case 1 – with focal epileptogenic activity. The local and distant (via neural network) effects of rTMS might be responsible for this improvement in this patient with multifocal epileptic activity.

Another important point in this treatment is the number of sessions. These two cases suggest that five sessions of rTMS might be superior to a single session. In this regard, much has been learnt from studies using rTMS for the treatment of medication-resistant depression. Several trials have shown that a prolonged rTMS course has an additional benefit of this strategy. Rumi *et al.* demonstrated the relationship between clinical antidepressant effects and number of rTMS sessions. In addition, several studies have shown that consecutive sessions of rTMS are safe. Loo *et al.* elegantly demonstrated, through a detailed and extensive cognitive testing, that the treatment with rTMS over a 4-week period is safe.

Finally, an interesting effect was observed in case 1 in whom the beneficial effect of the rTMS treatment continued to enhance even after the end of the treatment as shown by the number of ED after 15 days and 30 days of stimulation. Such an effect might indicate that plastic changes induced by rTMS might have occurred, e.g., synaptic strengthening (long-term potentiation and depression). This finding is reminiscent of observations in patients with stroke who received rTMS treatment for the treatment of aphasia.

Only a few studies have investigated the effects of rTMS in patients with refractory epilepsy and the results of these studies are mixed.[11,12,14,16] Further larger studies should explore the best parameters of stimulation in order to increase the magnitude and the duration of the rTMS effects. What seems critical is precise targeting of the epileptic focus, and given the rapid decay of the magnetic field with the square of the distance from the TMS coil, concentration on patients with foci in the cortical convexity seems indicated.

Technical case report: simultaneous EEG and TMS

In parallel to the probing of rTMS protocols for the treatment of epilepsy, new technological developments have been made rendering EEG recording online to TMS feasible. The continuous monitoring of EEG signals during rTMS in epilepsy research is of interest in several regards, e.g., for the early detection of TMS-induced epileptic discharges that could lead to a seizure or for the evaluation of the immediate beneficial effects of rTMS treatment during stimulation. However, EEG recording during TMS has proven difficult due to the artifact problem. This consists of magnetically elicited high-voltage peaks potentially saturating the EEG system.[18] To avoid TMS-induced contaminations of the EEG signal, two main methods have been proposed. One approach, introduced by Ilmoniemi and colleagues,[18,19] is based on special preamplifiers with sample-and-hold circuits and gaincontrol. This circuitry has been shown to block electrical contamination in the EEG hardware components, but necessitates switching off the preamplifier during the TMS pulse.[18] Others have proposed slow-rate limiting preamplifier modules to allow for continuous EEG recording without saturation of the EEG signals despite TMS pulse delivery.[20,21] The latter approach is devoid of any loss of data, as the preamplifier output does not have to be pinned to a constant level for the duration of the TMS pulse. It does however not fully prevent the magnetically elicited voltage peak from proceeding into EEG hardware components leading to electrical contaminations of short duration that however can be corrected offline to the recordings.[21]

Technical case: online EEG during 1 Hz rTMS

EEG monitoring online to TMS is illustrated in Figure 160.1, that depicts interictal scalp EEG of a patient with pharmacoresistant epilepsy before (Figure 160.1a) and during the application of 1 Hz rTMS (Figure 160.1b). This patient showed regular epileptic spikes that were generated both with or without TMS and that were clearly independent from TMS (see Figure 160.1b). The patient tolerated TMS well and no seizure occurred either during or in the first 24 hours after rTMS. EEG monitoring in epilepsy patients is useful to immediately discontinue the rTMS trial in case EEG abnormalities are induced by TMS.[22] In addition, being able to assess the immediate impact of TMS on epileptic discharges provides new possibilities for epilepsy research that, we hope, go beyond the use of EEG to document the long-term effects of rTMS treatment.[11–13] More information on the mechanisms how rTMS interferes with the generation of epileptic activity is definitely needed to further develop rTMS into an effective, alternative treatment strategy for pharmacoresistant epilepsy. Finally, online EEG recording may allow to develop a system of EEG-guided TMS by which the pulses of TMS could be precisely timed with the epileptic spike for maximal efficacy and to prevent progression of seizures.

Experimental case report: EEG-guided TMS in rat seizure model

TMS is emerging as a safe new therapeutic tool in epilepsy. In simple terms, TMS can be delivered during the interictal phase to reduce seizure frequency, or during the ictal phase to abort ongoing seizures (such as status epilepticus). Encouragingly, and as demonstrated by the patients illustrated above, a few human trials demonstrate the capacity of interictal TMS to reduce seizure frequency.[10–12] However, the potential for ictal TMS to terminate ongoing seizures has not been extensively studied. In part, this research has been limited by lack of adequate animal models and the difficulties of recording artifact-free EEG during TMS.

For experimental purposes, animal models, particularly rat epilepsy models, offer two important advantages: (1) time-coupling of seizure and TMS, and (2) the capacity

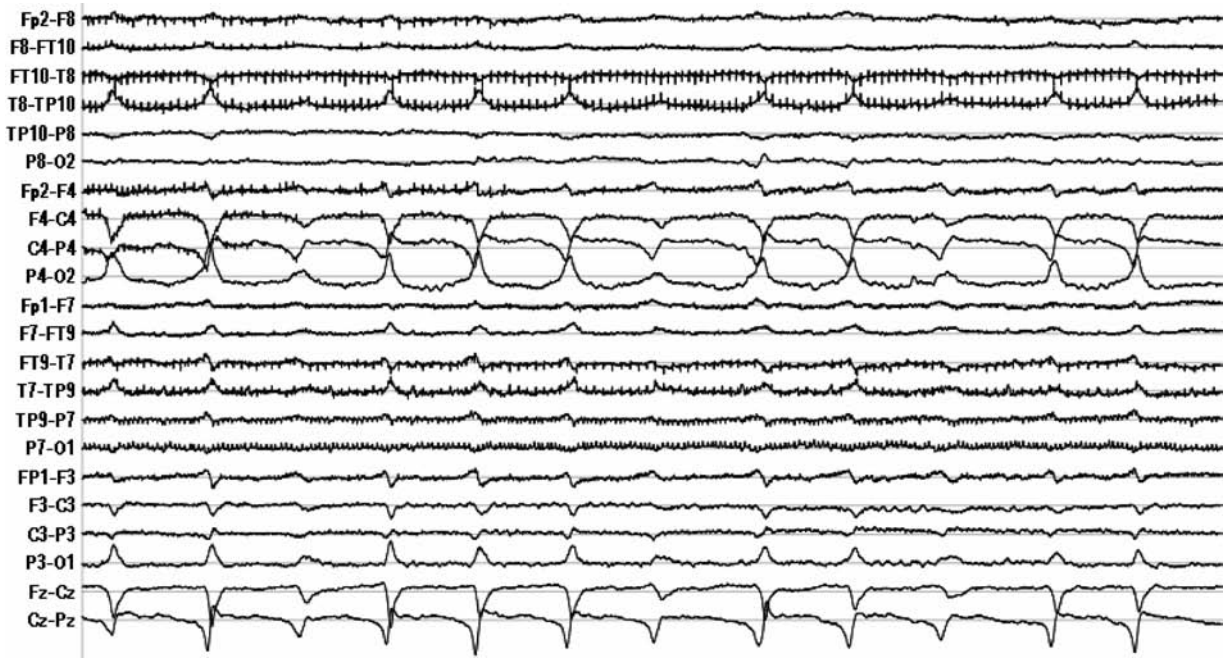

Figure 160.1 EEG monitoring during rTMS. Interictal EEG was recorded from 23 electrodes before rTMS treatment in a patient with pharmacoresistant complex partial epilepsy and regular spikes originating from parietal cortex (A) and during the application of 1 Hz rTMS over the spike origin (B). The spike origin was identified through interictal EEG, spike-triggered fMRI[28] as well as source localization algorithms in the patient's own MRI[29] and the TMS coil was places over this site using a Neuronavigation device. The TMS-induced artifacts correspond to the vertical black lines associated with each pulse, only transiently interfering with the EEG signal. In this example, the artifact lasts for maximally 15 ms after the TMS discharge. Plastic-body electrodes were used to prevent scalp burns due to overheating.[17,30] The protocol was approved by the local ethical committee and the patient gave written informed consent to stimulation. (courtesy of Dr. Margitta Seeck).

to generate large numbers of seizures to measure the therapeutic TMS effect. With respect to the first rat model advantage, the investigator can precisely time TMS delivery relative to seizure onset, or alternatively time the delivery of a convulsant relative to the TMS. For instance, a delay in pentylenetetrazole (PTZ)-induced seizure onset and reduction in incidence of status epilepticus was shown in rats pretreated with 1,000 pulses of 0.5 Hz rTMS.[23] With respect to the second advantage, large seizure numbers provide a readily-quantifiable outcome measure when investigating the potential of TMS to shorten average seizure duration. This was recently demonstrated in kainite induced seizures whose duration was abbreviated by EEG-guided 0.5 Hz rTMS.[24]

Furthermore, seizures in animal subjects can be timed to start during continuous EEG recording such that the electrographic seizure onset and offset, as well as timing of the TMS pulse can be analyzed online. This can provide a means of real-time assessment of anticonvulsive TMS effects, and forms the basis for EEG-guided TMS treatment of seizures.

A schematic of the methods for TMS in gently-restrained seizing rats is shown in Figure 160.2. With this method, the torso is restrained with broad straps such that the limbs, tail and head have full freedom of movement, but the rat cannot propel forward or backward.[24] This enables clinical as well as electrographic seizure monitoring while maintaining the TMS coil in a relatively fixed position overhead. The pictured setup is welltolerated by rats who show no apparent signs of distress during the restraint or TMS.

Experimental case reports: EEG-guided anticonvulsive TMS

The application of EEG-guided TMS is shown in Figure 160.2 where two spontaneous seizures appear in close proximity. The first (with onset before the displayed tracing) was not treated. The second seizure was treated by TMS applied as soon as the ictal pattern was recognized. A series of similar seizures are seen in Figure 160.3 that shows a comparison of seizures in a spontaneously-epileptic Long Evans rat treated with the TMS coil over the rat's head, with the coil over the rat's tail (sham control), and untreated seizures (untreated control) in the same animal.

Discussion

A natural extension of the pilot work with EEG-guided TMS is the development of a closed-circuit system where (1) the ictal EEG is recognized by an automatic seizure detection system, (2) TMS is delivered to the seizing subject, and (3) the EEG is reanalyzed to determine whether another TMS pulse should be delivered if the ictal pattern continues. Another series of experiments that can follow from the preliminary rat seizure work are the investigation of optimal TMS timing relative to the seizure onset, and at a finer time scale, relative to the spike-wave complex. That is, triggered seizures in animals may provide the opportunity to test whether seizure abortion is more likely when the TMS pulse is delivered at a particular phase of the spike-wave complex akin to a cardiac pacemaker that is phase-locked to the QRS complex.

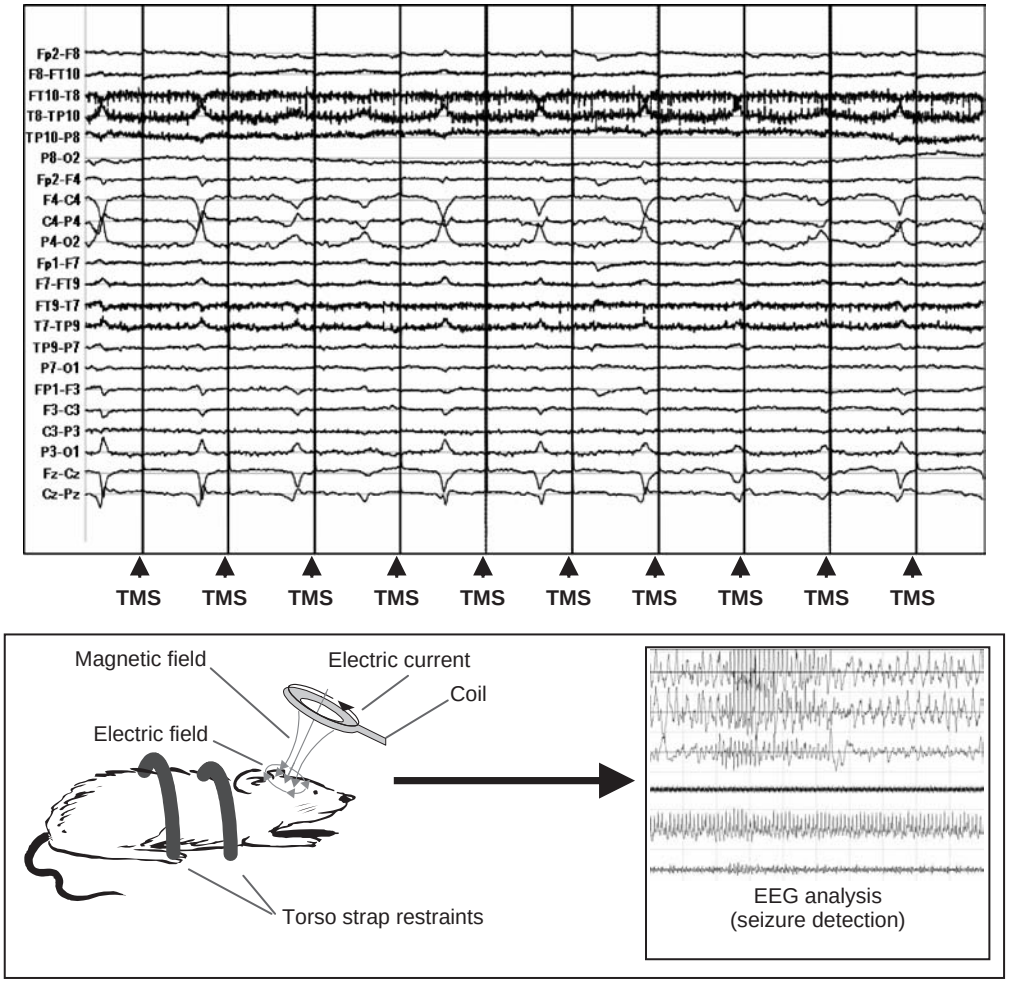

Figure 160.2 Schematic of rat with torso restraint, TMS coil and EEG. Torso restraint permits clinical observation of seizures and full access of head to the TMS coil. EEG (and EKG) can be analyzed in real time by experimenter to trigger TMS device.

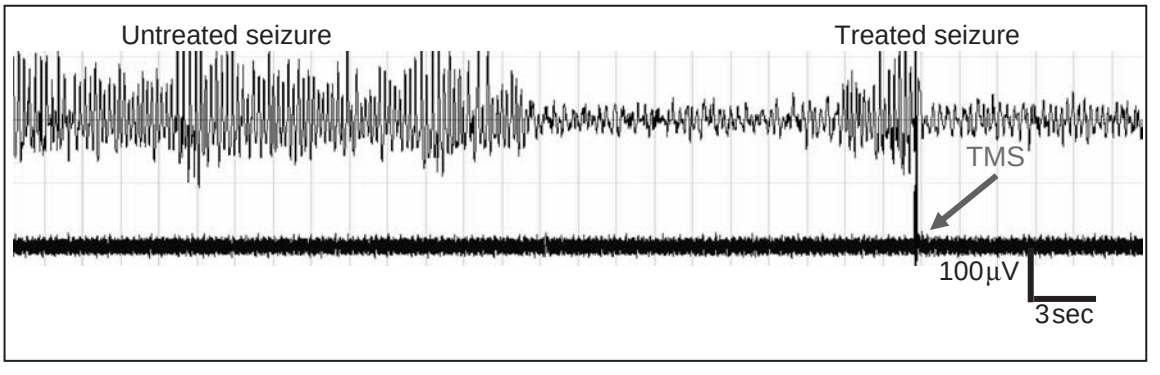

Figure 160.3 Treated and untreated spontaneous seizures. Online seizure analysis permits reliable seizure detection and real-time assessment of TMS anticonvulsant effect.

In addition to investigating the capacity of TMS to abort seizures, animal models offer a means to evaluate the potential for TMS to interfere with epileptogenesis. For example, kainite-induced status epilepticus reliably leads to spontaneous recurrent seizures in rats a after a several-week seizure-free latent period.[25,26] This latent phase during which epilptogenic changes that lead to a net increase in cortical excitability and eventually to spontaneous seizures provides a potential therapeutic target for low-frequency repetitive TMS. The hypothesis to test during the latent phase is that low-frequency repetitive stimulation that may decrease cortical excitability can interfere with the epileptogenic process.

Furthermore, as changes in synaptic efficacy resembling long-term potentiation (LTP) may be involved in epileptogenesis, low-frequency repetitive TMS provides an opportunity to

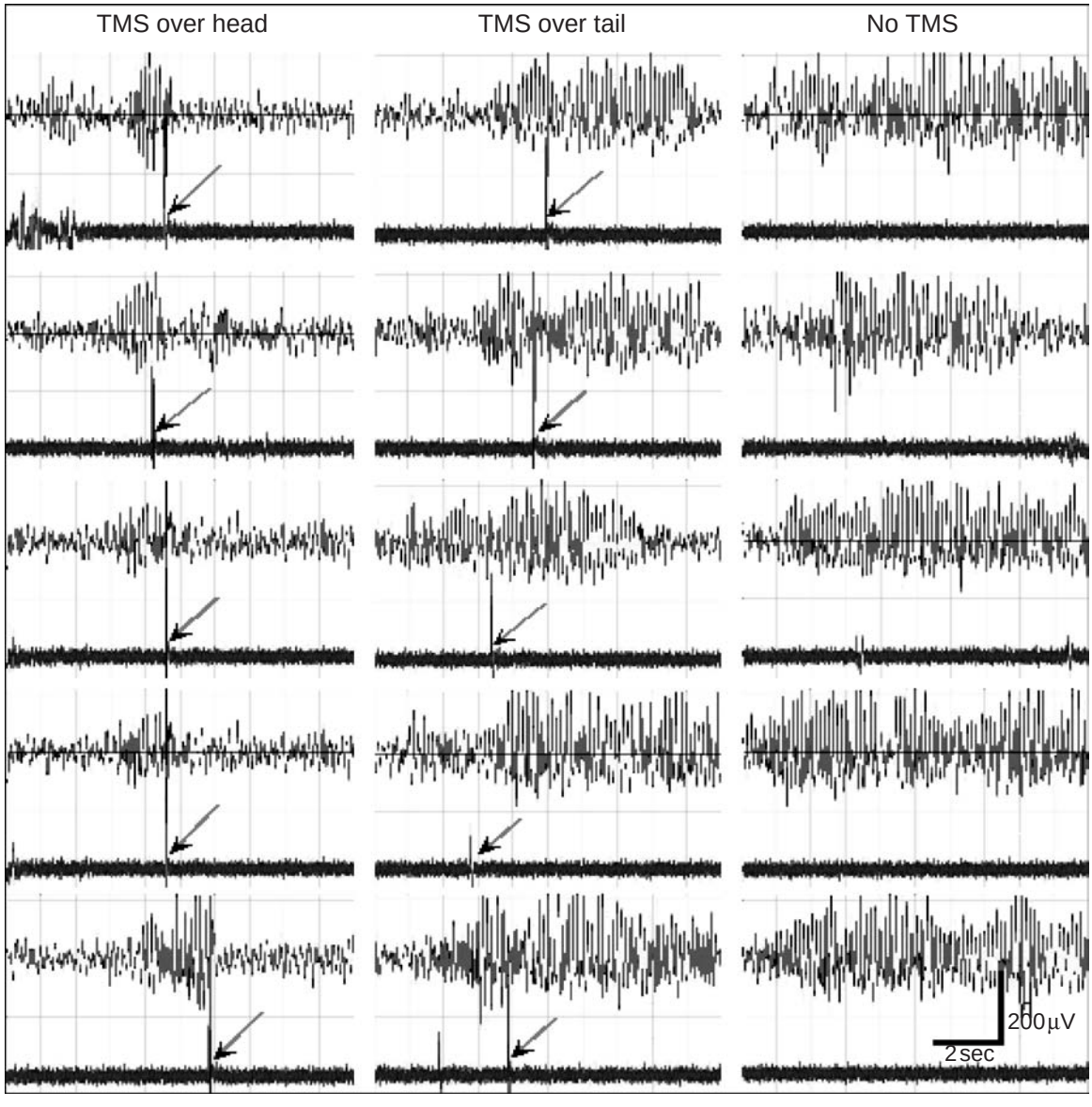

Figure 160.4 Spontaneous seizures aborted with overhead TMS. EEG (black tracing) and TMS output (blue tracing) were recorded for a spontaneously-seizing rat. Arrows point to time of TMS discharge. Seizure detection was performed by real-time visual EEG review – the EEG was monitored for ictal discharges and the TMS was triggered as soon as an ictal pattern was recognized. Five consecutive seizures were treated with coil over the rat's head (left column), five with coil over tail (center column) and the last five were untreated (right column). Each seizure treated with coil overhead terminated with rapid return to normal EEG. (See Color plates.)

investigate whether it can reverse the epileptogenigc process, perhaps by inducing changes resembling ling-term depression (LTD) that is LTP's inhibitory counterpart. In this regard, investigators working with rat models can take advantage of the extensive LTP and LTD literature[27] to evaluate the effects of repetitive TMS in vivo, ex vivo and in vitro, and compare them to the large body of work with direct cortical and hippocampal stimulation–such work should provide valuable insight into the therapeutic mechanisms of repetitive TMS.

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161 Surgery in a patient with medically intractable gelastic seizures and a hypothalamic hamartoma

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Introduction

Hypothalamic hamartomas are non-neoplastic congenital malformations resembling gray matter, composed of hyperplastic neuronal tissue. They are of varying size and usually take the form of nodules attached to the ventral hypothalamus and tuber cinereum or mamillary bodies.[1] These relatively rare lesions may be asymptomatic but are often associated with precocious puberty and/or an unusual epileptic syndrome characterized by gelastic seizures, behavioral disturbance, and suboptimal response to antiepileptic drug treatment.[2]

Gelastic epilepsy is characterized by pathological ictal laughter and often begins in childhood. In addition to the laughing spells, these patients have concomitant seizures of other types.[3–4] Morbid personality disorders and progressive cognitive deterioration further complicate the gelastic epilepsy related to hypothalamic hamartomas.[5–7] The management of affected patients remains difficult and controversial.[8] In this chapter, we report our surgical experience in a 3-year-old boy who was admitted to our service for investigation of longstanding uncontrolled gelastic seizures and associated generalized attacks. The case effectively illustrates the difficulties in the management of this challenging condition.

