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Epilepsy Surgery: Principles and Controversies

edited by

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To our wives, Chiyen and Marnie, for years of understanding, support, and encouragement, and our teachers, George Ojemann and the late Sidney Goldring, whose pioneering work in epilepsy surgery has benefited generations of physicians and patients.
Great progress has been made in the treatment of epilepsy over the past 75 years. Although medication remains the first step when seizures begin, in some circumstances surgery is a superior remedy. For those in whom surgery is the right thing to do, all too often the person is not told about the surgical option and spends years experiencing recurrent seizures, dealing with adverse effects of medications, and accruing the mental and psychosocial handicaps engendered by repetitive seizures. The severity and impact of these handicaps are underappreciated, in part because the problems appear gradually over years and decades. When the epilepsy begins in childhood, the handicaps materialize insidiously from stagnation of development rather than overt regression or loss of previously acquired ability and knowledge.

The work of Sillanpää and colleagues documented how costly years of unrelenting seizures can be. They followed a large cohort of Finnish children with epilepsy for more than three decades. Twenty percent died, mostly due to seizure-related causes. Survivors who were still having seizures had substantially reduced educability, reduced chance of finding a life partner, a twofold heightened risk of being childless, and a threefold risk of being jobless.

Although surgery is no panacea, many people for whom epilepsy surgery is the superior option never consider it or do not consider it early enough. As a result, surgery remains underutilized.

Given the great progress with and proven effectiveness of epilepsy surgery, why is it not used more readily and more extensively? Several reasons come to mind. A main one is the lack of knowledge and acceptance among professionals about the role and efficacy of epilepsy surgery. Culturally based fears and misconceptions about epilepsy are shared by some professionals and laypersons alike. Similarly, many professionals are reluctant to embrace brain surgery as an elective treatment for a chronic condition like epilepsy. Other likely contributors include lack of financial resources and lack of access to care. However, a major barrier is the lack of awareness of the role and benefits of epilepsy surgery among professionals who treat epilepsy.

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The mystery, uneasiness, and misconception that have historically shrouded epilepsy continue today. In the past, people with epilepsy have been variously reviled and revered, depending on the cultural context of seizures and on how the culture interprets epilepsy. Hippocrates, writing on epilepsy in 400 B.C., argued that epilepsy was not sacred but rather the consequence of natural brain afflictions. Hippocrates’ insight notwithstanding, causation(s) of epilepsy long went undefined, and over the millennia the condition was attributed to demonic possession, divine possession, over-active libido, and other supernatural factors. Today, misconceptions about the cause of seizures persist among the isolated and uninformed, as was eloquently articulated by Anne Fadiman’s 1998 book *The Spirit Catches You and You Fall Down*.

Convulsions are so dramatic and frightening to behold that they predictably spawn apprehension and alarm. Parents of children who witness their child’s first convulsion are terrified and fear for their child’s life. Even after witnessing tens or even hundreds of seizures, most parents never come to view their child’s seizures with equanimity. During the pre-surgery, pre-antibiotic era, before the days of imaging and skilled neurosurgery, the onset of seizures often represented preterminal, end-of-life events. Seizures that occur in public are sure to disrupt. One of the names the Romans gave to epilepsy was *morbus comitialis*, indicating that epileptic attacks spoiled gatherings of the people. Today a convulsion in a physician’s waiting room exerts a predictably disruptive impact.

Nonconvulsive seizures elicit more varied reactions, misunderstandings, and complex cultural rationalizations about what the cause might be. Although they are less intrusive, over time they too are hazardous and accrue the psychosocial consequences enumerated above. In this setting, when the inevitable question “Do repeated symptomatic nonconvulsive seizures hurt the brain?” comes up, the answer is yes. Yes they do.

Whereas seizures disrupt on an unpredictable timetable, are certain to evoke reactions from bystanders, and are loaded with cultural implications, the burden of epilepsy is intensely personal. It is personal for those who have it; for their friends, lovers, and family; and for the professionals who care for them. Strong personal relationships develop between patients and their physicians and between physicians and their mentors and teachers. There can be little doubt that the repeated partial seizures of Hughlings Jackson’s wife attracted and held his attention to epilepsy and stimulated his eventual discernment of how the brain works.

People with epilepsy and their families often face difficult choices deciding which treatment to choose. Strong partnerships evolve as patients, families, and physicians consider options and make tough decisions. These include choices of medications, the extent to which activities should be restricted, and whether to undergo surgery for epilepsy. These types of decisions become easier to weigh as the alternatives and risks are clear: when the boundary between what is known and what is unknown has been charted. Joined by expert coworkers, colleagues, and mentors, John Miller and Dan Silbergeld have identified the key landmarks in the surgical treatment of epilepsy and point the way to territory where the exploration is incomplete.

This book is important for several reasons. It is thoughtful and well focused. It addresses pivotal questions and identifies areas in need of ongoing refinement. The point-counterpoint format for illuminating controversy frames areas where

\(^b\) And many cases still go undiagnosed and undefined.
alternative approaches exist and where no particular protocol has emerged as the best. However, the real reason the book is so important draws from the impact that well-executed epilepsy surgery can have on the lives of those for whom it is the best treatment.

A few months ago at Sidney Goldring’s memorial service, a letter from one of his former patients was read aloud. The passages that follow are excerpted with permission from the author, and her words demonstrate why this book and the work that is related to its contents are so important.

I am writing to thank you for the impact that you have had on my life. I have met many people who have influenced me and touched my life, but you changed my life profoundly. When you operated on me, it made so many other things in my life possible. My grades in college began to soar. Once I wasn’t having 15 seizures a day I had more energy and was able to concentrate more. I completed my Bachelor’s and Master’s degrees. I am now working as a therapist in an in-patient psychiatric clinic. I will be changing to an out-patient position within a matter of weeks. I have been living and working here in Charlotte for about ten years now. I bought a house two years ago and I am enjoying responsibilities of home ownership. Although I am not married and have no living children, I am “happily single” at this point. Looking back I never dreamed that I would live this long, even though the surgery went beautifully. Here I am after eighteen years still going strong.

It seems impossible to find the right words to thank you for what you have done for me. Thank you for overcoming whatever challenges you may have faced over the years. I am a life that was changed. I am forever in your debt and forever grateful. I hope this letter somehow gets to you and finds you doing well. Thank you again.

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Preface

Epilepsy is one of the most common neurological disorders. Nearly all patients with recurrent seizures receive medical management, and many respond well, but seizures in more than one-quarter of patients are not adequately controlled, and patients suffer long-term morbidity, disability, and underemployment as a consequence. Neurosurgical intervention is the best treatment for many of these medically intractable patients. Over the past 50 years, neurosurgical treatment of epilepsy has become progressively more sophisticated, and more widely available, so that there are now hundreds of specialized epilepsy surgery centers around the world, as well as a broad consensus on the fundamentals of selecting surgical candidates, performing the presurgical evaluation, and techniques of the surgical resection. Although several very excellent and comprehensive books on epilepsy surgery exist, this book takes a different approach. In addition to presenting the current state of the art, we highlight the evolving and unresolved questions in epilepsy surgery, and in this way bring out the limitations of current techniques and future directions the field must take.

Significant controversies exist regarding almost every aspect of epilepsy surgery. Human epilepsy is an extraordinarily diverse condition. It has many underlying etiologies, with seizures arising from many different regions of the brain. The presurgical workup aims to determine the site of origin of a patient's seizures (“the epileptogenic zone”), and to determine if that region can be safely removed without injury to brain regions that mediate key neurological functions (“essential cortex”). The methods we have to do this are imperfect, and a successful outcome is not assured. Because of this, epilepsy surgery is constantly evolving, with new technology to better locate the epileptogenic zone and essential cortices being continually introduced or perfected, and new surgical approaches being developed to improve outcome and make neurosurgical treatment available to more patients.

In addition, there have been few definitive clinical trials of neurosurgical therapies. A controlled, randomized study of temporal lobectomy has been performed and confirms the superiority of surgery over continued medication trials in these intractable patients. The unfavorable natural history of intractable epilepsy has been well characterized, and the benefits of surgery in optimal candidates are so dramatic that these findings are not surprising. However, many other questions, for example, the relative merits of the standard temporal lobectomy and the selective amygdalohippocampectomy, involve
much smaller alleged outcome differences and cry out for randomized studies. As this text will make evident, clinical trials of surgical therapy are extraordinarily difficult to design and execute, and Class I evidence has rarely been obtained. As a result, ongoing controversy will continue to be inherent to the field.

The backbone of the book is a series of reviews of steps in the comprehensive process of epilepsy surgery, from selection of surgical candidates to the presurgical workup through techniques of the resection itself, assessment of outcome, and on to postoperative rehabilitation and vocational training. Each section is followed by a series of essays on controversies regarding many of the topics reviewed. Diverse opinions were solicited from experts who have published on the contested topic. Sometimes these editorial chapters present starkly divergent viewpoints; more often they are parallel and converge from different viewpoints to find common ground. These chapters represent current opinion as of 2005 but will continue to evolve after publication. The book ends with a section on investigational techniques and therapies.

The heart of every comprehensive epilepsy surgery program lies in the multidisciplinary case conference where neurologists, neurosurgeons, neuropsychologists, neuroradiologists, rehabilitation specialists, and others collaborate to make surgical decisions. Each specialty contributes its own skills and insights to the meeting to develop an understanding of the significance and limitations of the presurgical data and predict the chances of seizure control with the proposed procedure and the implications of the probable outcome for an individual’s life. The complexity of this process arises not only from the controversies inherent to the subject, but also from the diversity and heterogeneity of human epilepsy. Frank and lively discussions often lead to the realization and acknowledgment of the limitations of both diagnostic methods and the scientific evidence upon which surgical decisions are made. Often, new investigations and clinical trials result from these debates. This text was inspired by this intellectual excitement of the epilepsy surgery conference. We hope that it will bring new insights to all who treat epilepsy.

John W. Miller, M.D., Ph.D.
Daniel L. Silbergeld, M.D.
Acknowledgments

The editors would like to express their appreciation for the many individuals who aided in the conception and creation of this book. We would especially like to thank Jinnie Kim, of Taylor & Francis, who shared in the conception and planning of this volume over several years. It could never have occurred without her patience and guidance. We would also like to thank our colleagues around the world for their suggestions and advice—most, ultimately, became contributors. Finally, we would also like to thank Paula Garber of The Egerton Group, production editor of this text.
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Part One

Who Is a Surgical Candidate?
INTRODUCTION

Epilepsy has been known to mankind since the earliest civilizations. Effective pharmacological treatment has been available since the latter half of the 19th century, following the discovery of the anticonvulsant properties of the bromides. The number of antiepileptic drugs (AEDs) has slowly increased throughout the 20th century, thanks mainly to serendipity. In the 1990s, drug discovery programs saw nine new chemical entities with novel mechanisms of action added to the therapeutic armamentarium. Over the same period, our understanding of the natural history and prognosis of epilepsy has progressed at a rapid pace. There are convincing epidemiological data to show that over 30% of patients will never achieve lasting control of seizures with AED therapy (1–4). There is, however, no consensus as to what constitutes drug-resistant epilepsy. In epidemiological studies, authors have defined pharmacoresistance differently in terms of number of AED regimens and time since diagnosis (5–9). The terms “refractory epilepsy,” “intractable epilepsy,” “drug-resistant epilepsy,” and “pharmacoresistant epilepsy” are used interchangeably in this context. Whichever term is employed, it encompasses a multidimensional disorder in which intractable seizures cause deleterious neuronal plasticity with progressive cognitive decline, multifactorial psychosocial dysfunction, impaired quality of life, and increased morbidity and mortality (10).

Defining pharmacological intractability is of great importance in deciding the timing of epilepsy surgery in suitable patients. Its irreversible nature, together with fear of complications, induces a natural degree of reluctance in patients and doctors alike who tend to consider surgery as an acceptable option only when all pharmacological strategies have been exhausted. This perception of epilepsy surgery as a “last resort” has resulted in patients suffering seizures unnecessarily for many years (11–13). Defining a situation where additional medical treatment is unlikely to be successful will help optimize the timing of surgery as well as facilitate pharmacological decision making.
The term “epilepsy” covers a wide range of disorders with the common symptom of recurrent unprovoked seizures. The issue of pharmacological intractability is intricately linked to prognosis for each epilepsy syndrome (14). Our understanding of the natural history of the different syndromes, however, is incomplete. Benign epilepsies with onset in childhood usually, but not always, have an excellent prognosis and many patients enter remission regardless of AED treatment. Juvenile myoclonic epilepsies often respond well to AEDs, but have a high rate of recurrence if treatment is withdrawn (15). The long-term prognosis of adult-onset epilepsy is less clear. Data from longitudinal studies suggest that patients largely fall into two categories—those entering remission early and those remaining refractory from the outset (4,16,17). In a recent study in patients undergoing temporal lobectomy for refractory epilepsy, 26% and 8.5% had a history of one and five years remission, respectively (18). Thus, there appears to be a small group of patients in whom the seizure disorder displays changing behavior over time. Nonetheless, in the majority of patients, the early course of epilepsy is a reliable indicator of the long-term outcome (19–21).

AIMS OF TREATMENT

The definition of “intractability” is easier to arrive at if the aims of treatment are clearly defined. The ideal outcome is complete control of seizures with no adverse drug effects, enabling individuals to return to full, productive lives consistent with their innate abilities. Many people in whom complete seizure control is not achieved are able to maintain a near normal lifestyle with only minimal restrictions. This concept of “acceptable control” aims at limiting the number and severity of seizures but with a tolerable drug burden and few side effects. Acceptable seizure control in such situations may depend on the patient’s expectations and the epilepsy syndrome, but should be regarded as an option of last resort. Academic achievement and intellectual development were significantly improved in children whose seizures were well controlled (22,23). Even relatively infrequent mild seizures can impact adversely on quality of life (24). In some severe epilepsy syndromes of infancy and childhood associated with neurological morbidity and intellectual impairment, however, complete seizure freedom will often be an unrealistic expectation (25). In adults, the onset of epilepsy results in loss of driving privileges and restricted employment options. Reversing these requires demonstration of complete control of seizures over an extended period of time in most countries. Seizure freedom is thus the all-important treatment goal for every patient.

PSEUDO-INTRACTABILITY

Patients fail pharmacotherapy for a variety of reasons. Erratic adherence to treatment, diagnostic error, failure to attend for follow-up, and lifestyle factors can all contribute to a poor outcome. While these individuals can be considered treatment failures, they are not pharmacoresistant. Pharmacoresistance should be diagnosed only in patients who have a secure diagnosis of epilepsy, have failed a range of appropriate AEDs at adequate dosages, and adhere religiously to their treatment regimens.

Failing to respond to appropriate doses of the first or second AED should call for, in the first instance, prompt review of the diagnosis (26). Common diagnostic
pitfalls include non-epileptic attack disorders (NEADs) and incorrect classification of seizure types or epilepsy syndromes. Video-electroencephalogram (EEG) monitoring is the only reliable method by which accurate diagnosis and classification of the epilepsy can be carried out, and this technique should be made available to all patients failing drug therapy before epilepsy surgery is contemplated. NEADs are common and constitute a large proportion of cases referred for evaluation (27,28). Diagnosis can be challenging as NEADs often coexist with epilepsy, or may develop as substitutes for seizures once the epilepsy is controlled (29). Psychological factors, such as anxiety or stress, physical and sexual abuse, and dysfunctional relationships, are present in the majority of patients (30). Episodes are often triggered by emotional factors, usually witnessed by family or friends, and are characterized by variable, semipurposeful movements and rapid recovery. Syncope can also cause convulsions, which may be mistaken for epileptic seizures (31). Reflex anoxic events are often provoked by pain, anxiety, or on assumption of upright posture and are commonly preceded by facial pallor, visual symptoms, and diaphoresis. Tilt table testing can aid diagnosis. Cardiac investigation to exclude potentially serious arrhythmias, such as prolonged QT syndrome, may be indicated in some cases.

Erroneous classification of seizure types and epilepsy syndromes can result in unsuccessful pharmacological treatment. Physicians are often reliant on descriptions given by third parties to arrive at a diagnosis. Subsequent errors, e.g., generalized absences misdiagnosed as partial seizures, can lead to inappropriate drug selection. The wrong choice of AEDs can worsen control of some seizure types. Carbamazepine, phenytoin, gabapentin, and tiagabine, for instance, can all exacerbate myoclonic jerks and generalized absences (32). Video-EEG monitoring will facilitate accurate classification of seizures and rationalization of drug therapy in doubtful cases.

Non-adherence to medical treatment can be an insidious factor resulting in therapeutic failure. This problem may be present in up to 50% of patients attending epilepsy clinics and can be assessed by asking patients about medication-taking habits, by measuring serum drug concentrations, and by using automated monitoring devices (33). If the variability among three serum trough concentrations at steady state is less than 20% to 25%, good compliance can be assumed (33). AED treatment is often lifelong and so patients may miss the occasional dose. Abuse of alcohol and recreational drugs can cause seizures and non-adherence to AED treatment. Similarly, sleep deprivation and stress are common precipitants. Social and lifestyle factors should, therefore, be taken into account when evaluating the efficacy of drug treatment. Good motivation is needed to continue treatment lifelong, and this can depend on the perceived adverse consequences of further seizures and the presence or absence of side effects. Thus, effectiveness of AED treatment is determined by both efficacy and tolerability (34).

REFRACTORY EPILEPSY—PROGRESSIVE OR DE NOVO?

Whether drug resistance occurs de novo in patients with epilepsy or arises as a result of repeated seizures is a subject of debate. The concept that “seizures beget seizures” was introduced by Gowers in the 19th century and was reinforced by the writings of Rodin in the 1960s (35,36). A long history of epilepsy and high numbers of pretreatment seizures were thought to correlate with a poor outcome. This view was supported by Reynolds and colleagues in the 1980s and early treatment of seizures was considered the key to preventing the emergence of drug-resistant epilepsy (37,38).
Repeated seizures have been shown to result in neuronal loss and mossy fiber sprouting in the hippocampus, which in turn can cause more seizures by forming excitatory recurrent circuits (39–41). Neuropsychological studies have shown cognitive decline in patients with refractory epilepsy, the severity of which can be correlated with duration of epilepsy (42). Cross-sectional magnetic resonance imaging (MRI) studies have demonstrated smaller hippocampal volumes ipsilateral to the seizure focus in patients with temporal lobe epilepsy and uncontrolled seizures (43,44). Longitudinal studies employing repeat MRI of the brain have demonstrated progressive hippocampal and temporal neocortical volume loss and have suggested that neuronal loss correlates with number of seizures (45,46). Thus, in mesial temporal lobe epilepsy, hippocampal sclerosis appears to be both the cause and consequence of seizures.

On the other hand, studies in patients sustaining 100 or more generalized seizures before seeking to medical attention have shown that a similar proportion go into remission as patients treated after suffering only a few seizures (47). Moreover, treatment with AEDs after the first unprovoked seizure does not affect the long-term outcome despite preventing more seizures in the short term (48–50). In our own series of 780 patients with newly diagnosed epilepsy, duration of epilepsy did not have a bearing on eventual outcome. Several studies have demonstrated a relationship of high initial seizure frequency with poor outcome (36,38,51–53). However, detailed analyses of data from observational studies have suggested that this is true only for patients suffering complex partial seizures (54). It is likely that the epileptogenic process responsible for the high frequency of partial seizures is inherently pharmaco-resistant (4).

CAUSES OF DRUG RESISTANCE

Despite advances in the field of cell biology, our understanding of the processes of epileptogenesis at the molecular, cellular, and tissue levels remains incomplete. A few well-defined epilepsy syndromes of infancy and childhood have a clear genetic basis (55). These usually result in altered ion channel structure and may be associated with catastrophic epilepsy (56). The nature of the underlying lesion has a strong influence on the prognosis (57,58). Hippocampal sclerosis (HS) and disorders of neuronal migration are commonly found in patients with drug-resistant epilepsy, as are cerebral tumors and serious head trauma. Why such lesions result in hyperexcitability of neurons and hypersynchronized discharge of a large number of neurons in these individuals, however, is not fully understood. Several hypotheses have been proposed (59). These include ontogenic abnormalities in brain maturation, alterations in neuronal networks and glial properties in seizure-prone areas, and the phenomenon of kindling and reorganization of cortical tissue in response to seizure-induced disturbances in oxygen supply.

HS is the most common pathological finding in temporal lobe epilepsy in surgical studies. Indeed, it is the most common underlying cause for medically refractory temporal lobe epilepsy (57,58,60). HS is characterized by tissue shrinkage, cell loss, and reactive gliosis in all hippocampal subfields as well as the entorhinal cortex. This process may be triggered by an initial precipitating injury, such as febrile convulsions (61,62). The characteristic features on MRI are an atrophic hippocampus, increased signal on T2 weighted images and fluid attenuated inversion recovery (FLAIR) sequences, and decreased signal on inversion recovery sequences (63,64). HS coexists with a second pathology, most commonly cortical dysplasia, in a small proportion of cases (60,65).
Disorders of cortical development have been increasingly recognized as a cause of epilepsy. In recent years, there has been a greater understanding of their genetic bases, clinical presentations, and the mechanisms of epileptogenesis (66). Lissencephaly, the most severe abnormality of neuronal migration, is characterized by absent (agyria) or decreased (pachygyria) convolutions. Subcortical band heterotopia (SBH) is at the mild end of the agyria–pachygyria spectrum and shows simplified gyral pattern with increased cortical thickness. Bilateral periventricular nodular heterotopia (BPNH) consists of confluent and symmetrical subependymal nodules of gray matter located along the lateral ventricle, particularly along the ventricular body. These lesions have high intrinsic epileptogenicity (67). The epileptogenic zone often extends beyond the visualized area, and intraoperative electrocorticography may be required to ensure adequate resection.

Intracranial mass lesions, particularly low-grade gliomas and gangliogliomas, can be identified in approximately 15% of patients with intractable epilepsy (68). Dysembryoplastic neuroepithelial tumors are an uncommon cause of epilepsy in young people (69,70). Modern imaging techniques allow accurate characterization of structural lesions, but histological diagnosis may be required to exclude malignancy.

Inflammatory disorders affecting the brain often cause refractory epilepsy. Encephalitis usually produces neocortical epilepsy. However, both encephalitis and meningitis can result in HS if they occur early in life. The risk of epilepsy is greater in patients with residual neurological deficits (71). Infections and infestations are important etiological factors in the developing world. Neurocysticercosis is widely prevalent in Latin America, Asia, and sub-Saharan Africa. It is thought to be the most common cause of acquired epilepsy, although no studies have examined its relative contribution to all incident cases (72). Prognosis for seizure control in neurocysticercosis is usually good and many patients are able to stop AEDs after successful antihelminthic treatment (73). Nevertheless, its preventable nature offers the opportunity of reducing the disease burden of epilepsy in developing countries.

Autoimmune mechanisms, both cellular and humoral, may be associated with seizure production. Rasmussen's encephalitis, a rare disorder mainly of children, is characterized by intractable partial seizures, unihemispheric inflammation with progressive neurological deficit, and association with antibodies directed against the glutamate receptor GluR3. It may respond to treatment with intravenous immunoglobulins and other immunomodulants, but some patients require radical surgery for control of seizures. Autoantibodies directed against GluR3 receptors may also be found in patients with partial epilepsy who do not meet the diagnostic criteria for Rasmussen's encephalitis (74). Patients with other autoimmune conditions, such as systemic lupus erythematosus, are at increased risk of developing epilepsy (75). Higher prevalence of glutamic acid decarboxylase, anticardiolipin, and antinuclear antibodies has been reported in patients with epilepsy compared to controls (76–78). Immunologic mechanisms, however, appear to play a causative role in only a minority of patients with pharmacoresistant epilepsy.

**DRUG TRANSPORTER PROTEINS**

Patients with pharmacoresistant epilepsy are, by definition, resistant to all AEDs. This raises the possibility of a common mechanism. Their possible extrusion from the intended site of action by multidrug transporter proteins has received much attention in recent years. Multidrug transporters are ATP-dependent efflux proteins,
which include the P-glycoprotein (PGP) and multidrug resistance–associated protein (MRP) family. PGP is a transmembrane glycoprotein, which is present in many organs (e.g., intestine, kidney, liver) as well as contributing to the integrity of blood–brain and blood–testis barriers. Its natural function is believed to be absorptive, excretory, and/or protective (79). Many AEDs may be substrates for PGP (80). Studies in mice have shown that deletion of the multidrug resistance gene-1 (MDR1) gene, which codes for PGP, results in higher brain concentrations of several lipophilic AEDs (81,82). The MRP family, which at present has seven members (MRP1–MRP7), acts not only as an organic anion transporter, but can also transport neutral organic drugs. They have overlapping specificity with PGP, with some AEDs being substrates for both.

Increased expression of MDR1 gene was first identified in surgically resected tissue from the brains of patients with refractory partial epilepsy in 1995 (83). Since then, higher brain MRP1 and MRP2 levels have also been demonstrated (80). Increased expressions of PGP and MRP1 have been found in reactive astrocytes and neuronal elements of focal cortical dysplasia, dysembryoblastic tumors, and HS, compared to histologically normal adjacent tissue (84,85). These lesions are commonly associated with refractory epilepsy. PGP- and MRP- mediated efflux of AEDs from the site of origin of seizures resulting in inadequate intraparenchymal concentrations could be one of the processes underlying drug resistance.

GENETIC FACTORS

Several genetic factors modify the pharmacodynamics and pharmacokinetics of AEDs and can influence the response to treatment. Polymorphisms in genes coding for metabolizing enzymes of the cytochrome P450 family can alter metabolic activity and affect serum levels and brain concentrations for substrate AEDs (86). Despite their potential influence on AED concentrations, polymorphisms of the cytochrome P450 superfamily of enzymes have not been shown to be associated with drug resistance in epilepsy. Single nucleotide polymorphisms (SNPs), which are stable heritable alterations of single nucleotides distributed through the genome, are the genetic markers of choice in pharmacogenomic studies. They can be found in the coding regions of genes causing translational changes in proteins or regulating gene expression if they occur in promoter regions. An SNP in the MDR1 gene resulting in increased expression of the gene and higher levels of PGP has been claimed to be associated with a greater likelihood of drug resistance (87). However, this has not been shown to predict response to individual AEDs in patients with newly diagnosed epilepsy (88).

WHEN IS EPILEPSY INTRACTABLE?

For physicians treating epilepsy, there are several questions that need to be answered before a diagnosis of drug-resistant epilepsy can be made and nonpharmacological management considered. How long should one persevere with AED treatment before diagnosing pharmacoresistance? How many regimes should be tried before the epilepsy is designated as refractory? Should combinations be tried early on and, if so, which ones? Are some combinations better than others? If so, for which patients?

Longitudinal studies in children and adults suggest that the natural history of epilepsy can usually be recognized early in the course of the disorder (4,19,89). In the
Glasgow series, 83% of patients entering a prolonged seizure-free period did so within a year of starting treatment with their first ever AED (Fig. 1). Interestingly, 54% reported no further seizures after taking the initial dose. Only 7% entered remission more than three years after starting treatment. Similar patterns have been observed in other studies (90). Patients who continue to have seizures after the first few treatment years have a low chance of subsequent remission and should be evaluated in a comprehensive epilepsy program.

With the large number of AEDs currently available, it is not possible to try all combinations. What is the number of AEDs that the patient has to fail before the chance of subsequent success is sufficiently low to designate the seizure disorder as pharmacoresistant? No drug can be effective in all patients and so those who have not responded to one AED may benefit from an alternative (91,92). In the Glasgow series, 50% of the patients entered a remission period of 12 months or more with their first ever AED, whereas those who received a second and third monotherapy only entered remission in 32% and 27% of the cases, respectively. The chance of successful monotherapy dwindled with each failed AED. Most patients who went into remission on AED monotherapy did so at moderate dosage (Fig. 2). However, if the first well-tolerated AED failed to control the seizures due to lack of efficacy, only a modest percentage of patients subsequently became seizure-free (4).

Since the early 1980s, monotherapy has been considered the gold standard for the pharmacotherapy of epilepsy (93). Polytherapy was thought to produce a higher incidence of toxicity, more cognitive side effects, and complex pharmacokinetic interactions without substantially improving outcomes. This view has slowly altered in recent years. The emergence of nine new chemical entities, all licensed initially as adjunctive treatment for difficult-to-control epilepsy, has moved combination therapy higher up the treatment agenda. In addition, some combinations have been suggested to be particularly useful and could succeed when monotherapy with individual drugs had failed (94–101). A randomized study comparing initial monotherapy with

**Figure 1** Time to achieving response (greater than 12 months of seizure freedom) in 780 patients with newly diagnosed epilepsy.
duotherapy in patients with newly diagnosed epilepsy reported no differences between
the two groups with regard to seizure control and neurotoxicity (102). Patients who
develop idiosyncratic reactions or have intolerable adverse effects on low doses of
their first AED should be treated with alternative monotherapy. If suboptimal seizure
control is achieved at a maximally tolerated dose of the first-choice AED, a reason-
able approach would be to reduce the dose of the first drug and add a second (26).

Combinations of more than two drugs rarely produce seizure freedom, but may
be unavoidable in patients with frequent seizures not responding to duotherapy
(101). Basing choices on mechanism of action of the individual AEDs has been
proposed as a “rational” approach to polypharmacy (103). Predominant modes of
action are known for the older AEDs, and mechanisms have been proposed for some
of the newer ones (104). Accumulating clinical evidence suggests that combinations
of AEDs that possess different pharmacological properties are most likely to produce
favorable outcomes (105). The most successful approaches may be with a sodium
channel blocker in partnership with a drug affecting gamma-aminobutyric acid
(GABA) receptor function or one possessing multiple mechanisms of action (92,105).

PREDICTING INTRACTABILITY

Predicting the development of intractable epilepsy could help target early specialist
intervention and optimize treatment outcomes. Studies of prognosis should be popu-
lation based, prospective, and should follow patients from the same point in the
course of their epilepsy (e.g., first seizure, start of treatment, etc.) to minimize bias
(106). Separate univariate analyses can give a distorted picture. Multivariate analysis
will best allow the relevance of each factor to be assessed (107).

Seizure types and epilepsy syndromes have the strongest influence on prognosis.
Several studies, especially in adults, have reported that patients with localization-
related epilepsies are more likely to be drug resistant than those with idiopathic

![Figure 2](image)

Monotherapy doses producing seizure freedom in patients with newly diagnosed
epilepsy.
generalized epilepsies (1–4,108,109). Similarly, the presence of mixed seizure types predicts a poor outcome in adults and children (16,52,86,108–110). In our series, both localization-related epilepsy and multiple seizure types were significantly associated with uncontrolled epilepsy (Table 1).

Remote symptomatic seizures (those occurring more than a week after a cerebral insult) have consistently been associated with a poor outcome (8,17,53,90,108,110). Perinatal hypoxia or intracranial injury resulting in neonatal seizures can cause epilepsy in later life in approximately 30% of infants (111). The relevance of perinatal injury to prognosis in adult onset epilepsy is less clear cut. Patient-reported birth trauma did not predict outcome in our series. However, posttraumatic epilepsy was associated with a poor prognosis, with only 35% of such patients achieving seizure freedom, whereas 70% of patients with cerebrovascular disease were fully controlled on medication (Table 1). This suggests that the nature of the cerebral insult has a bearing on prognosis.

Onset of epilepsy in children before the age of 12 months can lead to a poor prognosis (8,110,112). Some studies in adults have also reported an association between young age at onset and later intractability (108). Multivariate analyses of prognostic factors in children and in adults have found no independent correlation between age at onset and prognosis (9,19,107). These differences are likely to reflect the epilepsy syndromes prevalent in the various age groups. In our series, the outcome for senior citizens (age >65 years: 85% remission) was substantially better than that in younger adults (age 20–65 years: 57% remission). Adolescents (age <20 years: 65% remission) also fared better than did the general adult population.

Table 1 Remission Rates in Relation to the Presence or Absence of Risk Factors in 780 Patients with Newly Diagnosed Epilepsy

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Present (%)</th>
<th>Absent (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>56</td>
<td>62</td>
<td>NS</td>
</tr>
<tr>
<td>Learning disability</td>
<td>59</td>
<td>59</td>
<td>NS</td>
</tr>
<tr>
<td>Birth injury</td>
<td>74</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Febrile convulsions</td>
<td>34</td>
<td>60</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Family history</td>
<td>44</td>
<td>61</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>52</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Serious head injury</td>
<td>35</td>
<td>62</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Clustering of seizures</td>
<td>43</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Medical problems</td>
<td>59</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>43</td>
<td>62</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Neurological deficit</td>
<td>56</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol-/drug-related seizures</td>
<td>29</td>
<td>64</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Localization-related epilepsy</td>
<td>57</td>
<td>66</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Multiple seizure types</td>
<td>54</td>
<td>62</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Abnormal surface EEG</td>
<td>63</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Abnormal brain imaging</td>
<td>60</td>
<td>59</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.
wider population (47). Studies in adults and children have found a correlation between number of seizures over unit time (seizure frequency) and prognosis (8,17,107,109). We found a significant correlation between increasing number of pretreatment seizures and likelihood of subsequent "refractoriness" (Fig. 3).

The presence of neurological deficits in children, especially associated with mental retardation, is indicative of a poor prognosis (17,19,89,109). This effect is less pronounced in adults, although reports of such an association exist in this literature as well (105). In our study, the presence of neurological deficits in newly diagnosed patients did not affect the likelihood of remission. Similarly, patients with learning disability developing epilepsy in adolescence and adulthood did not fare worse than individuals with normal intellect.

We found a strong relationship between psychiatric comorbidity and uncontrolled epilepsy (Table 1). Psychiatric problems are more frequent in patients with epilepsy, and this association with refractory epilepsy has been reported before (107). There is emerging evidence to support a close relationship between epilepsy and depression (114). Impaired memory at the outset may also be predictive of a poor outcome (108). These features could be markers of greater underlying cerebral dysfunction. AEDs do not modify the underlying epileptogenic process, but merely suppress their external manifestation, namely the seizures (115,116).

Approximately 3% of children manifesting febrile convulsions develop epilepsy in later life (117). Complex febrile seizures (i.e., those that are prolonged, focal, or recur within the same day), preexisting neurological deficit, and family history of epilepsy all confer a higher risk. Patients who develop epilepsy following febrile convulsions appear more likely to be pharmaco-resistant (Table 1). There is, of course, an association between febrile seizures in infancy and the development of HS in later life (62).

Family history of epilepsy can be associated with a poor prognosis in children and in adults (17,107). Genetically mediated mechanisms causing seizures could be responsible for determining the response to drugs in patients with idiopathic epilepsy.
syndromes. However, we also observed a correlation between a positive family history in first-degree relatives and the subsequent development of uncontrolled localization-related epilepsy.

Some studies, mainly in children, have reported correlation of background slowing and focal spike and wave activity on a surface EEG with a poor outcome (17,108,110). Others have not shown the EEG to be independently predictive of outcome (9,107). Timing of this investigation in relation to the onset of seizures is important in determining its prognostic value. Findings on routine interictal EEG did not correlate with outcomes in newly diagnosed epilepsy across a range of ages and syndromes in our series (Table 1).

Several studies have found response to the first AED to be the strongest predictor of long-term prognosis (4,6,21,53). Patients whose seizures continue despite adequate doses of an appropriate, well-tolerated AED have a low chance of subsequent remission. In our study, only 27% of patients failing to respond to the first drug subsequently entered remission. The outlook was poorer for those whose seizures did not respond to initial monotherapy owing to lack of efficacy (21% remission) than those failing treatment due to intolerable side effects (48% remission). Only 14% of patients failing a second drug regimen subsequently ever became seizure-free.

CONCLUSIONS

Approximately one in three people with epilepsy never achieve lasting remission. These individuals suffer the physical, psychological, and social consequences of intractable seizures and an escalating drug burden (10). Refractory epilepsy represents a massive drain on health care resources. While there is a clear need for new AEDs with novel mechanisms of action, there is also a requirement to better target available treatments. Identification of patients likely to be unresponsive to pharmacotherapy will facilitate earlier specialist intervention. Epilepsy surgery is a much neglected form of effective treatment the world over.

Advances in cerebral imaging and molecular biological techniques have allowed greater insights into the mechanisms underlying seizure generation and propagation. However, this knowledge is far from complete. The processes underlying drug resistance also remain largely unclear (116). Epidemiological studies have identified some factors that correlate with poor prognosis in children and adults. Pharmacogenomic approaches employing sophisticated genotyping and bioinformatics technologies promise greater predictability of response with individual AEDs. Long-term data are required to assess prognosis in each epilepsy syndrome.

Early response to treatment is a powerful predictor of outcome in newly diagnosed epilepsy. Thus, a patient who does not achieve seizure control with the first two or three drug regimes (including combinations) within the first two to three years of starting treatment is unlikely ever to achieve remission and can usually be considered to have pharmaco-resistant epilepsy (4). A uniform definition of intractable epilepsy remains elusive, however. When AEDs produce less than complete control of seizures, the decision to pursue nonpharmacological treatments should be made on a case-by-case basis taking into account the patient’s expectations, the likely prognosis, the available expertise, and the potential risks and benefits of each course of action. An orderly approach to the management of each epilepsy syndrome will optimize the chance of perfect seizure control and help more patients achieve a fulfilling life (26).
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Determining Pharmacological Intractability


Chapter I-1  
The Definition of Intractability Is a Function of Epilepsy Syndrome

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From an electroclinical as well as from a pathophysiological point of view, epileptic syndromes are very heterogeneous. They are also very heterogeneous in their response to antiepileptic drug (AED) treatment (1–3). As mentioned by Mohanraj and Brodie (Section I), seizure types and epilepsy syndromes have the strongest influence on prognosis. There is some evidence that one of the most important factors for delineating prognosis is the epileptic syndrome itself and the related underlying cause of the epilepsy. It is well known, for example, that the seizures in children with Lennox–Gastaut syndrome are generally refractory to AED, although seizures in children with absence of epilepsy are generally easy to control with well-adapted AED. In adults, most of patients with juvenile myoclonic epilepsy are seizure-free when treated with adequate AED (4). The questions of the intractability of epilepsy in patients with symptomatic and cryptogenic partial epilepsy and the main predictors of intractability in these patients continue to be debated. Criteria for determining medical intractability might vary among the different epileptic syndromes, with the etiology of a patient’s seizures being an important factor in determining the probability of achieving seizure control. This chapter reviews the available data on the relationships between intractability and epileptic syndromes in partial epilepsies. Various definitions of intractability have been proposed (Section I), this chapter defines patients to have intractable epilepsy when their seizures are not completely controlled with well-tolerated AED.

The main feature differentiating cryptogenic and symptomatic partial epilepsies is the etiology of the disease. We focus on the relationships between prognosis and etiology and between prognosis and the location of the epileptogenic zone.
IS INTRACTABILITY RELATED TO THE ETIOLOGY
OF THE EPILEPTIC SYNDROME?

Various prognostic criteria of intractability have been described, such as age at onset, remote symptomatic epilepsy, status epilepticus, focal electroencephalographic (EEG) abnormalities, complex partial seizures, and an abnormal neurological examination (5–8). Most of these criteria are associated with the existence of symptomatic or cryptogenic epilepsy. Further, few have studied the relationship between epilepsy etiology and the likelihood of seizure control. Nevertheless, one recent study by MacDonald et al. (9) reported that the most important factor was the number of seizures in the early phase of epilepsy and that etiology was less important, but other studies have reported large differences in the intractability according to etiology. In a follow-up study to the British National General Practice Study of Epilepsy, Cockerell et al. reported that patients with vascular epilepsy had a twofold higher rate of five-year remission than patients with brain tumors, suggesting that vascular epilepsy is easier to control with AED than epilepsy associated with brain tumors (6). We recently reported a study conducted in 581 young patients (aged 18–55 years) with recent cryptogenic ischemic stroke in whom occurrence of late seizures was very infrequent. The risk of first late seizure was 3.1% within one year and 5.5% within three years (10). Among them, only 11 of the 20 patients experienced seizure recurrence on AED, and most were seizure-free at the end of the follow-up, suggesting that epilepsy is rare after stroke. Seizures, if they do occur, are easy to control in young cryptogenic stroke patients. On the other hand, temporal lobe epilepsy (TLE) is often medically refractory. Most patients with TLE have mesial TLE (MTLE) associated with hippocampal sclerosis (HS) (Fig. 1). MTLE could be considered as a model of intractable epilepsy and is the most frequent type of epilepsy treated with surgery.

A few other large studies have assessed the occurrence of medical intractability in relation to the cause of epilepsy. Stephen et al. reported a study of 550 adult

![Figure 1](image1.png)  
**Figure 1** Hippocampal sclerosis is one of the major prognostic factors in epilepsy. T2-weighted cerebral MRI section shows a left hippocampal sclerosis.
patients in which 43% of the patients had persistent seizures, with the cause of the epilepsy being clearly related to the probability of achieving freedom from seizures (11). HS was associated with the poorest prognosis. Van Paesschen et al. also clearly showed in a study of 66 patients with newly diagnosed epilepsy that patients with hippocampal sclerosis had a worse prognosis than patients with other magnetic resonance imaging (MRI) abnormalities or with a normal MRI (12). In this study, all patients with HS had recurrent seizures despite AED treatment. In another large, prospective, hospital-based study conducted in 2200 patients, including 238 patients with partial epilepsy associated with HS we clearly demonstrated that HS is one of the main factors of intractability with 89% of the patients with TLE and HS having recurrent seizures (Fig. 2) (2). This very high percentage can be compared to other epileptic syndromes with recurrent seizure rates ranging from 18% with idiopathic generalized epilepsy to 65% with symptomatic partial epilepsy and 55% in cryptogenic partial epilepsy (Fig. 3). In patients with symptomatic partial epilepsy, the underlying cause of the epilepsy was also an important prognostic factor, with 46% of patients with post-stroke epilepsy having persistent seizures despite AED, 50% of patients having vascular malformation, 65% of patients having brain injury, 76% of patients having malformation of cortical development, 89% of patients having HS, and 97% of patients having partial epilepsy associated with HS and an associated malformation of cortical development in the temporal lobe (Fig. 2). When focusing on patients with TLE and hippocampal abnormalities, patients with HS had more severe epilepsy than patients with hippocampal malformations (13). Some isolated case reports also suggest that the type of malformation is related to the prognosis of epilepsy, but this point needs to be confirmed by controlled studies. Focal cortical dysplasia and dysembryoplastic neuroepithelial tumors seem to be more difficult to control than other malformations of cortical development, such as heterotopia.

Figure 2  Prognosis of partial epilepsy is a function of the MRI-detected brain abnormalities. Source: From Ref. 2.
IS INTRACTABILITY RELATED TO THE LOCATION OF THE EPILEPTOGENIC AREA?

This point has seldom been investigated. In our study conducted in 2200 patients, we reported that in patients with partial epilepsy, temporal lobe epilepsy was more frequently associated with drug-resistant seizures than other types of partial epilepsies, such as frontal lobe epilepsy, occipital lobe epilepsy, or parietal lobe epilepsy (2). The multivariate analysis demonstrated that the main factor of intractability is the

Figure 3  Intractability is related to epileptic syndromes. Source: From Ref. 2.

Figure 4  In temporal lobe epilepsy (TLE), hippocampal sclerosis is the main prognostic factor. Source: From Ref. 2.
presence of an associated hippocampal sclerosis (Fig. 4). Nevertheless, other studies are needed to further investigate this point.

CAN INTRACTABILITY BE PREDICTED?

Published evidence would suggest the answer is “yes” for several types of epilepsies, such as idiopathic generalized epilepsies, several types of symptomatic or cryptogenic generalized epilepsies, idiopathic partial epilepsies, and probably for partial epilepsy associated with various brain abnormalities such as HS (2). But response to drugs cannot be predicted accurately for an individual patient, and all clinicians have seen in their own practices seizure-free patients with an epilepsy that is usually highly medically refractory and also patients with frequent seizures who suffered from a well-known easy-to-control epilepsy syndrome.

Intractability remains a poorly understood, multifactorial phenomenon. Recent pharmacogenetic studies have provided new insights into the causes of intractability (14). Sisodiya and colleagues demonstrated that overexpression of drug-resistant proteins, such as multidrug resistance gene-1 (MDR1) P-glycoprotein and multidrug resistance-associated protein 1 (MRP1), correlated with cellular resistance to AED in brain tissue obtained in patients with refractory epilepsy associated with dysembryoplastic neuroepithelial tumors, focal cortical dysplasia, and HS (14). MDR1 transports some AEDs and MRP1 may also do so. Expression of these proteins was demonstrated in glia and neurons, which do not normally express these proteins. It is suggested that overexpressed resistance proteins lower the interstitial concentration of AEDs in the vicinity of the epileptogenic pathology and thereby render the epilepsy resistant to AEDs.

In conclusion, identification of an epileptic syndrome and of an associated brain lesion can help in the definition of intractability and in the prediction of prognosis (15). Further studies are needed to investigate the prognosis of partial epilepsy according to the type of brain abnormalities associated with these epilepsies. These studies will also help to better identify good candidates for early surgery in partial epilepsy.

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Chapter I-2
The Role of New Antiepileptic Medications in the Determination of Intractability

Chapter I-2a: Trials of New Antiepileptic Medications Are Needed to Demonstrate Intractability

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INTRODUCTION

Antiepileptic drugs (AEDs) are the main method of therapy for the overwhelming majority of patients with epilepsy. The goals of medication therapy are an optimal quality of life, no seizures, and no medication side effects. Although a favorable response to therapy is easy to recognize, it is often difficult to identify the point at which pursuit of the above goals using an additional AED trial is futile. No international consensus exists for a functional definition of “pharmacologic intractability” despite intense research and its importance to both the patient and society. It has been suggested by Mohanraj and Brodie (Section I) that “Pharmacoresistance should be diagnosed only in patients who have a secure diagnosis of epilepsy, have failed a range of appropriate AEDs at adequate dosage, and adhere religiously to their treatment regimens.” Although clear and concise, this proposal leaves unanswered a fundamental question: which AEDs are necessary and sufficient to be included in a practical working definition of pharmacoresistance?

This chapter proposes that the “range of appropriate AEDs” should include at least one of the new AEDs. The various options for AED therapy are often arbitrarily grouped chronologically into old AEDs and new AEDs. Old AEDs include phenobarbital (PB), phenytoin (PHT), carbamazepine (CBZ), valproic acid (VPA), and primidone (PRM). During the past 15 years, nine new AEDs have been approved
around the world including felbamate (FBM), gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), tiagabine (TGB), topiramate (TPM), vigabatrin (VGB), and zonisamide (ZNS).

There is substantially more rigorously obtained scientific data about the new AEDs compared to the old AEDs. This difference in data volume results from the more increasingly demanding regulatory requirements for AED approval over the past 70 years.

Despite the disproportionate volume of randomized controlled trial (RCT) data for the new AEDs, the majority of patients with epilepsy around the world are still treated initially and then subsequently with one or more of the old AEDs. For example, for a 12-month period ending in December 2003, four old AEDs (PB, PHT, CBZ, and VPA) accounted for 58% of all AED prescriptions for children less than 19 years (1). PB is the most commonly used initial AED in children under 11 years (1).

Multiple RCTs have demonstrated similar efficacy between old and new AEDs in the treatment of newly diagnosed untreated epilepsy but this patient population is not our focus. No double-blind RCTs directly and purposely compare the efficacy or effectiveness of old and new AEDs in patients with epilepsy uncontrolled by one or two trials of old AEDs. New AED double-blind RCTs involving adults or children with treatment-resistant seizures use the primary outcome variables of short-term efficacy or effectiveness (2–7). The outcome variable of both clinical relevance and importance for a determination of pharmacologic intractability is long-term (>6 months) seizure-free rates. Two types of new AED studies examining patients with presumed treatment-resistant epilepsy use long-term seizure-free rates as an outcome variable: (i) prospective long-term open label extensions of double-blind RCTs and (ii) prospective open label cohort studies. Reports of long-term seizure-free rates from four new AEDs (LEV, LTG, OXC, and TPM) will be used to illustrate these types of studies. As patients are predominantly treated with old AEDs, these studies illustrate that new AEDs can be efficacious in many patients in whom old AEDs have not been efficacious. This finding supports the proposal that pharmacoresistance can not and should not be defined solely by trials of old AEDs.

OPEN-LABEL EXTENSIONS OF DOUBLE-BLIND RCTs

Seizure-free rates in the open-label long-term extension phase of randomized, controlled, double-blind trials have been reported for OXC (n = 2) (8,9), LEV (n = 1) (10), and TPM (n = 3) (11–13) (Table 1). In the open label extension phase, the new AED dose is not fixed, titration is not forced, and medication adjustments more closely mirror clinical practice.

The long-term (48 weeks) seizure-free rate in adults who participated in a mono-therapy substitution dose-controlled OXC study was 6.6% (8). These patients previously had inadequate seizure control on one or two AEDs (49% were taking CBZ, 24% were on PHT, and 14% on VPA) with a median baseline seizure frequency of 7.8 seizures per 28 days. Similarly, in the two-year open-label extension phase following a double-blind placebo-controlled trial of OXC in 233 children with previous treatment-resistant partial seizures, 5% of the patients reached and maintained seizure freedom for the full two years. The most common AEDs of patients entering the trial were CBZ (49%), VPA (20%), LTG (19%), and PHT (16%). The group’s baseline partial seizure frequency was 13.0 seizures per 28 days (9).
Table 1  Seizure Freedom During Open-Label Extension Phase of Double-Blind Clinical Trials

<table>
<thead>
<tr>
<th>Seizure type or syndrome (patient population) (Ref.)</th>
<th>AED</th>
<th>Number of patients</th>
<th>Baseline seizure frequency (median)</th>
<th>Duration of seizure freedom</th>
<th>Rate of seizure freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial seizures (adults) (8)</td>
<td>OXC</td>
<td>76</td>
<td>7.8 per 28 days</td>
<td>48 weeks</td>
<td>6.6%</td>
</tr>
<tr>
<td>Partial seizures (children) (9)</td>
<td>OXC</td>
<td>233</td>
<td>13 per 28 days</td>
<td>2 years</td>
<td>5%</td>
</tr>
<tr>
<td>All types but 93% had partial seizures (adults) (10)</td>
<td>LEV</td>
<td>1422</td>
<td>8.68 per 4 weeks</td>
<td>Last 6 months</td>
<td>11.7% (CI: 10.1; 13.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Last 12 months</td>
<td>8.9% (CI: 7.4; 10.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Last 6 months</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Last 6 months</td>
<td>GTCs: 16%; All types: 7</td>
</tr>
<tr>
<td>Partial seizures (children) (11)</td>
<td>TPM</td>
<td>83</td>
<td>22 per month</td>
<td>Last 6 months</td>
<td>15%</td>
</tr>
<tr>
<td>GTCs of nonfocal origin (adults and children) (12)</td>
<td>TPM</td>
<td>131</td>
<td>GTCs: 4.4 per month; All types: 17.5 per month</td>
<td>GTCs: 16%; All types: 7</td>
<td></td>
</tr>
<tr>
<td>Lennox–Gastaut syndrome (13)</td>
<td>TPM</td>
<td>97</td>
<td>Drops: 90 per month; All types: 238 per month</td>
<td>Last 6 months</td>
<td>Drops: 15%; All types: 2</td>
</tr>
</tbody>
</table>

*Abbreviations: AED, antiepileptic drug; OXC, oxcarbazepine; LEV, levetiracetam; TPM, topiramate; CI, confidence interval; GTCs, generalized tonic-clonic seizures.*
Long-term seizure-free data have been reported for 1422 adults with treatment-resistant epilepsy participating in clinical trials as part of the LEV development program (10). The cohort’s mean duration of epilepsy was 21.9 ± 12.7 years at study entry with a median seizure frequency of 8.68 seizures per four weeks. The follow-up data from the last 6 and 12 months of LEV therapy demonstrated 11.7% (confidence interval, CI: 10.1; 13.5) and 8.9% (CI: 7.4; 10.5) were seizure-free, respectively. Overall, 4.6% (CI: 3.5; 5.8) of the study population was seizure-free from the first dose of LEV until the last treatment day or the cut-off date (10).

Three TPM double-blind, randomized, placebo-controlled, adjunctive therapy trials [pediatric partial seizures, n = 83 (11); generalized tonic–clonic seizures of nonfocal origin, n = 131 (12); and Lennox–Gastaut syndrome, n = 97 (13)] reported six-month, open-label extension seizure-free data. In the three trials, the median monthly baseline seizure frequency was 22 partial onset seizures, 4.4 generalized tonic clonic seizures, and 90 drop attacks, respectively. At the last study visit, seizure freedom for more than six months was achieved by 14% to 16% of TPM-treated patients for the target seizure type (partial seizure, generalized tonic–clonic seizures, or drop attacks) (11–13).

**PROSPECTIVE OPEN-LABEL COHORT STUDIES**

Prospective open-label cohort studies tend to be more reflective of clinical practice in comparison with open-label extension phases of double-blind studies. As such, these types of reports provide a different perspective on the efficacy and tolerability of the new AEDs and reinforce the concept that new AEDs should be tried prior to declaring a patient’s epilepsy as pharmacoresistant. Four reports involving three different new AEDs (LTG, LEV, and TPM) illustrate the value of trials of new AEDs in patients previously described as pharmacoresistant (Table 2).

In a cohort of 200 adults and children with treatment-resistant epilepsy treated with LTG adjunctive therapy and followed-up for at least six months, 35% became seizure-free (14). Two old AEDs (CBZ, VPA) were the most common concomitant

<table>
<thead>
<tr>
<th>Table 2  Seizure Freedom During Prospective Open-Label Cohort Studies</th>
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<tbody>
<tr>
<td>Seizure type or syndrome (patient population) (Ref.)</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>All types (adults and children) (14)</td>
</tr>
<tr>
<td>Partial epilepsy (children and adults) (15)</td>
</tr>
<tr>
<td>All types (adults) (16)</td>
</tr>
<tr>
<td>All types—84% were partial seizures (adults) (17)</td>
</tr>
</tbody>
</table>

*Abbreviations: AED, antiepileptic drug; LTG, lamotrigine; LEV, levetiracetam; TPM, topiramate.*
AEDs that were withdrawn or reduced following initiation of LTG therapy. LTG demonstrated efficacy over a variety of partial onset and generalized onset seizures. Only 6.5% stopped LTG due to side effects. A separate study of LTG adjunctive therapy in a cohort of 41 adults and children with treatment-resistant partial epilepsy (mean age 12 years, range 3–25, mean seizure frequency 3.6 seizures per day) found that with 12 to 48 months of follow-up, 14.6% of the group became seizure-free. At the time of study entry, 73% of this study’s patients were on two or more AEDs with the most commonly used concomitant AEDs being CBZ, VPA, and PB (15).

Among 98 patients with treatment-resistant epilepsy (various seizure types, average age 39.8 years, and 14 seizures per month) followed-up for one year, 14% became seizure-free following introduction of LEV adjunctive therapy (16). Seventy-four percent of the patients were taking two or more concomitant AEDs at study entry with CBZ (53%), TPM (26%), VPA (22%), and PHT (20%) being the most common. Lastly, six-month seizure-free data were reported for a long-term open-label study of TPM in a cohort of 292 adults (mean age 33 years) with various types of treatment resistant epilepsy (17). The overall six-month seizure-free rate for the 196 patients who had completed more than six months of TPM therapy was 10%. The six-month seizure-free data for the separate subgroups of patients with partial onset and generalized onset seizures receiving TPM were 9% ($n = 163$) and 35% ($n = 43$), respectively (17).

**CONCLUSION**

Today most patients with epilepsy are treated with one or more of the old AEDs. As these clinical trial results demonstrate, even patients with chronic uncontrolled epilepsy can experience long-term seizure freedom when treated with one of the new AEDs. There is more data illustrating the clinical utility for OXC, LEV, LTG, and TPM than for FBM, GBP, TGB, VGB, or ZNS. The long-term seizure-free rates in these trials indicate that pharmacoresistance cannot and should not be defined solely by trials of old AEDs.

**REFERENCES**

1. IMS Health’s National Disease and Therapeutic Index (NDTI) Audit with data on a Moving Annual Total basis for the 12-month period ending in December 2003.
Chapter I-2b: The Development of New Medications Has Not Substantially Affected Intractability

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Many patients with epilepsy are not seizure-free with medical therapy. Their epilepsy has been termed refractory, intractable, or medication resistant. Prior to designating a patient as having intractable epilepsy, one must determine that the events being
treated are truly epileptic seizures. Epilepsy monitoring units report that 25% to 50% of patients referred for medication-resistant seizures do not have epilepsy (1). In addition, the medications used must be appropriate for the epilepsy syndrome or seizure type. For example, carbamazepine can exacerbate myoclonus or absence (2), and tiagabine has been reported to induce absence status epilepticus (3). Other factors like medications that exacerbate seizures, alcohol or substance abuse, incomplete compliance with antiepileptic drug regimens, and sleep deprivation must be eliminated. Unfortunately, even when all these factors are considered, most studies estimate the frequency of medication resistant epilepsy at about 30% to 40% (4), or approximately one million patients in the United States alone. The biological mechanisms behind medication resistance are poorly understood and likely differ depending on factors like the epilepsy syndrome or the presence of a structural lesion. Eight new antiepileptic drugs and one new device have been approved in the United States since 1993. This is a remarkable achievement considering that no new antiepileptic therapies were approved in the previous 15 years. All these drugs were tested as adjunctive therapy in randomized controlled trials against placebo in patients whose seizures had not responded to trials of multiple AEDs. The Food and Drug Administration (FDA) required that the drugs show statistically significant superiority in seizure control. These studies designed for regulatory approval typically measured outcome as percent seizure reduction or frequency of subjects showing a 50% or more reduction of seizures (the so-called responder rate). Total seizure reduction ranged from 25% to 52% depending on the drug and dose (5,6).

These drugs are now used throughout the world, but have they really made an impact on patients with medication-resistant seizures? The seizure-free rates from these trials are more sobering and range from 1% to 4%. Even in open-label extension or postapproval phase 4 studies where doses could be individualized, patients were less refractory and biases inherent in open-label trials might inflate response rates, the number is only 20% at most (7).

The seizure-free rate after one year in the medical treatment arm of a randomized controlled trial of surgery for temporal lobe epilepsy was 8% (8). In addition, some patients who are initially seizure-free may relapse after months or years (9). From the patient's perspective, a 50% seizure reduction (defined as efficacious) likely has little impact on health-related quality of life (HRQOL). Such a seizure reduction will rarely permit a patient to drive a motor vehicle or improve employment. A recent study showed that the only meaningful reduction in seizures associated with a significant improvement in HRQOL was a 100% seizure reduction.

Are there differences among drugs that can help match the drug to the patient? The mechanisms of actions of the AEDs are deduced from animal and basic laboratory studies.

Some of the new AEDs like tiagabine have well-defined mechanisms (inhibiting GABA reuptake) while others like topiramate likely have multiple mechanisms (10), and years of study have not completely elucidated the mechanism of levetiracetam (which also failed the initial efficacy screening tests in animals). Whether these mechanisms are the ones conveying efficacy in humans with epilepsy is not clear. Recent genetic studies have shown that some uncommon epilepsy syndromes are related to defects in ion channels, but it is not likely that these defects are common causes of medication resistance (11). With such a poor understanding of what makes patients medication resistant, it is hard to give credence to speculation that choosing a drug based on mechanism of action is likely to lead to improvements in efficacy. Mohanraj and Brodie (12) (Section I) suggest that accumulating clinical evidence
supports combining drugs with complementary mechanisms of action, but there are no data from randomized controlled trials supporting this speculation.

Are there more potent AEDs that should be preferred after a patient fails to become seizure-free on the first treatment? There have been no direct head-to-head comparison trials among the new antiepileptic drugs. One approach that can mimic such a trial is a meta-analysis. Meta-analysis is a statistical analysis that combines or integrates the results of several independent clinical trials. These studies looked at all the new AEDs plus valproate (the only one of the older drugs that was tested in a randomized controlled add-on trial against placebo) (5,6). The overall conclusion of these meta-analyses is that all the treatments were significantly better than placebo when all studies at all dosages were analyzed. There was a trend that topiramate and levetiracetam were the most effective, and gabapentin and the vagus nerve stimulator were the least effective, but these differences were not statistically significant when odds ratio was used as the comparison. Analysis of withdrawal rates thought to represent an overall measure of tolerability similarly showed no differences among AEDs. There are many potential drawbacks to a meta-analysis of randomized controlled trials of AEDs. The drugs may not have been used at optimal doses or titration schedules which may have exaggerated adverse effects or underestimated efficacy.

Should we use particular AEDs because they are disease-modifying or neuroprotective? Animal models provide strong evidence that status epilepticus and even single seizures can cause neuronal injury and increased seizure susceptibility and that certain AEDs may reduce or prevent neuronal injury and synaptic reorganization in these models. In addition, research suggests that some AEDs may not only suppress seizures but may interrupt the epileptogenic process to be disease-modifying. These data support the notion that epilepsy can be progressive and that progression can be halted with drug intervention (Table 1) (13).

Unfortunately, data from clinical studies are less robust and conclusive that epilepsy is progressive. Clearly, some epilepsies are not—calling into question the notion that “seizures beget seizures” or even that “seizures beget neurobiological changes that beget seizures.” However, an all-too-frequent experience for clinicians is observing what seems to be a slow, inexorable decline of certain patients when seizures do not remit, especially patients with temporal lobe epilepsy. As time passes, not only does disability become more entrenched as the patient misses more educational, employment, and social opportunities, but cognitive function and memory also seem increasingly affected. For these patients, epilepsy seems to be progressive in psychosocial and perhaps neurobiological dimensions, with outcomes worsening as the interval of active epilepsy lengthens. Thus there may be both biological

<table>
<thead>
<tr>
<th>Table 1 Progressive Epilepsy: Conflicting Evidence</th>
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<tbody>
<tr>
<td><strong>Pro (Animal Evidence)</strong></td>
</tr>
<tr>
<td>• Neuronal injury after SE and single seizures</td>
</tr>
<tr>
<td>• Increased seizure susceptibility in kindling models</td>
</tr>
<tr>
<td>• Neuronal injury and reorganization inhibited by some AEDs</td>
</tr>
<tr>
<td><strong>Con (Clinical Evidence)</strong></td>
</tr>
<tr>
<td>• Natural history of remission despite frequent seizures in some syndromes</td>
</tr>
<tr>
<td>• Time to remission unchanged by early AED intervention</td>
</tr>
<tr>
<td>• AED prophylaxis ineffective</td>
</tr>
</tbody>
</table>
progression making the seizures more difficult to control as well as psychosocial progression that enhances the negative impact of seizures on quality of life. However, freedom from seizures following epilepsy surgery in temporal lobe epilepsy has been associated with decreased mortality and significant improvements in employment, personal/social relationships, and quality of life (14), underscoring the potential for interrupting progressive decline, at least in certain psychosocial domains. This then raises the question of whether disability could be reduced and outcomes improved even further by shorter intervals of active epilepsy.

The current evidence for a progressive nature of epilepsy is suggestive but not convincing. For now, clinicians must continue to provide each patient with the best seizure control possible, keeping in mind that earlier achievement of a seizure-free state may have better long-term outcomes.

Are there particular AEDs or drug combinations that should always be tried before epilepsy surgery is considered? A randomized trial comparing temporal lobe surgery to continued medical treatment showed a dramatic superiority of surgery (7). A new randomized trial of early temporal lobe epilepsy surgery is in progress (15). Although many theories and speculations pervade the literature, there is a paucity of evidence that any particular AEDs combination based on mechanism of action or other considerations is most effective.

But epilepsy surgery is a viable option for only a subgroup of patients with medication-resistant epilepsy, and there are currently a limited number of sites that can do the time-consuming and complex evaluation necessary. In contrast, any licensed practitioner with a modest amount of training can try different AEDs. In this sense, AEDs will likely make a larger impact on the problem of medication-resistant epilepsy than surgery, even though the drugs have a much lower seizure-free rate.

It is our obligation to move resources to studies that will improve epilepsy surgery outcomes and lower adverse effect rates. Imaging research has made great strides in the past 15 years and has much promise, especially in functional magnetic resonance imaging. We must also educate practitioners, who treat people with epilepsy, about the availability of epilepsy surgery as an effective and safe option. In parallel, we should aim for higher goals in AEDs development like double-digit seizure-free rates and disease modification rather than merely statistically significant superiority over placebo in our patients who need much more.

REFERENCES

Chapter I-3
Intractability in Children and the Role of the Ketogenic Diet

Chapter I-3a: When to Consider Children with Seizures for Surgery: Intractability and the Role of the Ketogenic Diet

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“INTRACTABILITY” DOES NOT MEAN THAT SEIZURES ARE UNCONTROLLABLE WITH ALL MEDICATION

Many neurologists feel that in the absence of a lesion, surgery should be the last resort in the management of difficult-to-control seizures and should be used only when the seizures have been proven intractable. They use almost every medication serially and in combination before recommending a surgical evaluation. The true definition of intractability is resistant to control. When can you identify seizures that are, or will be “resistant to control”?

As has been shown by Kwan and Brodie (1) and discussed in Section I, 47% of individuals with epilepsy become seizure-free with their first anticonvulsant medication. Fourteen percent required a second drug or a third drug before becoming seizure-free. Many of those who required a second drug had discontinued their first medication because of lack of efficacy, rashes, or side effects. When the first drug was discontinued for those reasons, almost half the patients became seizure-free with a subsequent medication. When the first drug was ineffective, only 11% of the patients became seizure-free with a second drug. Individuals with symptomatic or cryptogenic seizures were almost twice as likely (40%) to have persistent seizures as those who had idiopathic seizures (26%). Kwan and Brodie (1) and Engel (2) conclude that patients with
correctable structural abnormalities should be considered refractory when they have failed two medications.

WHEN SHOULD PATIENTS BE CONSIDERED FOR SURGERY?

Some believe that patients should be considered for surgery when their seizures are intractable. I would go even further. I believe that surgery should be the first treatment considered when an individual has recurrent seizures. If a child with seizures does not respond to the first anticonvulsant medication used properly, or to the second if the first caused side effects, an evaluation for surgery should be initiated as the epilepsy is likely to be difficult to control. If the child is found to have a structural lesion, or has focal seizures arising in an accessible location, then surgery should be strongly considered. If the seizures are multifocal or there is evidence of abnormalities on both sides of the brain, then more anticonvulsants should be used before the seizures are considered intractable and a surgical evaluation is undertaken.

SEIZURE SURGERY SHOULD NOT BE RESERVED FOR THOSE WITH “INTRACTABLE” SEIZURES AND SHOULD NOT BE A LAST RESORT

Intractability or difficulty in control should not be the only criteria for considering surgery. Surgery should also be considered when the effects of the seizures and of the medications on the child’s quality of life outweigh the risks of the surgery and its consequences and when there is decreasing likelihood of becoming seizure-free. The effects of the seizures on the individual’s quality of life will depend on the seizure type frequency and severity, and on the time of day in which they occur. The effects may also vary with the child’s other handicaps (if any), and even with the child’s age and where they live. For an adult, the seizure’s effects may vary with the individual’s occupation and the accessibility of public transport. The effects of seizures are very individual. The sum of the consequences and effects of the seizures should be compared to the risks and benefits of the proposed seizure surgery.

The risks and consequences of the surgery will depend on the location of the lesion, the need to remove eloquent tissue, and the child’s age and ability to recover function. The risks will also depend on the skill and experience of the team evaluating the patient and of the surgeon.

NOT EVERY NEUROSURGEON WITH ACCESS TO AN EEG MACHINE AND A SCALPEL SHOULD BE DOING EPILEPSY SURGERY

The following case(s) show how considerations of surgery must be very individualized.

1. A child has a single focal seizure. Her computed tomography (CT) and magnetic resonance imaging (MRI) scans show a focal (presumably benign), circumscribed lesion in the anterior temporal lobe. The electroencephalogram (EEG) suggests that the seizure originated from the lesion. This child with an accessible, structural lesion has a high likelihood of not responding to medication and a high probability of being cured by surgery without causing deficit. Even if her seizures
are controlled with medication, will she need it for the remainder of her life? Surgery should be considered and discussed early in her course.

2. A child has a single focal seizure. His CT and MRI scans show a similar focal (presumably benign), circumscribed lesion. However, his EEG shows multiple spikes on both sides of the brain and the child’s development is slow. The slow development and the bilateral EEG findings suggest that he may have bilateral problems. We would try medications and see his response, keeping in mind that he may still have a surgical lesion.

3. A child has a single focal seizure. Her CT and MRI scans show diffuse bilateral cystic encephalomalacia more prominent in the left temporal lobe. The EEG suggests that the seizure originated from this left temporal lobe. We would treat her with medication, and perhaps the ketogenic diet. However, if the seizures remained refractory to treatment, and if the seizures were affecting her quality of life, we would evaluate her further, to see if she was a candidate for surgery.

The term “intractable” should be replaced by the terms “refractory” or “difficult to control.” Surgery should be considered early in the course of the child with epilepsy and evaluation for surgery should be pursued early in that course when focal lesions are found in favorable locations, or when the semiology of the clinical seizures suggests a focal onset to the epilepsy. Surgery should be performed when the potential benefits of the surgery outweigh its risks and consequences. Informed decisions about the risks and potential benefits of the evaluation and the surgery should be made by the patient and the family with the advice of the physician.

WHAT IS THE ROLE OF THE KETOGENIC DIET IN DEFINING INTRACTABILITY?

There is no role for the diet in assessing intractability. For those few neurologists who still consider that surgery should be done only as a last resort, the ketogenic diet presents another last resort.

The ketogenic diet has been shown to be effective in children with difficult-to-control seizures (3–5). It is relatively less effective in those children with structural lesions than in those without such lesions. Since the diet is usually used for only two years, one would expect that when structural lesions are the cause of the epilepsy, the seizures are likely to return when the diet is discontinued. This, however, is not always the case.

If the patient has a resectable lesion, we would suggest that resection is preferable to further medications or to the ketogenic diet. If the lesions are not resectable, the ketogenic diet may be preferable to continued attempts to achieve control with newer medications or with medication combinations. The ketogenic diet may allow children who are refractory to many medications to achieve some (and occasionally complete) seizure control without the side effects of polytherapy.

We usually reserve the diet for children who have failed two medications, but when seizures (such as infantile spasms) are know to be poorly responsive to medications, we may advocate the diet even earlier in the child’s course, and even as the first therapy. Children with the Lennox–Gastaut syndrome, tuberous sclerosis, and infantile spasms (6) may be controlled by the ketogenic diet without the multiple side effects of steroids or the ocular consequences of vigabatrin. Families may state that even when the diet has not been effective, they feel better for having tried it before
embarking on the surgical evaluation. The diet does not appear to substantially affect growth (7) or lipids (8). Details of the diet may be found in the The Ketogenic Diet: A Treatment of Epilepsy (5).

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Chapter 1-3b: Intractability, Operability, and the Role of the Ketogenic Diet

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THE CONCEPT OF INTRACTABILITY

The increased recognition of surgery as a potential cure for epilepsy in carefully selected patients has generated the need for criteria defining eligibility and optimal timing of surgery. If surgery is considered for better seizure control only, and not because of a cerebral lesion that needs to be resected (e.g., tumor or AVM), it would be very unusual to proceed with surgery unless some degree of resistance to medical treatment has been established. The term used for this resistance to medical treatment is a matter of semantics and of definition. Defining medical intractability for
the purpose of eligibility for surgery is meaningful and important. However, declaring a patient who is not a surgical candidate as being intractable will help neither the patient nor the physician. There is generally no accepted definition of intractability. The definition of medical intractability has to be based on the type and number of therapeutic steps that have failed despite adequate trials. No single step in the treatment defines intractability. After each drug failure, the statistical probability of seizure control by the next step is lower but this probability never reaches zero. The certainty that a patient will remain refractory to medications can only be approached in an asymptotic manner, and intractability could be defined as a probability of less than 5% that seizure control will be achieved by any additional medications.

It seems that the criteria that are applied practically for medical intractability in the context of epilepsy surgery have shifted over the past 10 to 15 years. The notion that was applied in the past was inspired by a concept of failure of virtually available antiepileptic drugs, alone or in combination. It should be pointed out that the number of available antiepileptic drugs at the time was much smaller than now. Currently, it is generally accepted that failure of a rather small number of drugs is sufficient to justify surgical intervention. This shift in the concept of intractability has been supported by several published observations suggesting that resistance to medical treatment can be established early. The study by Kwan and Brodie (1) has been widely quoted already. This study revealed that, among patients with focal onset seizures who failed to be controlled by an adequate trial of a first medication, only 11% could be controlled by a second or third therapeutic step. In this analysis, the concept of adequate trial excluded drug failure due to an early reaction that precluded the achievement of good therapeutic levels. Gilman et al. (2) evaluated 21 children who were referred for epilepsy surgery and who did not meet pre-established intractability criteria. These criteria consisted of (i) trials of first-line antiepileptic drugs (carbamazepine, phenytoin, and valproate) as monotherapy and at least one combination, (ii) use of these medications at the maximal tolerated dose, and (iii) trial of one adjunctive second-line drug. In all of these 21 children, the omitted steps were completed. Only one patient became seizure-free and one additional patient had more than 90% reduction in seizure frequency. In a similar study in adults, Hermanns et al. (3) used failure of three major drugs at the maximal tolerated dose as intractability criteria. When 74 patients referred for epilepsy surgery without having met these criteria underwent the missing therapeutic steps, seven of them (9.5%) experienced more than 80% seizure reduction and none became seizure-free.

Predictors of intractability were assessed in 120 children with temporal lobe epilepsy by Dlugos et al. (4). Two years after seizure onset, 45 (37.5%) had remained refractory to medications. In bivariate analysis, the three best predictors of intractability were early risk factors for epilepsy, a temporal lobe abnormality, and failure of the first antiepileptic drug. Logistic regression analysis singled out failure of the first antiepileptic drug as the best predictor.