Clinical presentation

The patient was born at 40 weeks gestation by spontaneous vaginal delivery as the older of a set of non-identical twins. The patient's mother reported an uneventful pregnancy. He had good Apgar scores and had mild neonatal hyperbilirubinemia. He was discharged home within 36 hours of birth. However, in the following days, the patient experienced what later were identified as gelastic seizures. Over the next few months, he continued to have episodes of pathological laughter. It was noted that at 6 months of age, spells typically lasted less than 5 seconds and occurred up to 20 times per day. These brief but repetitive episodes persisted in the first year of life but remained largely unrecognized until the patient was 18 months old. At that time, he had a usual non-emotional laughing spell lasting a few seconds, but contrary to all previous episodes; this attack was followed by a generalized tonic-clonic seizure. He was referred to a regional epilepsy center for investigation of the 'new onset' seizure.

Over the subsequent months, the patient continued to experience approximately 20 gelastic seizures and seven to 20 generalized seizures per day. At this time, he was started on vigabatrin. However, not finding any change in the frequency or severity of the seizures, the parents decided to discontinue the anticonvulsant and refused any further antiepileptic medications.

His developmental milestones were also somewhat delayed. He was crawling at 8 months and began walking at 16 months. At that time, his gross and fine motor skills were felt to be marginally below the normal range. From a speech and language developmental perspective, the patient had a vocabulary of six to eight words at 14 months of age.

Over the following year, the patient's seizures continued to worsen. In addition to gelastic and secondary tonic-clonic seizures, he started having drop attacks primarily involving the head. During this period, the patient began to regress developmentally. His level of interaction and communication deteriorated. He also failed to develop any new motor or language skills and, in fact, lost the few words he had spoken previously. Behaviorally, he became very aggressive with frequent temper tantrums.

The patient was normocephalic with a slight strabismus with alternating esotropy. The motor and sensory, as well as the rest of the neurological examinations were within normal limits.

Video-EEG evaluation

In typical severe cases of hypothalamic hamartoma, an association is seen with slow spike-wave with or without multifocal (typically frontal or temporal) epileptiform abnormalities.[9–10] In addition, some seizures can closely resemble complex partial seizures of temporal or frontal origin on clinical and ictal EEG criteria.[11–12] Despite ictal recordings which may demonstrate the cortex as the site of origin of seizures, cortical resection uniformly is ineffective in treating the seizures.[3] These hamartomas are now known to be intrinsically epileptogenic and the site of origin for gelastic seizures.[12–14]

In our patient, EEG video telemetry revealed two electrographic and clinical seizure types. Clinically, the patient appeared afraid and made guttural sounds at seizure onset. This was followed by an emotionless laugh. The patient also had head drops and associated arm extension. Electrographically, an eletrodecremental pattern was observed followed by generalized slow wave and at times intermingled generalized spike and wave complexes. Figure 162.1 demonstrates rhythmic sharp activity starting in the left frontal region rapidly becoming rhythmic spikes. Head drop attacks were associated with generalized sharp waves. Seizure duration was between 50 and 75 seconds. Interictally, a generalized epileptiform abnormality was observed. Additionally, a bifrontal epileptiform abnormality with right-sided predominance was also noted.

Neuroimaging

The intimate association of the hamartomas to the mamillary bodies appears to be crucial for genesis of seizures.[15] In our patient, high-resolution magnetic resonance imaging scans demonstrated a well-defined, rounded soft-tissue mass in the region of the tuber cinerium (Figure 162.2). The lesion measured 12 mm in diameter and was isointense to gray matter on both T1- and T2- weighted sequences. The lesion did not enhance following administration of gadolinium. The mass showed heterogeneous signal intensities on the FLAIR images. There was no evidence of restrictive diffusion. There was no hydrocephalus associated with the hypothalmic hamartoma and no other lesions were identified.

Neuropsychological testing

The isolated hypothalamic hamartoma patients are known to perform poorly on the Woodcock-Johnson Battery, a broad cognitive ability standard score.[4,16] No correlation has been found between age at seizure onset and cognitive abilities. However, the frequency of gelastic and complex partial seizures do negatively correlate with the broad cognitive ability score.[17] A conclusive correlation between age at seizure onset or seizure frequency, and verbal or nonverbal abilities remains to be elucidated.

In our patient, progressive worsening of cognition and behavior was noted on the neuropsychological examination performed at the time of surgery. The evaluation showed moderate mental deficiency, borderline developmental quotients, and delayed speech. In addition, he had behavioral problems that encompassed hyperkinesias, aggressiveness, and autistic features.

Surgical management and outcome

Microsurgical excision of the hypothalamic hamartoma was proposed to the patient's parents given the intractability of the seizure disorder, the developmental regression, and behavioral and cognitive disabilities. Despite earlier views to the contrary, there is now good evidence that these clinical features are caused, directly or indirectly, by the hamartoma. Furthermore, there is now ample evidence that long-lasting control of seizures or even seizure freedom can be achieved by complete removal, destruction, or disconnection of the hypothalamic

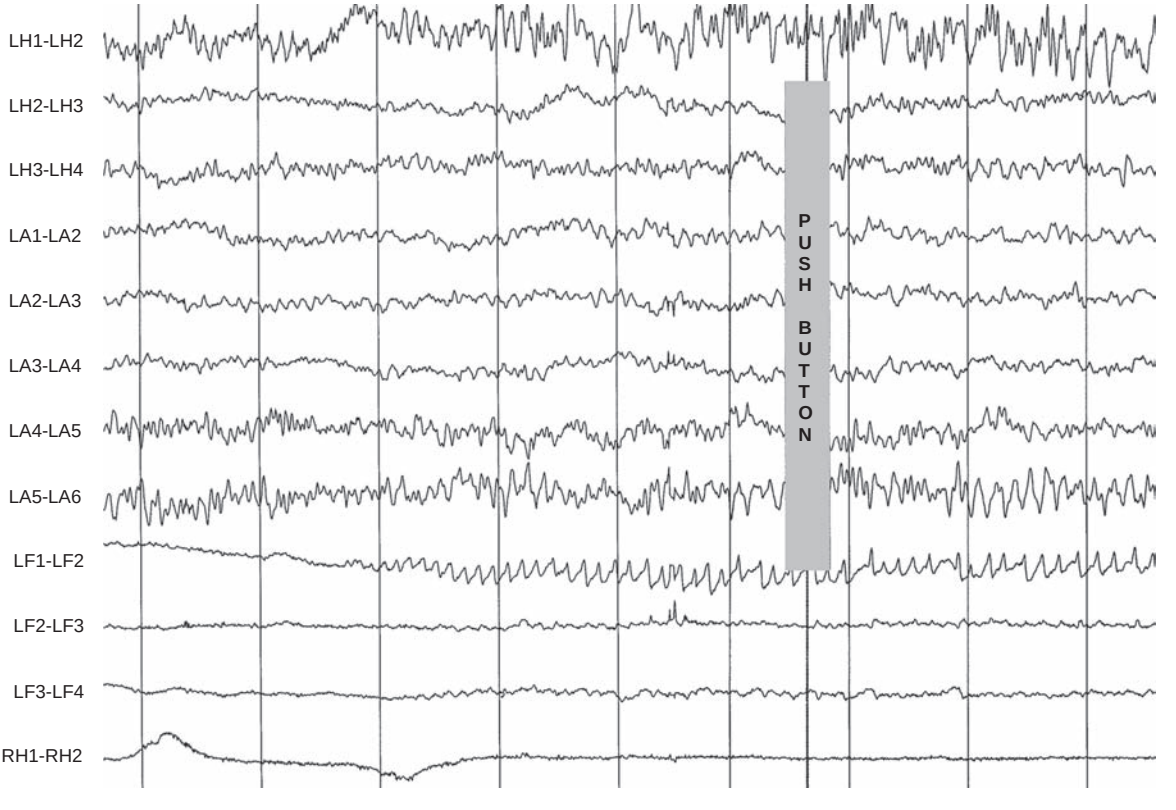

Figure 162.1 Preoperative scalp-EEG showing rhythmic sharp activity at LF1–LF2 rapidly becoming rhythmic spikes with push button denoting clinical seizure.

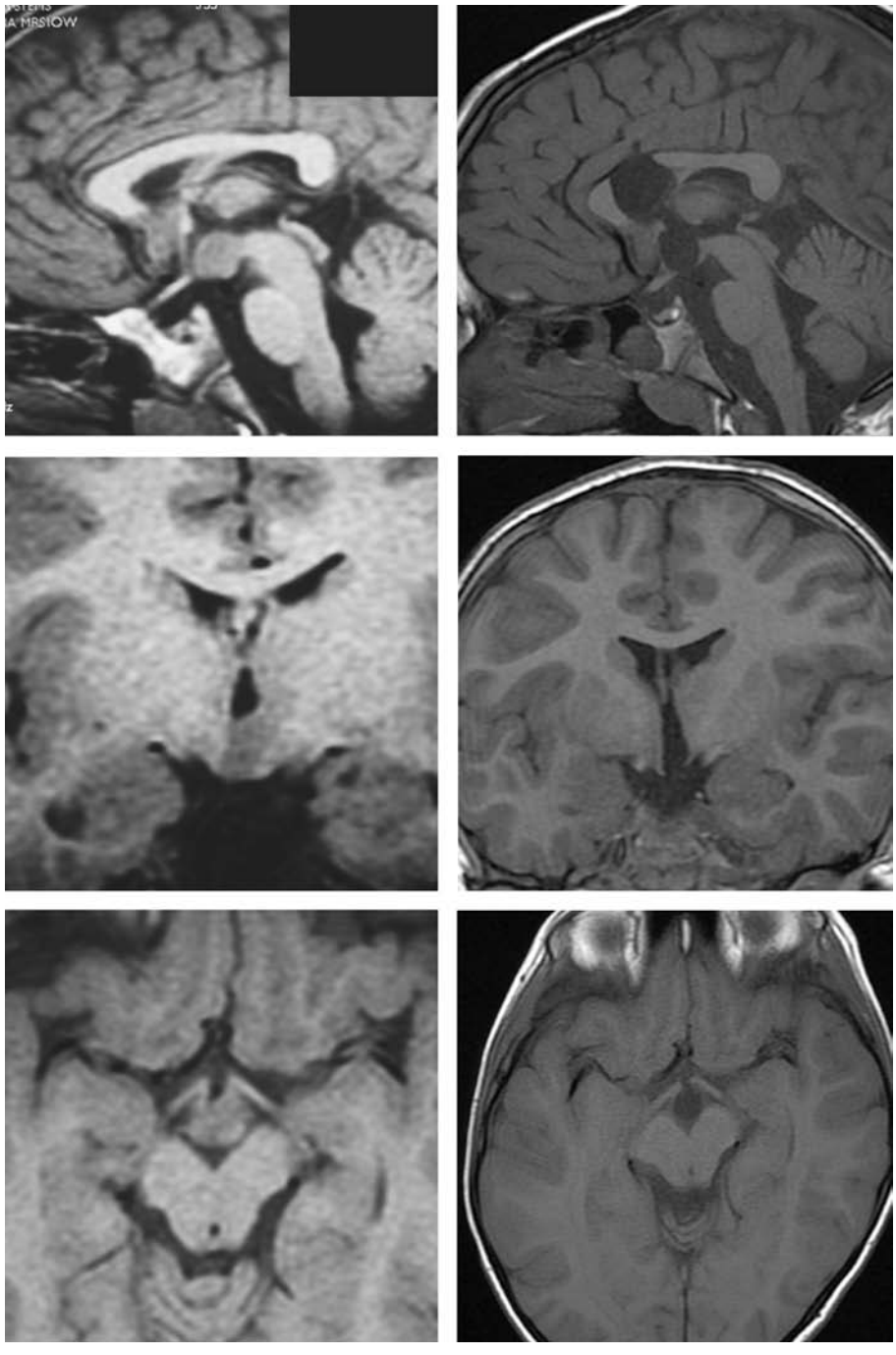

Figure 162.2 High-resolution MRI scans of demonstrating a well-defined, hypointense, non-enhancing hypothalamic hamartoma measuring 12 mm in diameter. Sagittal, coronal, and axial views obtained preoperatively (left panel) and following surgery (right panel).

hamartoma. Multiple surgical approaches and techniques have been described and should be tailored according to the surgical anatomy of the lesion and the surgeon's experience. We have used the traditional surgical approaches such as the transcallosal anterior interforniceal, the pterional, and the subfrontal translaminal terminalis approaches for resection of hypothalamic hamartomas. Because the main component of the hamartoma was within the third ventricle, it was felt that the interhemispheric, anterior transcallosal route, as described by Rosenfeld,[18] would be best suited for this patient. Craniotomy using frameless stereotaxy was performed. The corpus callosum was split and the two leaflets of the septum pellucidum and the columns of the fornix were separated, providing direct entry into the third ventricle at the level of and anterior to the foramina of Monro. Clear and direct visualization of the intraventricular component of the hamartoma was possible. Using a microdissector and an ultrasonic aspirator, complete removal of the lesion was achieved. Differentiation of the hamartoma from the ventricular walls and mamillary bodies can be a challenge. The lesion is typically slightly firmer and more gray compared to the surrounding neural structures. The plane of the third ventricle, the mamillary bodies posterolaterally, and the pia above the interpeduncular cistern provide resective surgical margins.

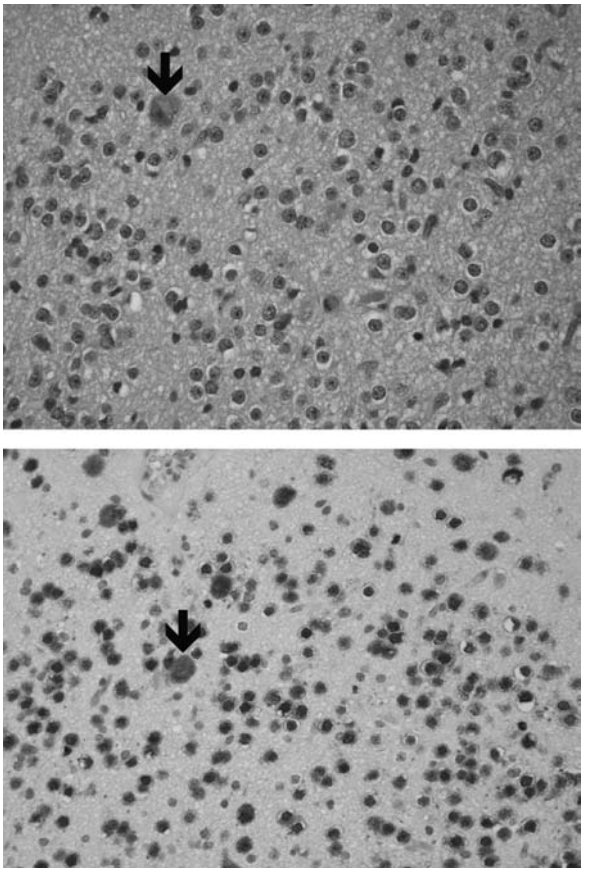

Figure 162.3 Histology of a hypothalamic hamartoma. Upper panel: On a routine H&E stain, there are both large neurons (ganglion cells; arrow) and smaller neuronal cells called 'neurocytes'. They are surrounded by a neuropil-like matrix. Lower panel: When stained immunohistochemically with an antibody against NeuN, a neuronal marker, both cell types are intensely positive (arrow, ganglion cell). (Original magnification 400× on both images. Photomicrographs courtesy of Dr. S. Albrecht, Dept. of Pathology, Montreal Children's Hospital.)

Postoperatively, he became seizure free and is no longer taking any antiepileptic medications. His overall behavioral functioning after surgery was significantly improved. He also showed considerable progress in his cognitive development, both verbal and nonverbal. However, he developed diabetes insipidus requiring desmopressin (DDAVP).

Histopathological analysis

Histological examination of the surgical specimens revealed a disorganized mixture of scattered large, neurons similar to those commonly found in the normal tuber cinerium. These mature hypothalamic neurons were interspersed with clusters of neurocytoid cells with round, monotonous nuclei and clear cytoplasm (Figure 162.3). These cells stained intensely for NeuN, a marker for mature neurons, and were surrounded by a fine fibrillary matrix positive for synaptophysin immunostaining. Immunocytochemistry with GFAP showed scanty astrocytes and oligodendrocytes without neoplastic differentiation. No mitotic figures were seen with absence of MIB1 positivity. There was no evidence of microvascular proliferation or necrosis.

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162 Surgery in a patient with focal epilepsy and dual pathology

N Foldvary-Schaefer

Clinical history and examination

LK is a 53-year-old right-handed woman with seizures since the age of 13 months. She was the full-term product of a normal pregnancy, labor and delivery. She had a generalized motor seizure of unknown duration at 13 months of life without fever. Her mother was told she had 'injured a vein on the right side of her brain'. She developed recurrent afebrile seizures in childhood, beginning with nausea often accompanied by a sensation ascending into her neck and a feeling of having a 'lump in her throat'. This was followed by an arrest of activity with unresponsiveness, staring and drawing up of the left arm, occurring 15–20 times per month. Isolated auras occurred over a dozen times per day. Generalized motor seizures occurred in the order of once per year and she had one episode of generalized convulsive status epilepticus and two episodes of nonconvulsive status epilepticus in the two years prior to presentation. Seizures proved resistant to a variety of antiepileptic drugs in monotherapy and polytherapy including phenobarbital, mysoline, phenytoin, valproic acid, carbamazepine, gabapentin, felbamate, topiramate, lamotrigine, oxcarbazepine and levetiracetam.

Her past medical history was positive for hypertension, depression and viral myocarditis. She was married with two adult children. She did not drive. She had 12 years of education and was last employed part-time for a medical answering service five years prior.

The neurological examination revealed poor short-term memory, slow response time and bilateral gaze-evoked nystagmus. The gait was wide-based and she was unable to tandem.

Presurgical noninvasive epilepsy monitoring unit evaluation

Noninvasive video-EEG was performed using the 10–20 system electrode placements and additional anterior temporal scalp electrodes. The interictal EEG revealed intermittent slowing in the right temporo-parietal region (Figure 162.1a). Rare sharp transients were seen in the right temporal region but no definite epileptiform discharges were recorded (Figure 162.1b).

Two auras and three seizures were recorded. Auras were described as a sensation of nausea ascending to her neck. Seizures began with her typical aura evolving to staring, unresponsive and subtle oral automatisms (repetitive swallowing) during which time the patient continued to speak and follow commands. During this phase, the left arm began to assume a dystonic posture by drawing up repeatedly, each time in a nonsustained fashion. All seizures were secondarily generalized with more prominent clonus on the left side. In one seizure, this was preceded by left face clonic activity.

The seizure classification was: abdominal aura → right hemisphere automotor seizure → left face clonic seizure → generalized asymmetric clonic seizure.

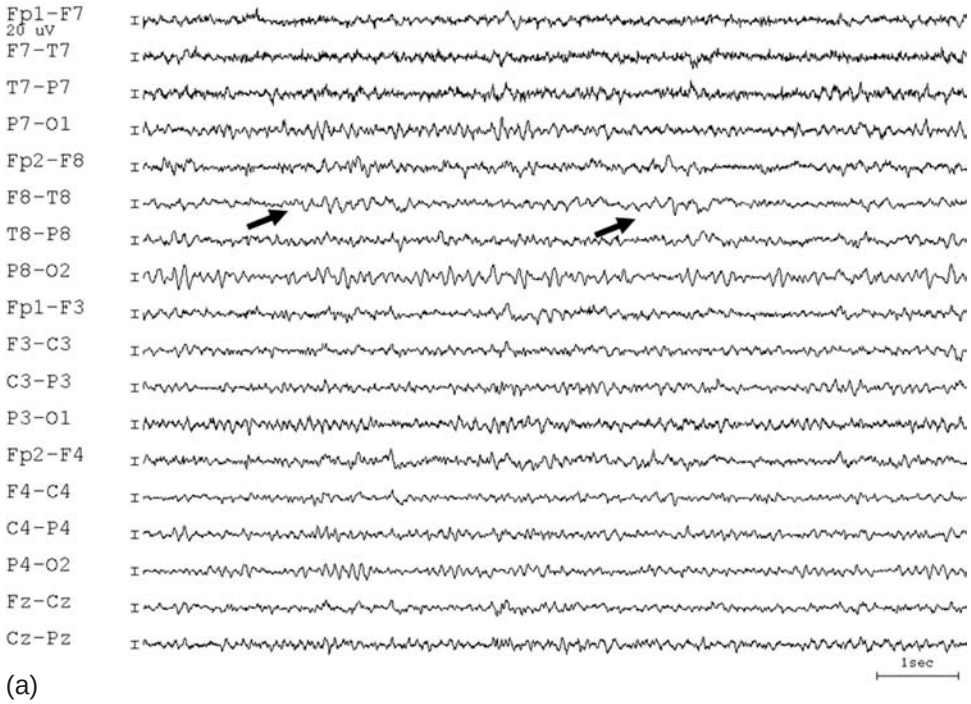
The video illustrates the following features:

- The patient notified her husband at the time of her aura and described it as nausea ascending to the neck.
- Several seconds later, she had repetitive swallowing movements but continued to speak, name an object and follow commands. During this time, the left arm drew up toward the chest repeatedly, but was not sustained.
- This evolved to left face clonic activity that was prolonged.
- The final phase is a generalized clonic seizure in which the clonus is asymmetric, initially restricted to the left face and arm. Toward the end of the seizure, the right arm develops clonus while the left arm becomes extended.