The available evidence strongly suggests that, after two to three adequate drug trials, the probability of successful medical treatment of epilepsy has reached values that are so low that epilepsy surgery becomes a justifiable option. However, there can be no universal definition of intractability for the purpose of epilepsy surgery. There are at least two reasons for this. First, intractability is not evenly distributed among patients with epilepsy of different etiologies. Second, certain patients are more promising surgical candidates than others. In other words, operability differs among patients. In a large group of 2200 patients followed at
a referral center for one to seven years, Semah et al. (5) determined the long-term outcome of medical treatment according to the etiology of the epilepsy (Table 1). These data suggest that patients with partial epilepsy have less than 50% probability of having their seizures controlled by medication. Among patients with temporal lobe epilepsy, this proportion is 30% or less. Only one of ten patients with hippocampal sclerosis was controlled by medication, and patients with so-called dual pathology (hippocampal sclerosis and cortical abnormality) could be considered to be intractable at the time of diagnosis. Such numbers may well influence the extent to which medical therapy will be pursued before surgery is considered. Another factor that is even more likely to influence the timing of surgery is the operability. An example of good operability would be mesial temporal sclerosis in the nondominant hemisphere, whereas frontal lobe seizure without identifiable structural abnormality represents an example of lesser operability. In the end, the timing of the decision to proceed with surgery in a given patient will be based on an individual assessment of the probability of success of medical therapy based on the etiology, medical intractability, and operability.

### EPILEPSY SURGERY AND THE KETOGENIC DIET

In the assessment of medical intractability in the context of epilepsy surgery, the ketogenic diet cannot be excluded as one of the therapeutic steps. Indeed, the ketogenic diet should be considered in some patients. Although published data on sequential response to antiepileptic drugs are now available, no comparable data are available for the ketogenic diet, because it has never been included in any sequential analysis of treatment response. However, the available information on response rates to the ketogenic diet for various seizure types has grown in recent years (6-9). It is reasonable to assume that the majority of patients enrolled in these studies of the ketogenic diet had previously failed to respond fully to at least two antiepileptic medications. This does allow some comparison with the response to an additional antiepileptic drug at a similar stage in sequential treatment. Overall, responses to

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**Table 1** Underlying Cause of Epilepsy as a Major Prognostic Factor for Intractability

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percent controlled (&gt;1 yr seizure-free)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic generalized epilepsy</td>
<td>82</td>
</tr>
<tr>
<td>Cryptogenic partial epilepsy</td>
<td>45</td>
</tr>
<tr>
<td>Symptomatic partial epilepsy</td>
<td>35</td>
</tr>
<tr>
<td>Extratemporal partial epilepsy</td>
<td>36</td>
</tr>
<tr>
<td>Head injury</td>
<td>30</td>
</tr>
<tr>
<td>Dysgenesis</td>
<td>24</td>
</tr>
<tr>
<td>Temporal lobe epilepsy (TLE)</td>
<td>20</td>
</tr>
<tr>
<td>TLE with hippocampal sclerosis (HS)</td>
<td>11</td>
</tr>
<tr>
<td>TLE without HS</td>
<td>31</td>
</tr>
<tr>
<td>Dual pathology (HS + cortical abnormality)</td>
<td>3</td>
</tr>
</tbody>
</table>

*Source: From Ref. 5.*
the ketogenic diet compare quite favorably to responses to additional antiepileptic drugs after failure of two or more drugs (6–9). In a review of 11 studies, Lefevre and Aronson reported that a greater than 90% seizure reduction was achieved by 32%, and 16% of patients became seizure-free (8). Based on such responses, one could argue that the ketogenic diet should be considered in every patient before proceeding with epilepsy surgery. However, further analysis may limit the role of the ketogenic diet in this context. The ketogenic diet is used more frequently in patients with generalized epilepsy than in patients with focal onset seizures, whereas the majority of potential epilepsy surgery candidates have focal epilepsies.

In a retrospective analysis of 134 children treated with the ketogenic diet by Maydell et al. (10), 100 patients had generalized seizures and only 34 had focal seizures. In addition, the results were better for generalized seizures (42% with >50% seizure reduction at one year) than for focal seizures (24% with >50% seizure reduction at one year), although the difference was not statistically significant.

Finally, considering that the use of the ketogenic diet is always limited in time, there are no data regarding seizure relapse rates following discontinuation of the ketogenic diet in seizure-free patients, specifically in the patients with focal onset seizures that might be candidates for epilepsy surgery. But not all patients considered for epilepsy surgery have focal onset seizures, the exception being those considered for corpus callosotomy. These patients often have Lennox–Gastaut syndrome or similar secondary generalized epilepsies with drop attacks. These patients also tend to have a favorable response to the ketogenic diet and should all be tried on the ketogenic diet before being considered for surgery. The same applies to patients with generalized epilepsies being considered for vagus nerve stimulator implantation.

REFERENCES

INTRODUCTION

Epilepsy is a diverse condition, with only a subset of epilepsy syndromes being amenable to neurosurgical treatment. Candidacy for surgery and the likelihood of subsequent seizure control is determined by anatomy—whether epilepsy is focal or generalized, and the sites of seizure origination, and etiology. In this chapter we present an overview of the epilepsies, organized by these two attributes, outlining how surgically remedial syndromes may be recognized and evaluated, and expected surgical outcomes.

LOCALIZATION-RELATED EPILEPSIES

Focal epilepsies are by far the most important group of surgically treated seizure disorders, as seizure-freedom is most often a possibility with surgery, whereas this is not the case for generalized epilepsies.

Temporal Lobe Syndromes

The majority of adult complex partial seizures likely originate within the temporal lobes, most often the mesial structures, and this is the most important group of syndromes treated with resective surgery. As discussed in Chapter XIV-43, it has now been documented in a randomized, controlled clinical trial that patients with
previously uncontrolled temporal lobe epilepsy are more likely to achieve seizure control with surgical, rather than medical therapy (1).

Mesial Temporal

Clinical Characteristics. The mean age of seizure onset for mesial temporal epilepsy for both genders is in the latter half of the first decade (2). Patients with temporal lobe epilepsy due to mesial temporal sclerosis (MTS) often have a history of febrile seizures, though most studies of patients with febrile seizures do not demonstrate an increased risk of adult epilepsy (3).

Commonly reported auras include epigastric sensations, smells, fear, sadness, déjà vu or jamais vu, or auditory hallucinations. Seizures originating from mesial temporal structures often involve characteristic semiologies such as behavioral arrest, mouth movements including lip smacking and chewing, ipsilateral hand movements, head turning, contralateral arm posturing, (both dystonic and tonic) (4). Postictal nose rubbing may be seen, the wiping hand most commonly is ipsilateral to the seizure focus, but can also suggest a contralateral onset (5). Most seizures originating from the temporal lobe are either simple partial or complex partial in nature, however they may later progress to generalized tonic and clonic activity.

Interval periods between epilepsy onset and evaluation at a referral center may be characterized by periods of absent or infrequent seizure activity, particularly prior to adolescence, but later progression to refractory epilepsy. There is often a considerable delay, 18 years on average at our center, between seizure onset and ultimate referral for epilepsy center evaluation and surgical resection.

Pathophysiology. MTS is the most common pathology in mesial temporal epilepsy with changes including neuronal loss and hippocampal gliosis particularly within CA1 and CA3 as well as the granule cell layer of the dentate (6). CA2 cells are less prone to these changes. Animal models suggest the dentate undergoes sprouting of mossy fibers and aberrant neuronal networks, possibly decreasing effective inhibition of seizure and epileptogenesis (7). Similar pathological changes may also occur in patients without seizures, particular in the setting of hippocampal sclerosis dementia, which has clinical features resembling frontotemporal dementia (8). Pathological changes are also present outside the hippocampus—Chapters II-4c and II-4d discuss the possible role of extrahippocampal areas in epileptogenesis. MTS may exist in combination with pathology in other regions of the ipsilateral cerebral hemisphere (“dual pathology”) (9) and familial cases also occur (10). Chapter II-4a discusses current ideas on the pathogenesis of MTS, and the evidence on whether it may be produced by neurological insults early in life.

Mesial temporal epilepsy may also exist with other pathologies, including neoplasms, vascular malformations, and dysplasia. On some occasions, microscopic cortical dysplasia or microdysgenesis are seen in mesial temporal regions (11), but its role in the development of epilepsy and MTS is controversial (Chapters II-6a and II-6b). Some mesial temporal lobe epilepsy cases have no changes on magnetic resonance imaging (MRI) (Chapter II-5). In such cases, surgical specimens may show nonspecific gliosis, end folium sclerosis (12,13), or no definite pathological changes, even in cases when the resection results in seizure control.

EEG Findings. Intertitial and ictal recordings in temporal lobe epilepsies are reviewed in detail in Section V. Noninvasive EEG findings typically include anterior mesial temporal interictal spike or sharp wave activity. Some cases may also have independent contralateral temporal spikes, or even extratemporal spikes, with the
proportion of such cases varying depending on referral patterns and surgical case selection (14). The absence of interictal activity on EEG can suggest an extratemporal origin (15). Noninvasive ictal recordings are variable, but frequently show widespread attenuation followed by the appearance of rhythmic or irregular frequencies that may or may not show lateralized or localized features (14).

**Neuroimaging.** Neuroimaging of temporal lobe epilepsy is reviewed in detail in Sections VI and VII. In patients with presumed MTS, fine cut MRI sequences through temporal lobes structures typically show hippocampal atrophy, presumably correlating with neuronal loss, and, in some cases, progressing over time (16). FLAIR and T2 signal changes correlated best with GFAP positive reactive astrocytes within the dentate (17). Changes consistent with hippocampal sclerosis have also been documented in both asymptomatic relatives of patients with familial temporal lobe epilepsy, and in others with no personal or family history of epilepsy (18,19).

**Treatment Outcomes.** The majority of patients receiving neurosurgical treatment for medically intractable temporal lobe epilepsy achieve seizure control—68% to 69% in one retrospective international survey (20), and 58% at 12 months postoperatively in a randomized controlled trial (1). Factors favoring a good outcome include hippocampal atrophy on MRI, unilateral hypometabolism on positron emission tomography, and interictal epileptiform abnormalities confined to the resected temporal lobe (21–24). Outcomes of temporal resection are further discussed in Section XIV.

**Lateral (Neocortical) Temporal**

**Clinical Characteristics.** While mesial and lateral temporal lobe epilepsy may not be reliably distinguished on the basis of ictal semiology, some seizure symptoms may suggest lateral temporal onset. An experiential aura is often found reported in lateral temporal epilepsy, while an epigastric aura was more often found with mesial temporal seizures (25). Although in this study (25), vocalization, speech, facial grimace, postictal cough, late involvement of the contralateral arm and hand and late oral automatisms occurred similarly, another study (26) reported that lateral temporal lobe seizures lacked features common in mesial temporal seizures, including automatisms, contralateral dystonia, searching head movements, body shifting, hyperventilation, and postictal cough or sigh. In addition, mesial temporal epilepsy patients had an earlier age of epilepsy onset and were more likely to have a prior history of febrile seizures, central nervous system (CNS) infection, perinatal complications, or head trauma (26).

**Pathophysiology.** Lateral temporal epilepsy may be associated with cortical dysplasia, vascular malformation, low-grade focal neoplasia such as dysembryoplastic neuroepithelial tumors, gangliogliomas, and pleomorphic xanthoastrocytomas, or other pathologies such as gliosis from traumatic injury (27). A lateral temporal zone of epileptogenesis may coexist with MTS, representing dual pathology. Removal of both the epileptogenic zone and hippocampal atrophy present in dual pathology has been associated with better surgical outcomes than removal of either the lesion or the hippocampus alone (28).

**EEG Findings.** While noninvasive interictal and ictal EEG findings in lateral temporal epilepsy are similar to those in mesial temporal epilepsy, features have been described which may raise a suspicion of lateral temporal origination. Chief among the scalp EEG findings suggestive of lateral temporal epilepsy is a rhythmic electrographic discharge of lower frequency than mesial temporal cases, with a tendency for
this activity to be distributed over the hemisphere, rather than maximal over the ipsilateral temporal region (26).

**Neuroimaging.** Neuroimaging issues are similar to other neocortical epilepsies. Existence of MRI findings (Section VI) such as foreign tissue lesions—neoplasms or vascular malformations, as well as cortical atrophy or dysplasia may be crucial in raising the possibility of a lateral temporal epileptogenic zone, but hippocampal changes may coexist. Flumazenil positron emission tomography (PET) (Chapter 50) may ultimately be of value in identifying neocortical abnormalities in patients with nonlesional epilepsy.

**Treatment Outcomes.** Although seizure control rates (Engel Class I) as high as 79% have been reported in temporal neocortical epilepsy (29), outcomes depend on case selection and epilepsy etiology. A retrospective survey combining temporal and extratemporal neocortical epilepsy indicated an overall 67% seizure-free rate with lesional epilepsy (19). Nonlesional epilepsies have an overall significantly less favorable outcome with a recent report (30) noting a 37% seizure-free rate.

**Extratemporal Syndromes**

*Frontal*

**Clinical Characteristics.** Frontal lobe epilepsies constitute from 11% to 25% of surgical series (31). Frontal lobe seizures tend to be shorter in duration than temporal lobe seizures, occur more frequently and in clusters, may have a more abrupt onset of clinical manifestations, and there may be a history of status epilepticus (31–34). Frontal lobe seizures may occur predominantly during non-REM (Rapid Eye Movement) sleep (34). A number of distinct semiologies have been described, including motionless staring (“pseudoabsence”), violent and bizarre automatisms with kicking, thrashing, sexual automatisms and vocalizations, contralateral clonus, and contralateral tonic posturing (31–34). Although these subtypes may not reliably localize to a particular frontal region, more often focal clonic seizures are seen with seizure origin in the frontal convexity; tonic seizures are most often seen with origin in the supplementary motor area, and seizures resembling typical temporal lobe seizures with orofacial automatisms are often seen with seizures arising from the orbitofrontal region (34).

**Pathophysiology.** This is similar to other neocortical epilepsies and includes neoplasms, vascular malformations and dysplasia (27). The anterior frontal and temporal poles are prone to injury from traumatic forces with resultant encephalomalacia, gliosis, and posttraumatic epilepsy.

**EEG Findings.** Noninvasive EEG recording may be useful in some cases of frontal lobe epilepsy. Interticial epileptiform abnormalities are reported to arise from the ipsilateral frontal region in 68% (35). Occasionally interstitial abnormalities may be absent, or, if located near the midline, may be difficult to reliably lateralize. It is common for ictal changes to be absent, to be obscured by artifact, or to be diffuse or absent, particularly with seizures of mesial frontal origin. The presence of focal beta activity at electrographic seizure onset on scalp recording is a predictor of good surgical outcome (36). Noninvasive EEG localization of frontal lobe epilepsy may not reflect what is found with later invasive monitoring; in one series 23% of patients undergoing invasive monitoring thought to be frontal from non-invasive recordings had other sites of seizure origination (37).

**Neuroimaging.** Neuroimaging issues are similar to other neocortical epilepsies.
Treatment Outcomes. Reported outcomes are quite variable, with seizure-free outcome ranging from 23% to 67%, with the existence of a structural lesion being the key predictor of a good result (32,37,38). The results of EEG monitoring also predict outcome—one series reported that in 46% of invasively monitored patients with presumed frontal epilepsy a single clear focus was not found, with only 10% of such patients becoming seizure-free postoperatively (37).

Parietal and Occipital

Clinical Characteristics. Unlike frontal or temporal epilepsy, parietal seizures may have more striking sensory or integrative phenomena such as sensory changes, pain, vertigo, or visual changes (39,40). Ictal symptoms that suggest an occipital origin include visual manifestations, dots, lights, and ictal blindness (41). Eye deviation or ictal nystagmus may be seen with medial occipital foci. Additionally, the sensation of seeing a persisting vision of what was previously seen (palinopsia) can suggest an occipital seizure origin (42). In some cases, semiology of parietal and occipital seizures may resemble that of temporal or frontal lobe seizures, presumably due to patterns of seizure propagation.

Pathophysiology. The most common findings are developmental abnormalities (including focal cortical dysplasia, periventricular heterotopia, subcortical band heterotopia, and polymicrogyria), vascular (including post cerebral infarction, cavernous malformations, AVMs, and bilateral occipital calcification associated with celiac disease) or low grade tumors (43–45). Occasionally hippocampal sclerosis may be associated.

EEG Findings. Although noninvasive ictal EEG can be localizing or lateralizing in the majority of extratemporal cases (46), occipital lobe epilepsy is more likely to be characterized by bilateral or diffuse ictal changes. False localization or lateralization is reported to occur in 28% of occipital and 16% of parietal seizures (46). Another study (47) reported localizing ictal EEG in 70% of occipital lobe epilepsy patients, but only 10% of parietal cases.

Neuroimaging. Neuroimaging issues are similar to other neocortical epilepsies. A syndrome of occipitotemporal epilepsy has been described, which may respond to occipital and temporal resection, but not to standard temporal lobectomy with hippocampal resection (48). This condition is associated with a neuronal migration disorder, but is poorly characterized with scalp EEG recording (48). Functional MRI is of value to characterize ipsilateral essential visual cortex when occipital resection is planned (49).

Treatment Outcomes. The majority of patients are seizure-free postoperatively (40,50). Seizure control (40) was better after tumor resection (85% excellent/good) than dysplasia (45%). Presence of clearly lateralizing auras or seizure semiology also is a favorable factor (50).

Lesional Syndromes

Tumors

While metastatic and highly malignant cerebral neoplasms may cause epilepsy, in such cases, the primary treatment goal is diagnosis and institution of appropriate treatment for the tumor. Epilepsy surgery typically deals with benign or low-grade neoplasms, where the main treatment goal is seizure control. Many of these tumors, however, have potential for transformation into a higher grade
malignancy, and, on occasion, additional treatment with radiation or chemotherapy may be instituted. In one large neurosurgical series of 207 patients treated for tumor-related epilepsy, 53 patients had astrocytomas or oligodendrogliomas, and 154 had an assortment of low-grade tumors—gangliogliomas, dysembryoplastic neuroepithelial tumor, pleomorphic xanthoastrocytoma, or pilocytic astrocytoma (51). Three astrocytomas and one ganglioglioma had grade III histology. Resection resulted in an overall excellent outcome (82% seizure-free, and 4% tumor recurrence at five years) (51), with complete tumor resection predicting the best outcome (51–53).

**Gangliogliomas.** Although ganglioglioma represents only a small percentage of all primary cerebral neoplasms (54), it is a common finding in surgical series for chronic tumor-related epilepsy (51,55–58). Most are found in the temporal lobe and consist of both dysplastic neurons and neoplastic glial cells, and the majority display CD34 reactivity, a stem cell epitope not expressed in normal brain (55). Seizure-free rates of 63% to 84% have been reported (51,56,57), with one series (51) reporting a 3% tumor recurrence risk at two years.

**Dysembryoplastic Neuroepithelial Tumor.** These are characterized by small, round oligodendroglia-like cells, astrocytes, and immature neurons with a multinodular, nodular or diffuse arrangement (59). In one third, dysplastic neurons and abnormal cortical lamination is present in adjacent cortex (59). Most are in the temporal lobe, and they are associated with childhood onset partial seizures (59). On MRI, dysembryoplastic neuroepithelial tumors (DNETs) are intracortical lesions without mass effect or edema and decreased signal on T1-weighted images (60). Prognosis for both the tumor and seizures is excellent if it can be completely removed (51,59).

**Astrocytomas and Oligodendrogliomas.** Epilepsy can also result from astrocytomas, or oligodendrogliomas, making up about one-third of series of tumors associated with chronic seizures (51,61). The great majority of these patients are seizure-free after surgery, and even patients with grade II or III astrocytomas had a 10-year tumor recurrence of only 25% (51). This lower risk of recurrence (51,53) may be because of the occurrence in some chronic epilepsy patients of a prognostically more benign isomorphic subtype of diffuse astrocytoma, characterized by histology with low cellularity with little mitotic activity with highly differentiated, but infiltrating astroglial elements (62).

**Other Tumors.** Chronic epilepsy can also result from a number of other benign or low grade neoplasms, including meningiomas (63), pleomorphic xanthoastrocytomas (64), and pilocytic astrocytomas (51). All are associated with a good chance of seizure control and low risk of recurrence if they can be completely removed (51).

**Developmental Abnormalities**

**Focal Cortical Dysplasia (FCD).** FCD is a common cause of refractory epilepsy. The age of epilepsy onset varies from infancy to adulthood, being earlier if there is an associated family history of epilepsy (65). FCD is characterized pathologically by abnormal neuronal layering with columnar disorganization, abnormal dysmorphic, or giant neurons with or without balloon cells (66). Three subcategories have been proposed: (i) architectural dysplasia, characterized by abnormal cortical lamination and ectopic neurons in white matter; (ii) cytarchical dysplasia, with giant neurofilament-enriched neurons and altered cortical lamination, and (iii) Taylor-type cortical dysplasia, where giant dysmorphic neurons and balloon cells are associated with cortical laminar disruption (67).
Histopathological similarities suggest a relationship of Taylor-type FCD to tuberous sclerosis, which is supported by reports of alteration of the TSC1 gene in this type of FCD (68). There is an effort to further revise FCD classification and arrive at a consensus terminology (69).

On MRI, FLAIR or T2 sequences may show indistinct gray white differentiation, broad gyri, thickened cortex, abnormal sulci, or focal enlargement of overlying subarachnoid space or ventricles adjacent to the dyplasia (70). With Taylor-type FCD with balloon cells, MRI changes are most often in extratemporal regions and are characterized by a hyperintense funnel-shaped subcortical zone tapering toward the lateral ventricle (71,72). Architectural dysplasia without balloon cells is more commonly seen in temporal lobes, more often shows focal hypoplasia, and may be concomitant with hippocampal sclerosis (73). About one-third of FCD patients have no evidence of the dysplasia on MRI performed at a referral center (73).

EEG changes may be somewhat characteristic. Electrocorticography may display a distinct, constant interictal activity (“continuous epileptiform discharges”) (74), consistent with the view that portions of FCD consist of intrinsically epileptogenic tissue (66,75), although this pattern may occasionally also be seen in patients with gliosis without dysplasia (75). This activity is detectable on scalp EEG recordings in a minority of cases (76).

The majority of patients become seizure-free after resection of FCD (67–79), with complete removal of the imaged dysplasia being a strong predictor of good outcome. In one study, Taylor-type FCD had the best reported surgical outcomes (75% Engel class Ia), while 50% of cytoarchitectural dysplasia and 43% of architectural dysplasia cases were seizure-free (67).

Tuberous Sclerosis Complex (TSC). TSC is an autosomal dominant disorder with variable expression, which affects multiple organs (80). Two genes are responsible for the disease, TSC1 identified on chromosome 9q34, and TSC2 on chromosome 16p13 (81). Major cerebral findings in TSC are cortical tubers, white matter abnormalities, subependymal nodules, and subependymal giant cell astrocytomas. Cortical tubers consist of non-neoplastic cortical hamartomas, with increased numbers of tubers correlating with greater seizure severity (82). Seizures occur in approximately 90% of patients with onset usually in the first decade and consisting primarily of partial seizures, although infantile spasms and the Lennox–Gastaut syndrome can occur (83). An epileptogenic tuber may represent the principal spike focus with highest amplitude and most frequent spike frequency (84).

Epilepsy surgery in medically intractable patients has led to seizure control in 30% to 67% in different series (85–88). TSC patients usually have multiple tubers and multimodal investigation including interictal scalp and long-term video-EEG monitoring, brain MRI, positron emission tomography (PET) and ictal single proton emission computed tomography (SPECT) studies are used to identify the epileptogenic tuber to be resected (84,89–92). Prognosis for seizure control with epilepsy surgery has been shown to be more favorable in patients with normal development at the time of operation (93). Vagus nerve stimulation may be considered in medically intractable patients where resective surgery has failed or is not an option (94).

Sturge–Weber Syndrome. Sturge–Weber syndrome is manifest by facial port-wine stain in the territory of the trigeminal nerve with ipsilateral leptomeningeal angiomatosis. It is frequently a progressive congenital neurological disorder with contralateral hemiparesis, developmental delay and often difficult to control seizures (95), as well as glaucoma (96). MRI with gadolinium is the most accurate test to
evaluate the extent of intracranial involvement (97,98). If severe hemiparesis is present, hemispherectomy has an excellent chance of achieving seizure control and preventing further developmental deterioration (99–101). Further details about clinical aspects, indications for hemispherectomy, and surgical outcome are discussed in Section III and below in the discussion of hemispheric syndromes.

Schizencephaly. Schizencephaly is a neuronal migration disorder that develops before the end of the second month of gestation. It is characterized by thickened four-layered gray matter lined clefts usually in the frontoparietal region, extending from the pial surface to the ventricular system. The wall of the clefts may be widely separated (open-lip schizencephaly) or closely apposed (closed lip schizencephaly) (102–104). Diagnosis is by MRI (104,105) with unilateral cases being more frequent than bilateral. Schizencephaly is frequently associated with other CNS malformations including polymicrogyria, heterotopias, and septo-optic dysplasia (105–107). Some familial cases have been associated with EMX2 mutation (108). Patients with bilateral schizencephaly have more severe cognitive and motor deficits (109). Seizures usually begin in late-childhood (104,110), with seizures onset often being earlier, and more severe in bilateral cases (105,107,111,112). The epileptogenic zone may lie in the cortical mantle lining the schizencephalic cleft or in associated developmental malformations (104,105,107). Epilepsy surgery may be considered in selected medically refractory patients (111,113); however, even with complete excision of the electrical defined epileptogenic zone, typically significant abnormal cortex will not be resected, implying a lower chance of seizure freedom.

Hypothalamic Hamartoma. Hypothalamic hamartomas are rare lesions that may be associated with precocious puberty or epilepsy. They consist of well-defined masses of mature ganglionic tissue of variable differentiation, usually attached to the tuber cinereum or the mammillary bodies. The pedunculated form is more commonly associated with precocious puberty, whereas the sessile form may be associated with gelastic seizures (114). They are also often associated with cerebral or extracerebral congenital abnormalities, including microgyria, heterotopia, cysts, callosal defects, polydactyly, facial anomalies, and heart defects (114). The presence of active neural tracts connecting the hamartoma to hypothalamic nuclei may explain precocious puberty in many of these patients (115).

Gelastic seizures, the hallmark of the epileptic syndrome, consist of a brief, repetitive, stereotyped attack of laughter, and appear early in childhood. During the first decade, a generalized epileptic encephalopathy develops, characterized by tonic, atonic, and other seizure types in association with slow spike-wave electrographic discharges, cognitive deterioration, and behavioral problems (116,117). The response to antiepileptic therapy is poor. Brain MRI shows nonenhancing isointense or hypointense lesion on T1 images, and hyperintense signal on T2 images (118).

At one time, it was hypothesized that gelastic seizures originated in the temporal lobe because of epileptiform discharges in the temporal or frontotemporal regions on scalp EEG and suggestion of ictal onset in the anterior mesial temporal region (119,120). However, temporal resections are ineffective and temporal pathology is unrevealing (120). Later, evidence emerged that hypothalamic hamartomas are indeed epileptogenic (121,122). Ictal SPECT during typical gelastic seizures demonstrate hyperperfusion in the hamartoma and adjacent hypothalamus (122) and ictal depth electrode recording shows discharges during gelastic attacks strictly confined to the hamartoma (116,119,120,122,123). Furthermore, pathological examination of the hamartoma surgical specimens from patients with gelastic seizures demonstrates dysplastic neurons (122).
Complete or nearly complete microsurgical removal of the hypothalamic hamartoma is technically difficult but may lead to seizure control in a majority of patients, and, if performed early, to improvement of behavioral and cognitive problems (114,117,122–125). Stereotactic radiosurgery has also been used, but its long-term results are not yet established (126–128).

**Vascular**

**Arteriovenous Malformations.** Cerebral arteriovenous malformations (AVM) may present with intracranial hemorrhage or seizures (129–132). AVMs carry an annual risk of developing de novo seizures of 1%, with a good prospect of control on antiepileptic medication (130). Another study of 141 patients showed a higher incidence of epilepsy with male sex, age less than 65 years, AVM size of more than 3 cm, and temporal lobe location (129). In the same study, good seizure control was associated with short seizure history prior to treatment, seizures associated with intracranial hemorrhage, and generalized tonic–clonic seizures.

Computed tomography may show calcification and hypointensity; enhancement is seen after contrast administration and may show the AVM nidus or the draining vein (133,134). MRI can provide critical information on localization and topography, showing an inhomogeneous signal void on T1- and T2-weighted sequences, commonly with hemosiderin suggesting prior hemorrhage (135). However, MRI cannot exclude the presence of micro AVMs (134). Magnetic resonance angiography can provide noninvasive data but may not provide details such as intranidal or feeding aneurysms, comprehensive data on venous drainage patterns or subtle AVM nidus characterization (136). Cerebral angiography is the gold standard for assessment of angioarchitecture and blood flow before treatment planning (134).

AVMs require therapeutic intervention, if possible, in the majority of cases given the risk of hemorrhage and development of seizures (137). Nowadays, there are three available treatment options: embolization, microsurgery, and radiosurgery, sometimes used in combination. Embolization is usually indicated before surgery or radiosurgery for large AVM or nidus volume more than 10 cm (134,138). In addition, palliative embolization may be used in large nonsurgical or nonradiosurgical AVMs in patient with progressive neurological deficit secondary to high flow or venous hypertension (138). Seizure control can be achieved after surgical resection, with a 70% to 83% seizure-free postsurgical outcome (139,140). Stereotactic radiosurgery with gamma knife, proton beam, or linear accelerator is used for AVMs with nidus volume less than 10 cm or located in deep structures or functionally eloquent brain regions (134,138). The effect of radiotherapy takes months or years until the lesion disappears (131,143). Reports show 68% to 85% seizure freedom after radiosurgery for AVM (141–143).

**Cavernous Malformations.** Cavernous malformations (CMs) comprise 5% to 13% of all CNS vascular malformations (144), and are found in 0.4% of MRI series (145). They are dense clusters of sinusoidal vascular spaces without intervening brain parenchyma, which undergo repeated hemorrhage followed by reactive angiogenesis within the lesion and development of dystrophic calcifications (146). Multiple lesions occur in 20% to 40% of cases, especially when familial (147–149). CM may also develop “de novo” in some patients, and new lesions have appeared after brain surgery or radiation therapy (150). Seizures are the most frequent presenting symptom, and are the major cause of morbidity (144,146,151,152). Unlike AVM, CMs have a relatively low risk of hemorrhage of approximately 1% per year (146). MRI is the most sensitive diagnostic tool for evaluation of CM. It demonstrates a well-defined lobulated lesion
on MRI, with a characteristic hypointense surrounding ring of T2 weighted spin-echo or gradient echo parenchyma, related to hemosiderin and ferritin deposits (135,153). They are most often not visualized by cerebral angiography.

Surgery in medically intractable CM-related epilepsy is reported to result in 50% to 97% postoperative seizure-freedom (154,155). Surgery includes lesionectomy plus corticectomy, with removal of the surrounding epileptogenic zone, which may be defined by invasive intracranial monitoring (144,156) (see Chapters IX-28a and IX-28b). Earlier removal of CM may improve overall outcome (151,157,158). While radiosurgery has been used when the CM lies in surgically inaccessible regions (157,159,160), it is not yet established as a treatment for CM-related intractable epilepsy.

**Venous Malformations.** Venous malformations are developmental anomalies of the normal brain venous drainage (161,162), and are usually found incidentally on MRI. Imaging studies show characteristic caput medusae in the late venous phase of angiography with a normal circulation time and a normal arterial phase (163), appearing as a stellate contrast-enhanced mass (164).

Cerebral venous malformations may occasionally be associated with seizures but they usually respond well to antiepileptic medication and are only infrequently treated surgically (165). Venous malformations are often associated with AVMs or cavernous angioma (166,167). In such cases, the suggested approach is removal of the associated vascular malformation with preservation of the venous malformation to avoid postintervention complications (165,168).

**Stroke.** Remote symptomatic epilepsy caused by cerebral injury from cerebral infarction or hemorrhage is common after age 60, and may occasionally be refractory to antiepileptic medications. Surgery is occasionally a consideration, particularly with congenital and childhood-onset vascular insults which will be discussed further under Hemispheric Syndromes below.

**Hemispheric Syndromes**

These may have presumed developmental, genetic or autoimmune etiologies, or be the result of perinatal insults such as stroke or infection. Onset is early in life, with associated hemiparesis, hemisensory deficit, homonymous hemianopsia, and developmental delay. The epilepsy has a variable course but may be severe and disabling.

**Conditions Amenable to Hemispherectomy**

Hemispherectomy can be highly effective in treating intractable adult epilepsy associated with hemispheric syndromes when epilepsy is intractable and a static severe contralateral neurological deficit exists. The surgical procedure and variants are discussed in detail in Section XI.

**Prior Cerebral Infarction.** Prenatal and perinatal vascular occlusions may result in hemiplegic syndromes and make up approximately one quarter of surgical hemispherectomy series (169,170). These insults may lead to porencephalic cysts, often with mild associated cortical architectural abnormalities, or even hippocampal sclerosis (171,172). Good seizure control may follow hemispherectomy if there is a good correlation of clinical, imaging, and electroencephalographic findings (173–175). For example, one series reported seizure freedom or greater than 75% seizure reduction in 91% of patients with a vascular etiology (170).

**Hemimegalencephaly.** Hemimegalencephaly is a dysplastic malformation characterized by overgrowth and abnormal architecture of an entire cerebral
hemisphere, presenting with early onset epilepsy, hemiparesis, hemianopsia, and severe developmental delay (176). It may be sometimes associated with phakomatoses such as neurofibromatosis (177), Klippel–Trenaunay syndrome (178), hypomelanosis of Ito (179,180), linear nevus sebaceous of Jadassohn (181,182), and Proteus syndrome (183). Histopathology shows severe disorganization of white matter and cerebral cortex with presence of migrational disorders and giant neurons or astrocytes (184,185). The contralateral hemisphere may also contain developmental abnormalities.

Structural imaging evaluated by brain MRI is notable for enlarged affected hemisphere and presence of thickening of the gray matter, pachygyria, ventricle abnormalities, calcifications, hypoplasia of the corpus callosum, and, occasionally, schizencephalic cleft. It is also useful for evaluation of the structural integrity of the contralateral hemisphere (176,186). SPECT and 2-[18F]fluoro-2-deoxyglucose-PET (FDG-PET) have also been used to evaluate the functional integrity of both hemispheres (187,188). Although hemispherectomy often leads to dramatic reduction in seizure frequency, the rate of seizure freedom is significantly less with hemimegencephaly and other developmental etiologies of hemispheric epilepsy (175,181)—in one series, only 31% of these patients were seizure-free (170).

**Extensive Unilateral Cortical Dysplasia.** Extensive unilateral cortical dysplasia is sporadic nonfamilial, dysplastic abnormalities of unknown genetic and molecular basis. The clinical presentation consists in contralateral hemiparesis, developmental delay, and medically refractory epilepsy. If there is concordance of imaging and EEG findings, surgical resection can lead to good seizure control (72,189), but, as mentioned in the previous paragraph, seizure control occurs less often than with nondevelopmental etiologies (170,175,181).

**Sturge–Weber Syndrome.** The nature of Sturge–Weber syndrome has been discussed earlier under the chapter section titled “Developmental Abnormalities.” In this syndrome, seizure onset early in life often progresses to severe intractable seizures, contralateral hemiparesis, and developmental delay (95,96). Unilateral cutaneous nevus does not exclude bilateral cerebral involvement (190) but surgery has been performed in cases where one hemisphere is responsible for the majority of the seizures (99). If severe hemiparesis is present, hemispherectomy has an excellent chance of achieving seizure control (99–101), for example, with 81% of patients seizure-free in one series (99) with age at surgery not a factor in the outcome.

**Rasmussen’s Encephalitis.** Rasmussen’s encephalitis is a progressive disease characterized by medically refractory focal epileptic seizures, progressive neurological deficit resulting in acquired hemiparesis, intellectual deterioration, and progressive unilateral hemispheric atrophy. Definitive diagnosis is based on pathology findings with presence of chronic inflammatory encephalitis with perivascular lymphocytic cuffing and microglial nodules in the cortex (191,192).

Serial brain MRI demonstrates slowly progressive ipsilateral brain atrophy, particularly affecting the frontoinsular region and the head of the caudate, with increased signal on T2-weighted images in the cortex and white matter of the affected cerebral hemisphere, and ipsilateral lateral ventricular enlargement (193,194). Cerebrospinal fluid (CSF) exam may demonstrate elevated lymphocyte count and protein levels (195). Some will also have positive glutamate receptor antibodies (GluR3) although this is a not a specific finding (196). Early in the course of disease immunomodulatory treatment including gamma globulin intravenous infusion, high-dose steroids, and plasmapheresis has been advocated to delay the course of the disease (197).
Hemispherectomy has a very high chance of achieving seizure control and cognitive improvement (198). Partial resections in those patients with only slight or moderate hemiparesis result in suboptimal seizure control and do not prevent further neurological deterioration. Section III further discusses the roles of medical and surgical treatment for Rasmussen’s encephalopathy.

**Risks and Functional Consequences of Hemispherectomy**

Even in patients with severe hemiparesis, postoperatively there is often decreased motor function with hypotonia, but typically returning to baseline after the first six months postoperatively (169,199). The cognitive and behavioral impairments associated with hemispheric syndromes may be profound, and in some patients, a goal of hemispherectomy is to prevent further progression of cognitive and behavioral deficits. The best predictor of cognitive skills at follow-up is etiology, with patients with developmental causes being more impaired (200). Cognitive skills at follow-up were similar to preoperative scores for selected patients with severe preexisting hemispheric syndromes (200).

Risks of the surgical procedure itself are discussed in Section XI.

**GENERALIZED EPILEPSIES**

**Lennox–Gastaut Syndrome**

**Clinical Characteristics**

Lennox–Gastaut syndrome (LGS) begins in early childhood and is defined by an electroclinical triad with multiple seizures types, particularly tonic seizures, atypical absence and drop attacks; an EEG with interictal generalized 1.5–2.5 Hz slow spike and wave activity and bursts of generalized paroxysmal fast activity during sleep; and the presence of cognitive delay (201–203).

**Pathophysiology**

LGS is subdivided into cryptogenic and symptomatic groups. Cryptogenic cases, with no identifiable cause, account for 25% to 30% of patients and are characterized by normal neuroimaging findings and normal development prior to seizure onset (201). Symptomatic cases have etiologic factors such as neonatal hypoxic-ischemic encephalopathy, perinatal and prenatal vascular insults, perinatal meningoencephalitis, cerebral dysgenesis, tuberous sclerosis, Down’s syndrome, head trauma, hydrocephalus, brain tumor, or radiotherapy (203). About 10% to 25% have a prior history of infantile spasms (204).

**Ictal Semiology**

Tonic seizures are the most characteristic seizure type, and occur during wakefulness and sleep. During a typical tonic episode, the neck and trunk flex, the arms raise in a semiflexed or extended position, the legs extend, the facial and masticatory muscles contract, the eyes deviate upward, and autonomic changes may occur (203,205). During atypical absences there is progressive, incomplete impairment of consciousness followed by gradual recovery. Purposeful motor activity, drooling, changes in postural tone, and irregular eyelid or perioral myoclonus may be seen (206). Drop
attacks frequently lead to falls and injuries. They may be secondary to brief or prolonged tonic seizures, myoclonic events or loss of tone (207).

**EEG Findings**

The interictal EEG shows diffuse slowing and also anterior dominant generalized spike or polyspike and slow wave discharges, with a frequency most commonly between 1.5 and 2.5 Hz. In addition, 10–25 Hz generalized paroxysmal fast activity may occur during non-REM sleep (203,204).

Ictal events have distinct electrographic patterns. During tonic seizures there is low amplitude suppression or generalized paroxysmal fast activity with a concomitant gradually increasing of muscle contraction (203,204). Atypical absences show bisynchronous, high amplitude, 1.5–2.5 Hz spike and slow wave activity (204,206). Drop attacks have heterogeneous electrographic findings. When more than 1 sec in duration, they may be associated with a run of low amplitude fast rhythm or high amplitude spike wave discharges. Myoclonic drop attacks may show generalized spike wave or polyspike wave discharges, and atonic seizures may have generalized polyspike and wave discharges with loss of tone associated with the slow wave component (203).

**Neuroimaging**

MRI is helpful in evaluating CNS abnormalities in the symptomatic group, and most often shows evidence of diffuse or multifocal processes. PET may infrequently show more restricted focal abnormalities that have been used as a guide for surgical resection in a small number of selected cases (208,209).

**Natural History and Treatment Outcomes**

The long-term outcome in LGS is generally poor with multiple seizures refractory to antiepileptic drugs, mental retardation, and frequent episodes of status epilepticus, (210) with the patients often requiring institutional care. The use of polytherapy with high doses of antiepileptic medications also can worsen cognitive problems. Poor outcome is usually seen in symptomatic LGS, especially if preceded by infantile spasms, onset of seizures before age three years, high frequency of seizures with several episodes of status epilepticus, and the persistence of diffuse slowing of the background and generalized spike–slow wave discharges (201,211,212). Drop attacks are the most refractory to treatment.

Corpus callosotomy may provide reduction of drop attacks (213,214). The typical approach is a partial anterior corpus callosum section, followed by a completing posterior section at a later date in selected patients that fail to respond to the first procedure. A detailed description of the surgical techniques of corpus callosotomy is in Section X. As discussed in that section, the goal of corpus callosotomy is a reduction in the number of tonic and atonic seizures, although a reduction in the number of generalized tonic–clonic seizures may sometimes be seen. Vagus nerve stimulation is also considered as a palliative option and is discussed further below (215,216).

**Generalized Epilepsy Syndromes Not Amenable to Corpus Callosotomy**

Corpus callosotomy is not considered for idiopathic generalized epilepsies such as childhood and juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized
tonic-clonic seizure upon awakening. In severe medically refractory cases, palliative vagus nerve stimulation (VNS) therapy may reduce seizure frequency [217].

VAGUS NERVE STIMULATION

VNS is discussed in detail in Section XII. The Food and Drug Administration (FDA) approved the device in 1997 as therapy for management of medically refractory partial epilepsy in patients older than 12 years [218–221]. It delivers intermittent stimulation to the left cervical vagus nerve trunk by implanted electrodes connected to a subcutaneously placed pulse generator located below the clavicle. Multicenter randomized clinical trials confirmed the long-term safety, efficacy, feasibility, and tolerability of VNS, as well as the durability of the device [221–226]. Side effects are usually mild and may include hoarseness, cough, dyspnea, headache, nausea, tingling sensation in the throat, or sleep disturbance. Neuropsychological testing has not detected adverse effects on cognition [227,228].

Analysis of five controlled multicenter U.S. trials of VNS in focal epilepsy (454 patients) showed a median reduction in seizure frequency of 35% at one year, 44.3% at two years, and 44.1% at three years [225]. Despite this, it is not a substitute for epilepsy surgery, because, unlike resective neurosurgery, VNS very infrequently makes patients with intractable epilepsy seizures free [225]. Rather, VNS efficacy is comparable to that of a variety of antiepileptic medications [229], although its adverse effect profile is quite different from these medications. Its role in treatment of intractable epilepsy should be judged in this context (Chapter XII-36).

SUMMARY AND CONCLUSIONS

The epilepsies are made up of diverse syndromes, which differ greatly in etiology, anatomy, and natural history. This chapter has demonstrated that epilepsy syndrome determines how judging surgical candidacy, the presurgical workup, and operative planning will be approached. Prerequisites for epilepsy surgery include medical refractoriness (Section I) and the presence of an epileptic condition that is severely affecting aspects of the patient’s life, including health, social, and cognitive development (Section III), relationships, and employment (Section XVI). These factors are interdependent, for judgments regarding medical refractoriness can only be made in reference to the chance of a successful outcome, which is largely a function of the epilepsy syndrome (Section I).

REFERENCES


Who Is a Surgical Candidate?


Who Is a Surgical Candidate?


Chapter II-4

The Anatomy and Pathophysiology of Mesial Temporal Epilepsy

Chapter II-4a: Is Mesial Temporal Sclerosis Caused by Early Childhood Neurological Insults?

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Early childhood seizures have long been reported in association with later development of intractable temporal lobe epilepsy (MTLE) with mesial temporal sclerosis (MTS). These findings, mainly from retrospective human studies, appear to conflict with extensive animal data which demonstrates a relative resistance of the immature brain to early seizures. We will present the view that the question of whether early seizures, such as febrile seizures, “beget” MTLE with MTS is as yet unanswered and the occurrence of MTS may be dependent on age, prior neurologic injury, nature of the insult, and genetic considerations.

MTLE with MTS DEFINED

MTLE with MTS consists of partial seizures beginning in mid-to-late childhood, with a clear increased incidence of complex febrile convulsions or other predisposing insults in the first five years of life. The magnetic resonance imaging (MRI) appearance of an atrophied hippocampus with high gradient-echo signal supports the diagnosis.

Pathological examination of the hippocampus and associated tissues shows mostly neuronal cell loss and gliosis at CA1 and end-folium, with relative sparing
of transitional cortex. There are also structural and functional glial changes, synaptic reorganization (not limited to the mossy fibers and supragranular layer of the dentate gyrus), and dentate granule cell dispersion.

**WHAT IS THE RELATIONSHIP BETWEEN EARLY SEIZURES AND MTS/MTLE IN HUMAN STUDIES?**

Although MTS is rarely identified in children, retrospective studies identify an association between febrile seizures (1), prolonged initial seizures or other early precipitating injuries, particularly before age five (2), and MTS noted later in life. Unfortunately, prospective evidence is scant. The association between febrile seizures and ensuing epilepsy may be related to preexisting pathology (3). If prolonged febrile seizures were causally associated with MTLE, then the risk of MTLE should be reduced with febrile seizure prophylaxis; however, this is not the case (4). These findings support the hypothesis that both febrile seizures and subsequent MTS/MTLE are related to parallel processes.

MRI findings consistent with MTS have been reported both to be present (5) and absent (6) in infants prospectively evaluated following prolonged febrile seizures. Multicenter, prospective studies will be needed to determine whether seizures early in life produce MR changes associated with subsequent epileptogenesis. One such study is underway, supported by NINDS (Shinnar PI).

**DO RESULTS FROM EXPERIMENTAL MODELS CLARIFY THE RELATIONSHIP BETWEEN PROLONGED SEIZURES/STATUS EPILEPTICUS AND HIPPOCAMPAL CHANGES?**

Seizure-induced hippocampal injury in animal models of seizures and status epilepticus (SE) is age-related. The discussion of age-dependent features in rats must be prefaced by contrasting the rat lifespan to the human lifespan (7). The rat is born precociously, equivalent to a premature human newborn, and at seven to eight days is considered equivalent to a human full term newborn. Rats begin puberty between 33 and 38 days of age, and reach adulthood by 55 to 60 postnatal days.

Following SE in adult rodents, a chronic epileptic state emerges characterized by neuropathological changes resembling MTS (8). These findings are relatively absent in immature animals. Although pups below P20 are more prone to develop acute seizures and status epilepticus, their hippocampi are strongly resistant to seizure-related injury in the pilocarpine (9), kainic acid (10), and kindling (11) models (12).

These findings cannot be explained by a decreased involvement of the hippocampus at the younger age. Metabolic mapping studies demonstrate that the hippocampus is highly active at all ages tested in the kainite and kindling models (13,14). Proposed physiologic mechanisms for the resistance of the immature hippocampus include altered GABAa receptors (15), higher GluR2 levels (16), and resistance to effects of lactate (17) in immature pups.

The resistance of the immature hippocampus is not absolute, and neuropathologic changes following seizures may be evident in certain models. Following corticotropin-releasing hormone (CRH)-induced SE, degeneration is evident in CA3 pyramidal neurons postsynaptic to mossy fibers (18). Mossy fiber sprouting without neuronal loss has been documented after exposure to 15 daily pentylenetetrazol-induced
convulsions (19) and recurrent flurothyl-induced brief seizures (20) in immature animals. Additionally, behavioral or cognitive changes may be demonstrated following early seizures, even in the absence of neuropathology (21), although these changes are less severe than in adult animals.

Hippocampal excitability following SE in animal models is also age related; “both” neurophysiologic changes and the development of epilepsy appear to be similarly age related. The younger the animal, the lesser the likelihood of spontaneous seizures. Spontaneous seizures may occur if SE occurs after P21; two-thirds or more will develop chronic epilepsy (22). Of rats that develop epilepsy, approximately one-third manifest only spontaneous seizures, one-third have only handling-provoked seizures, and one-third have both (23). Rats younger than PN21 do not develop spontaneous seizures in the pilocarpine (24) and kainate (25) models of SE, or following febrile SE (26). There may be, however, evidence of long-term enhanced hippocampal excitability to subsequent convulsant exposure as age increases from P10 to P20 in some models (26) but not others (25). This should be contrasted with the universal increases in seizure susceptibility seen in adult models. Interestingly, repetitive seizure, i.e., kindling, permanently alters the seizure susceptibility at all ages (7).

Seizures early in life, however, modify the brain even in the absence of documented neuronal loss. Neonatal SE on PN4 inhibits brain DNA synthesis and reduces seizure threshold for several weeks, in the absence of histological changes (27). Increased excitability may be related to functional alterations in gene expression in hippocampal neuronal populations. Expression of the genes encoding the hyperpolarization-activated depolarizing current may be reduced following prolonged seizures on PN10 (28), and changes in the high-voltage calcium current amplitude and a faster inactivation of the high voltage-activated, slowly inactivating calcium (HVA) current have been demonstrated in CA1 and dentate granule neurons following SE (29). A proepileptogenic circuit related to intense bursts of neuronal activity thus may render the immature hippocampus highly excitable to future hippocampal excitants. The significance of these changes must be interpreted with caution however, as they may represent compensatory changes without specifically being the cause of future epileptogenicity.

All these studies have been performed in normal rodent brains. Other variables may affect the susceptibility of the hippocampus. Enhanced epileptogenesis is associated with the presence of neuronal migration disorders (30) and perinatal ischemia (31). The release of cytokines such as interleukin-1B (IL-1B), which has proconvulsant properties (32), is increased with infection-related seizures, and in fact, the presence of high IL producer alleles has been linked to MTLE in human studies (33). Changes in cytokine gene transcription after SE are age dependent (34) and very limited in rats younger than PN21. Other aspects of genetics likely contribute to seizure susceptibility in the rat, as in humans. More extensive studies are forthcoming.

CONCLUSIONS

The sequelae following exposure to prolonged seizures in most experimental models emerges as a spectrum. At one end of this spectrum is the full syndrome of MTS with chronic epilepsy in the adult, while at the other end of the spectrum is a normal-appearing hippocampus with no spontaneous seizures in the immature animal. Clearly, between these two extremes, there exists a range of neuropathologic or neurophysiologic manifestations which may occur following prolonged early seizures,
and the outcome is likely affected by age, genetic predisposition, presence of underlying brain disease, and specific infectious insults. The possibility of a “two-hit hypothesis,” where an early insult renders the hippocampus more excitable to a second, later insult, also emerges from the current experimental literature. However, from the animal data, no firm conclusion can be reached linking seizures in the immature brain as the cause of the later development of chronic epilepsy with classic MTS.

Similarly, in human studies, the question remains: Does the association between early seizures, particularly febrile seizures, and MTLE with MTS represent a specific cause and effect, or are these parallel processes with a common pathologic substrate? This cannot be resolved without long term outcome studies, which have not been completed to date.

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Chapter II-4b: The Role of the Hippocampus in Mesial Temporal Lobe Epilepsy: Historical Perspective

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This chapter presents the evidence that the majority of medically intractable, but surgically treatable, temporal lobe epilepsies are attributed to anatomic pathology and anomalous physiologic firing patterns in remnant neurons and aberrant synapses in the hippocampus alone.

HISTORY OF MESIAL TEMPORAL LOBE EPILEPSY AND HIPPOCAMPAL PATHOLOGY

In 1825, Bouchet and Cazauvieilh described brain autopsy specimens from 18 epileptic patients, 14 of them were classified as having “alienation epilepsy” with auras with the characteristics typical of what we now know as hippocampal epilepsy. The authors did not actually realize that the postmortem Ammon’s horn damage was directly related to these seizures. In 1880, Sommer summarized all the available reports on epileptic patients with postmortem brain evaluations, noting asymmetric hippocampal atrophy in 76 of 90 patients. More recent studies support this observation (1). Although Sommer could not define the source of this hippocampal atrophy, he clearly believed it was an etiological element of epilepsy. Bratz also emphasized that epileptic attacks were the result of hippocampal pathology, although he did not suggest its cause (2).

In 1927, Spielmeyer proposed that hippocampal neuron loss resulted from ischemia due to various conditions, most often status epilepticus. Scholz (3) extended
this notion by coining the term “ictal damage” (3) but later raised the critical question of whether or not such ischemic neuronal loss can become epileptogenic (4).

In 1941, Jasper and Kershman (5) reported recording electroencephalogram (EEG) spikes in the temporal neocortex and laterally as deep as the fusiform gyrus, concluding that the most vigorous EEG spikes were found in the cortical “rhinencephalon” deep to the lateral temporal lobe.

By 1948, the diagnosis of temporal lobe epilepsy was often based on EEG recordings with “low temporal spiking.” Gibbs persuaded Bailey (6) to perform cortical resections or lobectomies to treat these seizures. However, the success rate was only a 50% reduction in seizures in about 50% of cases, with no correlation between the amount of cortex removed and outcome. Therefore, it appeared that the zone of epileptogenesis was not in the cortex overlying the hippocampus or hippocampal gyrus.

By the 1950s, other surgical epilepsy teams had developed the “en bloc” temporal lobe resection, which excised the hippocampal formation, including the hippocampus, in a single, intact specimen. When examined postoperatively, hippocampal sclerosis was present in 90% of the cases of temporal lobe seizures (7,8). Because of this work, it was important to verify that seizure onset occurred first in the hippocampus before spreading to neocortical areas.

Over the past 30 years, the findings from the University of California, Los Angeles, (UCLA) epilepsy program has addressed these issues (9–14). This program studied patients with medically intractable temporal lobe epilepsy, and many had scalp EEG showing bitemporal, independent discharges or diffuse temporofrontal discharges. Routine scalp EEG recordings were not very diagnostic if surgical treatment was being considered. It was decided to develop a method for long-term in-patient video monitoring synchronized with chronic direct brain stereotactically implanted (SEEG) recordings to allow correlation with standardized behavioral observations to search for the origin of temporal lobe epilepsy. Over the years, the accuracy of stereotactic guided electrode implants was significantly improved to increase the computational resolutions in neuroimaging of multimodal image analysis systems for simultaneous display in each patient of computed tomography (CT), magnetic resonance imaging (MRI), digital subtraction angiography (DSA), and positron emission tomography (PET) scans adjusted for common coordinates (15).

There were two constants over the years in this series: (a) the arrays of depth electrodes, and (b) the use of standard “en bloc” anterior temporal lobe lobectomies. The standard bilaterally symmetrical recordings included the amygdalae and the anterior, middle, and posterior pes hippocampi and parahippocampal gyri, allowing comparison between the seizure and the contralateral sides. The plane orthogonal to the midline through the temporal lobes and medial to the temporal horn was used for implants to avoid major vessels and for reliability in the basic science studies. Standard “en bloc” anterior temporal lobectomy meant that the entire anterior 5.5 to 6 cm of the temporal lobe from the middle temporal gyrus medial to the cisternae of the hippocampus removed in one piece so that it could be studied in its proper anatomic orientation.

HIPPOCAMPAL NEURONAL FIRING DURING EPILEPTOGENESIS

While macroelectrode SEEG and radiographic markers defined the boundaries of the epileptogenic lateral neocortex compared to the more mesial archicortex—the
hippocampus, we reasoned that the physiologic properties of neurons might provide even better localizing information. In 1971, we developed a simple method for chronically recording extracellular action potentials at all SEEG sites. Bundles of fine wires (40 μm diameter each) were inserted through each cannula macroelectrode, forming sprays of nine microelectrodes protruding about 5 mm from the end of the cannula (16). Ipsilateral to the hippocampal seizure focus, when interictal SEEG sharp waves were recorded from the nearby cannula tip and had fast rise times (e.g., <16 ms base to peak), then the fine wires detected single or multiple action potentials. However, bursts of action potentials also occurred in the absence of regional SEEG sharp waves, indicating that neurons may fire without generating large field SEEG “spikes” (17,18). During the low-amplitude, high-frequency SEEG activity, variable firing rates followed until the clonic SEEG phase, where a reliable excitation of neurons occurred during the sharp SEEG waves and strong inhibition during the following slow SEEG waves (18). Our data strongly suggest that the neuronal population that depolarizes synchronously determines the extent of seizure propagation. Hence, the neuronal “pool” in the hippocampus fired rapidly, recruiting adjacent neurons, many of which projected diffusely to other sites, such as to the subicular complex and entorhinal cortex.

SUBCLINICAL AND CLINICAL SEIZURES

To test the hypothesis that neurons increase their firing rates in a region of hippocampus or amygdala that has SEEG seizure waves, it was necessary to record both SEEG and extracellular action potentials from the same microelectrodes permitting spatiotemporal correlations between neuronal firing, SEEG patterns, correlations with the spread of SEEG seizures, and behavioral alterations during ictus. One of the most important distinctions was between the seizure intensity, i.e., subclinical or clinical alterations correlated with the electrophysiological changes in the hippocampus (18). Subclinical seizures were typically prolonged discharges from a focus that had a typical SEEG seizure onset pattern and ipsilateral propagation but no significant changes in the majority of neurons. Even though we had limited sampling of neurons for each subclinical SEEG seizure, we would expect to randomly detect increased firing if, for example, only 25% of the neurons were recruited during such mild SEEG seizures. However, in seven of nine subclinical seizures there were no detectable increases in single or multi-unit firing despite the presence of SEEG seizure waves recorded by the same microelectrodes. There were 10 neuronal recordings for each of the nine subclinical seizures (90 units) and only six neurons increased firing by two times or more at some point in the SEEG seizures. This supports our previous report on subclinical seizures (16); however, the estimate of 7% recruitment of neurons (6 of 90 units) during subclinical seizures is a new finding that may help to explain why there is normal consciousness, memory encoding and recall during such abnormal ipsilateral hippocampal SEEG waves.

There was no consistent relationship between the neuronal firing pattern and the SEEG pattern to distinguish between subclinical and clinical seizures. However, when an SEEG seizure (with movements) occurred, there were always a few neurons that increased firing bilaterally in the hippocampi. When the clinical seizures were limited to auras, units rarely fired. Since there were only three seizures with auras and three with movements, it is difficult to quantitatively compare the relative...
percentage of units recruited during auras versus those with increased psychomotor seizures. However, the best estimate is 4 of 29 units in three aura seizures or 14% neuronal recruitment, which is roughly twice the number of neurons estimated to fire in subclinical seizures. By contrast, during three behavioral seizures 12 of 33 neurons increased firing in the hippocampus, indicating that 36% of hippocampal neurons are recruited, providing greater synaptic divergence to bilateral temporal lobe structures and propagating to more neocortical areas (18). However, these numbers are only estimates from a limited number of spontaneous types of temporal lobe seizures. These data suggest the relative degree of neuronal recruitment that may generate seizures of increasing severity. Similar conclusions were found by Babb and Crandall (17). In two other published papers with hippocampal microelectrode recordings during spontaneous seizures, there were clear increases in hippocampal multi-neuronal firing coincident after the spread of the SEEG seizures into the hippocampus from their occipital lobe focal SEEG onset (19,20).

**HIPPOCAMPAL SEEG PATTERN AND NEURONAL FIRING DURING SEIZURES**

As indicated earlier, most hippocampal SEEG seizure onset patterns recorded with microelectrodes were similar with decreased amplitude at the start and a modal frequency of 9 to 15 counts/sec. During the onset period, which usually lasted two to five seconds neuronal firing rate increases were most likely to occur. With subclinical seizures or auras, neuron firing rates did not usually increase; whereas local firing did increase for behavioral seizures. The increased neuron firing, however, was usually shorter than the SEEG pattern, and the firing often stopped when the SEEG pattern slowed (17). Even during the most significant SEEG seizure onset pattern, the population of neurons needed to fire for seizure propagation is surprisingly small, and neither the rate nor the duration of single cell firing is great. Rather, it appears that in the various human focal SEEG seizures, brief synchronous firing of neurons in the epileptic focus is sufficient to sequentially activate neurons one or several synapses away.

**MODEL OF FOCAL HIPPOCAMPAL SEIZURE GENESIS AND PROPAGATION**

These studies of local SEEG seizure patterns and neuronal firing during spontaneous seizures cannot fully define seizure mechanisms in human temporal lobe epilepsy, but do suggest a feasible model of focal epileptogenesis and seizure propagation. First, SEEG seizure onset waves are probably generated by synchronous excitatory postsynaptic potentials (EPSPs) in a relatively numerous and widespread population of neurons constituting a very large “epileptic pool.” This is supported by the fact that virtually all of the nine microelectrodes record the same SEEG seizure patterns even though their tips may be 3 to 5 mm apart. However, despite such widespread EPSPs, most of the depolarizations are sub-threshold for spike generation. Apparently as few as 7% actually increase discharge rates during SEEG seizure waves that clearly propagate to other hippocampal regions: e.g., from anterior to middle Ammon’s horn. With more distant and widespread propagation, typical of complex partial seizures, more focal neurons actually discharge, presumably in order to recruit more neurons
several synapses away and interfere with normal function, i.e., produce an aura or a clinical seizure.

Our data suggest that possibly 36% of neurons discharge rapidly to promote widespread seizure propagation and behavioral seizures, which would have to involve the motor cortex to elicit automatisms or partial complex body movements. A second important and consistent finding was that the duration of SEEG seizure onset waves was much longer than the “burst” of associated discharges from nearby focal neurons, suggesting that for any given instant only a small percentage of neurons in the epileptic focus fire repetitively. This leads to the conclusion that these “triggered” cells trigger other cells synaptically and this sequential activation of other synaptic targets propagates seizure activity. It is surprising that so few neurons actually fire in the hippocampus preceding propagation of SEEG seizure patterns to the neocortex and the clinical seizure.

Finally, although SEEG seizure patterns distant from the focus (first onset pattern) are easy to detect, there appear to be even fewer neurons firing at distances or at propagated sites. For example, during a clinical-behavioral seizure propagated SEEG seizure patterns are seen ipsilaterally and contralaterally, but neuronal firing is only slightly increased when compared to the firing at the hippocampal focus. This lack of widespread recruitment sufficient to cause action potentials may be due to lack of temporal or spatial summation either of which would contribute to supra-threshold regenerative depolarization. In short, our data strongly suggest that there is a population of focal neurons that depolarize synchronously and are more likely to discharge. The percentage of neurons that discharge apparently determines the extent of seizure propagation and eventual seizure severity.

This model of seizure genesis is based on spontaneous temporal lobe seizures where neuronal recordings were limited to the archicortex, that is, the dentate gyrus and hippocampus. Although in humans, the true archicortex represents only approximately five percent of the volume of the temporal lobe, nevertheless, the major structures of the temporal gyri (fusiform, inferior, middle, and superior temporal cortices) do not appear to primarily initiate temporal lobe seizures, except for the rare instances of epileptogenic tumors. Although the sampling limitation of 12 microelectrodes for each seizure seems problematic, the microelectrodes were placed in the same structures for all patients. Hence, it is valid to compare the SEEG seizure patterns in these structures in estimating the relative firing rates and patterns for different seizure onsets and propagation.

HIPPOCAMPAL PATHOLOGY AND REACTIVE SYNAPTOGENESIS

Although it has long been known that peripheral axons with distal damage may regrow and reinervate skin or muscle groups previously denervated, regeneration of central axons, severed near their cell bodies, did not grow and reinervate target skin or muscle. Liu and Chambers (21), however, did find intraspinal de novo growth of dorsal root axons that reinervated motoneurons previously denervated. Studies of adult mammalian brain axons have failed to demonstrate true functional, compensatory axonal regeneration. This is best illustrated by the presence of irreversible scotomas, dysphasias, and paralyses following lesions to specific neocortical regions.

Rose et al. (22) demonstrated postlesional neocortical collateral axon “sprouting” in rabbits whose ages ranged from four weeks (immature) through full adulthood.
Ionizing radiation was limited to certain cortical laminae (e.g., layer four), while sparing nearby layers or adjacent laminae. They found microscopically that all the lesioned zones were eventually filled in by axonal sprouts because the fibers ran in abnormal directions and formed denser, irregular networks, demonstrating adult central nervous system (CNS) collateral axon ingrowth to a denervated zone. They suggested that throughout life such mature mammalian central neurons have the capacity for continuous axon growth, especially if their axon collaterals are intact and if the neurons are physiologically active. Finally, they commented that “even dendrites can sprout,” which were findings reported by Lafora (23), and “considered incontestable” by Ramon y Cajal (24).

During the 1970s, the concept of collateral axonal sprouting and reactive synaptogenesis was studied using well defined lesions of the entorhinal cortex inputs to the rat hippocampal fascia dentata (25). In hippocampal epilepsy, the extensive cell losses result in many areas of axonal denervations and reinnervations (26). The best-studied example of synaptic reorganization is the mossy fiber sprouting into the inner molecular layer, a finding observed in all patients with hippocampal epilepsy (26–28). “Inhibitory” gamma-aminobutyric acid (GABAergic) axon sprouting into the inner molecular layer has also been reported (9). Synaptic reorganizations by excitatory mossy fibers and by GABA axons as related to seizure sensitivity and hyperexcitability in human epileptic hippocampus may provide mechanisms explaining neuronal firing localized to the hippocampus proper.

In human epileptic hippocampus, electron microscopy of Timm-stained mossy fibers has demonstrated that, in the inner molecular layer, the most frequently found asymmetric synapses are mossy fiber terminals, as indicated by large vesicles with Timm granules (10). In the outer molecular layer, asymmetric synapses have smaller boutons and smaller vesicles with no Timm granules, forming synapses from the perforant path axons of the entorhinal cortex. The appearance of the mossy fiber terminals, synaptic clefts, and postsynaptic densities in the epileptic inner molecular layer supports the conclusion that these synapses are functional and probably excitatory (10). This leads to the concept that synaptic reorganization of damaged hippocampus leads to aberrant mossy fiber monosynaptic excitatory feedback or feedforward circuits that would be maladaptive and contributory to seizure susceptibility. In addition, there are anomalous GABAergic terminals throughout Ammon’s horn, terminating on both pyramidal cell bodies and on their dendrites. These GABAergic synaptic reorganizations are further evidence that following damage to the hippocampus, the remaining neurons and their axons will provide collateral axon innervation to denervated synaptic zones. It seems unlikely that either too much excitation or too little inhibition alone explains epileptogenesis. Enhanced inhibitory mechanisms could synchronize the membrane potentials so a greater population of neurons reach firing threshold simultaneously, allowing the next mossy fiber recurrent excitation to trigger seizures in an otherwise cell-poor region.

CONCLUSION

Mesial temporal epilepsy is focal hippocampal epilepsy. This conclusion is based on extensive and diverse evidence, which includes pathological studies, invasive SEEG recording, recordings of neuronal activity, and surgical outcomes.
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Chapter II-4c: The Epileptic Focus in Mesial Temporal Epilepsy Is in Both the Hippocampus and the Entorhinal Cortex

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INTRODUCTION

The hippocampus (HC) has been implicated since the late 19th century as causing what we now identify as complex partial seizures typical of temporal lobe epilepsy (TLE). It was then that Wilhelm Sommer first described selective loss of neurons in hippocampal area CA1 of patients suffering from nonconvulsive seizures. Since that time, it has become clear that this characteristic pattern of mesial temporal sclerosis (MTS)—with cell loss and gliosis predominating in hippocampal areas CA1, CA4, and the hilus of the dentate gyrus, but sparing CA2, CA3, and dentate granule cells—is present in the majority of patients with intractable temporal lobe epilepsy (1). Because the outcome of patients with TLE undergoing anterior temporal lobectomy with hippocampectomy is improved in the setting of proven MTS, the hippocampus has remained a focal point of research into the underlying cellular and molecular causes of epilepsy. Understanding of the role of other parahippocampal brain regions, such as the entorhinal cortex (EC), in the pathogenesis of epilepsy has been slower to develop. Undoubtedly this is because of the far subtler
alterations of cellular anatomy that occur in that six-layered neocortex compared to
the striking changes in the simplified cellular laminae of the HC. Nonetheless, there
is a growing appreciation of the interrelated behavior of the various “limbic” tem-
poral lobe structures, and their derangements in TLE. This chapter will review the
evidence for and against the exclusively hippocampal causation of TLE, and whether
the EC can be shown to play a role.

ANATOMIC CONSIDERATIONS IN TEMPORAL LOBE FUNCTION

The temporal lobe comprises several interconnected areas which are the principal
ictal sites of origin in TLE (Fig. 1). At the functional center of the temporal lobe
is the hippocampal formation, which abuts the temporal horn of the lateral ven-
tricle. The hippocampal formation consists of the HC proper (Ammon’s horn),
which is subdivided into four cytological zones (CA1–CA4), and the dentate
gyrus (DG), which is separated from the HC proper by the hippocampal fissure;

Figure 1  Anatomy of medial temporal lobe structures. Coronal brain section shows the relationship of the parahippocampal gyrus to the hippocampal formation. Pyramidal neurons in layer II of the EC project via the perforant path to DG granule cells. A secondary projection from the EC includes layer III pyramidal neuron axons synapsing onto CA1 hippocampal pyramidal neurons. Within the hippocampus, the classical “trisynaptic” pathway consists of DG cells projecting via the mossy fibers (mf) to CA3 pyramidal neurons, which, in turn, project to area CA1 via the Schaffer collaterals (sc). The primary output of the hippocampus to the temporal lobe consists of CA1 pyramidal neurons projecting to the subiculum and the EC. Abbreviations: EC, entorhinal cortex; DG, dentate gyrus.
the interleaved laminae of the HC proper and the DG are usually collectively referred to as the “hippocampus.” The circuit formed by the projection of the DG to area CA3 (the mossy fibers), and from CA3 to CA1 (the Schaffer collaterals) is termed the “trisynaptic” pathway. The clear anatomic definition of this circuitry, and the fact that it can be captured largely intact in a transverse tissue slice of the HC, has led to its widespread use in in vitro physiology experiments. However, it would be incorrect to think of the hippocampal formation as a series of functionally separate “slices”—rather, anatomical and physiological evidence suggests that activity within the hippocampus propagates along the septotemporal axis as well as within the transverse plane (2).

Hippocampal area CA1 is contiguous with the subiculum, which flows to the EC, both a part of the parahippocampal gyrus. Cytologically, the three-layered archicortex of the HC proper transitions gradually to the six-layered isocortex of EC (3). The collateral sulcus divides the parahippocampal gyrus from the three gyri of the temporal neocortex. Axons of CA1 pyramidal neurons form the main outflow of the HC, bifurcating to send processes along the alveus to form the fimbria/fornix, and into the subiculum and EC. The former pathway is the hippocampal projection to the thalamus and septal nuclei; the latter forms the hippocampal output to the temporal lobe. There is anatomic evidence of a projection from HC pyramidal neurons to the contralateral HC via the hippocampal commissure, which may play a role in bitemporal seizure propagation (4).

The inputs to the HC arise principally in the EC (aside from cholinergic afferents from the septal nuclei which project via the fornix). The projection from the EC to the DG forms the perforant path. While this pathway has been appreciated since the time of Cajal, more recently it has become clear that the perforant path in fact comprises two topographically separate pathways from separate cells of origin in the EC (5). The classical perforant path input to DG largely arises from EC layer II neurons, and is distributed to DG granule cells, and CA3 and CA2 pyramidal neurons. A separate perforant path component is formed by projections from layer III neurons, and this is distributed to CA1 and subiculum; this latter pathway also has a rostral–caudal topography, such that more rostrally-located layer III neurons more strongly project to area CA1 (2,6). This layer III projection to CA1 has been identified on physiological as well as anatomical grounds, providing excitatory input to the distal dendrites of CA1 pyramidal neurons (7). Thus the EC is connected to the HC via two separate projections resulting from two distinct neuronal populations, raising the intriguing question of whether these two systems may be differentially involved in epileptogenesis.

EVIDENCE FROM ANIMAL MODELS FOR INVOLVEMENT OF THE HIPPOCAMPUS OR ENTORHINAL CORTEX IN TEMPORAL LOBE EPILEPSY

Support for the primacy of hippocampal pathology in TLE has come from the development of animal models of TLE, such as the kainate and pilocarpine models (8). In these models, application of a convulsant agent (kainate, a glutamatergic agonist; pilocarpine, a muscarinic acetylcholine agonist) produces acute status epilepticus. After termination of the status with benzodiazepines, the animals recover and after a latent period go on to have chronic, spontaneous seizures. The neuronal pathology produced by these models is widespread, affecting CA1 and CA3 HC, olfactory
cortex, neocortex, substantial nigra and thalamus, and appearing within 24 hours after the acute status (9). This neuropathology is generally assumed to result from excitotoxicity occurring during recurrent seizures, as application of these drugs in the presence of anticonvulsants does not produce widespread pathology. The cell loss in the HC is reminiscent of MTS, with the greatest loss of neurons occurring in CA1 pyramidal neurons, followed by CA3 pyramidal neurons, but with relative sparing of DG granule cells. Invasive EEG recordings in experimental animals support the idea that the HC shows the first signs of electrographic discharge compared to overlying cortex, both during the acute status episode and later during recurrent seizures (10). However, the studies documenting seizure onset in these rodent models have tended to be few and anecdotal, and have not systematically probed seizure onset from varying brain regions, i.e., EC versus HC.

In vitro brain slice preparations have allowed investigation of epileptiform activity in neurons under controlled experimental conditions. Using standard techniques to elicit neuronal hyperexcitability, such as elevated extracellular potassium concentration, CA3 pyramidal neurons fire synchronized bursts of action potentials that propagate to area CA1 and resemble interictal EEG spikes. Such activity can drive ictal-appearing prolonged electrographic discharges in CA1, suggesting that the intrinsically burst-prone CA3 produces interictal spikes which then trigger ictal discharges in CA1 and other temporal lobe areas (11,12). However, a different perspective on the role of CA1 in promoting epileptiform activity was gained from a recent in vitro study performed using hippocampal slices from patients with MTS in which interictal-like spiking activity was seen not in CA1 or CA3, but in the subiculum. The authors hypothesized that loss of afferent input from the sclerotic CA1 caused a reorganization of inhibition in the subiculum, followed by hyperexcitability of subicular principal neurons (13).