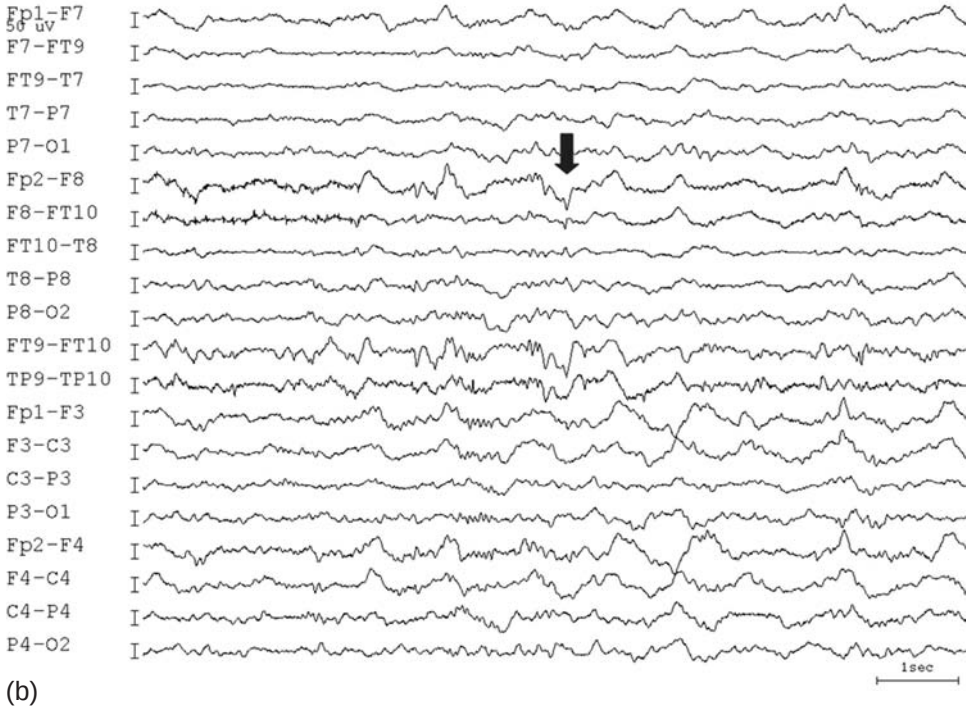
Auras were not accompanied by discernable EEG change. Seizures were accompanied by right hemispheric rhythmic delta, maximal in the temporal region, beginning 8 to 32 seconds after clinical onset (Figure 162.2a, b). This pattern later spread to the left hemisphere and did not evolve in frequency (Figure 162.2c).

Neuroimaging

High-resolution MRI demonstrated slight asymmetry of the head and body of the hippocampal formations with the right being smaller than the left on T1-weighted coronal images (Figure 162.3A). Increased signal on the FLAIR sequence was observed in the body and tail of the right hippocampal formation (Figure 162.3B). An area of susceptibility artifact (Figure 162. 3D, arrow) was observed on the T2-weighted images in the right parietal region in the area of the angular gyrus, thought to represent an area of prior hemorrhage or occult arterial venous malformation. Corresponding to this area on the T1-weighted images, the gyrus was somewhat small, although the cortical mantle was thought to be normal in thickness (Figure 162.3C).

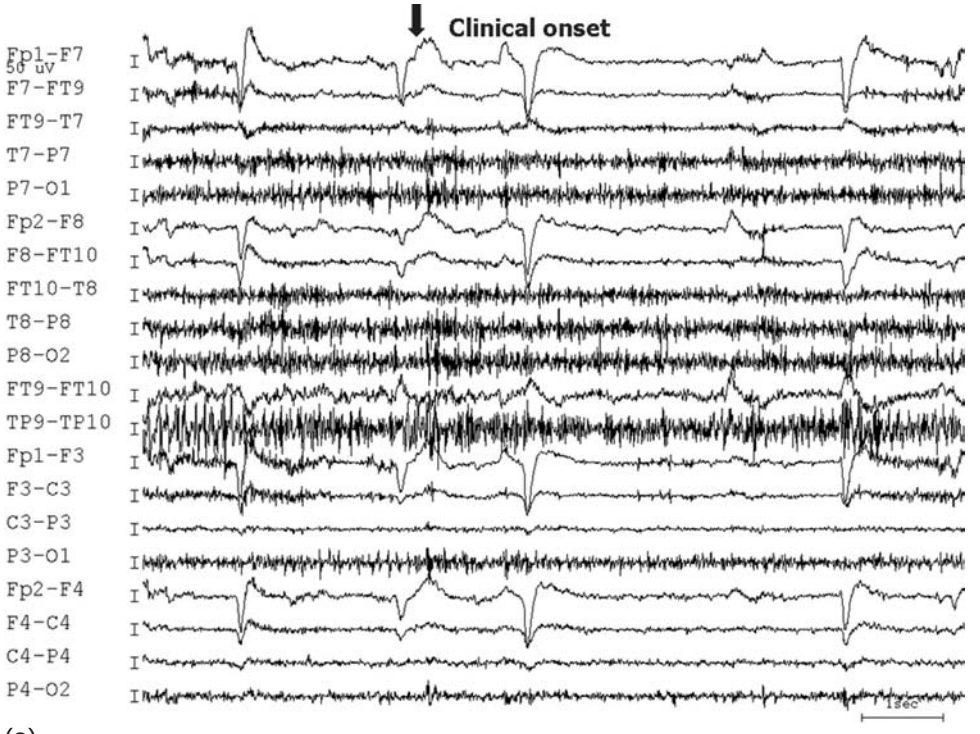


(a)

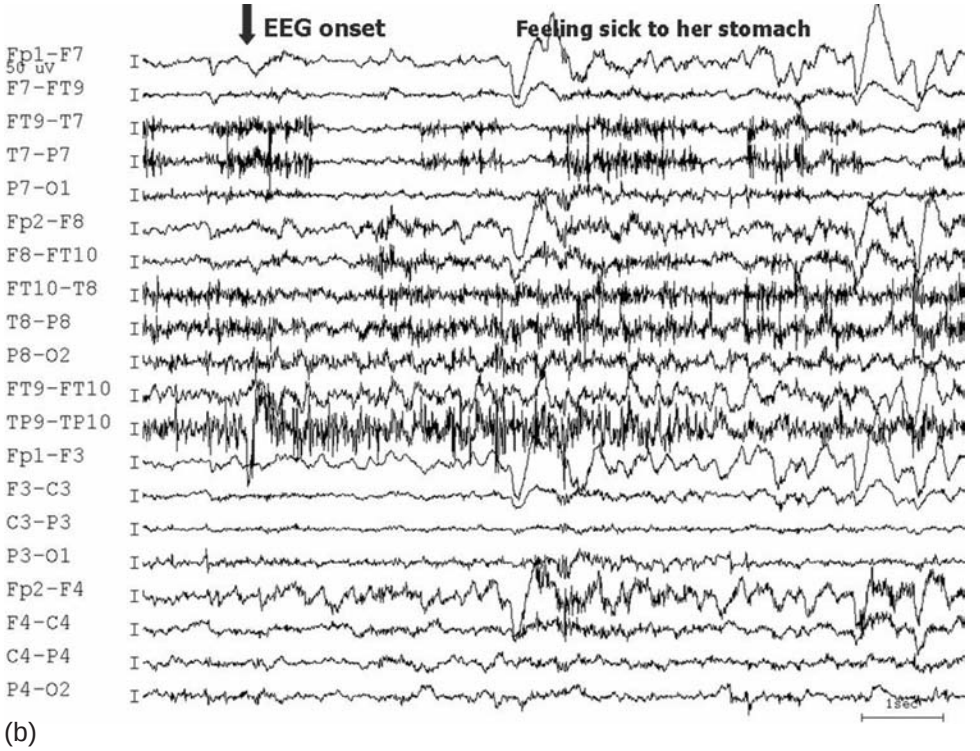


(b)

Figure 162.1 Interictal EEG demonstrating intermittent right temporo-parietal slowing (a) and rare sharp transients in the right temporal region (b). No definitive epileptiform discharges were observed.



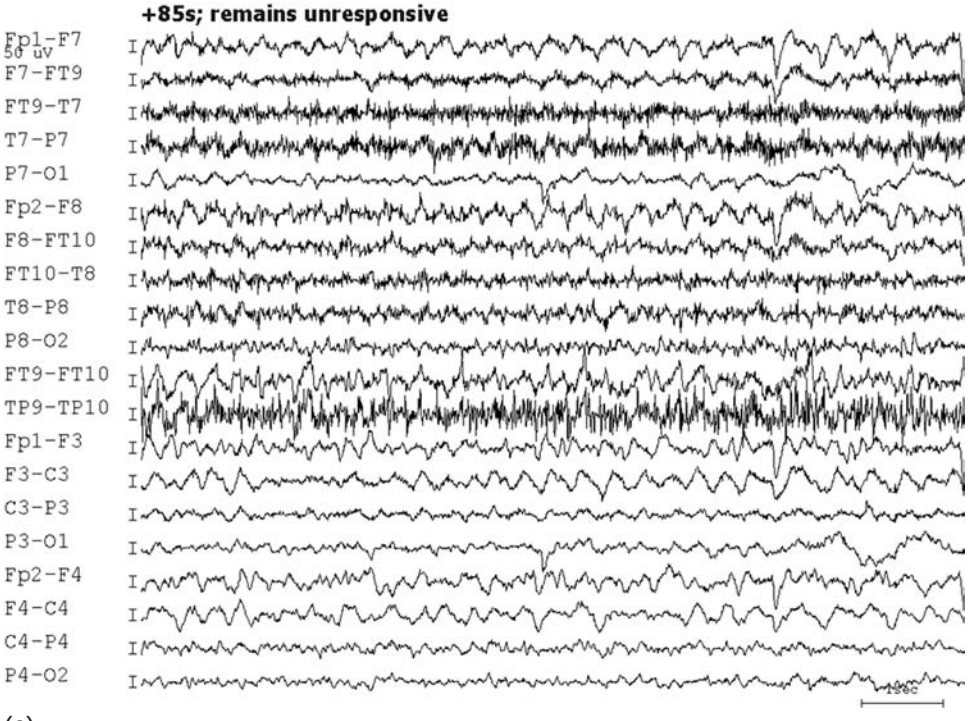
(a)



(b)

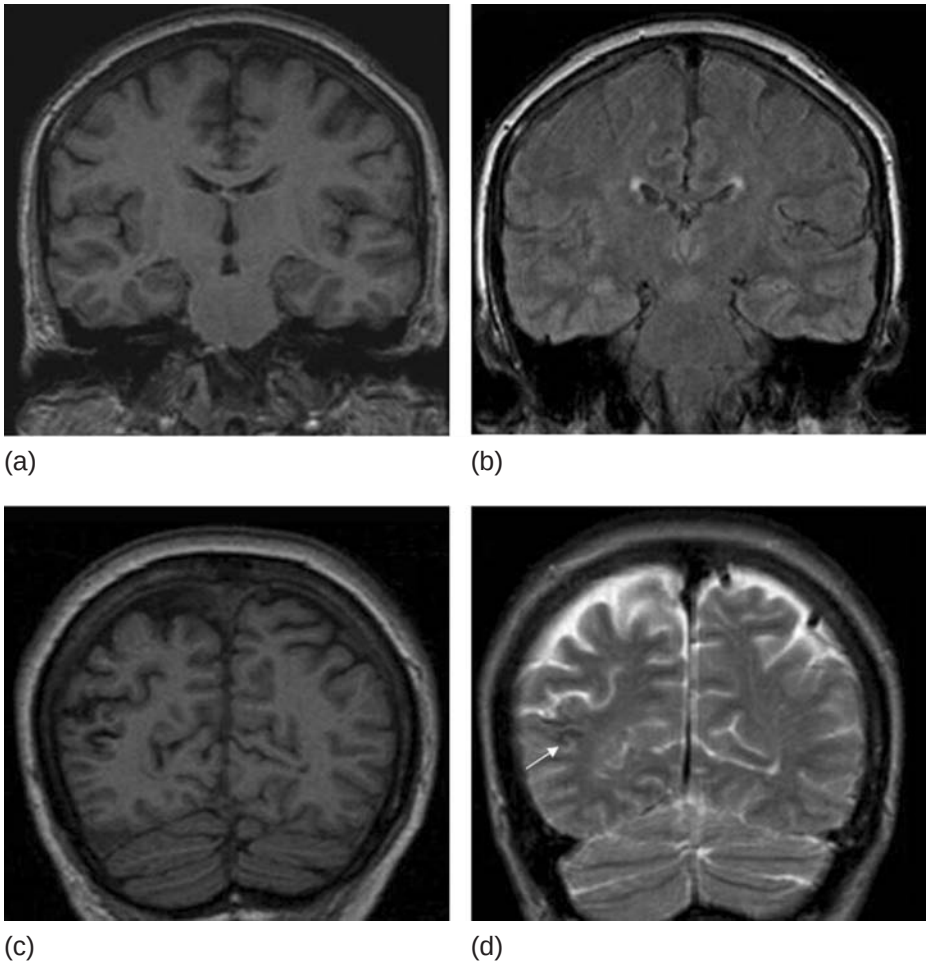
Figure 162.2 Ictal EEG during a typical automotor seizure preceded by an aura of nausea. The clinical onset preceded EEG onset from 8 seconds. Rhythmic delta was observed over the right hemisphere, maximal in the temporal region, gradually evolving to the left hemisphere.

Continued



(c)

Figure 162.2 cont'd



(a) (b)

(c) (d)

Figure 162.3 High-resolution MRI demonstrating mild right hippocampal atrophy (a) and increased signal intensity (b). An area of susceptibility artifact in the right lateral parietal lobe in the region of the angular gyrus (d, arrow) is seen on the T2-weighted image, thought to represent an area of prior hemorrhage or occult arterial venous malformation. Corresponding to this area on the T1-weighted image (c), the gyrus is somewhat small, although the cortical mantle is normal in thickness.

Neuropsychological testing

Neuropsychologicical testing revealed low-average general intellectual functions (Full Scale IQ: 91; Verbal Comprehension Index 81; Perceptual Organization Index 81; and Processing Speed Index 76). On tests of higher cognitive functioning, the patient was mildly impaired on a measure of visual search and ability to follow sequential procedures and a more complex task of selective attention. She was moderately perseverative on the Wisconsin Card Sorting Test and had some difficulty in both generating and maintaining problem-solving strategies. Measures of language functions were average, with the exception of markedly constricted verbal fluency and initiation and impaired sentence repetition. Oral and expressive reading skills were in the average and high average ranges, respectively. In contrast, math calculation skills were in the low average range. There was no evidence of significant visuo-constructional dyspraxia or spatial disorientation. Fine motor speed was normal bilaterally.

The patient was administered the Wechsler Memory Scale-III to assess learning and memory. Her overall span or Working Memory was constricted and in the borderline range (79). Her Immediate Memory Index score was 80 with a 17-point discrepancy between the Auditory Immediate Memory Index (92) and Visual Immediate Memory Index (75). Her delayed General Memory Index was in the borderline range (74) with a significant 33-point discrepancy between her Auditory and Visual Delayed Memory Index scores (92 versus 59, respectively).

Her score on the Beck Depression Inventory was 18, indicating a mild degree of affective distress.

Intracarotid amobarbital procedure

An intracarotid amobarbital procedure (IAP) was performed with bilateral injections of 200 mg and 175 mg in the left and right internal carotid arteries, respectively (the higher injection was required to produce an adequate hemiparesis). Both injections filled the ipsilateral ACA and MCA; limited crossover to the contralateral ACA was observed following the right injection.

The first verbal response was 03:45 minutes following the left injection and 00:00 minutes following the right injection, supporting left hemisphere language representation. Memory was impaired in the right hemisphere (retention score 44% after the left injection) and better in the left hemisphere (retention score 69% after the right injection). The pretest memory score was 100%. No abnormalities were identified on angiography.

Summary of presurgical evaluation and surgical plan

The MRI suggested the presence of dual pathology with a possible vascular malformation or remote hemorrhage in the right inferior parietal lobe and mild atrophy and increased signal intensity in the ipsilateral hippocampal formation, suggestive of hippocampal sclerosis. The seizure semiology (abdominal aura → right hemisphere automotor seizure → left face clonic → generalized clonic seizure) is consistent with right mesial temporal seizure origin. The interictal EEG finding of intermittent right temporo-parietal slowing is supportive of dysfunction in this area of the brain.

Findings on neuropsychological testing reflected some mild, fairly generalized neurocognitive deficits, although she manifested a relatively striking and circumscribed pattern of memory deficit for visual material, suggesting significant involvement of the right temporal region. She was judged to be limited risk for neurocognitive morbidity with respect to visual memory should she undergo a right temporal resection. The IAP findings were consistent with the neuropsychological testing, demonstrating impaired memory in the right (nondominant) hemisphere.

However, the lack of risk factors for epilepsy and absence of localizing epileptiform features on the ictal and interictal noninvasive EEG were somewhat unusual for isolated mesial temporal lobe epilepsy. On the other hand, parietal lobe epilepsy may produce poorly-localized seizures and a paucity of interictal discharges on noninvasive EEG, as seen in this case. Taken together, it was the recommendation of the Patient Management Conference to proceed with a subdural grid evaluation to better define the epileptogenic zone and map eloquent cortex.

Invasive evaluation

Subdural electrodes were placed over the right lateral temporo-parieto-occipital region (A plate – 8 × 6), the right temporal pole and inferior frontal gyrus (B plate – 4 × 4) and the anterior and posterior basal temporal surface (C and D plate, respectively – 2 × 6) as shown in Figure 162.4a.

Interictal spikes were seen very frequently (1 to 10 per 10-second epoch) in the mesial part of the C plate (contacts 7-1 > 2-8) representing 80% of interictal discharges (Figure 162.4a–b). Less frequent independent spikes were seen in the A plate (contacts 8, 9, 12, 13, 14, and 15), B plate (contacts 1, 5, and 6), C plate (contacts 3, 4, 9, and 10) and D plate (contacts 3, 4, 9, and 10). Spikes were observed at these locations every 1 to 2 minutes, each representing 5% of interictal discharges. In addition, low voltage repetitive spikes were seen nearly continuously in the anterior aspect of the parietal lesion involving contacts 28, 29, 36, 37, 38, 44, and 45 of the A plate (Figure 162.4c).

Eleven auras and 13 seizures were recorded over 10 days of monitoring. Seizure symptomatology was similar to that of the noninvasive evaluation (abdominal aura → right hemisphere automotor seizure). In two seizures, this evolved to left face and arm clonic activity and then to extension of the left and flexion of the right arm (sign of four) during the initial phase of the generalized motor seizure.

The first three auras, recorded during ongoing antiepileptic drug therapy, were not associated with EEG change. The ictal EEG was stereotyped for subsequent auras and clinical seizures and EEG onset preceded clinical onset by 10 to 76 seconds. EEG onset was characterized by low voltage fast activity appearing at the most mesial temporal contacts on the C plate (1, 7) as shown in Figure 162.5a. This pattern gradually spread to adjacent electrodes on the C plate (2, 8) and later to the inferolateral temporal lobe as shown in Figure 162.5b (arrows) after which the seizure spread more posteriorly.

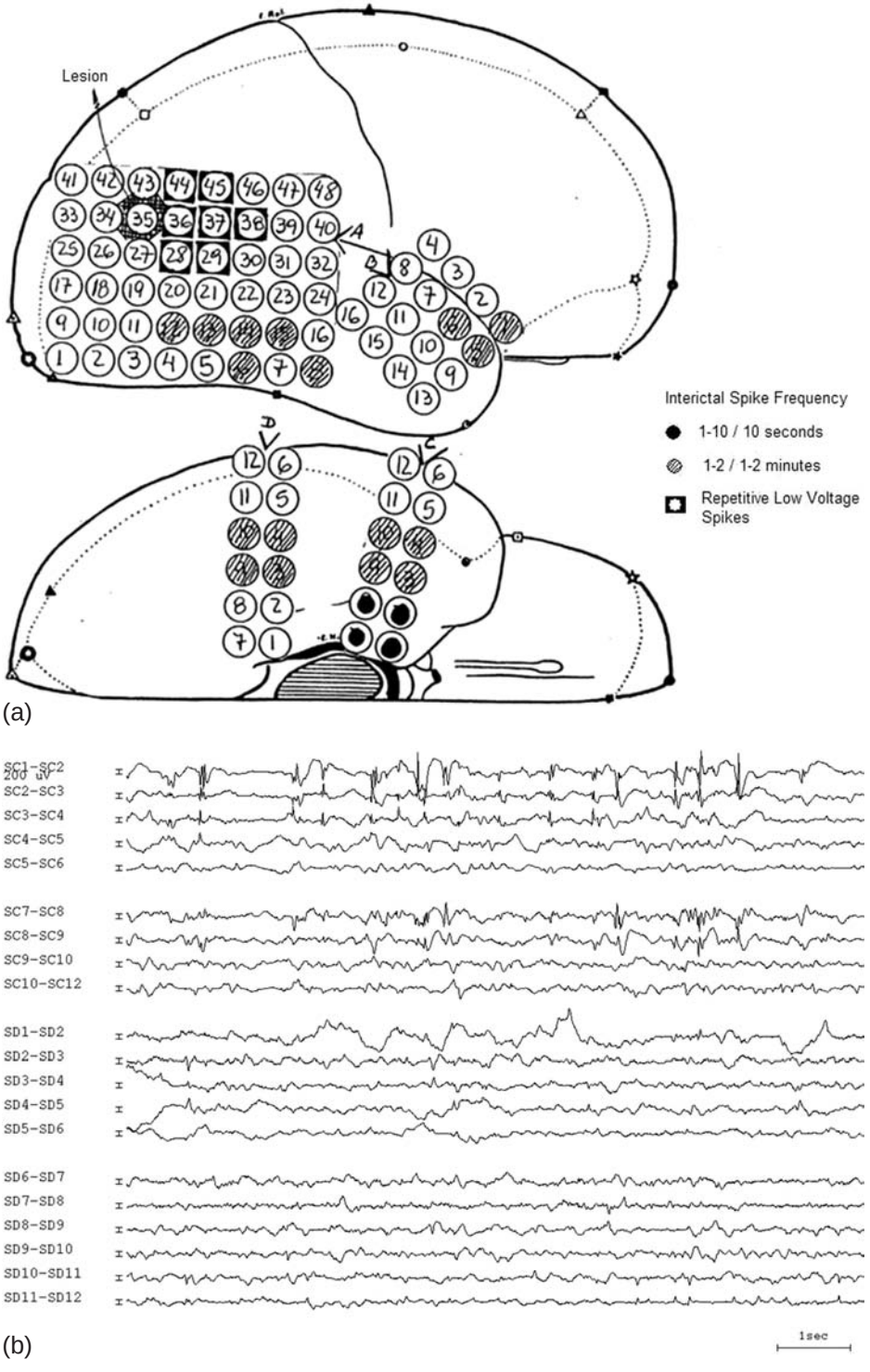
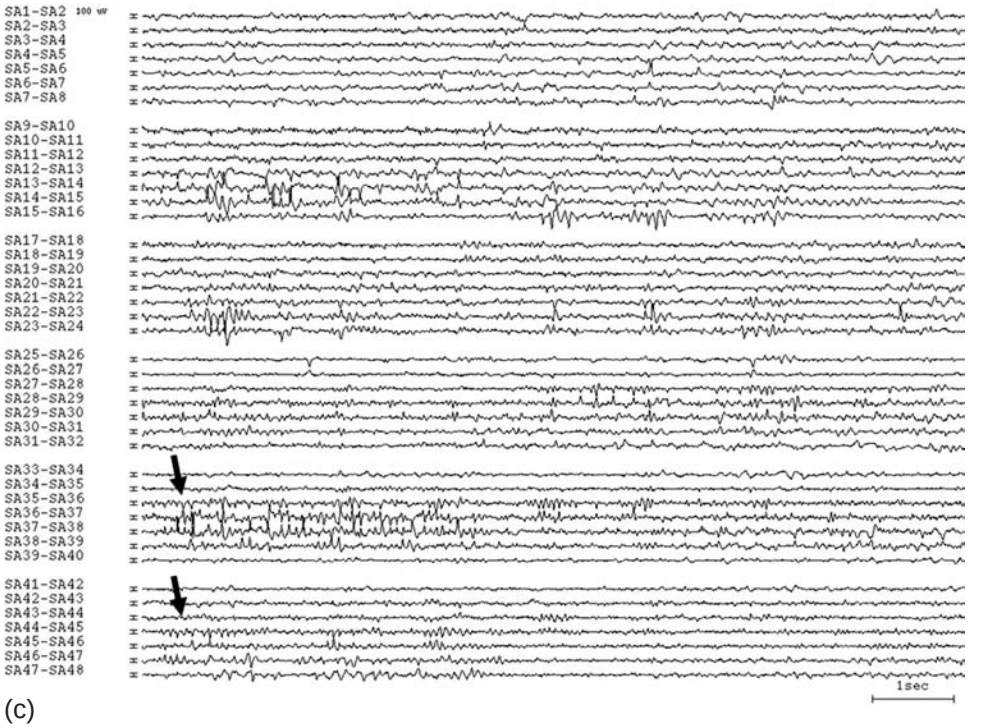


Figure 162.4 Invasive map showing electrode placement over the right lateral temporo-parieto-occipital region (A plate), temporal pole and inferior frontal gyrus (B plate) and mesiobasal temporal surface (C and D plates) and distribution of the various interictal populations (a). The most frequent spikes were recorded from the most mesial contacts on the inferior temporal strips at electrode contacts C1 and C7 (b).