Study of entorhinal pathology in animal models has followed from initial observations in human patients which found selective loss of layer III EC neurons in TLE resection specimens, either in the presence or absence of MTS (14). This pathology was most notable in the medial EC. Similar to what has been observed in human TLE, EC pathology in animal models has been limited to medial EC layer III pyramidal neurons, with relative preservation of parvalbumin-positive inhibitory interneurons, again suggesting that excitotoxicity was the mechanism of neuronal death (15). Surviving layer III EC pyramidal neurons are intrinsically hyperexcitable after status epilepticus, owing to a downregulation of dendritic voltage-gated channels (16). While layer II EC principal neurons are not as vulnerable as their layer III counterparts, they also become hyperexcitable in status epilepticus models, demonstrating prolonged firing and a deficit of GABAergic inhibition that does not appear to result from loss of inhibitory interneurons, but may reflect loss of layer III pyramidal neuron inputs (17). Together, these results point to increased excitability of EC neurons in TLE, which may influence the HC via the perforant path.

Despite this propensity of the EC to generate epileptiform discharges in vitro preparations, it has been experimentally difficult to demonstrate transmission of this activity through the perforant path and into the hippocampus proper. In vitro studies of DG granule cell physiology have established the relatively inexcitable behavior of these neurons in response to excitatory input, yielding the notion of the DG as a “gatekeeper” to the HC, filtering out potential proconvulsive input from the EC. Several pathological processes may alter the flow of activation from EC to HC in epilepsy, however. For example, under conditions which globally increase excitability (such as decreased extracellular Mg^{2+} concentration), both EC and area
CA3 can transmit epileptiform activity to each other, the so-called “dual focus” model of seizure initiation (18). The “gatekeeper” function of the DG may also become compromised by repetitive EC discharges (19), or by loss of DG hilar neurons (20). Another controversial possibility suggests that interictal spike-like discharges generated in CA3 which feedback through CA1 to the EC may in fact reduce EC excitability, such that loss of CA3 neurons as may occur in MTS would actually promote transmission of EC-to-DG ictal discharges; this theory would predict that interictal spikes are in fact anticonvulsive (21,22).

Finally, the secondary perforant pathway from EC to CA1 hippocampus is subject to inhibitory control via CA1 interneurons (23). Loss of these interneurons in TLE may predispose to hyperexcitability via enhanced propagation along this lesser-understood pathway (24).

EVIDENCE FROM HUMAN FUNCTION STUDIES

Data from human patients with TLE on the sites of seizure origin is undoubtedly more relevant than animal models, and correspondingly more difficult to obtain. Electroencephalographic (EEG) evidence has usually been gathered in the setting of intracranial EEG monitoring during presurgical evaluation for intractable TLE. One of the first studies to demonstrate the functionality of human EC-to-HC anatomic connections also confirmed that activity in the HC could propagate back to the EC, suggesting the possibility of a positive-feedback loop during seizure onset (25).

Much of the work studying the localization of seizure onsets within the temporal lobe has used depth electrode recordings, either alone or in combination with subdural electrodes, as this technique is best suited to distinguish onsets from HC versus nearby temporal neocortical sites. Using this technique, it appears that the most common pattern is the so-called “regional” onset, with ictal discharges appearing simultaneously in medial and lateral temporal structures (26). When a more localized onset pattern is seen (i.e., discharges appearing in only one or a few contiguous electrode contacts with 1 cm spacing), the medial structures overwhelmingly account for the majority of onsets, with the temporal neocortex rarely the unambiguous site of onset.

The finding of “regional” onsets might suggest an undetected common site of ictal origin, and indeed one technical limitation of depth electrode studies is limited tissue sampling, especially when inserted transversely into the HC. Studies from the yale epilepsy group have attempted to circumvent this problem by inserting depth electrodes along the longitudinal axis of the HC. Using this technique, they found a higher rate of medial temporal lobe onset (>90%), and did not observe any unambiguous neocortical onsets in 11 patients (4). Using this same technique to study ictal onsets from medial temporal lobe structures has not been as successful; simultaneous depth electrode recordings in EC and HC failed to show any consistent pattern in site of onset either among or within individual patients, with seizures often occurring in a “regional” pattern, i.e., in both EC and HC simultaneously (27). Again, one explanation for this inconclusive result may be that existing recording techniques may not have sufficient spatial resolution and tissue coverage to meaningfully address this question.

Pathological evidence has also contributed to the debate on the relative roles of the HC and EC in TLE. The correspondence of MTS and a good surgical outcome would imply that the anatomic sites of hippocampal cell loss correspond to the sites of ictal onset. Early work using transverse hippocampal depth recordings suggested
that this was the case (28), although a later study using longitudinal depth electrodes (thus sampling more points within the hippocampus) found no correlation between the two, with ictal onsets most frequently occurring in the more anterior segments of the HC, and atrophy (as visualized by magnetic resonance imaging, MRI) most pronounced in the posterior segments (29). This might suggest that vulnerable HC pyramidal neurons are bystanders in the pathological process, rather than the primary actors.

As mentioned above, the appearance of unilateral MTS on MRI is a positive prognostic factor for postsurgical seizure freedom in temporal lobe epilepsy, particularly when associated with ipsilateral interictal and ictal discharges (1). Because of improved neuroimaging techniques, presurgical identification of MTS has become more accurate and routine. Evidence has been accumulating that the EC also undergoes atrophy in TLE that is akin to MTS. Although radiological evaluation of the EC has been less routine than that of the HC, quantitative MRI evaluation has shown a bilateral reduction in EC volume in patients with TLE, with a more severe decrease ipsilateral to the ictal focus (30). A similar study in patients lacking imaging evidence of MTS also found EC atrophy that correlated with ictal lateralization 64% of the time, although in most of these patients histopathological evidence of MTS was seen postsurgically (31). Other investigators have found that EC atrophy correlates modestly with the extent of MTS, and is not an independent predictor of the epileptic focus (32). In concert with pathological evidence of cell loss in layers III and II of the EC in confirmed TLE, these findings support the idea that EC pathology is frequently associated with TLE, and at a minimum shows promise as a secondary imaging marker to noninvasively lateralize the seizure focus (14).

EVIDENCE FROM SURGICAL OUTCOMES

Perhaps the most compelling evidence for the relative involvement of various medial temporal lobe structures in TLE derives from the clinical outcome when they are surgically resected. Numerous studies have compared the results when patients with TLE undergo epilepsy surgery; however, interpretation of the rates of seizure freedom is complicated by the diversity of surgical approaches (e.g., anterior temporal lobectomy, selective amygdalohippocampectomy) as well as by the heterogeneous nature of the underlying substrate (e.g., MTS, nonlesional). Much of this evidence is reviewed elsewhere in this volume. However, existing studies delineate some broad trends on the causal roles played by the HC and the EC.

The presence of MTS is clearly favorable for long-term seizure freedom, virtually regardless of the surgical procedure used, clearly arguing the case for the causative role of HC pathology. An aggregate review of 32 studies from 29 epilepsy surgery centers found an overall seizure-free (Engel Class I) rate of 67% for patients with proven MTS on either neuroimaging or pathological grounds (33). This rate, encompassing a variety of surgical approaches as well as some patients with bitemporal involvement, compares favorably to that obtained when MTS is not evident on the presurgical workup. A retrospective study of patients undergoing either selective amygdalohippocampectomy (AHE) or standard anterior temporal lobectomy found equivalent outcomes with the two procedures when MTS was present (83–88% Class I outcome with unilateral MTS) but only 50% were seizure-free when MTS was absent (34). Additional factors which diminish the likelihood of success, regardless of surgical approach, include bilateral interictal EEG abnormalities or bilateral evidence of MTS (35).
If HC pathology is primary in the etiology of TLE, then it is reasonable to assume that surgical outcomes will depend on the amount of HC resected. However, this point is controversial. Considering the results obtained with AHE alone, several studies have found a correspondence between seizure freedom and total removal of the medial temporal lobe structures (with most AHE resections encompassing the parahippocampal gyrus, thus the subiculum and entorhinal cortex), while some advocate a tailored approach in which intraoperative monitoring guides the extent of resection (36–38). While not using a selective AHE technique, the only prospective, randomized study to examine the influence of the extent of hippocampal resection (combined with a fixed lateral temporal resection) found that the degree of seizure freedom correlated with the amount of HC removed (39). A radiographic analysis of surgical outcome versus resection extent for the various medial temporal lobe structures similarly concluded that seizure freedom primarily correlated with the volume of tissue removed (40). A secondary conclusion was that outcome covaried most with the extent of resection of the parahippocampal gyrus, and not the hippocampus itself, implicating either the subiculum or the EC as the epilepsy focus.

The question of whether either HC or EC resection alone is critical to seizure freedom has been infrequently directly tested. More selective AHE approaches that spare the EC have in general yielded unsatisfactory results. A surgical series where radiofrequency lesions of the amygdala and HC replaced resection and spared the EC produced seizure freedom in only 2 of 15 patients (41). Preserving the amygdala while resecting the HC and parahippocampal gyrus produced better results (60% of patients seizure-free or nearly so); interestingly, the authors concluded in a review of contemporaneous epilepsy surgery studies that the degree of EC resection was the principal determinant of the degree of seizure freedom (42). There has been only limited recent experience with lateral temporal corticectomy alone (sparing the HC and amygdala), with one study showing a seizure-free rate of 55% (43). Finally, the technique of gamma knife radiosurgery shows some promise as a curative modality that allows targeted disruption of medial temporal lobe structures while preserving lateral temporal neocortex. While its therapeutic efficacy is currently controversial (44,45), gamma knife radiosurgery may allow testing of clinical hypotheses as to the essential sites of epileptogenesis in TLE.

CONCLUSIONS

The evidence presented here supports the hypothesis that the EC participates in the pathogenesis of TLE along with the hippocampal formation. Given the functional interdependence of the two regions as demonstrated in in vivo and in vitro animal models, it may be meaningless to consider the epileptic focus as residing in one area or the other; rather, clinical neurophysiological data would suggest that this is a “regional” process. Existing surgical series have largely been inadequate to resolve the question, as most resective techniques do not discriminate between the HC and the parahippocampal gyrus. Further understanding may come from the study of extrahippocampal regions in patients with non-MTS TLE, or from the results obtained with highly selective surgical techniques, such as the gamma knife.

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Chapter II-4d: Extrahippocampal Regions Are Important in the Generation of Mesial Temporal Lobe Seizures

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INTRODUCTION

The extrahippocampal regions that are partially removed in most surgical treatments of mesial temporal lobe epilepsies (MTLEs) include the subiculum, the entorhinal cortex, the perirhinal cortex, the parahippocampal gyrus, and the basolateral amygdala (1). These regions are mutually interconnected with the hippocampus proper and with neocortical areas (2–4). Depth recordings have shown that seizure onset does not necessarily occur in the hippocampus proper. In a study by Wennberg et al. (5), about 67% of clinical seizures originated in the amygdala and in the parahippocampal regions compared with only 23% resulting from focal hippocampal onset. In another study from Spencer’s group, 29% of seizures originated in the entorhinal cortex and 47% simultaneously in the entorhinal cortex and hippocampus (6). Both groups report that seizure spread to neocortical areas and thereby manifestation of clinical symptoms is more likely if the entorhinal cortex is involved in seizure onset. Studies on the hippocampal pathology showed that loss of nerve cells is not restricted to the hilus and CA3 and CA1 region but also to the middle layers of the entorhinal cortex (7,8). This is reflected in reduced volumes of these regions in magnetic resonance imaging (MRI) studies (9,10). In a retrospective study of the Montreal group in patients with Engel Class I or II seizure outcome, significantly more entorhinal cortex was removed than in patients with Engel Classes III and IV outcome (11). In a recent study from our lab we found, in the pilocarpine model, that seizure frequency correlated in the pilocarpine model with cell loss in the hilus,
CA3 region, and middle layers of the entorhinal cortex (Fig. 1) but not with cell loss in area CA1 and cell loss in other layers of the entorhinal cortex. Indeed, cell loss in the medial entorhinal cortex has also been reported in studies using the kainic acid and the sustained stimulation model of status epilepticus with subsequent seizure development (12).

Why would the parahippocampal structures be ideal candidates for seizure initiation and seizure spread? These structures receive multimodal input from all sensory systems and distribute this information to the amygdala, the hippocampus, and the frontal cortex and back into neocortical areas as they play an important role

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**Figure 1** Lateral (LEC) and medial (MEC) entorhinal cortex of the rat. In both images the borders of the LEC and MEC are marked with arrows, and layers II, III, and IV/V are labeled with roman digits. (A) In the normal rat, layer III is of normal width. In the lower left corner the dentate gyrus shows a densely packed granule cell layer. (B) Entorhinal cortex of a rat with chronic limbic epilepsy after pilocarpine-induced status epilepticus. A cell loss occurred in all layers of the entorhinal cortex with the third layer being most affected. The granule cell layer of the dentate gyrus (lower left corner) reveals cell dispersion. Scale bar in both images: 500 μm.
in distribution of information to hippocampal and cortex memory stores (Fig. 2) (4). They have—unlike most neocortical structures—apart from the distribution mode at least four additional working modes as they serve to store and to recall information, serve for novelty detection, and to transfer information from the hippocampus into more permanent stores of the central nervous system (CNS). To this end, the perihippocampal structures are strongly interconnected with state-dependent formation of interconnected networks. For example, theta activity superimposed by gamma oscillations is frequently used when animals are exploring and it seems that synchronized gamma between entorhinal and hippocampal cortex favors storage of information (13–15) while sharp wave ripple complexes originating in the hippocampus may mediate memory consolidation. It is interesting to note that such activities can precede generation of seizures (16).

The intrinsic connectivity in the entorhinal cortex and intrinsic cellular properties may render this region particularly vulnerable to generation of seizures. Thus, layer V neurons project to superficial layers (17,18) which in turn project back to deep layers in the entorhinal cortex. Deep layer cells in the entorhinal cortex were shown to be potential pacemaker cells with intrinsic bursting when extracellular potassium concentration is elevated to 5 mM (19). These cells are strongly connected by recurrent excitatory collaterals and thereby facilitate synchronization and spread of activity not only within the columnar-like structures but also to neighboring areas (20,21). As the entorhinal cortex is also strongly innervated by the hippocampus and subiculum to which it sends information, it sits at a crossroad where seizure initiation and propagation is readily facilitated.
Studies on in vitro preparations in rats and mice have shown that agents which induce convulsant activity such as low magnesium or application of 4-aminopyridine initiate seizures in the entorhinal cortex and more rarely either in the subiculum or the temporal neocortex (22,23). The seizures that are generated in the entorhinal cortex propagate readily to the temporal neocortex but less likely to the hippocampus (24). This is changed when animals have been subjected to a kindling procedure or where the animals present with seizures following an experimentally induced status epilepticus (25). Also in these cases seizures usually start in the entorhinal cortex but propagate readily into the hippocampus either through the dentate gyrus or through the subiculum or the temporoammonic pathway (26,27). This is not to say that spiking activity in the hippocampus does not occur in these models and that under some conditions it may trigger seizure-like events in the entorhinal cortex from which the activity then propagates (28–30). In fact, some authors claim that interictal activity in the hippocampus may prevent seizure initiation in the entorhinal cortex (29,31,32). Thus, it appears that the entorhinal cortex and the other parahippocampal regions are critical for seizure spread and may, more often than previously thought, also be the site of abnormal connections and functionally altered networks which permit seizure development.

Studies on tissue from human patients have found a number of alterations, but so far very few studies were made on the human entorhinal cortex except for two studies showing distinct cell loss in layer III of the entorhinal cortex and other parahippocampal regions (7,8). Also, relatively little information is available on the alterations in the amygdala (8,33–35). In hippocampal slices, a number of alterations have been found, most notably increased bursting behavior in the CA1 region. It was therefore surprising to observe spontaneous interictal-like discharges in the subiculum of human patients (27,36). The properties of such interictal spikes correlated closely with the spikes recorded with foramen ovale or sphenoid electrodes as well as in-depth recordings. This spiking behavior was partially mediated by GABAergic mechanisms as bicuculline could abolish the behavior. Likewise, the generation of these discharges was blocked by AMPA type receptor antagonists such as CNQX. Whether the occurrence of such abnormal behavior is dependent on the degree of cell loss in the CA1 and CA3 sector is a matter of debate. While Cohen et al. (36) found such behavior in amygdalo-hippocampal sclerosis (AHS) patients, we showed such activity to be present also in cases lacking hippocampal sclerosis (27).

However, it remains to be seen whether comorbidity with depression, anxiety, and psychotic behavior depends on alterations in any of the different subfields of the hippocampal formation.

REFERENCES


Chapter II-5
What Is the Role of Surgery in MRI-Normal Temporal Lobe Epilepsy?

Chapter II-5a: MRI-Normal Mesial Temporal Epilepsy Is a Common, Surgically Remedial Condition

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Patients with temporal lobe epilepsy (TLE) who are candidates for surgical therapy have often been divided into those with evidence of mesial temporal sclerosis (MTS), who are considered to have “mesolimbic” epilepsy, and those without evidence for MTS, who are considered to have “neocortical” epilepsy. As indicated in an earlier publication (1), the author views this classification as incorrect. There is a third substantial group, patients without evidence of MTS, either on presurgical evaluation or pathological examination of the hippocampus, who have an epileptogenic zone in mesial temporal structures, and thus have “mesolimbic” epilepsy but not the changes of classical MTS. The evidence for this comes from temporal lobe resections in such patients. In a series of 44 patients with histologically normal hippocampi, who had temporal lobe resections tailored to the extent of interictal activity in the hippocampus, 61% had a Class 1 outcome (seizure-free or single seizure/year) at an average follow-up of 2.5 years (minimum 1.5 years), with the outcome the same for those with large or small hippocampal resections, so long as there was no interictal spiking in the remaining hippocampus (2). Moreover, the presence of interictal spikes in the residual hippocampus was highly predictive of an unfavorable outcome in this group, as it was in the group with MTS. In a separate series of TLE patients, who had imaging normal medial temporal lobes, and also had resections tailored to the extent of hippocampal interictal activity, 48% were seizure-free at an average follow-up of
over three years (minimum two years). Factors indicating a favorable outcome in that series were the presence of basal temporal ictal onsets, especially when associated with a unilateral temporal interictal focus (3). Seventy-eight percent of the patients in this last group with concordant unilateral interictal and ictal focus were seizure-free, an outcome not much different from that in patients with MTS and a unilateral interictal and ictal focus. All of this evidence points to medial temporal structures, and specifically the hippocampus as involved in the generation of seizures in these patients without MTS, and that those patients have a reasonable chance to become seizure-free after a temporal resection that includes mesial structures.

These patients seem to represent an increasing proportion of the TLE patients coming to resective surgery at tertiary epilepsy centers. They were 34% of our 1991–1995 series of temporal lobe resections (2), and 57% of the 1997–1999 series (4). The cause of this shifting proportion between MTS and non-MTS cases is not clear. One possibility is referral patterns, with clear MTS cases on imaging with a unilateral interictal and ictal temporal lobe focus not being referred to tertiary centers, but undergoing temporal resections locally. Another possibility is a decline in the incidence of MTS. Whether some of the TLE patients who do not have classical MTS have more subtle hippocampal pathologic changes remains controversial. Mathern and colleagues (5) related the present of subtle hilar neuronal loss to a favorable outcome in patients without the classical changes of MTS. We have a few patients with no evident hippocampal cell loss, but positive Timm staining suggesting reorganization in the granular cell layer (Born et al., unpublished). Thus, the cases with medial temporal foci but not classical MTS may represent a transition stage to that process. There is some evidence that the patients with medial temporal foci but not MTS are more likely to have a recurrence of seizures on long-term follow-up, although the recurrences are often a single seizure in one or a few later postoperative years (6).

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4. Miles AN, Dodrill CB, Ojemann GA. Postoperative decline in measures of verbal memory after dominant temporal lobe resections is proportional to the extent of medial resection. Epilepsia 2001; 42(suppl 7):304.
Chapter II-5b: MRI-Normal Medial Temporal Lobe Epilepsy Has a Less Favorable Surgical Outcome

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INTRODUCTION

Medial temporal lobe sclerosis (MTS) is the most common substrate responsible for epileptogenesis among the patients with temporal lobe epilepsy (1–3). The characteristic features of MTS on magnetic resonance imaging (MRI) include an atrophic hippocampus with hyperintense signal on long-repetition-time sequences (4–9). The degree of hippocampal atrophy correlates with the severity of pyramidal cell loss in CA (cornu ammonis) subfields (especially CA1) (10,11). Patients with MTS who are refractory to medical therapy have a 70% to 90% chance of achieving seizure freedom after anterior temporal lobectomy and resection of the epileptogenic medial structures (4,12,13).

The pathogenesis of hippocampal sclerosis may involve an early life-acquired injury, genetic predisposition, and/or secondary hippocampal atrophy associated with chronic epilepsy (14). However, reports suggest that up to 15% of the patients with the diagnosis of medial temporal lobe epilepsy (MTLE) may have normal hippocampal volumes on MRI (15,16). This subgroup of patients present with clinical and scalp electroencephalographic (EEG) findings consistent with MTLE; paradoxically, there is no appreciable hippocampal atrophy or T2-weighted signal changes on imaging even though the hippocampus is confirmed as the only ictal generator on long-term intracranial monitoring. This subgroup of MTLE has been referred to as paradoxical temporal lobe epilepsy (PTLE). We have previously reported the immunohistopathological changes of a similar group of patients (11). In this chapter, we will discuss the clinical syndrome of PTLE. This is a distinct syndrome with clinical features and surgical outcome different from those of MTS.

Previous studies have explored the clinical features of certain MTLE patients with normal hippocampal volumes. These studies included patients with increased T2 signal changes in the hippocampus on MRI (15,16) or incorporated patients who had not consistently undergone chronic intracranial monitoring (17). Such inconsistencies in methods of inclusion or evaluation may prevent meaningful comparison of patients across different series.
PREOPERATIVE EVALUATION

The comprehensive preoperative epilepsy assessment at the Yale epilepsy surgery program includes continuous video EEG recordings, high-resolution MRI designed for epilepsy patients, neuropsychometric studies, and intracarotid amytal evaluation (Wada testing). Patients also undergo positron emission tomography (PET) and single photon computed tomography (SPECT). There is no hippocampal atrophy or signal change on MR imaging among the PTLE cohort. Formal measurements of hippocampus volumes according to a previously described method (18) or detailed visual inspection by a blind reviewer may exclude hippocampal asymmetry.

INTRACRANIAL STUDY

In PTLE patients, as normal imaging does not direct the interpretation of semiologic and electrophysiologic data, an intracranial study is beneficial in the identification and resection of epileptogenic zone. When the MRI is normal and there is temporal scalp EEG lateralization, the paradigm for subdural electrode implantation includes placement of a small grid over the lateral temporal neocortex followed by one to two basotemporal strip(s) and one anteromedial strip along the long axis of the para-hippocampal gyrus (19). Hippocampal depth electrodes are implanted parallel or perpendicular to the long axis of the hippocampus. When EEG lateralization is not clear, the intracranial study consists of small bilateral temporal craniotomies and symmetrical placement of subdural strips and amygdalo-hippocampal depth electrodes. PTLE patients present with a unilateral medial temporal lobe ictal onset, from either the hippocampus or amygdala.

PATIENTS (YALE SERIES)

There was a paucity of a history of febrile seizures among the 12 patients with PTLE (Table 1). This finding is consistent with previous reports demonstrating the correlation between the presence of hippocampal signal changes and history of febrile seizures (14,20). The 8% incidence of febrile seizures among the PTLE patients is similar to the incidence reported among the general population (21). Our PTLE patients had other risk factors for epilepsy including trauma, meningoencephalitis, and perinatal injuries. Furthermore, they presented with their first seizures slightly later in life than our MTS cohort. These differences may highlight the underlying pathophysiological disparities between the PTLE and MTS patients. The higher incidence of seizure generalization among the PTLE patients may underscore the more extensive involvement of the neocortex in seizure network generation. All patients underwent anteromedial temporal lobectomy and en bloc amygdalohippocampectomy.

HISTOPATHOLOGY AND ELECTROPHYSIOLOGY

The neuronal counts in different CA sectors of the resected hippocampi demonstrated that the maximal extent of neuronal cell loss occurred most frequently in the CA4 sector among our six PTLE patients (average % cell loss = 38% range = 21–51%). The extent of CA1 subfield neuronal loss for the PTLE and MTS group was 20% (range: 0–59%) and 75% (range: 41–90%) (p = <0.001), respectively.
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/Gender</th>
<th>Feb seizure</th>
<th>Predisposing factors</th>
<th>Age at onset of seizure (yr)</th>
<th>Seizure duration (yr)</th>
<th>Video-EEG localization</th>
<th>Seizure onset based on intracranial EEG</th>
<th>F/U duration (mo)</th>
<th>Modified Engel outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30/M</td>
<td>None</td>
<td>Trauma</td>
<td>20</td>
<td>12</td>
<td>L temporal</td>
<td>3 L HC, 1 contralateral temporal neocortex</td>
<td>69</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>35/F</td>
<td>None</td>
<td>0</td>
<td>2</td>
<td>31</td>
<td>R temporal</td>
<td>7 R mid HC and 1 ipsilateral temporal neocortex</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>44/F</td>
<td>UK</td>
<td>0</td>
<td>1</td>
<td>43</td>
<td>R temporal</td>
<td>5 R HC, 2 inferior temporal gyrus</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>23/M</td>
<td>Yes</td>
<td>0</td>
<td>4</td>
<td>23</td>
<td>R temporal</td>
<td>R anterior and mid HC</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>16/M</td>
<td>None</td>
<td>Trauma</td>
<td>5</td>
<td>11</td>
<td>L temporal</td>
<td>3 L anterior HC, 1 L mid HC</td>
<td>37</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>17/F</td>
<td>None</td>
<td>Trauma</td>
<td>10</td>
<td>7</td>
<td>L hemisphere</td>
<td>3 L anterior HC, 1 R HC</td>
<td>175</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>50/F</td>
<td>None</td>
<td>0</td>
<td>34</td>
<td>16</td>
<td>R mid-temporal</td>
<td>R mid HC and PH gyrus</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>24/F</td>
<td>None</td>
<td>0</td>
<td>18</td>
<td>4</td>
<td>L temporal</td>
<td>L HC and PH</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>27/M</td>
<td>None</td>
<td>Trauma</td>
<td>8</td>
<td>30</td>
<td>R mid-temporal</td>
<td>R anterior HC</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>40/M</td>
<td>None</td>
<td>Trauma</td>
<td>34</td>
<td>4</td>
<td>R temporal</td>
<td>R HC</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>36/F</td>
<td>UK</td>
<td>0</td>
<td>8</td>
<td>28</td>
<td>R temporal</td>
<td>R HC</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>44/M</td>
<td>None</td>
<td>Trauma</td>
<td>21</td>
<td>26</td>
<td>L temporal</td>
<td>L HC/amygdala</td>
<td>35</td>
<td>4</td>
</tr>
</tbody>
</table>

*Abbreviations:* Feb, febrile; UK, unknown; HC, hippocampus; PH, parahippocampus.
Electrophysiological sharp electrode recordings of the dentate cells of the resected hippocampus in acute slice preparations revealed that the PTLE group was significantly less excitable than the MTS group \( p < 0.05 \).

**CONSIDERATIONS FOR RESECTIVE SURGERY**

In PTLE patients, a lack of pathology on MRI requires an intracranial study to determine the epileptogenic zone. A study by Holmes and others (17) has reported an improved surgical outcome among the temporal lobe epilepsy patients with normal MRI if the ictal onset localized to basal temporal regions. In comparison, none of their patients with lateral mid-posterior temporal seizure onset attained seizure freedom after surgery. They also reported an overall 48% rate of operative seizure freedom.

Despite a generous coverage of the candidate cerebral epileptogenic regions with electrodes and confirmation of the medial temporal lobe onset, only 50% (6 out of 12) of patients with PTLE attained seizure freedom after surgery as compared to 76% of those with MTS (Yale series). This former less satisfactory outcome may be due to factors such as the presence of bilateral hippocampal disease and/or dual pathology. Even though intracranial studies seem to have excluded bilateral temporal epileptogenicity in some of our patients, not all candidate cerebral regions could be covered with electrodes and sampling error may account for suboptimal seizure focus localization (22,23).

**REFERENCES**

Chapter II-6
What Is the Significance of Dysplasia Associated with Mesial Temporal Sclerosis?

Chapter II-6a: Dysplasia Associated with Mesial Temporal Lobe Sclerosis Is a Common Finding Related to Epileptogenesis

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DYSGENESIS IN THE TEMPORAL LOBE IN MTS

There is a well-documented association of mesial temporal sclerosis (MTS) with developmental pathologies or cortical malformations involving the temporal lobes. This suggests that they may occur together more than by chance alone and that they may share a common pathogenesis (1). Such pathologies include focal cortical dysplasia (FCD), low grade glioneuronal tumors, in particular, dysembryoplastic neuroepithelial tumors, and gangliogliomas and hamartomas. These may be located in the lateral temporal lobe or more medially in proximity to or involving the hippocampus. Cortical dysplasia is identified adjacent to up to half of low-grade glioneuronal tumors, suggesting that a disturbance in cortical development is a predisposition to these tumors which are more common in the temporal lobe than other sites. Macroscopic developmental abnormalities involving the hippocampal structure itself have also been observed in imaging and postmortem studies in patients with epilepsy, some associated with sclerosis, and in some cases probably predating sclerosis (2,3). All these reports therefore suggest an underlying predilection of the temporal lobe to developmental pathologies associated with epilepsy.
MILD DYSPLASIAS OF THE TEMPORAL LOBE IN MTS

In contrast to well-defined tumors and dysplasias, which are typically clearly seen on preoperative magnetic resonance imaging (MRI), there is greater scepticism regarding the identification, significance, and incidence of “mild dysplasias” or microdysgenesis with more subtle changes in cortical cytoarchitecture in patients with MTS. These are usually only identified on tissue sections by the pathologist. They include regions of neocortex with an increase of single or nodular collections of neurons in layer I and the white matter and poor distinction between cortical laminae. These dysplasias lack the presence of abnormal, giant, or dysplastic neurons and glial cells that characterize the more severe forms of dysplasia, as FCD Types Ib, IIa, and IIb (4). The diagnosis of mild dysplasias is therefore based on the identification of normal appearing neurons present in an “abnormal number or location.” It is also considered likely that there may be several subtypes of mild dysplasias with specific cytoarchitectural derangements perhaps arising from different developmental mishaps (4). It is acknowledged that a lack of clarity regarding the nomenclature of these lesions and different diagnostic criteria used by the examining pathologist has resulted in a lack of clear information regarding their incidence in temporal lobe epilepsy (TLE). Their identification may also depend on whether qualitative assessment alone or additional quantitative analysis has been applied in reaching the diagnosis. In parallel with the recent advances made using quantitative MRI for the detection of lesional abnormalities in TLE, microscopic quantitative methods are likely to be helpful tools in the future for more precise definitions of mild dysplasias.

QUANTITATIVE STUDIES OF WHITE MATTER NEURONS IN MTS

There have been several studies in the last decade detailing quantitative methods of analysis of mild dysplasias in TLE mainly regarding the white matter component (Table 1). It has been demonstrated that normal temporal lobe white matter contains more neurons than occipital or frontal lobe white matter (5). Further to this, all quantitative studies in MTS have suggested higher white matter neuronal densities in epilepsy patients compared to controls groups (Table 1, Fig. 1). Volume loss has been shown to involve the lateral temporal lobe structures in addition to mesial structures in some MTS patients in neuroimaging studies. This volume loss may be a reflection of cortical neuronal, neuropil, and myelin loss, and gliosis as a result of seizures. Certainly cortical gliosis, neuronal loss, perivascular white matter atrophy, and excess corpora amylacea are common observations in the pathological examination of MTS surgical specimens. As neuronal densities (cell number per area or volume) have been measured in most studies to date (Table 1) rather than absolute neuronal number, it has been argued that the increase in white matter neurons observed in epilepsy is merely a reflection of temporal lobe volume reduction. However, in one study in MTS patients, white matter neuronal densities did not correlate with GFAP-positive astrocytic densities (a measure of white matter gliosis) and cortical neuronal densities, suggesting they are independent of the atrophic processes (10). In the only study where total neuronal number was measured in TLE, 1.5 million neurons were identified in the Brodmann area 38 white matter compared to 1.2 million in controls; although this was higher in the epilepsy group it was not, however, significant (9).

The variation in the numerical data presented between studies (Table 1) may also reflect the differences in case selection and methodologies used. Although there
Table 1  Quantitative Studies of White Matter Neurons in Temporal Lobectomies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cases</th>
<th>MTS present</th>
<th>Counting method</th>
<th>Main method for identification of neurons (additional methods used in brackets)</th>
<th>Types of neurons counted</th>
<th>Region of temporal lobe white matter examined</th>
<th>White matter neurons in epilepsy</th>
<th>White matter neurons in controls</th>
<th>Significance given in study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardiman et al. (6)</td>
<td>49</td>
<td>Hippocampus not resected</td>
<td>Profile count (2D counting)</td>
<td>Nissl</td>
<td>Only neurons &gt;10μm diameter</td>
<td>“Deep” white matter all regions of temporal lobe examined</td>
<td>&gt;8/2 mm² in 43%</td>
<td>&gt;8/2 mm² in 0%</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Emery et al. (7)</td>
<td>22</td>
<td>86% of cases</td>
<td>Profile count (2D counting)</td>
<td>Nissl (and MAP2 immunostaining)</td>
<td>Only neurons &gt;12μm diameter</td>
<td>Anterior temporal lobes</td>
<td>4.11/mm² (mean)</td>
<td>2.35/mm³ (mean)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Kasper et al. (8)</td>
<td>47</td>
<td>44% of cases</td>
<td>Profile count (2D counting)</td>
<td>Nissl</td>
<td>Large neurons</td>
<td>Not stated</td>
<td>&gt;10/HPF in 23%</td>
<td>&gt;10/HPF in 0%</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Bothwell et al. (9)</td>
<td>8</td>
<td>50% of cases</td>
<td>Design-based stereology (3D counting)</td>
<td>Nissl</td>
<td>All; neuronal volumes also measured</td>
<td>Brodmann area 38</td>
<td>1160/mm³ (mean)</td>
<td>750/mm² (mean)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Thom et al. (10)</td>
<td>31</td>
<td>100% of cases</td>
<td>Optical dissector (3D counting)</td>
<td>NeuN Immuno-staining (and Nissl)</td>
<td>All positive neurons (&lt; or &gt; than 10μm)</td>
<td>Lateral temporal lobe (all regions)</td>
<td>2164/mm² (mean)</td>
<td>1660/mm³ (mean)</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>
appears to be no significant regional variation in the density of neurons between gyri in the lateral temporal lobe white matter (10), there may be differences in the proportions of neuronal subtypes between the deep and superficial white matter. Therefore the area of white matter selected for pathological analysis should be considered and standardized for future comparative studies. It also remains possible that differences in tissue preservation and shrinkage between surgically removed and optimally fixed MTS tissue and postmortem control tissue may influence neuronal density measurements using either stereological or simple counting methods; surgical control tissue should therefore be used where available. An increase in size or hypertrophy of white matter neurons in epilepsy, including MTS cases, has also been shown and considered to reflect disrupted development or differentiation (9). If this is a common phenomenon, larger neurons may be “over-counted” in MTS if simple two-dimensional (2D) cell profile techniques are used rather than modern design based stereological cell counting methods, as the former are “biased” towards the inclusion of larger cells. Stereological methods may therefore be the preferred tool for more accurate white matter cell density estimates. Using the optical dissector method, the range of white matter neuronal densities in over 90 MTS surgical specimens is shown in Figure 2. In this figure, the range of densities of neurons in the white matter in these patients appears to be normally distributed and a bimodal picture distinguishing a

Figure 1 (A) White matter neurons of varying morphologies in lateral temporal lobe in a patient with MTS, labeled with neuronal nuclear marker NeuN (bar = 60 μm). (B) An excess of white matter neurons in normal appearing cortex adjacent to a region of focal cortical dysplasia (Taylor type/IIB—see Ref. 4) (NeuN immunostaining; bar = 150 μm). (C) Neuropeptide Y positive neurons and processes in the white matter of the parahippocampal gyrus in patient with MTS (bar = 60 μm). (D) An excess of neurons in the white matter in the vicinity of laminar heterotopia immunolabeled with antibodies to GAD (bar = 60 μm). Abbreviations: MTS, mesial temporal sclerosis; GAD, glutamic acid decarboxylase. 
separate group with MTS and white matter neuronal dysgenesis from MTS alone is not apparent. Neuronal densities in MTS have been shown to overlap with control range of values (7,9,10). Therefore, it remains to be clarified at which point neurons in the white matter are regarded as present in increased or “pathological” numbers.

In summary, the data gathered so far universally support the argument that MTS patients have greater densities of white matter neurons. Refinements in protocols for their identification may lead to consistency in the diagnosis of white matter dysgenesis in MTS between centers. Further questions that should also be addressed are the developmental origins and nature of these neurons, and if and how they are functionally connected to abnormal neuronal circuits in MTS.

**ORIGIN AND SUBTYPES OF WHITE MATTER NEURONS IN MTS**

During cortical development the region between the cortical plate and the proliferating neurons in the ventricular zone comprises the subplate and the intermediate zone which will become the future white matter. The subplate neurons are some of the earliest neurons to appear in corticogenesis and form temporary targets for the guidance of efferent and afferent axonal connections of neurons in the overlying cortex. Subplate neurons comprise pyramidal neurons, fusiform, polymorphic, and multipolar neurons. Precursor cells also migrate tangentially from the ganglionic eminence and settle within the subplate forming local connections (11,12). The diversity in subplate neuron morphology is reflected also in the range of neuro-active substances expressed by these cells including NPY, GABA, and calcium-binding proteins and

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**Figure 2**  Box plot of the distribution of white matter neurons in the lateral temporal lobe in 90 surgical specimens from patients with hippocampal sclerosis. The neurons were identified with NeuN neuronal marker and counted using the optical dissector method. The mean density was 2238/mm³ (SD = 735).
these neuronal subtypes are unevenly distributed (11,12). As the brain matures it is likely that the majority of these neurons undergo programmed cell death but some persist as interstitial neurons in the white matter. The role of these persistent neurons in the normal mature brain is unknown.

It is yet unclear whether the excess white matter neurons in MTS represent abnormal survival of subplate cells which may reflect sustained connectivity of these cells to the overlying cortex. An alternative hypothesis is that white matter neurons are heterotopic cortical plate cells which have failed to complete migration; this may in turn relate to a defect of radial glial cells or abnormalities of the molecular–cellular signals controlling migration. Mixed neuronal populations, including both excitatory and inhibitory neurons in the white matter are likely. Using immunohistochemistry markers to distinguish neuronal subtypes is likely to identify more white matter neurons than can be seen with Nissl staining alone (10), and the relative proportions of these cells may be critical.

WHITE MATTER NEURONS IN OTHER EPILEPSY-RELATED PATHOLOGIES

In studies of macroscopic neuronal heterotopias in the white matter (gray matter laminar and nodular heterotopia) in patients with epilepsy there is accumulating data regarding the origins and functional status of these lesions. In many patients, mutations in genes necessary for normal cortical neuronal migration, as Filamin 1 and doublecortin, have been identified. Tracing studies suggest connectivity between neurons in the nodules and overlying cortex in both humans and animal models and intrinsic epileptogenicity of these nodules has been shown (13–15). Within heterotopia both glutamatergic (pyramidal) and inhibitory interneurons are observed (14,15), but there may be a reduced representation of inhibitory interneurons, which results in excitatory overbalance (16). In addition, an excess of single neurons may be observed in the white matter adjacent to the heterotopia (Fig. 1) (14), hinting at a developmental relationship of these lesions with microdysgenesis.

In FCD, a lesion which is established as highly epileptogenic, although the main dysplastic lesion involves the cortex, heterotopic cells in the white matter are commonly seen (Fig. 1). In many cases, the underlying white matter is hypomyelinated and a trail of abnormal neuronal and balloon cells is seen extending in a wedge-like process toward the lateral ventricle, the so-called transmantle dysplasia. These observations in better characterized pathologies involving white matter suggest that it would be presumptious at this point to dismiss the excess of single white matter neurons in the temporal lobe associated with MTS as “epiphenomena” before determining their exact relationship to the process of MTS, cortical dysplasia, and epileptogenesis.

CORTICAL LAYER I ABNORMALITIES ASSOCIATED WITH MTS

Quantitative studies also have suggested an increase in cortical layer I neurons, in particular Cajal–Retzius cells in mild dysplasias and in association with MTS (17,18). Cajal–Retzius cells are important in cortical development through the reelin-signaling pathway and abnormalities of this cell population may be either a
primary or secondary manifestation of the cortical dysgenesis (12). In addition, quantitative histological studies in hippocampal sclerosis surgical specimens have also identified an abnormal persistence of Cajal–Retzius cell in the dentate gyrus (19,20) and recent work also suggest a link between these cells and abnormal migration of granule cells (21), a common finding in hippocampal sclerosis (20). Abnormalities of the reelin-signaling pathway have more recently been implicated in the patho-etiology of other malformative lesions associated with epilepsy including FCD and gangliogliomas. Hippocampal dysplasias are observed in the reeler mouse and neuronal dysgenesis involving mesial temporal lobe structures have been identified in the Ihara rat model with spontaneous seizures supporting a relationship between these subtle cytoarchitectural cellular abnormalities and epilepsy (22).

**RELATIONSHIP OF THE PRESENCE OF MILD DYSPLASIA TO POSTOPERATIVE SEIZURE OUTCOME IN MTS PATIENTS**

There is no clear information as yet regarding the presence of mild dysplasias in MTS and how this influences postoperative outcome in terms of seizure control (6,8,10,23). Factors to consider when making such calculations include the type of operative procedure (i.e., extent of resection) and the presence or not of additional epileptogenic pathologies, particularly the severity of MTS. As mild dysplasias, in particular white matter neuronal dysgenesis, are not as yet clearly defined with current functional and structural imaging, it is possible that their resection may be only partial. Postmortem studies, following temporal lobectomy, indeed suggest that in some cases mild dysplasias may be more widespread (24).

**FUTURE WORK**

It is clear that more precise characterization of mild dysgenesis in association with MTE is warranted with the adoption of uniform diagnostic criteria and terminology for these lesions. Current information suggests that future work should be addressed in the characterization of the subtypes, functional status, developmental origins, connectivity, and electrophysiological properties of white matter neurons in mild dysplasias associated with MTS in surgically resected tissues. Single cell molecular biology on microdissected cells may also allow study of differential gene expression in isolated cell populations. Improved in vivo imaging using advanced MRI techniques and functional imaging may allow detection and better localization of these abnormalities in patients with MTS. Improved detection and recognition will allow clearer information regarding the incidence and relationship to MTS of these abnormalities.

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Chapter II-6b: Increased White Matter Neurons in Temporal Lobe Epilepsy: An Epiphenomenon

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CORTICAL DYSPLASIA AND TEMPORAL LOBE EPILEPSY

The phenotypic characteristics of lesions described as “neuronal heterotopia” associated with epilepsy are quite variable and range from grossly apparent, subcortical islands of gray matter to scattered, apparently increased, individual mature neurons of the subcortical white matter. Although most types of heterotopia are considered to represent a failure of neuronal migration, this condition could also result from a failure to terminate the generation of immature neurons so that they continue to be produced after their appropriate guidance cues (e.g., radial glia) have involuted. (1–3). While large subcortical (linear or band) heterotopias are clearly malformative, with some types having a well described genetic basis and clear clinical relevance, the clinical significance of scattered individual subcortical neurons (often referred to as “heterotopic neurons”) remains enigmatic.

Heterotopic neurons have been often described in surgically resected temporal lobes showing other, rather distinct, pathologies such as mesial temporal sclerosis. The latter is the most common histopathologic change observed in temporal lobe resections for focal epilepsy, being identified in about 60% of cases (4,5). Other focal pathologies encountered in temporal lobe epilepsy include neoplasms, malformative lesions, vascular malformations, and cortical scarring due to an acquired process (infectious/inflammatory/traumatic etc.). While more comprehensive discussions of pathologic findings associated with intractable epilepsy are available (6–8), there is little hard data to address the relationship between focal temporal lobe pathologies and neuronal heterotopia. For this chapter, we shall briefly consider the spectrum of neuronal
heterotopia and focus on the finding of “individual (heterotopic) white matter neurons,” which are often discussed in the context of “microdysgenesis.” We assert that the latter is most likely an epiphenomenon, having little to do with the clinical and electrical characteristics of temporal lobe epilepsies.

Neuronal heterotopia refers to neurons that reside outside of their normal location in the brain (9). In the cerebral hemispheres this usually means the presence of gray matter or neurons in the underlying white matter or periventricular region. While the relationship of such lesions to the clinical and electrophysiologic manifestations of epilepsy is still poorly understood, the likelihood that a particular type of neuronal heterotopia is truly the cause of seizure activity is probably related to the severity of the lesion.

The most striking neuronal heterotopias, consisting of islands of gray matter, are described as subcortical or periventricular and can be nodular or diffuse. Two types of familial heterotopia, subcortical band heterotopia and X-linked periventricular heterotopia, result from single gene defects and have a high incidence of epilepsy (10,11). Sporadic cases of subcortical heterotopic gray matter also have a strong clinical association with epilepsy. Human studies that have recorded electrical seizures activity in macroscopic heterotopias (12) and documented that they are metabolically active (13,14) support the proposition that heterotopic gray matter may serve as an initiator of clinical seizures.

Cortical dysplasia is a general term that encompasses any condition that results in a pathological malformation of cortical development. It includes conditions with extensive brain involvement such as lissencephaly, agyria/pachygyria, hemimegalencephaly, and heterotopic gray matter and more confined lesions such as focal cortical dysplasia (FCD). First described in association with epilepsy by Taylor et al. (15), FCD may produce gross anatomical abnormalities with widening of a gyrus and blurring of the gray/white matter interface. Currently, FCD is used to describe a lesion that involves the full thickness of the cerebral cortex from pia to white matter, while the term “microdysgenesis” (see below) refers to isolated abnormalities in cell size, number, and position within the cortex and subcortical white matter (6,16). In addition, FCD often produces a macroscopic abnormality that can be identified in clinical diagnostic studies such as magnetic resonance (MR) imaging. Neurons and glia comprising FCD can demonstrate abnormalities of cellular commitment, migration, and connectivity. These include enlarged neurons with bizarre morphologies, abnormalities of spatial orientation and location, and altered patterns of cytoskeletal protein expression (17). The most strikingly abnormal cells are called balloon cells. They are large cells, often with rudimentary cytoplasmic processes, that can stain simultaneously for glial fibrillar acidic protein (suggesting glial lineage) and vimentin (which, along with nestin is an intermediate filament protein expressed by neuroepithelial stem cell/progenitor cells). The occasional identification of neuronal antigens in these cells (18) suggests that balloon cells have failed to make a definite lineage choice along neuronal or glial lines, implying an abnormality that occurred during the first trimester (7).

Microdysgenesis (or microdysgenesia) is a term originally used by Meencke and Janz (19,20) to describe a constellation of microscopic abnormalities seen in people with epilepsy. It includes the presence of “partially dystopic” neurons in the molecular layer of the cortex, indistinct boundaries between the gray matter and white matter and layers one and two of the cortex, a columnar organization of the cortical neurons in layers two to six, and increased numbers of neurons in the cerebral white matter. Over the years, other microscopic findings have been added to this list. While the
appearance of many of these abnormalities suggests disordered development (i.e., a pathological process), these lesions have the most tenuous etiologic role in epilepsy (6). One concern is that these subtle lesions have often been identified in surgical specimens from epilepsy patients without direct autopsy or non-epileptic controls.

For example, one type of microdysgenesis termed “glioneuronal hamartia” refers to irregular clusters of small oligodendrocyte-like cells that are often mixed with mature neurons. They are often identified in temporal lobe resections from patients with intractable epilepsy (21–23). These microscopic lesions do not produce grossly visible masses and are not apparent by clinical imaging. While “hamartias” have been attributed to abnormal migration or proliferation in the developing nervous system, similar microscopic foci can be identified in the caudal amygdala adjacent to the temporal horn of the lateral ventricle in about 80% of individuals without epilepsy (24). This is an example of a process that was felt to be maldevelopmental or “dysgenetic” because it was most often encountered in surgical material with distorted brain anatomy and the normal occurrence of such “oligodendrocyte-like” cells, in non-epileptic young adults, was not generally appreciated.

Based on the previously mentioned considerations, the incidence of microdysgenesis in temporal lobe epilepsy is difficult to know. Some authors may be reporting changes that are considered normal by others. Conversely, some of these findings have proven to be present in normal brains and the proposed pathological finding becomes ones that require a quantitative assessment of certain cells types in certain areas, a level of analysis that is often not feasible on a routine clinical basis. This raises the possibility that the incidence of microdysgenesis may be grossly under-reported in most clinical series. Using non-quantitative histological analysis, Nordborg et al. (25) reported microdysgenesis in 17% of 79 adults that underwent cortical resections for intractable epilepsy (76% of these cases were temporal lobe resections).

**DEFINITION OF INCREASED SINGLE WHITE MATTER NEURONS**

The purpose of the current chapter is to address a specific question: do increased numbers of white matter neurons represent a cause of temporal lobe epilepsy? It is first important to clearly define what is meant by increased numbers of white matter neurons. We are addressing reports of increased density of otherwise normal-appearing neurons in the white matter of the temporal lobe; a finding that has been proposed to represent one form of microdysgenesis. Since no reports have documented abnormal morphology of these isolated white matter neurons, the question of increased density alone will be considered so that our analysis can be restricted to quantified data that can be compared between studies. We are not addressing more gross abnormalities of cortical development such as frank accumulations of heterotopic gray matter that have been discussed in the previous section.

It is first important to note that the presence of neurons in the subcortical white matter is not an abnormality. These sparse, isolated neurons are called interstitial neurons and are found throughout the cerebral hemispheres (for review, see Ref. 26). Chun and Shatz (27) have shown that, in cats, interstitial neurons are survivors of the earliest generated cortical neurons. In embryonic development, the earliest neurons form the preplate, or primordial plexiform layer (28,29). The neurons that form the cortical plate migrate into the preplate and divide it into the (outer) marginal zone and the (inner) subplate. Although the subplate involutes in the early postnatal period, interstitial white matter neurons in adult cats and monkeys appear to be remnants of
this embryonic structure (27,30). However, this hypothesis has been contested by researchers working with human tissue (31). Neurons of the subplate appear to play a critical role in cortical development and regional specialization. They are the first-generated (28), they make the first synaptic connections (32), they send the first corticofugal projections (33), and their selective destruction can lead to loss of thalamic afferent input (prenatal ablation) (34) and loss of ocular dominance columns in the visual cortex (postnatal ablation) (35).

Morphological descriptions of deep white matter neurons include those with fusiform and stellate somata (27,30) as well as inverted pyramidal cells (36). In cats, interstitial neurons are immunoreactive for interneuron markers including GABA, neuropeptide Y, somatostatin, and cholecystokinin (27). These morphological and neurochemical data have led to the assertion that most interstitial neurons are inhibitory interneurons. This view has been challenged by a morphological study in human tissue where the authors reported 90% of interstitial neurons to be pyramidal cells and 10% to be non-pyramidal cells (31). White matter neurons can also contain the enzymes nitric oxide synthase and NADPH-diaphorase (26,37). Using whole cell recordings, all interstitial neurons tested showed physiological properties of functional neurons and 80% showed intrinsic firing properties usually associated with inhibitory interneurons (37). Dendrites of interstitial neurons extend throughout the cerebral white matter and may extend into the overlying cortex (36,37). The majority of interstitial neurons send axonal projections into the overlying cortex, although some send axons into the descending white matter (36) and some deep white matter neurons send axons into the hippocampus (37). Overall, the likelihood that an interstitial neuron will have dendritic or axonal processes in the overlying cortex decreases as the location of the soma resides deeper in the white matter (37). Beyond this basic information, little is known about the role of interstitial neurons in cortical function.

Although, the presence of neurons in subcortical white matter in humans is widely acknowledged (30,31), quantitative studies of these neurons have been scarce. Meencke (38) reported that neurons in the white matter of the inferior frontal gyrus had a mean density of 5.7 neurons/0.005 mm³ in brains from 22 autopsy controls. This number was elevated in brains from people with traumatic epilepsy and even more so in people with primary generalized epilepsy. He also noted that the density of interstitial neurons declined with advancing age in controls. More recently, Rojiani et al. (39) performed two-dimensional cell counting techniques to quantify the density of white matter neurons in the frontal, temporal and occipital lobes of 20 autopsy controls ranging in age from 23 to 67 years. They found that white matter neurons were a normal finding in all three areas and that the temporal lobe had a significantly higher density of these neurons (mean = 2.35 neurons/mm²) than the frontal and occipital lobes. However, this study did not show a significant effect of age on neuronal density.

QUANTIFICATION OF SINGLE WHITE MATTER NEURONS IN TEMPORAL LOBE EPILEPSY

The first papers that related increased numbers of white matter neurons to epilepsy involved frontal lobe interstitial neurons and primary generalized epilepsy (19,20,38). In these papers, the authors reported findings of microdysgenesis (described above) in 15 cases of primary epilepsy. Increased numbers of frontal white matter neurons was one of the pathological features that they described. In two of the papers (19,20),
In 1988, Hardiman et al. (41) reported an increased density of temporal lobe white matter neurons in people with refractory temporal lobe epilepsy. They compared specimens from 50 neocortical temporal resections with 33 age-similar controls. They found that white matter neurons were seen in 96% of surgical specimens and 72% of controls. However, white matter neuronal densities more than eight neurons/2 mm² were seen only in epilepsy specimens. This finding was present in 43% of the surgical specimens. The authors proposed that microdysgenesis may be an “important morphologic substrate for seizures in some people.” It is not known how many, if any, of these patients had mesial temporal sclerosis.

In 1997, Emery et al. (42) conducted a similar study comparing temporal lobe white matter neurons in 22 anterior temporal lobectomy specimens and 22 age-similar controls. They confirmed that neuronal densities were higher in the lobectomy group (4.1 neurons/mm² compared to 2.4 neurons/mm² in controls). Of the 20 surgical specimens where the hippocampus was available for histological evaluation, 19 had mesial temporal sclerosis. Although the cell counts are encouragingly similar between the two studies, Emery and colleagues proposed a different explanation for their findings, suggesting that the increased density of white matter neurons may be due to a loss of white matter volume in the temporal lobes of patients with intractable temporal lobe epilepsy.

Thom et al. (43) performed a quantitative study of temporal lobe white matter neurons using the optical dissector method. They compared 31 surgical specimens from people with temporal lobe epilepsy to 15 control specimens. This study included small neurons with somal diameters <10 μm, neurons that were excluded in the previous studies. They confirmed that neuronal densities were significantly higher in patients with temporal lobe epilepsy compared to controls and that the small neurons comprised about half of the white matter neurons in both groups. Perhaps in order to address the hypothesis of Emery et al. (42), they tested for and found no significant correlation between the degree of white matter gliosis and the density of white matter neurons in temporal epilepsy specimens. For technical reasons, no comparison was made in the degree of gliosis between the two groups.

Kaspar et al. (21) evaluated temporal lobectomy specimens for several features of microdysgenesis and compared them to age-matched autopsy controls. They found that >10 single white matter neurons per high-power field were present in 23% of surgical cases but were not seen in autopsy controls (although white matter neurons at lower densities were commonly seen in controls). Interestingly, two clinical studies found that increased white matter neurons were predictive of good post-surgical seizure control (41,43) while the study of Kaspar et al. (21) found just the opposite.

**REDUCED WHITE MATTER VOLUME IN TEMPORAL LOBE EPILEPSY**

Although they have used different methods, all of these quantitative studies have measured density of temporal white matter neurons rather than total numbers. This
is due to several stereological constraints including the fact that the entire temporal lobe is never removed at surgery and the fact that the posterior boundary of the temporal lobe is, to some degree, arbitrary. Since neuronal density is a function of cell number per unit volume, the possibility exists that the increased density of white matter neurons in temporal lobe epilepsy is a result of reduced white matter volume rather than increased numbers of white matter neurons. This alternative explanation has been supported by several volumetric studies of the temporal lobe in patients with temporal lobe epilepsy. In 1996, Breier et al. (44) developed a semiautomated analysis of T1-weighted MR images of the temporal lobes by thresholding for white matter-intensity pixels and measured volumes in 31 patients with temporal lobe epilepsy and 13 age-matched controls. They found significant asymmetry in temporal lobe white matter volumes in patients with temporal lobe epilepsy and that the volume was reduced on the side of the seizure focus. Two other MR-based studies have confirmed a reduction in temporal lobe white matter volumes (on the side of seizure initiation) in people with intractable temporal lobe epilepsy compared to age-matched controls (45,46). White matter volume loss has not correlated with any significant clinical features in these patients such as seizure duration or age at onset. At this time it is unknown if this finding represents part of the underlying pathological substrate of the epileptic condition or is simply a result of the effects of prolonged seizures or antiepileptic medications on the brain.

SIGNIFICANCE OF INCREASED DENSITY OF WHITE MATTER NEURONS IN TEMPORAL LOBE EPILEPSY

After reviewing the available literature, it is clear that the presence of some “heterotopic” neurons in the white matter is a normal finding. In addition, there appears to be a higher density of these neurons in the temporal lobe compared to the frontal and occipital lobes. There is good documentation that the density of white matter neurons is increased in people with intractable temporal lobe epilepsy. But there is also good documentation that temporal lobe white matter volumes are reduced in the same condition. Therefore the most parsimonious interpretation of these studies would be that the increased density of white matter neurons in temporal lobe epilepsy represents a normal complement of these neurons distributed in a reduced volume of white matter. One study that might alter this position would be quantitative cell counts and white matter volumetrics in the same specimens to see if the degree of white matter loss actually accounts for the degree of increased density in white matter neurons.

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Dysplasia Associated with Mesial Temporal Sclerosis

Section III  
Surgically Treatable Epilepsy Syndromes in Infancy and Childhood

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INTRODUCTION

Severe epilepsy during infancy and childhood may be associated with developmental stagnation or regression. The descriptive term “catastrophic epilepsy” has been used to describe this picture. Without intervention, the affected child’s outlook for cognitive achievement remains guarded (1,2). Surgical treatment may be appropriate in this setting if the epilepsy is severe, medically refractory, and caused by a focal epileptogenic lesion.

EPIDEMIOLOGY OF INFANT AND CHILDHOOD EPILEPSY

The frequency of epilepsy is high in infants and young children compared with adults (3,4). The incidence of epilepsy is highest in the first year of life (4–6) with 20,000 to 45,000 children diagnosed with epilepsy annually and up to 325,000 American children between the ages of 5 and 14 having active epilepsy (7). Approximately 20% of all seizures in children under the age of three years begin during the first month of life and nearly 17% begin within the first 15 days of life (8). Children with developmental disabilities tend to have an increased seizure risk, lower age of epilepsy onset, multiple seizure types, and high pharmacoresistant rate of seizures (7,9–12).

Malformations of cortical development (MCD) and low-grade developmental tumors are common etiologies in infants and children with catastrophic epilepsy presenting for surgery. In the Cleveland Clinic series (13), MCD and low-grade tumors were found in 90% of infants under the age of three years, in 70% of children, and in 57% of adolescents. In the Miami Children’s Hospital series (14), MCD accounted for 68%, developmental tumors 23%, and peri- and postnatal lesions in 10% of infants.
under the age of three years. Hippocampal sclerosis does not emerge as a common cause of surgically remediable epilepsy until later in childhood and adolescence (13).

**GOALS FOR SURGERY IN CATASTROPHIC EPILEPSY**

In part, the diagnostic evaluation must have consideration for distinct outcome concerns in the pediatric population. In addition to seizure control, there is a high priority of long-term developmental gain, optimization of cognitive performance, and increased social development. Some patients may have improved development gains after surgery. Bourgeois et al. (15) demonstrated that some patients had cognitive improvements in function and behavior after surgery. In a report of 12 infants, Wyllie et al. (16) found “catch-up” development in several infants with catastrophic epilepsy who underwent epilepsy surgery. In five patients with intractable seizures, Matsuzaka et al. (17) showed that early epilepsy surgery before the demonstration of developmental delay allowed the continuation of development, while delaying surgery until development delays were found resulted in continued delays. Asarnow et al. (18) found that compared with prior studies of developmental outcome, 24 children with infantile spasms who underwent epilepsy surgery had better developmental progression. Progression was more robust if they were relatively young and had high level of presurgical developmental attainments. Unfortunately, even with seizure freedom, epilepsy surgery may not result in enhanced neurological developmental gains (14,19). It is unclear what additional factors may be involved in normal progression of development in the context of intractable seizures, and what obstacles need to be removed or altered to restart normal neurological progression. Likely, the underlying pathological etiology, extent and area of epileptogenic zone, and seizure burden influence final outcome.

Risks and benefits of the surgical procedures themselves must be considered. The perioperative mortality in two pediatric epilepsy surgery series was 1.3% from the Cleveland Clinic (13) and 1.2% from the Miami Children’s Hospital (20). The risk may be higher in infants with small blood volumes and extensive brain lesions requiring multilobar resection or hemispherectomy. Because of risks for perioperative mortality, surgery should be reserved for infants with serious epilepsy and developmental compromise (2). However, the risks for surgery must be balanced against the risks of uncontrolled seizures treated medically, estimated at 1 in 295 per year in a pediatric study (21). In an adult series, the elimination of seizures after temporal lobectomy reduced mortality rates to those seen in the general population, indicating that the long-term risk of continued medical treatment is higher than the risk of epilepsy surgery in suitable candidates (22).

Another important risk of epilepsy surgery is the possibility of incurring new postoperative neurological deficits. The risk may be higher in infants and young children requiring extensive resections or hemispherectomy, coupled with age-related difficulties in mapping eloquent cortex in the immature brain (23,24). However, developmental plasticity of the immature brain may allow the recruitment of other brain regions or areas for proper function. For example, resection of eloquent cortex may result in only minor residual motor or language deficits when surgery is performed in a developing brain (25). In the presence of developmental focal lesions, the re-localization of the function because of plasticity can occur as the brain matures (26,27). Although plasticity with reorganization of eloquent functioning is related to the age of the patient, little data exist concerning what functions are age-related and
at what age that functional plasticity ceases. For instance, some transfer of language capabilities to the right hemisphere has been demonstrated even in older children (age 7–14 years) who underwent left hemispherectomy for Rasmussen’s encephalitis (28).

**PRESURGICAL EVALUATION OF THE SURGICAL CANDIDATE**

Although the major tenets of candidate selection are analogous to the adult patient, there are added complexities in the evaluation process that occur in the infant and young child. Various pediatric epilepsy centers have slightly different approaches for the surgical workup of the infant or child with intractable seizures. However, the information gathered reflects the fundamental requirements for proper candidate selection.

**Medical Intractability**

The cornerstone of what constitutes a surgical candidate is the presence of intractable and disabling focal seizures. However, what defines medical intractable or pharmaco-resistant seizures in adults is not fully accepted, especially in infants and children. The failure of two antiepileptic medications, with or without one trial of polytherapy over a period of two years, has been considered intractability to medication in the adult patient (29,30). Camfield and Camfield (31) have recommended that intractability should be considered after the failure of three first-line antiepileptic medications in the pediatric population. It appears unlikely that trials of more than two to three medications would significantly increase numbers of patients achieving seizure freedom (30). In infants with many seizures every day, the duration of drug trials may be brief. Waiting two years to determine intractability would be too long in an infant with daily seizures and developmental stagnation or regression.

There are some studies suggesting that some predictors of medical intractability exist in the pediatric population. Four studies have shown that remote symptomatic etiology and earlier age of seizure onset were predictors of intractable seizures (32–35). In two of these studies, high seizure frequency was a predictor of medical intractability (32,33). Berg et al. (32) found that infantile spasms, while Sillapaa (34) found that status epilepticus predicted intractability. Ko and Holmes (35) noted that tonic seizures as well as simple partial seizures were predictors. Poor response to short-term antiepileptic therapy (33) and failure of the initial antiepileptic drug trial (30) were also predictors of medical intractability. Further studies are needed to confirm predictors of medically intractable seizures within the context of seizure duration and epilepsy substrate.

**Seizure Semiology**

The clearest candidates for epilepsy surgery have stereotypic partial seizures. However, this is not always found in the younger child. The development of eloquent cortex alters the clinical seizure expression in the younger child, making evaluation of seizure semiology problematic even with the utilization of extensive video recording (36). In infants <3 years and those who have significant developmental delay, clinical assessment of level of consciousness and localizing semiology limits declarative features of focal onset (37–39). This is particularly true in preverbal children. Detection of an aura, automatism, hand/arm dystonic posturing, and level of consciousness during a seizure may not
be present or easily discernable in the younger child. In 23 children younger than three
years, only three patients had motor features characteristic of partial seizure onset (37).
In a larger series from the Cleveland Clinic, 76 children under the age of three years had
seizures suggestive of nonlocalized related seizures, but were rendered seizure-free after
focal cortical resection (39). However, as eloquent cortex matures, defining features
may become more evident. Nordli et al. (40) have demonstrated that after six years,
the prevalence of aura, automatism, and dystonic posturing becomes more evident.
Brockhaus and Elger (41) have found that tonic posturing becomes more asymmetric
with age, although this was not found in other studies (40). While localizing features
may be seen in the pediatric age group, declarative features of focal onset may not
be present because of immaturity of eloquent cortex.

Infants with focal epileptogenic lesions may present with epileptic spasms.
MCD are most common but spasms may also occur in the setting of developmental
tumor or perinatal infarction. The typical age of epileptic spasm onset is between
4 and 10 months of age. Characteristically, the spasms later remit with other seizure
types developing. The hypsarrhythmic electroencephalogram (EEG) consists of diffuse
high-amplitude poorly organized background activity with multifocal epileptiform
transients during the awake state. Often a suppression-burst pattern is seen during
sleep. Magnetic resonance imaging (MRI) is critical to identify surgical remediable
lesions. Positron emission tomography (PET) scanning may also be helpful to identify
focal hypometabolic regions, which may be foci of cortical dysplasia on pathological
analysis (42).

Important clues to the surgical candidate with infantile spasms can be focal
findings on neurological examination, such as hemiparesis with decreased sponta-
neous movement on one side of the body. The EEG may give hints for focal seizure
onset, displaying asymmetry or focal slowing of faster rhythms. History may also
reveal focal or partial seizures before the onset of epileptic spasms. The seizure semi-
ology may include asymmetric spasms. The best surgical candidates are those with
focal MRI lesions congruent with focal EEG findings, neurological examination,
and PET hypometabolic region.

The poor developmental outcome of infants with medically refractory spasms
would suggest that if congruent findings identify a surgical candidate, the surgical
elimination of seizures represents a significant advantage. Improved developmental
gains, socialization, and skills of daily living can accompany seizure freedom (18).

Physical Examination

The immature brain can also limit focal findings on the physical examination.
Hemiparesis during infancy may only be subtly expressed, as the corticospinal tracts
and motor systems are still undergoing maturity. One may only see decreased spon-
taneous movement of the extremities on one side of the body. Skin lesions may be
subtle but can provide clues to Sturge–Weber, tuberous sclerosis complex (TSC), or
epidermal nevus syndrome. Moderate-to-severe developmental delay is present in
more than 75% of infants and young children presenting for surgical evaluation
(13,15,39,40), and such patients may not be able to fully comply with the neurological
examination so that subtle focal findings are blunted. Furthermore, some infants and
children may have focal epileptogenic lesions without localizing clinical seizure semi-
ology or focal neurological deficits. These limitations necessitate careful evaluation
of multiple modalities of physical examination, video-EEG, and neuroimaging with
the convergence of these investigations becoming paramount for patient selection.
Video-EEG Monitoring

Video-EEG monitoring with seizure recording is one of the foundations of the surgical evaluation. However, the interictal EEG can also yield important information concerning the presence of an epileptogenic focus, help in characterization of seizure type and epilepsy syndrome, and provide important information concerning the epileptogenic zone. Some important localizing clues are focal slowing, focal attenuation of fast rhythms, or persistently present focal epileptiform discharges. However, multiregional interictal discharges can also be seen in children with a potential surgical lesion (43), complicating the surgical decision.

The detailed analysis of the seizure by video and EEG has been vital to the identification of the infant and child surgical candidates. Visualization of clinical semiology of seizure onset can be the most informative aspect of the study. Early finding of eye and head version, focal motor movements, unilateral dystonic posturing, automatisms involving one body part, and aura may be suggestive of focal seizure onset. The EEG during an event may lateralize to a particular brain region, corroborating the clinical semiology. In select situations, invasive electrode monitoring may help define epileptogenic zones and tailor resections, when involvement of eloquent cortex needs to be elucidated or neuroimaging is nonlesional. The Miami Children’s Hospital group has found subdural EEG helpful in localization of eloquent cortex and epileptogenic zone, even in young infants (23,24,44,45). However, subdural studies carry some risks (46,47).

MRI is critical for the localization of the epileptogenic substrates such as MCD and tumor. Conventional MRI imaging is generally sufficient to characterize a relatively large lesion, but subtle MCD and small lesions may only be visualized using three-dimensional acquisitions and image reconstruction. The type of lesion determines the optimal acquisition sequences. For example, some MCD are better visualized against immature white matter in neonates with the contrast of fast T2-weighted images (48). Fluid-attenuated inversion recovery imaging is especially useful in detecting signal abnormalities in the hippocampal formations of patients with mesial temporal sclerosis (48–51).

The presence of an MRI-detected lesion has important prognostic value in outcome. When present on MRI, complete removal of the lesion may confer better outcome. For instance, detection of an MCD on MRI and complete resection resulted in seizure freedom in a higher percentage of patients than those with only partial resection (52,53). Those patients without MRI lesions or only nonspecific findings may have a worse outcome (14).

MRI detection of focal MCD in the infant and young child has unique problems. The immaturity of the myelination process presents a less distinct gray–white junction on MRI. At the same time, loss of distinctive gray–white junction can represent focal MCD. Compounding the difficulty in detection of MCD is the maturation-dependent change in signal intensity of T1- and T2-weighted images, as the brain matures from caudal to cephalad and from dorsal to ventral (54). Furthermore, focal MCD exists along a spectrum, ranging from a subtle area of indistinct gray–white junction or abnormal thickening of the cortical mantle to a large cleft lined by polymicrogyric cortex from ventricle to pia surface (55). Depending on the age of the child and the degree of MCD, detection by MRI may be challenging.
PET scanning may add important information and may be an independent measure of focal lesions. PET defines metabolically abnormal brain regions correlating with the epileptogenic focus (56). This may be especially important in the immature brain where the pattern of myelination is not fully developed. PET can identify MCD when it is otherwise difficult to detect (16,39,57).

Ictal single photon emission computed tomography (SPECT) may aid in the presurgical evaluation of some children (58). Sensitivity of SPECT depends on the ability to inject isotope early in seizure propagation, as delays in injection may show seizure spread rather than seizure onset (59). Currently, SPECT is complimentary in helping to define the epileptogenic zone rather than being of independent importance. SPECT data must be evaluated with the other presurgical investigations with awareness of the spatial resolution. Recently, studies have suggested that the probability of seizure freedom is significantly higher in patients with nonlesional extratemporal epilepsy, when surgery involved a focal lesion based on subtraction SPECT with co-registration on MRI than when it did not (60,61).

Other refinements in imaging techniques are being developed for detecting the epileptogenic zone in older children and adults, including diffusion-weighted MRI, magnetic resonance spectroscopy, and functional MRI. However, these methods have not been widely tested in the pediatric population.

Neuropsychological Assessment

An essential component in the presurgical evaluation is the battery of neuropsychological tests used to measure global intelligence, language, memory, and motor skills. The integration of test results identifies deficits that correlate with the patient’s underlying neurophysiological and neuroanatomic lesion. Deficits may be useful in lesion localization to corroborate the results from other studies. Results of testing are also used to predict the risk of functional loss after a specific type of surgery procedure. Children may present problems because of cognitive immaturity, although the Wada intracarotid amobarbital test has been used in children as young as five to six years (62). However, Wada results, especially for memory, may not be informative for those with IQs less than 70 (62).

SURGICAL PROCEDURES

The epileptogenic substrates typically found in infants and children result in distinct spectrum of surgical procedures. The majority of epilepsy surgeries in infants are extratemporal or multilobar resections or hemispherectomies (13,14,16). Various hemispherectomy techniques are used in different clinical situations and at different centers (Section XI). Anatomic hemispherectomy, which involves resection of the frontal, parietal, and occipital cortices along with a complete temporal lobectomy and insular resection, is the oldest of the surgical techniques (63). Although an effective surgical treatment, this procedure entails risk of the serious late complication of superficial cerebral hemosiderosis (64). This has not been reported in modern series since the advent of computerized tomography (CT) and MRI, however, and it is possible that the earlier cases involved hydrocephalus. Peacock et al. (65) recommend anatomic hemispherectomy in patients with a small lateral ventricle, in those with dysplastic syndromes because of the high risk of hemorrhage and firmness of the tissue, and in very young children. Other techniques were developed in response to the
late complication of anatomical hemispherectomy: functional hemispherectomy (66,67), hemispherotomy (68,69), Oxford modification of anatomic hemispherectomy (70), modified lateral hemispherotomy (71), and hemidecortication (72). Functional hemispherectomy or hemispherotomy have the advantage of reducing infection, hemorrhage, and hydrocephalus by minimizing the calvarium entrance site and volume of removed tissue (73). In addition, compared with anatomic hemispherectomy, functional hemispherectomy reduces the risk for superficial cerebral hemosiderosis with the same degree of seizure control (66). The lateral modified hemispherotomy was associated with the least intraoperative blood loss, shortest intensive care stay, and lowest complication rate in one study (71). Further studies are in progress to assess the relative efficacy of functional, modified anatomic or complete hemispherectomy in the setting of various clinical settings such as perinatal infarction, Rasmussen syndrome, or hemispheric MCD.

THE APPROACH TO PEDIATRIC EPILEPSY SURGERY IN SPECIFIC CLINICAL SETTINGS

The infant and child present unique complexities to surgery because of their innate epilepsy substrates and physiology. Tailoring the surgery to the type and extent of lesion requires comprehensive evaluation and strategies to optimize outcome, in respect to both seizure freedom and developmental outcome.

Malformation of Cortical Development

Cerebral cortical development can be divided into three broad categories: cell proliferation, neuronal migration, and cortical organization (74). The stage where the arrest/abnormality occurs produces a distinct spectrum of malformations ranging from focal cortical dysplasia to profound alteration of the cortical architecture (74–76). Despite differences in their gross appearance, all malformations share similar pathological findings of cortical dyslamination, neuronal ectopia, and bizarre giant cells with neuronal and glial elements (74,77). Furthermore, these lesions have an intrinsic epileptogenicity associated with them (78,79). Consistent with infants and children having innate abnormalities as epilepsy substrates, malformations are the most frequently cited pathologies in this age group coming to epilepsy surgery.

Scalp EEG may show high-amplitude activity (often >150 μV) and paroxysmal fast activity (15–25 Hz). In addition, rhythmic discharges with or without epileptiform morphology may be seen (80). Electroencephalography of focal lesions usually shows multiple EEG seizures, repetitive bursting discharges or continuous rhythmic spiking (79,81). MRI may be helpful in identifying the presence of MCD and the approximate region of the epileptogenic zone, but may not demonstrate the true extent of the cortical dysplasia (52,82). Functional imaging with PET and seizure onset ictal SPECT may aid in defining the extent of the lesion (16,42,81).

Early surgical series with patients having MCD showed limited success with only 11% to 35% of patients becoming seizure-free (53,83,84). One series showed a seizure-free rate of 52%, with a mean follow-up of 3.6 years (13). Another series from the Cleveland Clinic suggested that 50% to 60% seizure freedom can be seen (52). The surgical series from the University of California, Los Angeles (UCLA) showed 65% seizure-free at two years but only 33% seizure-free at 10 years of follow-up (85). It is unclear whether length of follow-up alters seizure freedom or if refinements in
neuroimaging may have influenced surgical outcome. Results may be less favorable in particular types of malformations such as schizencephaly (86) and nodular heterotopía (87). Further studies with more defined subpopulations and seizure reoccurrence over more prolonged time periods are needed.

**Hemimegalencephaly**

Hemimegalencephaly is a disorder of uncontrolled neuroepithelial proliferation or decreased apoptosis (74). It occurs as an idiopathic, poorly understood developmental event or within a neurocutaneous syndrome (74,88). Two of the more common neurocutaneous syndromes with hemimegalencephaly are linear sebaceous nevus syndrome and hypomelanosis of Ito (89,90). A spectrum of abnormality may exist and cerebral size of the affected side may be related to clinical severity (91,92). Histopathological findings are similar in both idiopathic and syndromic types (93). Patients with frequent seizures soon after birth or infantile spasms during the course of their disease have poor prognosis, with a high probability of death during status epilepticus (94).

The natural history of frequent and pharmacoresistant seizures associated with hemimegalencephaly led to the development of hemispherectomy for seizure control (94,95). In a small early series from the Cleveland Clinic, seizure-free outcome after functional hemispherectomy tended to be less frequent in infants with classical hemimegalencephaly than in those having hemispheric malformations with atrophy or relative sparing part of one lobe (96). In infants with persistent seizures after functional hemispherectomy, video-EEG most often gave evidence of onset in the transected hemisphere. These results suggested that complete disconnection of epileptogenic tissue might be more difficult in the setting of classical hemimegalencephaly, severe malformation, and disordered deep hemispheric anatomy. Studies are in progress to assess the efficacy of modified anatomic or complete hemispherectomy in this clinical setting.

**Tuberous Sclerosis Complex**

Tuberous sclerosis complex is an autosomal dominant genetic disorder with variable penetrance, affecting multiple organ systems (97). Neurological involvement is common with epilepsy in ~90% of patients, with onset usually beginning sometime in the first decade (98). Although infantile spasms are common in TSC during infancy, partial seizures affect a higher proportion of patients overall (99). The signature lesion is the non-neoplastic cortical hamartoma or tuber (74), with increased number of tubers correlating with greater seizure severity. In some cases, one tuber may be predominant in the generation of seizures. One study indicated that in such cases a tuber that is well defined, larger compared with other tubers, or contains a nidus of calcification is likely to be the epileptogenic tuber (100).

Although TSC patients have multiple tubers with each having the potential to be individual epileptogenic zones, the removal of a single tuber may successfully improve or alleviate seizures (100). Ictal video-EEG may show rapid secondarily generalized discharges that are apparently bilaterally synchronous discharges (100,101) with the clinical semiology of generalized tonic spasms. An epileptogenic tuber may represent the principal spike focus with highest amplitude and most frequent spike frequency (75). When EEG, MRI, and ictal SPECT findings are convergent on a tuber(s) that is surgically resectable, the prognosis for surgery may be favorable (102,103).
Small surgical series indicate seizure freedom in about 39% to 67% of patients with TSC (78,102,104,105). When the scalp EEG, SPECT, and MRI findings of the largest tuber or tuber with nidus of calcification are congruent, the percentage of seizure freedom increased to 70% (100). In the Miami Children’s Hospital series, those patients who became seizure-free experienced decreased seizure activity and improved cognition and behavior by parental report (100). Recently, a multistage surgical approach with resection of multiple seizure foci located in bilateral hemispheric locations has shown significant seizure reduction with improved neurocognitive outcome in two patients (106,107). As more patients undergo multistage surgery for multiple epileptogenic tubers, the utility of aggressive surgical resection may reduce seizure and neurocognitive burden in an otherwise refractory population. However, the long-term outcome from epilepsy surgery is guarded as it is unknown whether the remaining tubers could activate, or removal of the epileptogenic focus could modify potential secondary epileptogenic areas.

**Developmental Tumors**

In the classification of Barkovich et al. (74), dysembryoplastic neuroepithelial tumor (DNET), ganglioglioma, and gangliocytoma are malformations because of abnormal neuronal and glial proliferation or apoptosis associated with disordered cortex. Seizures are a common presentation in patients with developmental and slow growing cerebral tumors.

DNETs are benign lesions that are usually detected clinically as a result of seizure activity, without signs of increased intracranial pressure, acute neurological deficit, evidence of growth, or changes in the lesion (108). Histologically, these lesions consist of small cells having the appearance of oligodendrocytes with admixed neurons. Lesions are often cystic and are associated with MCD (109). On MRI, both T1- and T2-weighted sequences have characteristics comparable with gray matter, although calcifications with isolated or multilobulated cystic lesions may be present (110). The epileptogenic zone may not be the actual DNET itself, but the associated dysplastic tissue in the adjacent cortex (81,111). Intraoperative electrocorticography, surface EEG ictal onset, as well as subdural electrocorticography have shown the epileptogenic zone to be encompassing the tumor (81).

Gangliogliomas are also usually detected in the context of seizures. A large study from Children’s Hospital of Philadelphia demonstrated that almost 50% of children expressed seizures as their presenting symptom, with over 60% having seizures over the course of the disease (111). Temporal lobe was the most common site with parietal and frontal lobes also found (111). Histologically, both neuronal and glial atypia are found in small, well-demarcated lesions. When neuronal elements predominate, the lesion is termed gangliocytoma and when glial elements predominate, the tumor is a ganglioglioma. These lesions comprise 4% to 8% of pediatric brain tumors but comprise up to 22% of patients undergoing epilepsy surgery (112,113). Calcification and cysts may be seen within the tumor, and the lesions may be seen in association with cortical dysplasia (114). In the Children’s Hospital of Philadelphia surgical series, 78% of patients were seizure-free on no seizure medication after surgery and 18% had improvement in seizure frequency (111). In a Cleveland Clinic series of 15 patients, total removal of the lesion appeared to be the most important factor predicting a seizure-free outcome (114).

Patients with low-grade gliomas often present with seizures, as do those with DNET or ganglioglioma (115). The radiographic findings of low-grade glioma are
similar to DNET (108). Packer et al. (116) reported that 45 of 47 patients with total or near-total resections were seizure-free. Their data suggested an association between short duration of seizures and good outcome.

Children with developmental tumors appear to be excellent surgical candidates. Seizures as the presenting symptom appear to be a favorable prognostic sign.

**Hypothalamic Hamartoma**

Hypothalamic hamartomas consist of heterotopic hyperplastic tissue within the interpeduncular cistern or within the hypothalamus, near the tuber cinereum and mamillary bodies (117). Characteristic of this syndrome are gelastic or laughing seizures, with other seizure types usually present (117). Many patients also have severe behavioral problems and precocious puberty (118). Reports have noted spiking within the hamartoma detected by depth EEG, and electrical stimulation of the hamartoma may induce gelastic seizures (119,120). In addition, ictal SPECT may reveal hyperperfusion within the hamartoma but not in the cortex (120). Surgical resection or radiofrequency lesioning of the hypothalamic hamartoma can result in cessation of gelastic as well as tonic and atonic seizures (120,121), with improvement of behavior and cognition (122).

**Hippocampal Sclerosis**

In contrast with the experience in adults, hippocampal sclerosis is relatively uncommon among pediatric candidates for epilepsy surgery (13,85). When present in children, hippocampal sclerosis may frequently be associated with cortical dysplasia (123–125).

In temporal lobe epilepsy caused by hippocampal sclerosis or other etiologies, seizure symptomatology may vary by age. Seizures tend to be bland in young children, with prominent automatisms manifesting after four to six years of age (40,41). The EEG is localizing in most patients, with rhythmic theta/alpha discharges, focal attenuation, or low-voltage fast discharges as early localizing ictal features. In some, the earliest EEG feature may be the cessation of focal spikes. Hamer et al. (39) showed that interictal anterior temporal spikes tended to be more confined in patients with hippocampal sclerosis, than in patients with temporal lobe epilepsy caused by tumors of the amygdala and hippocampus. Adult patients with hippocampal sclerosis on MRI and congruent interictal epileptiform discharges have excellent surgical outcomes (126).

Predictive factors may vary (127), but outcome after mesial temporal resection appears comparable in children compared with adults (13,52). In one study looking at long-term outcome with a 15 year follow-up, seizure freedom declined from 88% of patients at two years to 60% at 15 years (128). This reduction in seizure freedom over time was also seen in an adult series, showing 90% of patients seizure-free at two years and 62% at >10 years (129). Despite some late recurrences, surgical results remain superior to those achieved with antiepileptic drugs in refractory patients.

**Cavernous Malformations**

Vascular malformations are a potential cause of epilepsy. Arteriovenous malformations are epileptogenic with 17% to 40% of patients having the initial symptom of seizures (130). Data in the pediatric age group are sparse. Capillary telangiectasias are also thought to be epileptogenic, however, there are no pediatric series in the
literature. Venous angiomas, the most prevalent vascular malformation, have an unclear relationship to epilepsy (130).

In contrast to arteriovenous malformations and venous angiomas, most cavernous malformations present with seizures. Cavernous malformations are dense clusters of sinusoidal vascular spaces without intervening brain parenchyma, which undergo repeated hemorrhage and development of dystrophic calcifications (131). Lesions are commonly isolated but may be multiple in up to one-third of cases, especially when familial (132). MRI demonstrates spherical lesions with a characteristic hypointense surrounding ring of T2-weighted spin-echo or gradient-echo parenchyma, related to hemosiderin and ferritin deposits. In a small series with large literature review, epilepsy was reported in over 45% of patients (133). Lesionectomy in 11 out of 18 children with intractable seizures resulted in seizure freedom postoperatively (134). In another series of 51 children with malformation and seizures, 70% were seizure-free with the rest having persistent seizures. Seizure freedom was related to shorter preoperative duration of seizures, total number of seizures, and female sex (135). Earlier removal of malformation may improve outcome in this condition.

Sturge–Weber Syndrome

The neurocutaneous syndrome, Sturge–Weber syndrome, is a sporadic disease with leptomeningeal venous angioma and ipsilateral facial hemangioma (port-wine stain or nevus flammeus). The nevus can be absent in ~5% of patients (136). The etiology of the neurological manifestations is the chronic ischemia of the cortex underlying the leptomeningeal venous angioma (137). A progressive cortical ischemia produces hemiparesis in 30% to 56% (138,139) and mental retardation in 60% (140), with a strong association of seizures with mental retardation. Seizures are seen in 70% to 90% of children with this syndrome (139,140) and usually begin before the age of one year (141). The seizures are usually partial motor involving the contralateral limbs or secondarily generalized, however, generalized seizures can be seen. A high percentage of patients, >95%, have been shown to have abnormal interictal EEG patterns (139). The most common feature was attenuation of background activity (74%), with only 22% having both attenuation of the background activity and epileptiform spikes. Contrast-enhanced MRI is the most accurate imaging study for demonstrating the extent of the pial angioma (142). Calcifications mask the enhancement on CT and therefore, MRI with contrast is more sensitive in revealing the extent of enhancement (142). Depressed glucose metabolism on PET (143) and decreased regional blood flow on 133Xenon SPECT (144) confirm severe functional abnormality of the cerebral cortex underlying the angioma. In one series (145), 36 of 45 patients (80%) were seizure-free after surgery.

In ~50% of patients with Sturge–Weber syndrome, seizures are either controlled by medications or undergo spontaneous remission (138,146). The decision to perform epilepsy surgery and the correct timing of surgery is controversial. Seizures often occur in bursts with temporary control by medications. This makes the decision to proceed with surgery for these patients difficult and the usual decision-making paradigm problematic during periods of relative seizure freedom (147). On the contrary, some suggest that early surgery might reverse the process of gradual cognitive decline that can attend this syndrome (148). In one study (149), cognitive delay was significantly correlated with seizure intensity in the early period, but not with the age of seizures onset, degree of hemiparesis, or the presence of ongoing seizures. A retrospective questionnaire review from Johns Hopkins University (147) suggested that age at
surgery did not have an adverse effect on seizure or cognitive outcomes, with most patients seizure-free. However, the impact of surgery on long-term cognitive outcome is not yet clarified.

**Rasmussen's Encephalitis**

Rasmussen's encephalitis is an acquired progressive inflammatory disease characterized by intractable focal or lateralized seizures, often with epilepsia partialis continua (150,151). A slow, progressive neurological decline follows seizure onset, with development of hemiparesis, hemianopsia, cortical sensory loss, and speech deterioration over the next 1 to 20 years. The inflammatory process is usually limited to one hemisphere and remains unilateral with only rare progression to the contralateral hemisphere. Atrophy accompanies the inflammatory involvement and usually is a later finding on neuroimaging. However, recent advances in MRI scanning have shown that focal abnormalities can be seen as early as four months after disease onset. One study showed that seven of eight patients had focal atrophy involving the insular cortex and extending also to ipsilateral frontal, temporal, or parietal areas (152). As the disease progressed, atrophy is seen in the precentral gyrus, inferior frontal gyrus, and cerebellum over the first year of the disease (153).

Age of onset is usually between 14 months and 14 years, although later onset has been reported (151). There is no sex preference and before the onset of epilepsy, development is usually normal. There is a preceding infectious or inflammatory event in about one-third of the cases (151). Isolated focal seizures with a motor component are the usual presentation, which become intractable to medication. Epilepsia partialis continua occur in over half of patients. The EEG usually shows polymorphic slowing over the affected hemisphere, with epileptic abnormalities intermixed. Serial EEGs show progressive flattening of the background activity over the affected hemisphere with persistence of the multifocal slow epileptiform abnormalities (154). Death from chronic encephalitis is unusual but may occur (151).

Surgical intervention early in the course of the syndrome may preserve residual function and optimize seizure control (155). In the Montreal Neurological Institute series, limited cortical resection was ineffective, while hemispherectomy was effective in abolishing the seizures in 42% of patients and was thought to prevent cognitive deterioration (156). In two separate surgical studies, hemispherectomy resulted in seizure freedom in 67% of patients in the UCLA series (71) and 65% in the Johns Hopkins series (157). Language recovery was noted in older children, 7 to 14 years, undergoing left hemispherectomy (28). However, more studies are needed to address whether early surgery may enhance cognitive retention and seizure freedom.

**Congenital Vascular Injuries**

Vascular congenital hemiplegia and intractable epilepsy most frequently arise from pre- or perinatal hypoxic-ischemic injuries as a result of unilateral vascular accidents. The majority of patients have evidence of middle cerebral artery infarction with and without porencephaly (158,159) or smaller arterial branches having no predilection for the middle cerebral tree (159). Smaller numbers of patients have evidence of perinatal ischemic insults (158) and sinus thrombosis (160). Most patients express seizure semiology consistent with the epileptogenic area affected. However, the extent of the epileptogenic zone does not always correlate with extent of the MRI lesion and neurological deficit (161). When patients express moderate or
severe hemiparesis and seizures arising from multiple regions or diffusely within the damaged hemisphere, hemispherectomy represents the surgical option of choice (160). In the UCLA series, 73% of 27 patients were seizure-free (71), while 81% of 16 children at Johns Hopkins (157) and 82% of 11 patients from the Great Ormond Street Hospital for Children in London (158) became seizure-free after hemispherectomy. Although the series from the Cleveland Clinic did not separate children from adults, 84% became seizure-free following hemispherectomy (161). When compared with the other candidate lesions for hemispherectomy, Rasmussen encephalitis and MCD, infarction/ischemia lesions represent the highest incidence of seizure freedom following surgical resection (71,157,158). There is also a strong indication that the type of hemispherectomy may influence seizure outcome, as those patients who underwent functional hemispherectomy or modified hemispherotomy had a significantly higher seizure freedom percentage when compared with the anatomical procedure (71).

CONCLUSION

Epilepsy surgery is an important treatment of catastrophic epilepsy syndromes in infants and children with medically intractable seizures as a result of focal or hemispheric epileptogenic lesions. The adverse seizure and neurobehavior outcomes in the setting of failed medical therapy have provided justification and rationale for this innovative treatment. The current diagnostic tools of video-EEG, neuropsychological testing, MRI, PET, and ictal SPECT scanning have demonstrated that particular epilepsy syndromes can be effectively treated with favorable outcomes. Seizure freedom has been in the range of 60% overall, comparable with that seen in large adult surgical series. Issues include surgical timing, neural plasticity, and the goal of improved neurobehavior outcome.

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Who Is a Surgical Candidate?


For those children with epilepsy who are likely to benefit from surgery, there has to be a timing for the surgery that is optimal. If surgery was the only treatment option, this optimal timing would be defined as the time point when it becomes apparent that the seizures are not going to subside spontaneously. However, medical therapy of epilepsy is always the first step and it is considered to be associated with less risks and with less permanent consequences than surgery. Consequently, as stated in Section I, “if surgery is considered only for better seizure control, and not because of a cerebral lesion that needs to be resected (e.g. tumor or arterial venous malformation), it would be very unusual to proceed with surgery unless some degree of resistance to medical treatment has been established.” Resistance to medical treatment in this context is usually referred to as medical intractability and this concept has been amply discussed in Section I. Medical intractability is a relative concept. In the context of the eligibility for a surgical approach to the seizures, medical intractability should imply that the benefit versus risk ratio of surgery is estimated to be higher than for any further treatment option, including vagus nerve stimulator implantation. The point in time at which this conclusion is reached can be considered to be the optimal timing for surgery. As stated earlier, the criteria for medical intractability seem to have changed over time. What may have been considered appropriate timing in the past is now often considered late, and what is now considered appropriate timing, might have been regarded as early intervention in the past.
The issue of early surgical intervention has already been addressed over the past 10 to 15 years by several authors who have previously addressed many of the issues that will be discussed here (1–5).

The present discussion is entitled “What are arguments in favor of early intervention?” As intervention should always be optimally timed and should not be “early” or “late,” this discussion will focus on factors that have influenced the shift in timing over the years, and factors that would justify a surgical intervention “sooner rather than later.” Presumed or established factors that may contribute to a shift toward earlier surgical intervention can be divided into four main categories:

- Earlier identification of medical intractability
- Increased experience and comfort with surgical intervention in infants and children
- Expanded spectrum of conditions that may benefit from epilepsy surgery in infants and children
- Evidence that earlier surgical intervention can improve overall long-term outcome.

EARLIER IDENTIFICATION OF MEDICAL INTRACTABILITY

The issue of medical intractability has been amply covered earlier in this book. There is little doubt that, during the past decade, published data as well as widespread clinical experience at epilepsy surgery centers have generated a consensus that a good probability of medical intractability can be accepted after fewer therapeutic steps than had been previously perceived (6,7). This widely accepted concept of early identification of medical intractability must be recognized as a strong impetus for earlier surgical intervention. Acknowledgment of medical intractability is a crucial element in the benefit versus risk equation of the surgical decision. Once it becomes apparent that the probability of substantial seizure reduction or seizure freedom is much higher following a contemplated surgery than with any number of further medical interventions, the potential risks of the surgical intervention are more justifiable and acceptable. However, one can never be entirely sure that the patient will not experience a spontaneous remission at some point in the future. Indeed, Selwa et al. (8) have assessed the long-term outcome (average more than four years) in 34 patients who were evaluated for possible epilepsy surgery, but were considered to be inadequate surgical candidates. Somewhat unexpectedly, seven (21%) patients achieved seizure remission for an average of 2.5 years.

INCREASED EXPERIENCE AND COMFORT WITH SURGICAL INTERVENTION IN INFANTS AND CHILDREN

Even after Falconer (9,10) demonstrated the feasibility and benefit of epilepsy surgery in children in the early 1970s, this therapeutic approach remained initially limited to very few specialized centers. Widespread application of the surgical approach to the treatment of various forms and causes of epilepsy in children began in the 1980s and grew rapidly in the 1990s. During the past two decades, an increasing number of centers have accumulated experience with steadily growing pediatric series involving various types of surgeries and younger patients (11–18). As a result,
an increasing number of centers have become experienced with epilepsy surgery in children and it became possible to evaluate the success rates and the risks associated with this approach in large samples of pediatric patients.

Extensive experience with the procedures involved, as well as an improved assessment of success rates and risks undoubtedly make it easier to consider and recommend surgery for epilepsy at an earlier stage in the treatment sequence. Overall, success rates following epilepsy surgery in children and in infants have been found to be similar to those achieved in adults. Certain epilepsy surgeries are performed almost exclusively in children, because of neural plasticity and because of the nature of the underlying pathology, such as hemimegalencephaly, Sturge–Weber syndrome, and symptomatic infantile spasms. Some of these patients have very severe epilepsies and surgery can be of substantial benefit even when complete freedom from seizures is not even expected. In general, there is no evidence from published data that complications from epilepsy surgery are more common in children and infants than in adults, although it has been suggested that infants may be at higher risk of perioperative mortality (4). Nevertheless, the fact that success rates and risks of epilepsy surgery in children and infants do not differ appreciably from results obtained in adults, and that several centers now have extensive experience with this therapeutic approach in children, represents strong arguments in favor of early intervention.

EXPANDED SPECTRUM OF CONDITIONS THAT MAY BENEFIT FROM EPILEPSY SURGERY IN INFANTS AND CHILDREN

Epilepsy in infants and children may be caused not only by serious congenital abnormalities associated with severe and invariably intractable seizures, but also by conditions known to cause progressive neurological impairment over time, such as tuberous sclerosis, Sturge–Weber syndrome (19–21) and Rasmussen’s encephalitis (22). Infants and children may also have severe epilepsies referred to as “catastrophic epilepsies” or epileptic encephalopathies, such as West syndrome and Lennox–Gastaut syndrome. Some of these syndromes may benefit from surgery. In these syndromes, the concept of epileptic encephalopathy implies that the epileptic activity in general, rather than the seizures per se, cause a global functional impairment of mostly higher cortical functions. Control of the epileptiform activity, by any means, is often associated with significant developmental and cognitive progress. Another clinical situation that is specific to the pediatric age group is the association of epilepsy and language regression. It has been shown that these patients can benefit from surgery (23).

In Sturge–Weber syndrome, a progressive hemispheric atrophy is common, with functional decline. Seizures may often become increasingly refractory to medications. This poor prognosis can justify surgery even if the surgery causes new deficits, because seizure control can be achieved at the price of deficits that are expected to occur spontaneously during the future course of the disease (19). However, even in this syndrome, the prognosis cannot be established with certainty, both in terms of seizure control and in terms of a hemiparesis (20).

EVIDENCE THAT EARLIER SURGICAL INTERVENTION CAN IMPROVE OVERALL LONG-TERM OUTCOME

It appears intuitively evident that, in a child who would indeed have experienced no remission of seizures at any time, an earlier surgical intervention should be
associated with a better long-term outcome overall. This improved long-term outcome would be expected to affect predominantly psychosocial aspects of the patient’s life, but also a reduction in the morbidity associated with seizures, and freedom from adverse effects associated with antiepileptic drugs if these can be successfully discontinued. In addition, the higher plasticity of the brain at a young age suggests that infants and young children would be more likely to transfer functions affected by a surgical resection. A good example is the transfer of language function after a hemispherectomy. A more questionable argument for early surgical intervention could be the development of a secondary and ultimately independent focus of epileptogenesis in the presence of an active primary focus (2).

Although the above benefits from early intervention are likely, objective evidence is limited. The only benefit from successful surgery that does not need documentation is the additional time period of improved quality of life. If successful surgery is performed, for instance, three years earlier in a given child than in another child with the identical clinical presentation, the first child will have benefited from three additional years of life without seizures and from earlier discontinuation of antiepileptic drugs. This in itself is an undeniable benefit. The important question, however, is whether the first child will also be better off than the second child 10 or 20 years after the surgery.

Developmentally, early childhood is a very vulnerable period. The relative extent of development, learning and maturation is much greater between the ages of two and five years than between the ages of 22 and 25 years. Delays or setbacks are likely to be caused by epilepsy and its treatment. These include functional impairment, restrictions of activities and morbidity as a result of seizures, side effects from medications, missed school, overprotection, lowered self-esteem, and reduced social interaction. These factors are not only likely to have a greater impact at an earlier age, but are also likely to cause a psychosocial gap. This gap may be impossible to fill completely, even after the individual is “cured” from the epilepsy by the surgical intervention. It is reasonable to assume that this gap will widen further, the longer the epilepsy remains uncontrolled on medication. Although these theoretical considerations appear plausible, they are rather poorly documented. Unequivocal documentation would require controlled studies with long-term follow-up over many years. Such controlled studies are difficult or even impossible to perform. One could conceivably use historical controls, such as patients who, in the past, underwent surgery for comparable conditions at a later age than more recent cohorts of patients. However, other parameters may also have changed over the years, such as surgical approaches or side effects of available antiepileptic drugs. Because of the importance of determining the optimal timing for epilepsy surgery, and because of the paucity of data regarding this issue, it has been argued that a randomized controlled trial would be ethically justifiable (24,25).

There has been a longstanding concern that epilepsy at a young age may have negative neurodevelopmental consequences. It has been recently reported that childhood-onset temporal lobe epilepsy appears to be associated with an adverse neurodevelopmental impact on brain structure and cognition (26). This deleterious effect on the brain was found to be generalized, affecting predominantly white matter volume. The developmental outcome of 24 children who underwent surgical resection for intractable infantile spasms was assessed by Asarnow et al. (27). Their mean age at surgery was 20.8 months. In comparison with their presurgical performance, their developmental quotient was significantly higher two years after surgery, although it was normal in only four patients. Two factors associated with a better
outcome were a higher level of development before surgery and a younger age at surgery. Wyllie et al. (15) reported the surgical outcome in 12 infants evaluated for surgery at 2.5 to 24 months (mean 12.4 months) of age for so-called catastrophic epilepsies. At a mean follow-up of 32 months after surgery, six patients were seizure-free, three had rare seizures, and two had worthwhile improvement. Several of the patients with improved seizure control were said to have had marked “catch-up” developmental progress. Duchowny et al. (28) described their experience with 26 children in their first three years of life who underwent a cortical resection for medically intractable epilepsy, and were followed for at least one year. Results were very good in terms of seizure outcome, with 16 being seizure-free and four having a > 90% seizure reduction. Interestingly, the families of patients who were seizure-free perceived an acceleration in development, but this perception could not be confirmed by developmental assessments. Meyer et al. (11) reported a series of 50 patients who underwent a temporal lobectomy. Their mean age was 15.8 years at the time of surgery and the average duration of their epilepsy before surgery was 7.5 years. Although 78% became seizure-free, there was no change in their Wechsler Intelligence Scale. However, those with a shorter time between seizure onset and surgery were more likely to experience an improvement in verbal and perceptual intelligence quotients.

In conclusion, there are arguments for and against early surgical intervention in pediatric epilepsy (Table 1). In carefully evaluated and selected cases, a strong case for early intervention can often be made.

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Temporal lobectomy can be an effective treatment for medically refractory seizures when seizures localized to the temporal lobe are unresponsive to traditional therapies [e.g., treatment with antiepileptic drugs (AEDs)]. While the primary goal of surgery is to eliminate seizures, secondary goals include preservation of cognitive function and improved quality of life. Recommendations for early surgical treatment have been based, in part, on the assumption that alleviating seizures early in development will minimize or perhaps even eliminate the long-term cognitive and psychosocial consequences associated with chronic epilepsy. This chapter will discuss some of the evidence for such claims, and provide a framework for further study to address the question of long-term outcome following epilepsy surgery in children.

THE RATIONALE FOR EARLY SURGICAL INTERVENTION IN TLE

Epilepsy often begins during childhood or adolescence, and although some forms of childhood epilepsy remit before adulthood, localization-related epilepsy may persist into adulthood. One of the most common forms of localization-related epilepsy, complex partial seizures of temporal lobe origin [temporal lobe epilepsy (TLE)], is associated with significant cognitive and psychosocial deficits. Despite the success of surgical intervention performed during adulthood with respect to seizure control, cognitive and psychosocial deficits may not resolve even among patients with good seizure outcome. This may be because seizures disrupt development during the period in which the foundation for many of these important intellectual and psychological functions is laid, and eliminating seizures during adulthood does not provide the same opportunity for “recovery” as early intervention may. It is reasonable to speculate then, that preventing the emergence of these deficits prior to their becoming intractable will result in better functional outcome in all spheres.

Cognitive Deficits Associated with Epilepsy

TLE is associated with a distinct pattern of cognitive deficits that is well described in adults. Memory deficits are among the most commonly reported cognitive impairments, often manifested as material-specific (e.g., verbal vs. visual) memory impairments that can be traced to lateralization of seizure onset (left vs. right, respectively) (1). TLE is also associated with disorders of verbal comprehension and verbal
expression (most prevalent in dominant hemisphere TLE) (2,3), disorders of written language processing (e.g., dyslexia and dysgraphia) (4,5), and nonverbal information processing (more prevalent in nondominant hemisphere TLE) (6,7). TLE is also associated with nonlateralized findings and may include clinically significant attention problems (8), speed of information processing, and executive functions (9). Although these deficits are less adequately described in children with TLE compared with adult samples, there is evidence that cognitive impairments emerge relatively early in development. For example, there is a high comorbidity of learning disabilities in school-age children with epilepsy (10) regardless of side of seizure lateralization. In addition, many children with TLE demonstrate a pattern of memory impairment related to side of seizure onset that is similar to the deficits observed in adults (11,12). Deficits in language processing, attention, and executive functions may also emerge early in association with seizures.

Cognitive development is also vulnerable to side effects of AED treatment. Short-term side effects of AED use include diminished speed of information processing, impairments in attention and concentration, psychomotor speed, and reaction time. Treatment with multiple AEDs increases the likelihood of cognitive side effects, as well as the severity (13); surgical candidates are most likely to have failed trials of several medications, as well as have been treated with polytherapy, making them most vulnerable to iatrogenic effects of AEDs. Although adult studies seem to indicate that the effects are transitory and reversible, there is a lack of adequate information regarding the long-term effects of most AEDs on cognitive development in children (14,15).

Psychiatric and Psychosocial Consequences of Epilepsy

The psychiatric comorbidities of epilepsy have long been recognized, and include references to disturbance of personality and interpersonal relations, affective symptoms, and psychiatric illness. Early studies suggested the existence of an “epileptic personality” syndrome (16,17a–b) that included distinct behavioral characteristics that were associated with impaired interpersonal effectiveness. Although the notion of an “epileptic personality” has since been discredited (18), psychosocial issues including diminished social function and dissatisfaction with interpersonal relations are common and occur in children as well as adults. Children with epilepsy report diminished quality of life, citing factors such as school problems (19), peer relations, and development of autonomy (20).

In addition, the existence of unusually high rates of depression and anxiety among patients with epilepsy compared with other chronic medical conditions has been recognized (21). There is also mounting evidence that emotional symptoms appear in childhood, with rates of depression and anxiety among children with epilepsy estimated as high as 50%. Clinically significant mood disturbances have been found among children with seizures even when psychological concerns are not primary symptoms or overtly recognized (22).

Based on these factors, it is relatively easy to make a compelling case for early surgical intervention. Eliminating the disruptive influence of seizures and potential side effects of long-term AED usage on cognitive, emotional, and psychosocial development would be expected to produce improved long-term outcome resulting in a more socially and economically productive adult.

Despite the logic inherent in the rationale for early surgery, there are arguments to the contrary as well. First, seizures are likely to be a symptom of an underlying
neurological condition [e.g., mesial temporal sclerosis (MTS)], and may not themselves be the primary cause of the deficits. Thus, eliminating seizures in children by removing epileptogenic substrate may not “prevent” cognitive impairments as they are already becoming evident by the time surgery is indicated because of the underlying abnormal substrate. Early temporal lobectomy may produce the same persistent deficits that result from surgery in adulthood, as the temporal lobe region may already be dysfunctional when removed. Second, the argument that early surgery may produce fewer deficits because there is greater plasticity in function at earlier ages has been based, in part, on data showing recovery and reorganization of basic language functions following early left hemisphere injury, but has not yet been convincingly demonstrated in other cognitive functions like memory. The window for such plasticity is not known, and may be past by the time a child is considered for surgery. Early evidence suggests that temporal lobectomy in children does produce cognitive deficits similar to those observed in adults, although the follow-up is not sufficient to determine if “plasticity” will result in more favorable long-term outcome (see the following summary of studies).

There is also the problem of identifying appropriate surgical candidates at an earlier age. In cases of catastrophic epilepsy, or epilepsy associated with a known cause (e.g., tumor) or predictable course (e.g., Rasmussen’s), surgical decision-making is straightforward. However, in TLE the course is not well understood and identification of patients who will go on to develop intractable epilepsy is imprecise at best. Although ~10% may develop intractable epilepsy early in the course of their disease (23), the majority have a long latency between onset of seizures and intractability. This is especially true in epilepsy that begins in childhood and early adolescence (24). The solution of early surgical intervention is therefore confounded by the problem of early identification. Few would argue for temporal lobectomy as a prophylactic measure in cases that may remit or remain well controlled with AED monotherapy.

THE DATA

There have been several reports of temporal lobectomy in children, with seizure outcome similar to or better than adult series (25). However, despite the early recognition of the potential for improved function in cognitive as well as psychiatric/psychosocial domains, many outcome studies fail to adequately document the long-term benefits of temporal lobectomy outside of seizure control. Studies that have examined cognitive and psychosocial outcome have been relatively limited, and the results mixed.

Several studies have found stable or improved intellectual functioning following temporal lobectomy (26). In a multicenter study of children and adolescents who underwent temporal lobectomy, the average group mean IQ scores demonstrated no significant decline in verbal function, and modest improvements in the Performance IQ of children regardless of surgery side. However, although group means were stable after surgery, there were several individuals who demonstrated declines, and negative outcome was more likely following left temporal lobectomy. Although apparently indicating favorable cognitive outcome, studies that focus on IQ as a primary outcome measure may not detect clinically relevant changes in other cognitive functions, such as language and memory. IQ scores represent a composite of skills, and may be relatively insensitive to changes that more detailed cognitive assessment may reveal. Dlugos et al. (27) found significant language and memory deficits that were not reliably identified by IQ testing in a small sample of patients who had temporal lobectomy.
Recent reports of memory outcome following temporal lobectomy in children suggest that children may be at risk for the same types of memory deficits as adults (28,29) although other studies have suggested that there is no significant change in memory following temporal lobectomy (30).

There are few studies that have examined post-TLE psychosocial outcome. However, in a recent study that also included pre- and postoperative assessment of cognitive function (IQ), neuropsychological function (memory, academic achievement, attention), family relations, and psychosocial function, no significant changes were observed in any domain—one year after surgery (31) despite good seizure control outcome. This study also included a nonsurgical comparison group followed over the same time interval, which allows for determination of the degree to which changes would be expected had surgery not occurred. Although this study challenges the clinical lore regarding the enhanced benefits of early surgery, it should also be noted that the follow-up period was relatively brief (one year postoperatively), which may not be sufficient time for benefits to be realized. Nonetheless, it does serve as a reminder that clinical assumptions about outcome need empirical verification, particularly with respect to invasive treatment modalities.

CONCLUSIONS

While short-term outcome studies (e.g., one to two years) are promising, there remains a paucity of information regarding the long-term outcome of epilepsy surgery performed in childhood and adolescence. In general, the literature regarding outcome of temporal lobectomy in childhood suffers from several deficiencies.

First, duration of follow-up is inadequate to determine whether the expected benefits of early surgical intervention are realized, and whether they persist into adulthood. Typical “long-term” follow-up studies are one year, and there are no studies to date that report on the adult status of patients who underwent temporal lobectomy in childhood with respect to cognitive, psychosocial, economic, or other outcome parameters. While long-term prospective studies are obviously needed to provide this information, it would also be desirable to perform retrospective studies of children who underwent temporal lobectomy who are now adults to determine whether there is a lasting, positive impact on cognitive and psychosocial function. This can provide a more immediate answer to the critical question of the risk–benefit equation in children.

Second, there is a lack of specificity in the outcome measures, with studies either referring to vague outcomes, or employing more global indices such as IQ. Only a few studies that provide information regarding more specific abilities such as language or memory are currently available, and these suggest that the risk of cognitive morbidity associated with temporal lobectomy in children is similar to that of adults. Long-term studies that include more comprehensive assessment of neuropsychological function are also needed. A comprehensive understanding of the more detailed cognitive outcomes that may occur can lead to more effective interventions and remediation in children that do have some type of postoperative cognitive morbidity.

In conclusion, while the benefits of temporal lobectomy have been well demonstrated in adult populations, so have the risks. In children, the benefits may be the same or greater, but as of yet the data to support this are not available; moreover, early studies appear to suggest that the risks are similar for children as in adults. Further studies are needed to investigate more detailed cognitive outcomes over a longer period of time.
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Chapter III-7c: Epilepsy Has Significant Effects on Social and Educational Development: Implications for Surgical Decisions

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The long-term social and educational outcome of children with epilepsy is influenced by the following factors: seizures, medication, associated impairments, and public attitudes.

A small number of existing long-term studies show that, in children with epilepsy, the great majority of seizures can be successfully treated with antiepileptic drugs (1–4). After a few years from onset of seizure freedom, the antiepileptic medication can be discontinued in half the patients.
In a cohort of 176 children with epilepsy derived from an unselected population of ~500,000 and followed for 30 years (5), 47% were in terminal remission of five or more years without medication and a further 17% with medication. Sixty percent were socially well-adjusted and completely independent in activities of daily living, while 40% were in need of some help or completely dependent or living in institution.

To see the effect of epilepsy per se on medical, social and educational development, subjects with uncomplicated epilepsy were selected from the study population. They numbered 100 and were compared with general population controls matched for age, sex, and domicile. On 35-year’s follow-up, 77% of these patients were free from seizures. In multivariable analysis, a favorable long-term seizure outcome was associated with good early effect of drug therapy, epilepsy with other than complex partial seizures or atonic seizures, or any seizures with nonsymptomatic etiology (5).

Relapses after five years or longer remission occurred in more than one-third of patients. A long-term follow-up of patients with childhood-onset epilepsy (M. Sillanpää, submitted) showed that 36% experienced one or more relapses. The only independent predictor of relapse was symptomatic or cryptogenic etiology of seizures. Temporal lobe epilepsy and presence of mental retardation were approaching significance as risk factors of relapse.

Subjects with uncomplicated epilepsy had a significantly higher chance of having only a primary education than controls (49% vs. 23%) with a 2.0- to 2.5-fold relative risk for no more than primary education. Similarly, they were more likely to lack vocational training compared with controls (69% vs. 52%) with a 1.3- to 1.4-fold risk for no vocational training, independently of whether the epilepsy was acquired or idiopathic, or whether they were on medication or not. Furthermore, the risk of not being married or cohabiting, or being childless was two to three times higher among epilepsy patients than controls. They also had a lower than expected chance of being employed or having a driver’s license (5). As a conclusion, epilepsy per se may have long-reaching social and educational consequences in the life of an individual regardless of seizure occurrence or use of medication. In agreement with the Nova Scotia pediatric epilepsy study (6), poor social outcome of normally intelligent people with epilepsy is mainly predicted by factors other than the biological features of epilepsy.

The assessment of the quality of life using SF-36 scale and Impact of Epilepsy Scale showed that patients on medication, whether they had seizures or not, had worse scores than either patients in remission off medication, or controls. They also had higher unemployment rates and lower socioeconomic status. These differences were not associated with differences in education or seizure frequency (M. Sillanpää et al., unpublished data). Both the occurrence of seizures versus no seizures and the use of medication versus no medication correlated separately with the social outcome of patients with epilepsy. Only those who have become seizure-free at the early stage of therapy and whose medication has been discontinued can cope with everyday social and attitudinal requirements as competently as other individuals.

Approximately 15% to 20% of patients with epilepsy are not completely seizure-free and must continue antiepileptic medication. Furthermore, virtually as great a proportion of patients have intractable epilepsy. Intractability appears most commonly in children with partial epilepsies with secondary generalization, infantile spasms, Lennox–Gastaut syndrome, and temporal lobe epilepsy (5–8). Predictors of poor long-term outcome of seizures are presence of brain structural pathology, high intensity of seizure propensity, and poor early effect of drug therapy.

Neurological impairment accompanying epilepsy, including cerebral palsy and mental retardation, have, not unexpectedly, strong and long-reaching social...
and educational consequences. By definition, patients with epilepsy and cerebral palsy or mental retardation have symptomatic epilepsy. In particular, mental retardation or any other learning disorders affect social and educational outcome (2,6,9). In a prospective long-term follow-up series of 150 patients with incidence of childhood-onset epilepsy, mental retardation occurred in 33%. Of patients with symptomatic epilepsy, 76% were mentally retarded. Compared with matched subjects with epilepsy of normal intelligence, the mentally retarded were significantly more likely to have past febrile seizures, an age of epilepsy onset before six years, or to have the Lennox–Gastaut syndrome. Despite the prevailing concept of gloomy seizure outcome in the mentally retarded, a five-year or longer terminal remission was achieved by 80% of mentally normal, 64% of mildly mentally retarded and 52% of severely mentally retarded patients (10). As stated above, the mentally retarded are at an increased risk of relapse, however. Psychotic disorders occur in 3% to 5% of people with epilepsy (11,12) with any kind of psychosomatic symptoms occurred in 40% compared with 6% of general population controls (13).

Attitudes and prejudices may greatly affect the life of people with epilepsy. Epileptic disorders are invisible impairments which cause sudden and unexpected attacks, the sort of events that may make other people embarrassed and evoke negative attitudes and prejudices. Particularly in children, epilepsy often causes underestimation of the child’s learning potential among parents and school authorities, and either overprotection and negligence. The consequences are underachievement in learning performances and social skills followed by poor self-esteem, decreased motivation in daily life and subsequent depression and “learned helplessness.” These processes are closely bound to the occurrence of seizures and to use of medication.

What can surgical measures do to improve the social and educational outcome of children with epilepsy? It may stop or reduce seizures, and allow discontinuation of medication, with subsequent decrease of overprotection, negligence, and social pressures.

Potential surgical candidates are children whose epilepsy appears intractable, whose brain disorder is not progressive, who are operable, and whose seizure and functional status is likely to become good or satisfactory. There is no universally accepted definition of intractability. Camfield and Camfield (14) defined this as failure of three antiepileptic drugs to completely control seizures, with at least one seizure every two months during the last year of follow-up. Some have extended this follow-up to two years (5,15). Concurrent mental retardation is a strong risk factor for persistent seizures. Patients who have both intractable epilepsy and mental retardation or other major developmental disability are now also accepted as potential surgical candidates (16,17). Some reservations might be made in case of severe mental retardation. Careful preoperative deliberation is needed, if psychosis is associated with the epilepsy disorder. Successful epilepsy surgery is only possible if the family can be made to understand the goals, limitations and potential risks of the operation, and if the surgical intervention can be integrated in the child’s whole program of rehabilitation.

Epilepsy undoubtedly affects the life of patients with epilepsy in many ways. Children at developmental age are at particular risk. Occurrence of seizures and continuing medication are defining factors in the child’s life. All medical measures are needed to minimize their direct and indirect effects. Good seizure control followed by antiepileptic medication withdrawal, environmental acceptance and social support enables the full attainment of the child’s spiritual potential and his or her future social competence as an adult.
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Chapter III-8
What Are the Roles of Medical and Surgical Management in Rasmussen’s Encephalitis?

Chapter III-8a: The Role of Early Surgery in Rasmussen’s Syndrome

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ARGUMENTS FOR EARLY SURGERY IN RASMUSSEN’S SYNDROME

Rasmussen’s syndrome (also termed Rasmussen’s encephalopathy or Rasmussen’s encephalitis) is a progressive, unilateral disease, primarily (or exclusively) of children. It is characterized by focal and unilateral seizures refractory to anticonvulsant medication, a progressive hemiparesis, and increasing dysfunction of the affected hemisphere (1,2). Its pathology consists of perivascular round cell infiltration, microglial nodules, astrocytosis, and spongy degeneration which originally was believed to suggest a chronic viral encephalitis, hence the original name “Rasmussen’s encephalitis.” Multiple studies have failed to reliably reveal a viral etiology (3).

The clinical diagnosis is now usually sufficiently clear that an experienced physician can make a presumptive diagnosis over the telephone. In a typical case, a previously well child, aged 2 to 10 years, has a seizure, and soon thereafter develops increasingly frequent, persistently focal, seizures, sometimes manifest as epilepsy partialis continua. The seizures spread from the initial focal area to include adjacent and eventually widespread areas of the ipsilateral cortex. The refractory focal seizures, the focality on the electroencephalogram (EEG), and the lack of a space
occupying lesion on magnetic resonance imaging (MRI) scan rules out most other causes. The MRI may, or may not, show focal atrophy. Biopsy of the affected area, searching for the hallmark pathology, is neither necessary to confirm the diagnosis nor advisable, as the pathology is spotty and may vary from 1 mm to another within the same gyrus of the brain (3). Biopsy may also interrupt the blood–brain barrier and increase the progression of the disease (J.M. Freeman, personal observation).

The seizures of a child with Rasmussen’s encephalopathy are always progressive, although with a variable time course, and are refractory to all anticonvulsant medications. The immunopathology and response to treatments are similar to an autoimmune disease (3–5) and both the seizures and the neurological symptoms may respond transiently to steroids, to intravenous immunoglobulin (IVIG), or to plasmapheresis (6,7) (see Chapter III-8b). However, the symptoms and the seizures usually recur within three to four weeks after such treatments and become increasingly resistant to the therapies. At this time (2005), the only established therapy that will cure the seizures and allow the child to resume a satisfactory life is hemispherectomy (1,8,9).

In reviewing their experience in Montreal (10), Rasmussen stated, “Limited cortical resections carried out early in the course of the disease ... are clearly ineffective in protecting the patient from further neurological deterioration.” He had found, by experience, that when the seizure focus was resected, the seizures inevitably recurred and the disease progressively involved the remaining tissue of that side of the brain. However, at the time, he was reluctant to advocate a hemispherectomy until the hemiparesis was complete, for fear that the surgeon would be blamed for creating the child’s permanent hemiplegia.

In our 1993 report of 12 cases of Rasmussen’s syndrome (1) we stated our rationale for early hemispherectomy. We continue to believe that as the hemiparesis that results from the surgery is also an inevitable consequence of the disease process itself, the motor deficit caused by the surgery only results in earlier, but not necessarily a worse hemiparesis. In each of those reported cases, we, and the families, wished that the surgery had been performed earlier. Now, after more than 50 hemispherectomies for Rasmussen’s encephalitis, we continue to recommend hemispherectomy early in the course of the disease. We did not, and have not defined “early,” as each child differs in the rate of progression of their disease; in the degree of disability caused by the seizures; and in the effects of the treatments. Each family also differs in their acceptance of our surgical recommendation. Our policy is to inform the family that Rasmussen’s syndrome inevitably progresses to paralysis, but that only when the child reaches the stage when the seizures are sufficiently incapacitating, and the family has realized that the surgery is inevitable and asks us for the hemispherectomy, will we perform it. Surgery for this condition is virtually never an emergency.

After hemispherectomy, all children with Rasmussen’s syndrome will walk, with a mild hemiparetic gait, often with a short leg brace at first. Most will run. Gait rarely poses a substantial problem for the child. All children will have movement at the shoulder, and flexion at the elbow, but none will regain useful function at the wrist or the hand. For all such children, the affected hand remains a helper hand (8,9). All our children with Rasmussen’s are in school, and when old enough may be in college, or employable (11). Only 5% have residual handicapping seizures, almost inevitably because of tissue which was left behind. None have developed seizures from the other side. A few have “ghosts,” feelings as if they were going to have a seizure, but without the change in function or in the EEG (8,9).
The most difficult decisions about performing a hemispherectomy occur when the left hemisphere is involved. A left hemispherectomy will, in most children, involve loss of speech, but the speech will always return. The older the child, the longer it will take to regain speech in the right hemisphere and the greater the difficulty in regaining speech (12). The younger the age of a left hemispherectomy, the quicker and more completely speech returns. The electrical activity of the left hemisphere seems to inhibit transfer of speech to the right hemisphere (personal observation). Therefore, we strongly prefer to do a left hemispherectomy at the youngest possible age.

That said, we have performed a left hemispherectomy in two patients ages 13 and 14 and in both speech has progressively returned over one to two years. Their speech is sufficiently fluent that both are in college, although some word-finding problems remain.

Hemispherectomy surgery comes in several forms. Anatomical hemispherectomy has largely been abandoned. At Johns Hopkins we have mainly done hemidecorticetomies (13). Others have advocated functional hemispherectomies in which the mid-section of the brain is removed and the frontal and occipital areas are disconnected. Still others advocate hemispherotomies, keyhole disconnections, and perisylvian disconnections of the two hemispheres. It would appear that the outcome from each of these surgeries depends more on the experience and skill of the neurosurgeon and on the completeness of the disconnection of the epileptic tissue than on the type of surgery performed. No comparisons of the various types of surgery are available.

In recent years it has become increasingly apparent that Rasmussen’s encephalopathy is an autoimmune disease (3–5), and that therapies directed at altering the immune response such as steroids, IVIG, and plasmaphoresis (6,7) (see also following chapter), will temporarily modify the seizures and sometimes the symptoms. Immunotherapy, as discussed in the next chapter by Drs. Gibbs and McNamara, may ultimately allow us to avoid this mutilating but very beneficial surgery.

Immunosuppression therapy in which the immune cells are wiped out with cytoxan and the immune system reconstituted by the child’s own cytoxan-resistant progenitor cells has been reported to more permanently alter the immune system (14) and has been used in severe myasthenia gravis (15). As of this writing (September 2005) immunosuppression therapy has been utilized in two children with Rasmussen’s encephalopathy with promising results (E. P. G. Vining, personal communication). We consider these results to be very preliminary and the procedure to be highly experimental. However, we eagerly await a therapy that is less invasive than hemispherectomy and which will also completely halt this progressive disease.

SUMMARY

Until we have less invasive and heroic therapies available, hemispherectomy in one of its forms remains the only therapy which provides long-term control of the disabling seizures. The physical effects after early surgery are identical to the inevitable outcomes of the condition itself. The earlier onset of the hemipaesis and, of the language problems attendant to early surgery have allowed these children to get on with their lives, to avoid the years of constant seizures and of the side effects of the ineffective medications. Earlier is better, once the family has realized the inevitability of the disease process.
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Chapter III-8b: Immunotherapy for Rasmussen’s Encephalitis

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Rasmussen’s encephalitis (RE) is a rare form of human epilepsy that typically begins in the first decade of life and is characterized by progressive destruction of a single cerebral hemisphere. RE is characterized by intractable partial seizures and devastating neurological signs including hemiparesis, language deficits, and dementia that parallel the degeneration of the single cerebral hemisphere (1). As seizures in patients with RE are particularly resistant to anticonvulsant therapy, a functional hemispherectomy has become a common treatment modality; however, this intervention inevitably leaves patients with severe residual neurological deficits (1,2).

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of RE is incompletely understood, yet evidence for an autoimmune mechanism contributing to the pathogenesis has emerged over the past decade. The starting point for this evidence originated in a serendipitous occurrence in the laboratory of Dr. Steve Heinemann at the Salk Institute in La Jolla, California, U.S.A. Dr. Scott Rogers, then a postdoctoral fellow in Dr. Heinemann’s laboratory, was seeking to raise antibodies to the recently cloned AMPA subtypes of glutamate receptor; toward that end, Dr. Rogers immunized more than 50 rabbits with recombinant fusion proteins that included sequence from the extracellular domain of multiple receptors. Interestingly, two of three rabbits immunized with a protein including the GluR3 subtype of glutamate receptor developed severe epileptic seizures (3). The illness of the rabbits together with the similarity of the histopathology of the epileptic rabbits to that of human RE led to several hypotheses: the rabbits became ill because of an autoimmune attack on GluR3 protein; RE itself was an autoimmune disease; and one autoantigen of RE was GluR3. This led to the discovery that a subset of patients with RE exhibited serum IgG antibodies to GluR3 and relevant controls did not. This circumstantial evidence for an autoimmune mechanism led to treatments of children with RE aimed at removing serum IgG (3,4). Direct evidence of an autoimmune mechanism in this disease emerged from the dramatic improvement in neurological signs together with an 80% reduction in seizure frequency following a series of plasma exchanges (PEX) that removed serum antibodies. Other groups followed and demonstrated that selective removal of IgG by PEX using a Protein A affinity column produced a long-lasting improvement in seizure frequency and neuropsychological
deficits in a 16-year-old girl (5), confirming and supporting previous findings (3,4). Together these findings demonstrated a humoral (antibody-mediated) autoimmune mechanism in the pathogenesis of the disease. Importantly, the clinical response of these patients to removal of serum IgG suggested the source of the IgG to be B cells residing outside of the central nervous system. While earlier reports suggested that glucocorticoids effected improvement in some patients (6), the beneficial effects could have been secondary to an inflammatory (not necessarily autoimmune) etiology or another effect of glucocorticoids.

The beneficial response to removal of antibodies not only implicated an autoimmune mechanism but also provided a plausible explanation for how antibodies might contribute to the seizures and cell death seen in RE. That is, subsequent immunohistochemical studies established evidence of IgG and complement activation products in human RE brains (7). This led to further studies which established that activation of the terminal pathway of the complement cascade is sufficient to induce seizures and cell death (8). Together these findings advanced IgG activation of the complement cascade as a plausible effector mechanism for the phenotype of RE (8–10). An alternative explanation emerged, namely that antibodies themselves activate glutamate receptors and might be excitotoxic (11).

Like multiple sclerosis (MS), the autoimmune effectors in RE appear to include both humoral and cellular mechanisms. By contrast, the autoimmune effectors in myasthenia gravis are almost exclusively humoral. Circumstantial, but not direct, evidence favors the presence of cellular immune mechanisms in the pathogenesis of RE. One observation favoring a cellular mechanism is that removal of circulating antibodies effects dramatic improvement in some but not all patients with unambiguous RE (4), suggesting that a cellular immune mechanism may contribute to disease in the nonresponders. Additional studies have provided circumstantial evidence for a role of cell-mediated immunity in the pathogenesis of RE. Restricted populations of T cells have been identified in RE brains using PCR techniques for quantitative assessment of T-cell gene transcripts; these have likely expanded from a limited number of T cells that responded to discrete antigenic epitopes and are consistent with an antigen-driven process (12). More recently, Bien et al. (13) used confocal laser microscopic analyses of immunohistochemical studies and identified CD3- and CD8-positive T cells in RE brains; a subset of the T cells expressed granzyme B and lay in direct apposition to major histocompatibility complex class I positive neurons, raising the possibility that neurons underwent apoptosis due to a T-cell-mediated cytotoxic reaction. Although controls did not include other types of epilepsy such as temporal lobe epilepsy, these findings nonetheless raise the possibility that a cellular immune effector might contribute to the pathogenesis of RE.

THERAPEUTIC IMPLICATIONS OF AN AUTOIMMUNE MECHANISM FOR RE

The standard treatment for RE is a functional hemispherectomy. Given the evidence for an autoimmune mechanism in the pathogenesis, the question arises as to whether immunotherapy might replace the devastating consequences of a functional hemispherectomy. While immunotherapy holds enormous promise for the future, the limitations inherent in contemporary immunotherapy warrant caution in such approaches. For example, immunotherapy is often ineffective and associated with substantial
unwanted effects in some diseases with autoimmune mechanisms such as systemic lupus erythematosus (SLE) or MS. In comparison with RE, much more extensive investigations of the immune mechanisms have been conducted for SLE and MS. Likewise, many clinical trials of diverse immunotherapies have been performed. Despite both preclinical and clinical investigations, immunotherapy is palliative, not curative, in SLE and MS and is ineffective in many patients. The uncommon occurrence of RE contributes to the fact that no prospective, controlled clinical trial of an immunotherapy has been performed. Likewise, the lack of an animal model of RE in a mouse or rat limits preclinical studies of immunologic mechanisms. Together these factors account for the limited insight into optimal immunotherapies for RE.

Given the uncertainties regarding optimal immunotherapy for RE at present, we favor functional hemispherectomy early in the course of RE when it arises in the first decade of life. Language function is affected little if at all as a consequence of hemispherectomy in the first decade. The elimination of seizures and apparent arrest of disease progression as early as possible constitute acceptable trade offs despite the persistent neurological deficits caused by the hemispherectomy (14).

In some instances, however, a functional hemispherectomy is simply not a viable alternative. For example, we have encountered cases of RE beginning in adulthood in which the hemisphere dominant for language is attacked. In other rare instances, the disease process has invaded both hemispheres in a child. Under these circumstances, immunotherapy is the only viable option. What immunotherapies might be considered under these circumstances? At the outset it is important to realize that no prospective, controlled studies of any immunotherapy have been completed, to the best of our knowledge. Thus, anecdotal observations in limited numbers of individuals provide the basis for selecting a given therapy. Given this state of knowledge, we favor beginning with therapies with least harmful side effects and moving sequentially to more aggressive options. It is important to include a skilled clinical immunologist in the selection and implementation of the therapies outlined below.

The immunotherapeutic regimens considered include the following. We favor starting with a course of PEX and followed by intravenous immunoglobulin (IVIG) at the end of the course, using a protocol described by Andrews et al. (4). An alternative used by Hart et al. (6) reported success with IVIG alone or in combination with steroids. Pulse doses of corticosteroids (solumedrol 20 mg/kg/day tapered to withdrawal over two weeks) have been demonstrated to be effective in the treatment of status epilepticus in RE (15). Lack of response to therapies targeting removal of antibodies raises the possibility that therapies targeting T cells may be effective. Given the observation of CD8-positive T cells in RE brains, another consideration is tacrolimus that has been used for transplant rejection (16). If such options proved ineffective, an option warranting careful consideration consists of immunoablative high-dose cytoxan without stem cell rescue, as has been used successfully for a limited number of patients with other autoimmune diseases (17). A final, and in our view viable alternative, is bone marrow transplantation (BMT). BMT has been demonstrated to significantly ameliorate symptoms or “cure” a few patients with SLE (18). In closing, improved insight into the etiology and autoimmune mechanisms of RE together with rapid progress in therapies of other autoimmune disorders in humans will hopefully guide design and implementation of immunotherapy for RE and one day render functional hemispherectomy for this condition obsolete.
ACKNOWLEDGMENTS

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Chapter III-9
The Role of Neurosurgery for the Landau–Kleffner Syndrome

Chapter III-9a: Landau–Kleffner Syndrome: A Review

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INTRODUCTION

Landau–Kleffner syndrome (LKS) is an age-related epilepsy syndrome of childhood characterized as an acquired aphasia associated with seizures and a paroxysmal EEG. Although this disorder is rare, it has generated considerable interest, research and hypothesis about the etiology of the aphasia and its serious language sequelae. Studies in the natural history of LKS suggest that if the paroxysmal disorder and aphasia persists for three years, the majority will suffer permanent language dysfunction, significantly altering their quality of life. Early recognition of this syndrome and aggressive medical management in the first year or two is proposed. For those who face failure of medical management either due to lack of efficacy or treatment side effects, referral to an experienced surgical center for full evaluation in year two is suggested. The permanent language sequelae is not dramatically altered, even if the paroxysmal EEG abnormality is eliminated, if this process has persisted for three years or longer (1,2).
HISTORICAL PERSPECTIVE

In 1957, Landau and Kleffner reported six children with a syndrome of “acquired aphasia with a convulsive disorder.” They described an aphasia that developed over days to months that then persisted for two weeks to several years. The associated seizures included grand mal, petit mal, and myoclonic seizures. The paroxysmal EEG abnormality was bilateral, most prominent over the temporal lobes. While the relationship between the aphasia and EEG abnormality was not perfect, the severity of the language disturbance did correlate with the severity of the paroxysmal disturbance on EEG. They hypothesized that the persistent convulsive discharge in brain tissue responsible for linguistic communication results in a functional ablation of these areas responsible for normal language behavior. This “functional ablation” hypothesis was supported by the fact that these aphasic children had good performance on nonverbal intelligence tests and their consciousness and reactivity were not altered as would be expected in petit mal status (3).

Since that time well over 200 published case reviews have been published (4–6). The EEG abnormality is predominantly bilateral posterior temporal spike or spike wave that is activated by slow wave sleep. Most observers agree that the ultimate language outcome correlates with age of onset of this epileptic disturbance as well as its severity, bilateral anatomic location, and the duration of the active phase.

EPIDEMIOLOGY

The frequency of LKS cannot be accurately ascertained. Using the strict criteria outlined above, it is a rare disorder. There have been 81 cases reported in the literature from 1957 to 1980 and 117 cases reported between 1980 and 1996 (4–6). Dugas et al. reported one new case per year at a Parisian psychiatric clinic (5,6).

PATHOPHYSIOLOGY

Landau–Kleffner syndrome develops during a period of cortical synaptogenesis when the basic functional circuitry is being established. Synaptogenesis involves an overabundant growth of axonal processes and synaptic contacts thought to be twice the number found in adults. Neuronal activity or synaptic use is the major factor determining which will be eliminated or pruned. The environment plays the crucial role in the establishment of permanent synaptic contact. If a significant paroxysmal disturbance is present in the cortex undergoing this age-dependent synaptogenesis, it acts to strengthen synaptic contacts that are not appropriate for the underlying behavior. The paroxysmal electrical disturbance in LKS reinforces inappropriate synaptic contacts in the developing temporal-parietal cortex, producing a permanent language dysfunction. This proposed hypothesis of the basic mechanism underlying LKS predicts that, if unsuccessfully treated, those children affected earlier in this period of synaptogenesis will suffer the most severe neuropsychological sequelae after the epileptiform disturbance remits in early teenage years. Several authors have confirmed these findings in their series (7–12).

CLINICAL PRESENTATION

LKS is an acquired epileptic aphasia or auditory agnosia, occurring in a normal child with age-appropriate language skills. It is associated with paroxysmal EEG
abnormalities with or without apparent seizures. There is no structural abnormality on magnetic resonance imaging (MRI) scan sufficient to account for the language deterioration. This disorder begins most commonly between the ages of three and eight years of age. The onset may be subacute or stuttering and initially consists of a loss of verbal understanding. Soon, however, speech output is affected and paraphrasic and phonologic errors appear. In the most affected cases, the child becomes entirely mute and displays an auditory agnosia, failing to respond to nonverbal sounds such as the ringing of the telephone or knock on the door. Behavioral disorders such as hyperactivity and attention deficits are common. In the more severely affected children disinhibition, psychosis, and autistic behavior are manifested (13).

Seizures vary in type and frequency but most commonly are eye blinking, ocular deviation, head drop, and minor automatisms with occasional secondarily generalized convulsions. They have a variable relationship to the language deficits with 20% to 30% of patients reporting no behavioral seizures. The seizures follow a benign course in most and are readily treated with most antiepileptic drugs (AEDs). The seizures subside by mid-teenage years. The language disturbance, however, has a less benign prognosis. Early on the symptoms may show marked fluctuations and even spontaneous recovery within weeks or a few months of onset. If the aphasia and associated paroxysmal EEG disturbance persists for two or more years, complete recovery is very unusual; such patients may expect linguistic difficulties throughout their lifetime (5,14).

**DIAGNOSTIC EVALUATION**

The diagnostic evaluation in suspected LKS requires a careful developmental history, physical, and neurologic examination. Careful documentation of premorbid language, cognitive and behavioral function is necessary through developmental history, school, and intellectual testing. All children with suspected LKS need careful neuropsychological testing by a specialist experienced in testing linguistic and non-linguistic function. This testing is critical in separating children who suffer LKS from the much more common pervasive developmental delay (PDD). The child with LKS will display deficits in language-related intelligence with near-normal nonlanguage intelligence and social/behavioral function.

Laboratory testing includes structural and functional neuroimaging (4,15). Prolonged outpatient EEG with a sample of slow wave sleep induced with amitryptiline, 1–2 mg/kg by mouth two hours before recording has been used as a screening method to identify those patients with continuous spike and wave in slow wave sleep (CSWS). The EEG pattern consists of a continuous 1.5–5 Hz spike and wave. It may make up 80% to 90% of slow wave sleep. This abnormality fragments or disappears during rapid eye movement sleep. The distinctive feature of the CSWS of LKS is that the spike and wave has a posterior temporal predominance.

Closed circuit TV–EEG monitoring is performed if the screening EEG is positive and especially for those where surgical treatment is being considered. More sophisticated neurophysiologic investigation such as computerized amplitude mapping, dipole source localization, magnetoencephalography (MEG), and intracranial EEG recording are useful in the patient where surgery is seriously considered (16,17).

These tests most often localize the epileptic foci to the posterior superior temporal gyrus with a tangential dipole across the sylvian fissure. The negativity is superior and positivity inferior, indicating the origin to be on the dorsal surface of the superior temporal gyrus in the area of Heschl’s gyrus. Methohexital suppression
test often will demonstrate the apparent bilateral discharge is often a unilateral discharge with rapid bilateral synchrony. The propagation interval between the two discharges is in the order of 20 milliseconds. MEG studies have also demonstrated similar time lags between temporal discharges.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of LKS is at times difficult. The disorder is most commonly confused with PDD, especially when there is an abrupt regression of language skills in seemingly normal children. The most important distinguishing feature is that other nonlanguage skills and intelligence are abnormal in those with PDD. However, when language skills are most severely affected, only careful neuropsychological testing makes it clear that the patient best fits into the category of PDD. What makes this distinction even more difficult is that children with PDD and autistic regression may be associated with paroxysmal EEG disturbance. However, this EEG disturbance is not CSWS. In addition, patients with autistic regression most often show a multifocal epileptic focus, not the posterior temporal location of LKS (4,13).

Developmental dysphasia is another disorder that may mimic LKS. Children with this condition do not develop age-appropriate language at the usual time. Like patients with LKS, they often have normal neurological examinations and nonverbal intelligence. EEG abnormalities are uncommon and continuous spike and wave has not been reported. A family history of delayed language development is often reported.

The acquired idiopathic localization-related epilepsies of childhood are more difficult to separate from LKS pathophysiologically but are easily distinguished clinically. These disorders have a more subtle effect on cognitive function either because of a less severe paroxysmal disturbance or that the cortex involved is more “silent.” There have been a number of case reports of patients with CSWS without detectable cognitive dysfunction (7). However, the severity of spike and wave and duration of the active phase of CSWS were not documented. It is probable that these cases are a subset of CSWS with an older onset and shorter duration of active phase. Finally, benign childhood epilepsy with centro-temporal (BECT) spikes is clinically distinguished from LKS by the absence of acquired aphasia. However, BECT is probably a more benign subset of CSWS with less active paroxysmal disturbance in clinically more silent cortex. A number of behavioral disturbances and learning disorders have been described in BECT and other benign-acquired epilepsies (18,19).

**TREATMENT**

As discussed earlier, the clinical seizures in LKS are for the most part not severe and readily treated with most AEDs. They tend to be self-limited and occur during the active phase of CSWS. However, the paroxysmal EEG disturbance does not respond well to AEDs.

The data from the Venice colloquium reported that valproate alone or in combination with a benzodiazepine, usually clobazam, was the treatment of choice (20). Other AEDs that were successfully used include vigabatrin, ethosuximide, phenobarbital and, more recently, zonisamide.

Corticosteroid therapy, either with ACTH or prednisone, is reported to have favorable and long-lasting effects. The use of corticosteroids, especially in new onset disease during the active phase, may produce medical remission. The recommended dosing of ACTH (80 U/day with three month taper) or prednisone (60 mg/day with
A three month taper has been proposed (21). Prednisone pulse dose therapy two days per week has been tried to lessen steroid-induced side effects. However, there may be relapse with steroid reduction and some children require corticosteroids for months to years to prevent relapse.

The long-term use of corticosteroids is fraught with side effects, including weight gain, Cushingoid appearance, hypertension, glucose intolerance, electrolyte abnormalities, sleep disturbance, and mood/behavioral changes cited. More serious adverse effects including cataract formation, immune dysfunction, proximal myopathy, and pathological fracture have been reported (21). The risk versus benefit must be carefully deliberated and discussed with the caregivers, primary care physician, parents, and families. Side effects of corticosteroids are often judged acceptable in children with early onset of an active phase of severe spike and wave because this group is at highest risk for residual neuropsychological sequelae.

Our practice is to treat initially with valproate with or without a benzodiazepine. If the epileptiform activity and cognitive dysfunction persists or worsens, a course of prednisone 3–5 mg/kg/day is suggested with careful physical and laboratory follow-up. If there is clinical and EEG response after the first month, an attempt to convert to alternate day dosing is attempted in the second month of therapy. A slow wean is continued in the third month if there has not been clinical or EEG signs of relapse. Serial EEGs, including recording of slow wave sleep, is necessary during the steroid treatment to determine both initial efficacy as well as possible relapse during steroid wean.

**SURGICAL TREATMENT: MST FOR LKS**

Surgery for Landau–Kleffner is only considered after an exhaustive trial of medical therapy and a thorough presurgical evaluation is completed. The most important part of the presurgical evaluation is eliminating patients with autism or autism-spectrum disorder. In these cases, the epileptiform activity is likely a secondary phenomenon in a more widespread neurological disorder, and thus, is not appropriate for surgical treatment. Presurgical evaluation commonly includes video-EEG, MEG, MRI, and neuropsychological testing. Patients who are selected for surgery are those who have near-normal nonverbal intelligence, are severely disabled by ongoing paroxysmal activity for at least one year, and have a single, unilateral epileptogenic zone. Because of the rapid propagation of spike and wave epileptiform discharge from one hemisphere to the other, it is occasionally difficult to determine the side of origin. In cases where laterality of onset is in question, MEG is performed. If necessary, bilateral epidural electrodes are placed in parallel to the sylvian fissure. Methohexital suppression test may also be of use.

The surgery involves a routine craniotomy under general anesthesia exposing the perisylvian cortex. In more recent cases, MEG data has been imported into an image guidance system in order to minimize the opening and target the MEG findings (16,17). Electrocorticography is performed. The sylvian fissure is then opened to expose the insular and deep branches of the middle cerebral artery under the microscope. In most cases the epileptogenic zone is in the posterior portion of the left sylvian fissure. The opening is large enough in length and depth to accommodate the insertion of at least six electrodes into the fissure to the depth of the insula. Electrocorticography at this stage usually shows the epileptiform activity to be predominantly on either the temporal or the fronto-parietal operculum. In some cases, the epileptiform discharges are distant from likely speech cortex. In these circumstances, resection of
the epileptogenic cortex is carried out. This is usually the case in the less common right-sided cases. In most cases, the area in question undergoes subpial transection at 5 mm intervals. Repeat electrocorticography is performed and guides any further transections in adjacent areas. In most cases, multiple subpial transection (MST) is only necessary in the sylvian fissure and immediately surrounding the fissure. After hemostasis, routine closure is performed. Postoperative management must take into account the inevitable, but moderate, swelling that typically occurs with MST.

In the original publication describing surgical treatment of LKS, Morrell et al. described indications, surgical technique, complications, and outcome in 14 patients. All patients were aphasic prior to surgery for at least two years despite aggressive medical therapy. At follow-up, seven of the 14 recovered age-appropriate speech without need of speech therapy, four had reacquired speech but required speech therapy, and three had no benefit. There were no permanent complications. In a follow-up publication by the same group, Grote et al. (22) gave a detailed analysis of language outcome in the patients from the original publication. The factors found to be most predictive of long-term language improvement in patients who had surgical treatment of LKS were the length of time since surgery and the duration of LKS prior to surgery. Language outcome was positively correlated with longer interval since surgery and negatively correlated with duration of LKS prior to surgery. Interpretation of this data must be made in light of the small sample size and the retrospective nature of the study. The number of patients who have undergone surgery for LKS at this institution has grown to over 30. Analysis of outcomes in this population is ongoing.

Since the report by Morrell (15), several other groups have published results from surgical treatment of LKS. Irwin et al. (23) reported results in five patients. In their series, all patients had a significant improvement in seizures, behavior, and language that corresponded to a decrease in electrographic continuous spike and wave. Kolski and Otsubo (24) reported results of surgical treatment in seven patients with ‘malignant rolandic-sylvian epilepsy.’ Most of these patients did not have LKS by the usual criteria. They found significant improvement in seizure outcome, but no improvement in neuropsychological measures.