(c)

Figure 162.4 cont'd Low voltage fast activity was recorded from electrodes corresponding to the anterior aspect of the parietal lesion (c).

Electrical stimulation of the four posterior rows of the A plate did not identify any eloquent areas. The patient was able to read, write and recognize pictures during the stimulation and no seizures were produced.

Summary of invasive evaluation and surgical plan

The subdural grid evaluation gives evidence of a large irritative zone involving the temporal lobe both mesial and lateral (although the mesial temporal region was most active) and the inferior parietal lobe near the MRI lesion. However, seizures arise from the anterior part of the right mesial temporal lobe, spreading relatively late to the parietal region. The seizure semiology suggests right mesial temporal origin. As a result of this evaluation, an anterior temporal resection including mesial temporal structures and resection of the parietal lesion was recommended. The patient was judged to be at no significant risk for neurological deficits related to the proposed resection.

Surgical procedure and outcome

The patient was taken to the operating room where the right temporoparietal craniotomy flap was reopened and subdural electrodes removed. Subsequently, a 3.5 cm lateral temporal resection was performed. The inferior temporal horn was then opened and the right amygdala and hippocampus were resected with microsurgical techniques. Attention was then directed to the posterior aspect of the incision, where there was a 2.2 cm calcified lesion in the right parietal lobe at the posterior aspect of the sylvian fissure. This was resected in its entirety using bipolar technique and microdissection.

The pathological findings are shown in Figure 162.6. The hippocampal specimen demonstrated focal neuronal loss and gliosis consistent with hippocampal sclerosis (Figure 162.6a). The parietal specimen revealed abnormal proliferation of blood vessels associated with dystrophic calcification consistent with a vascular malformation (Figure 162.6b). The temporal neocortex revealed focal leptomeningeal chronic inflammation and gliosis. The amygdalar specimen was relatively unremarkable.

During the first 2 years postoperatively, auras were reduced to approximately two per day and were less intense, although similar in character. She was otherwise seizure free. Thereafter, seizures recurred gradually increasing to approximately four per month despite toxic antiepileptic drug levels. Seizures were similar in character to those described preoperatively.

The postoperative MRI is shown in Figure 162.7. There is a parenchymal defect in the right temporal pole and resection of the amygdala and head and body of the hippocampal formation (A, C). Another parenchymal defect is noted in the region of the right angular gyrus (B, C) where the calcified lesion was resected.

Neuropsychology was repeated 6 months postoperatively. Findings are compared with preoperative scores in the table below (Table 162.1.) The 6-month postoperative assessment indicated some deterioration in general perceptual organization abilities and nonverbal fluency, in addition to less efficient higher executive functions. However, her performance on other neuropsychological measures, including verbal and visuospatial memory tasks, improved. Antiepileptic drug

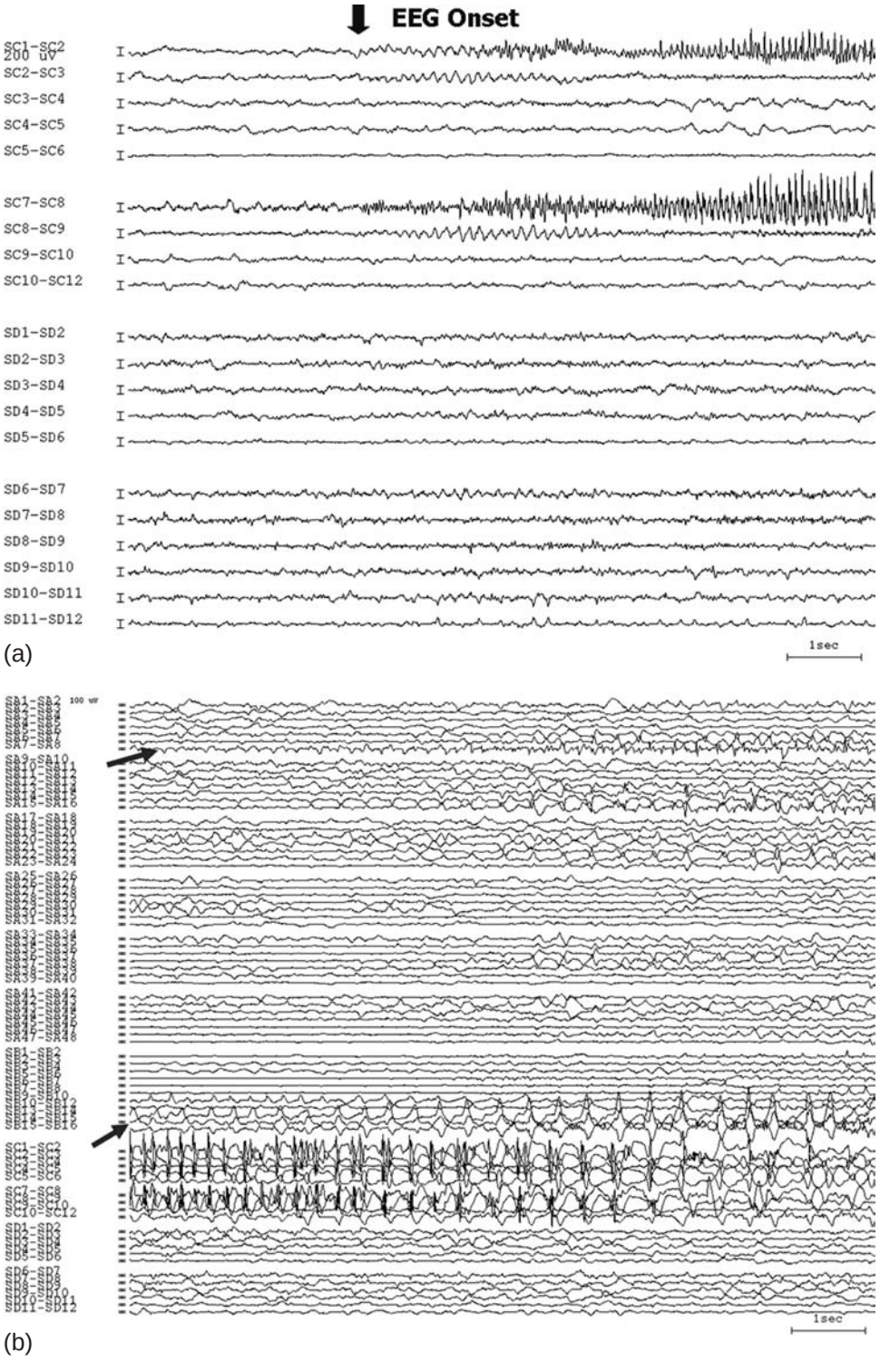
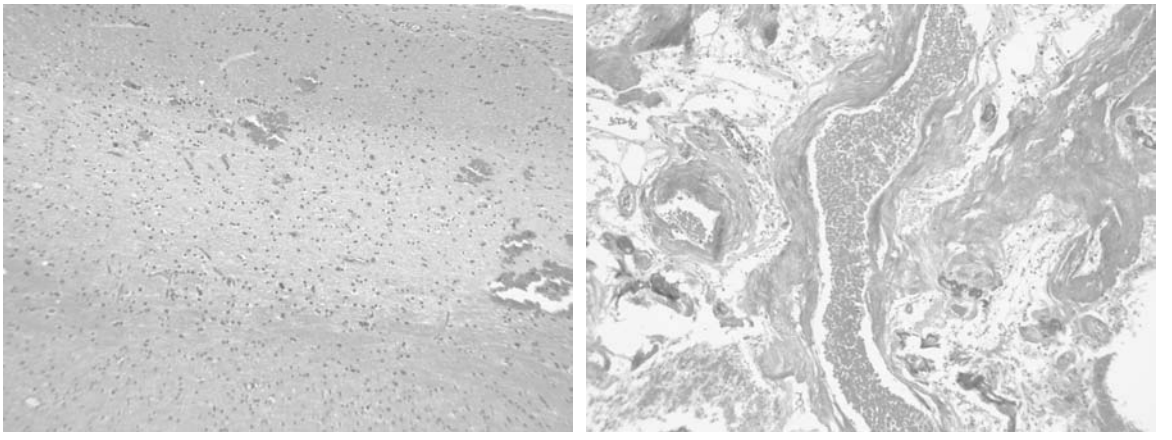
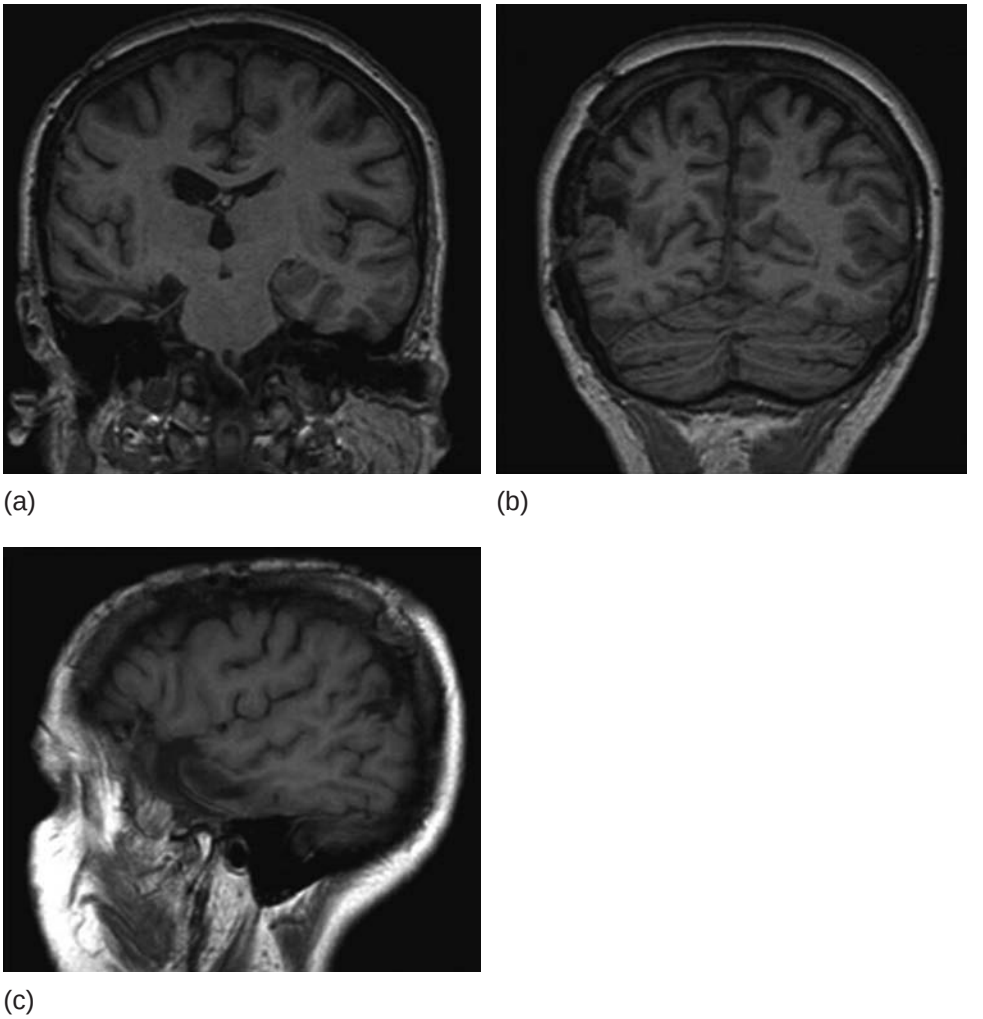


Figure 162.5 Ictal invasive EEG recordings showing the ictal onset (a) with low voltage fast activity at electrode contacts C1 and C7 suggesting mesial temporal origin. Approximately 20 seconds later, the pattern spread to the inferolateral temporal lobe on the A and B plates and as indicated by the arrows in (b).



(a) (b)

Figure 162.6 Pathological specimens showing a section from the Sommer sector (CA1) region of the hippocampus showing marked loss of neurons and gliosis consistent with hippocampal sclerosis. (a) hematoxylin and eosin, 100×). The parietal specimen shows abnormal proliferation of blood vessels associated with dystrophic calcification consistent with a vascular malformation (b); hematoxylin and eosin).



(a) (b)

(c)

Figure 162.7 Postoperative MRI demonstrating resection of the hippocampus (a), temporal pole (c) and inferior parietal lesion (b, c).

Table 162.1 Neuropsychological test scores

Measure	Preoperative	Postoperative
Verbal comprehension index	91	91
Perceptual organization index	91	78
Processing speed index	76	86
Working memory	79	85
Immediate memory	80	100
Auditory immediate	92	102
Visual immediate	75	97
Delayed general memory	94	96
Auditory delayed	92	111
Visual delayed	59	88

therapy (carbamazepine and topiramate) and other medications were similar at both testing intervals.

Noninvasive EEG monitoring was repeated 5 years after surgery to evaluate for reoperation. This evaluation revealed continuous slowing and frequent interictal discharges in the right temporal region (maximum T8>P8) as shown in Figure 162.8. Six seizures were recorded, characterized by an aura of nausea evolving to staring and unresponsiveness with subtle oral and manual automatisms. Seizure semiology was similar to that recorded preoperatively. All seizures were localized to the right temporal region, maximum at T8 (Figure 162.9), suggestive of seizure origin from the residual temporal lobe. The patient is considering whether she would like to proceed with further surgical options.

Conclusion

This case illustrates some of the challenges in the surgical treatment of patients with dual pathology. Many of the features of this case, including seizure semiology, MRI and neuropsychological testing, strongly implicated an epileptogenic zone in the mesial temporal structures. However, the noninvasive EEG did not provide supportive localization

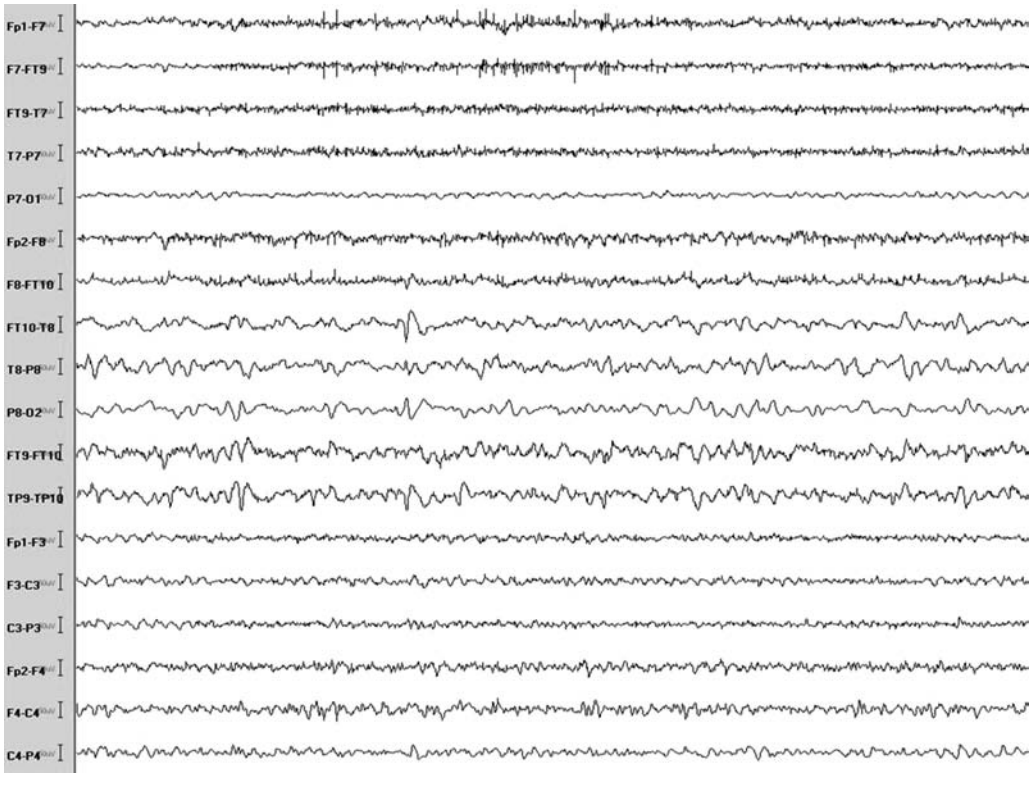


Figure 162.8 Postoperative noninvasive monitoring revealed continuous slowing and frequent interictal discharges in the right temporal region.

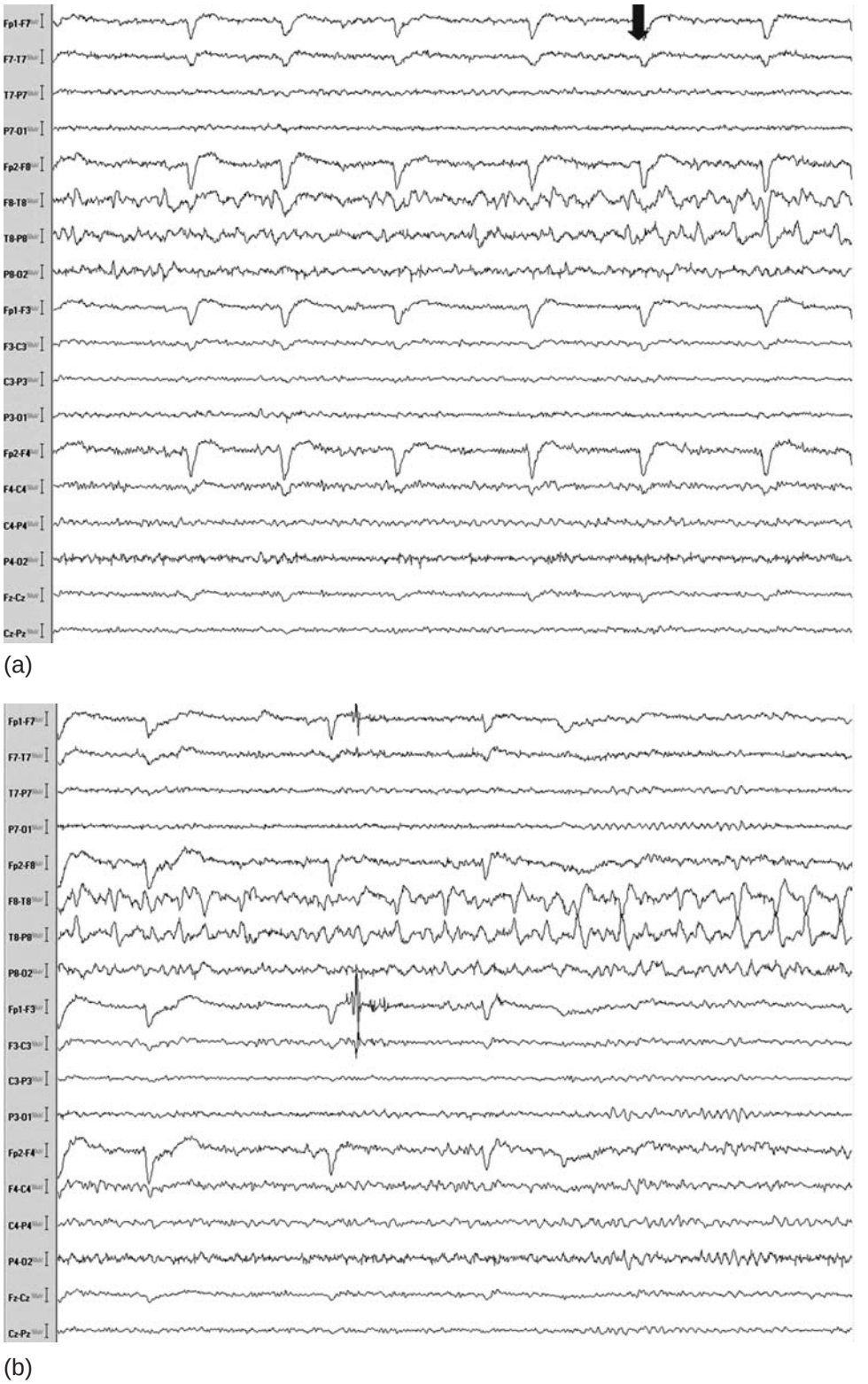


Figure 162.9 Postoperative ictal EEG of a habitual seizure characterized by nausea evolving to an automotor seizure. EEG onset (arrow) begins with repetitive spiking in the right temporal region, maximum at T8 (a) evolving in the same distribution on the next 10-second epoch (b). This pattern is suggestive of seizure origin in the residual temporal lobe.

and in fact, suggested the possibility that seizures may be arising from the lesion in the right parietal lobe and propagating to the temporal lobe. Findings of the invasive evaluation helped to clarify that the epileptogenic zone was in the temporal lobe, in the face of a much larger irritative zone. The planned procedure was to include both lesions. The unfavorable seizure outcome likely relates to an incomplete resection of the lateral and basal temporal lobe based on postoperative noninvasive EEG recordings. In settings such as this, the goal of the planned surgery is to perform a complete resection of both lesions and surrounding irritative tissue, sparing eloquent areas.