Polkey (25) reported a series of seven patients in which all cases were LKS and all had been mute for at least six months. Five patients had surgery on the left side and two had surgery on the right side. Two patients had significant and sustained language improvement, four had early improvement followed by a period of transient deterioration that cleared, and one patient had no improvement. Paetau et al. (26) reported surgical results in one patient. Although this patient had a dramatic resolution of the continuous spike and wave discharges, she did not make significant language recovery.

LONG-TERM PROGNOSIS

While the long-term prognosis for the seizure disorder is good with <20% of patients suffering from persistent, usually rare seizures, the long-term prognosis for the neuropsychological consequences is not nearly as good as once thought. Mantovani and Landau (7) reviewed the long-term prognosis of nine patients with LKS 10 to 28 years after onset. Language function was normal in <50%. Other series agree that language dysfunction in some degree persists in the majority (27,28). Even with successful resolution of the CSWS with either drug therapy or surgery, permanent language sequelae is expected if the active phase of CSWS has had a duration greater than two years. Only by early recognition, aggressive medical treatment and surgical evaluation and treatment before two years of duration will we be able to successfully treat this devastating disorder.
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Chapter III-9b: The Role of Surgery in Landau–Kleffner Syndrome

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Landau–Kleffner syndrome (LKS) is a rare devastating neurologic illness of childhood. It was first described in 1957 in a cohort of children with acquired aphasia and seizures (1). After attaining age-appropriate speech, children develop an acute or subacute verbal auditory agnosia and various types of seizures typically between the ages of three and eight years. This regression is associated with several
types of seizures. Children with LKS also exhibit behavioral disturbances ranging from mild hyperactivity to autistic-like behavior. The electroencephalogram (EEG) in the awake state can be normal or reveal paroxysmal abnormalities. These abnormalities are usually bilateral and most prominent over the temporal regions. The abnormalities are activated by slow wave sleep where the EEG reveals generalized spike-wave discharges which at times become continuous. Neuroimaging shows no demonstrable lesions sufficient to explain the patient’s symptoms (2). Though the seizures are usually easily controlled, the language disturbance is unrelenting, leaving some children mute. Spontaneous remission is rare (3). Mantovani and Landau (4) reviewed the long-term prognosis of nine patients 10 to 28 years after onset. They found that language was normal in <50%. The majority of patients continued to have significant language deficits and had difficulty leading a normal life (2,4).

All available antiepileptic drugs (AEDs) have been used alone or in combination for treatment. These medications are usually effective in treating the seizures but have little effect on the EEG abnormalities, (5) which are hypothesized to contribute to the severe language disturbances (2). Corticosteroid therapy (ACTH or prednisone) can be efficacious in ablating the EEG abnormalities, and is temporally associated with improvement in language skills in some children with LKS. Unfortunately, the high doses required for effectiveness pose formidable risks. Further, both clinical and electrographic relapses can occur with steroid tapers, leading to children requiring treatment for months to years, increasing deleterious effects (6). Steroid treatment is not always effective. Marescaux et al. (7) found improvement in three children with the use of high-dose steroids, but significant speech deficits persisted.

The gravity of the clinical syndrome, lack of effective long-term treatments, and poor cognitive and developmental prognosis, has led to the search for effective surgical procedures. Generalized EEG patterns are traditionally a contraindication to surgery, but the methohexital suppression or intracarotid amobarbital test combined with EEG dipole mapping often shows that children with LKS have a unilateral primary epileptogenic region that generates the severe generalized abnormalities in sleep (6).

Morrell et al. (6) described the outcome in 14 children with LKS who underwent multiple subpial transection (MST). MST is a type of disconnection procedure whose goal is curative, but is most often palliative. Primate visual and other studies show that projections involved in cortical function are primarily vertically oriented while fibers responsible for spread of epileptiform discharges are horizontally oriented. By selectively disrupting the horizontal fibers and preserving the vertical, the spread of epileptic discharges could be inhibited without affecting normal function (8). Transections are carried out with concurrent electrocorticography ideally, until all signs of epileptiform discharges cease. Most abnormalities are localized to the speech area, i.e., the superior and middle temporal gyri well as the perisylvian region. Prior to surgery, no child used language effectively for communication for at least two years. Seven of the 14 children recovered age-appropriate speech and were in a regular class without services. Four children showed marked improvement; they were able to speak and understand verbal instruction and were requiring speech therapy. Improvement was gradual, with first words usually occurring three months postoperatively. Most children had substantial improvements by six months. Of the three remaining, two did not fully satisfy criteria for LKS and the last patient had chronic encephalitis. Five patients had a recurrence, three of these did not present with the typical features of LKS. There were no deaths nor any permanent neurological deficits. In this surgical study there were many more patients with improved
neurologic status in comparison with historical outcomes in children left untreated or treated with medical therapy.

Since Morrell’s initial work, several other groups reported outcomes of children undergoing MSTs in LKS. Sawhney et al. (9) described three patients with LKS who showed substantial recovery of speech after MSTs. One child produced complete sentences within two weeks after surgery, the other had fluent language but required speech therapy. The last made slow progress speaking only with single words. All children had behavioral improvement.

Grote et al. (10) studied four children with LKS who were treated with MSTs and also found significant improvements in receptive and expressive language abilities. Maximal improvements were achieved from three to six years after surgery. Children with longer periods of language impairment prior to surgery were less likely to show significant postoperative improvement in receptive vocabulary abilities. One child contracted meningitis and one other had a stroke from which they mostly recovered. The authors believed that the cognitive improvements seen in these children exceeded the level of improvement attained in children with spontaneous remissions.

Irwin et al. (11) described five children with LKS who underwent MSTs and observed that language and behavior improved dramatically in all patients, but not to an age-appropriate level. A greater interest in communicating and behavioral improvement was apparent almost immediately. The biggest improvement in language occurred during the first year postoperatively. Seizures were eliminated. One child required extension of the transection after recurrence of electrical status epilepticus in sleep, and had good results after the second surgery with sustained improvements.

Temporal lobectomy has also been used to treat LKS. Cole et al. (12) reported two children with LKS who showed marked improvement in language and behavior after temporal lobectomy. The patients were essentially mute prior to surgery. One patient was speaking in full sentences, though slightly dysarthric 10 months postoperatively. Subsequently there was some deterioration in language skills, but the patient was lost to follow-up. The second patient underwent regression at approximately age five years and underwent surgery as an adult. By then she had severe behavioral disturbances and utilized sign language. One year later her communicative abilities improved, though some difficulties still persisted.

There is some experience in the use of surgical procedures for LKS variants. Neville et al. (13) reported two children with partial epilepsy and autistic regression. One child had a tumor and underwent a temporal lobe resection. The other child had a more classical presentation of LKS. Initially the patient was treated with steroids with some improvement in language comprehension, hyperactivity, and aggression. He remained socially indifferent. He underwent MSTs, and within a few days the child became more interactive and began using sign language. He continued to improve over the next six months, utilizing sign language effectively. Though incomplete, he showed remarkable progress from his preoperative state.

Nass et al. (14) reported seven children with autistic regression. All underwent MSTs and one case also had a temporal lobectomy after failure of medications. All had modest improvements in receptive more than expressive language functions. Concentration, attention, and eye contact also improved. The behavioral improvements were not always sustained.

There is a role for surgical intervention in the treatment of LKS. MST and temporal lobectomy are safe and effective procedures. In many cases, recovery of cognitive abilities occurs soon after, but most patients require at least six months
to exhibit sustained improvements. Even though patients may not recover fully because of the severe nature of this condition, any improvement in behavior or language is encouraging. Delay of surgery may limit maximal benefit. Cases in which the desired surgical outcome is not obtained maybe to the result of a more refractory case in which the epileptogenic zone is more widespread or bilateral, or there are co-morbid neurological disorders that contribute to the cognitive deficits. The surgery may allow for the reacquisition of language function by halting epileptiform discharges that interfere with optimal pruning following synaptogenesis and allows for a reacquisition of language (10).

Patient selection and the timing of surgery are not well defined as it is unclear which patient may remit spontaneously. There is some evidence that the earlier the abnormal discharges are eliminated, the better the surgical outcome (10). Some surgical series are skewed from patients included in studies who may represent variants of LKS, thereby altering outcome measures. The outcome is extremely variable and random in patients treated with medications. Current data does not allow us to compare efficacy of the various treatments. More collaborative, multicenter work needs to be done in recording the natural history and efficacy of the available treatments. This will enable practitioners to provide better care and better advice to parents faced with this grave condition.

Patients with LKS who meet traditional criteria and have failed at least two AEDs and a trial of steroids, and in whom there is no evidence of improving language after two years of treatment, are potential candidates for surgery (1). When the presurgical evaluation supports a unilateral and restricted epileptogenic area, the benefits of surgery appear to outweigh the risks. Magnetoencephalography (MEG) is a modern technique that records magnetic activity by utilizing interictal discharges. It is helpful in localizing the origin of seizure activity. In some patients with LKS, MEG has been used to locate the focus of the epileptiform abnormalities (2). As this technique becomes more readily available and affordable, its application to LKS should become more beneficial. Parents must understand that we are unable to offer precise odds regarding spontaneous recovery without surgery or the degree of language recovery with surgery. However, the longer the duration of language dysfunction and number of medical treatment failures are poor prognostic factors for spontaneous recovery. In such cases, the physician and parents should ask themselves how they would view the risk/benefit ratio of surgery if they were the affected child and faced a future life without meaningful language function.

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Neurology for the Landau–Kleffner Syndrome

Chapter III-9c: Epilepsy Surgery Is Not Useful for the Landau–Kleffner Syndrome

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The evidence for the effectiveness of multiple subpial transection (MST) for Landau–Kleffner syndrome (LKS) does not substantiate the perioperative risks of surgery and the elimination of other therapies, based on the currently available scientific and clinical data.

Since its introduction in 1989 by Morrell, the MST technique has been both controversial and seductive for the epileptologist and neurosurgeon. It is an operation in which the association fibers traveling along the longitudinal axis (the fibers...
important for electrical spike propagation) at the surface of the gyrus are interrupted while leaving the vertically arrayed motor fibers intact (preserving function). Often fibers on the sides and the base of the gyri are left intact which may explain why this procedure is rarely curative and instead mostly palliative. Furthermore, with the young brain’s plasticity, the ability to adapt to partial disruptions of epileptogenic pathways over time needs to be factored into the long-term results of this procedure, in a syndrome such as LKS, which can be self-limiting. Clearly there are no randomized studies, which compare the outcome of MST in LKS to the natural history of nonoperated controls or to the current best medical therapy in the treatment of this protean syndrome. In fact, MST does not uniformly fulfill its proposed indication in LKS—to cure the seizures and improve long-term language recovery (1,2). In a study of the natural history of LKS, one investigator concludes, “It is of interest that the outcome and pattern of spontaneous recovery is similar to that following surgery… These similarities suggest that MST brings forward the onset of Stage III but, as so far determined, this has little impact on the eventual language outcome.” (1).

After drawing these conclusions, Irwin et al. (2) argues that MST is worthwhile based on its seizure and behavioral problem reduction in patients who are essentially in crises. However, seizures of patients with LKS are typically mild, even absent in some, and almost always subside before the age of 15, leaving reduction of behavioral problems as the only real benefit from surgery. In any invasive, destructive procedure such as MST, there must be evidence of a sustainable outcome and one that exceeds the benefits of medical therapy or the natural history of nonoperated controls. MST is often not effective alone in abolishing seizures. Neither of those two criteria have been demonstrated in studies published to date. Careful analysis of the cases published by Morrell et al. (3) demonstrate that many patients who undergo MST experience a seizure reduction but only about half are seizure-free for extended follow-up. Luders et al. (4) have noted that the critical mass of cortex required for synchronization of electrical activity is at least 5 mm. Therefore, it is reasonable to conclude that multiple transections spaced 5 mm apart may suppress much electrical activity and many seizures but certainly will not be guaranteed to obliterate all electrical activity. Thus, MST does nothing but hasten the inevitable outcome of LKS while incurring all of the complications involved in an invasive surgical procedure.

PERIOPERATIVE COMPLICATIONS

Though MST has been associated with low morbidity and mortality, the technique contains the typical risks of craniotomy (bone flap infection, etc.) and a few of its own complications. In the first series of MST for LKS two cases of small infarcts were seen out of a total of 14 patients (5); in the 1999 study of 14 patients by Grote et al. (6), one patient contracted meningitis and another suffered a stroke from which she “largely recovered.” Though not specific to MST of the language cortex, a broader and more accurate picture of the complications involved in MST can be drawn from the 2002 meta-analysis of MST for intractable seizures. In 53 patients who underwent MST without resection, 19% had persistent deficits including hemiparesis (5), memory decline (4), and partial visual field loss (1). This study further suggests that MST with or without resection leads to an increase in partial seizures for 15% to 20% of patients. In fact, 10% of patients with complex partial seizures and 16% of patients with simple partial seizures worsened postoperatively.
While these numbers may not apply to those undergoing MST for LKS, they certainly do not support the case for surgery. MST also has several technical complications, especially in its original format. Wyler et al. noted that MST is technically difficult and can cause subpial hemorrhage, while Pierre-Louis et al. reported cystic cavitation (7–9). Though these complications have been addressed in the modification by Wyler et al., cortical damage like the inadvertently severed input–output connections reported by Kauffman remain a problem in the use of this procedure and continue to be seen to this day by those of us who use the technique (8,9).

ALTERNATIVE THERAPY

In a 2002 report by Mikati et al. (10), intravenous immunoglobulin (IVIG) completely resolved symptoms of LKS in the two patients who were free of prior brain insults, supporting a previously proposed autoimmune etiology behind “pure” LKS (11). These numbers are small but promising. It seems logical to pursue this route before surgery, as it is far less invasive and curative rather than palliative. In summary, the long-term results of MST in LKS simply remain to be proven in a randomized study against nonoperated controls. The scientific evidence for MST in LKS is not yet conclusive.

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Part Two

The Presurgical Workup
Section IV
Integrative Neuropsychology in the Preoperative Workup of the Epilepsy Surgery Patient

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INTRODUCTION

The value of neuropsychology in the preoperative evaluation of the epilepsy surgery patient has been recognized for many years. In March, 1990, a National Institutes of Health (NIH) Consensus Panel on Surgery for Epilepsy wrote “to be effective and comprehensive, the staff of a center should include neuropsychologists” (1). The panel further stated that to localize the epileptic foci, psychological tests were “essential for the evaluation of varied cerebral functions, including memory and language.” The use of the intra-arterial amobarbital procedure (IAP) was also recommended in surgery centers “to localize language function and to assess memory preoperatively.” A more recent report, the 2001 Report of the National Association of Epilepsy Center, similarly recommended that neuropsychological services be included for both third- and fourth-level centers for epilepsy (2).

The above recommendations were made based upon the literature and experiences of professionals (neurologists, neurosurgeons, psychologists, etc.) from well-established epilepsy surgery centers. Neuropsychologists contribute in many different ways to the preoperative evaluation of the surgical patient. In the present day, mainly because of the financial restraints of hospitals and clinics, the roles of the neuropsychologist in surgical centers may be more limited than previously seen in the larger comprehensive epilepsy centers. Even as consultants to the epilepsy team rather than an interactive member, neuropsychologists play an important part in the presurgical evaluation.
CLINICAL NEUROPSYCHOLOGY AND THE NEUROPSYCHOLOGICAL APPROACH

The most effective utilization of a clinical neuropsychologist is as an integral member of the preoperative epilepsy surgery team. The clinical neuropsychologist working in the epilepsy center is usually trained in clinical psychology with specialized training in neuropsychology. Because of the complexity of the issues in the neuropsychology of epilepsy, additional internship or fellowship in epilepsy has been recommended. To develop a neuropsychological profile or interpretation the clinical neuropsychologist of epilepsy utilizes principles of psychology, brain behavior relations, and the neuropsychological effects of epilepsy. (For several recent reviews of neuropsychology of epilepsy see Refs. 3–5.) This knowledge is applied to data obtained from a variety of sources. The data used by the neuropsychologist include medical and psychosocial history of the patient, psychiatric/personality assessments, observations, and neuropsychological measurements from neuropsychological testing, IAP behavioral testing, functional magnetic resonance imaging (fMRI), and intraoperative language mapping (6,7). The neuropsychologist is trained to be aware of potential factors that can negatively impact the validity and reliability of the behavioral data collected, including potential confounding factors such as reduced motivation, attention problems, mood, and external distractions (8). Particularly in the epilepsy patient, the neuropsychologist is also aware of potential interference of a recent seizure on the patient’s current cognition, with knowledge that the type and severity of the seizure factors determine the nature of the negative impact (9,10). Potential medication effects on behavior and test data and profile are recognized (11–14). If possible, questionable neuropsychological data are repeated, although costs, schedules, and potential confounds by repeated assessments may play a role. Nevertheless, the neuropsychologist is cognizant of the validity and reliability of the data and conveys as appropriate the limitation of behavioral information to the epilepsy surgery team.

As additional medical and neuropsychological information becomes available on a patient, additional tests or reinterpretation or extension of the initial neuropsychological impression can occur. For example, an unexpected frontal lobe lesion identified by the MRI may require increased frontal lobe behavioral assessments for clarification of its behavioral impact. Also, the finding of right hemisphere language dominance by the IAP can influence the interpretation of neuropsychological testing results (15). Thus, the neuropsychological evaluation and interpretation becomes integrated with the medical information as the latter develops during the presurgery epilepsy workup.

CLINICAL APPLICATION VS. RESEARCH

In an attempt to obtain objective evidence of the relative contribution of neuropsychology to the preoperative workup, the statistical and methodological approaches have frequently favored using one cognitive measure from the neuropsychological evaluation. However, the clinical neuropsychological evaluation is not synonymous with an isolated cognitive score; in the clinical setting a blind interpretation of one behavioral score does not occur. While select test indices may indeed be highly sensitive to the functional integrity of specific brain regions involved in epilepsy (such as auditory word-pairs delayed-learning, and the left hippocampus),
the neuropsychological significance of any one score requires integration with other
test data as well as other relevant patient information (16,17). A simplified example
of the difficulty to extract clinically useful information from one score is illustrated by
the findings of a recent MRI study (18). In this report, low scores on a verbal memory
measure (retention of logical prose) were found to be useful in lateralizing a left
temporal lobe seizure onset in patients who had bilateral atrophy of the hippo-
campus. However, in review of the individual cases, the authors indicated that the
low verbal memory score was not diagnostically helpful in the presence of low overall
intellectual functioning. This reported exception is consistent with the interpretation
of low memory scores in the clinical setting where the over intellectual level of a
patient could influence the interpretation of an isolated cognitive measure.

There have been limited studies addressing the relative value of the clinical
interpretation versus individual scores in the epilepsy surgery population. A recent
study of anterior temporal lobe (ATL) surgery candidates found that scores on
individual memory tests were less predictive of seizure laterality than skilled clinical
interpretations of neuropsychological profile (19; for additional examples and discus-
sion see Chapter IV-10a by Dr. Dodrill). Unfortunately, the generality of findings
from such studies are difficult since variations can exist across surgical centers both
as to the training and experience of the neuropsychologist as well as variations in the
behavioral tools and indices used. Nevertheless, it is apparent that much of the
published literature does not adequately address the effectiveness of neuro-
psychology during the actual workup of patients in many epilepsy centers.

ROLES OF NEUROPSYCHOLOGY

The following is an overview of the various roles of neuropsychology in the evalua-
tion of epilepsy surgery patients. ATL surgery is the most frequently performed
epilepsy surgery and has been the most well-researched one. Discussion will focus
on the adult ATL patient; the reader is referred to Reference 20 for a review of neuro-
psychology and epilepsy surgery in children.

Behavioral Outcomes Research

To Identify the Cognitive Sequelae of Standardized Resections

One of the earliest roles that neuropsychology played in the neurosurgical treat-
ment of epilepsy and one that continues to be invaluable and irreplaceable is the
evaluation of the cognitive effects of different surgical approaches. By comparing
postoperative scores with preoperative baseline performance, neuropsychology has
documented that, in addition to controlling seizures, epilepsy surgery can impact
cognition. Many of the earlier neuropsychological studies reported on the cognitive
sequelae of a standardized ATL surgery for epilepsy (21). However, the surgery
parameters and its impact may not have been as consistent as previously thought.
A recent MRI study reported variations in the extent of resections in supposedly
standardized ATL surgeries (22). In addition, dynamic postoperative changes appar-
ently can occur in the remnant (nonremoved) tissue (23). While these variables were
found to relate to the extent of postoperative cognitive change, the main cognitive
sequelae of ATL surgery are sufficient robust to be fairly consistent in publications
reported among the different surgical centers.
It has been recognized for 50 years that memory, in particular, is at risk following ATL surgery. Following a resection of the anterior portion of the left language TL, including the anterior hippocampus, and surrounding neocortical tissue, verbal memory skills are likely to decline, particularly in the auditory modality (24,25). In addition to memory, in a significant number of patients, select language skills, such as visual confrontation naming, are at risk for decline following the left-dominant ATL resection (26,27). Lowered nonverbal memory scores have been associated with a right ATL resection, although the consistency of finding such a decline has not been at the same level as reported earlier (28–31). The failure to replicate the findings of a relationship between nonverbal memory changes and right ATL resections may be because of a number of factors, including change in patient characteristics, surgical approach, diagnostic procedure to guide the surgical parameters, postoperative testing intervals, sensitivity of the measures, and gender (32–34). Bilateral TL surgery for epilepsy was performed as a control for bilateral onset seizures, but resulted in a severe permanent amnestic syndrome, affecting both verbal and nonverbal memory (35).

Yet despite the well-documented risk for memory decline following ATL surgeries, there have been a few reports of postoperative increase in select cognitive functions in the seizure-free patient (36–39). Practice effects have been suggested as a factor relating to increased postoperative operative scores, but the issue remains open. These selective cognitive increases would be consistent with improvement in brain metabolic functions that have been documented outside the resected area following successful surgery, decreases in postoperative medications regime, and patients’ subjective report of postoperative memory improvement (40,41). Such select improvements, however, should be considered in relation to the potential broad-spectrum verbal memory declines that can occur following a left language-dominant ATL resection.

To Aid in Refining the Surgical Parameters
The goal of epilepsy surgery is to control seizures with the minimal impact on quality of life domains such as cognition. Neuropsychological studies have helped to identify surgical parameters that may negatively impact cognition. The language and verbal memory declines associated with left ATL resections have been studied most extensively because of the frequency of the surgery and the negative impact that these cognitive impairments may have on the patient’s overall functioning (42). A decrease in naming skills (visual confrontation naming), sometimes seen following a left language-dominant ATL resection, has been found to relate to the extent of lateral neocortical tissue removal, with greater naming problems with more extensive resection of the lateral neocortex (26,43). Also, a more extensive lateral neocortical excision in a left ATL resection has been reported to relate to greater difficulties postoperatively in the auditory learning of prose material (44). On the other hand, using a word-list learning task to compare outcomes, patients who underwent a lateral TL lesionectomy showed less decrease postoperatively than either a left ATL lobectomy or left selective amygdalohippocampectomy (45). Although “less may be better,” there is sufficient that type and extent of cognitive changes vary as a function of the surgical parameters of the left TL resection. Thus, in order to appreciate the differences in cognitive sequelae among various surgical approaches, a variety of verbal learning and memory indices should be utilized as outcome measurements.
To Appreciate the Overall Impact of Cognitive Change Following Epilepsy Surgery

For almost three decades, clinical research has consistently shown that controlling seizure activity with epilepsy surgery relates to improvement in a number of facets of quality of life. Such improvements have been documented with a variety of quality of life indices (also see Chapter II-4c) (46–49). Although improvement in quality of life is likely to occur in the seizure-controlled patient, the contribution of cognitive problems to overall quality of life of the epilepsy surgery patient has only recently been appreciated (42,50). The degree of improvement in quality of life following seizure control with surgery appears to be compromised in part by cognitive and memory declines (51). Figure 1 shows the nonadjusted relationship of overall quality of life scores of a group of middle-aged epilepsy surgery patients to verbal memory scores, derived from the recall of prose, a task similar to conversational language. Stepwise regression had identified both seizure control and logical prose as independent predictors of quality of life (51).

The overall impact of cognitive changes in the epilepsy surgery patient deserves further research. As noted previously, there have been several different verbal memory indices used in outcome studies, and it is likely that the quality of life impact of the different memory indices would not be identical. Also, the self-reported complaints of memory in the epilepsy patient are not strictly related to verbal memory scores and can reflect broader neuropsychological domains such as level of verbal skills, i.e., word fluency and vocabulary (52). Thus, in order to better appreciate the findings of surgical outcome studies, the quality of life impact of the varied

Figure 1 Overall quality of life scores of temporal lobe surgery patients plotted against a verbal memory score, prose–immediate recall, with simple regression lines shown. Both overall quality of life scores and prose–immediate recall scores were obtained at a long-term follow-up, mean 12.9 years after surgery. Regression analyses showed that seizure frequency accounted for 27% of the variance in quality of life scores, with verbal memory score accounting for 15%.

(A) Patients who were seizure-free at the long-term follow-up (n = 34). (B) Patients who had at least one seizure the previous year (n = 10). Small square, left temporal lobe patients; up-pointing small triangle, right temporal lobe patients. Source: From Ref. 51.
cognitive changes, including comparisons among the different verbal memory measures, is imperative. Yet, there is the individual patient factor; in the clinical setting, the degree of impact of cognitive and memory problems on the overall quality of life of individual surgery patients can vary, as the expectations, goals, and occupations of patients are not heterogeneous (53).

Both the early and late cognitive sequela of epilepsy surgery are being addressed by neuropsychological research. Surgery-induced memory changes, at least reflected by select memory measures, are long-standing (51). As the epilepsy surgery patient ages, there is concern that age-related changes in memory imposed upon an already compromised memory system will result in such a lowered functioning level that late additional negative impact on the patient’s quality of life may occur. Long-term follow-up studies are addressing these concerns and the effect of age on cognition and other quality of life indices in the epilepsy surgery patient (51,54).

To Predict Cognitive Change in the Individual Epilepsy Surgery Patient

A universally accepted role of the neuropsychologist as a member of an epilepsy surgery team is to provide information regarding the likelihood of postoperative cognitive decline in the individual patient. Following ATL surgery for epilepsy, memory problems are the greatest cognitive risk and are more likely to follow a left dominant than a right nondominant surgery. The memory problems occur primarily in verbal memory. Yet, following left ATL surgery, there is marked variability among patients as to the extent of verbal memory loss (29). While surgical approach and other surgery-related variables clearly impact the likelihood of postoperative cognitive changes, there are a number of other nonsurgical factors that have been shown to influence the type and extent of cognitive change. Considerable research has been undertaken to identify predictive factors of the postoperative verbal memory decrease. This information may affect surgical decisions and can provide potential patients with information to make informed medical choices. Factors found to have prognostic value relate to brain organization, compensation, and plasticity, including functionality of the tissue to be removed and the functionality of the tissue not to be removed (55,56).

Factors

Non-epilepsy–Related Factors. In general, females have been reported to be more advanced in verbal skills than males and thus less likely to have marked problems with verbal skills both before and after ATL surgery (57). However, it is not clear that gender affects the verbal memory decline from pre to postoperative (58). With right TL surgery, females may be more at risk for a related decline in visual memory (34).

Hemispheric language dominance has been shown to relate to postoperative changes of left ATL surgeries. Left ATL surgery in an individual with genetically determined left-handedness and right hemisphere language dominance is less likely to result in verbal memory decline than in a patient with left hemisphere language dominance (59). (However, see Ref. 60 for the probability of language shifting in the nonneurological compromised patient).

Epilepsy-Related Factors. A number of seizure-related factors relate to postsurgery cognitive outcome. Clearly, surgical parameters such as extent of lateral
cortex removed, lesionectomy versus standard, and left language dominant versus nondominant resections will impact the probability of specific cognitive outcomes.

**Age-Related Factors.** Other epilepsy factors that have been found to correlate with postoperative cognitive declines include age of seizure onset, age of the initial precipitating event, and age at surgery. Early age of onset of seizures and age of the initial precipitating event relate to the probability of interhemispheric language reorganization, particularly transfer of language dominance to the right hemisphere with early left hemisphere onset seizures or insult (59,61). Intrahemispheric reorganization of functions in the left hemisphere dominance patient has likely occurred in some patients with early left TL seizures onset or early event as these patients are less likely to have language and verbal memory declines after left ATL surgery (50,62,63). Thus, in the patient with late age of onset of epilepsy or late age at the initial precipitating event, reorganization of function associated with the epileptic tissue has not likely occurred; thus, consequently, these patients have a higher risk for postoperative cognitive decline than those with early insults.

There are several reports that the older an individual is that undergoes left ATL surgery, the more likely that postoperative naming and verbal memory declines will occur (26,27). Such findings imply reduced plasticity of the older brain, although with select functions older may mean late twenties (26).

**Tissue Integrity.** A substantial amount of research during the last decade has confirmed that the integrity of the tissue to be removed relates to the postoperative cognitive change. The removal of relatively intact and functional brain tissue is more likely to result in a loss of function than the resection of sclerotic or atrophied tissue.

**Anatomical Integrity.** Both qualitative and quantitative analyses of the resected hippocampus have shown that removal of a sclerotic hippocampus results in less postoperative memory decline (16,63–66). Following a left ATL resection, patients with no or mild hippocampal sclerosis are at greatest risk for the broad-spectrum verbal memory decline and thus generally considered at risk for a negative impact on overall quality of life. There are, however, individual differences in cognitive outcome among patients within the hippocampal pathology groups. When examining outcome on a patient-by-patient basis, many patients undergoing left-sided ATL who have moderate to severe hippocampal sclerosis were also at risk for further memory decline (67). Although this risk to the memory may be selective, the quality of life impact of additional memory decline on an already compromised memory system is not known. The subgroup of patients with hippocampal sclerosis who are at risk for further verbal decline deserves further investigations both in terms of social impact of the decline and the identification of predictive indicators for those most likely at risk. For example, recent research suggests that the type of hippocampus sclerosis may play a role in cognitive outcome, as patients with classical Ammon’s horn sclerosis appear to demonstrate fewer cognitive declines after ATL surgery than those with atypical sclerosis (39).

With the introduction of high-resolution MRI, the preoperative anatomical integrity of both the tissue to be removed and that of the tissue not resected have been associated with cognitive changes in the epilepsy surgery patient. Both MRI-determined hippocampal atrophy and elevated (i.e., abnormal) hippocampal T2 signal have been related to postoperative memory decline after left or right ATL surgeries (68,69). Bilateral hippocampus atrophy identified by MRI associated with left temporal lobe onset is associated with worse verbal memory before and after temporal lobe surgery than bilateral atrophy association with right temporal lobe
surgery or right temporal lobe epilepsy (70). Coexisting abnormalities identified by MRI have also related to postoperative memory decline (71).

**Physiological Integrity.** The pattern of hypometabolism identified with fluodeoxyglucose (FDG-PET) has been associated with the anatomical integrity of a temporal lobe seizure focus (72). Thus, the lack of hypometabolism in an affected left mesial temporal lobe onset, not unexpectedly, relates to greater postoperative verbal memory decline (73).

**Cognitive Integrity.** The neuropsychological data provide preoperative information as to the cognitive integrity of the to-be-resected tissue as well as the supposedly noninvolved brain (74). Thus, in the left temporal lobe surgery patient, it is not surprising that a high preoperative verbal memory skills (indicating a cognitively intact hippocampus) would predict greater loss or drop after surgery than a low preoperative score (75). While guidelines exist to predict the risk of postoperative decline based solely upon preoperative neuropsychological functions, in general neuropsychological findings are combined with other prognostic indicators to provide the best predictive value.

**IAP.** Five chapters in this volume are devoted to the IAP so the subject will be only briefly discussed. The IAP was originally developed to determine hemisphere language dominance prior to surgery and the IAP still plays this prognostic role in the epilepsy surgery patient (76). Depending upon the surgical parameters, language dominance in the surgical hemisphere warns against potential language-related postoperative deficits and verbal memory declines. After reports of marked memory problems following unilateral resection(s) of the mesial temporal lobe, the IAP was adapted to test for memory functions following pharmacological ablation of the to-be-resected hemisphere (77–79). There are inherent difficulties with the procedure to replicate the proposed surgery, and there are a varied number of IAP techniques currently in use making generality across centers problematic (80,81). Although there are no known current surveys of surgical centers’ usage of the IAP to predict a severe postoperative memory loss, most of the large epilepsy centers attend closely to the IAP results following injection of the proposed hemisphere. Depending upon the experience and confidence of the centers in their IAP protocol in this function, such concerns could lead to further investigations or changes in the surgical decisions.

The utility of an IAP to predict specific memory (less than fully amnestic) changes following epilepsy surgery entails a protocol that compares the performances of patient following the left and right injections. The use of the IAP in this regard, while used in many centers, is not universally accepted, as evident by the discussions in Chapter IV-11c by Dr. Dodrill. However, Drs. Loring and Meador et al. (53) have published extensively on the ability of their IAP protocol to predict specific memory loss. A review of their research can be found in Chapter IV-11b.

**Prediction of Cognitive Loss**

Many of the factors associated with cognitive decline following epilepsy surgery are related, which results in confusion as to the independent contributions of the factors. For example, early age of onset of seizures and brain insult are related to brain organization as well as to hippocampal sclerosis (63,82). Age factors in many investigations are correlated, with age of onset and age at surgery also correlating with duration of seizures. Both the anatomical and physiological integrity of the involved tissue have been related to cognitive functioning (65,66,83). Considerable research has been aimed at identifying those factors that are most predictive of postoperative
cognitive decline and provide independent information from the other factors. Various statistical approaches (e.g., multiple regression, logistic regression) using various combinations of predictors have been used in prognostic models. Reliable change indices and regression-based norms have been found to be complementary methods to address test–retest performance of individual patients who undergo epilepsy surgery as well as the more general investigation of cognitive outcome after epilepsy surgery (84). Cognitive outcome measures in these research endeavors have consistently included an index of verbal memory, typically using either indices from a verbal list learning task or recall of prose.

Neuropsychological procedures provide data as to the cognitive integrity of brain regions, information that the other prognostic indicators reviewed above do not provide. Thus, it is not surprising that in statistical models of multiple potential predictive variables, cognitive measures universally emerge as a significant independent predictor of postoperative cognitive decline. For example, using logistic regression analysis to predict reliable change index values of a list-learning task, preoperative score on the list-learning task and age at surgery were independent predictors for decline on the list-learning task following a left-sided temporal lobe surgery (57). In a subsequent study, the IAP was found to contribute additional independent predictive information (85). A study from the Minnesota group reported that failing the IAP with both left and right hemisphere injections, higher preoperative memory testing, and male gender were all associated with greater declines in memory after left temporal lobe surgery (86). In this latter study, MRI results, age of onset, and age of damage were not independent predictors. Another group from the University of Rochester, using logistic regression analyses, similarly found that preoperative memory testing and IAP results predicted cognitive outcome, with side of surgery and qualitative MRI findings also contributing independent predictive information (88).

It is not known to what extent the statistically-derived weights of the various predictive models are used in the surgical centers to predict cognitive change in the individual patient. There are sufficient published studies on prognostic variables to enable identification of those patients most at risk (and those least at risk for cognitive decline), with those at most risk having left-sided surgery, late onset, male gender, left hemisphere language dominant, and no or little evidence of compromised integrity of the tissue to be resected). However, it is the patient with inconsistent prognostic indicators that poses the greatest challenge. In these latter cases, the clinical team considers the risks identified from the various sources, in light of expectations and needs of the individual patient.

To Aid in Identifying the Epileptiform Area

The results of neuropsychological procedures cannot independently diagnose an epileptiform area, but has been reported to be helpful when combined with other diagnostic information. Both the neuropsychological assessment and the IAP provide information as to the integrity of brain regions, with information from both procedures providing information as to possible inter- and intrahemispheric brain-behavior reorganization. The neuropsychological information may suggest the extent of more diffuse brain involvement, hemispheric lateralization associated with the greater cognitive involvement and in some cases intrahemispheric localization of dysfunction (74). The diagnostic significance of the neuropsychological findings is considered in light of other evidence, including medical, electrophysiological and imaging data that implicate an epileptiform area.
A review of the published literature using neuropsychological testing to aid diagnosis in the epilepsy surgery patient is provided by Dr. Dodrill in Chapter IV-10a. Drs. Stroup, and Sherman in Chapters IV-10b and Chapters IV-10c provide an excellent overviews of issues involved in the neuropsychological evaluation of the epilepsy patient and Dr. Swanson in Chapter IV-10c address the limitations of neuropsychological testing to assess regional brain dysfunction in this population.

Historically, neuropsychological procedures have been used to provide confirmatory information (6,88). If data from neuropsychological procedures (neuropsychological testing evaluation or IAP) suggest an area of dysfunction outside the area suspected to be the epileptiform area, further investigations as to the significance of these findings to the seizure onset are usually undertaken. For example, patients who show both verbal and visual memory deficits preoperatively tend not to be seizure-free after temporal lobe surgery, suggesting that neuropsychology had identified an area of dysfunction that was associated with another or the primary seizure onset (89). The lack of neuropsychological evidence of cortical dysfunction does not preclude a localized epileptiform area. However, in certain cases the lack of lateralization by neuropsychological testing and IAP may indicate further invasive, depth-recording studies. It has been suggested that invasive testing is indicated if there is evidence of bitemporal mesial sclerosis on structural imaging or electrophysiologically, and additional information from functional imaging, neuropsychology testing, and IAP also does not help to lateralize the epileptogenic zone (90). It has also been suggested that neuropsychological procedures are more valuable in one epilepsy population than in another. In the mesial temporal lobe epilepsy patients, the IAP results were found basically confirming other evidence of localized brain disruption, but in patients with neocortical or mesial frontal epilepsy, results from the IAP provided more valuable information regarding localization that ultimately alter surgical management (91).

**To Aid in Distinguishing Seizures vs. Non-epileptic Seizures**

The contribution of neuropsychology in this role is most useful when the video-EEG shows negative results (92).

**To Aid in Planning Rehabilitation and Intervention**

Neuropsychology plays a role in identifying cognitive and social/personality weaknesses existing preoperatively that may need to be addressed to maximize postoperative functioning. Information as to predictive change in language and memory should be included in the planning with suggestions as to potential helpful interventions for the postoperative status (93).

**THE NEUROPSYCHOLOGICAL TOOLS**

Much of the research on neuropsychological and epilepsy surgery has utilized data collected during the clinical neuropsychological evaluation of the patient. The more comprehensive neuropsychological testing protocols in use cover a broad range of brain functions. In most evaluations, the following cognitive domains are assessed: intelligence, attention and concentration, language skills, visuospatial skills, executive functions and other abilities associated with frontal-lobe functions,
learning and memory (74). However, it is likely that with the increased difficulties of reimbursements for neuropsychological assessments and financial strains on hospitals and clinics, assessment batteries may become more streamlined.

Based upon the recent clinical research literature, the following tests occurred frequently in the preoperative workups of the epilepsy patient:

**General intelligence:** Either from one of the Wechsler Scales or estimates from a subtest or several subtests (94–96).

**Attention and conceptual tracking:** Trails-Making (97), Wisconsin Card Sorting, Digits and Arithmetic Reasoning Subtests from a Wechsler Scale.

**Language:** Wechsler’s expressive vocabulary subtest, a visual confrontation naming test, usually the Boston Naming 60, although there is emerging evidence that auditory naming may be more sensitive than visual naming to left temporal lobe dysfunction or at least provide complementary information; Verbal Fluency (COWAT, Category Naming, or both) (98–102).

**Visual–perceptual and visual–perceptual–motor skills:** Wechsler Block Design, Judgment of Line Orientation, Drawing Tasks such as the Rey-Osterrieth (103,104). Varied Visual Memory Tasks, including Rey-Osterrieth Delay, Nonverbal Selective Reminding Test, WMS Visual Reproduction, Immediate and Delayed (104–106).

**Verbal memory:** Verbal memory has been the focus of much of the neuropsychology and epilepsy surgery research. The following is a sampling of varied research indices of verbal memory.

**Recall of prose from the Wechsler Memory Scales** (106). Indices have included immediate, delayed and/or percent retention. The task is somewhat similar to conversational learning and has been related to an overall quality of life score (51). Higher percent retention scores preoperatively have been related to a greater decrease in postoperative decline (81). The percent retention score has been found to be diagnostically useful in patients with left temporal lobe seizures and bilateral atrophy on the MRI (18).

**Unrelated auditory word-pairs from the Wechsler Memory Scales** (106): Indices: Learning and Delayed Recall. The learning of auditorily presented word pairs has been well known to be consistently impaired with left ATL surgery (107). Strong associations have been reported between learning and retention of unrelated word pairs and left hippocampal sclerosis and atrophy, with delayed recall of the word pairs a more sensitive index (16,17,108).

**List-learning tasks:** California Verbal Learning Test, Selective Reminding Test, or Rey Auditory Verbal Learning Tests (96,109,110). Indices included learning across trials delayed recall scores (following an interference), the interference trial, delayed recall score, and percent retention. Research has suggested that list learning across trials may be related to general language competence, and that the learning score may also be more sensitive to neocortical temporal lobe structures than to the left mesial temporal lobe or hippocampus (30,45). Delayed recall or loss of recalled information appears to be sensitive to the preoperative integrity of left hippocampus (45,111). This delayed retention score was also reported to relate to reported memory complaints in epilepsy patients (52). Of note, however, others have failed to identify a relationship
between list learning performance and either presence of hippocampal sclerosis or lateralization (67).

SUMMARY

Clinical neuropsychology has played varied roles in the preoperative workup of epilepsy surgery patients. These have included cognitive outcome research, prognostic studies of cognitive change, confirmation of the epileptiform area, aid in diagnosis of non-epileptic seizures, and planning of postsurgical rehabilitation. Expertise in brain behavior is certainly not limited to clinical neuropsychology, and some of the more specialized procedures, such as fMRI and intraoperative language mapping, have also involved professionals other than clinical neuropsychologists (e.g., neurologists, neuroscientists). These latter brain behavioral tools are addressed elsewhere in this volume (Chapter IV-11a-c, and Chapter VIII-21a–c). While epilepsy centers may vary in the utilization of clinical neuropsychology, all surgery centers engage clinical neuropsychology in at least one of the roles described. Clinical neuropsychology provides information as to the cognitive functioning of the epilepsy surgery patient, and as the risk of cognitive sequelae is associated with epilepsy surgery, clinical neuropsychology will continue to be invaluable in the workup of these patients.

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Chapter IV-10
The Use of Neuropsychological Testing to Locate the Epileptogenic Zone

Chapter IV-10a: Is Neuropsychological Testing a Useful Predictor of the Epileptogenic Zone?—Review of the Literature

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INTRODUCTION

The possible use of neuropsychological tests to help identify the lateralization and localization of the electrical focus in patients with partial epilepsy has immediate appeal. For one thing, neuropsychological testing is completely noninvasive, and while it does require effort, there are very few risks involved. For another, it approaches the brain from a very different perspective than the electroencephalogram (EEG), and the likelihood therefore exists that it might provide complementary information to the EEG with the possibility of enhanced prediction beyond which it is possible with either area alone. However, one must critically review the studies that have been done in the area before conclusions can be drawn about the possible usefulness of neuropsychological testing in this context. That is the intention of this chapter.

PRELIMINARY COMMENTS ABOUT NEUROPSYCHOLOGY

Human neuropsychology is rooted behavioral neurology, experimental psychology, and psychometrics. Traditionally, it has sought to evaluate the brain from the...
viewpoint of cognitive functioning. Tests have been included based upon their demonstrated ability to reflect the functioning of the various structures in the brain. This has been typically accomplished through studies of discrete brain lesions and their impacts upon neuropsychological tests. The general viewpoint has been that for a test to be “neuropsychological,” it must have a demonstrated relationship with the nervous system. This is the “neuro” part of the term. Without such a demonstrated relationship, it is merely a psychological test. The general belief has been that without such a demonstrated relationship between the nervous system and the test, one can hardly use the test to make inferences about the nervous system. Furthermore, as the functions of the brain are complex and varied by nature, there is no hope that a single test will provide an adequate description of the function of any particular brain. That being the case, it is important to validate a group of tests together, so that the validity of each test can be established as an indicator of brain functions, and also the relative validities of the tests as well as the interrelationships of the tests with one another can be established. As is obvious, it is also important to include tests sensitive to the full range of cortical areas.

Until 10 to 15 years ago, the general philosophy just described was the stance assumed by most neuropsychologists, probably including the largest group of neuropsychologists who demonstrated an influence by Reitan and Wolfson (1). However, in the last decade, neuropsychologists have concluded that especially with the progress made in neuroimaging, their services are no longer desired in terms of lateralizing and localizing brain lesions. Instead, many persons in the field have chosen to focus upon the identification and measurement of underlying constructs which might shed light on how the brain works as a whole. The constructs at hand most commonly include “executive functioning,” “working memory,” “episodic memory,” “semantic memory,” “perceptual speed,” and the like. Based upon assumptions of what constructs particular tests measure, many neuropsychologists today commonly select tests more to reflect these constructs than to reflect brain condition. This is consistent with their view that they should focus upon cognitive domains and the underlying constructs they imply.

The thrust of the movement described in the field of neuropsychology is away from localizing and lateralizing brain-related problems. In epilepsy, this means that there is currently diminished interest in using neuropsychological tests to assist in the location of the epileptogenic zone. The result is fewer investigations in the area and less knowledge about the sensitivity and specificity of the tests being used within this context. Nevertheless, a review of the most important information will now be undertaken.

**LITERATURE REVIEW**

There have already been at least two published reviews of this area (2,3). These reviews show that there are actually a large number of studies that are potentially relevant to the ability of neuropsychological tests to lateralize or localize the focus. However, instead of citing numerous papers, the approach that has been taken here is to hone in on those studies most directly relevant to the question at hand and to refer to the broader literature selectively. A total of 13 studies were found of direct relevance to the question at hand, and pertinent information about each of these investigations is summarized in Table 1.

Table 1 shows that in the majority of studies, a substantial number of patients was studied and that these patients were always surgical candidates evaluated in large epilepsy centers. In all cases, the patients utilized were primarily or solely adults.
<table>
<thead>
<tr>
<th>Author, date (Ref.)</th>
<th>Patients studied</th>
<th>Findings related to general NP performance</th>
<th>Findings related to lateralization of test results</th>
<th>Findings related to localization of test results</th>
<th>Findings related to variables other than neuropsychological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bengzon et al., 1968 (4)</td>
<td>50 patients with excellent surgical outcomes; 54 with poor outcomes</td>
<td>No relationship found and no relationship with general intelligence found</td>
<td>Nonlateralizing results found more often with poor (49%) than good (27%) outcomes. Good outcomes more often associated with right (40%) than with left (20%) hemisphere deficits</td>
<td>Localization of deficits to the temporal lobes more likely to be associated with a good (58%) than a poor (31%) seizure relief outcome</td>
<td>Neuropsychological data fell in the middle of other predictors of relief from seizures including EEG, age, seizure history variables, radiology variables, and surgical variables. Types of variables not combined or compared on strength of prediction</td>
</tr>
<tr>
<td>Bidzinski, 1971 (5)</td>
<td>100 patients with TLE</td>
<td>Better intelligence associated with more seizure relief after surgery</td>
<td>Not studied</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Wannamaker and Matthews, 1976 (6)</td>
<td>14 patients</td>
<td>Greater impairment on NP tests associated with poorer relief from seizures after surgery</td>
<td>Not studied</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Lieb et al., 1982 (7)</td>
<td>36 patients</td>
<td>Better intelligence associated with greater seizure relief after surgery</td>
<td>Not studied</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Dodrill et al., 1986 (8)</td>
<td>100 patients, divided into predictive</td>
<td>Better scores on WAIS Digit symbol, Marching test,</td>
<td>79% of patients lateralized to the correct side had good relief</td>
<td>Not studied</td>
<td>4 EEG variables plus 4 psycho/neuropsychological variables most predictive together;</td>
</tr>
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and crossvalidational groups

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Outcome/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williamson et al., 1993 (9)</td>
<td>67 TLE (37 LT, 30 RT) with excellent surgical outcomes</td>
<td>MMPI Hysteria, and MMPI Paranoia related to better relief from seizures after surgery. 15/30 (50%) of RT cases had neuropsychological findings concordant with side of surgery; 34/37 (92%) of LT cases were concordant (73% concordance overall) do not know if the psychologist making the ratings was blinded. 35 (52%) had neuropsychological localization to the temporal lobes; 27 of these had LT seizure origin and 8 had RT seizure origin.</td>
</tr>
<tr>
<td>Hermann et al., 1995 (10)</td>
<td>77 patients (48LT, 29 RT)</td>
<td>Not studied. Warrington Recognition Memory Test insensitive preoperatively to differences between the LT and RT groups.</td>
</tr>
<tr>
<td>Hermann et al., 1997 (11)</td>
<td>107 patients (62 LT, 45 RT)</td>
<td>Much general cognitive impairment in both groups in intelligence, academics, language, visual-spatial, but not in attention and executive functions. No main effect for laterality—memory not an effective discriminator between the overall RT and LT groups. Verbal memory worse in LT group if moderate/severe MTS present; some indices of visual-spatial memory worse in both RT and LT groups if moderate/severe MTS present.</td>
</tr>
</tbody>
</table>

(Continued)
### Table 1  Selected Review of Studies Reporting Data on the Use of Neuropsychological Tests to Identify the Epileptogenic Zone or to Predict Relief from Seizures After Surgery (Continued)

<table>
<thead>
<tr>
<th>Author, date (Ref.)</th>
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<th>Findings related to general NP performance</th>
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<th>Findings related to variables other than neuropsychological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kneebone et al., 1997 (12)</td>
<td>81 patients (32 LT, 49 RT) with excellent surgical outcomes</td>
<td>Not studied</td>
<td>WMS-R and Warrington Recognition Memory Test verbal vs. visual discrepancy scores performed poorly and called most cases inconclusive</td>
<td>Not studied</td>
<td>Wada test much better in lateralizing the focus than either test of memory</td>
</tr>
<tr>
<td>Loring et al., 2000 (13)</td>
<td>101 patients (51 LT, 50 RT)</td>
<td>Memory assessment scales global memory not different across the groups</td>
<td>Visual Memory discrepancy score distinguished LT and RT, but 1/3 of patients with 14 point discrepancies lateralized incorrectly, and most were indeterminate; overall classification: LT 55%; RT 60%</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Test Battery</td>
<td>Outcomes</td>
<td>Laterality</td>
<td>Summary</td>
</tr>
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<tr>
<td>Moser et al., 2000 (14)</td>
<td>44 patients (26 RT, 18 LT) with excellent surgical outcomes</td>
<td>Full battery of tests given but results not supplied for overall level of performance</td>
<td>Language and verbal memory distinguished the groups, but nonverbal memory, motor, and visuoconstructive did not</td>
<td>Not studied</td>
<td>Neuropsychological tests alone discriminated lateralization more poorly (66% correct) than MRI (86% correct) and EEG (89% correct). MRI + EEG = 93% correct; MRI + EEG + NP = 95% correct</td>
</tr>
<tr>
<td>Ogden-Epker and Cullum, 2001 (15)</td>
<td>56 patients (27 LT, 29 RT)</td>
<td>Only 4 of 19 test measures differentiated the groups, none pertaining to verbal memory</td>
<td>Ratings by the neuropsychologist concordant with surgery side in 70% of LT, 62% of RT, and 66% overall</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Akanuma et al., 2003 (16)</td>
<td>125 patients (66 LT, 59 RT) including tumors, atypical speech, and all surgical outcomes</td>
<td>Not studied</td>
<td>Of WAIS-R, WMS Logical Memory and Rey Complex Figure, only VIQ distinguished the groups with 58% accuracy</td>
<td>Not studied</td>
<td>Wada test variables clearly superior to neuropsychological tests in distinguishing between the groups</td>
</tr>
</tbody>
</table>

**Abbreviations:** TLE, temporal lateral sclerosis; MRI, magnetic resonance imaging; EEG, electroencephalogram; MTS, mesial temporal sclerosis; VIQ, verbal IQ; WMS, Wada memory scale; LT, left temporal; RT, right temporal; NP, neuropsychological.
(age 16 and over), and typically, lesional cases beyond mesial temporal sclerosis (MTS) were eliminated as were cases with atypical speech lateralization, those with foci outside the temporal lobes, and in some cases, persons who were not right handed. Note is made that while the elimination of such subjects helps to clean up the sample and might therefore improve the accuracy of prediction of focus localization by neuropsychological tests, the practicing neuropsychologist must also deal with these other cases. Therefore, the rates of correct prediction reported here may be mildly increased beyond those obtainable in an everyday clinical setting.

Another general finding of interest is that efforts to localize the EEG focus with neuropsychological tests seem to have seriously begun with patients grouped according to the likelihood of seizure relief following epilepsy surgery. While such an approach may seem somewhat indirect, it is potentially very useful, since if good and poor responders can be identified by these tests in advance, it is evident that the tests must have located brain-related structures and functions which are of inherent interest in epilepsy.

For each investigation, four different types of data are summarized. First, the use of general test measures such as overall intelligence to predict overall outcome in terms of seizure relief was done in 10 of the 13 investigations. Scanning down the third column of Table 1 reveals that in most cases where this was attempted, there were, in fact, one or more connections between general overall performance and relief from seizures. In every case, where a relationship was discovered, better performance was associated with a greater likelihood of seizure relief after surgery. While this is of general interest in a foundational way, the relationships noted are of limited importance with regard to our basic topic at hand, and we will therefore move on.

The second type of data obtained and reported in Table 1 pertains to lateralization of the focus by neuropsychological tests. This is of much greater interest than the very general indicators just reported, and it is clear that this was the focal point of most of the studies, three early papers being the exception. In the remaining 10 papers, some degree of success in utilizing neuropsychological tests to lateralize the focus was routinely reported. However, this did not achieve statistical significance always, and in a number of cases, the findings which were reported were sufficiently small that they are of uncertain practical value. The most favorable findings were reported by Williamson et al. (9), with 92% of the left temporal cases having lateralized neuropsychological findings concordant with the side of surgery, although only 50% of the cases with a right temporal focus being concordant with surgery. The overall correct concordance rate was 73% which is a little better than what Moser et al. (14) reported (66% correct overall), as well as the 66% that Ogden-Epker and Cullum (15) identified. The results are also better than the 58% correct classification noted by both Loring et al. (13) and Akanuma et al. (16). It is wondered if the neuropsychological ratings were made blindly in the Williamson et al. (9) investigation and if a lack of blindness could have resulted in an artificially inflated hit rate. Regardless of whether or not this is the case, it is clear that in the typical investigation, no more than two-thirds of the patients can be correctly lateralized by neuropsychological procedures alone, even when efforts have been made to make the groups as free as possible of the potentially contaminating factors seen in clinical practice.

At least a moment should be spent on why the neuropsychological predictors are not stronger. One outstanding reason, not commonly recognized, is that neuropsychological tests are more closely related to slow waves on the EEG than to spikes. This was shown years ago in a series of papers undertaken in Seattle where painstaking spike-counting studies were done, as well as one on slowing in the EEG (17–19). In these investigations, EEG slowing was clearly more related to performances on the
neuropsychological tests than were epileptiform discharges of any type, and especially focal epileptiform discharges, which are, of course, the topic of interest rather than generalized discharges. It also appeared that the EEG slowing was more related to performances in everyday life than the epileptiform discharges, a finding which was consistent with the purposes of neuropsychological tests to begin with. Other reasons for the relatively weak relationship between the laterality of the focus and the neuropsychological tests can be given, but the reason pertaining to EEG slowing is highlighted here as it is easy to miss.

One more observation about the data in the lateralization column of Table 1 needs to be drawn to the attention of the reader before moving further into the table. The observation is that while most investigators have in mind that tests of memory and especially verbal memory are their best lateralization indicators, the data in the table are not especially supportive of this assertion. Where memory indictors had been sorted out specifically among the 10 studies reporting results on lateralization, there is not a single study which reported a high level of success in lateralizing the focus with memory measures. On the contrary, in five cases where memory results were specifically studied and reported upon, the results were identified as disappointing, and in the remaining two cases where memory was reported upon specifically, the results were mixed (10–16). It is evident that the entire matter of using current tests of memory as indicators of lateralized hemispheric dysfunction needs to be thought out more thoroughly.

The next column in Table 1 pertains to localization of the focus by neuropsychological test results. Only three groups of investigators even approached this area, no doubt because of the difficulties in so doing (4,9,11). In two of the three cases, a neuropsychologist had to make judgments based upon a battery of tests, and exactly how this was done is difficult to specify. While some positive findings were reported in these three investigations, perhaps the best that can be said is that this is an area worthy of further exploration.

As the title of this chapter implies, we are looking for not just any kind of statistically significant relationship that has been eked out of the data, but for a “useful” relationship. Neuropsychological results therefore need to contribute to the predictive value of other variables of similar cost and risk in order to be useful. The last column in Table 1 deals with this matter. There are five investigations in which data on variables other than neuropsychological variables were reported. In the first of these, no effort was made to compare the potency of the neuropsychological variables in identifying the epileptogenic focus with that of a host of other variables (4). An examination of the data that were presented, however, indicates that the neuropsychological variables were somewhere in the middle in terms of predictive power. In a second investigation, four neuropsychological variables did add to four EEG variables in predicting relief from surgery (8). In two other studies, neuropsychological variables were compared with those arising from the Wada test, and in both cases the Wada test was much more closely related to the side of focus than were the neuropsychological measures (12,16). In the final study, the neuropsychological measures were inferior to MRI measures and to the EEG in predicting relief from seizures after surgery (14). In that study, adding the neuropsychological measures to the MRI and the EEG combined increased the correct prediction only slightly.

CONCLUSIONS

The evidence shows that there likely is some relationship between neuropsychological test results and the epileptogenic focus. However, a review of the literature does not
show a consistent relationship, and certainly the relationship is not as strong as for the MRI and the EEG. Therefore, any assertion that neuropsychological tests results constitute a “useful predictor” of the epileptogenic zone must be reviewed with care.

REFERENCES

INTRODUCTION

Comprehensive neuropsychological assessment of epilepsy surgery candidates serves several purposes, including prediction of postoperative risk of memory and language decline, diagnosis of disorders associated with cognitive deficits, determination of need for supportive services, identification of disabling medication effects on cognition, and assessment of patient quality of life (1–3). As a result, neuropsychological assessment has become a necessary component of the comprehensive presurgical workup of patients in specialized epilepsy centers (4). However, despite its utility in these domains, one issue remains controversial: the value of neuropsychological testing in predicting the epileptogenic zone. The best analysis of current findings is that, while the primary role of neuropsychology is not to localize the seizure focus, neuropsychological testing, in certain circumstances, can serve as a useful adjunct to increase prediction accuracy in surgical candidates.

TEMPORAL LOBE EPILEPSY (TLE)

Temporal lobectomy accounts for the majority of surgeries at epilepsy surgical centers (5). Studies have shown that patients with left temporal lobe epilepsy (TLE)
perform poorly on neuropsychological tests of verbal learning and memory, whereas those with right TLE have more difficulty on tests of visual learning and memory (6–10). In particular, tests requiring a patient to learn a series of items over several learning trials appear to be most sensitive to lateralization, relative to single-trial learning tests (11). The lateralizing success of such learning paradigms is in part dependent upon the extent of hippocampal involvement required for the task, as shown by studies relating extent of mesial temporal sclerosis (MTS) to severity of verbal memory impairment (12,13). For instance, in TLE patients with no hippocampal pathology (e.g., amygdala atrophy alone), learning is often intact (14). Tests of naming, and in particular auditory naming, have also shown considerable success in differentiating left from right TLE patients prior to surgery, with rates of up to 85% accuracy in correctly lateralizing TLE patients (15,16).

Neuropsychological measures are also useful in predicting seizure lateralization when used in conjunction with other data such as Wada test results and clinician ratings. For example, combining verbal IQ and Wada correctly lateralized the side of seizure onset in 80% to 90% of TLE patients, while Wada in conjunction with tests of visual and verbal memory correctly predicted lateralization in 87% of TLE patients (17,18). Clinician ratings based on pattern analysis of comprehensive test batteries have yielded promising results. In one study, neuropsychologists’ ratings of probable lateralization of seizure focus correctly predicted laterality in 73% of TLE patients, and another provided correct classification in about two-thirds of TLE patients (19,20). A positive predictive value as high as 93% has also been reported, using stringent cutoff criteria based on a battery of tests to determine lateralization (21).

EXTRATEMPORAL EPILEPSIES

Frontal lobe epilepsy (FLE) is the second most common epilepsy subtype seen at surgical centers (22). However, identifying frontal foci can be challenging due to inherent difficulties in capturing epileptiform activity of deep structures (i.e., orbitofrontal or mesial cortex) on surface EEGs, and because of the pattern of seizure propagation (23,24). Thus, the diagnosis can only be confirmed with either invasive means or confirmation of correct localization following excision of frontal lobe cortex (23). As a result, any noninvasive preoperative technique that serves to increase prediction accuracy in this patient group would be of considerable value. While not as well studied as TLE, neuropsychological investigations of FLE are beginning to identify a potentially specific pattern of test results. For instance, researchers have found difficulties with aspects of executive functioning, including attention, response selection, initiation, and inhibition, in FLE patients compared to TLE patients (25–29). Although further study is warranted, increasing prediction accuracy in FLE using neuropsychological tests may prove of significant utility. Patients with epileptogenic zones outside the frontal and temporal lobes are less common, and as a consequence, have been inadequately studied from a neuropsychological perspective.

POSTICTAL ASSESSMENT

Traditionally, neuropsychological testing is conducted during the interictal period in order to capture “baseline” cognitive performance (i.e., unadulterated by adverse
ictal or postictal cognitive effects). However, postictal testing demonstrates excellent sensitivity and specificity to lateralization and, to a lesser extent, localization, of the epileptogenic zone using several paradigms. Computerized verbal and visual recognition memory testing in the postictal period resulted in approximately 88% correct lateralization with regard to side of seizure focus, based on a small study of TLE patients (30). Similar paradigms have also been used to assess interictal and postictal functioning in FLE, TLE, and controls, with 89% correct group classification using postictal test results (31). Specifically, patients with frontal lobe onset showed no change in memory performance, while patients with right and left TLE had difficulty with postictal visual and verbal memory tasks, respectively. In addition, significantly better prediction of lateralization and localization of the seizure focus using a postictal neuropsychological test battery as compared to interictal test results has been reported in TLE (32). Lastly, 100% accuracy was demonstrated when the length of time required to demonstrate error-free performance on a simple reading task was used postictally to lateralize the epileptogenic focus in TLE (33). This method has demonstrated an even higher degree of accuracy than other noninvasive preoperative measures, including ictal and interictal EEG, MRI, and interictal neuropsychological test results (33).

MULTIFACTORIAL PREDICTION MODELS

Neuropsychological data have been shown to add predictive power to neural network models, logistic regression models, and other multifactorial prediction models aiming to identify the epileptogenic zone (34,35). Although the relative additive power of cognitive tests is typically small, neuropsychological testing increases accuracy, and unlike many other methods, can be gathered noninvasively. Given the consequences of incorrect lateralization in surgical candidates, small increments in accuracy are of significant importance, particularly from the perspective of the individual patient.

METHODOLOGICAL DIFFICULTIES

In order to definitively evaluate the utility of neuropsychological testing in increasing the accuracy of epileptogenic zone prediction, one must effectively control for a number of potentially confounding factors. These include: (1) the standard for correct localization; (2) findings suggesting that localization-related epilepsy represents a diffuse process; (3) research design, including neuropsychological test selection; (4) the impact of psychological variables, including the contribution of effort; and (5) heterogeneity within patient groups.

First, the “gold standard” for determining whether or not the epileptogenic focus is correctly identified is seizure outcome. If the preoperative neuropsychological results agree with the site resected, and the patient is seizure-free, it is assumed that the cognitive profile correctly lateralized (and possibly localized) the focus. This is, however, an imperfect criterion. Not all surgeries successfully eliminate the entire epileptogenic zone, either due to the need to spare eloquent cortex, or because the epileptogenic zone extends beyond the resection margins. Additionally, in some cases the neurosurgeon may perform a more conservative resection based on the
preoperative cognitive profile, resulting in decreased potential for a seizure-free status despite correct identification of the focus.

Relatively new findings suggest that in some instances, localization-related epilepsies, and in particular TLE, may represent a diffuse process (36). Whether the widespread magnetic resonance imaging (MRI) changes and general cognitive deterioration represent the etiology of the disease or the consequence of intractable seizures is not known. Regardless, neuropsychological findings are unlikely to pinpoint a focal deficit in the context of diffuse dysfunction.

Study design can serve to reduce the localizing value of tests, including temporal factors regarding testing time (i.e., interictal vs. postictal), as reviewed above. The selection of neuropsychological measures may also obscure results. There is inconsistency among studies, and as an example, a “memory” measure using single-trial learning will not demonstrate comparable ability to lateralize or localize as will learning-to-criterion paradigms.

Psychological variables may also confound results, given the recognized effects of depression and other emotional disorders on cognitive test performance (37). Additionally, effort may account for a significant proportion of the variance in individual test measures, again obscuring results at the group level (38).

Lastly, patient variables will influence predictive capabilities. For example, testing patients on their usual antiepileptic drug (AED) dosage versus testing patients while being weaned from medications may confound results, given the cognitive effects of certain AEDs. In most cases, subject groups do not represent homogenous epilepsy subtypes and this can also have a significant impact on test results. As a case in point, TLE patients with MTS will likely have deficits in learning and retention that are not seen in patients with neocortical TLE. Thus, disregarding MTS status in TLE patients may dilute deficits at the group level and reduce prediction accuracy. Along these same lines, patients with an epileptic focus in a well-defined brain region may still differ in terms of etiology (e.g., tumor, dysplasia) or epilepsy characteristics (e.g., seizure frequency, seizure severity). In addition, neuropsychological testing as an index of seizure lateralization or localization might not be useful in patients with comorbidities (e.g., other neurological or psychiatric disorders), atypical language, or diffuse brain dysfunction.

CONCLUSIONS

In sum, neuropsychological data is useful in localizing the epileptogenic zone, but with certain caveats. First, neuropsychological test results are most useful for lateralization and localization in specific patient groups such as TLE, and may be useful in FLE. Second, the most promising line of investigation is postictal testing. Though there have been few studies to date, the generated data have been encouraging. Third, several issues confound interpretation of data involving neuropsychological prediction, not the least of which is the choice of criterion. Finally, the limitations of neuropsychological tests in identifying the epileptic zone in no way take away from their primary role in identifying preoperative risk factors and describing pre- and postoperative cognitive and psychosocial functioning in epilepsy surgery candidates.

Indeed, neuropsychological tests are best seen as adjunctive methods to increase prediction accuracy, to be used in concert with the rest of the tools available to the epilepsy surgery team.
REFERENCES

Chapter IV-10c: Neuropsychological Testing Is of Limited Value for Predicting the Epileptogenic Zone

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Historically, neuropsychological test data has been described as useful for detecting lateralized brain dysfunction in the context of focal seizure disorders (1). While some research supports the use of neuropsychological testing to detect material-specific memory deficits, primarily in patients with seizures originating in the dominant temporal lobe (TL), there are significant issues that limit the usefulness of neuropsychological tests for localization or lateralization of seizure foci (2). These issues include: (i) the lack of sensitivity and specificity of neuropsychological tests, (ii) the diffuse effects of seizures, treatment, and the pathogenesis of epilepsy, and (iii) functional reorganization.

SENSITIVITY AND SPECIFICITY ISSUES

Few empirical studies support the use of neuropsychological testing for lateralization or localization of seizure foci preoperatively. Qualitative clinical interpretations of neuropsychological test data corresponded with side of seizure focus in only 66% of cases (3). Further, while electroencephalography (EEG) and magnetic resonance imaging (MRI) are of high lateralization value (93% when combined), neuropsychological testing adds little additional value (2%) to MRI and EEG (4). In a recent study, the lateralizing value of neuropsychological test scores, intracarotid sodium amytal testing, EEG, MRI, and seizure variables were examined using binary logistic regression. Only verbal IQ showed a significant lateralizing value (58%), but this value is only marginally better than chance (5).

When single tests or domains are examined, there have not been consistent differences between candidates for resection in the left versus right hemisphere on measures of verbal–performance IQ differences, figural and verbal fluency, and naming (2,6–8). Verbal–visual memory score discrepancies were significantly different between left and right TL seizure groups, but over one third of the patients with a 14-point verbal–visual memory discrepancy were classified incorrectly with regard to laterality of seizure focus (9). Moreover, separate verbal and visual memory factors were not found in a sample of 245 patients with epilepsy using factor analysis on the Wechsler Memory Scale-III, one of the most widely used memory tests (10). Thus, group differences in neuropsychological profiles of patients with left and right seizure foci are not reliably found and neuropsychological testing lacks sensitivity for predicting an individual patient’s side of seizure focus.
Moreover, even when preoperative group differences have been found, there is little evidence that neuropsychological test data can go beyond interhemispheric lateralization to intrahemispheric localization of the epileptic zone in focal seizure patients. For example, it would be difficult to conclude that a patient with deficits in language and executive functions has a left frontal lobe focus since executive dysfunction is found in patients with TL seizure foci (11). Multiple studies have documented differences between left and right temporal lobectomy groups, but data supporting the difference between pre-surgical patients with left and right seizure foci are less compelling (12).

THE DIFFUSE EFFECTS OF SEIZURES, TREATMENT, AND THE PATHOGENESIS OF EPILEPSY

Seizure and medication variables lead to generalized cognitive impairment as well as extratemporal anatomical abnormalities that may interfere with detection of focal deficits. Neuropsychological tests used to localize the seizure focus are also sensitive to cognitive deficits caused by (a) initial precipitating events, diseases, or injuries that affect brain regions beyond the seizure focus, (b) distributed cerebral dysfunction caused by seizure disorders, (c) coexisting disorders such as mental retardation or developmental learning disabilities, and (d) cognitive side effects of antiepileptic medication. These factors may lead to a misleading profile of lateralized deficits (e.g., in the case of verbal learning disabilities) or to generalized cognitive impairment.

Many pathophysiological mechanisms for epilepsy such as traumatic brain injury, central nervous system infection, perinatal stroke, neurodegenerative disease, abnormalities of cortical development, and rarer etiologies such as tuberous sclerosis and neurocysticercosis lead to diffuse or multifocal brain dysfunction. Cognitive testing is sensitive not only to deficits associated with the seizure focus but also to deficits in functions subserved by other brain areas affected by the pathophysiological process. Posttraumatic epilepsy is associated with scars, abscess formation, depressed skull fractures, and hematomas that may lead to a focal seizure disorder (13). However, more extensive cerebral dysfunction is often present in association with diffuse axonal shearing or coup contre coup injuries (14). While the pathogenesis of most seizure disorders is idiopathic, even patients with mesial temporal lobe epilepsy (TLE), the most localized and surgically remediable focal seizure disorder, have generalized cognitive impairment (2,15). More specifically, in patients with mesial temporal sclerosis, laterality of seizure onset was not associated with differences in verbal or nonverbal intelligence, language, naming, or academic achievement. Only verbal memory deficits were noted in patients with left hemisphere seizure foci. Thus, while there was some value to the material specific (verbal only) memory deficits, considerable generalized impairment is also noted in patients with mesial temporal sclerosis, indicating that TLE is associated with diffuse effects.

Examination of extratemporal structural abnormalities in patients with TLE indicates volume loss in total cerebral tissue and the corpus callosum (16,17). Volume reductions were observed in frontal, parietal, and temporal regions in patients with TLE. Reductions in cerebral tissue volumes were associated with reduced cognitive functioning providing structural and functional correlation of the disseminated effects of seizures (16). Childhood onset TLE has a significant neurodevelopmental impact with generalized neuropsychological deficits and reduced white-matter tissue volume (18). Thus, TL seizures or their cause are associated with
generalized cognitive impairment that correlates with structural gray and white matter changes that extend beyond the temporal lobe and beyond the epileptogenic hemisphere.

Focal seizure can have a generalized effect on intelligence and memory. Seizure variables such as age at onset of epilepsy, duration of seizure disorder, status epilepticus, and history of having experienced more than 100 convulsive, generalized or secondarily generalized tonic clonic seizures are known to correlate with overall IQ attainment and decreased cognitive functioning across multiple domains (19–21). This diffuse effect of seizures on the brain hinders the ability of neuropsychological testing to localize seizure foci. In a large multicenter study of 1141 seizure patients, regression analyses were conducted to determine whether visual, verbal, and delayed memory were related to the following predictor variables: age at seizure onset, duration of seizure disorder, laterality of seizure focus, temporal versus extratemporal dysfunction, sex, speech dominance, and handedness (22). Age at seizure onset was a significant predictor of general memory, verbal memory, and delayed recall. Verbal memory deficits have been the primary difference reported between those with left and right seizure foci. However, in this large sample, laterality of seizure focus was not a predictor of verbal memory. Laterality of seizure focus was a predictor of lower verbal IQ in patients with left seizure foci. However, age at seizure onset correlated more highly with verbal IQ than did laterality. Overall, early age at seizure onset is the most robust predictor of reduced intellectual and memory functioning. This indicates that focal seizures or their cause and treatment affect the brain diffusely making it difficult to detect lateralized dysfunction with neuropsychological testing.

Comorbid disorders such as mental retardation and learning disabilities are associated with global impairment or lateralized deficits that may be unrelated to the seizure focus. Visual spatial impairments are seen in patients with nonverbal learning disabilities, and individuals with verbal learning disabilities may have profiles characterized by verbal cognitive deficits including reduced verbal IQ, verbal memory, mental processing, and visual scanning speed in addition to deficits in academic skills such as reading and spelling (23,24). Cognitive tests have been found to be less sensitive to laterality of seizure focus in patients with language based learning disabilities (25).

Antiepileptic medications are known to result in reductions in attention, psychomotor speed, and language (26). For example, reduced attention, memory, and word fluency have been reported in association with topiramate (27,28). Intelligence was significantly lower in children given phenobarbital for febrile seizures compared to those given a placebo suggesting generalized adverse neurocognitive effects associated with some antiepileptic drugs (29). These generalized or lateralized (language) deficits may interfere with interpretation of psychometric test data for the purpose of seizure lateralization.

**FUNCTIONAL REORGANIZATION**

Cerebral reorganization with shift of language to the right hemisphere occurs in patients with early left hemisphere brain injury (30). The sparing of language at the expense of nondominant hemisphere functions is known as crowding (31). Thus, left hemisphere seizure disorders may lead to cognitive profiles that appear to lateralize to the right hemisphere. Even if the profile of pathological left handedness with crowding is recognized (visual spatial deficits, preserved language, and poorer motor
performance with the right hand), often there are varying degrees of reorganization making interpretation of such profiles difficult.

In summary, neuropsychological testing has limited predictive value for preoperative detection of lateralized brain dysfunction relative to MRI, EEG, the intracarotid amobarbital procedure and functional neuroimaging (32–37). Factors associated with the diffuse effects of seizures and treatment, comorbid disorders, functional reorganization, and burgeoning evidence of distributed extratemporal structural abnormalities in patients with TLE limit the usefulness of neuropsychological testing for localizing the epileptogenic focus. However, neuropsychological testing remains an integral part of the comprehensive evaluation prior to epilepsy surgery as it can be used for understanding the effects of seizures on cognition, determining whether progressive decline or adverse effects of antiepileptic medications are occurring, assessing possible contraindications for surgery, and for predicting cognitive, psychosocial, and seizure outcome after temporal lobectomy (22,38,39).

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Chapter IV-11
Is the Wada Test a Useful Predictor of Memory Outcome?

Chapter IV-11a: Review of the Role of the Intracarotid Amobarbital Procedure (IAP) in Memory Assessment and Predicting Memory Outcome Following Anterior Temporal Lobectomy

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HISTORICAL BACKGROUND AND UNDERLYING ASSUMPTIONS

In 1958, Penfield and Milner (1) described two patients who presented with significant memory impairment following unilateral temporal lobectomy. The underlying assumption was that the contralateral temporal lobe harbored an unknown lesion such that, following surgery, the patients’ memory function declined to a level consistent with patients who had undergone bilateral temporal lobectomy. This assumption was later proven to be accurate in one of the cases in whom autopsy data were available (2). Driven by the need to prevent similar devastating memory outcomes in unilateral temporal lobectomy patients, Milner et al. (3) adapted Juhn Wada’s intracarotid amobarbital procedure (IAP) for assessing language lateralization to the study of memory lateralization in preoperative epilepsy surgery patients.

The IAP involves injection of amobarbital (or another anesthetic agent) into the internal carotid artery thereby resulting in a temporary disruption of function in those brain regions supplied by the internal carotid artery. Language, memory,
or other cognitive tests can be performed during the period of hemisphere anesthe-
tization, and the patient’s performance during each injection can be used to infer the
relative contribution of the two hemispheres to the tested behavior. The IAP
memory protocol was based on the rationale that the ipsilateral injection would
essentially mimic the effects of a temporal lobectomy and thus, provide a method
of assessing the potential impact of surgery on memory function. A number of
studies have demonstrated that the critical memory structures resected during an
anterior temporal lobectomy are functionally inactivated during the IAP injection
(4,5). Milner and colleagues’ goal with IAP memory assessment was to evaluate
the contralateral temporal lobe’s ability to sustain memory in order to prevent a
postoperative global amnesia (3).

The emphasis on the contralateral temporal lobe’s functional ability during
ipsilateral injection reflects the functional reserve model that stipulates that predic-
tion of cognitive risk is based on the functional reserve of the nonresected tissue. This
model stands in contrast to the functional adequacy model that argues that the func-
tional integrity of the tissue to-be-resected provides the best indication of memory
outcome following surgery (6). The functional adequacy model posits that greater
decreases in memory are evident if the tissue to be resected is relatively functional
(as assessed by neuropsychology, hippocampal volume measurements, or with the
IAP memory protocol).

Also implicit in Milner and colleagues’ thinking was the concern that an
ipsilateral temporal lobectomy could result in a global amnesia (if the contralateral
temporal lobe was dysfunctional) (3). For a number of years, the underlying impetus
for completing IAP memory assessments with temporal lobectomy candidates arose
out of the concern that unilateral temporal lobectomy could result in a global amnesia
reminiscent of Scoville and Milner’s seminal case report on HM (7). More recently,
Loring et al. (8) estimated that the risk of sustaining a global amnesia, similar to that
manifest in HM, is probably less than 1% following unilateral temporal lobectomy.
Because of the very low likelihood of sustaining a global amnesia following unilateral
temporal lobectomy, the emphasis on the IAP has shifted from predicting a frank
global amnesia to assessing memory risk along a continuum, including identifying
patients at risk of sustaining more subtle deficits.

RELIABILITY ISSUES

It is essential to review the reliability of the IAP prior to beginning a discussion of the
validity of the procedure in predicting memory outcome following anterior temporal
lobectomy. As has been well documented elsewhere, there are multiple challenges to
obtaining reliable memory data in an IAP assessment (8). The IAP is a stressful, inva-
sive procedure. Patients can respond with a wide variety of emotional and/or beha-
vioral presentations. The assessment must be completed in a very brief time frame
during which the patient might be transiently aphasic or have a transient visual field
defect due to perfusion of the posterior arterial system. Patients might be significantly
confused or stuporous. Seizures during the IAP are also not uncommon.

To date, only one peer reviewed study has been published assessing the reliabil-
ity of the IAP. McGlone and MacDonald (9) presented data on a set of patients who
had repeat IAP assessments. They employed an adaptation of the original Montreal
Neurological Institute (MNI) memory protocol. Alternate form reliability of the
memory protocol was assessed in 10 patients who underwent 18 repeat injections
of the same hemisphere. Major changes in memory classification (i.e., pass/fail) occurred in eight of the 18 repeat injections. Seven of the eight changes were associated with clearly identifiable variations in situational factors (e.g., technically unsatisfactory first injections, clear deterioration in cognitive function between the two assessments). Eight of the initial injections were judged to be technically satisfactory. Seven of those eight satisfactory cases yielded identical memory classifications (i.e., pass/fail) on repeat injection.

Other studies examining the reliability of the memory protocol of the Wada test have been published in abstract form (10,11). In general, these authors have not found good test–retest reliability data. Recently, Loddenkemper et al. (12) reported on a large series of patients who underwent the IAP at the Cleveland Clinic Foundation. A total of 1249 consecutive IAPs on 1190 patients between 1989 and 2001 were reviewed. Fifty-three patients (4%) underwent a second IAP and three patients (0.24%) underwent a third IAP. Most often, the IAP was repeated due to obtundation and inability to assess memory or language lateralization. Retest intervals ranged from 1 to 1119 days (median = 95.5 days). Language lateralization findings were always replicated on repeat IAP testing. In contrast, the memory results were inconsistent in 63% of the cases.

The reliability of the IAP memory protocol appears to be hampered by a variety of challenges inherent in the procedure itself (transient confusion and specific neurological deficits, a short time frame in which to assess complex cognitive abilities, etc.). The reliability studies reported focus primarily on a subset of patients who needed repeat testing due to concerns regarding the validity of the initial IAP test. Consequently, it is not unreasonable to expect relatively low reliability coefficients. To date, nobody has reported the test–retest reliability of the IAP memory protocol in a group of patients consecutively referred for IAP testing. These data are crucial to obtaining an accurate estimate of the reliability of the IAP in assessing memory function.

VALIDITY STUDIES

Another historical challenge to evaluating the IAP has been the significant variability in different protocols used across various epilepsy centers. This has hampered neuropsychologists’ ability to replicate findings across centers and to apply published results from one epilepsy center to the memory protocol used at another center to help guide clinical decision making. This point was highlighted in a study by Dodrill and Ojemann (13) who examined the utility of a variety of IAP memory protocols in predicting postoperative memory performance following anterior temporal lobectomy.

The authors compared the Seattle memory protocol to the MNI memory protocol as well as a self-report of IAP memory performance. Their data revealed an overall higher hit rate in predicting verbal memory decline following anterior temporal lobectomy with the Seattle procedure (67%) compared to the MNI (46%) or self-report protocols. Loring and colleagues also found that stimulus type and the timing of the IAP memory assessment were important variables. Real items were superior to line drawings of objects in discriminating left versus right anterior temporal lobectomy patients (14). In addition, memory items presented shortly after injection (i.e., 50–55 seconds) were more sensitive to detecting laterally temporal lobe dysfunction than memory items presented approximately 4 minutes 30 seconds following injection (15). These studies highlight the fact that
research findings published from one center cannot be indiscriminately applied to the IAP memory protocol used at another center. They also support the argument for the use of a standardized IAP memory protocol, with well-documented reliability and validity, in all epilepsy surgical centers.

Multiple studies have been published examining the convergent validity of the IAP memory protocol as an index of temporal lobe dysfunction. Convergent validity is good when a test is highly correlated with other tests that measure the same construct. Milner's (16) initial studies from the MNI documented that the IAP memory protocol was sensitive to seizure focus. Jones-Gotman (17) later replicated these findings and found a failure rate of 41% following the contralateral injection versus 15% following the ipsilateral injection in patients with a unilateral temporal lobe focus. Many more studies have been published since these initial reports supporting the utility of the IAP memory protocol as an index of seizure laterality (e.g., 18-20) and extent of hippocampal sclerosis (18,20-23). These data provide evidence supporting the convergent validity of the IAP memory protocol as an index of temporal lobe dysfunction in epilepsy patients.

The criterion validity of the memory protocol of the IAP has also been addressed. Criterion validity reflects the relationship between test scores and a measure of decision outcomes or criteria (e.g., memory performance). The criterion measures can be assessed at the same time in a preselected group of patients (e.g., concurrent validity). Alternatively, the criterion measures can be assessed after making decisions based on the test being evaluated, thereby allowing the predictive validity of the test to be assessed against some predetermined criterion.

McGlone et al. (24) examined the concurrent validity of the IAP memory protocol. They measured the performance of a group of 15 amnesic patients on a four-item adaptation of the MNI's memory protocol. The underlying hypothesis was that a recognition memory task designed to predict global amnesia during an IAP should be sensitive to the memory deficits evident in patients with amnesia due to neurological disease. McGlone and colleagues defined amnesia as memory scores falling 1.5 standard deviations below the norm. The additional category of global amnesia was reserved for those patients who failed to recognize the examiner when she returned to the room following a five-minute interval. McGlone et al. (24) found that the globally amnesic patients performed in the impaired range on the IAP memory protocol (with no drug injection), but that the memory protocol was insensitive to the more common amnesic disorders. Carswell et al. (25) completed a similar study using the Medical College of Georgia IAP memory protocol. The memory protocol was administered to two patients (without drug) who met the working definition of amnesia proposed by Jones-Gotman et al. (26). All two of the amnesic patients performed at or below chance level on the memory items suggesting that the memory protocol is sensitive to a global amnesic syndrome.

Criterion validity can also be addressed by examining the ability of the IAP memory protocol to predict memory outcome. Unfortunately, studies examining the criterion validity of the IAP memory protocol are confounded in that many centers exclude patients from surgery on the basis of the IAP memory results. Furthermore, several centers do not routinely have all epilepsy surgery candidates complete an IAP evaluation. Thus, there are multiple potential sources of bias in the published studies. The ultimate test of the IAP's ability to predict memory outcome has not been reported. This would involve completing IAP memory evaluations on a consecutive series of temporal lobectomy surgical candidates. All patients would proceed to surgery regardless of the results of the IAP. Such a study would permit an
accurate characterization of the true sensitivity and specificity of the IAP memory test in identifying postoperative memory outcome. For obvious reasons, such a study is viewed as unethical by many and is unlikely to ever be undertaken.

Despite the absence of definitive studies, the predictive validity of the IAP memory evaluation has some indirect support. Unilateral temporal lobectomy has resulted in a profound, irreversible amnesia in two reported cases. These devastating outcomes were predicted on the basis of the IAP memory evaluation and provide examples of true positive cases (27,28). These reports must be contrasted with Barr’s (29) case report of a patient who “passed” the memory protocol following ipsilateral injection and went on to present with a transient global amnesia following temporal lobectomy.

A number of published studies have examined the utility of the IAP memory protocol in predicting postoperative memory outcome. These studies will be reviewed in rough chronological order. The literature highlights the changes evident over time in reliance on the functional reserve versus functional adequacy models to a model that encompasses both models. In addition, these data indicate that the ability of the IAP memory protocol to predict postoperative memory is dependent on a number of variables including choice of predictor variable (i.e., ipsilateral, contralateral, or asymmetry memory score), side of surgery, and age at initial injury.

In 1990, Loring et al. (30) reported on a series of 10 patients who underwent unilateral temporal lobectomy despite failing the IAP memory evaluation with ipsilateral injection (i.e., testing contralateral memory function). None of the patients presented with a postoperative amnesia, although material-specific declines in memory were apparent. These data challenged the traditional functional reserve model. Rausch and Langfitt also found very limited support for ipsilateral injection IAP memory scores in predicting postoperative memory outcome (31). Wyllie et al. (32) demonstrated that ipsilateral injection IAP memory scores did not predict postoperative memory outcome. However, their data suggested that a comparative score, taking into account the memory scores following both the ipsilateral and contralateral injections, demonstrated potentially greater clinical utility. Loring et al. (33) reported similar, more robust, findings in their use of a memory asymmetry score that incorporated data from both the ipsilateral and contralateral injections together. Interestingly, neither ipsilateral nor contralateral injection memory scores alone predicted postoperative memory in their sample.

In contrast, studies published slightly later documented the predictive validity of the contralateral injection memory score in predicting memory outcome (e.g., 29,34,35). For example, Kneebone et al. (34) demonstrated significantly greater postoperative verbal memory deficits in patients who “passed” their contralateral injection IAP memory test (indicative of relatively well preserved ipsilateral memory function). These findings were evident whether the memory score was used as a dichotomous variable or a continuous variable. Patients with higher contralateral injection IAP memory scores showed the greatest decline in verbal memory following left temporal lobectomy. These data have largely been interpreted as consistent with the functional adequacy model. Similar findings in support of the functional adequacy model are lacking in patients who have undergone nondominant temporal lobectomy.

There are also more recent data in favor of the traditional functional reserve model, particularly in patients with evidence of early injury or ipsilateral mesial temporal sclerosis. Jokeit et al. (36) found right hemisphere IAP memory performance predicted postoperative memory outcome in patients with left (dominant)
temporal lobe epilepsy. The authors also found that age of first risk was a significant predictor of memory decline following surgery when IAP results were not entered into the prediction equation. Patients who sustained temporal lobe damage at an early age had a better memory prognosis than those who suffered temporal lobe damage later in life. They used these data to hypothesize that transfer of memory function to the right hemisphere can occur in some patients with dominant (left) temporal lobe seizures and that the ability to transfer these functions depends on the age of the patient at the time of the initial injury. These findings were very similar to those later reported by Bell et al. (37) who found that the right IAP memory score was predictive of postoperative memory in patients with left (dominant) temporal lobe epilepsy with evidence of hippocampal sclerosis or with an early age of seizure onset. Chiaravalloti and Glosser’s data also provided support for the functional reserve model. They found that the IAP memory score following ipsilateral injection (reflecting the functional ability of the contralateral temporal lobe) best predicted postoperative verbal memory (38). Finally, a recent study by Sabsevitz et al. (39) provided support for the independent contribution of both the ipsilateral and contralateral IAP scores in predicting postoperative memory following left (dominant) temporal lobectomy.

Lineweaver et al. (40) recently reported some preliminary findings of an ongoing multivariate study designed to examine the utility of a variety of preoperative variables to predict postoperative memory outcome. Their results supported both the functional reserve and functional adequacy models and demonstrated that the IAP memory scores contributed unique and significant information in predicting postoperative memory function. Declines in verbal memory were associated with the presence of hippocampal atrophy in the hemisphere contralateral to the side of resection and poor performance on the IAP after ipsilateral injection (reflecting poor contralateral memory function). These findings support the functional reserve model. However, both the functional reserve and functional adequacy models assisted in predicting visual memory outcome. Memory scores on the IAP following ipsilateral injection (measuring contralateral memory function) contributed to the prediction of visual memory outcome (in support of the functional reserve model). However, the strongest predictors of visual memory outcome were baseline visual memory scores, with better preoperative visual memory scores associated with greater declines following surgery (in support of the functiona adequacy model).

In contrast to Lineweaver et al.’s data, Chelune and Najm (41) found overwhelming support for the functional adequacy model in their multivariate study assessing the utility of multiple preoperative variables in predicting postoperative memory outcome. Their data revealed that side of surgery, extent of hippocampal volume loss, and baseline neuropsychological function all provided unique information regarding the prediction of postoperative memory. Interestingly, IAP memory scores did not significantly add to these variables in predicting memory following surgery. Stroup et al. (42) completed a similar multivariate study. In their study, the ipsilateral IAP memory score (following contralateral injection) contributed additional unique information to predicting postoperative memory. It is likely that the differences evident in these multivariate studies reflect differences in the IAP protocols and neuropsychological measures used. Larger, more definitive studies are needed which can control for a variety of potentially important moderating variables (e.g., age of initial injury) to better ascertain the unique contribution of the IAP memory protocol in predicting postoperative memory.
CONCLUSION

The IAP memory protocol was developed to help identify patients at risk of global amnesia following unilateral temporal lobectomy. Over time, the emphasis on predicting the very rare probability of a global amnesia has shifted toward predicting memory loss along a continuum. The original test was based on a number of underlying assumptions, including the importance of the functional reserve of the contralateral hemisphere in predicting postoperative memory. The functional reserve model has been challenged, and there are many studies that support the functional adequacy model that asserts that postoperative memory function is best predicted by assessing the functional integrity of the tissue to be resected. More recent data suggest that components of both models may be accurate, but that important patient variables need to be considered in making these predictions. There are significant challenges to obtaining reliable data with the IAP. Despite this, there are a number of published studies supporting the convergent, and to a limited extent, criterion validity of the IAP memory protocol. Multivariate regression studies have found that the IAP memory results provide unique information that can assist in predicting memory outcome following surgery. What has not been addressed is whether the addition in predictive power the IAP provides justifies the medical risks and financial costs associated with the procedure.

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Chapter IV-11b: The Wada Test Is a Useful Predictor of Memory Outcome

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Before any discussion of whether the Wada test is a useful predictor of memory outcome, particularly in patients undergoing anterior temporal lobectomy, a few comments about the test itself are necessary. Unlike formal neuropsychological tests, which are standardized and administered with explicit instructions and scoring criteria, the Wada test is better conceptualized as a method or technique. Although
the overall application of hemispheric anesthesia using a short-acting barbiturate remains fairly constant across centers, various methodological differences in the approach to Wada testing make it difficult to generalize results from one Wada memory procedure to another, particularly when significant technical differences exist (e.g., dosing, stimulus material, memory paradigm, etc.). Similar outcomes and findings with a different Wada method will attest to the robustness of any particular findings; however, the absence of replication with alternative Wada procedures may simply reflect methodologic differences between approaches.

There are several issues implicitly raised by asking if the Wada test is a useful predictor of memory outcome. The first is whether the Wada test by itself can predict memory decline, and the second, which is probably the issue of greater concern, is whether Wada memory provides unique information regarding memory outcome. These questions, of course, are impossible to completely answer from a statistical and methodological standpoint since a large series of patients would need to undergo surgery without respect to their Wada memory results. To the extent that centers use Wada memory results as part of their preoperative evaluation, the predictor and dependent variables are no longer independent, and patients may be excluded or have their surgery modified based upon their Wada memory results. To the extent that a center discounts the usefulness of Wada memory data, the Wada test is probably not performed on anything approaching a consecutive patient series.

The Wada memory procedure that we developed at the Medical College of Georgia (MCG) relies on the presentation of eight real objects for approximately four to eight seconds each beginning 45 seconds following injection of 100 mg of sodium amobarbital (1,2). Our memory measure is obtained by recognition testing after return to baseline and at least 10 minutes postinjection in which memory objects are individually presented in a semirandom sequence. The eight targets are interspersed with 16 foils and are individually presented; the subject responds “yes” or “no” to indicate if each object had been previously shown. One-half the number of false positives is subtracted from the total correct to control for response bias and guessing.

This approach to Wada memory testing has been successful, and has predicted amnesia when other measures including baseline neuropsychological memory material-specific asymmetry did not (3). This case was a 27-year-old mixed-handed male who had an uncomplicated febrile seizure at nine months with recurrent seizures beginning around age five years. He had impaired verbal memory but normal visual spatial memory; because the Wada demonstrated complete right hemisphere language dominance, this pattern was considered to be consistent with right temporal impairment. Magnetic resonance imaging (MRI) scans were normal and revealed no hippocampal asymmetry. Intracranial and strip electrode recording from different institutions suggested right temporal seizure onset. At the time when this patient was tested, our Wada protocol also assessed memory for material presented several minutes into the procedure, and the patient recognized 3/5 items following both left and right injections. He underwent a right anterior temporal lobectomy at a different institution, and became amnesic with little memory improvement over time. In addition to demonstrating a relationship between a reversed pattern of Wada memory asymmetry that indicated a risk for postoperative amnesia, this case also illustrates the risk of using a Wada memory results from an outside institution with a different procedure when assessing postoperative memory risk. The early object memory performance in this patient was discounted since it was not common at the time to test memory for material
presented soon after drug injection (c. 1989), and the late item memory performance (3/5 bilaterally) suggested no unusual memory risk.

The other case that we present was evaluated more recently (c. 2000), and was a 21-year-old right-handed male who had an uncomplicated febrile seizure at nine months and developed recurrent seizures at seven years of age (4). MRI revealed left medial hippocampal sclerosis and ictal/interictal EEGs indicated clear left temporal lobe seizure onset. On baseline neuropsychological testing, he obtained superior verbal memory and average visual memory. Following left hemisphere injection, he obtained a corrected Wada memory score of 7.5/8 and following right hemisphere injection, he obtained an 8/8 Wada memory score. Thus, the clinical history and seizure patterns suggested no memory risk although the Wada scores and neuropsychological testing did. The patient had dropped out of college due to increasing seizure frequency and subsequently underwent left anterior temporal lobectomy. Postoperatively, his delayed verbal memory index on the WMS-III declined from 124 to 108 at one-year follow-up, and his Selective Reminding CLTR score declined from 53/72 to 26/72. Although he had much greater difficulty with his schoolwork, he was seizure-free with an improvement in his QOLIE score from $T = 47$ (average) to $T = 61$ (above average) and was apparently enjoying his college experience to a greater degree despite being more challenged academically due to his memory difficulty.

The prediction of no postoperative risk to recent memory, akin to proving the null hypothesis, cannot be statistically answered. In our experience, we have not had patients “pass” the Wada memory component yet develop a persistent amnesia following anterior temporal lobectomy. Wada results are interpreted within the context of the entire preoperative workup findings and no fixed pass or fail criterion is used. They may assume more or less importance in the decision-making process depending on the results from other tests and established clinical risk factors for memory decline. In this framework, we consider the Wada results to suggest no unusual risk, moderate risk, or significant risk. Significant risk may result in a decision to either not perform surgery or to modify the surgical procedure (e.g., temporal tip resection sparing hippocampus).

The MCG Wada memory protocol has been validated using a variety of approaches by demonstrating a relationship to hippocampal volumes, seizure onset laterality, prediction of memory decline following language dominant temporal lobectomy, and even seizure outcome (5–8). In addition, Wada testing provides predicative value about postoperative memory decline that is not simply redundant with other behavioral measures such as neuropsychological testing (9,10). It is largely due to the different validation studies that we have performed on our Wada procedure that our approach to Wada testing was adopted by the multicenter trial examining outcomes following anterior temporal lobectomy (ERSET Study).

There is clearly some inherent test–retest variability with Wada memory results, and we will typically repeat Wada testing if we get a pattern of Wada results that is inconsistent with other studies. We consider Wada memory results particularly helpful in the context of left temporal seizure onset patients with hippocampal atrophy. Patients with normal hippocampal volumes can be expected to display memory decline following language dominant resection (11,12). It is those patients who have presumed hippocampal sclerosis, but in whom the temporal lobe region retains significant functional capacity, that the Wada memory test and neuropsychological memory testing provide the greatest independent information regarding memory outcome.
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INTRODUCTION

In answering the question of predicting memory loss after surgery, one must distinguish between global amnesia and material-specific memory. The reason for the distinction between these two types of memory is because the answers to them are very different.

GLOBAL AMNESTIC SYNDROME

The original purpose of the Wada test with regard to memory was in fact to presage global amnestic losses in memory rather than material specific memory losses (1). That it is successful in this context has been demonstrated with an occasional exception (2–4). In 956 Wada procedures done by the author of this chapter using a recall memory paradigm with testing during drug presence (“Seattle procedure”), there has never been even one case of global amnestic syndrome after surgery without the Wada test clearly warning of this possibility (5). The clear warnings included dramatic failures of more than one type of memory that could hardly be missed. Therefore, it appears that the Wada test is able to presage such losses, at least in the majority of cases.

MATERIAL-SPECIFIC MEMORY LOSSES

The second type of memory pertains to material-specific memory loss, and especially with regard to verbal memory when one is operating on the same side as speech. Memory losses of this type are often very important, even if not truly devastating. This is a far more common problem than global amnestic loss, and, in the experience of the author, it is this type of loss that represents the type of loss where there is the greatest disagreement.

The controversy about whether or not the Wada test is a useful predictor of memory change in this context is best answered by a review of the world’s literature on this topic, and this is provided in Table 1. A review of the table reveals that there was some positive finding reported between Wada memory scores and changes in
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<th>Author(s), date(s) (Ref.)</th>
<th>Patients studied</th>
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<td>Bell et al., 2000 (6)</td>
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<td>Chelune et al., 1993; 1995 (7,8)</td>
<td>63 LT</td>
<td>WMS-R</td>
<td>Cleveland Clinic procedure</td>
<td>Changes in verbal memory related to the IAP score arising from the injection &lt;em&gt;contralateral&lt;/em&gt; to the EEG focus</td>
<td>Baseline memory and IAP memory simultaneously made predictions of memory changes after surgery on the left</td>
</tr>
<tr>
<td>Chelune and Najm, 2000 (9)</td>
<td>39 LT, 33 RT</td>
<td>WMS-R Verbal Memory Index with reliable change criteria for loss</td>
<td>Cleveland Clinic procedure</td>
<td>Wada memory variables (% recall after ipsilateral and contralateral injections) not evaluated alone in relation to verbal memory loss</td>
<td>Multivariate procedures showed that (1) side of surgery, (2) hippocampal volume ratio, and (3) baseline verbal memory all contributed to a prediction of memory loss. Age, age at seizure onset, sex, and both Wada variables did not significantly contribute to the predictive equation</td>
</tr>
<tr>
<td>Chiaravalloti and Glosser, 2001 (10)</td>
<td>42 right and 28 left</td>
<td>CVLT, Graduate Hospital Facial Memory Test</td>
<td>Glosser et al. (1995)</td>
<td>Asymmetry and IAP injection &lt;em&gt;ipsilateral&lt;/em&gt; to the EEG focus related to changes on the CVLT</td>
<td>Not done</td>
</tr>
<tr>
<td>Dodrill and Ojemann, 1997 (5)</td>
<td>96 left and 76 right cases</td>
<td>WMS (I)</td>
<td>Three different IAP procedures</td>
<td>Change in memory related to Seattle procedure only and to injection &lt;em&gt;ipsilateral&lt;/em&gt; to the EEG focus</td>
<td>Not done</td>
</tr>
<tr>
<td>Authors</td>
<td>Samples</td>
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<td>Findings</td>
<td>Notes</td>
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<tr>
<td>Dodrill et al., 2002 (11)</td>
<td>29 LT, 19 RT (no overlap in sample with Dodrill and Ojemann, 1997)</td>
<td>WMS (I) and AVLT—composite score</td>
<td>Three different IAP procedures</td>
<td>Changes in verbal memory related to the Seattle procedure only, and to the injection ipsilateral to the EEG focus</td>
<td>Baseline verbal memory, side of surgery, and unilateral hippocampal sclerosis on MRI all made independent predictions of memory change (Wada test dropped out)</td>
</tr>
<tr>
<td>Jokeit et al., 1997 (12)</td>
<td>27 left cases</td>
<td>WMS-R</td>
<td>German version with 20 items for recognition</td>
<td>IAP pictorial score contralateral to the focus correlated with verbal memory on one story but not on another story</td>
<td>15 variables simultaneously considered showed that level of preoperative memory was related with both stories, and the IAP simultaneously related with one story only</td>
</tr>
<tr>
<td>Kneebone et al., 1995 (13)</td>
<td>32 LT, 31 RT</td>
<td>WMS-R</td>
<td>Cleveland Clinic version</td>
<td>LT patients passing memory testing with injection contralateral to EEG focus had more verbal memory loss than those who failed</td>
<td>Not done</td>
</tr>
<tr>
<td>Loring et al., 1995 (14)</td>
<td>17 LT, 17 RT, all seizure-free one year postsurgery</td>
<td>WMS-R, selective reminding, complex figure</td>
<td>Use of eight solid objects with postdrug recognition testing with 16 foils and correction for guessing</td>
<td>LT patients only had verbal memory losses if ipsilateral and contralateral Wada memory scores were asymmetric</td>
<td>Not done</td>
</tr>
<tr>
<td>Loring et al., 2002 (15)</td>
<td>44 LT patients</td>
<td>WMS-R Logical Memory</td>
<td>Same as Loring (1995)</td>
<td>Asymmetry in Wada memory scores predicted memory change after surgery</td>
<td>Preoperative memory level and Wada asymmetry scores both contributed to changes in memory after surgery</td>
</tr>
<tr>
<td>Ojemann and Dodrill, 1987 (16)</td>
<td>20 LT</td>
<td>WMS (I)</td>
<td>Seattle procedure (Dodrill and Ojemann, 1997)</td>
<td>No significant relationship between Wada scores and memory change</td>
<td>Preoperative verbal memory level was related to loss with higher preoperative memory</td>
</tr>
</tbody>
</table>
Table 1  A Comparison of Studies That Report Data on Changes in Material-Specific Memory After Surgery as Related to the Wada Test (Continued)

<table>
<thead>
<tr>
<th>Author(s), date(s) (Ref.)</th>
<th>Patients studied</th>
<th>Tests of memory</th>
<th>Wada procedure</th>
<th>Prediction of memory change after surgery using Wada test alone</th>
<th>Wada test with other procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rausch and Langfitt, 1991 (17)</td>
<td>11 LT, 12 RT</td>
<td>WMS (I)</td>
<td>Procedure with verbal, visual, and general memory items</td>
<td>Wada memory scores obtained with the injection ipsilateral to the EEG focus related to verbal memory change in LT patients only</td>
<td>Not done</td>
</tr>
<tr>
<td>Sabsevitz et al., 2001 (18)</td>
<td>21 LT</td>
<td>WMS-R, Selective Reminding</td>
<td>Loring et al. (1994)</td>
<td>Ipsilateral, contralateral, and asymmetric Wada scores related to SR but not to WMS; asymmetry strongest</td>
<td>Not done</td>
</tr>
<tr>
<td>Stroup et al., 2003 (19)</td>
<td>58 LT, 74 RT</td>
<td>CVLT, WMS-R with reliable change criteria for loss</td>
<td>Six solid objects and two pictured objects in a multiple choice recall/recognition paradigm</td>
<td>Wada results not evaluated alone in the prediction of memory loss</td>
<td>Strongest to weakest (but statistically significant) predictors: (1) side of surgery; (2) MRI; (3) delayed verbal memory; (4) Wada (score obtained contralateral to EEG focus); (5) immediate verbal memory</td>
</tr>
<tr>
<td>Wyllie et al. (20)</td>
<td>20L, 17 R</td>
<td>WMS-R</td>
<td>Usual procedure but with an asymmetry memory score in addition to unilateral memory scores</td>
<td>No Wada memory score was significantly related to memory change</td>
<td>Not done</td>
</tr>
</tbody>
</table>

Abbreviations: WMS, Wada memory scores; EEG, electroencephalogram; LT, left temporal; RT, right temporal; SR, selective reminding.
memory after surgery in 12 of the 15 empirical studies found. However, the following observations were also made:

1. In 10 of the 12 studies where a positive finding was reported, only a single positive relationship was found even though several Wada variables and several memory variables had typically been evaluated. In most instances, the positive findings were not clearly beyond those expected by chance.

2. Groups with EEG foci on the right never showed a change in memory after surgery related to a Wada variable.

3. No visual-spatial measure was ever shown to be related to a Wada measure. The only exception was Jokeit et al. (12), but this finding appeared to be the product of chance because of a large number of predictors and a small number of subjects.

4. Regarding the lateralization of the Wada memory variables, there is little consensus with the important variable found to be the injection contralateral to the surgery in four studies, ipsilateral in four studies, asymmetry between the two injections in two studies, and a combination of more than one of these possibilities in two studies. In the remaining three investigations, no relationship between any Wada score and memory change could be demonstrated. Thus, while a number of studies report a relationship between the Wada and memory change after surgery, it is evident that consensus is lacking even as to which injection(s) provide scores that will predict memory change.

5. When the relative potency of the Wada variables and other variables were compared in the prediction of memory change after surgery, the Wada variables were routinely less potent than other variables. In just three papers did the Wada test demonstrate any predictive capability in the presence of even one other predictive variable, and in each of these cases the Wada variables were secondary in predictive power to other non-invasively obtained variables, especially including (i) preoperative memory level, (ii) MRI findings, and (iii) side of surgery (8,15,19). In the other four cases where a comparison had been made between the Wada test and one or more noninvasive variables, the Wada test was inferior to the noninvasive variables. In no case was it shown that the Wada test provided a practically useful enhancement of prediction of memory loss after surgery (such as even a 5% improvement in the identification of at risk patients) when the three noninvasive variables just mentioned were also used.

CONCLUSIONS

The evidence shows that the Wada test likely does help to presage the possibility of a global amnestic syndrome, and in that sense it is useful in the area of memory, even if that adverse outcome rarely occurs. However, in the much more common instance of material-specific memory loss after surgery, 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. Especially in view of the invasive nature of the Wada test, it is incumbent upon people taking other positions on this point to supply data supporting the contention that the Wada test provides additional useful predictive information when better and noninvasively obtained variables are readily available.
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Chapter IV-12
When Is the Wada Test Necessary for Temporal Lobectomy?

Chapter IV-12a: The Wada Test Is Needed for Temporal Lobectomies

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The intracarotid amobarbital (Wada) procedure, introduced into the preoperative evaluation for epilepsy surgery by Wada and Rasmussen (1) at the Montreal Neurological Institute during the early 1960s, has been effectively used over the years to determine speech/language dominance, as a measure of memory functioning, and as a predictor of outcome in terms of neurocognitive dysfunction and seizure relief (2–5). There have been numerous versions of this procedure and decision rules for its use. Some epilepsy centers only obtain Wadas in select cases, while others, like our own at the University of Washington (UW) Regional Epilepsy Center, continue to complete this procedure with virtually all patients undergoing epilepsy surgery. 

Deciding whether to employ the Wada procedure essentially boils down to a risk–benefit analysis, with two primary objections being put forth by those individuals who have opted to limit or eliminate its use. These objections include: (i) the belief that complications associated with neuroangiography outweigh the information that can be gained by the procedure, or (ii) the belief that equivalent information can be obtained through less invasive techniques. The risks associated with neuroangiography

For a description of the Wada procedure used at the University of Washington, please see: Dodrill CB, Ojemann GA. An exploratory comparison of three methods of memory assessment with the intracarotid amobarbital procedure. Brain Cogn 1997; 33:310-323.
include the complications that are associated with any invasive medical procedure (e.g., infection, discomfort), bleeding associated with the site of catheter insertion, and the possibility of stroke or arterial dissection. Traditionally, serious complications have been estimated to occur in less than one percent of all Wada cases (6). However, despite this small risk, one would opt to forego the Wada if it did not provide relevant information that could not be obtained in a less invasive fashion. In this regard, some have proposed that certain surgical procedures pose little threat to speech/language functioning or verbal memory (7). For example, some epilepsy centers would not complete the Wada procedure with right-handed patients who are undergoing right temporal lobectomy, as they would assume that atypical speech in such individuals is a statistical rarity. Others have argued against the continued use of the Wada procedure, suggesting that equivalent information can be obtained through noninvasive methods [e.g., functional magnetic resonance imaging (fMRI), functional transcranial doppler (fTCD) ultrasonography] (8–10).

We believe that our own Wada data strongly support the completion of this procedure for both cerebral hemispheres in all presurgical temporal lobectomy patients who are not at increased risk of complication from undergoing neuroangiography because of other health factors. Based on the speech lateralization results of nearly 800 Wadas completed in our laboratory, atypical speech occurs more frequently in an epilepsy population than it is predicted to occur in a healthy adult population (11). Although less than 1% of all healthy right-handers are thought to have right-sided speech lateralization, nearly 7% of our epilepsy patients who are right-handed and right-footed exhibited atypical speech lateralization. This number rises if you include patients who are right-handed but left-footed, the latter variable representing a factor that most epilepsy centers do not even measure. Of note, atypical speech is observed in approximately 4% of patients who are right dominant for both handedness and footedness that are undergoing right-hemispheric surgery (11,12). Although this group is the least likely to demonstrate atypical speech of all of the permutations for side of surgery and handedness/footedness variations, this rate is still more than four times greater than the risk of serious complication associated with the Wada. Therefore, it appears much more likely that one will encounter atypical speech than a serious adverse complication related to the Wada, even in surgical situations that many epilepsy centers would consider to pose little threat to language. Feedback from our neurosurgeons suggests that the false positive rate in these atypical speech cases is rare, based upon evidence from electrocorticography and the occurrence of acute postoperative language dysfunction (G. A. Ojemann, personal communication, 2003).

The second major reason that some epilepsy centers omit the Wada from their presurgical workup involves the belief that the same information can be obtained using less invasive techniques. While noninvasive procedures such as fMRI and fTCD have great potential for complementing or perhaps even supplanting the Wada procedure, neither has been sufficiently developed to date to allow for routine clinical implementation. Both of these procedures have shown promise in their ability to lateralize language functions, yet not all studies have shown complete concordance with the Wada procedure and stimulation mapping (8–10,13). Perhaps of greater importance, memory paradigms that reliably activate temporal lobe structures are still in development with fMRI and are completely lacking with fTCD. Several recent fMRI studies have reported consistent activation of mesial temporal and frontal structures (14,15). However, it can be difficult to interpret activation patterns, as fMRI defines volumes of brain that show changes in activity correlated with a
specified task but does not define those regions whose activity is necessary for this
task. In addition, although reliable memory paradigms will undoubtedly be devel-
oped with fMRI, it has been pointed out that there is a fundamental difference
between the methodologies of functional imaging and the Wada. Functional imaging
represents an activation paradigm while the Wada is an inactivation technique. Func-
tional imaging highlights which brain structures are necessary to perform a given
cognitive task while the Wada demonstrates whether or not a specific function can
be supported when part of the brain is inactivated. In this sense, the Wada seems
to more accurately model the impact of resective surgery. While we hope that the
Wada will someday be replaced by some of these promising functional techniques,
it is possible that these tests contribute information that is complementary rather than
redundant. Once reliable activation paradigms are available, research will be required
to determine their clinical relevance. This would include determining the relationship
between these alternative, non-invasive procedures and the Wada, pre- and postsur-
gical neurocognitive scores, and outcome variables.

Finally, the Wada procedure contributes independent information regarding
memory functioning that can be used to assess risk of postoperative memory decline,
provides further confirmation of presumed seizure lateralization in cases where more
invasive procedures are being considered (e.g., intracranial electrodes), and can be of
use in predicting postoperative seizure occurrence (5,16–20). While the Wada mem-
ory test has been shown to contribute only a small percentage of unique variance
when compared to other variables (e.g., age of seizure onset, side of speech) used

to predict risk of memory decline following epilepsy surgery, it can prove useful in
the individual case (7,21). For example, we quite often obtain Wada findings that
lead to changes in surgical planning, with results sometimes even contributing to
the decision not to pursue surgery. Overall, we currently suggest that all patients
receive bilateral Wada studies for the determination of language representation
unless contraindicated on clinical grounds (e.g., some individuals may be at greater
risk of experiencing an adverse event secondary to neuroangiography due to the
presence of significant vascular disease).

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Chapter IV-12b: The Wada Test May Not Always Be Needed Prior to Mesial Temporal Resection

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The intracarotid amobarbital procedure (IAP) or “Wada test” is considered the “gold standard” for the presurgical workup of patients considering resective surgery for treatment of epilepsy. The primary use of the Wada test currently is to (i) determine speech and language lateralization, (ii) predict possible memory deficit, (iii) obtain supportive evidence of localization of seizure focus, and (iv) predict seizure outcome following surgery (1). However, findings from studies examining the utility, reliability, and validity of the Wada test vary. Furthermore, the Wada test is costly and an invasive procedure with potential morbidity. Despite these shortcomings it is nearly universally applied by epilepsy centers throughout the world (2). Given the limitations and risks associated with this procedure, it may not be clinically necessary for the Wada test to be included in the presurgical workup of all patients. In this chapter, we will suggest that the Wada test may not be necessary for patients who are right-handed, surface EEG and clinical seminology indicate a right mesial temporal epileptogenic region, have no evidence of an early left hemisphere insult, and have clear magnetic resonance imaging (MRI) evidence of right mesial temporal sclerosis.

A critical factor for the reliability of the Wada test is the variability associated with the procedure itself from center to center. Other than the vessel selected for injecting the drug there is little that is standard about the Wada test (1). There is significant variability in the procedures used, type of stimuli, timing of stimuli, drug delivery, method of determining drug effect, and criteria for “passing” and “failing.” All of these factors severely limit the ability for one to compare findings from various centers and make conclusions about the efficacy of the Wada test.

In order for a test to be valid it first has to be reliable. There are reports in the literature of patients who have failed the Wada test and were retested and subsequently passed the second procedure (3). However, most of these studies do not adequately test the reliability of the procedure since repeat Wada testing is typically only done when results are atypical, thought to be due to technical difficulties, or the patient becomes obtunded. Despite the previously mentioned limitations of the Wada test, it is an extremely effective test for language lateralization (2).

It has been generally accepted that patients with evidence of early left hemisphere damage have a greater probability of right hemisphere language dominance or bilateral language organization compared to other epilepsy candidates or the general population. In a large series of 396 patients, Rasmussen and Milner in 1977 (4) reported that among patients with no clinical evidence of early damage 96% were left hemisphere dominant. In a more recent series of 103 patients undergoing Wada testing...
as part of their diagnostic workup for epilepsy surgery, only two patients showed exclusive right hemisphere language dominance (5). The authors concluded that language restricted just to the right hemisphere is rare, and previous reports may be due to an artifact of dichotomizing a continuous variable. Furthermore, among right-handed individuals with right temporal lobe epilepsy (TLE) characterized by right mesial temporal sclerosis postoperative language disturbance is rarely reported.

Although the Wada test is a robust test for language lateralization, its reliability for predicting postoperative severe amnesia is not well established. Furthermore, the false-positive (memory failure) rate is high. Novelly and Williamson (3) reported that 21 of 25 patients who failed the Wada test went on to pass repeat Wada testing using lowered drug dosage but otherwise identical procedures. In addition, of the 21 patients who went on to have surgery, none of them experienced postsurgical memory impairment. It is difficult to determine the validity of the Wada test in predicting those at risk for an amnesic syndrome when the relatively high percentage rate of failures is contradictory to the rare incidence of amnesia following unilateral anterior temporal lobectomy (ATL). The utility and accuracy of any diagnostic test is determined by its positive and negative predictive value, sensitivity, and specificity (6). Furthermore, the predictive value is going to be affected by the prevalence of the phenomena in question. Thus, if overall prevalence rates are low (which is the case of global amnesia following unilateral ATL) most positive tests will be false positives (fail their Wada test but do not show postoperative amnesia). Given the low base rate of global amnesia and poor predictive value of the Wada test concerning global amnesia, in addition to the general question regarding the utility, reliability and validity of the procedure, it does not seem clinically indicated to use the Wada test purely to predict the presence or absence of global amnesia following ATL.

It may be rare to observe global amnesia following ATL but more mild memory changes are not uncommon following a temporal lobectomy. The material-specific memory hypothesis suggests that the left mesial temporal lobe is important for auditory–verbal memory, and similar regions in the right hemisphere are utilized for visual–spatial memory (7). Although studies examining left hippocampal/mesial temporal lobe integrity have consistently showed that this area is crucial for verbal memory functioning, research has not reliably shown a relationship between visual–spatial memory and the right hippocampal system (8,9). Verbal memory performance has been found to be associated with left hippocampal volume; however, findings regarding right hippocampal volume and visual–spatial memory are inconsistent (9,10). Studies investigating the role of the Wada test in predicting material-specific memory changes postsurgery often find a relationship between verbal memory performance on the Wada test and postsurgical outcome in left ATL patients, but a similar association between visual–spatial memory scores on the Wada test and outcome following a right ATL has not been consistently demonstrated (11,12). Kneebone et al. (12) suggested that the lack of a relationship between Wada test performance and post-surgical memory changes in right TLE patients may be because of (i) the simplicity and weak construct validity of many visual–spatial memory tests, (ii) the possible confounding role of verbal mediation in visual–spatial memory tasks, (iii) functional correlates of the right hemisphere may not be as closely tied to its anatomic substrates as those in the left hemisphere, and (iv) possible functional reorganization of the right hemisphere. In summary, the research and clinical observations to date do not show a significant relationship between visual–spatial memory performance and right hippocampal integrity. Furthermore, studies have not consistently demonstrated a relationship between performance on the Wada test and memory changes following
a right ATL. Therefore, it does not appear to be clinically indicated to conduct Wada testing on a patient with right mesial temporal seizure onset for the purpose of predicting possible post-ATL visual–spatial memory deficits.

Previously, it was mentioned that the Wada test is sometimes utilized by epilepsy centers to provide confirmatory evidence of seizure focus and to predict seizure outcome following surgery. Although the use of the Wada test to determine language lateralization and to predict post-operative memory deficits is well established, these later uses are still somewhat investigational (1). Given the relationship found between memory performance on the Wada test and left hippocampal pathology (e.g., volume or cell count) many investigators use the results from Wada testing as supportive evidence of seizure focus (13–15). Perrine et al. (15) were able to correctly classify approximately 70% of seizure focus lateralization based on Wada testing memory performance. Related to the Wada test’s ability to correctly predict seizure lateralization is its usefulness in predicting seizure relief following ATL. Although in some cases the Wada test may provide confirmatory lateralizing information, it is unlikely in patients with clear right mesial temporal epilepsy that the results from the Wada test would be more predictive than MRI findings suggesting right hippocampal atrophy and confirmatory surface EEG. However, this is an empirical question that to date has not been addressed.

In summary, although the Wada test is currently used to predict language lateralization and postsurgical memory outcome at most major epilepsy centers the reliability and validity of the procedure, particularly in terms of global amnesia and visual memory outcome is weak. Furthermore, the procedure carries with it significant morbidity and cost. Wada testing is one of the most expensive diagnostic tests in the presurgical evaluation. Substantial research and clinical evidence suggests that the Wada test is clinical indicated in patients with a left or bilateral hemisphere focus, or when other diagnostic tools yield unclear or contradictory information. Despite the questionable reliability and validity associated with the procedure, and the unclear relationship between Wada testing memory performance and visual–spatial deficits following right ATL, the Wada test is considered the “gold standard” even for patients with convincing right mesial temporal lobe epilepsy in most surgical epilepsy centers. However, the risks and costs associated with Wada testing may outweigh the usefulness of the procedure in patients with clear MRI evidence of right mesial temporal sclerosis, a seizure seminology consistent with a right temporal seizure focus, right-hand dominance and no evidence of an early left hemisphere lesion. Furthermore, the Wada test may not provide any additional diagnostic or predictive information in this subset of epilepsy patients. Future studies need to empirically investigate the utility and usefulness of the Wada test in individuals with unequivocal right mesial temporal lobe epilepsy.

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Section V
Neurophysiological Studies in the Epilepsy Presurgical Evaluation

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The goal of the presurgical evaluation of a patient with medically refractory epilepsy is to determine if the subject has an epileptogenic focus that can be safely resected without causing unacceptable neurological deficits. As functional measures, neurophysiological studies are indispensable elements in formulating this determination. This review examines the various neurophysiological studies, emphasizing the role each may play in the context of the goal of presurgical assessment. The discussion includes summaries of the noninvasive and invasive methods that are now routinely employed to define the epileptogenic zone, and a consideration of extraoperative neurophysiological techniques used in functional brain mapping of surgical candidates.

STANDARD ELECTROENCEPHALOGRAPHY

Methodology

The electroencephalogram (EEG) has been available to clinicians for over 70 years, and to this day remains the single most important laboratory tool in evaluating patients with epilepsy, or suspected epilepsy (1). Findings from routine EEG have formed the basis of classifying seizures. In most EEG laboratories, subjects are recorded for 30 to 45 minutes. Typically, up to 21 metallic electrodes, usually made of gold, tin, or silver–silver chloride, are applied to the scalp with a conductive gel in locations that are in accordance with the international 10:10 system (2). Electrodes to monitor eye movements and electrocardiogram are also utilized. Minute electrical signals are conducted from the subject to EEG machine through the applied electrodes, where the signals are subtracted, amplified, and filtered. Electrical frequencies between 0.1 and 70 Hz are analyzed in most commercially available alternating current EEG machines.

The specific EEG patterns that correlate with the diagnosis of epilepsy are spike and sharp wave discharges. It is the distribution and morphology of these epileptiform discharges (EDs) that have allowed for the current dichotomous
classification scheme of localization-related and generalized seizures and epilepsy syndromes. An initial EEG will record EDs in about 50% of patients with proven epilepsy, and about 90% will show EDs after two or three recordings (3). However, even in unequivocal epilepsy, EDs are absent in a minority (about 5%) of subjects (4).

“Activation methods,” including hyperventilation, stroboscopic stimulation, eye-opening and closure, and sleep induction, are used in many laboratories to increase the yield of recording EDs (5). Nonepileptiform abnormalities, which may be focal or diffuse, may also be seen on the standard EEG.

**Significance**

From the viewpoint of identifying the epileptogenic zone, interictal findings on the standard EEG may at times provide important clues. When consistently observed on prolonged or serial recordings, exclusively unilateral, unifocal EDs on scalp EEG are highly predictive of seizure onset in that region in both temporal and extratemporal focal epilepsy (Figs. 1 and 2) (6–9). Particularly in regard to intractable frontal lobe epilepsy, the presence of unilateral frontal convexity EDs is highly predictive of ictal onsets (10). The fortuitous circumstance of unilateral, unifocal, interictal EDs is observed in 10% to 20% of potential surgical candidates. In other chapters of this textbook Cascino, Sazgar, and Henry debate the question as to whether ictal EEG recordings should be obtained for every person considered for epilepsy surgery, or whether in some instances the interictal EEG findings alone will suffice. There is evidence that there may be a subgroup of patients with temporal lobe epilepsy where ictal EEG recordings provide no additional information, and

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**Figure 1** Interictal spikes were observed exclusively over the right basal temporal regions in this subject with refractory temporal lobe epilepsy. Note phase reversals at Sp2. Scalp electrode placement and nomenclature followed standard 10–20 guidelines. **Source**: From Ref. 2.
do not affect postsurgical outcome, provided that the clinical, neuroimaging, and neuropsychological data are not discordant with the interictal EEG (11).

Nonepileptiform abnormalities in patients with epilepsy are rarely specific enough to be useful in identifying the epileptogenic region, with the possible exception of unilateral, temporal, intermittent, rhythmic delta activity, a finding that has been associated with the site of ictal onset (12,13).

Standard EEG is safe, relatively inexpensive, and routinely available. Evaluated in conjunction with other data, the interictal findings on occasion provide strong clues to the epileptogenic zone.

There is also convincing evidence that the standard EEG has an important role in the postsurgical evaluation, and should probably be included as a routine part of the patient follow-up evaluation. In particular, postoperative recordings may be very useful in assessing prognosis after surgery. Investigators have shown that after temporal lobectomy for intractable epilepsy, the presence of interictal EDs on the side of resection appears to be strongly associated with persistence of postoperative seizures (14,15). In subjects with preoperative independent bitemporal spikes, finding

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**Figure 2** In this subject with intractable frontal lobe epilepsy, interictal discharges were observed only over right frontopolar regions. Note the sharp waves at Fp2.
postoperative EDs on the side contralateral to the side of resection during non-rapid eye movement (NREM) sleep is one other factor that may portend an unfavorable outcome (16).

The standard EEG does have limitations. Because of brief recording times, clinical seizures are rarely recorded (except by chance), and unless consistent, unifocal EDs are observed, this technique can not be relied upon to yield unequivocal insight into the epileptogenic zone. The interictal EEG in epilepsy is frequently normal, or may demonstrate diffuse or nonspecific abnormalities, or the presence of bilateral or multifocal EDs.

LONG-TERM SCALP EEG-VIDEO MONITORING

Long-term scalp EEG-video monitoring (LTM) has two main purposes. The first function is diagnostic, and LTM is frequently used to evaluate patients when the nature of the presenting problem is uncertain. About 25% to 30% of patients referred to epilepsy centers for difficult epilepsy prove to have non-epileptic events (17,18). In still other instances, even when epilepsy is strongly suspected, LTM is often required to establish the epilepsy syndrome and to separate localization-related from generalized epilepsies (19). The second function of LTM is to define the epileptogenic region in the medically refractory localization-related epilepsies, and for the majority of subjects who are considered for epilepsy surgery, LTM is the cornerstone of the evaluation. The results of LTM are analyzed in conjunction with the clinical, neuro-imaging, and neuropsychological findings. Postsurgical outcomes are generally best when all the data are convergent (20–22).

Methodology

Analog or digital EEG-video recordings permit the documentation and synchronization of both the clinical and electrographic features of the epileptic seizure. The use of video cassette recorders provides a practical method for monitoring. Single or multiple cameras are used, and, along with the EEG, the data are stored on magnetic tape. Cameras that use infrared light can be used in darkened rooms. EEG electrodes are applied to the scalp in a manner and locations similar to that used during standard EEG. Collodion is used to improve the stability of scalp electrodes used during LTM.

The use of digital EEG-video monitoring allows for montage reformatting, application of quantitative techniques, automatic spike and seizure detection, and digital filtering. Computer-assisted monitoring is more efficient and eliminates the need for paper storage and data can be stored on computer disks.

The huge amount of information generated by hours or days of LTM requires some means of data reduction. This is usually accomplished by selecting clinical events that are reported by the patient, identified by nursing or hospital personnel, or signaled by automatic event-detection. The audiovisual and corresponding EEG data is then saved for off-line review, including EEG several minutes before, during, and several minutes after the seizure. During the analysis of data collected during LTM, clinical manifestations of patients’ seizures are carefully correlated with ictal EEG patterns. The times of onset of the first clinical and electrographic changes of each ictus are determined. Generally, a greater degree of confidence is placed on seizure localization when initial EEG changes precede initial clinical signs. One method of reducing the
interictal EEG, used at the University of Washington Regional Epilepsy Center includes saving 30 seconds of data every 5 minutes for off-line review.

At most centers, patients are hospitalized and studied continuously for consecutive days, while antiepileptic medications are tapered or withdrawn completely in order to efficiently record the subjects’ seizures. The number of seizures that need to be recorded varies from patient to patient, but most often a minimum of three to five clinical events are documented. Some individuals may find continuous hospitalization inconvenient or exceptionally uncomfortable, and for this reason outpatient LTM as been explored by some as an alternative mode to obtain ictal recordings. Several investigators report that there may be subset of patients for whom several days of outpatient LTM only can yield results comparable to inpatient evaluation (23,24).

In addition to simultaneous audiovisual and EEG recordings that follow routine 10–20 scalp electrode placement, many centers routinely implant sphenoidal electrodes in potential surgical candidates. Sphenoidal electrodes have been reported to detect basal-temporal discharges but whether sphenoidal electrodes offer a significant advantage over anterior-midtemporal scalp electrodes is debatable (25). Kanner and Binnie discuss this issue in other chapters of this book.

Scalp Ictal EEG Recordings

Complex partial or secondarily generalized tonic–clonic convulsions are usually accompanied by the onset of lateralized rhythmic discharges that are evolving over time in frequency, amplitude, and location. Rhythmic patterns in the theta range (3–7 Hz) are the most common initial ictal EEG manifestation of partial seizures (Fig. 3) (26). However, rhythmic patterns in the delta (1–3 Hz) or alpha (8–12 Hz) range, paroxysmal fast patterns (>13 Hz), repetitive spike discharges, focal or diffuse voltage attenuation (<10 μV), and focal arrhythmic patterns constitute other possible scalp ictal EEG correlates of focal seizures (27–29).

The presence of ictal EEG patterns that consist of rhythmic theta patterns is a well-recognized accompaniment for seizures of medial temporal lobe origin (26).

Figure 3  Ictal EEG patterns recorded from an individual whose interictal EEG is displayed in Figure 1. Note the rhythmic 5–7 Hz patterns that begin over the right basal temporal regions.
However, scalp ictal EEG recordings may also have important localizing value for seizures that originate in other regions as well. Surface EEG can localize in as many as 70% of cases, including the majority of patients with medial temporal, lateral frontal, and parietal lobe seizures, and can lateralize onsets in most subjects with lateral temporal lobe epilepsy (30). On the other hand, in subjects with medial frontal or occipital lobe seizures, the scalp EEG may frequently yield inconclusive or misleading results (30). In some series investigators have observed that the surface EEG may be accompanied by discrete focal changes at ictal onset in 10% to 70% of patients with neocortical epilepsy, even in occipital seizures, and therefore provides useful localizing information in these cases (31). The duration of discrete or regional initial ictal EEG changes is typically found to be shorter for the neocortical epilepsies, especially for frontal and parietal lobe seizures, than for medial temporal lobe seizures.

Beyond the role that surface ictal EEG patterns play in localization of seizure onset, the frequency, patterns of spread, and termination of these patterns may provide useful information regarding postoperative outcome. Focal beta (paroxysmal fast) discharges in the setting of frontal lobe seizures (seen in about 25% of cases) is highly associated with a good postoperative outcome in either lesional or non-lesional frontal lobe epilepsy (32). Ictal EEG patterns have been reported to be predictive of outcome following corpus callosotomy in adults (33). When the scalp ictal EEG in medial temporal lobe epilepsy demonstrates contralateral propagation, postsurgical outcome is usually worse than if ictal patterns remain lateralized to one side (34). Similarly, if ictal patterns continue on the side opposite the seizure origin, following termination of ictal activity on the side of origin, a poor outcome is predicted (35). The presence of unilateral postictal EEG delta patterns is often associated with side with the side of seizure onset in temporal lobe epilepsy (36).

In contrast to the information that scalp EEG usually provides in analyzing complex partial or secondarily generalized tonic–clonic convulsions, the majority of surface ictal recordings of simple partial seizures are not accompanied electrographic changes (37).

### Seizure Semiology

Clinical features of partial seizures vary greatly from one subject to the next. Specific signs clearly must represent origin and regional spread of ictal discharges in the brain. Most complex partial seizures last in duration less than two minutes, although from one subject to the next huge variation is possible, from ictal duration of a few seconds to many minutes (38). By definition, complex partial seizures are accompanied by some alteration in mental status, ranging from clouding of awareness or confusion to complete loss of consciousness.

At times clinical features of partial seizures may yield information that suggests regional localization or hemispheric lateralization. Temporal lobe seizures are frequently preceded or accompanied by an initial “aura” of subjective symptoms such as epigastric discomfort, feeling of déjà vu, or affective complaints such as fear, anxiety, or panic. This may then be followed a “stare,” then orofacial and extremity automatisms (e.g., chewing or mouthing movements, lip-smacking, eye-blinking, fumbling of the hands, rubbing) and changes in behavioral responsiveness. If the attack is accompanied by dystonic posturing of one upper extremity or hand, ictal origin from the contralateral side is possibility. Unilateral nose-rubbing has been suggested to lateralize ictal onset to one side in temporal lobe epilepsy. Vocalization or even formed words may accompany the ictus. If language is impaired following
a seizure for more than one or two minutes, the seizure may arise from the side of
language dominance. Unilateral clonic jerks suggest ictal origin from the opposite
cerebral hemisphere. Frontal lobe seizures have a tendency to be brief and repetitive,
and be associated with more elaborate or complex automatisms than those
usually observed during temporal lobe seizures. Occipital lobe seizures are frequently
accompanied by visual symptoms, and parietal lobe attacks, by unilateral sensory
complaints. Head-, eye-, or body-turning may occur during seizures that originate
from temporal or extratemporal regions.

Secondarily generalized tonic–clonic seizures may begin with initial clinical signs
and symptoms of subjects’ partial seizures, with the convulsive phase of the seizure
lasting usually one or two minutes. The convulsive phase may occasionally be “incom-
pletely” generalized, with tonic–clonic activity affecting one side more than the other.

In practice, the clinical signs and symptoms of partial seizures are so variable
from one subject to the next, and exhibit such overlap from different regions of
origin, that the usefulness of semiology, by itself, for purposes of localization is
a matter of considerable debate. Lachhwani, Kotagal, Cheng-Hakimian, and
Wilensky discuss the usefulness of seizure semiology in other chapters of this book.
However, careful consideration of both the clinical and EEG features frequently
permits differentiation of medial temporal from neocortical epilepsies, and the
lateralization of ictal onset in temporal lobe epilepsy (39,40).

**Intercital EEG During Scalp LTM**

Although the main function of scalp LTM is to document the electroclinical
manifestations of the patient’s seizures, the interictal EEG obtained during monitoring
may also provide valuable information. In many respects the utility and limitations
of the interictal LTM EEG is identical to that of the standard EEG. Though observed
in a minority of patients, exclusively unifocal interictal EDs are highly predictive of the
site of seizure origin (9,11,34). In other regards, in subjects with temporal lobe epilepsy
and normal magnetic resonance imaging (MRI), finding exclusively unilateral anterior
temporal interictal EDs during LTM that are concordant with ictal onsets predicts
excellent postsurgical outcome (41). When scalp LTM studies suggests that seizures
may be bitemporal in origin, a preponderance (>75%) of interictal EDs to one side
is one of several favorable lateralizing factors, indicating both that it is reasonable to
proceed with invasive monitoring, and that a good postsurgical outcome is possible
(42). The occurrence of EDs during sleep stages may also be important. Specifically,
unilateral EDs during REM sleep may be predictive of the site of seizure origin in
temporal lobe epilepsy (43). Other investigators have found that in refractory lesional
frontal lobe epilepsy, an absence of diffuse or generalized interictal discharges is a
favorable predictor of postoperative outcome (44).

**Scalp LTM: Summary**

Scalp LTM offers many advantages. Most importantly, a careful review of the of the
ictal events, including both clinical and EEG characteristics, analysis of the interictal
EEG, and correlating this data with the neuroimaging and neuropsychological
findings, will define the epileptogenic zone in at least 60% to 70% of medically refrac-
tory patients referred for epilepsy surgery. It is also noninvasive, resulting in a gen-
ernally safe procedure. The limitations of LTM include the need for hospitalization
(often for many days), consumption of resources, and expense. Finally, for some candidates, noninvasive studies alone will prove to be inadequate in defining the seizure origin, necessitating the need for invasive studies.

INVASIVE LTM

Rationale

The electrical properties of the tissues surrounding the brain (meninges, cerebrospinal fluid, skull, muscle, scalp, hair) are such that, in effect, these tissues function as a lowpass filter, and “smear” electrical signals generated by the cerebral cortex and propagated to the scalp (45). The resulting loss and reduction in amplitude of faster frequencies and reduction in spatial resolution of cortically generated electrical activity will mean that in some cases it is impossible to localize, or even lateralize, ictal onsets from scalp recordings. When this occurs it becomes necessary to bypass the tissue “barriers” surrounding the brain to obtain specific knowledge of the epileptogenic zone through direct ictal EEG recordings. These recordings are obtained either from the subdural or epidural spaces or from within the cerebral parenchyma. In other situations, if the data obtained from the noninvasive assessment are discordant (e.g., ictal EEG onsets suggest different location from MRI lesion), or if surface EEG recordings suggest that seizures arise independently from either cerebral hemisphere, invasive studies are necessary in order to pursue the possibility of surgical therapy.

The precise strategy of invasive LTM must be individualized for each surgical candidate, taking into account information obtained from the noninvasive assessment (46). In general terms, if the main clinical question to be answered is one of lateralization of seizure onsets, then depth or subdural strip electrodes are implanted bilaterally in homologous regions. Wyler, in Chapter V-14, discusses in more detail the relative merits and limitations of depth and strip electrodes monitoring (47). If localization of ictal origins is the main concern, then subdural grid electrodes are placed, so as to cover broad areas of the cerebral surface on one side. Often supplemental strip or depth electrodes are implanted on the side of the grid to obtain additional coverage. On occasion, invasive LTM will need to be a staged process, with the first stage consisting of bilateral strip or depth electrode recordings to solve the lateralization problem, followed later by subdural grid recordings to resolve the precise localization of the epileptogenic zone. In general, invasive studies are more likely to be performed in subjects with extratemporal than in temporal lobe epilepsies. At the University of Washington Regional Epilepsy Center, for example, in the decade 1993 to 2002, the majority of neocortical resections were based on the results of some form of invasive monitoring, while less than one-third of temporal resections were based on intracranial EEG recordings.

Methodology

Techniques of recording and analyzing data obtained from invasive LTM are in principle no different from that of scalp LTM. The data is reduced by audiovisual playback of clinical events reported by the subject, observed by medical or nursing personnel, or detected by computer methods. The interpreting physician carefully correlates these events with the electrographic changes, noting the onset of first clinical signs or symptoms in relation to the initial ictal EEG changes. The origin
and spread of ictal EEG patterns are documented. Regular, periodic samples of interictal EEG recordings are saved for off-line review.

Length of time of invasive recordings, as with scalp LTM, is individualized for every patient. Antiepileptic medications are withdrawn and several of the habitual seizures are recorded. For depth or subdural strip electrodes recordings patients can be monitored continuously for days or even weeks.

Subjects with subdural grid electrodes require a more limited recording time because of the greater risk of infection, and many neurosurgeons believe that grids should usually be removed 7 to 10 days after implantation.

**Depth Electrodes**

Because depth electrodes penetrate brain parenchyma, they are used to directly record from gray matter that is otherwise inaccessible by other means. The usage of this mode of invasive recording is necessarily restricted to certain regions, most commonly including amygdala, hippocampus, and cingulate gyrus (48). Recently, investigators have reported that, although neocortical regions are generally studied with subdural electrodes, there may be situations where the epileptogenic zone that is found in regions of focal lesions (e.g., cortical dysplasias) buried beneath the cortical surface, are more efficaciously studied with depth rather than subdural electrodes (49).

Commercially available electrodes have 4 to 12 contacts typically spaced 5–10 mm apart. Some modern electrodes are constructed of nichrome alloy materials to allow for MRI compatibility. Depth electrodes are inserted by the neurosurgeon through burr holes, the locations of which are dependent on the nature of the clinical problem for each individual patient. The electrode insertions follow standard stereotactic techniques to assure accurate placement (50).

As with other forms of scalp or invasive long-term monitoring, depth recordings are performed referentially, and can be reformatted and filtered as desired. Although depth recordings can yield excellent resolution of ictal onsets, a major limitation is limited spatial sampling (51). One can never be entirely certain that seizures actually originate from sites demonstrated by the invasive recordings. For this reason, in many centers where depth electrodes are employed, scalp recordings are also used simultaneously to corroborate the results obtained from depth recordings (stereoelectroencephalography).

Depth recordings do carry risk of complications. Intracerebral hemorrhage is the most serious and may occur in 1% to 4% of subjects (52). It is not known if depth electrodes carry definite, clinically relevant risks of functional impairment as a result of usage. As an alternative to reduce the morbidity associated with depth electrodes, some investigators have advocated the use of endoscopically placed temporal horn, intraventricular electrodes, in conjunction with subdural electrodes (53). The precise role of intraventricular monitoring in the presurgical assessment requires further evaluation and comparison with other methodologies.

**Subdural Strip and Grid Electrodes**

Less invasive than depth electrodes, strip and grid electrodes are placed in the subdural space. Commercially available electrodes are made of stainless steel or platinum and embedded in Silastic or Teflon material. The contacts are typically 4 mm in diameter, 0.7 mm thick, and placed 10 mm apart (center-to-center). Strip electrodes have 1 to 10 contacts on each strip, while grid electrodes may have up
to 64 in an $8 \times 8$ array. The precise number of contacts for the strips and the design and number of electrodes of the grid array is tailored for each individual patient.

The most common strategy for use of strip electrodes is to place these through burr holes bilaterally and symmetrically over the regions of interest. For example, in temporal lobe epilepsy, if the lateralization of onset of seizures is in question, strips are placed over both basal and lateral temporal regions. If there is concern that seizures may originate from either frontal or temporal lobes, bilateral strips may be placed over the convexity and inferior (orbitofrontal) surface of the frontal lobes as well over basal and lateral temporal lobe regions (Fig. 4).

Subdural grid placement requires a craniotomy for implantation. They are only used unilaterally, when there is no question concerning the lateralization of ictal onsets. Grid recordings have the distinct advantage of good spatial sampling, and are therefore indicated when the precise onset of seizures requires clear definition. Typically, grids are used in subjects with neocortical seizures, and are placed over the convexity of the hemisphere so as to cover portions of frontal, lateral temporal, parietal, or occipital cortex, the precise locations of which are determined by each patient's clinical problem (Fig. 5). Spatial coverage in some subjects may be enhanced

Figure 4 Subdural EEG strip recording of a seizure in the individual whose interictal discharges are shown in Figure 2. Cortical strip electrode placements: right and left lateral-orbitofrontal regions (ROFA–H and LOFA–H); right and left superior frontal regions (RSFA–D and LSF A–D); right and left mesial-inferior temporal lobes (RMTA–D and LMTA–D); right and left lateral temporal areas (RLTA–D and LLTA–D). All seizures arose from the right orbitofrontal cortex (ROFH). Abbreviation: EEG, electroencephalogram.
by placement of strip electrodes in regions adjacent to the grid. The nature of subdural grids is such that they frequently cover portions of sensorimotor cortex and essential language and can therefore be utilized for mapping of these critical regions (see below). Placement of subdural electrodes may at times be very difficult because of adhesions or bridging veins and for this reason, some neurosurgeons have utilized epidural electrodes instead. However, the resolution of epidural recordings is generally inferior to those of subdural recordings.

Subdural electrodes, especially grids, carry some risks, including delayed subdural hematoma, infection, epidural hematoma, and brain swelling (54,55).

Intracranial Ictal EEG Recordings

Invasive ictal EEG recordings are much less subject to artifactual distortion compared to scalp recordings. They may show a variety of patterns marking seizure onset, including voltage attenuation, increased amounts of rhythmic potentials, including faster frequencies (>12 Hz), repetitive spike or multiple spike complexes, or combinations of these. The timing of the first electrographic ictal changes relative to the first clinical manifestations of the seizure is of critical importance. If clinical manifestations precede electrographic changes, the most likely explanation is that the electrodes are not on or near the epileptogenic region. On the other hand, if the reverse is true, the probability is much greater that the invasive electrodes are properly placed.

More importantly, this information carries prognostic implications. In difficult temporal lobe epilepsy requiring bilateral subdural electrode recording, the greater the duration in time between EEG onset and clinical seizure onset, the greater the probability of a postoperative seizure-free outcome (56).
Careful analysis of the intracranial ictal EEG in regard to focal onset, waveform morphology, and timing and distribution of spread may yield additional information. Low voltage faster frequencies and sinusoidal rhythmic waves at seizure onset are more likely to be associated with a good postoperative outcome than other patterns (57,58). Stable, reproducible ictal onsets in recurring seizures and persistence of ictal discharges in the same regions from beginning to end of the seizures are associated more often with favorable outcomes than if these factors were not present (58). In neocortical temporal lobe epilepsy, grid recordings that demonstrate discrete focal or sublobar onset, anterior temporal origin, and slow progression times are all features that are related to seizure-free outcomes (59). Similarly, in neocortical seizures of extratemporal or temporal origin, the types of ictal propagation patterns correlate with predicting outcome. Patients with seizures of slow, contiguous spread of ictal patterns (>1 second) over cortical areas have significantly better outcomes than those with fast contiguous spread, while subjects with noncontiguous ictal spread have the poorest outcomes of all (60).

In subjects with temporal lobe epilepsy, the location and extent of ictal onset, based on intracranial strip or grid recordings, may be associated with outcome. In patients who have documented ictal onsets that include involvement of posterior basal temporal or posterior parahippocampal gyrus, a favorable outcome may not result, even when the resection encompasses those regions, and where ipsilateral mesial temporal sclerosis is present (61).

Widespread, prominent, irregular slow wave patterns (0.5–7 Hz) are often observed during and after temporal lobe seizures. Such slowing, which may affect bilateral frontal and ipsilateral parietal association neocortex, and which is distinct from the faster, rhythmic ictal patterns that emanate from the temporal lobe, may represent the neurophysiologic correlate of functional clinical impairment that is observed during complex partial seizures (62).

Recent research suggests that most currently available EEG recording systems and EEG analysis methods may be inadequate to precisely localize ictal-onset zones in neocortical epilepsy. Systems in clinical practice typically utilize a dynamic range that discards biologically important high-frequency oscillations that are found in the epileptogenic brain. Based on invasive EEG recordings, investigators have shown that 60–100 Hz oscillations are highly localized to the region of seizure onset in neocortical epilepsy. These fast oscillations are found in the ictogenic zone interictally, and are present during the several minutes prior to the onset of the clinical seizure (63). These findings may have important implications for future research and in the development of clinical EEG monitoring systems.