SECTION 22

Appendices

163 Essentials for the establishment of an epilepsy surgery program

MG Campos, HB Pomata, MA Vanegas, and AC Sakamoto

Introduction

This chapter presents small differences compared to the last version published in 2001[1] because there has not been sufficient progress in technology to improve the results of epilepsy surgery, nor was the introduction of new antiepileptic drugs (AEDs) able to produce changes in the control of seizures in surgical candidates. In this context, the main new issues to consider are the following: first, the fact that epilepsy surgery programs have had great development worldwide in recent years[2–4] and, second, that resective epilepsy surgery has succeeded in establishing a good seizure outcome. A prospective and randomized study of temporal lobe resection showed a result of 58% of seizure-free patients 1 year after surgery.[5] In observational studies, 41–56% of patients were seizure free within 10 years of follow-up.[6,7] These results are better than those obtained by the best new AEDs (see Chapter 32).

In the adult population, at least 20% of epilepsy patients have uncontrolled seizures with rational AEDs.[8–10] This percentage is even greater in children.[11,12] On average, approximately 10% of the whole epileptic population could be considered good candidates for epilepsy surgery. However, less than 2–4% of potential candidates are actually surgically treated in developed countries like Germany and the United States. The number of patients with refractory epilepsy without surgical alternatives is higher in developing countries.[1]

An adequate presurgical selection is basic to optimize the studies.[13–16] In a multicenter study of epilepsy surgery, only 30% of the patients who had undergone presurgical evaluations for resective epilepsy surgery were not ultimately subjected to this form of surgery. The abnormal MRI and consistent localized EEG findings were associated with having undergone surgery.[17] The success of epilepsy surgery depends upon the early identification of potential surgical candidates as well as the selection from this group of ideal candidates destined to have a postoperative seizure-free outcome.[6,7,18,19]

Epilepsy surgery can be classified as curative, when the goal is seizure-free patients, or palliative, when the target is to decrease the frequency of seizures. Diverse surgical procedures – such as disconnections, subpial transections, and comissurotomies – can reduce the seizures. Usually, the intent of curative surgery contemplates a resection of tissue; this procedure is a definitive and nonreversible surgery, with risks similar to those of other neurosurgical interventions. Nevertheless, the mortality and morbidity rates of epilepsy surgery are lower compared with other intracranial neurosurgical procedures.[5–7,18–20]

Epileptogenic zone (EZ) is defined as the minimum amount of tissue that must be excerpted to produce seizure freedom. Success – meaning seizure-free patients – depends on the correct resection of the EZ and good assessment of the eloquent brain near the EZ (language areas, motor cortex, sensory cortex, etc.). False localization of the EZ can lead to dramatic and adverse consequences such as: (a) persistence of epileptic seizures due to the incomplete or erroneous resection of the EZ, and (b) new neurological deficits due to resection of 'normal' and functionally eloquent cortex. Therefore, prevention of postoperative neurological deficits and reduction of morbidity to a minimum level involve careful and extensive presurgical testing and solid knowledge of the functional anatomy of brain cortical areas.

Presurgical evaluation and surgery require a well-trained multidisciplinary team of specialists in epileptology, clinical neurophysiology, neurosurgery, neuroradiology, neuranesthesiology, and intensive care medicine as well as pediatry, psychiatry, neuropathology, psychology, and other fields, since all risks need to be carefully weighed and only minor new neurological deficits should be acceptable.[1,15,21,22]

The low cost of the new methodologies is reducing the technological 'gap' between developed and developing regions and will certainly help the establishment of new epilepsy surgery centers in the whole world.[2–4] Based on the previous information, it is thus essential to establish more epilepsy surgical programs in developed countries and to ensure their creation in developing countries.

In order to perform a rational evaluation and treatment of patients with intractable epilepsy, we elaborated recommendations to establish two different levels of epilepsy surgical centers. One considers the *absolute minimum requirements* for an entry-level or *basic epilepsy surgery center* (BESC) while the other refers to the ideal conditions and qualifications or the *gold standard* for an *advanced or referral epilepsy surgery center* (AESC) (Table 163.1) nevertheless, these considerations do not negate the existence of the many centers around the world that remain between both categories.

Table 163.1 Minimum requirements for basic and advanced epilepsy surgery centers

	Basic epilepsy surgery center	Advanced epilepsy surgery center
Patients	Children Adolescents Adults	Infants Children Adolescents Adults
Types of surgeries	Temporal lobectomies Extratemporal (extralimbic) lesional resections, excluding eloquentareas Callosotomies	Temporal lobectomies Extratemporal (extralimbic) lesional/ nonlesional resections, including eloquent cortex Functional hemispherectomies, hemispherotomies Callosotomies Multiple subpial transactions Special surgical techniques (vagus nerve stimulation)
Video-EEG monitoring	Digital EEG – minimum of 32 channels 24-hours monitoring Noninvasive monitoring (additional + sphenoidal 'Less invasive' monitoring (foramen ovale)	Digital EEG – minimum of 64 channels 24-hours monitoring Noninvasive monitoring (additional + sphenoidal Invasive monitoring (foramen ovale, subdural strips and grids, epidural electrodes, depth electrodes)
Structural imaging	High-resolution 1.5-T equipment (0.5–1.0 T acceptable)	High-resolution 1.5-T equipment
Advance MRI techniques[a]		MR volumetric quantification MR spectroscopy Functional MRI T2 relaxometry 3D reconstruction Curvilinear reconstruction Coregistration and experimental techniques
Functional Imaging[b]	SPECT (optional study)	SPECT (interictal/ictal studies) PET MSI MEG
Electrocorticography	Intraoperative (optional)	Intraoperative
Cortical stimulation	Intraoperative (optional)	Intraoperative Extraoperative
Neuropsychological tests	Children	Children
Wada test	Adults Optional	Adults Yes
AED monitoring	Yes	Yes

[a] MR, magnetic resonance; 3D, three-dimensional; MEG, magnetoencephalography.
[b] SPECT, single-photon emission computerized tomography; PET, positron emission tomography; MRSI, magnetic resonance spectroscopic imaging.

Epilepsy surgical programs

Epilepsy surgical programs must always be part of a comprehensive epilepsy program and should not become an isolated issue in a medical institution.

Diffusion of epilepsy surgical programs to the community

First, it should be emphasized that – due to the particular characteristics of developing countries – the design of epilepsy surgery programs must include medical and social education for the communities which are far away from the primary epilepsy centers, as part of their pre-established tasks and budgetary considerations. This means that it is not reasonable to expect the personnel in charge of public health to be aware of, and able to appreciate the surgical options for refractory epilepsy patients. The surgical programs themselves must research and design the mechanisms and resources for diffusion of this option, which may include cooperation and coordination with the national organization in charge of primary healthcare. To cite an example, in Mexico, the Epilepsy Priority Program, which is a Federal State-funded organization and is in charge of primary epilepsy care, has been instrumental in coordinating the surgical program's efforts to discover knowledge of the surgical option. Contrary to what happens in Europe and North America, patients in developing countries usually do not independently seek other options for treatment due to their limited access to the Internet and health journals as well as the widespread fatalistic conception of disease as God's will. Thus, recognition of other modalities or alternatives for treatment depends solely on the primary medical caregivers, whose information and training must fall under the responsibility of the surgical programs.

Selection of candidates for presurgical evaluation

All patients with medically intractable epilepsy should be viewed as potential candidates for surgery. The exceptions to this rule include patients with generalized cryptogenic/ idiopathic epilepsies, and patients with epilepsy associated with progressive neurological diseases (except for Rasmussen's encephalitis). Even children initially classified as having

benign focal epilepsy, if not satisfactorily controlled, should be fully investigated, since some of them may eventually be found to have symptomatic focal epilepsy associated, for example, with perirolandic cortical dysplasia.

Definition of refractory

There is not a determinate seizure frequency to define refractory epilepsy. Seizures must interfere with the patients' quality of life (QOL) and fail to be controlled by at least two first line AEDs trials in monotherapy at the maximum tolerated doses. Usually a minimum of 2 years of medical treatment is carried out in most of the adult cases. The resistance to pharmacotherapy has to be established by a neurologist with a special training in the treatment of the epilepsies.

Establishment of patient's commitment

Presurgical evaluation will be offered to patients who are refractory to medical treatment and who are considered to be potential candidates for epilepsy surgery. Patients and their family will be counseled about the nature and risks of the various tests to be performed during the presurgical evaluation, as well as the postsurgical seizure outcome and potential morbidity and mortality risks of the surgical procedure. Patients will be asked to sign an informed consent. Only patients who have the intention to complete the presurgical evaluation will be entered in the protocol. This, however, does not preclude the patients' right to stop the evaluation at any time or to refuse surgery at the completion of the presurgical evaluation.

Special groups

Temporal lobe epilepsy (TLE)

TLE associated with mesial temporal sclerosis is the most common and intractable type of epilepsy. Also, unilateral medial temporal lobe resections have the best postsurgical seizure outcome.[5,20,22–25] In adults, 70–80% of the epilepsy resective surgeries are performed in temporal lobe[1,17,24,25] while around 80% of these patients do not need invasive presurgical evaluation, which means that approximately 60% of all the resective epilepsy surgeries can be performed in a BESC. We have recommendations of exclusion criteria for TLE in BESC, but some of these patients can be evaluated in AESCs (Table 163.2).

Table 163.2 Recommendations of exclusion criteria for temporal lobe epilepsy in basic epilepsy surgery centers

1 – Controlled epilepsy.
2 – Progressive medical disease.
3 – Patient or family who is not interested in surgery.
4 – Uncertain ictal onsets on scalp EEG.*
5 – Language involved in epileptogenic zone.*
6 – Normal MRI.*
7 – Memory ipsilateral to the mesial temporal sclerosis.*

* The last four exclusion criteria are not meant for advanced epilepsy surgical centers.

Extratemporal lobe epilepsy (ETLE)

ETLE is associated with several specific problems with respect to epilepsy surgery. Many times, the origins of seizures may not be limited to a circumscribed anatomic region and seizures can be widespread within the same lobe or hemisphere and even on the contralateral side. Another problem is the eloquent cortex (motor, sensory, language, etc.), which could surround or be part of the EZ. Several patients with ETLE need precise mapping of the eloquent cortex through invasive presurgical evaluation with subdural electrodes or complex functional techniques; these cases must be treated at AESCs. Extralimbic epilepsies (neocortical extratemporal and temporal) associated with focal lesion, outlying to the eloquent cortex, can generally be properly evaluated and treated at BESCs and AESCs.[26,27]

Children with intractable epilepsy

The epilepsy surgery must be considered very soon (6–12 months) in children with uncontrolled seizures, because many brain functions are affected with refractory epilepsy – such as the brain maturation, cognitive development, brain plasticity, etc. Special attention should be given to infants and younger children with catastrophic epilepsy, who require a high degree of selection to begin presurgical study, which should define cortical abnormalities and normal function, type of surgery, etc. We believe that genuine pediatric epilepsy centers should be considered as AESCs, especially for babies and young children, and all members of their team ought to fulfill the established standards for AESCs. Older children can be operated at BESCs, when they have diagnostics and need surgical approaches similar to those of adults.

Presurgical evaluation

Presurgical evaluation is a series of tests whose main objective is to localize the EZ. No single test provides definitive information,[1,14,15,22,28] which is the reason why convergence between different tests is essential to properly select the candidates and reach a better definition of the surgical strategy. To this purpose, presurgical evaluation includes several modalities of different features.

Imaging

Structural imaging

Magnetic resonance imaging (MRI)

Usually, brain MRI is performed before the video-EEG monitoring. MRI is the most important structural test of the presurgical evaluation and should be considered as absolutely essential to the process of identifying candidates for surgery. MRI will be performed with at least a 0.5 Tesla machine (but ideally with a high resolution 1.5 Tesla machine). The MRI must always be guided by the clinical features; for example, when TLE is suspected, both axial and coronal 2 mm cuts (and ideally 1 mm) will be performed in the hippocampus axis (30° from cranial basis). Sequences will include T1, T1-inversion recovery (IR), T2, and fluid attenuance inversion recovery (FLAIR).

For AESCs, high resolution MRI is absolutely essential. AESCs need also to have the capability to perform one or more of the various modalities of advanced MRI techniques, such as volumetric quantification, spectroscopy, T2 relaxometry, 3D reconstruction, curvilinear reconstruction, functional MRI (fMRI), co-registration techniques, and experimental methodologies. MRI can be repeated according to the video-EEG results.

Computerized tomography (CT)

CT can be perform in developing countries, where parasitic infections are endemic, in order to detect calcified lesions.

Functional imaging

We recommend these evaluations according to the video-EEG findings.

Single-photon emission computerized tomography (SPECT)

Currently, SPECT is available mostly in BESCs but is not obligatory in these centers. We need two examinations, interictal and ictal; the second is usually performed during the video-EEG monitoring, but the injection time is fundamental.

Positron emission tomography (PET)

This is a metabolic exam which should be performed in AESCs.

Inpatient video-electroencephalographic monitoring

Noninvasive studies

Continuous scalp video-electroencephalographic (video-EEG) monitoring will be performed with sphenoidal or at least anterior temporal electrodes using digital systems with a minimum of 32 channels. EEG data will include analysis of interictal nonepileptic abnormalities, interictal epileptiform activity and ictal activity. Patients and family members will be asked to review the recorded seizures to insure that their typical seizures were captured during the monitoring study. The interictal and ictal activity should be concordant and demonstrate a seizure focus. In patients with TLE, only those with hippocampal sclerosis or a lesion in anterior temporal region and concordant interictal and ictal data will be considered for surgery in BESC. EEG data must be concordant with neuroimaging and neuropsychological findings. To facilitate seizures, the AED dose will be reduced at the discretion of the treating neurologist.

Neuropsychological evaluation

The neuropsychological evaluation of adults will include a determination of full scale, verbal and performance intellectual quotients (IQs), measures of concentration and language functions, as well as the evaluation of immediate and delayed visual and verbal memory processing. This evaluation will be performed with the patient at full doses of AEDs and with a minimum seizure-free interval of one day. The main goal of the neuropsychological study will be to identify those patients at risk for postsurgical memory deficits.

In children and handicapped patients, studies will be tailored to the patients' cognitive status. Wada Test (Intracarotid amobarbital test) is necessary at AESCs. Indications and technical aspects are discussed elsewhere in this book.

Psychiatric evaluation

A formal presurgical evaluation must be performed in all patients, in order to diagnose acute psychiatric disease. Depressive states or other comorbidities should be diagnosed and treated before the surgery.

Epilepsy conference

When the above studies are completed, the patient data will be discussed in an interdisciplinary conference attended by the neurologist (epileptologist), neurophysiologist, neuroradiologist, psychiatrist, neuropsychologist, and neurosurgeon as well as the nurses and EEG technicians. At the end of the conference, patient and family will be given a recommendation to proceed (or not) with a surgery. The probabilities of seizure freedom will be estimated together with the risks of the surgical procedure, including the risks of memory deficits and other potential morbidities that will be explained in details.

Invasive studies (only in AESC)

Studies with invasive video-EEG monitoring will be considered in the following cases: (1) patients with discordant interictal and ictal data; (2) patients with discordant EEG and MRI and/or neuropsychological data; (3) patients whose EZ is suspected to override eloquent cortex.

Surgery (second hospitalization)

A neurosurgeon with special training in epilepsy surgery will perform the procedure. The main goal of the surgery will be to achieve a complete resection of the EZ sparing eloquent areas as well as normal tissue. Whenever possible, the neurosurgeon will attempt to make 'in-block resections' in order to provide temporal lobe tissue for neuropathologic analysis.

Neuropathology

A good neuropathology analysis of the surgical tissue is basic to determinate the type of lesion and evaluate the prognosis of the seizure control.

Follow-up

Outpatient visits with the neurologist will be scheduled postsurgically one month after surgery and then every 3–6 months during the first year and thereafter according to the patients' status. A postsurgical EEG and MRI will be performed not earlier than three months after surgery. Neuropsychological evaluation should be repeated at least 6 months postoperatively.

Other evaluations

It is strongly recommended that every center includes social evaluations in its protocol and planning of the rehabilitation and postoperative QOL of these patients, given their long-standing difficulties in coping with a chronic and handicapping condition such a medically intractable and severe epilepsy. It is felt that most of these patients, besides social problems, also face difficulties in interpersonal relationship within their nuclear family; for that reason, the practice of including a family therapist in some centers is encouraging. In terms of follow-up evaluations, epilepsy centers should be prepared to follow the QOL parameters. *Seizure-free patients are the target, but a best QOL for our patient is the main objective.*

Multiprofessional team

Epilepsy surgery is only possible through the laborious work of a highly qualified and dedicated multiprofessional team, including the following key personnel (Table 163.3).

Epileptologist

An experienced adult and/or pediatric epileptologist with training in presurgical methodologies is a key professional in the core team of the multidisciplinary group involved in the selection of candidates for epilepsy surgery. Epileptologists should be trained at an AESC, where the whole armamentarium of presurgical methodologies is available, and where the decision process regarding interpretation of presurgical data, indications for surgery, definition of surgical strategies, criteria, and the like are fully and clearly established. They should be board certified, or have equivalent qualifications in countries where this certification is not applied. BESCs should have an adult and/or a pediatric epileptologist, depending upon their surgical program (adult, pediatric, or both). However, it is recommended that AESCs have both fully trained adult and pediatric epileptologists. The minimum duration of training at an AESC is 1 year.

Clinical neurophysiologist

In most epilepsy centers, epileptologists are also fully qualified clinical neurophysiologists; otherwise, an experienced adult and/or pediatric clinical neurophysiologist is also essential to the multidisciplinary team. They should also be board certified (or the equivalent) and have comprehensive training in clinical neurophysiology methodologies, including EEG, video-EEG and evoked potentials. The qualifications are basically similar for BESCs and AESCs; however, clinical

Table 163.3 Minimum qualifications of epilepsy surgery center multiprofessional team

Key personnel	Basic epilepsy surgery center	Advanced epilepsy surgery center
Epileptologist	Board-certified neurologist (or equivalent qualification) with 1 year special of training in an AESC	Board-certified adult neurologist (or equivalent qualification) with 1 year of special training in an AESC Board-certified pediatric epileptologist (or equivalent qualification) with 1 year of special training in an AESC
Clinical neurophysiologist[a]	Board-certified clinical neurophysiologist (or equivalent qualification) with training in conventional EEG, evoked potentials, and video-EEG monitoring (should have at least 1 year of special training in an AESC)	Board-certified clinical neurophysiologist (or equivalent qualification) with training in conventional EEG, evoked potentials, and video-EEG monitoring (should have at least 1 year of special training in an AESC
Neurosurgeon	Board-certified neurosurgeon (or equivalent qualification) with 6 months of special training in an AESC)	Board-certified neurosurgeon (or equivalent qualification) with 12 months of special training in an AESC)
Neuropsychologist	Three months of special training in neuropsychological methologies in an AESC	Six months of special training in neuropsychological methologies in an AESC
Neuroradiologist[b]	Board-certified neuroradiologist (or equivalent qualification) ideally with 3 months of training in an AESC	Board-certified neurologist (or equivalent qualification) with special training in in advanced imaging techniques
Anesthesiologist	Board-certified anesthesiologist (or equivalent qualification) with experience in neuroanesthesiology	Board-certified neurologist (or equivalent qualification) with experience in neuroanesthesiology
Psychiastrist	Board-certified psychiatrist (or equivalent qualification)	Board-certified psychiatrist (or equivalent qualification)
Nurses	Preferentially trained in an AESC	Preferentially trained in an AESC
EEG technician	Preferentially trained in an AESC	Preferentially trained in an AESC
Other support personnel (social worker, psychologist, family therapist, etc.)	Integrated in the multidisciplinary team	Integrated in the multidisciplinary team

[a] In many centers, a neurologist is trained and board certified in both epileptology and neurophysiology.
[b] In selected centers, neurologists are trained and board certified in neuradiology.

neurophysiologists at AESCs need to be additionally trained in the interpretation of chronic invasive recordings.

Neurosurgeon

An experienced and board-certified neurosurgeon (or the equivalent) is also a key person on the team. It is recommended that surgeons working in a BESC have an additional 6 months of training in an AESC, and surgeons working in an AESC have at least 12 months of additional training in epilepsy surgery techniques.

Neuropsychologist

The requirements for neuropsychologists are similar for BESCs and AESCs. It is recommended that neuropsychologists involved in presurgical evaluation have a minimum of 3–6 months training in an AESC.

Neuroradiologist and nuclear medicine specialist

An experienced an board-certified neuroradiologist and nuclear medicine specialist (or the equivalent) are also essential to the multidisciplinary team, as structural and functional imaging become more and more essential and central to the decision process involved in the selection of candidates and the definition of surgical strategies. In addition, AESCs require professionals with special training in advanced imaging techniques.

Neuroanesthesiologist

An experienced and board-certified anesthesiologist (or the equivalent) is also an important professional in the multidisciplinary team, especially in those circumstances where intraoperative evaluations such as electrocorticography and cortical stimulation are employed.

Psychiatrist

As mentioned earlier, an experienced and board-certified psychiatrist (or the equivalent) should also be a member of the presurgical evaluation team, ideally evaluating all patients included in the program, or at least acting as a consultant in selected cases.