**Interictal EEG During Invasive LTM**

The purpose of invasive LTM is to document the electroclinical features of an individual patient’s seizures. However, some useful information may be gleaned from the analyses of interictal data. Quantitative studies of interictal subdural EEG data have shown that electrodes showing highest spike frequency, highest spike amplitude, and leading spike were part the seizure onset in the majority of instances (64). Similarly, there is a high correlation between the zones of the earliest spike in each spike cluster and seizure origin (65). On the other hand, other investigators find that interictal spikes in intracranial regions that extend beyond the area of intended resection may portend a poor surgical outcome (66).
Invasive LTM: Summary

Invasive LTM represents the final step in determining the epileptogenic zone. It is a necessary part of the evaluation in a substantial number of epilepsy surgery candidates. The precise strategy for placement of intracranial electrodes is based upon information acquired during the noninvasive assessment and is individually tailored for each patient. Invasive LTM is expensive and associated with some risk of morbidity. Because of unavoidably limited coverage of brain areas that may be sampled with invasive electrodes there is also the risk that the critical regions of ictal origin will be missed altogether. However, unless, or until, technological advances demonstrate that consistent and reliable information concerning seizure origins can be obtained noninvasively, there is no substitute for direct brain recordings for some patients.

“MINIMALLY INVASIVE” LTM

Over the last two decades some investigators have utilized techniques that may retain some of the benefits of invasive recordings with depth or subdural recordings, but with probably less risk of complications. These techniques, often referred to as “minimally,” “intermediate,” or “semi-invasive” in nature, however, do not completely eliminate risks and their precise role in the presurgical evaluation of difficult epilepsy is not completely established.

Foramen Ovale Electrodes

Foramen ovale (FO) electrodes utilized in subjects with temporal lobe epilepsy and are inserted while the patient is under local or general anesthesia. FO electrodes may have up to 10 contacts and record from mesial temporal regions and are typically utilized simultaneously with scalp electrodes (67). They are reported to be superior to both sphenoidal and scalp electrodes and may be especially effective in documenting ictal onsets from posterior hippocampus (68). FO recordings may show clear unilateral mesial temporal ictal origin when surface recordings are nonlateralizing (69). On the other hand, other investigators have reported that FO electrodes provided no useful lateralizing information in subjects with normal MRI studies (70). As with other forms of invasive LTM, especially with depth recordings, FO electrodes offer limited spatial sampling, with the consequent potential for false localization of seizures that originate from regions other than mesial temporal structures.

Epidural (Peg) Electrodes

Epidural (peg) electrodes, also referred to as “sentinel” electrodes, are inserted through burr holes and are positioned in the epidural space. In centers that use these, peg electrodes, usually employed in conjunction with other techniques, are used to obtain epidural ictal recordings. They have also been used to determine placement of subdural grid electrodes, when data obtained from surface EEG or neuroimaging has been equivocal. The morbidity associated with peg electrodes has been reported to be very low (71).
INTRAOPERATIVE ELECTROCORTICOGRAPHY

Intraoperative electrocorticography (ECoG) was introduced into clinical practice in the 1940s (72). Based on recording of interictal spikes (EDs) by electrodes placed by the operating neurosurgeon on the exposed cortical surface, the procedure is employed to guide the extent of resection, usually for temporal lobe operations. The precise location of electrode placement is individualized for each patient. ECoG is typically conducted in stages that include both pre- and postresection recordings.

The role of ECoG as a tool in helping to determine resection limits and the prognostic significance of postoperative EDs has been a matter of debate. Some investigators find that intraoperative hippocampal ECoG may be used to predict the extent of hippocampal resection in temporal lobe resections (73). See the discussions by Farrell, G. Ojemann, and Schwartz in Chapter VIII-22 for a greater review of ECoG, including differing perspectives on the relative merits of the procedure.

Functional Brain Mapping

Extraoperative Mapping

The use of subdural electrodes, especially grids, provides an opportunity to investigate the functional location of critical brain regions prior to resection, including areas important for language, speech, motor function, and sensation. These areas are typically spared to reduce postoperative functional deficits. It is important to obtain functional mapping studies for each individual, as anatomic localization alone is not sufficient, and in fact may be misleading, because of the great variability that may exist in location of functional maps between subjects (74–76).

Cortical Stimulation. Extraoperative mapping may be accomplished by direct electrical stimulation of the cortex through subdural electrodes, using principles derived from direct cortical stimulation at the time of operation (77). Although parameters differ between centers, typical stimulation settings include delivery of a high-frequency (50 Hz) square pulse of 0.3 milliseconds duration with alternating polarity for two to five seconds. The stimulus intensity at each trial begins initially with a small current flow (0.5–1.0 mA) and is gradually increased until a maximal intensity of 15 mA is reached, epileptiform after discharges occur, or a “positive” response in regard to the function under study is obtained. For example, a continuous object naming task is often employed during language mapping. If naming is interrupted at a particular site during stimulation, then a positive response is recorded and that site is considered as “essential” for language (74). A common strategy for mapping through the grid is to stimulate pairs of adjacent electrodes simultaneously. Responses obtained at each pair are documented. The function under study, such as object naming, is presumed to be localized at the sites of the common electrodes in the pairs where positive responses are elicited.

Language maps demonstrated though disruption of object naming reveals, the location of sites essential for language. A given subject may have one or more essential language sites, usually, but not invariably in perisylvian locations, distributed over temporal, frontal, or parietal cortex (Fig. 6). Mapping may be accomplished in children as young as four years of age (78). Language sites, as documented by disruption of object naming or reading by cortical stimulation, appear to have a wider distribution in epilepsy patients with lower intelligence and poorer education, and worse verbal and memory skills (79). Location of essential language sites may
also be related to gender and intelligence (74). Category-specific naming deficits (living vs. nonliving objects) have also been identified by stimulation mapping, independent of simple object recognition. Regions identified as such were included in the resection and postoperative neuropsychological testing confirmed category specific naming deficits (80). Other aspects of language, such as verb generation, have also been studied with cortical stimulation; results from these investigations resemble those obtained from functional neuroimaging when both utilize a verb generation task (81). Furthermore, in patients who are bilingual, mapping studies have clearly established a significantly different anatomic distribution for each language, with both language specific and shared sites that support both languages (82). Verbal memory has been studied with extraoperative cortical stimulation, which has provided evidence that left temporal neocortex mediates aspects of verbal memory (83). Investigators who have studied ECoG topographic patterns of fast frequencies (gamma) during naming and reading tasks found that these patterns, with a few exceptions, are consistent with results obtained from cortical stimulation (84). This observation that may lead to speculation that detailed quantitative studies of the intracranial EEG may eventually shed considerable insight into the localization and dynamics of cognitive functions.

Motor and sensory functions have also been investigated through direct cortical stimulation of subdural electrodes (Fig. 7) (85). Both primary and nonprimary

Figure 6  Results of extraoperative language mapping are displayed in one subject with left temporal lobe epilepsy. The solid circles indicate sites of errors in naming (“essential language sites”) with cortical stimulation. The half-circles indicate regions where naming was slowed with stimulation.
motor cortices, such as supplementary motor area (SMA) proper have been delineated. Investigators have found that mapping of the somatosensory evoked potential (SEP) responses has identified the postcentral gyrus (86). High-frequency cortical stimulation and the mapping of the readiness potential (“bereitschaftspotential”) can effectively document precentral gyrus and SMA, while single pulse electrical stimulation to record motor evoked potentials has been advocated as means to complement high-frequency cortical stimulation to map the primary motor regions (87). Combining the results of cortical stimulation and functional MRI has been found very useful in studies of medial frontal motor areas (88). Extraoperative functional motor mapping of children as young as four years can also be accomplished, although in subjects with neuronal migration disorders, a higher current flow, and careful observation of afterdischarges, may be necessary for adequate mapping (89).

Evoked Potential Studies. The presence of subdural electrodes, depending upon precise location, has also allowed mapping of function through averaging of signals from sensory stimuli to obtain evoked potentials (EPs). In addition to SEPs of median or peroneal nerves to map regions post-central gyrus, auditory and visual evoked potentials can also be recorded (Fig. 8) (90,91). The human second sensory and SMA proper can also generate evoked potentials (92–94). The frontal eye fields have been reported to generate evoked potentials about 100 milliseconds after stimulation (95).
In Vivo Studies of Epileptogenesis. Some recent research has suggested that extraoperative cortical stimulation studies may improve understanding of the physiology and dynamics of neuronal circuits in epileptic cortex and help identify the hyperexcitable regions in surgical candidates. Investigators have shown that two types of epileptic discharges in response to single pulse stimulation can be recorded: “early responses” of EDs (within 100 milliseconds after stimulus) and “delayed responses” (EDs between 100 and 1000 milliseconds after stimulus). Only those cortical regions showing the delayed responses were significantly associated with sites of seizure onset (96). Further studies in this area are required to corroborate these findings and to firmly establish the role of direct cortical stimulation in defining the epileptogenic zone.

Intraoperative Mapping

Principles of intraoperative mapping of critical brain regions are similar to those employed during extraoperative studies. Details of this method are reviewed by Silbergeld (Chapter VIII-21a) and the merits of intraoperative language mapping are debated by G. Ojemann (Chapter VIII-21b) and Binder and Barbaro (Chapter VIII-21c) elsewhere in this volume.

FUTURE DEVELOPMENTS

Ideal neurophysiological studies should allow clinicians to safely and reliably determine both the epileptogenic zone and the critically important functional cortical regions that need to be avoided at the time of surgery. It is likely that technological advances will replace some existing methods, and allow for the noninvasive assessment of ictal onset and cortical functions in more surgical candidates than is currently possible. Recent
developments clearly make virtually certain that investigators will eventually extract much more information from the noninvasive evaluation in such candidates.

New techniques that expand and improve the frequency and spatial resolution of scalp EEG, combined with quantitative source localization techniques are likely to greatly improve the noninvasive localization of epileptic seizures. This should be particularly true when high resolution, dense array scalp EEG is coregistered with the subjects’ own MRI and sophisticated EEG source analysis methods are applied (97,98). Complementary information will be provided when EEG source analysis is combined with functional MRI (99–101). The ability to readily record very slow (direct current) EEG potentials at the bedside, a topic discussed by Vanhatalo, Kaila, Voipio, Miller, and Holmes in Chapter 48, will assist in lateralizing partial seizures, even in situations where standard alternating current EEG recordings fail to do so (102). On the other hand, recording fast oscillations (60 Hz and higher) will also likely prove to be important in defining the epileptogenic zone (63). Information obtained from magnetoencephalography (MEG) should complement the interictal data obtained from scalp EEG. See the review by Otsubo, Oishi, and Snead in Chapter 49 regarding the role of MEG in the presurgical evaluation (103,104). Novel methods of analyzing the EEG may lead to the very real possibility that epileptic seizures can be predicted, even from surface recordings, minutes or even hours, before they occur (105). If the ability to predict seizures is borne out by future research, novel methods of therapy may be possible.

New research into the spatiotemporal dynamics of human neocortex will be applied to the analysis of scalp-recorded EEG. Recent research has established the spatial frequency spectrum (“spatial Nyquist”) of the human EEG from both the pial surface and scalp by application of quantitative methods to dense array recordings (106,107). Other recent studies have demonstrated that it possible to quantify rapid changes in EEG synchronization with a high degree of both temporal and spatial resolution. These new findings will establish the groundwork to improve the ability to noninvasively relate scalp EEG to cortical function, both in normal and in abnormal states, including epileptic seizures (108).

REFERENCES


Chapter V-13

Sphenoidal Electrodes

Chapter V-13a: Sphenoidal Electrodes Should Be Used in Presurgical Evaluations of Patients with Temporal Lobe Epilepsy

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Sphenoidal electrodes (SEs) are multistranded silver, platinum, or stainless steel wire electrodes inserted under the zygomatic arch with the aim of targeting a position below the foramen ovale (FO) (1). Several studies found these electrodes to be very valuable in recording interictal and ictal epileptiform activity of mesial–basal–temporal origin (2–9). However, anterotemporal electrodes (ATEs) and basal–temporal electrodes have been found to yield comparable data to SEs, thus raising questions with respect to the need for their use (10–13). In fact, several major epilepsy centers have replaced SEs with ATEs in the presurgical evaluation of patients with seizures of presumed mesial-temporal origin. Wilkus et al. (14) found no advantage of SEs over ATEs in ictal recordings, while Krauss et al. (15) found comparable ictal data obtained with SEs and anterior "cheek" electrodes, which consist of gold-plated electrodes placed approximately one inch anterior to the standard site of SE insertion.

Clearly, the use of SEs in the presurgical evaluation of patients with seizures of presumed mesial-temporal origin remains controversial. I was assigned the task to defend the position in favor of their use in this chapter. The position I am defending, however, has two caveats: (i) If SEs are to be used, they should always be inserted under fluoroscopic guidance to ensure that their recording tips are positioned immediately below the foramen ovale (FO); and (ii) SEs need not be used in all presurgical video-EEG of patients with presumed temporal lobe epilepsy (TLE). I present the data in support of these views.
IF SEs ARE TO BE USED, THEY SHOULD BE INSERTED UNDER FLUOROSCOPY

Theoretical Concepts

The rationale for using SEs is based on placing their recording tips in a position immediately below the FO; that is, closer to mesial-basal epileptogenic zones and where the electrographic signal can travel without interposed bone. Indeed, the epileptiform discharges’ signal amplitude varies inversely with the square of the distance from the source (16). While bone attenuates amplitude, a breech in the bone, such as the FO, preserves amplitude.

When Do SEs Fail to Yield an Advantage Over ATEs?

When SEs are inserted under blind conditions, the recording tips commonly end up in a position at a distance from the FO, either anterior or posterior to it. These alternative subtemporal locations have the following disadvantages: an electrode positioned posterior to the FO requires recording through the thick (2 cm) petrous pyramid, while a position anterior or lateral to the foramen has the double disadvantage of recording through bone and at an increased distance from target limbic structures. A large electric field of interictal and ictal activity minimizes the impact of longer electrode–generator distances and the effect of bone attenuation. In such circumstances, recordings obtained with SEs positioned at a distance from the FO or with ATE would look the same, and it may not matter where in the infratemporal area SEs are positioned or whether epileptiform activity was being recorded with ATE. In addition, SEs placed anterior to the FO and ATEs yield comparable subtended angles to mesial-basal generators and hence, epileptiform activity would not differ at either electrode, no matter the extent of its electric field.

When Do We Expect SEs to Have an Advantage over ATEs?

When SEs are positioned immediately below the FO, they are closer to basal cortex and the lack of interposed bone greatly facilitates the recording of epileptiform activity with a restricted electric field to mesial–basal–temporal regions that results from synchronous epileptic discharges (that can often consist of vertical spike dipoles) in a relatively limited extension of (or projection to) basal–temporal cortex with no projection to temporal lateral neocortex that cannot be detected by ATEs or SEs placed at a distance from the FO. Inserting SEs under fluoroscopic guidance insures the placement of their recording tips immediately below the FO.

THE DATA

SEs Should Be Inserted Under Fluoroscopy

In an initial study, we demonstrated that recordings with SEs inserted under fluoroscopy (SEF) significantly improved the localizing yield of interictal and ictal data of 17 patients with intractable partial seizures of anterotemporal origin whose initial video-EEG recordings with SEB/ATE had failed to localize the ictal onset with a focal onset pattern (17). SEF detected a unilateral anterotemporal interictal focus in four patients in whom SEB/ATE had failed to record any interictal spikes, and
detected bitemporal independent interictal foci in one patient where SEB/ATE had only identified unilateral spikes. In nine other patients, the spike count obtained with SEF recordings increased by more than 100%, when compared to that obtained with SEB/ATE recordings. In addition, SEF recorded seizures with an anterotemporal focal onset pattern in 10 patients where SEB/ATE had failed to do so.

Various authors have reported that a majority of silver electrodes migrated outward along the insertion tract during the course of monitoring (2,18). In the above-cited study, we found that SEs made of platinum resist such displacement, and I therefore recommend using SEs made of platinum (17).

In a second study, we substantiated our hypothesis that the advantage of SEF over SEB/ATE recordings resides in the recording of epileptiform activity with a restricted electric field (19). Using the interictal and ictal data of the 17 patients from the previous study, we compared spike voltages at SEF, SEB, and ATE in sets of five randomly selected spikes per interictal focus, recorded in the course of the two monitoring studies. We represented the voltage differences as ratios, $V_{ATE/SEF}$ and $V_{ATE/SEB}$, and calculated a mean ratio for each spike set. The spike voltages were almost identical at SEB and at ATE (mean $V_{ATE/SEB} = 0.94$), while they were significantly higher at SEF than at ATE (mean $V_{ATE/SEF} = 0.66$; $P < 0.001$). In SEF recordings, the narrowest electric field contours were found among interictal foci which had only been recorded with SEF, which, in turn, were significantly smaller than those of interictal foci in which SEF yielded an increment of more than 100% in spike counts (relative to those obtained with SEB/ATE). These, in turn, had a significantly smaller contour than those of the interictal foci where SEF failed to yield any advantage over SEB/ATE ($p < 0.001$). In addition, $V_{ATE/SEF}$ of interictal foci in which SEF recorded seizures with a focal onset pattern were significantly lower than those of foci where SEF failed to do so ($p = 0.016$). Finally, $V_{ATE/SEF}$ did not differ from $V_{ATE/SEB}$ among interictal foci where SEF failed to yield any advantage over SEB/ATE ($p = 0.240$), or ictal ($p = 0.311$) recordings. These findings prove that SEF yield additional localizing data when recording epileptiform activity with a restricted field, provided that its recording tip is positioned below the FO. When distant from the FO, SEs can be expected to yield comparable data to those obtained with ATEs.

How Often Do SEs Yield Additional Data Not Obtained with ATEs?

While the above data suggested an advantage of SEF over ATE and demonstrated the rationale for their use, they do not imply that SEF need not be inserted in every monitoring study of patients with presumed TLE. We conducted a third study to determine the frequency with which SEF yield new localizing data not obtained with ATE recordings in a group of unselected patients with TLE and to establish a set of criteria for their use (20). We compared the ictal recordings of 156 seizures obtained with SEF and ATE from a series of 40 consecutive patients whose presurgical evaluation had demonstrated a unilateral ($n = 32$) seizure focus or bilateral independent ($n = 8$) seizure foci in anterotemporal regions. Four electroencephalographers reviewed the 312 ictal recordings, independently, and blind to the patients’ identity, to any presurgical data and to whether the recordings’ montage included ATE or SEF. The main outcome variables included: (i) a comparison of inter-rater reliability among the four independent raters of SEF and ATE ictal recordings, (ii) the number of correctly localized seizures with SEF and ATE recordings by at least three raters, (iii) the number of ictal foci in which all seizures were only localized with SEF, and
(iv) the number of seizures in which SEs identified the ictal onset five or more seconds earlier than ATEs. We found that inter-rater agreement among the four raters was significantly greater with SEF than ATE recordings ($P < 0.0001$). The number of seizures correctly localized by at least three raters was significantly greater with SEF ($n = 144$) than ATE ($n = 99; P < 0.0001$). All the seizures ($n = 36$, or $23\%$) originating from 14 ictal foci ($29\%$) in 11 patients ($27.5\%$) were only localized with SEF. This was a significantly more common occurrence in patients with bilateral independent ictal foci ($P = 0.04$). The ictal onset was detected at SEF five or more seconds earlier than at ATE in 67 seizures ($43\%$) originating from 33 ($69\%$) foci in 30 patients ($75\%$). In addition, we found that SEF had a significant advantage over ATE in the recording of seizures of patients with bilateral independent foci and with a normal MRI, but not in seizures of patients with a structural lesion. We concluded from these data that SEF facilitate the localization of anterotemporal ictal onset and in about one-fourth of patients SEF identify ictal data not localized or mislocalized with ATE recordings.

WHEN SHOULD SEF BE INSERTED?

a. In case of hippocampal atrophy:
The decision to insert SEF can be delayed until the first seizure is recorded and the interictal recordings of the first 24 hours have been reviewed. SEF will not be necessary in the case of patients with unilateral atrophy if ATE recordings demonstrate:

- A majority of spikes ipsilateral to the atrophic hippocampus.
- The first seizure has a focal or regional onset pattern (provided that all of the patient’s seizures are identical by history).

SEF should be inserted:

- If ATE recordings reveal bilateral independent spike foci with a relative frequency of 50/50 to 60/40.
- If ATE recordings reveal an ictal onset pattern that is lateralized or not localized.
- In case the patient’s seizures are not identical by history (excluding complex partial seizures that also evolve to secondarily generalized tonic–clonic seizures).
- In case of bilateral hippocampal atrophy.

b. The same criteria can be used in patients with a unilateral structural lesion in anterotemporal regions.
c. SEF should be inserted in patients with TLE and a normal MRI study.

REFERENCES

Chapter V-13b: Sphenoidal Electrodes Have Limited Value

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INTRODUCTION

The 10–20 system of electrode placement includes no electrodes over the anterior temporal region, of especial interest in epilepsy surgery (1). This deficiency may be remedied by use of alternative systems, or addition of anterior temporal electrodes (ATEs), typically 1 cm above the junction of the posterior and middle thirds of a line from the external auditory meatus to the external canthus, variously called T1/2, D9/10, or F9/10 (2,3). Several extensions of the 10–20 system have been proposed, which include electrodes over the temporal regions particularly for presurgical assessment (4). Further improvement of capture of temporal discharges has long been claimed from the use of basal electrodes, particularly sphenoidal electrodes (SEs) inserted through the mandibular notch to lie immediately below the foramen ovale (5).

Early studies showed SEs to be superior to the standard 10–20 placements for detecting temporal spikes but were biased by comparing waking scalp EEGs with drug-activated sphenoidal recordings and used only 10–20 placements, without electrodes in the anterior temporal regions, where spikes in mesial temporal epilepsy are usually largest (4,5). The superiority of SEs over standard 10–20 placements is nevertheless now well established and further discussion will focus on studies using non-standard basal electrodes, usually ATEs at the T1/2 site (6,7).

A weakness of both early and some recent studies is the exclusive use of bipolar montages. Without entering into the wider debate over different methods of derivation, there are compelling reasons why bipolar recordings are inappropriate for these specific investigations. Recognizing and identifying transients as epileptiform involves comparing amplitude and amplitude-duration ratio of candidate events with those of ongoing activity. The electrode spacing on the sphenoidal channels commonly used (e.g., A2–Sph2, Sph2–Sph1, Sph1–A1) is greater than that between the scalp electrodes and biased towards recording greater amplitudes on these channels. More fundamentally, the waveforms at these adjacent sites may be different or asynchronous, and the potential gradients displayed by subtraction in bipolar derivations reflect these local differences, rather than absolute amplitude. By contrast, if the discharges are unilateral, the intersphenoidal derivation, avoiding cancellation effects, maximizes the displayed amplitude at one SE.

Consistent but small differences are found by valid comparisons of spike amplitudes at SEs and ATEs. Partial withdrawal of SEs or the use of “mini-sphenoidals” inserted just under the skin makes little difference to the activity recorded (8,9). Binnie et al. (10), using multicontact electrodes, showed a shallow potential gradient from the sphenoidal site to the surface. The mean amplitude ratio between ATEs and SEs was 85%. Kanner et al. (11) ensured accurately placed SEs by...
fluoroscopy (FPSE). Comparing fluoroscopic with previous blind placement (BPSE), they found a mean ATE/FPSE ratio of 0.66 and ATE/BPSE of 0.94. This study is biased by including only patients in whom BPSE had failed to detect seizure onsets and may have been particularly ill-positioned, but the results suggest that Binnie et al. (10) had achieved an accuracy of localization approaching that of Kanner et al. (11) using FPSE.

Both SEs and ATEs are sited in tissue of low impedance, separated from the cranial cavity by the high impedance of the skull, which is breached by the high-conductivity pathways of the foramen ovale and the superior orbital fissure. Biophysical considerations predict a large potential difference between intracranial sites and these extracranial electrodes, a widespread surface field, not closely reflecting intracranial topography, a relatively small potential difference between adjacent extracranial electrodes, and a steep potential gradient through and adjacent to the foramen ovale, which are indeed demonstrable (12).

INTERICTAL STUDIES

Comparative studies show discharges at SEs are demonstrable with reduced amplitude at ATEs, with similar detection rates of recognizably epileptiform graphoelements.

Manzano et al. (13) found all SE discharges in 21 patients were seen at an ATE 1 cm below the external canthus, some 3–4 cm anterior to T1/2, but 11% were not typically “epileptiform.” Using T1/2, Homan et al. (14) doubled the detection of temporal foci compared with 10–20 alone in 24 patients, and found an 11% but non-significant increase in yield at SEs. Jennum et al. (15) found no advantage for detecting interictal spikes of SEs over zygomatic electrodes, but the latter were clearly superior to adjacent 1–20 scalp electrodes.

Binnie et al. (10) found that in 109 out of 111 patients, over 90% of interictal sphenoidal spikes were detectable and identified as epileptiform at an ATE just behind the frontozygomatic suture, some 3 cm anterior to T1/2. In the remaining two-subjects, 50% of spikes were detected. Thus, in all patients, investigation without SEs would have provided adequate diagnostic information. As noted above, Kanner et al. (11) asserted that SEs accurately located under fluoroscopy greatly improve detection of temporal discharges. In response, Fernández Torre et al. (12) sought to exclude errors in electrode placement using as an idealized sphenoidal location, the first extracranial contact on a bundle passing through the foramen ovale. Their ATE was placed behind the frontozygomatic suture. The deeper contacts allowed detection of discharges not identified extracranially and, of 2280 discharges in 20 patients, 70% were seen only at the intracranial contacts. Of the remaining 722, 4.15% were detected at the SE but not on the scalp and 3.04 at the ATE only.

ICTAL STUDIES

Krauss et al. (16) found no difference in lateralization or timing of seizure onsets in 22 patients recorded at SE versus cheek electrodes. Pacia et al. (17) compared SE and T1/2 seizure onsets, using reference derivation, in 31 patients with temporal lobe epilepsy (TLE) subsequently confirmed by intracranial recording. In 3 out of 11
patients with mesial TLE, seizure onset was detected first at the SEs. In 20 patients with neocortical epilepsy, onsets were simultaneous. They note the importance of referential derivation and the need for studies using other surface electrode sites. Again, using an “idealized” sphenoidal contact on a foramen ovale bundle, and an ATE just behind the frontozygomatic suture Kissani et al. (18) independently assessed sphenoidal and scalp onsets of 314 seizures. These were synchronous in 39.2%, earlier at the “sphenoidal” in 20.1%, and on the scalp in 24.2%. Ictal change was detected on the scalp but not at the “sphenoidal” electrodes in 5.4% and at the sphenoidal but not the scalp in 1.9%. Artifacts prevented comparison in 5.1%. SEs supplied additional information in 22 seizures (7%), in five because artifact obscured the scalp EEG.

Kanner et al. (19) employed four raters for ictal studies, correctly localizing 89.1% to 95.5% of seizure onsets in sphenoidal/scalp recordings and only 61.5% to 76.3% in montages with T1/2, but no SEs. The single illustration demonstrates the superiority of referential recording over bipolar from all sites, but does not use sensitivities optimized post hoc to demonstrate activities of different amplitudes on different channels in accordance with current digital EEG practice. As the seizure onset apparently precedes the start of the excerpt, it is impossible to determine whether an early change should have been recognized at the scalp electrodes.

Seeking to reevaluate traditional blind insertion of SEs, Mintzer et al. (20) employed two raters to assess independently 101 ictal EEGs in 31 patients. ATE and SE recordings were viewed in different montages with post hoc adjustment of display parameters. ATEs were located at T1 and T2 and SEs inserted without help of radiology. A small, clinically insignificant difference in seizure onset latency was found in 6% of seizures. One seizure onset was detected three seconds earlier at the sphenoidal contact; other seizures of the same patient did not show this small difference. Five percent of onsets were not detected at the SEs because of artifacts.

CONCLUSIONS

The reported differences are exaggerated by methodological factors: comparison of activated sphenoidal recordings with waking scalp EEG, reliance on bipolar derivation, suboptimal location of the comparator ATEs, and failure to optimize recording parameters. Kanner’s group shows inaccurate placement of SEs reduces their sensitivity, but the findings of Mintzer et al. (20) and of the King’s College group’s studies with foramen ovale electrodes suggest the gain of information with accurately placed SEs to be modest.

There is no doubt that, in mesial but not lateral TLE, interictal spikes produce signals of greater amplitude at SEs, by 20% to 40%, than on the scalp, and seizure onsets are occasionally recognized earlier, perhaps in some 5% of patients. The greater amplitude of spikes at the SE in mesial TLE may be of some value for discriminating this from lateral TLE. Sphenoidal recording rarely detects ictal or interictal epileptiform activity which cannot be found in the scalp EEG, provided appropriate, generally referential, methods of derivation are used, optimal anterior temporal electrodes sites are employed and recording parameters are optimized. The small increase in detection rate is rarely of clinical consequence but sphenoidal recording is useful in a small proportion, probably less than 5% of those patients with TLE, in whom scalp recording fails to detect expected temporal discharges.
This controversy raises other neglected fundamental issues, notably the roles of volume conduction and propagation in the genesis of scalp potentials, the topographic relationship of scalp and intracranial EEG, and the effects on this of the brain coverings and particularly of cranial foramina.

REFERENCES


Chapter V-14
The Role of Depth and Subdural Electrodes in the Workup of Surgical Candidates

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INTRODUCTION

Drs. Miller and Silbergeld requested this chapter by e-mailing me the following instructions: “…write a brief (about 3 page) opinion on controversies on the role of depth and subdural electrodes in the presurgical workup, particular of temporal lobe seizures when there is a question of lateralization. We want you to present arguments as to whether subdural strips are adequate and appropriate for the great majority of patients.” The problem, I told Dr. Miller, is that in all likelihood, I will have no real controversy to present on this issue. The controversy as it exists today is nothing like what raged in the late 1980s and early 1990s when magnetic resonance imaging (MRI) had yet to make a significant impact on the presurgical workup of potential candidates.

Over the years an unspoken consensus has evolved concerning the relative indications for using strip and depth electrodes in presurgical evaluations. I believe the only remaining controversy is the degree of anatomical localization within the temporal lobe required before a surgeon is comfortable in choosing surgery and the type of procedure to be utilized. In other words, is localization to the hippocampus (or even a localization along the axis of the hippocampus) necessary before deciding on temporal lobectomy?

This discussion will not consider grid electrodes, which have different indications than strip electrodes. A strip electrode is defined as a single linear array of disk electrode contacts whereas a grid is an array of multiple parallel rows of disk electrode contacts.

Advantages of depth electrodes. Depth electrodes can be placed to record from deep brain structures that strip electrodes cannot reach. Examples are hippocampus, the depths of cortical congenital abnormalities, and tumors such as hypothalamic hamartomas. Thus, they can record electrical activity that strip electrodes cannot record.

Disadvantages of depth electrodes. (1) Because depth electrodes require some form of stereotaxis for proper placement, the technique necessitates a strategizing and
fiducial localizing MRI prior to surgery. This adds additional expense. (2) Stereotaxic procedures usually require more operating room time than strip electrode placement. Both of these factors increase the cost to the procedure. (3) Usually only one electrode is inserted through each burr hole whereas multiple strips can be inserted through each burr hole.

Although the literature comparing the relative safety of strip versus depth electrodes is limited, it suggests both have equal risks for severe complications. However, I do not believe the literature accurately reflects the true complication rate of depth electrodes. I base this opinion purely from my personal experience of being contacted by lawyers representing patients who have suffered such complication. It would appear that the serious complication of intracerebral hemorrhage is associated with depth electrodes and not with strip electrodes. Because of any number of factors including an increasingly hostile legal system, there is little incentive to report such complications. Thus, there is little objective data to support my impression.

Advantages of strip electrodes. (1) They can be inserted with much less operative time and MRI preparation as required for depth electrodes. Thus, the total costs of an implant (assuming the same cost of electrodes) are less. (2) Strip electrodes record from vast expanses of neocortex whereas depth electrodes do not. (3) Multiple electrodes can be inserted through one burr hole.

Disadvantages of strip electrodes. They are not capable of recording from deep structures like hippocampus.

RATIONAL FOR THE APPLICATION OF DEPTH AND STRIP ELECTRODES

Intracranial recordings are undertaken for one primary purpose—to better define the location and/or confines of a suspected epileptic focus. Electrode grids are usually implanted over the cortical areas for the purposes of “mapping” once the laterality of a focus has been determined. In contrast, strip or depth electrodes are implanted mostly for the purpose of determining which hemisphere or lobe generates the seizures. For this reason recording are best made from gray matter and not from white matter. Thus, the most desirable location for such recordings is the cortical surface. Almost all cortical regions of concern, except for hippocampus, are accessible with careful strip electrode placement. Thus, one approach has been to use strip electrodes to lateralize and localize suspected extratemporal foci and reserve depth electrodes for cases in which the temporal lobe involvement is suspected but not lateralized.

An illustrative example is a patient with documented complex partial seizures and EEG evidence of temporal lobe onset but who lacks MRI evidence of mesial temporal sclerosis. Because such patients are not associated with the same excellent outcomes from temporal lobectomy as do typical mesial temporal lobe epilepsy patients, a rational surgical workup would include invasive monitoring employing a combination of depth electrodes (placed via the posterior route so as to sample as much hippocampus as possible) and strip electrodes implanted over the lateral temporal and orbital frontal cortices.

For all other nontemporal neocortical cases, strip electrodes should provide sufficient data to answer the question of laterality and to localize a general location. However, once this is done, additional recording with an implanted grid electrode may be necessary to develop a strategy for proceeding to cortical resection.
CONTROVERSY

Some surgeons have suggested that the exact location within the hippocampus can be mapped with long-term ictal recordings using depth electrodes or acute intra operative interictal recordings. This, the story goes, will allow the surgeon to “tailor” a resection to remove as little hippocampus as necessary and in doing so, preserve memory.

I believe the data for this approach are neither compelling nor evidence-based and believe that the best postoperative seizure results derive from a total removal of the offending hippocampus.

SUMMARY

Most of the controversy surrounding the relative indications or advantages of strip electrodes versus depth electrodes that raged in the late 1980s and in the 1990s has been removed by the ability to identify epileptogenic lesions by MRI. This is especially true for temporal lobe epilepsy associated with mesial temporal lobe sclerosis. For ambiguous cases however, invasive recording are often needed to determine a patient’s candidacy for surgery and under these circumstances, the choice of electrode type will be highly lesion-specific.
Chapter V-15: The Role of Noninvasive Video-EEG Monitoring

Chapter V-15a: Ictal Monitoring Is Not Needed in All Temporal Resections for Mesial Temporal Sclerosis

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The presurgical evaluation for patients with medically refractory temporal lobe epilepsy may include determination of seizure semiology, routine electroencephalogram (EEG), long-term inpatient video-EEG monitoring (LTM), neuroimaging, nuclear imaging studies, and neuropsychological assessment. The rationale for all of these studies is to accurately localize the epileptogenic focus and the site of seizure onset for surgical resection.

LTM for ictal recording has traditionally been used as the most important piece of information in surgical decision making in patients with refractory epilepsy. This technique allows for identification of seizure semiology, and electrographic seizure pattern. However, LTM in an inpatient hospital setting is costly and should be used judiciously. It requires admission to a hospital and tapering the antiseizure medications, which could be potentially harmful for patients with severe epilepsy. Despite discontinuing the medications, patients may not experience their typical seizures during one admission. Also, ictal EEG patterns may be technically more difficult to interpret than the interictal recordings. For the above difficulties, several
investigators have studied the predictive value of interictal epileptiform discharges (IEDs) as an alternative to LTM for determining the site of the seizure origin (1–7).

In a multivariate analysis of the predictive variables for a favorable surgical outcome in cortical resection as a treatment for epilepsy, Dodrill et al. (8) found a single EEG focus among the significant predictors of a seizure-free outcome. The patients who had seizures recorded during long-term monitoring studies were not significantly different in outcome from those selected by conservative interictal scalp EEG criteria.

Holmes et al. (2) studied 59 patients with medically intractable epilepsy who showed a consistent preponderance of unilateral focal interictal discharges. They compared the interictal findings with the ictal recordings in a subset of 48 of these patients whose ictal findings demonstrated a focal seizure onset. They found that if the interictal discharges were exclusive to a single region, there was a greater than 95% probability that all the recorded seizures would originate from the expected region.

Interictal epileptiform abnormalities in isolation have an error rate of 10% to 20% for prediction of unifocal temporal ictal onset. It is argued that the IEDs may be misleading in both false lateralization and false localization of the epileptogenic zone (1,4,9,10). The typical ictal events may arise from the contralateral temporal lobe (false lateralization) or from an extratemporal site (false localization). However, IEDs when combined with concordant structural lesion consistent with mesial temporal sclerosis (MTS) are found to be predictive of the site of seizure onset and a favorable operative outcome.

Our reported experience at the Mayo Clinic is among studies to point out the redundancy of ictal recording in the face of unilateral hippocampal atrophy and concordant EEG lateralization. Cascino et al. (1) reported 159 patients with intractable temporal lobe epilepsy (TLE) who underwent an anterior temporal lobectomy between 1988 and 1993. Routine interictal EEG findings showed a significant correlation with the temporal lobe of seizure onset. MRI-identified unilateral MTS correlated with the routine EEG studies and was a strong predictor of operative success.

Cambier et al. (6) studied 84 patients with intractable temporal lobe seizures undergoing anterior temporal lobectomy. All patients had MRI-identified hippocampal atrophy, routine interictal EEG, and ictal monitoring. Fifteen of those patients with unilateral hippocampal atrophy and concordant IEDs showed excellent surgical outcomes despite discordant or non-localizing ictal findings. Pataraia et al. (7) also found that ictal EEG provided no additional information in their 24 patients with unilateral hippocampal atrophy and unitemporal interictal spikes. However, they used the presurgical video-EEG monitoring data to obtain the interictal EEG discharges, not the routine outpatient EEGs.

Gilliam et al. (4) have found that compared to other combinations of test results, concordance of MRI and interictal EEG is most closely associated with a favorable surgical outcome. Interestingly, outcome in patients with concordant ictal EEG and MRI but nonlateralizing IEDs was significantly worse.

Cendes et al. (5) studied 184 consecutive patients with TLE and MRI volumetric studies in keeping with MTS. All of their patients with unilateral hippocampal atrophy had concordant interictal and ictal lateralization. In other words, unilateral hippocampal atrophy was a predictor of ipsilateral interictal epileptiform abnormalities with no false lateralization.

Table 1 summarizes the largest studies in the literature, which support the importance of focal interictal discharges (IEDs) in predicting the epileptogenic focus. The studies, which used a favorable surgical outcome as the end point, are identified.
All studies used ictal onset during the video-EEG monitoring as the gold standard for comparison. A few studies used high-resolution MRI to identify a concordant hippocampal atrophy.

We believe that unilateral hippocampal atrophy, when combined with lateralized interictal epileptiform discharges, could reliably predict the site of the seizure origin and a favorable operative outcome. A multivariate multicenter study will ultimately determine if ictal recording is mandatory in this subgroup of patients with TLE. Ictal monitoring is still indicated in case of suspected non-epileptic spells, and to determine ictal behavior and its disabling effects. Ictal EEG recording should also be saved for patients with normal MRI studies, bilateral MTS, discordant preoperative studies, independent bitemporal discharges, or normal routine EEGs.

**REFERENCES**


**Table 1 Studies That Support the Focal Interictal Discharges as a Predictor of Ictal Onset or a Favorable Surgical Outcome**

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Number of patients</th>
<th>Number with focal IEDs</th>
<th>MRI (HR)</th>
<th>MTS/IED concordance</th>
<th>Surgical outcome</th>
<th>Ictal comparison</th>
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<td>Holmes et al. 1996 (3)</td>
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<td>28</td>
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</table>

*Abbreviations: IED, interictal epileptiform discharge; MRI, magnetic resonance imaging; HR, high resolution; MTS, mesial temporal sclerosis.*
Chapter V-15b: Ictal Electroencephalographic Monitoring Should Be Performed Before Temporal Resection

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GENERAL CONSIDERATIONS

Ictal video-electroencephalographic (EEG) monitoring, using extracranial electrodes, is pervasively employed in presurgical epilepsy evaluations (1–3). Evaluation for epilepsy surgery can in principle be distinguished from evaluation for lesionectomy. When characteristic imaging or biopsy evidence indicates that an alien-tissue lesion has high potential to cause progressive cerebral injury (e.g., cerebral neoplasia) or catastrophic hemorrhage (e.g., certain vascular malformations), and seizures are rare or absent, prolonged video-EEG monitoring is not used in surgical planning. On the other hand, ictal video-EEG typically is used in patients with frequent, medically refractory seizures in combined lesion-epilepsy evaluations, for intended cure or control of an alien-tissue lesion and of epilepsy by a single procedure (4). In patients with refractory localization-related epilepsies, most lesions detected with imaging are ablative or developmental in character (5,6). Such sclerotic–encephalomalacic lesions and malformations of cortical development serve as major clues in the search
for a site of efficacious antiseizure resection, but these lesions do not in themselves require resection.

Given that certain types of lesions are highly associated with a single ictal onset zone in particular clinical scenarios, some have questioned whether ictal video-EEG adds sufficient additional information to justify the associated bother and expense (7–9). Many patients who have the combination of clinical characteristics consistent with mesial temporal lobe epilepsy (TLE), unilateral hippocampal sclerosis or other ablative-malformational lesions confined to one temporal lobe, and ipsilateral temporal lobe EEG spikes, and who do not have other MRI or interictal EEG abnormalities, will be found to have exclusively ipsilateral extracranial EEG ictal onsets. Retrospective selection of such patients from an epilepsy surgery series naturally will fail to detect additional localizing value and pseudoseizure-detecting value of video-EEG monitoring. Retrospective series may present data on “unilateral temporal” interictal EEG spikes without critical attention to the difficulties posed by non-pathological phenomena such as benign epileptiform transients of sleep, by variability in spike detection between EEG sampling during brief outpatient studies and prolonged in-patient monitoring, and by uncertainties due to various definitions of unilateral temporal spike “preponderance” versus truly unilateral spiking (10–13).

Ictal video-EEG with extracranial electrodes is generally safe and well tolerated, when performed by experts, so risk of adverse events is unlikely to limit use of continuous video-EEG monitoring. The expense of video-EEG monitoring may be a greater consideration in deciding whether to perform this study in all epilepsy surgery evaluations. Cost–benefit analyses will be imprecise until the clinical utility of video-EEG has been further defined. In general, ictal video-EEG is not very expensive, relative to diagnostic procedures that are used for other serious medical conditions. If expenditures are limited excessively, diagnostic accuracy could be reduced in care of pharmacoresistant epilepsies. Certainly pharmacoresistant epilepsies should be treated just as seriously as are atherosclerotic heart disease and other less-stigmatized chronic conditions, in which extensive diagnostic evaluations are performed before surgical therapy or simply to direct medical management. The cost-effectiveness of video-EEG monitoring has not been sufficiently studied to determine that ictal video-EEG should always be required for epilepsy surgery in developing nations. On the other hand, ictal video-EEG costs may be surprisingly low in developing nations (14).

No randomized, prospective, double-blind clinical therapeutic trials in TLE are available to direct our practice with regard to the efficacy and safety of performing temporal resection or other epilepsy surgery without first acquiring ictal EEG data. In designing such a study, a thorough review of retrospectively analyzed surgical series, and even of case reports and expert opinions, would be useful to frame the hypotheses and to consider the ethics of randomizing volunteers into video-EEG and no-video-EEG groups. This analysis might be organized by considering the types of essential presurgical information that can be provided by ictal video-EEG recording. One might then consider which of these types of information are essential but are potentially redundant with or replaceable by other types of information. The following discussion will consider information that supports ictal video-EEG (with extracranial electrodes) in planning epilepsy surgery of the temporal lobe. The discussion will assume that comprehensive history and examination, interictal scalp EEG, high-resolution brain MRI, and neuropsychometric testing are routinely available (and performed by epilepsy experts), when considering epilepsy surgery evaluation.
LOCALIZATION OF THE ICTAL ONSET ZONE WITH ICTAL VIDEO-EEG

Numerous empirical research studies and conceptual reviews have addressed various types of localizing information derived from ictal video-EEG monitoring with extracranial electrodes, which are useful in planning temporal resection for epilepsy (1–3,15–27). These types of information occur in particular clinical situations in which reported ictal semiology, clinical history, interictal scalp EEG, neuropsychometric, and brain MRI data usually are available before video-EEG monitoring.

Ictal recordings with extracranial video-EEG can provide these types of information:

1. Detection of a single region of ictal onset in patients whose other noninvasively acquired localizing information also detects this site, so as to strongly support temporal resection, without prior intracranial EEG monitoring. The concordance of different types of localizing information (which reflect cerebral structure, ictal dysfunction, and interictal dysfunction), in the absence of contradictory localizing information, can be so highly associated with a single site of mesial temporal ictal onsets that ictal EEG with intracranial electrodes would not provide additional information (17). Temporal resection after such evaluations reportedly is as efficacious as temporal resection based on intracranially recorded ictal EEG (28,29). Unfortunately, seizures recur after temporal resection in many patients who have “simple” evaluations, in which all noninvasively acquired data point to a single temporal lobe. Based on this, some would argue that the goal of epilepsy surgery evaluations should be to obtain as much noninvasively acquired data as possible, to exclude failures in detecting multiple foci of ictal onset and atypical seizure generators that simulate mesial temporal foci but lie beyond sites of mesial temporal resection (2). From this point of view, when ictal extracranial EEG localization confirms MRI and interictal EEG localization, the extracranial EEG monitoring might be viewed not as redundant but as essential in raising the certainty of correct localization to justify elective ablation of temporal lobe structures.

2. Detection of a single temporal lobe maximum of ictal onset in patients whose other noninvasive localization fails to detect this site, but does not contradict ictal EEG localization. Intracranial EEG monitoring may establish a single site of mesial temporal ictal onsets, which then is efficaciously resected, in a patient who earlier had ipsilateral temporal lobe ictal onsets on extracranial EEG, in the absence of any epilepsy-associated MRI lesion or in the absence of interictal EEG spikes (20). Thus, ictal extracranial EEG findings provide information independently of that provided by MRI and interictal EEG. Intracranial EEG recordings are generally used to confirm the extracranial ictal EEG localization, when brain imaging is normal; in such cases, the extracranial ictal EEG findings strongly support the decision to pursue nonlesional temporal resection and assist in selection of intracranial electrode sites (30).

3. Detection of a single temporal lobe maximum of ictal onset in patients whose other noninvasive localization provides contradictory evidence of some other ictal onset zone(s). When interictal EEG shows bilateral independent temporal lobe spikes in a patient who has unilateral temporal lobe ictal
onsets of extracranial EEG, intracranial monitoring often establishes that extracranial ictal EEG was correct in localizing this single ictal onset zone (20). When brain imaging shows a temporal lobe abnormality contralateral to the side of temporal lobe ictal onsets of extracranial EEG or shows an extratemporal abnormality, intracranial monitoring may establish that ictal EEG was correct (20). In some cases, extracranial ictal EEG may be falsely lateralized from a temporal lobe lesion and intracranial ictal EEG (20,22,31,32). Temporal-maximum ictal onsets on extracranial EEG, in a patient with contradictory MRI or other localizing information, serve to support the decision to pursue intracranial EEG recording and also assist in planning sites of intracranial electrodes.

4. **Detection of bitemporal independent ictal onset zones in patients whose other data suggests only a unilateral TLE.** Structural and functional imaging abnormalities often involve only one temporal lobe, in patients who ultimately are shown to have bilateral independent onsets of temporal lobe seizures. Intracranial recordings appear to be necessary to fully establish that mesial temporal ictal onsets are truly bilateral, but extracranial EEG ictal recordings appear to be the noninvasive test that most sensitively detects bilateral temporal ictal onsets (20).

5. **Detection of an extratemporal ictal onset zone, with or without a coexisting temporal lobe ictal onset zone, in patients whose other data suggests only a unilateral TLE.** This situation can arise in patients who have temporal lobe MRI lesions (20). If the temporal lobe lesion does not in itself require resection, temporal resection will be unlikely to fully control seizures and may incur new cognitive deficits in such patients.

6. **Detection of generalized-onset ictal EEG patterns, with or without a coexisting temporal lobe ictal onset zone, in patients whose other data suggests only a unilateral TLE or other partial epilepsy.** Some patients with symptomatic generalized epilepsies (SGEs) have temporal lobe seizures, in addition to generalized-onset seizures (33). Such patients may have focal temporal spikes as the only interictal epileptiform EEG abnormalities (33). Correct diagnosis of temporal lobe seizures might occur with failure to suspect the coexisting generalized-onset seizures, in the absence of definitive ictal video-EEG monitoring. In some SGE patients, resection of a temporal lobe might increase preoperative cognitive deficits and almost certainly would fail to control generalized-onset seizures. Rarely patients with TLE might also have coexisting primary generalized epilepsy, but these patients are more likely to enjoy full control of generalized-onset seizures with antiepileptic drugs (AEDs), and to benefit from temporal resection for partial-onset seizures.

Ictal intracranial EEG is considered the definitive technique in localization of an individual’s ictal onset zone(s), with caveats concerning the accuracy–safety balance between sampling numerous sites and increasing risks of complications with greater numbers of electrodes (20,34–38). Intracranial electrodes obviate many limitations of extracranial recording related to volume conduction effects, deeply located current sources, atypical propagation patterns, and common physiological artifacts. Complications of intracranial electrode placement at times are severe and irreversible (39). Intracranial EEG monitoring generally is performed only when no other procedure can answer questions of localization, but extracranial
EEG monitoring is reasonable when the certainty of correct localization can be increased. Localization by MRI might be considered always correct in anatomy but occasionally incorrect in specificity to epileptic excitability (i.e., the lesion constitutes a risk factor for epileptic excitability, but neurons at or near the lesion site do not actually generate seizures). Localization by ictal extracranial EEG might be considered always correct in specificity to epileptic excitability (i.e., when ictal discharges are detected with extracranial electrodes, they always indicate an actual epileptic seizure, not merely a high risk of a seizure), but sometimes incorrect in anatomy (in that atypical propagation patterns may generate seizures with misleading scalp topography). When localizations by MRI and ictal extracranial EEG are discordant, either MRI or ictal EEG may be correct in localizing a single ictal onset zone as determined with intracranial recording, or both may be partly correct when intracranial recordings show two independent sites of ictal onset. Concordance of localizations by MRI and ictal extracranial EEG thus provides a high degree of confidence that specificity to both anatomy and epileptic dysfunction has been achieved, both on conceptual and on empirical grounds.

Similar reasoning might be applied to the question of whether an epilepsy-associated MRI lesion and exclusively unifocal interictal extracranial EEG spikes, over the same temporal lobe, predict the ictal onset zone with extremely high certainty, so as to justify resection without any form of ictal EEG recording. Interictal spikes on scalp EEG are subject to the same limitations in relation to cerebral generators of EEG activity as are ictal discharges on scalp EEG. Not surprisingly, it is commonplace to record one or more sites of frequently occurring interictal spikes with intracranial electrodes, which were not detected with extracranial electrodes (37,40). Not all pathological, focal spikes are in fact associated with clinically evident epilepsy (41). Further, temporal-maximum interictal spikes are often recorded in patients who have psychogenic non-epileptic events (19). Thus, extracranially recorded interictal spikes clearly add little to the anatomical aspects of MRI localization, and do not add the complete specificity to epileptic excitability that is provided by ictal EEG recordings. While interictal magnetoencephalography (MEG) might more completely and specifically record interictal spikes than does scalp EEG, a complete determination of MEG spiking will not confer the specificity to epileptic excitability that is provided by ictal EEG recordings (42–45). Further, determination of MEG spiking will not exclude the occurrence of psychogenic non-epileptic events.

It must be allowed that TLE-with-HS might be a special syndrome, in which unifocal temporal spikes have an unusually high specificity to epileptic excitability. One retrospective study suggests that TLE patients with more frequent interictal spiking may be more likely to have refractory seizures and also more likely to have hippocampal sclerosis (46). Empirical studies might in the future establish that hippocampal atrophy, or certain other temporal lobe MRI lesions, and exclusively concordant temporal spikes on scalp EEG, in the absence of contradictory semiologic and other clinical information, always correctly predict the ictal EEG findings, so as to permit confident temporal resection in the absence of any ictal EEG recordings. Several reports have provided evidence that many patients with ipsilateral temporal lobe MRI and interictal scalp EEG spikes have ipsilateral limbic TLE that is successfully treated with resection (7–9). None of these reports are prospective series of patients studied with tests designed to detect evidence of extratemporal or bilateral temporal ictal onset zones, or of pseudoepileptic seizures, however.
EXCLUSION OF NON-EPILEPTIC SEIZURES WITH ICTLAL VIDEO-EEG

Video-EEG recorded during habitual seizures sometimes provides evidence that the medically refractory seizures are in fact psychogenic non-epileptic seizures, among patients who appear to have TLE based on history, interictal EEG and MRI (19,47–49). There appears to be little or no evidence that a patient who suffers from refractory temporal lobe seizures is in any way protected against other forms of epilepsy, against organic types of paroxysmal non-epileptic disorders, and against psychogenic pseudoepileptic seizures. Indeed, refractory TLE may predispose some individuals to development of psychogenic seizures (49). Many patients have both epileptic and psychogenic non-epileptic events. The psychodynamics of some TLE patients apparently shape their pseudoseizure semiologies so as to be more similar to complex partial seizure semiologies, than is the case among pseudoseizure patients who have no evidence of ever having had actual epilepsy (48). While neuropsychometry can reliably detect psychological dysfunctions that are highly associated with pseudoseizures, most individuals with psychological traumas and psychological dysfunctions in fact never generate pseudoseizures (50–53). Conversely, some patients with video-EEG-diagnosed pseudoseizures are not found to have any risk factors for pseudoseizures, based on comprehensive psychiatric interview and neuropsychometric testing (50–53). Thus, neurologists who believe that they can reliably determine which patients are certain not to have psychogenic non-epileptic seizures, based on neurological history and examination or on “gut feeling,” are likely in error. Currently, we must depend on video-EEG during habitual events not only to diagnose, but also to exclude occurrence of, psychogenic non-epileptic seizures.

In TLE presurgical evaluations, video-EEG is useful in the diagnosis of non-epileptic seizures in two particular situations:

1. **Detection of AED-unresponsive psychogenic non-epileptic seizures in patients who also have AED-responsive TLE and in patients who do not have active epilepsy.** Some patients with ablative or malformative temporal lobe MRI lesions, and with interictal temporal lobe spikes on scalp EEG, generate psychogenic non-epileptic seizures that simulate epileptic seizures (19). These patients may demonstrate psychogenic events early in the course of video-EEG monitoring, but have no epileptic seizures even during long periods off AEDs, or have epileptic seizures only after significant tapering or complete discontinuation of AEDs (19). When tolerable AED regimens are fully controlling epileptic seizures, epilepsy surgery is not a reasonable therapy.

2. **Detection of psychogenic non-epileptic seizures in patients who also have refractory TLE.** These patients might attain full epileptic seizure control with temporal resection, but may nonetheless remain disabled by ongoing non-epileptic seizures postoperatively. When quality of life and disability are not improved after epilepsy surgery, it is not always clear that simply controlling epileptic seizures justifies exposure to surgical risks. Some might argue that the psychogenic seizures should be addressed with psychotherapy, and psychogenic events should cease before exposure to any surgical risk. On the other hand, it is possible that controlling epileptic seizures might permit improved psychological functioning and thereby act indirectly to reduce psychogenic seizures. Perhaps there even are TLE patients in whom epileptic simple partial seizures consistently trigger disabling psychogenic events, and surgical control of the simple partial seizures might directly
terminate the dependent psychogenic events (54–56). These speculations have not been addressed empirically. The optimal place of epilepsy surgery in patients with coexistence of medically refractory complex partial seizures and uncontrolled psychogenic pseudo-epileptic events is unclear at present.

SUMMARY

Ictal video-EEG monitoring, using extracranial electrodes, often provides information in localizing the ictal onset zones in TLE that is not obtained with interictal EEG, brain imaging, and other noninvasive diagnostic techniques. The ability of continuous video-EEG monitoring to record multiple events particularly supports detection of bilateral and multifocal ictal onset zones, and detection of epileptic and non-epileptic events coexisting in one individual. These data can be used to improve patient outcomes, by improving surgical planning and sometimes by avoiding unindicated surgery. For example, a patient who has unilateral hippocampal sclerosis on MRI, with ipsilateral temporal spikes on interictal EEG, might be found to have bilateral independent ictal onsets on extracranial EEG (confirmed with intracranial recording), or might be found to have psychogenic events as the habitual, uncontrolled seizure type (with evidence that epileptic seizures are fully controlled on a tolerable AED regimen). Currently, one cannot reliably predict which patients will have information on video-EEG that contradicts or adds surgery-altering information to that provided by interictal EEG and MRI, so one cannot choose patients who will not benefit by ictal video-EEG so as to avoid unnecessary video-EEG monitoring. The costs of video-EEG monitoring are well within the expense range of diagnostic studies used to plan definitive therapies of disabling conditions in medically advanced societies. At this time ictal video-EEG monitoring should be performed before temporal resection in epilepsy therapy.

REFERENCES


Chapter V-16
Ictal Semiology and the Presurgical Workup

Chapter V-16a: Ictal Semiology Is Very Useful for Lateralizing Seizures in the Presurgical Workup

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INTRODUCTION

The goal of presurgical evaluation of patients with epilepsy is identification of the “epileptogenic zone.” Any surgical strategy is most likely to result in seizure freedom only if the epileptogenic zone can be removed in its entirety. Clinical history coupled with further careful attention to detail in analyzing seizure semiology by video-EEG recording form the touchstone of formulating the first hypothesis of “ictal onset zone” for a particular epilepsy patient. Supplemented with evidence from neuroimaging tools, a reasonable assumption for the epileptogenic zone may be made to then subsequently proceed with planning of surgical strategy. Since the advent of video EEG monitoring, it has been possible to document seizure evolution with precision, and new information continues to emerge about components of semiology, which may indicate an underlying brain region as their seat of origin. The reliability of these signs is not perfect (some less reliable than others) and it is imperative that the accuracy of description of a sign must be considered together with the specificity ascribed to it by way of existing data. Here we review the value of lateralizing signs in the presurgical planning of epilepsy patients and also elucidate some of the signs, which are not considered to have lateralizing value.
LATERALIZING SIGNS

Intuitively, it would seem that unilateral sensory or motor ictal phenomenon should implicate the contralateral hemisphere as their site of origin. However, the accuracy of various signs in predicting the hemisphere of origin differs. Commonly observed signs which have the highest positive predictive value include: early version, focal clonic movements, unilateral dystonic or tonic posturing, ipsilateral automatisms, and eye/mouth deviation. Although strictly a postictal phenomenon, hemiparesis during the period of recovery from a seizure is strongly predictive of a contralateral hemisphere of seizure origin. Signs that are less commonly observed, but have a strong predictive value when present, include ictal paresis, unilateral blinking, ictal vomiting, and asymmetric limb posturing during generalized tonic-clonic seizures.

Other signs such as version in the absence of secondary generalization, unilateral head tilt, and deviation of the head or eyes may not be as reliably lateralizing.

Version

Version is defined as clonic or tonic head and eye deviation, which is sustained, unquestionably forced, and involuntary, resulting in sustained unnatural lateral positioning of the head and eyes usually followed by secondary generalization to a tonic-clonic seizure. When used in this context, versive movements reliably implicate the contralateral hemisphere in 100% of instances (1). Nonversive head and eye movements are unsustained, wandering, or seemingly voluntary. Several authors have substantiated the lateralizing significance of early (<10 sec from ictal onset) version with strong interobserver agreement (1–4). It should be noted that accurate use of version as a contralateral lateralizing sign requires distinction from late versive movements during a seizure, which are more often ipsilateral to the hemisphere of origin as well as from all other types of head and eye turning (5).

Contrary to versive movements, ictal eye and/or head deviation may occur in a variety of circumstances and must be interpreted with caution, for it has very limited usefulness in lateralizing to the correct hemisphere of seizure onset. Nonversive head and eye deviation may occur ipsilateral to mesial temporal lobe seizure onset, in association with contralateral dystonic upper limb posturing, and may even occur later in the course of a seizure with an initial versive phase.

Dystonic or Tonic Posturing

Dystonic posturing is defined as sustained, involuntary, unnatural posturing of an extremity (commonly the distal upper extremity), associated with a rotatory component (6,7). When the proximal limb is involved, the progression from a more distal to proximal spread can be discerned.

Tonic posturing is a stiffening of one extremity (usually the upper) in simple flexion or extension, without associated rotation. It may follow the dystonic posturing during the course of ictal progression.

Dystonic posturing is indicative of contralateral hemispheric involvement with statistically significant positive predictive values (8,9). Although one study (8) found tonic posturing to have a high positive predictive value, the authors reported that this finding did not reach statistical significance.
Eye/Mouth Deviation
This sign has very good inter-observer agreement and is defined as a forced and involuntary clonic or tonic eye/mouth deviation (8). Deviation of the mouth was seen to be associated with secondarily generalized seizures in a majority of patients studied, and it indicated a contralateral hemisphere of origin in all instances (2).

Focal Clonic Movements
An early circumscribed clonic movement in the face, bulbar, or limb musculature with preserved awareness is a valuable localizing sign indicating seizure onset in or adjacent to the primary motor cortex (10,11). Hemiclonic activity ipsilateral to the hemisphere of seizure onset may also evolve from a generalized tonic–clonic phase of a secondarily generalized tonic–clonic seizure. A postictal hemiparesis, contralateral to the seizure onset, is usually present under such circumstances.

Ipsilateral Automatisms
Unilateral upper extremity automatisms could be the result of potentially bilateral automatisms with superimposed immobilization of the contralateral extremity. The immobilization of the contralateral extremity could be the result of a negative motor phenomenon such as lateralized ictal paresis or due to a positive motor phenomenon such as tonic/dystonic posturing. Ipsilateral automatisms correctly indicated the epileptogenic zone in all patients in one series (2).

Postictal ipsilateral nose wiping is also on the spectrum of ipsilateral automatisms manifest due to contralateral motor impairment of the upper limb, and it can provide reliable lateralizing information in greater than 90% of the patients when observed (12,13).

Ictal Speech
Clearly distinguishable speech, whether or not contextually appropriate, if present during ictus is indicative of epileptogenesis from the nondominant hemisphere. This sign must be used with caution, as presence of speech could be seen in four different settings: speech during isolated auras, ictal speech, postictal speech, and lastly in a patient with focal seizures who has bilateral independent representation of speech. Furthermore, adequate testing of language requires patient cooperation and technician participation, with potential for inter-observer disagreement during analysis of recorded video clip. These factors add to the difficulty in uniform interpretation and therefore previous reports have not found this sign to be always reliable (2,14–16).

Postictal Dysnomia
Postictal dysnomia is very likely to indicate ictal onset zone in the speech dominant hemisphere and is felt to be as a result of inactivation of the language areas by ictal activity. This sign may be observed in up to one-fifth of the epilepsy patients (2). Direct stimulation studies have demonstrated this phenomenon by stimulation of Broca’s, Wernicke’s, and the basal temporal language areas. Eliciting this sign requires
adequate testing and caution must be used to exclude dysnomia due to other reasons such as ictal or postictal state of altered awareness with confusion.

**Lateralized Ictal Paresis**

Lateralized ictal paresis is defined as an abrupt loss of tone in a limb during a seizure while the opposite side demonstrated movement. Examination must exclude increased tone or dystonia as an explanation of the absence of movement. Oestreich et al. (17) noted that although this sign was observed rarely (5 of 94 patients), when present it implicated the contralateral hemisphere in all instances (10,17).

**Unilateral Blinking**

Unilateral blinking is a relatively uncommon ictal phenomenon. When observed to be clearly unilateral and without any accompanying facial clonic movements or deviation of the mouth, it indicates epileptogenic zone in the ipsilateral hemisphere and serves as a reliable lateralizing sign. Wada first described this sign in a group of temporal lobe epilepsy patients (18). It may also be seen in extratemporal epilepsy patients as described in a series of 14 patients (frontal lobe epilepsy in five, nonlocalizable epileptogenic zone in three) (19). The epileptogenic zone could be lateralized in 12 of the 14 patients, with ipsilateral blinking present in 10 (positive predictive value 83% against EEG).

**Asymmetric Tonic Limb Posturing During Generalized Tonic Clonic Seizures**

Asymmetric tonic limb posturing (ATLP) or the “Figure 4 Sign” is sometimes observed during the course of a secondary generalized tonic-clonic seizure. One elbow is extended while the other is flexed during the tonic phase of the generalized tonic-clonic convulsions (GTCs). The extended elbow is contralateral to the side of ictal onset and it may be the only available lateralizing sign. In one series involving 57 patients, semiology implicated the correct hemisphere in 35 of 39 patients who had ATLP during their seizures with a very good agreement between observers (20).

**Automatisms with Preserved Responsiveness**

Psychomotor seizures typically result in automatisms with alteration in awareness. It has been noted that automatisms may also take place with minimal or no alteration in awareness and responsiveness. Such a constellation of automatisms with preserved responsiveness is found to reliably implicate the right temporal lobe (21,22). In a series of 123 patients with temporal lobe epilepsy, automatisms with preserved responsiveness were never found in left temporal epilepsy, and occurred in up to 10% of the right temporal cases (22).

**Ictal Vomiting**

In patients with symptomatic epilepsy, ictal emesis commonly implicates the non-dominant hemisphere. In a series of nine patients, documented by simultaneous video and EEG recordings, ictal epileptiform abnormalities were lateralized to the
right hemisphere and involved temporal lobe structures in all patients (23). Another report of two patients with ictal emesis (one with left and one with right hemisphere language representation) demonstrated ictal patterns regional to the corresponding nondominant hemisphere (24).

CONCLUSIONS

Lateralizing signs (Table 1) can provide information about the correct hemisphere of ictal onset in about 75% of the patients (2,4). Consistent recognition of these signs is achieved only by a strict adherence to established definitions. Studies systematically investigating clinical seizure semiology in pediatric patients indicate that although the overall frequency of lateralizing signs in children is lower compared to adults, there is no age-specific difference of lateralizing accuracy (4). Contralateral signs, (e.g., early version, dystonic posturing, eye/face deviation) have a high lateralizing value of up to 100% (1,2,6). Ipsilateral lateralizing signs (e.g., ipsilateral automatisms) show a correct lateralizing accuracy of up to 90% (6). Careful attention to history and documentation of seizure semiology is invaluable in presurgical evaluation of medically refractory patients with focal epilepsy.

However, one must not overlook the fact that despite a strict adherence to correct diagnostic criteria, in a certain proportion of the epilepsy patients, even the most robust lateralizing semiological features may implicate the wrong hemisphere. Astute observation of seizure semiology must be supplemented with additional electrophysiological and neuroimaging evidence in formulating a hypothesis for a potential epileptogenic zone in individual patients.

Table 1  Frequency and Predictive Value of Lateralizing Signs

<table>
<thead>
<tr>
<th>Sign</th>
<th>Frequency (%)</th>
<th>Correctly predicts side of ictal onset (%)</th>
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</thead>
<tbody>
<tr>
<td>Version (≤10 sec before generalization)</td>
<td>45 (31–58)</td>
<td>100</td>
</tr>
<tr>
<td>Dystonic LIMB posturing</td>
<td>37 (24–50)</td>
<td>94</td>
</tr>
<tr>
<td>Mouth deviation</td>
<td>34 (22–47)</td>
<td>92</td>
</tr>
<tr>
<td>Focal clonic movements</td>
<td>2.2a</td>
<td>100</td>
</tr>
<tr>
<td>Ipsilateral automatisms</td>
<td>21 (10–32)</td>
<td>100</td>
</tr>
<tr>
<td>Ictal speech</td>
<td>16 (6–25)</td>
<td>83</td>
</tr>
<tr>
<td>Postictal dysnomia</td>
<td>21 (10–32)</td>
<td>100</td>
</tr>
<tr>
<td>Lateralized ictal paresis</td>
<td>5.3</td>
<td>100</td>
</tr>
<tr>
<td>Unilateral blinking</td>
<td>1.5</td>
<td>83</td>
</tr>
<tr>
<td>Asymmetric tonic limb posturing</td>
<td>68b</td>
<td>85–94</td>
</tr>
<tr>
<td>Automatisms with preserved</td>
<td>5.6</td>
<td>100</td>
</tr>
<tr>
<td>responsiveness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ictal emesis</td>
<td>10c</td>
<td>87.5</td>
</tr>
<tr>
<td>Postictal nose wiping</td>
<td>60</td>
<td>89–100</td>
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</tbody>
</table>

aFrom Ref. 11.
bFrom Refs. 20 and 25.
cFrom Ref. 23.
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Chapter V-16b: Limitations of Ictal Semiology for Lateralizing Seizures

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INTRODUCTION

Ictal semiology has long been used in conjunction with video-EEG, radiology, and clinical findings to identify the epileptogenic zone during presurgical evaluation. Most epileptologists would agree that in cases with definitive and concordant EEG and radiographic findings, semiology contributes little. However, when these studies are ambiguous or conflicting, what is the value of semiology in the presurgical evaluation? This issue is discussed first in general terms, then using head version, dystonic posturing, and automatisms as illustrative examples. We do not wish to argue that semiology is without value. Our goal is to discuss the methodological limitations in the literature, and argue that most semiology signs have primarily a confirmatory role in seizure lateralization.

GENERAL ARGUMENTS

The lateralizing potential of ictal semiology is limited by physiology. Seizures may originate from silent cortex before spreading to eloquent cortex. In this case, the true epileptogenic zone is not detectable by semiology. Instead, the downstream eloquent cortex may be mistaken for the epileptogenic zone. Similarly, negative phenomena, which are more difficult to detect, may lead to the mistaken use of downstream positive phenomena to identify the epileptogenic zone.
There are several design limitations to the studies published in the current literature. First, the sample used in any study should be representative of the population of interest. In this case, the population of interest is patients undergoing presurgical evaluation. The sample predominantly used in the literature is retrospectively identified patients with good postsurgical outcome (please see following sections for detailed discussion). Unfortunately, this sample is by necessity not representative of the target population. The conclusions of studies using such samples have limited applicability to the clinical situation at hand. A prospective study with preoperative identification of the semiology sign, and analyzing surgical failures as incorrect lateralization of the sign, would be a conservative study design.

A related concern is the identification of a gold standard for correct lateralization. Correct identification of the epileptogenic zone defines correct lateralization. Postsurgical seizure freedom is possibly the strongest evidence available that the epileptogenic region was correctly identified and removed. Unfortunately, use of postsurgical outcome as the gold standard will underestimate the utility of the semiology sign as not all surgical failures can be reasonably attributed to incorrect lateralization. Correct lateralization but incorrect localization, insufficient area of resection, and overlap with eloquent cortex are reasonable additional explanations. Reevaluation of surgical failures with EEG to determine if the epileptogenic zone was correctly identified would improve the estimate but holds the problem that a new epileptogenic zone may have appeared in the interim. An alternative approach is to use localization by EEG and radiography as the gold standard. This, however, will necessarily contaminate the study with false lateralization of the epileptogenic region. A combined approach would involve preoperative identification of the semiology sign and analysis based on surgical outcome, with additional use of EEG and imaging results for judging surgical failures. Each of these gold standards is imperfect; concordant findings from studies using various gold standards would be the most convincing evidence.

Identification of the semiology sign is a surprisingly complex issue. The definition of the sign should be agreed on, and inter-rater reliability for its presence should be good. The kappa statistic has been used to evaluate the inter-rater reliability in a few studies, as will be discussed below. However, reviewers of ictal videos in these studies were mainly from the same institution. Coworkers over time may develop convergent viewpoints. Thus, for a true measure of inter-rater reliability, reviewers should be from multiple institutions. Second, reviewers should be blinded to clinical, EEG, and radiographic outcome. Blinding is difficult if a subset of patients with a particular characteristic (i.e., good postoperative outcome) is selected before entry into the study.

Having discussed the general concerns, we next flesh out our discussion using the examples of head version, dystonic posturing, and automatisms. These three signs were chosen for their reported high lateralization value (please see Chapter V-16a).

HEAD VERSION

Definition

The first group commonly credited with careful video-EEG analysis of spontaneous seizures with head version is Wyllie et al. (1). Versive head movements were defined as “clonic or tonic head/eye deviations, unquestionably forced and involuntary, resulting in sustained unnatural positioning.” Later, studies by Chee et al. (2), Olboch et al. (3), Bleasel et al. (4), and Marks et al. (5) defined a minimum duration
of sustained posturing. This duration varied from 3 to 10 seconds. Other studies included a requirement for degree of rotation of the head (5–7). Yet others included a requirement for neck extension or concomitant eye or torso rotation (8,9). Still others found a striking correct lateralization if head version occurred 10 seconds or less before secondary generalization, but not earlier (5,10). In contrast, others found a significant ipsilateral localization in “early” head turns (8,11,12). One study (11) found no head turns with a “forced quality” despite sample size comparable to the Wyllie et al. study but nevertheless found significance to nonforced head turning. It is clear that the current literature does not support a universally accepted definition of head version (Table 1).

**Inter-rater Reliability**

Several studies examined the inter-rater reliability of semiology signs (2,3). High reliability was reported (kappa statistic = 0.76 and 0.74, respectively), but almost all authors within each study were members of the same institution. This potentially limits the interpretation of reliability, as discussed in the section “General Arguments.”

**Blinding**

No study known to the authors used complete blinding. Almost all studies blinded seizure reviewers to EEG data. However, this is inadequate since by study design patient characteristics are known. For example, reviewers of studies using Engel Class I outcome as entry criteria know *a priori* that the patient being reviewed has a single, surgically accessible lesion and did well postoperatively.

**Sample Representativeness**

No study known to the authors used a sample representative of the population of patients undergoing presurgical evaluation. This limits the applicability of the study results, as discussed above.

**Gold Standard**

All studies reviewed by the authors used surgical outcome, ictal EEG, or concordance of studies in the presurgical workup as the gold standard for localization of the epileptogenic zone. These standards are limited, as discussed above.