Neuropathology

A pathologist trained in neuropathology, hopefully with experience in neuropathology of epilepsies, will be responsible for the analysis of the surgical tissue.

Nurses and electroencephalography technicians

These multidisciplinary team members should be preferentially trained at an AESC, or be locally trained by the other members of the multidisciplinary team in all special issues involved in the care and evaluation of epileptic patients. Support personnel should be given courses on basic clinical epileptology, basic clinical neurophysiology, surgical techniques, assistance of patients during seizures, instrumentation, and the like. EEG technicians, especially, are strongly encouraged to have additional exposure or training at an AESC.

Other support personnel

Many other support personnel are welcomed to the multidisciplinary team, and should actually be fully integrated to the group. This is the case for social workers, clinical psychologists, family therapists, occupational therapists, phonoaudiologists, physiotherapists, and rehabilitation therapists.

Concluding remarks

The definition of two classes of epilepsy surgery centers, which represent each end of a spectrum of epilepsy surgery centers, fulfills two major objectives: (a) to define minimum requirements for a BESC, protecting patients from mismanagement of their unfortunate condition; and (b) to define the gold standard of AESC; this gives clear directions for each individual center to continuously improve its infrastructure and personnel. These two limits are obviously theoretical and somewhat arbitrary. Most centers would be situated in an intermediate position between these two ends of the spectrum. However, centers that do not fulfill the minimum requirements for a BESC should not be admitted by medical societies or government institutions, due to the risks of inadequate treatment.

Another important point is related to the multidisciplinary team involved in the activities of an epilepsy surgery center. In these days of major technological breakthroughs that make sophisticated methodologies less costly and more widely available, it is even more critical that multidisciplinary team members at all epilepsy surgery centers fulfill the minimum intellectual and technical qualifications of the professionals responsible for the implementation of these methodologies and interpretation of the data generated by them. Sensitive neuroimaging techniques frequently reveal one or more lesions. However, the epileptogenicity of each detected lesion must be documented before 'lesion-based epilepsy surgery' can be recommended. In other words, we must define what each lesion produces in terms of epileptic signs and symptoms before deciding on a surgical strategy. In this sense, the role of an experienced epileptologist/clinical neurophysiologist/neurosurgeon is absolutely essential. Such individuals are ultimately responsible for the correct interpretation of the *whole set of presurgical data*, and for the *development of the best surgical strategy for each individual patient*. The active participation of all other professionals is also essential in terms of the final results of the interventions, if one considers not only the narrow and simplistic view of seizure outcome, but also the global functioning and quality-of-life issues.

Finally, it is also important that professionals involved in AESCs be motivated to develop research in addition to their clinical work. It is important not only to perform well established techniques, but also to stimulate innovative ideas and to generate new knowledge in the field. These characteristics and this scenario are extremely important not only for the patients (our ultimate goal), but also for the training of the new generations of professionals entering the field of epilepsy surgery.

Final considerations especially for developing countries

Technology

When considering minimal technological requirement for establishing an epilepsy center in developing countries (MRI, video-EEG), every effort should be made not to remain behind and thus deprive patients of the best available techniques for detection and delimitation of epileptogenic tissue and coexistent morbidity. At the same time, the country's specific needs and economical situation should be kept in mind to avoid a total foreign dependency. It cannot be sufficiently stressed that budgetary considerations in terms of equipment acquisition must contemplate not only the initial but also the maintenance and operational costs. It has often happened that working equipment is replaced by state of the art technology, which is later very difficult to maintain.

Personnel (physician)

It might seem somewhat paradoxical, especially in countries where lowincome is not limited to the patients but extends to young professionals as well, to state that establishing a much needed epilepsy center requires integration of a multidisciplinary group of experienced and trained professionals, when there are practically no AESC in that country. Thus, it is our suggestion that all existing AESC must include a well-designed and certified training program. We suggest the integration of an ILAE task force to address the regulation and certification of training programs, specifically for neurosurgeons. Due to the vast surgical procedures available today and the need to tailor resections and techniques according to each individual case and evidence-based delimitation of epileptogenic tissue, we consider that a neurosurgeon's training experience in an AESC should last at least 12 months.

Motivation

It is absolutely essential that seeking clinical and quality-of-life improvement for medically refractory epilepsy patients be the thriving force shaping any surgical program. This might certainly sound redundant, but it is the moral and ethical obligation of epilepsy surgery specialist to ensure that establishment of epilepsy centers is devoid of economical, political or prestige seeking interests. As is the case in many chronic incapacitating diseases, the patients and their families are particularly prone to embrace false expectations, and no effort incurred in by the multidisciplinary team to explain the procedure and outcome probabilities is superfluous.

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164 Classification of seizure outcome following epilepsy surgery

HG Wieser and K Schindler

Introduction

Any medical–and specifically any surgical–procedure may be beneficial to the patient or may cause harmful (side-)effects. Therefore, the decision to engage in any therapeutic action should be based upon thoroughly assessing risks and benefits. In addition, in these times of widespread forced savings in the public health care sector, physicians are more and more often faced with having to justify therapeutic measures from the point of view of cost-effectiveness. However, to be able to efficiently advise an individual patient about whether to undergo surgery for pharmaco-resistant epilepsy or to convince health care authorities to invest money in this kind of therapy we have to document its effectiveness. Thus, we need powerful tools to assess the outcome of epilepsy surgery. This is why in recent years so much effort has been put into developing classifications of seizure outcome following epilepsy surgery. Seizure rate and severity were chosen as the variables, because they were thought to be rather easily to quantify. In the following we will describe the classification systems of Engel[1] and the one put forward by the Commission on Neurosurgery of the International League Against Epilepsy (ILAE).[2] We will highlight some of their advantages and disadvantages and thereby illustrate the difficulties of developing a quantitative measure of postoperative seizure outcome. We conclude with an outlook on possible future developments.

Engel's classification of postoperative outcome

The most important obstacles to quantitative measures of postoperative outcome with respect to epileptic seizures were initially analyzed at the first Palm Desert conference in 1986[3] and reviewed again by Engel in 1993.[1] Eleven points were raised, which will be briefly summarized here, because firstly they gave rise to Engel's original classification and secondly because most of them are still pertinent today.

1. Early postoperative seizures used to be considered to not necessarily indicating a bad long-term outcome.[4] This opinion was founded on the belief that pathophysiological processes in the postsurgical brain might be similar to the ones occurring following cerebrovascular strokes[5] or traumatic injuries. In these clinical situations early seizures do not predict further seizure recurrence. Engel pointed out that in 1991 a study at the Cleveland Clinic had found early postoperative seizures of any type to be associated with poorer seizure outcome,[6] a finding that keeps being studied and supported by very recent investigations.[7] Because there seems to be no such thing as a benign seizure early after surgery ('neighborhood seizure'), all seizures should be counted to assess postoperative outcome, a practice which had not been (and still is not) widely applied.
2. Late pattern changes of seizure occurrence are well known. Engel described the situations when, following surgery, there is a very slow running down and finally stop of seizures or, on the contrary, when there is initial seizure freedom for many years and then suddenly a reoccurrence of epilepsy. In the former case it is hardly possible to separate natural disease history from a beneficial effect of surgery, in the latter a new epileptogenic process may be responsible for the seizures. Independent from the difficulties of delineating the underlying pathophysiological processes these slow or late changes of seizure occurrence underline that the postsurgical brain is undergoing dynamic changes, which should be accounted for in the classification used to assess postoperative outcome.
3. Seizure severity and the impact of seizures on the performance of patients has to be considered when assessing the outcome. Obviously it makes a big difference for a patient to have simple seizures only at night or having secondarily generalized seizures during the day. While the former ones will most probably not interfere with social interactions and therefore may turn out to be 'nondisabling', the latter ones will strongly affect the quality of life. Therefore, merely documenting the seizure rate will not account for the very different impact of different seizures.
4. Closely related to the severity of single seizures is the time pattern of their occurrence. Depending on the character of the single seizure, a clustering may cause less or more disability for the individual patient. Again, simply counting the number of seizures relative to a specified time period will not reliably reflect this important aspect.
5. Report reliability of the patients about the postoperative seizure occurrence may be affected by many factors, ranging from unawareness of seizures to the development of nonepileptic seizure events or lasting psychosocial needs to remain dependent. Because there is still no reliable surrogate marker of epilepsy, physicians have to continue to rely on the reports of the patients or persons close to them.

6. Changes of seizure status occur with duration of follow-up. Late pattern changes of seizure occurrence as discussed above may be considered just as an extreme case of this well-recognized fact, again highlighting the importance of thinking about epilepsy as a dynamic disease, i.e., a process that develops in time. In regard to seizure outcome measures these changes of seizure status imply a dynamic approach, too. For example, assessing the year-by-year outcome relative to the time of surgery will assess the outcome much better than simply pooling the data into pre- versus postoperative groups.
7. The initial patient populations have to be characterized as precisely as possible to finally yield a measure that allows comparing the results of different surgery centers. In addition, at least a crude characterization of the goal of the surgical intervention should be attempted, for example by prospectively declaring a 'curative' or a 'palliative' approach.
8. Pharmacological factors are important because when and how antiepileptic drugs are withdrawn may well influence the reoccurrence of seizures.
9. Psychosocial factors of seizure occurrence are very difficult to measure and are certainly not accounted for by simply reporting seizure rates. Quality of life may even become worse for some patients who are not able to cope with their own or others' expectations for their independence.
10. Surgical complications can cause neurological defects that influence postoperative seizure rate to the better or to the worse. On one hand complications might lead to more extensive damage of the epileptogenic cortex than would have been achieved by the planned resection alone. On the other hand unintended lesions may cause scars, which may become epileptogenic and cause a postoperative increase of (new kinds of) seizures. In any case, the occurrence of surgical complications should be accounted for when pooling data for comparison between different groups of patients.
11. The natural history of different epilepsy syndromes has to be considered to separate it from effects of surgery.

Until today it seems to be impossible to develop a classification of postoperative seizure outcome that deals satisfactorily with all these obstacles. Thus, compromises have to be made as exemplified by the classification scheme of Engel,[1] displayed in Table 164.1, which is an altered version of the originally proposed outcome classification recommended at the first Palm Desert conference.

This altered version is still a compromise insofar, as effects of seizures on quality of life as subjectively experienced by the individual patients were combined with qualitatively assessing the number of seizures. Furthermore, many of the eleven points discussed above were not considered for the sake of applicability. Though this classification was considered to be work in progress, as already indicated by its footnotes, it was adopted by many epilepsy centers and is still one of the most widely used schemes to assess postoperative seizure outcome.[8] Another often used classification scheme was developed by the International League Against Epilepsy and was intended to improve on some of the disadvantages of Engel's classification.

ILAE classification of postoperative outcome

During the Ninth International Symposium 'Epilepsy Surgery' held in Cleveland in 1998 the participants of the workshop on seizure outcome, W.T. Blume, D. Fish, E. Goldensohn, A. Hufnagel, D. King, H.O. Lüders, M.R. Sperling, and H.G. Wieser (Chairman), agreed on the following new classification (see Table 164.2).

Table 164.1 Engel's classification of postoperative outcome

Outcome	Definition
Class I	Free of disabling seizures[a]
A	Completely seizure free since surgery
B	Nondisabling simple partial seizures only since surgery
C	Some disabling seizures after surgery, but free of disabling seizures for ≥2 years
D	Generalized convulsions with AED withdrawal only
Class II	Rare disabling seizures ('almost seizure free')
A	Initially free of disabling seizures but has rare seizures now
B	Rare disabling seizures since surgery
C	More than rare disabling seizures since surgery, but rare seizures for the last 2 years
D	Nocturnal seizures only
Class III	Worthwhile improvement[b]
A	Worthwhile seizure reduction
B	Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not <2 years
Class IV	No worthwhile improvement
A	Significant seizure reduction
B	No appreciable change
C	Seizures worse

[a]Excludes early postoperative seizures (first few weeks)
[b]Determination of 'worthwhile improvement' will require quantitative analysis of additional data such as percentage seizure reduction, cognitive function, and quality of life.

Table 164.2 ILAE classification of postoperative outcome

Outcome	Definition
1	Completely seizure free; no auras
1a	Completely seizure free since surgery
2	Only auras; no auras other seizures
3	One to three seizure days per year; ±auras
4	Four seizure days per year to 50% reduction of baseline seizure days; ±auras
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ±auras
6	More than 100% increase of baseline seizure days; ±auras

Two main lines of reasoning led to the proposal of a modification of Engel's classification system (see Table 164.1). These were on one hand some disadvantages of Engel's classification and on the other the intention to apply additional design principles. The main disadvantages of Engel's classification were considered to be:

- Despite the fact that Engel's classification was already widely adopted in 1998, results from center to center could not be compared objectively. Engel's category 'worthwhile improvement' was ambiguous and therefore differently interpreted from center to center. Some centers asked for a 90% reduction, others accepted 50, 60 or 75% seizure reduction. Furthermore, the term 'worthwhile' was a judgement that may not be entirely justified. Hence, this term was felt to best be avoided. In addition, the baseline for seizure counting was not defined precisely.
- In order to facilitate comparison of epilepsy surgery with AED drug trials, where a '50% seizure reduction' was increasingly reported as an end-point, a surgical seizure outcome category '50% seizure reduction' was desirable.
- Totally seizure-free patients are lumped together with others who still have seizures. Although Engel's category IA refers to completely seizure free patients, in reality most centers did not report Engel's subcategories. Therefore the actual number of seizure-free patients remained obscure. However, the category of seizure-free patients is obviously the most important, both in regard to clinical as well as scientific discourse. Since from a neurophysiological point of view, there is no difference between auras and simple partial seizures, including completely seizure-free patients together with those still having auras into the same class was sought to be avoided.
- A category postsurgical 'worsening' of seizures was needed.

Besides the intention to improve on these disadvantages of Engel's classification the following designing principles and goals were stated for the new classification:

- The new classification system was designed to be as simple as possible. The previous experience of various groups dealing with outcome measures (ILAE Commissions on Epilepsy Surgery and Outcome Classification, etc.) had clearly shown that only a simple classification system had realistic chances for worldwide acceptance and application. The new classification was therefore designed to avoid difficult-to-define terms, such as 'worthwhile' and 'disabling'.
- The new classification system was devised to be applicable to an *individual person*, to a *sample population*, on *a year-by-year* basis, and most importantly *cumulatively to the 'last available outcome'*. In addition, its application was intended to be not sensitive to different seizure types in order to fulfill the needs of 'palliative' procedures, such as corpus callosum sections, where very often only one type of seizure is targeted.
- It was designed to reasonably handle the special difficulties that appear when dealing with status epilepticus and with the differentiation between nocturnal/diurnal seizures. Counting 'seizure-days' instead of an absolute number of seizures was considered a more practical measure. In this context a 'seizure-day' was defined as a 24-hour period.
- The new classification system was designed to better account for the fact that some patients have at rare occasions seizures that, however, *occur in clusters*, or even *status epilepticus*, in response to or associated with highly provocative situations, such as antiepileptic drug (AED) withdrawal. Taking this into consideration 'seizure-days' instead of an absolute number of seizures is again the preferred measure.
- Finally the classification system was made in a way that further refinements could be easily adopted. Examples are the categories 'last available outcome' and 'completely seizure free *since* surgery', or the 'running-down phenomenon' of auras. The study of the latter phenomenon certainly was facilitated with this new classification system.

While these designing principles aimed at many of the the most important obstacles to quantitative measures of postoperative outcome as sketched in the section above, some issues were left aside. The following points were discussed in depth, but finally not included:

- It was considered to be desirable to state whether a patient was seizure free on AEDs or without AEDs. However, two separate categories are not justified, because many seizure-free patients on AEDs will not risk a possible seizure recurrence associated with the termination of AED treatment. For this reason, i.e., the impossibility of delineating how many patients would be seizure free off AEDs, it was decided against splitting category 1 into 'seizure-free without AEDs' and 'seizure-free with AEDs'.
- 'Quality-of-life' outcome measurements were considered to be very important. However, it was either not reported or not comprehensive. The inclusion of the term 'worthwhile' in the seizure outcome classification may be clinically useful, but it might also prevent a more comprehensive quality of life assessment. It was agreed therefore to avoid a 'quality-of-life' measure in a seizure outcome classification and to use a 'quality-of-life' outcome scale separately and in parallel. 'Quality-of-life' outcome measurement should be comprehensive and reflect behavioral, schooling, occupation, psychosocial, self-sufficiency, marriage and reproduction, mental, and cognitive states.
- Some authors (see references in Taylor *et al.*[9]) have argued that an outcome classification should allow one to measure whether surgery reached the contracted aim

(individually formulated in precise terms) or not. Though this approach was considered to be interesting, it was concluded not to be possible to integrate such a measure in the new classification system.

- The fact that there was a growing need to measure postsurgical results in a way to allow 'cost-benefit' analysis was discussed, but finally felt to be better covered in an additional 'quality-of-life' classification. Nevertheless the proposed seizure outcome classification, when properly used on a year-by-year basis, provides cumulative outcome data that will permit more sophisticated analyses, also in this regard.

The ILAE classification is displayed in Table 164.2.

In the following we comment on some important points of this classification:

1. Seizure outcome class is determined dynamically, i.e., for each year at yearly intervals following the date of surgery. Patients often change from one classification to another from year to year.
2. Seizures during the first month postsurgery are not counted. This should, however, be specifically indicated (see Introduction Section).
3. An aura is defined as a simple partial seizure that is not observable by witnesses, i.e., a pure psychic experience, which does not affect the patient's function. Auras should be counted only if they are of short duration and are similar or identical to the auras the patient experienced prior to surgery. If the history is not clear, auras should not be counted. Postoperatively, a large number of patients are anxious and may report subjective feelings that are not epileptic.
4. Class 3 is included because it is quite common for patients to have 'rare seizures' postoperatively. These are often nocturnal and often tonic-clonic. It is practical experience that some patients may have these rare seizures on certain – usually provocative – occasions, and usually can cope with fairly well. For plain statistical reasons class 3 could otherwise be part of Class 4 >90% seizure-days reduction.
5. A 'seizure-day' is a 24-hour period with one or more seizures. This may include status epilepticus or seizure clusters.
6. The number of 'baseline seizure days' is calculated by determining the seizure-day rate during 12 months (at least 3 months) prior to surgery, with correction for the effects of AED reduction during diagnostic evaluation.
7. In Classes 4, 5, and 6 the change of seizure-free days with reference to baseline should further be detailed at least in 10% subcategories, or – better – in absolute numbers to allow for cumulative data reporting.
8. Class 5 means that the surgery did neither significantly improve nor significantly worsen the clinical situation of the patient. After a long discussion and advised by statisticians it was decided for the 100% increase of baseline seizure-days (versus 50%) on the argument that for mathematical and biological reasons it is justified to assume that seizure frequencies and their changes after surgery have a normal log distribution. This implies that a 50% decrease is equivalent to a 100% increase.
9. In the year-by-year reporting Class 1 should contain a subgroup 'completely seizure free *since surgery*; no auras' (see Table 164.3 and Figure 164.1). It is recommended that those patients being Class 1 without antiepileptic drugs are also separately reported.
10. The 'last available outcome' can be indicated in a separate column with the specification that a minimal follow-up of 1 year postsurgery is required. It should further be specified by mean±standard deviation, and minimal and maximal follow-up. It is understood that the last available year has to be taken into consideration. For example; a patient was operated on 5 September 1992 and is followed to end of July 1998. The period which counts for the 'last available outcome' would then be 5 September 1996 to 5 September 1997. Only where the length of the follow-up period is critical, the last available outcome can be calculated for the last 12-month period, i.e., in this example 31 July 1997 to 31 July 1998. It should be indicated whether the year prior to the last surgical anniversary or the last 12-month period is taken into account.

A practical example: long-term seizure outcomes following amygdalohippocampectomy

As a practical example how to report seizure outcome using the Engel and ILAE classification systems we display some results of the outcome studies of the Zürich amygdalohippocampectomy (AHE) series (10–13) as graphs in Figures 164.1 to 164.3. Data are plotted for postoperative years 1–15 (or 17 or 18), and the last available outcome (using the year prior to the last surgical anniversary). The number of patients at a given year can be easily added into such an outcome classification (Figure 164.3) or given as a table with the graphs (Figures 164.1 and 164.2). Note also that in these examples ILAE Class 1 has been split in order to report the number of patients who are 'completely seizure free *since* surgery' (ILAE Class 1a). For more detailed data on the AED treatment following AHE see Wieser and Häne.[12,13] Neuropsychological outcome data[14,15] and some quality-of-life data[16] of our Zürich AHE series have been summarized elsewhere.[11,14,15]

Quality of life

In a recent survey (August 2004) of the International Bureau for Epilepsy it was found that 56% of participating epilepsy patients linked their cognitive impairment with their epilepsy medication (alone or combined with their epilepsy). Of these, 45–50% felt that the cognitive and other effects of their epilepsy and its treatment had a moderate or severe effect on their work, education, leisure activities, families and relationships and 63% felt that the effects they had experienced had prevented them doing a particular activity or achieving a specific goal. These numbers underline the importance of quality-of-life assessments in epilepsy patients (see Trimble and Dodson, 1994).[16] Although we cannot deal here with this very important aspect of quality of life outcome studies, we shall mention several available valid inventories, such as.

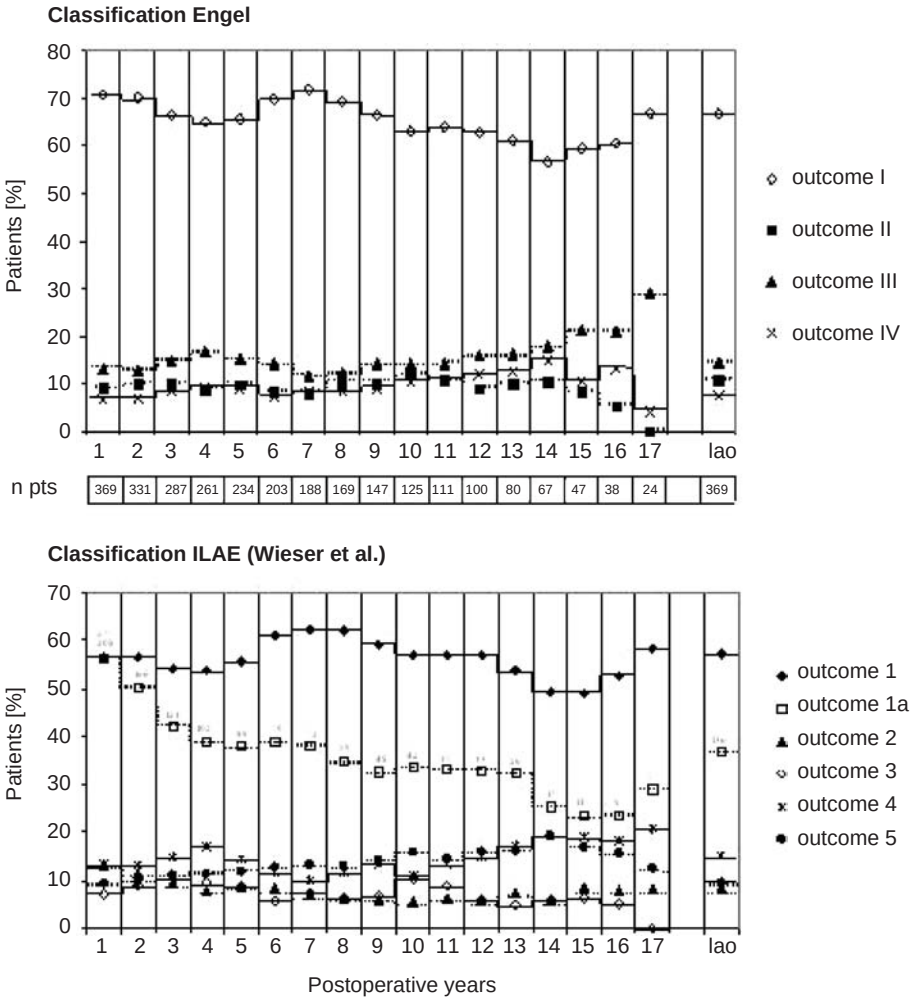


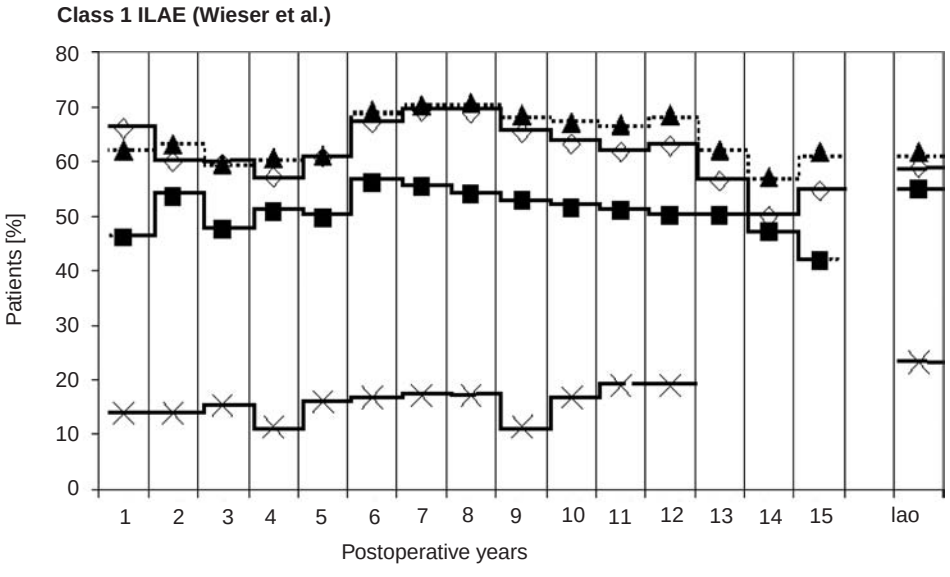
Figure 164.1 Year-to-year seizure outcome classification as well as last available outcome (lao) of the Zürich selective amygdalohippocampectomy series (1975–1999) with sufficient follow-up (≥1 year; n=369) according to Engel (see Table 164.1) and ILAE (see Table 164.2). No patient had an ILAE Class 6 seizure outcome. Years with fewer than 20 patients are not plotted. Numbers in boxes indicate the numbers of patients in the given year or overall. From Wieser et al., 2003[10] with permission.

- QOLIE-89 (Quality of Life in Epilepsy Inventory-89)
- ELDQOL (Epilepsy and Learning Disability Quality of Life)
- Likert scale of impact of treatment
- The Liverpool Quality of Life Questionnaire
- The Epilepsy Surgery Inventory–55 (ESI-55)
- The Washington Psychosocial Seizure Inventory (WPSI)
- The Adolescent Psychosocial Seizure Inventory (APSI)
- Quality of Life in Epilepsy QOLIE-31 (Version 1.0) Scoring Manual and Patient Inventory. Scoring Manual written by: Barbara G. Vickrey, Keneth R. Perrine, Ron D. Hays, Bruce P. Hermann, Joyce A. Cramer, Kimford J. Meador, Orrin Devinsky (Chair). Copyright 1993 RAND
- Quality of Life in Epilepsy QOLIE-10 (Version 1.0) Patient Inventory and Instructions for Use. Copyright 1993; Professional Postgraduate Services (a division of Physicians World Communications Group). Developed in cooperation with the QOLIE Development Group.

Outlook

Although considerable effort has been put in and success has been made during the last years with outcome measures, the interpretation of published reports on the long-term outcome of patients undergoing epilepsy surgery is still difficult because of several methodological issues. The lack of appropriate standard classification systems for both seizure outcome and quality of life outcome over time is one important reason.

The task to revise Engel's currently already widely used seizure outcome classification is certainly only justified if it is done in an as thoughtful manner as possible, and if it is generally accepted by the entire international epilepsy community. We feel that the ILAE classification has become a useful improvement, though it remains a special effort to calculate outcome on the basis of preoperative seizure days. While for retrospective studies many centers are not able to do this due to lack of preoperative data, or will use it in addition to the current Engel classification, we suggest the ILAE classification to be used for prospective studies, because of its discussed advantages.



n pts

lesional	189	161	140	127	113	98	92	82	73	61	56	52	40	33	23		189
non-lesional	180	170	147	134	121	105	96	87	74	64	55	48	40	34	24		180
curative	326	288	248	226	203	173	159	140	121	101	90	79	61	49	34		326
palliative	43	43	39	35	31	30	29	29	26	24	21	21	19	18	13		43
total	369	331	287	261	234	203	188	169	147	125	111	100	80	67	47		369

Figure 164.2 Year-to-year and last available seizure outcome in patients in ILAE Class 1 (completely seizure and aura free) stratified by lesional and nonlesional mesial temporal lobe epilepsy and by curative and palliative AHE. Lesional indicates gross structural lesion excluding hippocampal sclerosis; nonlesional indicates without visible structural lesion except hippocampal sclerosis and/or atrophy. Years with fewer than 20 patients are not plotted, but these patients are included in the last available (lao) outcome data. Numbers in boxes indicate the numbers of patients in the given year or overall. From Wieser et al., 2003[10] with permission.

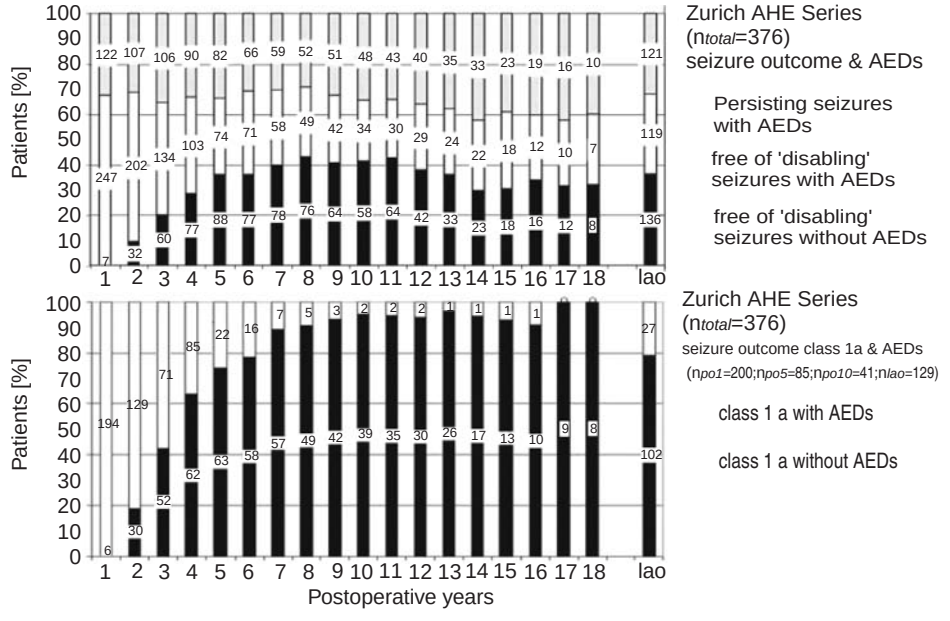


Figure 164.3 Annual distribution of amygdalohippocampectomy (AHE) patients stratified for seizure outcome and AED intake. This update covers the period 1975–2002 with a total of 468 AHE patients. With the requirement of a sufficient follow-up of ≥1 year and after exclusion of 'palliative AHEs' (*n*=43) and normal (*n*=15) or nonconclusive (*n*=16; too small sample size) histopathological findings the sample size consists of *n*=376. Top: Seizure outcome and AED intake for the total of *n*=376. Plotted is Engel Class I (free of 'disabling' seizures) *with* and *without* AEDs and Engel Classes II–IV (persisting seizures; all *with* AEDs). Bottom: Annual distribution of ILAE Class 1a (completely seizure and aura free since surgery) *with* and *without* AEDs. The number of patients in the given year or overall is indicated within the columns, and normalized to 100%. From Wieser and Häne 2003[12] with permission.

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165 Protocol for storage and processing of brain tissue for molecular studies

PB Crino

Introduction

The use of human brain tissue for epilepsy research has rapidly expanded over the past decade. Tissue resected during epilepsy surgery or obtained postmortem from epilepsy patients can provides a new window to view the cellular processes that are involved in epileptogenesis as well as the effects of recurrent seizures or chronic medications on neural systems. Indeed, our understanding of developmental malformations, mesial temporal sclerosis, and tumors has been greatly facilitated by human tissue studies. For many epilepsy syndromes animal models do not exist and human tissue studies provide the only means to learn about how these disorders affect the brain. Perhaps most exciting, however, is that new experimental methodologies to extract genomic DNA and mRNA from archival tissue samples now permits an in-depth analysis of the molecular mechanisms and genetic causes of virtually any inherited or sporadic epilepsy syndrome. With the advent of tissue microdissection an even finer experimental resolution can be gained. My laboratory has over 10 years experience with extraction and analysis of mRNA and DNA from human epilepsy tissue specimens. We have tried numerous protocols and optimization procedures to quantify mRNA expression, perform PCR, and sequence candidate genes; some have succeeded, many have failed. This chapter will provide an overview of the experimental strategies that can be implemented for tissue preservation, storage, and molecular analysis in human epilepsy. The goal will be to demonstrate how archival tissue research can provide exciting new discoveries in epilepsy pathogenesis.[1]

Background: why study genes in epilepsy?

The initial attempts at molecular analysis of human tissue were largely confined to in situ hybridization studies in particular, focusing on mesial temporal lobe epilepsy. These groundbreaking experiments provided pivotal new insights into molecular events that either heralded or followed intractable seizures. Of particular interest were experiments that defined altered expression of the family of immediate early genes such as c-fos in human epilepsy specimens.[2,3] From these results came the notion that seizures were associated with changes in gene and protein expression and furthermore suggested the exciting concept that seizures could alter gene transcription. The ideas that seizures could affect the expression of numerous genes opened a new door in epilepsy research and placed a 'molecular face' on epilepsy. Subsequent studies furthered this notion by demonstrating altered expression genes encoding a variety of candidate molecules including neurotrophins, neurotransmitter receptor subunits, and structural elements.[4–6]

More recently, the development of cDNA or oligonucleotide arrays (for a recent review, see ref. 7) has provided a high-throughput strategy to assay the differential expression of several thousand genes at once. Arrays are simply a solid support medium such as nylon or silica upon which is adhered either short cDNA sequences (oligonucleotides) that are portions of known genes or expressed sequence tags identified in existing gene databases or near full-length sequences of known genes (cDNAs). Arrays are probed with nucleic acid (either cDNA or amplified mRNA) tagged with a radioactive or a fluorescent nucleotide extracted from cells or tissues. Differential hybridization of the labeled DNA or mRNA probe to the oligonucleotide or cDNA sequence on the arrays determines the relative abundance of that gene. The array strategy permits quantification of numerous genes simultaneously so direct comparison of genes across families, functional clusters, developmental epochs, or in response to pharmacological manipulations can be made. The advent of array technology has provided a powerful strategy for evaluating changes in gene transcription in human epilepsy as well as in animal epilepsy models. An added benefit is that while arrays render a broad view of gene transcription, some conclusions can be made regarding altered expression of the encoded proteins. These data can then provide new insights into functional alterations in neurons or astrocytes that relates to epileptogenesis. Perhaps most intriguing is that for many specimens areas of tissue pathology are directly adjacent to morphologically normal tissue, thus providing a unique tissue control for gene analysis or gene sequencing (Figure 165.1).

Cataloging tissue

Most human tissue used in epilepsy research is obtained either directly from a neurosurgeon in the operating room,

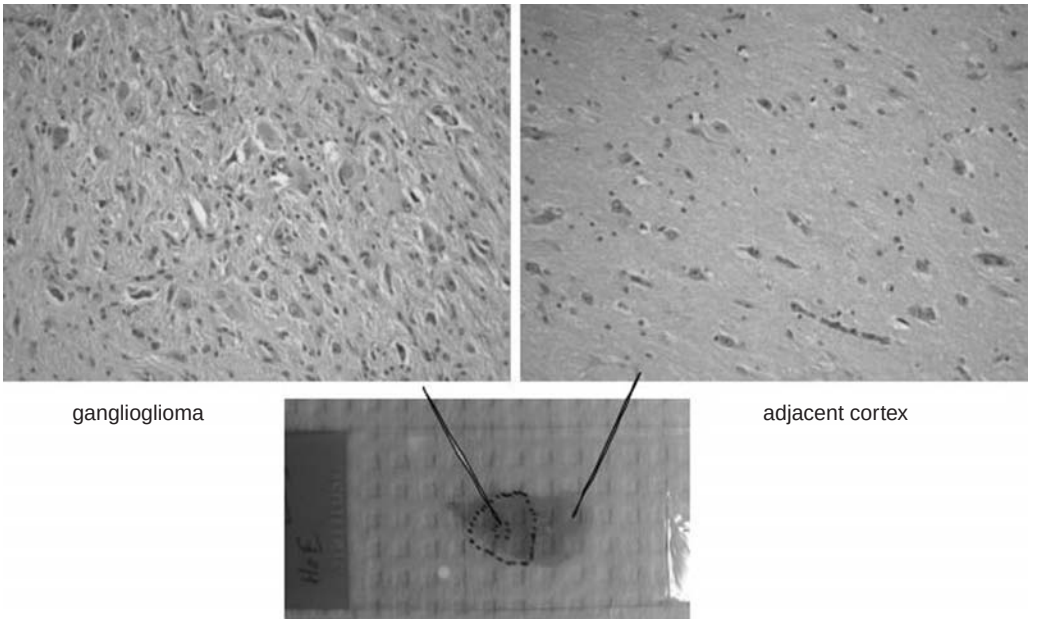

Figure 165.1 Top left, region of ganglioglioma directly adjacent to morphologically normal cortex (top right) resected from epilepsy patient for treatment of complex partial seizures. Tissue on same section (below) can be used en bloc or each region can be dissected for independent analysis (Hematoxylin and eosin stain).

through a pathologist, or from a tissue bank. In many institutions, a diagnostic pathology evaluation of resected tissue is needed prior to the use of tissue for research purposes and in general, removal of tissue directly from the operating room in a prospective paradigm requires patient consent. Retrospective collection of archival material typically does not require patient consent and is often deemed exempt from human studies institutional review. Many gene expression studies in other disorders for example cancers, have relied on tissue directly removed from the operating room. In our experience, procurement of tissue directly from the operating room can be limited by institutional review boards issues or issues relating to diagnostic accuracy in the resected specimens. For example, many pathologists will voice concerns over potentially missing low-grade neoplasms or other relevant pathological features in the tissue that is taken from the operating room. One strategy to surmount this is for investigators to use only the tissue that is needed and return the unused portion to the pathologist. Alternatively, we often have the pathologst 'sign off' on the material immediately after removal.

In view of HIPAA regulations on human research, it is of the utmost importance to maintain patient confidentiality. Unless specific phenotypic parameters are under investigation, investigators must avoid including patient identifying information in their research publications. It should be noted that birthdates, social security numbers, medical record numbers, and pathology/autopsy numbers are considered patient identifiers and thus cannot be used to label tissue in the laboratory. Nonetheless, it remains imperative to have some ability to track samples for a variety of reasons, e.g., collaboration, phenotypic analysis, request for more tissue, and thus a system should be designed for tissue identification and storage of necessary patient information. One strategy to assign each tissue sample a lab-specific number or label so that no member of the lab can identify the sample. A separate strictly confidential information database (for example, Excel) for each specimen is maintained (in duplicate) in a password protected, limited access file. Thus, an investigator can maintain tissue identity for research purposes but protect patient confidentiality. Prior to embarking on human tissue research, it is strongly suggested that investigators meet with appropriate protocol personnel at their home institutions to assure complete compliance with standards for human tissue research.

Tissue fixation and storage

A common myth is that resected tissue used for molecular analysis must be kept frozen or used immediately after removal. While it is true that frozen tissue yields high quality mRNA or DNA, paraformaldehyde or formalin fixed tissue can be used for both DNA and mRNA analysis.[8,9] Perhaps the most optimal situation for tissue analysis is to obtain both fresh, frozen, and fixed material although this may pose logistical procurement problems since specimens must typically be analyzed by a neuropathologist prior to experimental analysis. The use of fixed tissue has particular appeal since molecular analysis can be combined with tissue immunohistochemistry to define for example protein expression or to use protein expression as a phenotypic marker for cell specific mRNA analysis. In addition, it is much easier to obtain archival pathological material stored in paraffin than fresh frozen tissue.

As a general rule, frozen tissue is exquisitely sensitive to transient rise in temperature. Even 10–20°C changes can lead to mRNA and protein degradation over time. Frozen tissue should be maintained at −70°C in a frost controlled freezer. The freezer should have a backup power source with an alarm system should the internal temperature rise above −50°C. Contact persons and appropriate information should be displayed prominently near the freezer in case of emergencies.

A backup freezer should be identified in a nearby lab in case the power should fail to prevent loss of tissue.

In most cases, fixation for pathological preparation uses paraformaldehyde or 10% neutral buffered formalin. These protein cross linking fixatives afford excellent protein fixation but can make extraction of nucleic acids difficult. Boiun's fixative is occasionally used and combines picric acid with formalin and is very stringent. In general we avoid using Bouin's fixed tissue for nucleic acid work. Investigators may have little control over which fixative is used by pathologists, but if given a choice an alternative fixative to a crosslinking compounds is 70% ethanol with 150 mM sodium chloride which permits high yield and quality mRNA for array analysis.[10] Ethanols are denaturing fixatives and thus do not pose significant problems for nucleic acid extraction. In general for small blocks of tissue (less than 2 cm^3), a fixation period of 2–3 weeks may be effective, whereas for larger blocks or for example, whole brains or hemispheres, several weeks will be necessary. One issue that persists is whether there is a fixation time after which DNA or mRNA cannot be extracted from fixed tissue. In our experience, trial-and-error have been the norm and sometimes an initial failure to recover DNA can be overcome by manipulations of various protocols.

Tissue storage for nucleic acid work requires little else than space. DNA is perhaps the most stable biomolecule known and thus breakdown is unlikely even in fixed, paraffin-embedded tissue blocks. We have sequenced through several genes including *PTEN*, *TSC1*, and *TSC2* in genomic DNA extracted from paraffin-embedded tissue blocks stored for up to 5 years. That said, as tissue ages, DNA fragmentation may occur resulting in smaller sequence length available for analysis. DNA fragmentation becomes an issue when longer sequences are necessary to define gene mutations or polymorphisms (see below) or when using DNA to probe array platforms such as single nucleotide polymorphism (SNP) arrays. Paraffin blocks should be kept in cool, dark, dust-free boxes.

Work environment

DNA degradation is uncommon due to lab practice. In contrast to DNA analysis, mRNA work requires more care for success. The major difficulty with tissue-based mRNA experiments is overcoming mRNA breakdown by tissue and environmental RNAses. These ubiquitous enzymes are present in skin oils, expired breath, bacteria, and other benchtop contaminants and can easily degrade even large quantities of extracted mRNA. However, while RNAses have achieved an almost villainous status in some labs, we find that simply making all reagent buffers and solutions in DEPC (diethylpyrocarbonate, a potent RNAse inhibitor) treated water effectively does away with most RNAse contamination. Similarly, all glassware is autoclave sterilized and fresh plasticware is a must. Of course, all mRNA workers should wear gloves and a lab coat. For mRNA work, radiolabeling of the amplified mRNA is frequently necessary. Thus protocol approval and training of personnel by each institution's radiation safety office is mandatory.

Fresh tissue and frozen unfixed tissue is potentially infectious and thus universal precautions (gloves, eye protection, lab coat) should be implemented. While fixation of human tissue largely inactivates most pathogens, i.e., HIV, hepatitis B and C, we implement universal precautions for every day work with fixed human tissue as well. To start with, we make every attempt to ascertain HIV and hepatitis serology status in our patient samples and this data is usually available from existing tissue banks. For those working on epilepsy in association with known human pathogens, communication with institutional safety offices is requisite to insure safe practice for all lab staff. Transmissible spongiform encephalopathies are a particularly serious risk of working with human brain tissue. While it is believed that formalin fixation at least diminishes the risk of lab-related transmission of spongiform encephalopathy, the utmost care must be taken to protect lab personnel. As a general practice, gloves must be worn for *every* instance of contact with human brain tissue, whether it is during microtome sectioning, transfer of slides, or immunohistochemistry. We strongly recommend that investigator review their own institutional policies on working with human tissues and pathogens prior to embarking on human tissue research.

A final word about the work environment relates to responsibility and professionalism. Investigators working with human tissue must maintain respect for those individuals from whom tissue has been procured. While it is easy to look at blocks of tissue as 'data points' or 'sample numbers,' all human tissue specimens used in the lab are obtained following a major surgical procedure or patient death. Thus, each 2 cm^3 tissue block represents significant human suffering. This is especially important when communicating with families or support groups or grassroots funding agencies from whom these patients/tissues may be derived and lab staff should maintain appropriate respect for this fact. Of paramount importance is that the public perception of human brain tissue research can assume a 'ghoulish' overlay if not addressed in the appropriate context and with the necessary facts. Remember that the public may not realize that obtaining tissue from a tissue bank typically requires a processing fee and thus if not discussed openly, can lead to a misperception that tissue is 'for sale'. Similarly, it is vitally important that all human tissue research be approved by each institutional review board and that this approval is kept current. Imagine how the public might respond to learning of a scientist 'buying' brain tissue for 'experimentation without any approval'. Even worse, imagine how this would appear as a newspaper headline.

Extraction of genomic DNA

Analysis of genomic DNA provides a unique opportunity to study gene sequence in human tissue. For example, in monogenic disorders, if the genotype of a particular patient is unknown, it can be determined by direct sequencing of the candidate gene in genomic DNA from a tissue specimen (Figure 165.2). We have accomplished this for several genes in a variety of disorders such as hemimegalencephaly or tuberous sclerosis complex.[9] Of course, unless a lab is certified, results cannot be communicated to the patient or family member, nor can it be used for clinical practice, decision making, or counseling. However, reliable and reproducible results can be determined with published DNA sequence primers for most genes.

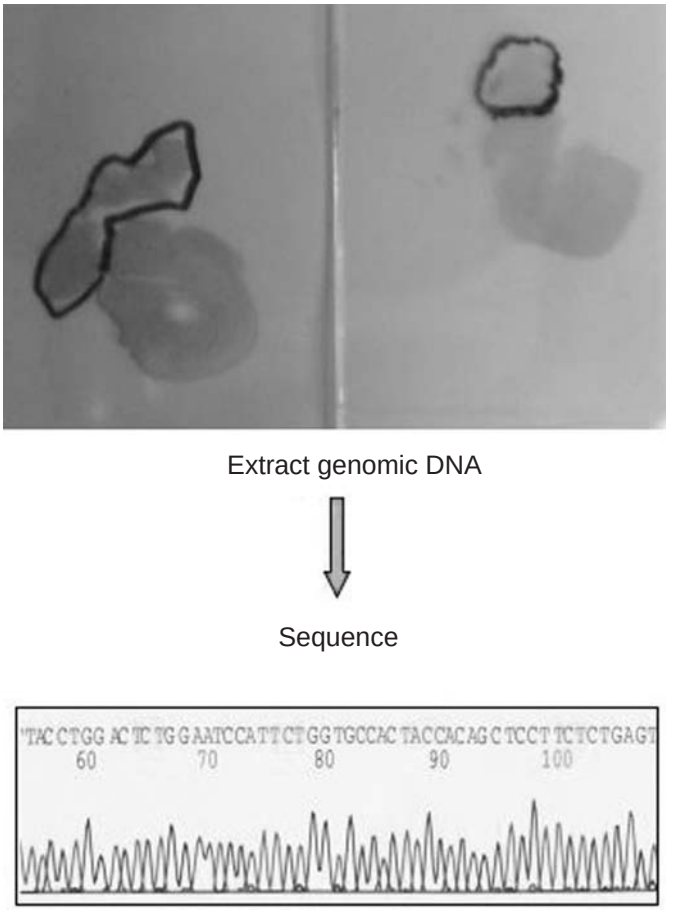

Figure 165.2 Specimen of mesial temporal lobe. Genomic DNA can be extracted from subregions defined by immunostaining (top left, glial fibrillary acidic protein)or morphology (hematoxylin and eosin, top right) and then sequenced to target select sequences.

There are several commercially available kits for DNA extraction. Initial steps in extraction include a Proteinase K step to reverse fixation and permit more effective DNA harvesting. Following Proteinase K, the tissue is treated with Tween or a similar detergent compound. DNA can be extracted with several commercially available kits. The quality of extracted DNA is then assessed by optical density (OD) measurement to determine concentration and purity as well as agarose gel analysis to determine the size of extracted products. An important issue is the quality of extracted DNA since older or poorly fixed samples may yield fragmented or degraded DNA that will be difficult to sequence. Poor quality DNA will appear as an excess of low molecular weight species on the gel. DNA extracted from paraffin embedded tissue can be used for PCR amplification, DNA sequencing and as a probe for DNA arrays including SNP arrays.

Analysis of mRNA in tissue specimens

The analysis of mRNA from fixed human tissue sections[11] provides a unique opportunity to define differential gene expression that may be pivotal in understanding the molecular pathogenesis of human epilepsy. For years, the analysis of gene expression was confined to in situ hybridization studies. The advent of cDNA and oligonucleotide arrays has provided a new strategy to define changes in the coordinate expression of numerous genes in a single experiment. While it is widely believed that gene expression analysis must be performed in fresh or frozen tissue, recent evidence suggests that mRNA analysis can be reliably performed in fixed paraffin embedded tissue. Furthermore, recent advances in microdissection technologies make it feasible to analyze differential expression in select brain regions or even within individual cell types.

The stability of mRNA can be quite variable from sample to sample and often there is degradation due to tissue RNAses. There is reasonable evidence suggesting that mRNA extracted from fresh or frozen tissue may be of superior quality when compared with mRNA extracted from fixed tissue samples. Isolation of mRNA from frozen tissue can be accomplished using one of several available commercial kits. We have used the TRIzol reagent which permits extraction of DNA, total RNA, and protein. The generation of mRNA from total RNA (mRNA, ribosomal RNA, and tRNA) requires annealing an oligo-dT primer to the poly A tail present on all mRNA followed by reverse transcription into cDNA. The cDNA can then be labeled with a radiotag or fluorchrome so it can be used as a probe for cDNA arrays. Alternatively, most commercial labs or university based nucleic acid core facilities will extract polyA mRNA and then generate a labeled cRNA probe for arrays.

In contrast, the extraction of mRNA from fixed tissue specimens requires a bit more technical expertise. A technology devised in the late 1980s known as in situ transcription (IST) provides a reliable strategy to generate cDNA from fixed tissue section mRNA (Figure 165.3).[12] During IST, cDNA is directly synthesized on a tissue section by annealing an oligo-dT(24) primer to tissue mRNA poly A tail overnight at room temperature. IST provided the necessary groundwork to later develop

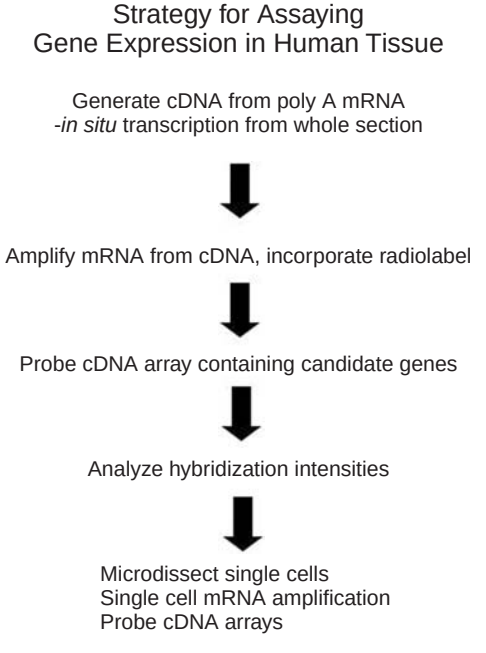

Figure 165.3 Overview of mRNA isolation and amplification strategy for fixed tissue specimens.

the technique of mRNA amplification so that mRNA in single cells could be analyzed. Coupled to the oligo-dT primer, is a promoter sequence for RNA polymerase that will be used in subsequent steps for mRNA synthesis. cDNA synthesized in IST reaction buffer (10 mM HEPES buffer pH 7.4, 120 mM KCl, 1 mM $MgCl_2$, 250 μM dATP, dCTP, dGTP, TTP) with avian myeloblastosis reverse transcriptase (AMVRT). Sections are washed in 0.5X SSC buffer. The cDNA can then be directly extracted from the section with sodium hydroxide and potassium acetate. The extracted cDNA from whole sections can be labeled with a radioactive or fluorescent tag to probe cDNA arrays. Alternatively, the extracted cDNA can be used to isolate or quantify mRNA by RT-PCR.

More recently, technologies have been developed to quantify mRNA in single cells.[8,11,13–15] This approach has in many ways revolutionized our ability to understand gene transcription in numerous disease states, i.e., epilepsy, Alzheimer's disease, Parkinson's disease, and HIV, and especially those with cell specific pathology. Single cell mRNA can be obtained from cells in culture, i.e., dissociated or tissue slice, or from fixed paraffin embedded tissue sections. For live cells, mRNA analysis can be combined with electrophysiology to provide a comprehensive view of cell function from gene expression to changes in cell firing. In live cells, a patch electrode can be used to aspirate the cytoplasm and transfer the contents into a microfuge tube for further reactions. In fixed cells in culture or tissue sections, single cell mRNA analysis provides an opportunity to analyze gene expression in a population of phenotypically defined cells, whether by protein expression using immunohistochemistry, or by cell morphology. Recent studies have demonstrated that mRNA can be extracted from single cells undergoing apoptosis identified by TUNEL.[16,17] Single cells may be microdissected from sections using a joystick driven microscalpel or by laser capture (Figure 165.4). Successful quantification of single cell mRNA has been achieved using the microscalpel technique whereas mRNA analysis in laser captured cells requires that a number of cells be harvested.

Following aspiration or microdissection, single cell mRNA amplification is performed in a microfuge tube with reagents that are commercially available (Figure 165.5). In the initial step, the oligo-dT-T7 promoter primer is hybridized to the dissected cell followed by cDNA synthesis with reverse transcriptase. cDNA synthesis is performed (oligo-dT(24)-T7 primer, 10 mM HEPES buffer pH 7.4, 120 mM KCl, 1 mM $MgCl_2$, 250 μM dATP, dCTP, dGTP, TTP with AMVRT) and then double-stranded template cDNA is generated with T4 DNA polymerase I (Boehringer-Mannheim). The double-stranded DNA is phenol:chloroform extracted and ethanol precipitated prior to use as a template for mRNA amplification. mRNA is amplified from the double-stranded cDNA template with T7 RNA polymerase. Unlike extraction of mRNA from whole tissue sections or from tissue homogenates, single-cell mRNA analysis requires an amplification step to generate sufficient quantities of mRNA for experimental analysis. It is imperative that the amplification kinetics be linear so that there is equal amplification of both low- and high-abundance mRNA in each cell. If not, then there may be an under- or over-representation of a particular mRNA based on its relative level of expression. The use of T7RNA polymerase, driven by a T7 promoter provides for linear synthesis of mRNA from double-stranded cDNA. Because the enzyme has high affinity for its promoter, each double-stranded DNA can be primed repetitively as a template for mRNA synthesis, culminating in an amplification of the copy number for any given mRNA. The reactions necessary for mRNA synthesis from cDNA are repeated, resulting in a 10^6-fold amplification of single cell mRNAs. Amplified mRNA serves as a template for a second round of cDNA synthesis with AMVRT and dNTPs, that is primed with N(6) random hexamers (Boehringer-Mannheim). cDNA generated from amplified mRNA is made double-stranded and serves as template for a second mRNA amplification incorporating ^{32}PCTP. Radiolabeled mRNA incorporating ^{32}PCTP is used to probe cDNA arrays.

Candidate gene expression analysis and cDNA arrays

In our lab, we have successfully probed arrays with nucleic acid extracted from human epilepsy specimens. These array

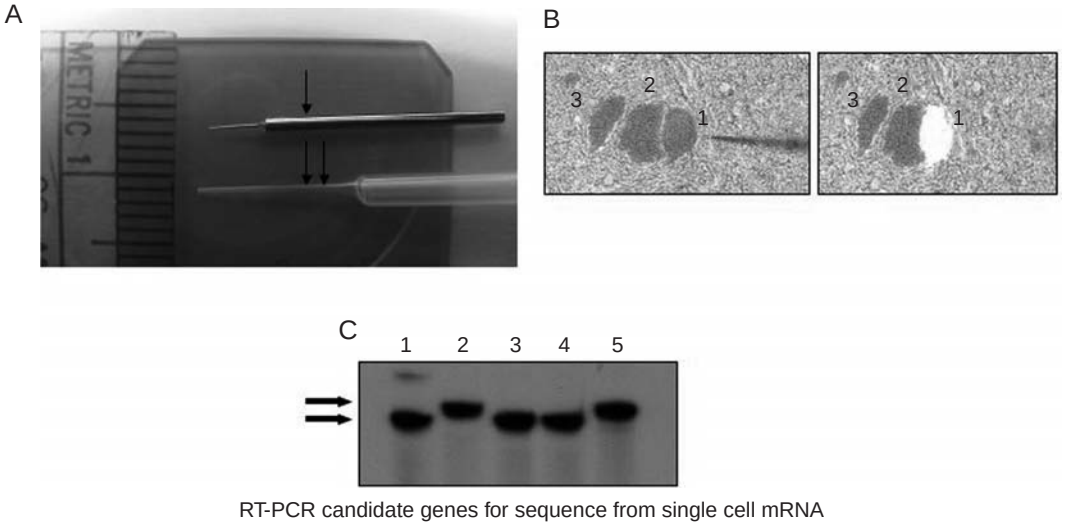

Figure 165.4 A, stainless steel microscalpel used to dissect single cells (arrow). Micropipette used to aspirate dissected single cells (double arrow). B, dissection of single immunolabeled cells from epilepsy tissue specimen. C, RT-PCR amplification of distinct genes from single microdissected cells in B.

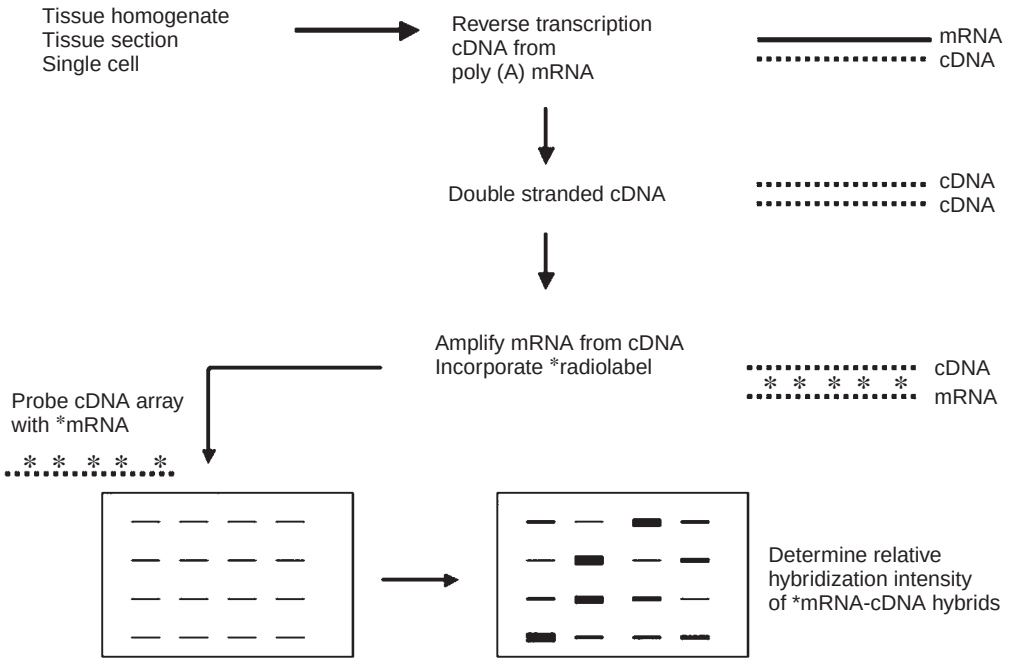

Figure 165.5 Schematic depiction of mRNA amplification procedure from human tissue specimens. On bottom right, different sized lines depict differential hybridization intensity of tissue mRNAs to cDNAs on the arrays (see also Figure 170.6).

platforms have lab-generated macroarrays (containing about 50 cDNAs),[19] small-scale commercial cDNA macroarrays (about 100 cDNAs),[9] and commercial arrays containing several thousand genes of interest. Lab-generated and some commercial arrays contain linearized, full-length plasmid cDNAs encoding genes of interest which are obtained by PCR or through collaborative efforts (Figure 165.6). The cDNAs are UV-crosslinked to the membrane. Analysis of larger scale commercial arrays such as those from Affymetrix or Agilent is not feasible with single cell mRNA and requires that mRNA amplified from multiple single cells or a tissue homogenate be used as a probe. As a general rule, arrays are screened in duplicate. 'Housekeeping genes' such as β-actin or GAPDH are included as to serve as positive hybridization controls. pBlueScript (PBS) and pUC18 plasmid cDNAs are used to define background levels of hybridization on each array platform. In our lab, a small arrays are hybridized with the radiolabeled mRNA probes for 24 hours in 6X SSPE buffer, 5X Denhardt's solution, 50% formamide, 0.1%SDS, and salmon sperm DNA 200 μg/ml at 42°C and then washed in 2X SSC.[18,19] Probed cDNA arrays are apposed to film or phosphorimage cassette to visualize the hybridization (Figure 165.6).

Troubleshooting

Often investigators new to nucleic acid work will try a protocol for mRNA extraction only to meet with failure and then frustration at repeated attempts. RNA work can be tricky and even experienced labs may have difficulty. First, make certain that the work environment is RNAse free and that all reagents, plasticware, and glassware are sterile and RNAse free. Wash all glass in DEPC-treated water and make as many reagents as possible in DEPC-treated water. Most commercially obtained enzymes are RNA free as are buffers and NTPs/dNTPs.

A second possibility is that there has been degradation of the mRNA in the tissue sample. This problem can be assessed in several ways. First, try to amplify mRNA from a whole tissue block to be sure that there is enough initial template for the polyA to bind the oligo-dT. Following the amplification and radiolabeling step, run an aliquot of the RNA on a 1% agarose denaturing gel, blot it, and appose it to film to determine if there is any mRNA. Alternatively, attempt to PCR amplify a high abundance message from the synthesized double-stranded cDNA compared with a known control sample. Finally, the tissue section can be stained with acridine orange, a fluorescent dye that labels single-stranded nucleic acids in cells (like mRNA). Cellular mRNA should glow a bright orange whereas DNA appears bright green.

If it appears that there is adequate mRNA for amplification, try to modify the reaction protocol. For example, fixed tissue sections can be treated with triethanolamine or 0.1N NAOH prior to oligo-dT hybridization. Alternatively, increase the concentration and exposure time for the Proteinase K and further diminish crosslinking fixation. The initial reverse transcription time can be increased to 24 hours to enhance cDNA synthesis. Similarly, the RNA polymerase step can be lengthened to 8 hours. If these measures are not helpful, it may be prudent to visit a lab that regularly performs mRNA analysis in human tissue. A full protocol is available on request from my laboratory.

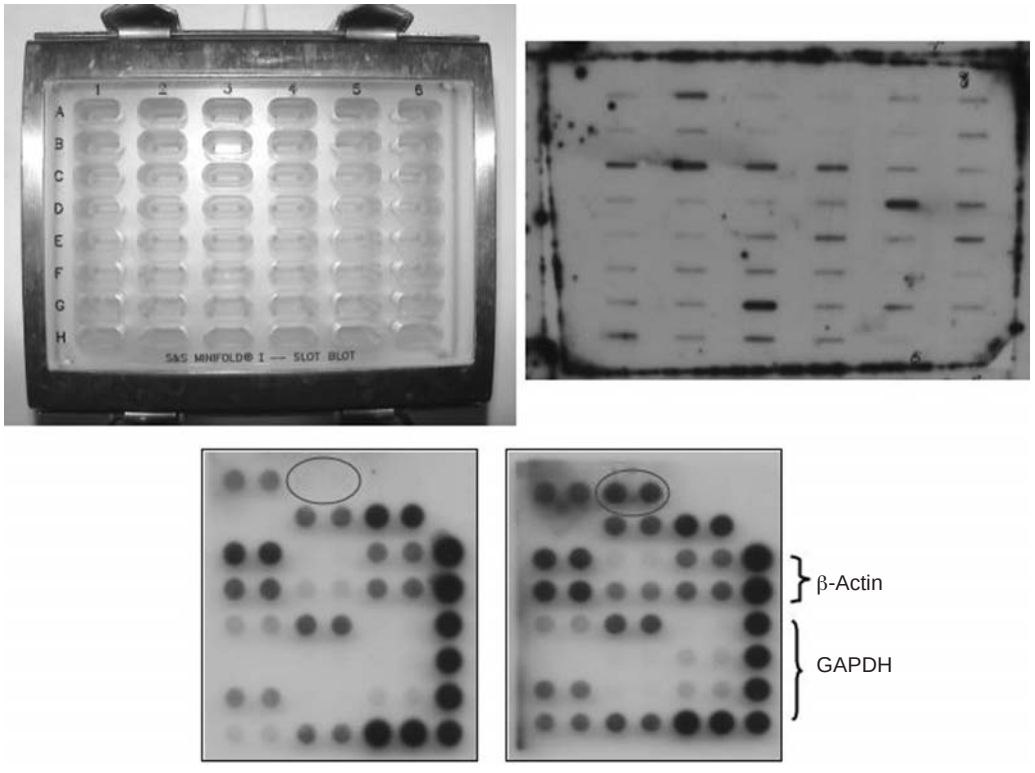

Figure 165.6 Candidate cDNA arrays used for gene expression analysis. Top left, plexiglass 'slot blot' apparatus. A single cDNA is placed in each well or slot that overlies a piece of nylon membrane. The membrane is dried and the cDNAs are UV-crosslinked to the membrane. When probed with radiolabeled mRNA, there is differential hybridization to select candidate cDNAs (top right; compare with schematic in Figure 170.5). Bottom, commercial cDNA arrays containing candidate cDNAs. Left, control tissue hybridization and right, array probed with cDNA from hemimegalencephaly specimen. Note differential hybridization of one gene pair (oval). Two genes, β-actin and GAPDH, are included on the array as 'housekeeping' genes to assess overall hybridization levels.

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