**Conclusions**

Despite the different definitions and designs used, the majority of studies from multiple centers have shown a reasonable lateralization value to head version in the samples tested. This suggests that semiology does have lateralization power, but its magnitude is unclear in the clinical scenario of interest because of the concerns outlined above.
<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Number of patients</th>
<th>Definition</th>
<th>Gold standard</th>
<th>Institution</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wyllie et al., 1986 (1)</td>
<td>39</td>
<td>“Clonic or tonic head/eye deviations, unquestionably forced and involuntary, resulting in sustained unnatural positioning”</td>
<td>Ictal EEG</td>
<td>Cleveland Clinic</td>
<td>27/39 patients, 100% contralateral</td>
</tr>
<tr>
<td>Kernan et al., 1993 (12)</td>
<td>29</td>
<td>Head deviation = &gt;15° and lasting &gt;3 sec; forced head deviation; “sustained, unnatural tonic or clonic movement”</td>
<td>EEG</td>
<td>New York University</td>
<td>More than 10 sec before secondary generalization: 91% ipsilateral; 10 sec or less before secondary generalization: 91% contralateral; forced: 89% contralateral</td>
</tr>
<tr>
<td>Jobst et al., 2000 (13)</td>
<td>26 (frontal lobe epilepsy)</td>
<td>Not distinctly defined. Early: occurred at beginning of seizure. Late: preceded by other clinical symptoms</td>
<td>Concordance of imaging, EEG, history, Wada; 80% Engel Class I, II</td>
<td>Dartmouth</td>
<td>Early: 7/10 patients contralateral; 1/10 ipsilateral. Late: 4/4 patients contralateral</td>
</tr>
<tr>
<td>Williamson et al., 1998 (11)</td>
<td>67 (TLE)</td>
<td>Not distinctly defined. Early: first half of seizure. Late: second half of seizure</td>
<td>Engel Class I outcome</td>
<td>Dartmouth; Univ. Penn.; Yale</td>
<td>Early: 33/34 patients ipsilateral. Late: 25/25 patients contralateral</td>
</tr>
<tr>
<td>Chee et al., 1993 (2)</td>
<td>38</td>
<td>“Clonic or tonic head/eye deviations, unquestionably forced and involuntary, resulting in sustained unnatural positioning.”</td>
<td>Seizure freedom (if TLE); 90% decrease in frequency (if ETLE)</td>
<td>Cleveland Clinic</td>
<td>17/38 patients, 98% contralateral, 2% ipsilateral</td>
</tr>
<tr>
<td>Olboch et al., 2002 (3)</td>
<td>14 (TLE)</td>
<td>“Clonic or tonic head/eye deviations, unquestionably forced and involuntary, resulting in sustained unnatural positioning.” &gt;5 sec</td>
<td>Engel Class I</td>
<td>Vienna</td>
<td>22 seizures, 100% contralateral</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Number of patients</th>
<th>Definition</th>
<th>Gold standard</th>
<th>Institution</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleasel et al., 1997 (4)</td>
<td>54</td>
<td>“Clonic or tonic head/eye deviations, unquestionably forced and involuntary, resulting in sustained unnatural positioning”</td>
<td>Seizure freedom (if TLE); &gt;90% decrease in frequency (if ETLE)</td>
<td>Cleveland Clinic</td>
<td>12 patients with TLE, 100% contralateral; 14 patients with ETLE, 100% contralateral</td>
</tr>
<tr>
<td>Marks and Laxer, 1998 (5)</td>
<td>55 (TLE)</td>
<td>“Appeared involuntary and forced,” “consisted of 45 degrees rotation or tilt,” “persisting &gt;10 sec”</td>
<td>Engel Class I</td>
<td>UCSF</td>
<td>60% contralateral, 40% ipsilateral; 100% contralateral if occurred within 10 sec of secondary generalization</td>
</tr>
<tr>
<td>Fakhoury and Abou-Khalil, 1995 (8)</td>
<td>32 (TLE)</td>
<td>“Forced, progressive, and accompanied with neck extension or if simultaneous head jerking occurred in direction of head turning.” &gt;2 sec and &gt;30°</td>
<td>Engel Class I, II, III</td>
<td>Vanderbilt</td>
<td>First head version 87% ipsilateral</td>
</tr>
<tr>
<td>Yu et al., 2001 (7)</td>
<td>82 (TLE)</td>
<td>“Active movement of the head and neck in the first 30 sec of sz which were carried through a range ≥15° and lasted ≥3 sec.” Tonic: “unquestionably forced head deviation, resulting in a sustained, unnatural positioning of the head”</td>
<td>Engel Class I</td>
<td>Taipei</td>
<td>Tonic in 66 seizures from 31 patients: 65% ipsilateral, 35% contralateral. 53/64 tonic or nontonic seizures that secondarily generalized: 83% contralateral</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Description</td>
<td>Location</td>
<td>Outcome and Notes</td>
<td></td>
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<td>-------------------------------</td>
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<tr>
<td>Chou et al., 2004 (10)</td>
<td>38 (TLE)</td>
<td>“Appeared involuntary and forced, tonic or clonic deviation of the head to one side”</td>
<td>Taipei</td>
<td>88% of 25 seizures contralateral; 100% of version before secondary generalization contralateral</td>
<td></td>
</tr>
<tr>
<td><strong>Negative studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robillard et al., 1983 (9)</td>
<td>24</td>
<td>First clinical manifestation of seizures; “marked”: forced, body, head, and eye rotation</td>
<td>Montreal</td>
<td>48% of 84 seizures ipsilateral, 52% of 84 seizures contralateral (did not separately analyze group with marked head turn)</td>
<td></td>
</tr>
<tr>
<td>Newton et al., 1992 (6)</td>
<td>42 (TLE)</td>
<td>“Major”: turning of head, eye, and trunk that was “marked, sustained movement that appeared forced or driven 45° or more”</td>
<td>Melbourne</td>
<td>6 seizures ipsilateral, 5 contralateral, 2 ambiguous</td>
<td></td>
</tr>
<tr>
<td>Quesney, 1986 (14)</td>
<td>19 (TLE)</td>
<td>“Tonic and forceful”</td>
<td>Montreal</td>
<td>7 seizures ipsilateral, 6 contralateral</td>
<td></td>
</tr>
<tr>
<td>Ochs et al., 1984 (15)</td>
<td>43</td>
<td>“Smooth, seemingly involuntary turning of the head to one side” “within 40 sec of the electrographic onset”</td>
<td>Montreal</td>
<td>53/106 seizures ipsilateral, 41/106 contralateral, 9/106 both</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations*: TLE, temporal lobe epilepsy; ETLE, extratemporal lobe epilepsy; UCSF, University of California San Francisco.
DYSTONIC POSTURING

The literature on dystonic posturing is fairly uniform (see Table 2 for details). The results of the studies consistently showed good lateralization value of dystonic posturing. The definition of dystonic posturing varies between centers but all include a bizarre and forced posturing of one side of the body. Inter-rater reliability in one study was good with a kappa value of 0.78 for temporal lobe epilepsy (4). However, as in the studies of head version, reviewers mainly belonged to the same institution. All but one study used postsurgical outcome as the gold standard; the last used EEG criteria. All studies used retrospectively identified samples that were not representative of the population undergoing pre-surgical evaluation. The blinding was incomplete, as study subjects were preselected for certain characteristics.

IPSILATERAL AUTOMATISMS

Automatisms are not well defined in the literature. Some studies do not define it at all; others specify a duration or type of movement (see Table 3). A few studies specifically mentioned the coexistence of both automatisms and dystonia in the same seizure (10,16,17). When both signs were present, 100% lateralizing value was found in one study (10). When seizures with automatisms alone were analyzed, no lateralizing value was found. This suggests the possibility that part of the predictive value of automatisms is because of the coexistence of dystonic posturing. Moreover, incidence of automatisms in patients with TLE varies from 9% to 81% (5,11). This suggests that the definition of automatisms used varies considerably between institutions. Kappa statistic is fair (0.65) in one study, but reviewers were from the same institution (2). As in the studies of head version and dystonia, the sample studied for automatisms was not representative of the population of interest. All were retrospective, and blinding was suboptimal. The gold standard used in all but one study was surgical outcome. Only one used EEG, clinical, and radiographic findings. Unlike the consistent results for dystonia, the lateralizing value of automatisms is less consistent than that of dystonic posturing, ranging from statistical non-significance to 100% predictive value.

CONCLUSIONS

In the preceding text we have tried to illustrate the complexity of the literature supporting the lateralization value of semiology using the examples of head version, dystonic posturing, and automatisms. The literature fairly consistently supports a strong lateralization value to semiology. However, no study in the literature met criteria of (i) prospective design, (ii) multicenter design, (iii) use of a sample representative of the population of interest, (iv) use of a definition of semiology achieved by consensus, with concordance tested statistically, (v) use of semiology as a truly independent variable (i.e., does not use the semiology in question to guide the presurgical workup), and (vi) report the predictive value against both gold standards of surgical outcome and localization by EEG and radiology. We conclude that while semiology can be useful in directing further evaluation, it cannot currently stand alone in surgical decision making.
<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Number of patients</th>
<th>Definition</th>
<th>Gold standard</th>
<th>Institution</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleasel et al., 1997 (4)</td>
<td>54</td>
<td>“Sustained (&gt;10 sec) forced, unnatural posturing of an upper extremity on one side of the body either in flexion or extension at the elbow and had a rotational component”</td>
<td>Seizure free or ≥90% reduction in frequency</td>
<td>Cleveland Clinic</td>
<td>19 patients with TLE: 92% PPV; 11 patients with ETLE: 100% PPV</td>
</tr>
<tr>
<td>Williamson et al., 1998 (11)</td>
<td>67 (TLE)</td>
<td>“Varied from bizarre, distorted posturing of a hand and arm (sometimes leg) to simple hand clenching and straightening”</td>
<td>Engel Class I</td>
<td>Dartmouth; Univ. Penn.; Yale</td>
<td>44/48 patients contralateral; 1/48 ipsilateral; 3/48 bilateral</td>
</tr>
<tr>
<td>Fakhoury and Abou-Khalil, 1995 (8)</td>
<td>32 (TLE)</td>
<td>“Unnatural, sustained positioning of one or both arms, including unnatural immobility of one arm relative to the other.” Subtle posturing was further evaluated by “fast forward review of videotapes.”</td>
<td>Engel Class I, II, III</td>
<td>Vanderbilt</td>
<td>160/167 seizures contralateral; 6/167 ipsilateral; 1/167 bilateral</td>
</tr>
<tr>
<td>Marks and Laxer, 1998 (5)</td>
<td>55</td>
<td>“Maintenance of a sustained, abnormal, contorted limb posture”</td>
<td>Engel Class I</td>
<td>UCSF</td>
<td>10 patients with sign, 90% contralateral</td>
</tr>
<tr>
<td>Kotagal et al., 1989 (16)</td>
<td>41</td>
<td>Same as Bleasel et al., 1997 (4)</td>
<td>Engel Class I</td>
<td>Cleveland Clinic</td>
<td>14/91 seizures, 100% contralateral</td>
</tr>
<tr>
<td>Chou et al., 2004 (10)</td>
<td>38</td>
<td>“Sustained, forced, unnatural posturing with a rotational component”</td>
<td>Engel Class I</td>
<td>Taipei, China</td>
<td>28 seizures, 96% contralateral</td>
</tr>
<tr>
<td>Dupont et al., 1999 (17)</td>
<td>60</td>
<td>“Sustained posturing”</td>
<td>Clinical, EEG, and radiographic findings</td>
<td>Paris, Belgium, Canada</td>
<td>37/39 contralateral; 1/39 ipsilateral; 1/39 bilateral</td>
</tr>
</tbody>
</table>
### Table 3  Studies of Ictal Automatisms

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Number of patients</th>
<th>Definition</th>
<th>Gold standard</th>
<th>Institution</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williamson et al., 1998 (11)</td>
<td>67 (TLE)</td>
<td>“Semipurposeful motor activity” with “consistency among different seizures”</td>
<td>Engel Class I</td>
<td>Dartmouth; Univ. Penn.; Yale</td>
<td>41 patients with sign; 37 ipsilateral, 4 contralateral, 13 bilateral</td>
</tr>
<tr>
<td>Marks and Laxer, 1998 (5)</td>
<td>55 (TLE)</td>
<td>&gt;10 sec, not otherwise defined</td>
<td>Engel Class I</td>
<td>UCSF</td>
<td>5 patients with sign, 80% ipsilateral, not statistically significant</td>
</tr>
<tr>
<td>Chou et al., 2004 (10)</td>
<td>38 (TLE)</td>
<td>“Rapid, repetitive, pill-rolling movements of the fingers or fumbling, grasping movements”</td>
<td>Engel Class I</td>
<td>Taipei, China</td>
<td>90 seizures; 89% ipsilateral; 94% with simultaneous contralateral dystonia</td>
</tr>
<tr>
<td>Kotagal et al., 1989 (16)</td>
<td>41 (mostly TLE)</td>
<td>Not defined</td>
<td>Engel Class I</td>
<td>Cleveland Clinic</td>
<td>13 seizures with automatisms only: 7 ipsilateral and 6 contralateral</td>
</tr>
<tr>
<td>Chee et al., 1993 (2)</td>
<td>38</td>
<td>Not defined</td>
<td>Seizure-free (TLE); &gt;90% seizure reduction (ETLE)</td>
<td>Cleveland Clinic</td>
<td>21% with sign, 100% ipsilateral</td>
</tr>
<tr>
<td>Dupont et al., 1999 (17)</td>
<td>60</td>
<td>“Stereotyped, nonpurposel, involuntary movement of the upper extremities”</td>
<td>Mix of clinical findings, EEG, and radiology</td>
<td>Paris, Belgium, Montreal</td>
<td>25 patients with TLE and sign; 3 contralateral, 1 bilateral, 21 ipsilateral, 2 patients with ETLE and sign; 2 contralateral, 2 patients with both seizure types and sign; 2 ipsilateral</td>
</tr>
</tbody>
</table>

*Abbreviations: TLE, temporal lobe epilepsy; ETLE, extratemporal lobe epilepsy; PPV, positive predictive value; UCSF, University of California San Francisco.*
REFERENCES

INTRODUCTION

Proliferation of cross-sectional imaging techniques over the last several decades has transformed the understanding, evaluation, and management of patients with epilepsy. Commonly applied imaging techniques range from the anatomic modalities of computed tomography (CT) and especially magnetic resonance imaging (MRI), to modalities reflecting metabolism or function including exams based on MRI data as well as the use of radioisotopes. Following a brief discussion of the role of CT, this chapter reviews the application of MRI in the standard clinical evaluation of the patient with epilepsy.

ROLE OF COMPUTED TOMOGRAPHY

Although no longer considered a standard for evaluation of the patient with epilepsy, CT is still useful in limited circumstances, notably when speed is paramount or when MRI is contraindicated. CT is indicated in emergency setting for evaluation of new-onset seizure patients with symptomatic causes including focal deficits, fever, trauma, persistent headaches, history of cancer, anticoagulation as well as in the elderly in whom acute stroke and tumors are the most likely causes (1,2). Compared to MRI, CT suffers from markedly inferior soft tissue contrast as well as beam hardening artifact.

Despite these limitations, CT depicts many of the pathologies that may underlie epilepsy, especially those associated with acute presentations such as hemorrhage, infarction, and mass lesions as well as obvious malformations and calcified lesions. Often CT serves as first-line imaging in acute presentation where urgent treatment may be merited. Patients with hemispheric pathology such as Sturge–Weber or with calcified lesions found in tuberous sclerosis may be adequately evaluated with CT. Small tumors, subtle cortical malformations and mesial temporal sclerosis may be
easily missed with CT. In general, patients with normal exams or with lesions judged incompletely characterized by CT will then proceed to MRI.

MAGNETIC RESONANCE IMAGING TECHNIQUES

Benefiting from superior soft tissue contrast, true multiplanar capability, absence of bone artifact and potential for high resolution, MRI has evolved into the unrivaled imaging standard for routine evaluation of the epilepsy patient. Beyond the impact on diagnosis and management of patients with epilepsy, MRI has influenced the understanding of epilepsy syndromes by shifting emphasis from electrophysiologic and clinical diagnosis to structural abnormalities underlying clinical and electrophysiologic manifestations (3).

Whereas CT imaging depicts one parameter, X-ray attenuation, MRI reflects a number of independent but related parameters reflecting the temporal dynamics of proton nuclei responding to changing magnetic fields. The parameters manifest in MRI include T1, T2, susceptibility effects (T2'), and proton density. Most MR sequences attempt to primarily demonstrate a single parameter although the resultant images are generally variably affected by others. Expansive MR development has yielded myriad imaging sequence approaches and options. The choice of optimal sequence and imaging plane depends upon suspected pathology and so is best done with clear communication between radiology and referring service following clinical evaluation.

MRI protocols attempt to optimize two approaches to lesion detection. In the first, tissue contrast is maximized generally through standard T2-weighted imaging or related techniques, especially fluid attenuated inversion recovery (FLAIR). Such imaging increases sensitivity to lesions that exhibit T2 differences from normal brain, most notably mesial temporal sclerosis. In the second approach to imaging optimization, resolution is enhanced through use of thin slices, especially with three-dimensional (3D) imaging acquisition that allows for reformatting in multiple planes. 3D thin slice imaging maximizes evaluation for subtle abnormalities which exhibit little or no T2 abnormality, most notably cortical dysplasia. In this application, the 3D sequence parameters are chosen to augment signal intensity difference between gray and white matter, thereby improving visualization of structural abnormalities. Before discussing the specifics of an MRI epilepsy protocol, a few comments attempting to clarify the alphabet soup of MRI sequences relevant to imaging epilepsy are warranted.

Rapid Acquisition and Resolution Enhancement (RARE), FSE, TSE

In 1986, Hennig et al. (4) demonstrated a technique for diminishing scan time in which multiple spin echoes were measured for a given excitation (i.e., multiple lines of k-space) rather than one k-space line, as is the case with conventional spin echo. The train of spin echoes was created through the use of a series of 180° inversion pulses that were applied after the creation of each echo. Originally labeled RARE, for rapid acquisition and resolution enhancement, the approach is now more commonly known by manufacturer labels—fast spin echo (FSE) and turbo spin echo (TSE). Although clearly faster, early implementations proved less sensitive in detection of subtle T2 lesions. Following further evaluation, it became apparent that the problem resided not with the concept but rather with the long TR values (4000 milliseconds or greater) initially employed. With proper choice of parameters, TSE/FSE is very similar to the
conventional spin echo method in lesion detection, while maintaining the advantage of reduced imaging time (5). The reduced imaging time may be used to limit motion in a restless patient or, as is the case with usual epilepsy protocols, may be traded for higher resolution imaging matrix.

**Use of Fast FLAIR and “White Matter Inversion Recovery”**

T2-weighted imaging provides superior parenchymal contrast in brain imaging. However, small T2-weighted hyperintense lesions may be obscured by adjacent, normally bright structures, most notably cerebrospinal fluid (CSF)—an occasional problem in evaluation of the hippocampus. FLAIR was developed to overcome this limitation through use of a magnetization preparation pulse applied prior to initiation of a T2-weighted imaging sequence. Here, an inversion recovery pulse is applied and the spins are then allowed to relax back partially to the equilibrium state as defined by their T1 characteristics. The imaging sequence is begun after a delay, $T_I$ for inversion time, when the tissue to be suppressed is at the null point (effectively, with no net longitudinal magnetization) on its course back to equilibrium. In FLAIR, the $T_I$ is chosen so that CSF is at the null point. The end result is a predominantly T2-weighted image with CSF suppressed through exploitation of its T1 relaxation characteristics.

The $T_I$ of CSF is long, so a fairly long time (2000–2500 milliseconds) must elapse between the inversion recovery pulse and the initiation of the imaging sequence. In early implementation, FLAIR was used with a spin echo sequence. Although the advantage of the technique was demonstrated, the imaging time (>10 minutes) was too long to gain widespread acceptance (6). More recently, FLAIR has been implemented with FSE/TSE sequence (fast FLAIR) yielding acceptable imaging times.

In a manner similar to FLAIR imaging, gray/white contrast may also be enhanced using an inversion recovery preparation pulse timed to suppress white matter signal relative to gray matter. The sequence is sometimes referred to as “white matter inversion recovery” (WMIR). In WMIR, an inversion recovery pulse is used with a modified inversion time, arrived at empirically, to maximize signal intensity difference between the two tissues.

**Typical MRI Epilepsy Protocols**

Typical protocols for MRI in evaluation of the epileptic patient begin with a standard noncontrast brain evaluation. Included are a T1 sagittal, a T2 axial, a T1 axial, and a FLAIR axial. Slice angulation is determined by common practice which varies by institution. A line drawn on the T1 sagittal from the anterior commissure to the posterior commissure (so called AC–PC line, Fig. 1A) is widely used. Standard slice thicknesses of 4–5 mm are employed usually with a skip between slices of 1 mm or so. This simple protocol provides significant information but does not optimally evaluate sometimes more subtle abnormalities.

Reflecting the importance of medial temporal lobe structures in lesional causes of epilepsy, protocols have been optimized to evaluate this region. In general, T2 or FLAIR sequences are performed in a near coronal plane oblique to be orthogonal to the long axis of the hippocampus (so-called “temporal lobe oblique,” Fig. 1B). The obliquity is best determined through inspection of an off-midline sagittal demonstrating the longitudinal extent of the hippocampus. Greater resolution improves visualization of the internal architecture of the hippocampus and thereby
enhancing diagnostic sensitivity and confidence. In MRI, higher resolution comes at the cost of signal-to-noise ratio (SNR) and so steps must be taken to improve SNR and thus avoid images unacceptably noisy or grainy. At our institution, we employ specifically designed surface coils that increase SNR at the level of the hippocampi. The dedicated coils allow for higher resolution (512 \times 384 matrix) WMIR images and T2 FSE images with satisfactory imaging times (Figs. 2 and 4). FLAIR provides for improved T2 contrast as well and is useful in evaluation of mesial temporal sclerosis (MTS) when performed using temporal lobe oblique orientation. In the author’s opinion, FLAIR has two deficiencies in this specific application. First, the hippocampi may normally appear somewhat bright compared to adjacent brain. Of course, asymmetry in signal intensity will help in detection of the abnormal

Figure 1  Midline (A) and off-midline (B) T1 sagittal used for prescription of imaging planes used in epilepsy protocol. In (A), midline T1 sagittal is presented with line drawn from anterior commissure to posterior commissure (AC–PC line). The line is used to identify the axial plane, thereby allowing more consistent identification of axial and coronal planes on individual patients. In (B), off-midline T1 sagittal allows identification of hippocampus (arrows). A line drawn perpendicular to the longitudinal axis of the hippocampus defines the so-called “temporal lobe oblique” plane—allowing for optimal inspection of the cross-section of the body of the hippocampus.

Figure 2  FSE T2 temporal lobe oblique coronal at level of mid-body of hippocampus demonstrates clear hippocampal atrophy and T2 high signal.
hippocampus but bilateral MTS does occur in some cases and so may be confused
with normal findings. As a second potential FLAIR deficiency, the sequence is not
readily performed with high resolution. Recognizing these potential limitations,
FLAIR temporal lobe oblique can be most helpful when higher resolution sequences
are motion compromised.

As an additional procedure in medial temporal lobe evaluation, a 3D T1
sequence (see below) may be performed in the temporal lobe oblique orientation.
The sequence provides contiguous thin slices (1–1.5 mm) that improve visualization
of anatomy, a capability sometimes helpful in challenging cases. The T1 sequence
lacks sensitivity to T2 changes, which are a common and useful finding in MTS but
provides superior depiction of atrophic changes. Additionally, the T1 3D sequence
is optimally suited to the application quantitative volumetric techniques used com-
monly in research studies and gaining increasing acceptance in clinical evaluation (7).

Detection of epileptogenic lesions outside the medial temporal lobe often pre-
sents a greater imaging challenge. In this MRI application, sequences which maxi-
imize contrast between gray and white matter while providing high resolution are
most useful. Three dimensional volumetric high resolution T1 gradient echo (GRE)
scanning with thin partitions is commonly applied. The 3D data set has the advantage
of providing thinnest possible slices while allowing for reformatting in arbitrary planes
as the specific imaging problem merit. The sequences vary subtly from one manu-
facturer to another and unfortunately no uniform system of nomenclature has been
adopted (8,9).

**MRI Protocol Choice**

Specific choice of MRI protocol depends on the technology available, the preferences
and experience of the interpreter, and critically the suspected type and location of
epileptogenic lesion. The type of pathology likely to underlie a given patient’s epi-
lepsy depends on multiple factors, especially age and duration of disease process.
The reader is referred to Table 1. Although a general protocol designed to evaluate
all epilepsy patients is an option, the patient’s interests will be better served through
crafting the protocol to specific lesion possibilities. Commonly, MTS is a prime
consideration in which case the MRI protocol should consist of a basic screening
exam with additional temporal oblique sequences, especially a high resolution T2
FSE, and at least one of WMIR, FLAIR, and 3D T1 gradient exam. If cortical
dysplasia is a main possibility, then a screening exam followed by a T1 3D gradient
is a good start. Ideally, the T1 3D exam is positioned to evaluate the area of brain
suspected as an epileptogenic focus as suggested by seizure semiology and EEG.
Sometimes a WMIR sequence favorably oriented to the cortex will improve diagnostic
confidence in subtle cases. On occasion, findings detected after review of the initial
imaging exam merit a second, more focused MRI evaluation.

**Use of Gadolinium**

In general, gadolinium is not necessary in patients with chronic epilepsy. In patients
who have a lesion suspicious for neoplasm, contrast is certainly helpful in further
characterizing the lesion. However, gadolinium is not helpful in evaluating MTS,
cortical dysplasia, or most atrophic processes. At our institution, contrast is not
part of the initial evaluation for patients with chronic epilepsy. In patients with
a more recent epilepsy presentation, especially older adults, the likelihood of
tumor as a cause for the symptoms is higher so contrast may be useful in the initial evaluation. Note that in this subgroup, a dedicated epilepsy imaging study may not be needed.

IMAGING OF SPECIFIC EPILEPTOGENIC DISEASE PROCESSES

Mesial Temporal Sclerosis

MTS is the most common pathology associated with temporal lobe epilepsy which is refractory to medical therapy. In epilepsy patients undergoing neurosurgical treatment, MTS is the single most common lesion (50–70%), followed by perinatal hypoxia or other insult (13–35%), tumors (15%), vascular malformations (3%), traumatic gliosis (2%), and developmental abnormalities (2%) (10). The identification of MR abnormality in patients with MTS, when correlated with EEG, serves as useful prognosticator for successful surgical treatment. In particular, a successful outcome after anterior temporal lobectomy has been observed in 70% to 90% patients with MR findings of MTS compared with 40% to 55% of patients in whom the MR is normal (11–13). It should be noted that MTS in and of itself does not prove the existence of refractory epilepsy as it has been observed in patients successfully treated medically (14).

Mesiotemporal or hippocampal sclerosis is characterized pathologically by pyramidal and granule cell neuronal loss in the cornu ammonis and gyrus dentatus often with hippocampal reorganization and evidence for changes in energy metabolism (15). Observed abnormal axonal sprouting and loss of interneurons relate to the altered balance of neuronal excitation and inhibition integral to the epileptogenicity of this lesion.

Primary findings seen on MRI in MTS are T2 high signal and atrophy of the hippocampus (Figs. 2–4) (16). Such findings may be quite subtle and so a concerted effort at obtaining the highest quality temporal lobe MR study should be made in

<table>
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<tr>
<th>Table 1 Epilepsy Cause by Age of Onset</th>
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<td>Age at onset (year)</td>
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<td>Infection</td>
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<tr>
<td>Hippocampal sclerosis</td>
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<tr>
<td>Vascular malformation</td>
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<td>Post-traumatic epilepsy</td>
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<td>Tumor</td>
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<td>Stroke</td>
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all cases. Other findings have been described in MRI as well, notably diminished gray–white matter differentiation, often referred to as loss of internal architecture. In cases with significant involvement of the hippocampal head, loss of the head interdigitations is observed (Fig. 4) (17). Secondary findings include ipsilateral atrophy of the fornix and of the mamillary body. One may also note atrophy of the white matter in parahippocampal gyrus between hippocampus and collateral sulcus (collateral hippocampal white matter). Additionally, atrophy of much of the adjacent temporal lobe has been described. These secondary findings are in general less helpful as they tend to be seen only in the more advanced MTS cases and may be misleading without the observation of the primary abnormality. As a manifestation of atrophy, ipsilateral enlargement of the temporal horn has been described. Asymmetric temporal horns sometimes occur normally so this nonspecific finding should be used with caution. Findings essentially never seen in MTS include enhancement and mass effect. Of course, the presence of mass effect should raise concern for underlying neoplasm.

Patients with MTS may have more than one lesion relevant to their epilepsy. The so-called dual pathology occurs in up to 15% of cases (18,19). Associated pathologies include cortical dysplasias, tumors, and vascular malformations (Fig. 5). Of these, cortical dysplasia is the abnormality most commonly observed in conjunction with MTS. Further evaluation, management and potential surgical treatment will be directly altered by the presence of a second relevant lesion so the search for pathology does not end with the observation of MTS. In general, the finding of dual pathology decreases the likelihood of successful surgical treatment. In many cases, both lesions merit consideration of resection.

Vascular Malformations

Vascular malformations may present with epilepsy. The most relevant example is the cavernous malformation (CM) for which the most common presentation is seizures (Fig. 5B) (20–22). Arteriovenous malformations may occasionally cause seizures although more typically will present with hemorrhage or other symptoms referable to mass effect. MRI is essentially 100% sensitive to CMs and will identify
Figure 4  Temporal lobe oblique WMIR (A) and FSE T2 (B) images demonstrate loss of interdigitations along with T2 high signal and atrophy in this case of MTS involving the pes hippocampus.

Figure 5  Dual pathology. FSE T2 temporal oblique coronal (A) shows MTS in mid-body of the hippocampus in this patient with a cavernous malformation adjacent to the pes and amygdala (B).
the majority of arteriovenous malformations. Although specialized MRI techniques are not in general needed to detect these lesions, MR does assist in lesion characterization and in many cases may be used to make a definitive diagnosis preoperatively. Key findings to identify in characterizing a CM on MRI include the presence of a complete hemosiderin ring, best seen with T2 sequence. Other characteristic findings include lack of adjacent edema (except in the setting of recent overt hemorrhage), reticulated internal architecture, and blooming of blood products on T2* (T2 GRE) sequence. The T2* sequence may also be used to identify lesions too small to detect without the benefit of susceptibility effects. Also, with gadolinium, one may identify developmental venous malformations often associated with CMs, thereby aiding further in preoperative planning.

Tumors

Although many neoplasms cause seizures, a subset present with chronic epilepsy and so fall into the preimaging differential diagnosis with cortical dysplasias, CMs, and MTS. Highly epileptogenic tumors occur most often in the temporal lobe or adjacent to cortex (23). The indolent tumors yielding chronic epilepsy include ganglioglioma, low-grade glioma, and dysembryoplastic neuroepithelial tumor (DNET). Within this subset, prediction based on MR of specific histologic type is difficult but educated guesses can be made. When cortically based, these often longstanding lesions may erode the inner table of the calvarium. Most of these tumors tend to be small and well localized with little edema or mass effect. Occasionally, a low grade oligodendroglioma may have achieved modest size (several centimeters) at time of presentation. Also, oligodendrogliomas may be suggested by the presence of calcification and of heterogeneous enhancement. Cysts are common with gangliogliomas (Fig. 6) (24). Occasionally, gangliogliomas may metastasize throughout CSF pathways with a pattern of multiple small subarachnoid cysts (25). For both DNETs and gangliogliomas, enhancement is variably present and when present tends to be focal or nodular (26,27). The classification of DNETs is somewhat controversial as they may not represent true tumors, noting their stable course and histology reflect a dysplastic process. On MRI, DNETs may exhibit a thick gyriform or nodular configuration. They may be small and exhibit signal intensity similar to CSF with T1 and T2 weighting, thereby confounding detection. FLAIR and T2 imaging tends to be the most helpful, at least at first inspection, in detection of all these tumors. The use of additional imaging planes and of gadolinium contrast is often helpful in further characterization.

Developmental Abnormalities

Developmental abnormalities represent a most challenging diagnosis in the patient with epilepsy. In addition to enhancing detection, MRI has greatly expanded our understanding of such pathology (28). Indeed, current classification schemes based largely on MRI findings have been developed (Table 2) (29). Superior resolution, gray–white matter contrast and multiplanar capability afforded by MRI again improve imaging evaluation. With respect to developmental abnormalities, although MRI detected lesions are often sources of epilepsy, the actual epileptogenic zone may differ from or be more extensive than the anatomic lesion. As such, even with an MRI detected lesion, surgical management demands invasive electrophysiologic monitoring in most cases. In the following, a few representative developmental abnormalities and their MRI appearance are presented.
Focal cortical dysplasias (FCDs) consist of abnormal neurons and glial cells arranged in disorganized manner in the cerebral cortex (30,31). When certain abnormal neurons are present, balloon cells, the FCD represents anomalous neuronal and glial proliferation. When balloon cells are not present, then the FCD is the result of abnormal cortical organization. Findings described with FCDs include obscuration of the gray–white junction, thickened cortex, abnormal sulcation, and cortical dimple with overlying CSF cleft (32). In the balloon cell variant of cortical dysplasia, often T2 high signal is present in involved subcortical areas. Figure 7 is provided as an illustrative example.

Schizencephaly differs from FCD in that a CSF lined cleft, usually lined by polymicrogyric cortex, connects pial surface to ependymal (33,34). As with FCDs, the abnormality may be bilateral and is seen commonly in the peri-Rolandic regions.

Figure 6  FLAIR axial (A), T2 FSE axial (B), postcontrast T1 coronal (C), and T2 FSE coronal (D) in patient with ganglioglioma. The FLAIR and T2 axial images show area of signal abnormality in the lateral right temporal in this patient with chronic epilepsy. The T2 FSE coronal confirms the finding to be either in the middle or inferior temporal gyri. No significant mass effect or volume loss is evident. The postcontrast T1 coronal suggests slight enhancement in the inferior aspect of the lesion. Findings were judged to be most suggestive of low-grade tumor. Pathologic diagnosis was ganglioglioma.

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Schizencephalies are subdivided into open- or closed-lip variants. Closed-lip lesions exhibit polymicrogyric walls which appose each other at one or more points whereas in the open-lip form the walls are always separated. In the closed-lip form, a “dimple” along the wall is the ventricle provides a clue to diagnosis. Figure 8 is provided as an illustrative example.

A disorder of both neuronal and glial proliferation, hemimegalencephaly results in enlargement of all or part of a cerebral hemisphere (Fig. 9) (35,36). Patients present early in life usually with intractable epilepsy, followed in childhood by hemiparesis and mental retardation. The disorder may be associated with neurofibromatosis type 1, Klippel–Trenaunay–Weber syndrome, and hypomelanosis of Ito. MRI confirms hemispheric enlargement along with ipsilateral enlargement of the ventricular atrium and classic straightening of the frontal horn. Ipsilateral white matter usually exhibits T2 high signal representing gliosis. Cortex in the affected hemisphere is dysplastic, variously exhibiting polymicrogyria, pachygyria, or agyria.

**Table 2** Classification System

1. Malformations due to abnormal neuronal and glial proliferation
   a. Generalized
      i. Decreased proliferation (microlissencephaly)
         - Microcephaly with simplified gyral pattern or microlissencephaly with thin cortex
         - Microlissencephaly with thick cortex
      ii. Increased proliferation (none known)
      iii. Abnormal proliferation (none known)
   b. Focal or multifocal
      i. Decreased proliferation (none known)
      ii. Increased and abnormal proliferation (megalencephaly and hemimegalencephaly)
      iii. Abnormal proliferation
         - Non-neoplastic: focal cortical dysplasia
         - Neoplastic (but associated with disordered cortex)

2. Malformations due to abnormal neuronal migration
   a. Generalized
      i. Classical lissencephaly (type 1) and subcortical band heterotopia (agyria-pachygyria-band spectrum)
      ii. Cobblestone dysplasia (type 2 lissencephaly)
      iii. Lissencephaly: other types
      iv. Heterotopia
   b. Focal or multifocal malformations of neuronal migration
      i. Focal or multifocal heterotopia
      ii. Focal or multifocal heterotopia with organization abnormality of the cortex
      iii. Excessive single ectopic white matter neurons

3. Malformations due to abnormal cortical organization
   a. Generalized
      i. Bilateral diffuse polymicrogyria
   b. Focal or multifocal
      i. Bilateral partial polymicrogyria
      ii. Schizencephaly
      iii. Focal or multifocal cortical dysplasia (no balloon cells)
      iv. Microdysgenesis

4. Malformations of cortical development, not otherwise classified

*Source: From Ref. 29.*
Abnormal neuronal migration results in ectopic gray matter. When the gray matter is in areas other than cerebral cortex, the resultant malformation is termed a heterotopia. Depending on the timing of migration interference, the heterotopias may be subependymal or subcortical in location. Presentation is highly variable with patients ranging from asymptomatic to mildly retarded (37–39). Heterotopias occur

![Figure 7](image1)

*Figure 7* In (A), a proton density axial shows an abnormality in the left frontoparietal region. Images reformatted in axial (B) and sagittal (C) plane from 3D T1 GRE sequence show the abnormality to consist of an area of thickened cortex adjacent to the Sylvian fissure associated with an anomalous deep sulcus, consistent with focal cortical dysplasia.

Abnormal neuronal migration results in ectopic gray matter. When the gray matter is in areas other than cerebral cortex, the resultant malformation is termed a heterotopia. Depending on the timing of migration interference, the heterotopias may be subependymal or subcortical in location. Presentation is highly variable with patients ranging from asymptomatic to mildly retarded (37–39). Heterotopias occur

![Figure 8](image2)

*Figure 8* In (A), a T2 axial shows abnormal cortex bilaterally with that on the patient’s right exhibiting a CSF lined cleft in direct communication with the ventricle (open-lip schizencephaly). In (B), series of contiguous partitions from a 3D T1 GRE sequence are presented. The presence of a CSF lined cleft is confirmed. No such cleft is present on the patient’s left; however, gray matter clearly extends from the cortex to the ventricle. On the T2 axial, a focal outpouching at the ventricle represents a “dimple”—as seen with closed-lip form of schizencephaly. If the “dimple” were not present then the abnormality would be more consistent with focal cortical dysplasia (transmantle cortical dysplasia).
in isolation as well as in combination with other anomalies, particularly relating to development of the corpus callosum and of the cerebellum. Epilepsy, usually partial, is the most common presentation. Imaging may be quite subtle, as even a single focus of heterotopic grey matter (heterotopion) may occur. As such, a 3D T1 GRE sequence is the most useful for reasons previously described. Conventionally, the heterotopias are subdivided into (i) subependymal, (ii) focal subcortical, and (iii) band heterotopia.

Individuals with isolated heterotopia generally exhibit a fairly mild clinical course with overall normal development and onset of seizures, usually partial, in the second or third decade. Patients with associated anomalies and with more extensive heterotopias often exhibit developmental delay in addition to seizures. Subependymal heterotopias may be roughly divided into two groups. Most affected individuals have heterotopias that are few and asymmetric. These are usually sporadic and may be associated with Chiari II malformations, and callosal agenesis. A second, smaller group of heterotopias are familial and exhibit heterotopias which essentially fully line the lateral ventricle walls (Fig. 10). A large cisterna magna has been specifically described in girls with X-linked subependymal heterotopia (38,40). Boys may exhibit associated cortical malformations, severe mental retardation, and syndactyly (41). In the familial group, mutations of chromosome Xq28 have been described (40–42).

As with subependymal heterotopias, the severity of clinical disturbance in patients with focal subcortical heterotopias varies greatly with the extent of the heterotopia (43). Patients so affected exhibit varying manifestations ranging from asymptomatic to severe developmental delay and hemiplegia. Nearly all patients with focal subcortical heterotopias develop epilepsy, usually in the first or second decade.

Band heterotopias or “double cortex” exhibit ribbons of ectopic gray matter between cortex and ventricles with white matter on both sides (44–47). Usually the ribbons are bilateral and fairly symmetric but significant variation exists. Patients
are generally symptomatic in childhood with presentation including seizures and developmental delay. Women are affected more than men. Although mostly sporadic, sex-linked dominant inheritance has been observed. Affected women may have sons with lissencephaly and daughters with band heteropia.

The key in diagnosing a heterotopia is identifying an area of tissue following gray matter on all sequences. Subependymal lesions tend to be nodular and to predominate near the trigone of the lateral ventricles. No nodules are seen along third and fourth ventricles. Subtle cases represent an interpreting challenge likely to be aided by use of T1 in the coronal plane, especially with thin sections provided by 3D T1 GRE sequences. Focal subcortical lesions appear as nodular masses of tissue exhibiting gray matter signal intensity. Mass-like indentation upon the adjacent

**Figure 10** T2 FSE axial (**A**), T1 axial (**B**), and off-midline sagittal T1 (**C**) reformatted from 3D sequence acquired in coronal plane in patient with extensive subependymal gray matter heterotopia. T2 FSE axial image (**A**) demonstrates nodular contour of ventricles due to ectopic gray matter (isointense to cortical gray matter on both T1- and T2-weighted sequences). T1 axial (**B**) depicts extensive lining of ventricles including trigones to temporal horns. On the T1 sagittal (**C**), gray matter lines visualized lateral ventricle including temporal horn and trigone. Note linear bridges of gray matter extending from subependymal heterotopia to cortex in the parieto-occipital region. The involved sulci are subtly abnormally deep and presumably represent dysplastic cortex.
ventricle allows for confusion with neoplasm. However, heterotopias lack edema and
do not enhance. Clues to the presence of a heterotopia include abnormalities of the
cortex overlying the lesion, including thinning of the cortex and shallow sulcation.
Inspection of the apparent mass-like effect on the ventricle proves that it relates to
distortion of the affected region and not the presence of a true mass.

Phakomatoses
Several of the phakomatoses result in epilepsy with tuberous sclerosis and Sturge–Weber
the most noteworthy examples. Although well-described clinical signs of these syn-
dromes exist, they can be subtle or sometimes not present and so diagnosis relies on
imaging. Both disorders can be diagnosed definitively with MRI.

Cortical tubers and subependymal nodules dominate the intracranial mani-
festations of tuberous sclerosis (Fig. 11) (48,49). The cortical tubers are characterized
by broad, flat gyri with subcortical white matter signal abnormality. The signal
abnormality varies with the stage of myelination. In neonates, the white matter exhi-
bits T1 high signal and T2 low signal. This pattern reverses with myelination. The
number and size of cortical tubers varies greatly. Subependymal nodules are recog-
nized as rounded contour abnormalities lining the ventricles. They should be dis-
tinguished from gray matter subependymal heterotopias which follow gray matter
on all sequences. In contrast, the subependymal nodules of tuberous sclerosis usually
exhibit T1 hyper- and T2 hypointensity. Calcification is present in the subependymal
nodules of older patients and may be detected with MRI by using a T2* sequence. Of
of course, CT is more useful for this specific imaging need.

Sturge–Weber or encephalotrigeminal angiomatous is characterized by lepto-
meningeal angiomatous proliferation associated with a facial port-wine stain in distri-
bution of the trigeminal nerve (50). The angioma enhances with contrast and is readily
identified with MRI. Associated findings include ipsilateral cortical atrophy with com-
pensatory calvarial thickening. White matter subjacent to the leptomeningeal angioma
exhibits T2 hypointensity until calcification alters this characteristic. In one-third of
cases, either the sclera or the ocular choroid exhibit a plexus of dilated small vessels.

Destructive Lesions Associated with Epilepsy
Trauma and stroke are major causes of epilepsy in young to older adults. In a
U.S.-based population study, one in seven epilepsy cases resulted from trauma
(51). Notably, the first recorded cortical resection for epilepsy was the removal of
a posttraumatic scar (52). Traumatic injuries most likely to yield epilepsy are those
associated with depressed skull fracture, penetrating injury, hemorrhage, and infec-
tion (53,54). Seizures associated with trauma may be classified as early or delayed
with the latter defined as occurring one week after the initial injury. Early seizures do
not presage posttraumatic epilepsy whereas late onset seizures do, with some 25% of
so affected patients going on to develop epilepsy. Although the pathology underlying
the development of epilepsy in such patients is not fully understood, it is associated with
the presence of cortical gliosis and tissue deposition of hemosiderin—both findings
optimally imaged with MRI (55,56).

A common cause of seizures in all adults, stroke becomes the most common
cause of seizures after age 50 (57,58). Although hemorrhage is regarded as epilepto-
genic, the most common stroke associated with epilepsy is nonhemorrhagic cortical
infarct—likely reflecting the overall greater incidence. Analogous to posttraumatic
epilepsy, delayed seizures following infarction increase the likelihood of subsequent epilepsy whereas early seizures alone carry a favorable prognosis (59–62). Gliotic tissue at the periphery of the infarct is thought related to the development of epilepsy.

In general, stroke and trauma do not represent a dilemma either in detection or in diagnosis. However, in select cases, MRI may assist in characterization and management of destructive brain epileptogenic lesions. In Figure 12A, a routine FLAIR axial demonstrates an area of abnormal signal in a 10-year-old with chronic epilepsy. On the basis of the FLAIR, the lesion is fairly nonspecific with differential considerations including gliosis, encephalomalacia, encephalitis and less likely tumor. As shown in Figure 12B, a high-resolution T2 coronal FSE was performed using surface coils positioned immediately over the abnormality. The superior resolution furnished by the exam unveiled detailed morphologic information allowing identification of distinctive gyri which were thinned more so at the base than at the apex. This observation along with the presence both of volume loss and of T2 hyperintensity in adjacent white matter leads to the specific diagnosis of ulegyria, a characteristic lesional pattern seen with perinatal ischemic injury. Subsequent surgical resection confirmed the preoperative diagnosis.

Infections Associated with Epilepsy

Central nervous infections of all varieties frequently cause seizures in the acute phase and depending on the type of infection and severity of initial injury may result in
chronic epilepsy. Seizures may be seen in viral infections that cause encephalitis. Herpes simplex is the most noteworthy, with some 40% of patients exhibiting seizures (63). In acute bacterial meningitis, seizures represent a frequent manifestation in children, occurring in the range of 40% (64). Bacterial infections complicated by cerebritis and especially abscess are prone to seizures. Indeed, one-fourth of cases of bacterial abscess present with seizures (65). Following the acute phase, gliosis or postabscess cavity may be observed and associated with epilepsy, which is sometimes intractable. Full characterization of such lesions, best done with MRI, is central to management and consideration of surgical treatment.

Tuberculosis central nervous system infection often causes seizures (66). Focal seizures may be associated with the presence of a focal lesion such as a tuberculoma. In the acute phase, 20% of children and 15% of adults exhibit seizures. In active disease, MRI with gadolinium is best to fully characterize the lesions.

Seizures occur at some point in the majority of cases of nervous system involvement with the helminthic infection cysticercosis (67–69). Reported incidences range from 56% to 92%. Distributed worldwide, cysticercosis is endemic in Africa, India, some of East Asia, Mexico, and Central and South America. Neurocysticercosis has been reported to be the most common cause of epilepsy in Peru (70). With increasing numbers of immigrants from these regions to the United States, seizures related to neurocysticercosis have increased greatly over the last few decades.

Symptoms of neurocysticercosis depend on the stage of the disease (71–73). Whereas early infection is generally asymptomatic, subsequent death of the parasite yields an inflammatory host response associated with symptoms. Common symptoms at this stage include seizures, headache and focal neurologic deficit. Late stages of neurocysticercal infection present commonly with epilepsy.
Imaging findings vary with the stage of disease and lesions at different stages occur simultaneously (Fig. 13) (74–76). In the earliest parenchymal stage (“vesicular stage”), thin-walled cysts without edema are noted at the gray/white junction. The scolex may be seen within the cyst as a small mural nodule. The cysts contents mirror CSF signal intensity on all sequences. A “colloidal stage” follows in which the cyst dyes and an inflammatory response ensues. Edema and peripheral enhancement are noted and the cyst contents become proteinaceous. Following this acute phase, resolving changes consist of less edema, an organizing thick enhancing rim or enhancing nodule follow (“nodular granular stage”). In this stage, mass effect is less and the lesions may be isointense on CT, making evaluation by MRI necessary. Finally, with full resolution of the cyst, adjacent edema and mass effect, all that may remain is a punctuate focus of calcification—so-called “calcified stage.” In this phase, CT is superior for identification of calcification although an MRI study may be made somewhat more sensitive to calcification with the addition of a T2 gradient-recalled (susceptibility) sequence.

Although parenchymal involvement by neurocysticercosis is most common, cysts may be found both in the subarachnoid space and within the ventricular system. Usually, such cysts follow CSF on all sequences and a scolex is not visualized. An associated inflammatory reaction may be present and associated with seizures.

### Possibly Immune-Mediated Disorders

Characterized by seizures along with progressive hemiplegia and psychomotor deterioration, Rasmussen’s encephalitis represents a leading cause of intractable epilepsy in childhood. Previously normal children develop seizures at ages ranging from 18 months to 14 years (77–80). Although seizure semiology varies, the most frequent pattern involves clonic movements, generally localized to the face and arms, persisting for long periods—a condition called epilepsy partialis continua. Other patients exhibit complex partial seizures, simple partial seizures and generalized tonic–clonic seizures. A devastating illness, patients usually decline in unremitting fashion that proves fatal unless involved areas of brain are resected. Numerous theories have been advanced to explain the phenomena with perhaps the most compelling suggesting an autoimmune mechanism related to the glutamate receptor (Chapter III-8) (81).
At pathology, the disease is characterized by extensive parenchymal injury with microglial nodules and perivascular T-cell lymphocyte infiltration (82,83). Atrophy involving cerebral cortex and white matter is pronounced in advanced stages. MRI findings reflect the pathologic changes. Early imaging studies may be normal but with time T2 hyperintensity and atrophy in affected areas will develop. Frontal and temporal lobe involvement is most common. With advanced disease, basal ganglia will exhibit T2 signal abnormality in two-thirds of cases.

CONCLUSION

Neuroimaging, with MRI, has evolved into standard evaluation along with EEG in patients with unexplained seizures. In the majority of cases, MRI provides definitive imaging characterization of lesional epilepsy. In order to maximize the potential of the technique, the protocol should be crafted to the needs of the individual epilepsy patient.

REFERENCES


Chapter VI-17: Will fMRI Replace the Wada Test?

Chapter VI-17a: Preoperative Assessment of Temporal Lobe Function with fMRI

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The ability of imaging methods to dynamically assess brain function represents a major breakthrough in cognitive localization. The reliable presence of left hemisphere, especially left frontal, blood flow changes in right-handed normal subjects lead to substantial efforts to develop imaging methods, particularly with functional magnetic resonance imaging (fMRI), that could lateralize cognitive function in the patient population (1). Certainly in the case of the preoperative evaluation of language and memory function, a noninvasive test that accurately assessed the lateralization of language and the “health” of medial temporal structures would have obvious relevance and be preferable to the current methods.

For both language and memory, the Wada (cerebral amytal) test has been the standard when presurgical information about dominance is desired. The Wada test appears to be highly predictive of the side of language dominance, and enjoys overwhelming anecdotal support, though little data exist to support the predictive value of the test (2). The ability of the Wada test to predict memory outcome is less impressive (3). The original intent of the “Wada memory” test was to avoid catastrophic amnesia following unilateral temporal lobectomy (4). This has not translated into a strong predictive value, using intracarotid amytal injections, for material-specific memory (e.g., verbal memory) following temporal lobectomy (4,5).

Certainly functional imaging does not make the same assessment of brain function as the Wada test. Anesthesia of the unilateral carotid distribution (of variable
extent depending on the particular vascular anatomy, potency of the drug, or other technical factors) would seem to mimic a similar large lesion of the brain, on a temporary basis. Functional imaging demonstrates areas of large blood flow changes (with small oxygen metabolism changes), linked to neuronal activity in an incompletely understood way. The relationship of activity during a specific task to the deficit expected after removal of such a regions may not be straightforward. Ultimately, comparisons about whether fMRI gives the same information as the Wada test should focus on which method, or combination of methods, give the greatest predictive power for presurgical decision making and functional outcome.

Another variable for both methods is the use of specific tasks to assess the highly diverse functions of “language” and “memory.” This is particularly an issue for fMRI, where tasks that are too simple (e.g., simple word reading) or too difficult, may not activate all language areas. For example, posterior language sites were not found in early blood flow studies of single word reading, but were evident for other word tasks, especially at a slower speed (1,6). In fact, some tasks that activate posterior language sites in normal subjects are derived from the cognitive psychology literature and only peripherally related to what most would consider a “language” task (7). Despite this, early efforts to demonstrate language lateralization were largely successful (8,9). These early series did not have large numbers of right-sided dominance cases; however, later larger series have suggested the general utility of functional MRI in most cases of temporal lobe epilepsy although the actual correlation with Wada appears to be 90% (2,10). Although a high number, better correlation can be obtained by assuming left-sided speech in right-handers. In extratemporal lobe cases, fMRI has a disconcordant rate of up to 25% (11).

Ideally, a language task will show strong lateralized activation during a simple word task (Fig. 1). When unequivocal, fMRI makes a strong prediction about the lateralization of language and can be quite dramatic as when “reorganization” is demonstrated following left frontal lesions (Fig. 2).

Some of the difficulty appears to be in handling “bilateral” language finding on fMRI and the precise method of how to determine language dominance remains controversial (12,13). Typically, frontal activation has been used to determine lateralization. Bilateral frontal lobe activation is very common in language fMRI studies, even in normal right-handed subjects, although left frontal usually is clearly larger than right frontal activity. Because of this bilaterality, lateralization indices are sometimes used to determine dominance, but magnitude comparisons may also be relevant. Further, posterior and frontal language regions have been reported to be incongruous (Fig. 3), although sometimes this lack of clear lateralization is shared by the Wada test as well (14–16). In summary, the best language task for language lateralization remains unclear, but emerging research is encouraging for the use of fMRI to determine language lateralization (13,17–20). The topic of fMRI localization of language is beyond the scope of this chapter, but is an even more uncertain tool in the clinical setting as used currently.

Another uncertainty in functional MRI is the interaction of the blood oxygenation level dependent (BOLD) response with pathology. Vascular activation can decrease around tumors (21). False lateralization of the BOLD response has been described following a seizure (22). Paradoxical increase in activation near a tumor (which could lead to false lateralization) has been described for a language task (22,23).

Functional MRI is a very promising tool as a non invasive marker of neuronal activity. The expected sensitivity and specificity of the test and its reliability for surgical planning are being addressed by a variety of groups and it is likely that the tool
A right-handed man with a history of aphasic events was found to have a hemorrhaged cavernous malformation in the left inferior frontal cortex (asterisk). After his aphasia resolved, fMRI using the same word task showed strong right-sided lateralization of language, confirmed by good surgical outcome following resection.

Figure 1  Left frontal activation in a right-handed woman with left temporal lobe seizures. A strongly lateralized activation is seen during a task where words must be categorized as living or nonliving.

Figure 2  A right-handed man with a history of aphasic events was found to have a hemorrhaged cavernous malformation in the left inferior frontal cortex (asterisk). After his aphasia resolved, fMRI using the same word task showed strong right-sided lateralization of language, confirmed by good surgical outcome following resection.
increasingly will complement current investigations. Developing reliable language paradigms that can be easily implemented in the clinical setting will improve the utility of language fMRI (24).

Determining the relative value of fMRI compared to the Wada test for assessment of memory function is confounded by the lack of predictive power of the Wada test itself (3). One possible limitation is the incomplete perfusion of medial temporal structures by an intracarotid injection, which has led some groups to consider posterior cerebral injections to assess memory function (25,26). This is not a procedure that has enjoyed widespread support, perhaps because of the higher morbidity, especially in less experienced hands. Despite these limitations, when the Wada test produces significant amnesia, it strongly suggests disease of the hemisphere opposite to injection (27). In fact, the Wada memory test can help lateralize the focus in cases of bitemporal electrical abnormalities (28).

Recent reports have found, in small series, lateralization of medial temporal lobe activation. Medial temporal lobe activation is not always apparent during memory tasks but is reliably found during various picture tasks (29). In cases of medial temporal epilepsy lateralizing fMRI activity has been found (30,31). However, these series have high incidence of mesial sclerosis which is an independent indicator itself of memory outcome following surgery. Another recent report found that fMRI lateralization predicted outcome of a picture memory test. A test that adequately predicts verbal memory performance postoperatively remains to be described.

**SUMMARY**

Functional MRI and the Wada test are likely complementary in their assessment of brain function and potentially with different relationships to postoperative outcome. In the rare instance when a direct assessment has been made both tests perform well in language lateralization, although false-lateralization with fMRI remains a concern,
and extreme attention must be paid to imaging methods, the language task chosen, and the specific analysis methods used to determine “dominance” in what is often a bilateral activation (2). The incomplete understanding of memory processes further confounds the situation for this function, as it seems neither fMRI nor Wada in isolation provides adequate predictive value of verbal memory decline. Nevertheless, the Wada test remains quite useful in identifying lateralized abnormalities of temporal lobe function and patients that might be at risk for a global memory decline. With Wada and fMRI in combination, and if structural MRI and neuropsychological data is included in the analysis, it is possible that postoperative outcome will be predicted with increasing accuracy.

REFERENCES

Chapter VI-17b: fMRI Could, in Principle, Replace the Wada Test

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A great deal of development and testing will be needed to learn if functional magnetic resonance imaging (fMRI) can replace the Wada test. Functional MRI must not only be shown to provide information equivalent to the Wada, but fMRI methods must be standardized and shown to be reliable and practical. These goals will require much effort to achieve, but are these efforts even worthwhile? Can fMRI in principle ever replace the Wada test?

An advantage of the Wada method is that it is a “lesion” test. The temporary deactivation of one hemisphere serves as a kind of preview of what would happen were the functionally relevant areas of one hemisphere surgically removed. Functional MRI, it has sometimes been argued, could never provide the same kind of predictive information. Who knows with certainty what is the functional significance of an “activation site” on fMRI? If fMRI cannot provide a preview of the effects of a lesion, so the argument goes, then the Wada test will always be needed to unambiguously confirm whether a postoperative deficit will occur. This is especially true for predicting postoperative amnesia after anteromedial temporal surgery, because surgery in this region can remove a substantial portion of the memory system. Patients who are unable to support memory functions in the unoperated hemisphere during Wada testing are at great risk of developing severe postoperative amnesia.

There are two problems with this logic. One is the assumption that Wada results are unambiguous. In fact, like any test, the Wada occasionally produces false-positive and false-negative results and is not perfectly reproducible (1–6). Under ideal circumstances, using a tightly standardized and optimized protocol and eliminating those cases contaminated by obtundation, insufficient sedation, crossflow, posterior cerebral perfusion, and so on, the Wada might be highly predictive of severe postoperative amnesia. The fact that this predictive capability is debated elsewhere in this volume, however, amply demonstrates that further development, testing, and standardization of the Wada would be welcome.

The second problem is the assumption that a lesion test is necessarily a better predictor of outcome than an activation test. In fact, predictive value in this setting could be obtained from any biologically valid measure of critical functional tissue. If poor outcome is highly correlated with resection of “activated” fMRI voxels, then fMRI will turn out to be highly predictive of outcome (this is a tautology and therefore hard to refute). Moreover, predictive value depends on a number of factors in addition to biological validity, such as sensitivity and measurement error. One test can be a less biologically valid measure of critical tissue but still be more predictive of outcome than another test if it provides a sufficiently more stable and reliable measure. There is thus no justification for the assumption that
a lesion test, simply by its nature, is more predictive of an outcome than an activation test.

Much testing remains to be done to learn how fMRI compares to the Wada test in predicting surgical outcomes, but some initial results are encouraging. Sabesvitz et al. (7) showed recently that preoperative fMRI measurement of lateralization of function in the temporal lobe predicted the degree of postoperative naming impairment after left anterior temporal lobectomy in a series of 24 patients. The fMRI test was a well-studied, standardized procedure shown previously to produce lateralization results similar to Wada language testing (8). Surgical resections were performed blind to the fMRI data and tailored using cortical stimulation mapping. All patients also underwent a standardized, quantitative Wada language test including naming, comprehension, repetition, counting, and reading subtests. Pre- to postoperative change on the Boston Naming Test was correlated with preoperative functional lateralization toward the side of surgery for both fMRI ($r = -0.64$, $p < 0.001$) and the Wada ($r = -0.50$, $p < 0.05$). The fMRI test showed 100% sensitivity and 73% specificity for predicting a significant decline in naming. The Wada showed 92% sensitivity and 45% specificity.

Are these results definitive? Are they applicable to all fMRI protocols? The answer to both questions is certainly “no.” This was a relatively small sample of subjects studied with a particular activation task producing a particular lateralization measure. It remains to be seen whether these results are reliable in larger samples, what range of fMRI protocols can produce similar results, and whether even better, more predictive fMRI and Wada protocols can be discovered.

There are also some initial results indicating that particular fMRI paradigms designed to produce activation in the medial temporal lobes are predictive of side of seizure focus in temporal lobe epilepsy and postoperative verbal memory decline after left temporal lobectomy (9–11). These studies are encouraging, but there is a clear need for much more extensive development and testing of such “memory” protocols and their ability to predict clinically relevant outcomes, including postoperative seizure control (12). This research will also need to include quantitative comparisons with Wada memory testing for predicting the same outcomes.

While efforts to replace the Wada test with less invasive tests are laudable, it is worth keeping in mind that fMRI and Wada testing might turn out to provide complementary information. For example, the predictive value of both tests used together might be better than either used alone (12). If so, the Wada test might continue to be necessary, at least in patients at high risk of a poor outcome. Thus, rather than “Can fMRI replace the Wada test?” the more relevant question might be “Does fMRI add useful information?”

REFERENCES

Chapter VI-17c: fMRI Is Not a Replacement for the Wada Test

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As a preface, I think I should note that the purpose of this brief commentary was to take the contrary side of the statement, “Functional magnetic resonance imaging (fMRI) can replace Wada testing” in the future. At the risk of taking on the role of apologist early in a debate, I point out that it is difficult to rebut the future. With that being said, or written, here I try to briefly point out some fundamentals that have made Wada testing useful in epilepsy surgery, some difficulties that fMRI will have to overcome to supplant Wada testing, and close with something a bit more controversial.

Wada testing is intended to isolate the cognitive function, particularly language and memory, of one cerebral hemisphere. The exact procedures and techniques for testing language, and especially memory, during Wada testing seem to have varied somewhat across locations and time. In recent years, there has been a trend toward procedural standardization to include presenting the patient with information during hemispheric anesthesia, and conducting of a delayed recall trial to determine the
retention of that information after the patient has returned to neurologic baseline. The amount of information recalled on the delayed recall trial is a measure of the non-injected hemisphere’s ability to learn and remember new information. This measure of memory has been associated with lateralization of ictal onset and postoperative memory ability in temporal lobectomy patients (1). In the author’s experience, Wada testing using a delayed recall paradigm is also predictive of verbal memory after left temporal lobectomy regardless of MRI-measured hippocampal volume (2).

Functional MRI techniques have the potential to measure the BOLD activation signal in each hippocampus, and other brain regions, during learning and memory tasks. Functional MRI has been utilized to lateralize language dominance (3,4). Functional MRI has been compared to Wada test results for memory lateralization purposes, and intrapatient reproducibility has been studied with an fMRI language protocol (5,6). While these studies have shown promising results, they have for the most part used relatively small groups of patients.

It has been pointed out, and it is worth mentioning again, that an activation task such as fMRI may not identify all brain regions involved in the activating task, and fMR activation protocols typically do not activate anterior temporal regions (3,7). Much like problems of nonstandardization in Wada testing, fMRI protocols can produce different results from the same activation dataset (8). The meaning of the fMRI signal with regard to anatomical support for memory functions may also be difficult. Unlike Wada testing, both temporal lobes, and particularly both hippocampi, contribute to the level of an individual patient’s memory performance during an fMRI memory task. So far, it does not seem that level of memory performance has been uniquely associated with the degree of activation in the neurosurgical region of interest. An fMRI protocol needs to measure the level of memory function supported by the neurosurgical region of interest, and thereby predict the extent of memory change when that region is resected. Perhaps this will be accomplished by a laterality ratio as has been done for language outcome, but the strength of the Wada test is the direct measurement of function of the surgical hemisphere regardless of pathophysiology (3). It could be assumed that patients with reduced hippocampal volume due to MTS would have a lower activated voxel count on fMRI due to the reduced tissue volume alone. Lateralization with hippocampal volume data was concordant with fMRI and Wada memory lateralization indices in seven of nine patients in one report utilizing adjustment for proportion of activated voxels (5).

The larger and more controversial question is whether routine Wada testing for temporal lobectomy patients is needed at all. The risk to auditory verbal memory and language associated with language dominant temporal lobectomy is well known. Nevertheless, patients experiencing global amnesia would seem to be quite rare, and population-based statistics on this degree of impairment do not seem available. Preoperative neuropsychological testing, MRI determined hippocampal volumes, T2 relaxometry, interictal EEG, and ictal EEG can all help predict seizure control and memory after temporal lobectomy. Wada testing can be useful in predicting verbal memory decline in language-dominant left temporal lobectomy patients even after MRI-determined hippocampal volume data are taken into account. Yet, the great majority of patients probably decide to proceed with surgery despite being told of the risks based on Wada testing, and it would be interesting to know the long-term outcomes of any patients who, based on Wada testing, decide not to have surgery. The extent to which care and understanding of a patient is changed by Wada testing may show that it is not necessary to perform Wada testing, or fMRI.
REFERENCES


Chapter VI-18
The Role of MRS in the Evaluation of Patients for Epilepsy Surgery

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INTRODUCTION

The aim of the presurgical evaluation of a candidate for epilepsy surgery is to find the answers to the following three questions: (i) From which brain region do the seizures arise and which other structures are involved in seizure spread? (ii) What is the risk that the resection of the primary epileptogenic zone will result in irreversible neurological or neuropsychological deficits? (iii) What are the chances of the patient being rendered seizure-free by the resection of this brain region? Very often, the identification of the epileptogenic focus also answers the questions regarding postsurgical deficits and seizure reduction.

Interictal and ictal EEG recordings in combination with careful observation of the seizure semiology are still considered to be the “gold standard” for the localization of the epileptogenic focus. Previously, invasive or semi-invasive intracranial EEG recordings were often unavoidable for this purpose; however, the development of several new structural and functional noninvasive imaging techniques has reduced the need for these invasive procedures. Magnetic resonance imaging (MRI), alone or in combination with relaxometry and/or volumetry, can depict structural abnormalities in the epileptogenic focus, while positron emission tomography (PET), interictal and ictal single photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS) detect functional abnormalities. In contrast to PET and SPECT, which contain information about just one functional modality, e.g., perfusion in SPECT or glucose metabolism in PET, MRS can detect abnormalities in three different metabolic pathways simultaneously: (a) N-acetyl-aspartate (NAA) as a measure of neuronal viability and functionality, (b) creatine/phosphocreatine which are important intermediates in energy metabolism, and (c) choline compounds
which reflect membrane turnover. It is the aim of this contribution to demonstrate to what degree MRS can help answer the three important questions of the presurgical exploration.

MRS AND MESIAL TEMPORAL LOBE EPILEPSY

Mesial temporal lobe epilepsy (MTLE) is the most common form of drug refractory epilepsy remediable by epilepsy surgery. Its histopathological hallmark, found in about 70% of the patients, is mesial temporal lobe sclerosis (MTS), which is characterized by neuronal cell loss and reactive gliosis in circumscribed regions of the epileptogenic hippocampus (1). Accordingly, the spectroscopic hallmark of MTS is a decrease of the neuronal marker NAA in the epileptogenic region. The decreased NAA can correctly identify the epileptogenic hippocampus in 86% to 100% of MTLE with MRI evidence of MTS (TLE-MTS). More importantly, decreased NAA, can identify the epileptogenic hippocampus in 70% to 80% of MTLE with normal MRI (2–9). Additionally, MRS also detects evidence for bilateral hippocampal damage in about 50% of MTLE (3,5,7). This is clinically important for two reasons. First, several studies have shown that a significant NAA reduction in the contralateral hippocampus is associated with an unsatisfactory postsurgical outcome. In TLE-MTS, the postsurgical outcome is good in up to 75% to 84% of the patients in whom the NAA reduction is restricted to the ipsilateral hippocampus but only in about 13% to 16% of the patients with bilateral hippocampal NAA reductions (10–12). A contralateral NAA reduction is also a predictor for an unsatisfactory postsurgical outcome in TLE with normal MRIs. However, in contrast to TLE-MTS, TLE patients with normal MRIs who have good surgical results are characterized by normal or only slightly reduced NAA in the ipsilateral hippocampus (13). Second, bilateral hippocampal NAA reductions may predict postsurgical neuropsychological deficits. The hippocampal formation is critically involved in the formation of episodic and semantic memory and thus bilateral hippocampal damage may result in persistent, global, anterograde amnesia. Therefore, the functionality, not only of the hippocampus to be resected, but also of the contralateral hippocampus, has to be assessed before surgery. Several MRS studies have demonstrated a good correlation between hippocampal NAA and pre- and postoperative memory performance (14–17). Because NAA not only reflects neuronal density but also neuronal functionality, MRS might even be better suited to assess memory function than structural exams, e.g., volumetry (18).

One of the most important limitations of MRS has been the spatial restriction of the measurements to rather small brain areas by the commonly used single voxel (SV) or single slice magnetic resonance spectroscopic imaging (MRSI) techniques while PET and SPECT were able to cover the whole brain. However, this has been changed by the development of multi-slice or more recently three-dimensional (3D) MRSI and automated postprocessing methods allowing the analysis of a large number of voxels. Several MRS studies using these techniques have demonstrated extrahippocampal and even extratemporal NAA reductions in MTLE (19–21). Such NAA reductions were found in the ipsi- and contralateral frontal lobes, especially frontal limbic and prefrontal regions, insula and ipsilateral temporal lobe and parietal lobe, i.e., reductions were found in regions involved in seizure spread in MTLE (22). As temporal and extratemporal NAA reductions were more pronounced in the ipsilateral hemisphere, they might also be helpful for the lateralization of the epileptogenic hippocampus.
and thus for the presurgical evaluation. However, further studies in a larger patient population are necessary to determine if in analogy to a recent PET study the distribution of extratemporal NAA reductions also predicts the postsurgical outcome (23).

MRS AND NEOCORTICAL EPILEPSY

In comparison to MTLE, there are only a limited number of MRS studies in patients with neocortical epilepsy (NE). This is mainly because of the special challenges MRS encounters in studying patients with NE. The clinical symptomatology and EEG findings in NE frequently only allow the identification of the epileptogenic lobe but not the exact spatial extent in the lobe from which the seizures arise, and it is difficult to cover an entire lobe appropriately with SV or single slice MRSI techniques. Furthermore, spectra from most neocortical regions are adversely influenced by artifact from skull lipids. These artifacts lead to loss of information from the most relevant regions for NE. In addition, the usual assumption that the epileptogenic focus is characterized by an isolated decrease of NAA is not necessarily true in NE, because NE is often associated with macro and microscopic malformations containing immature or undifferentiated cell elements.

Because frontal lobes contain a fair amount of interhemispheric gray matter and can be sufficiently covered with a single MRSI slice or two large SV, most studies in NE were done in patients with frontal lobe epilepsy. These studies demonstrated that decreased NAA correctly lateralizes the epileptogenic focus in 71% to 100% of patients with frontal lobe epilepsy (24–27). In addition to the decreased NAA, alterations of creatine, choline, and of the combined glutamine/glutamate peak were also found in NE, especially when associated with cortical malformations (26–28). However, in all these previous studies the measurements were restricted to the lobe suspected to contain the focus as determined by EEG or other techniques. In contrast, a recent multislice MRSI study done in our laboratory using slice selective inversion recovery and k-space extrapolation to remove the lipid artifacts tested the ability of MRS to identify the epileptogenic focus in NE without utilizing localizing information from other techniques. In this study, MRSI correctly identified the lobe containing the epileptogenic focus in 62% of the patients (70% of the patients with a MRI visible lesion and 55% of the patients with normal MRIs) and thus was comparable to or even better than other imaging techniques (29,30).

MRS may not only help with focus lateralization/identification in NE but depending on the population studied, “dual pathology,” i.e., an extrahippocampal lesion, e.g., a cortical malformation, in combination with hippocampal sclerosis can be found in up to 67% of the patients with NE (31–33). MRS can detect evidence of hippocampal damage in a high percentage of these patients (34). Because the surgical outcome is improved if the affected hippocampus can be resected with the extrahippocampal lesion, a reliable presurgical identification of “dual pathology” is of clinical importance not only for the surgery itself but also for the strategy of the presurgical evaluation (35).

CONCLUSIONS

For TLE, several studies have established the usefulness of MRS to answer the three important questions of presurgical evaluation: focus identification, outcome, and risk.
of postoperative deficits. The small number of studies in NE patients also shows promising results. While it is true that PET and SPECT may also be helpful in answering these questions, these techniques have other disadvantages and limitations, including the need for radioactive tracers and a specialized facility for their preparation.

REFERENCES


INTRODUCTION

Positron emission tomography (PET) is an in vivo functional imaging modality that allows visualization and quantification of tissue distributions of positron-emitting radiotracers. The technology is an adaptation of in vitro autoradiography and tissue counting techniques, which when combined with tomographic imaging, provides the equivalent of quantitative autoradiography in vivo (1). PET was developed as a research tool over 35 years ago, and began seeing clinical application not long thereafter. A detailed chronology of the interesting evolution of PET imaging and of the related development of organic positron-emitting radioligand chemistry and more recently of molecular imaging is beyond the scope of this chapter. Comprehensive
accounts of the development of these technologies can be found in studies by Ter-Pogossian (2), Frost (3), and Jones (4).

Brain imaging has been a major application of PET since the beginning, with epilepsy being a particular area of intense investigation. Kuhl et al. (5) were the first to demonstrate localized perfusion and metabolic alterations in PET scans of patients with partial epilepsy. In the interim since then, many other investigations have extended these early observations, contributing to both an enhanced understanding of the pathophysiology of epilepsy, as well as to the inclusion of functional imaging as a diagnostic tool in the evaluation of patients with intractable epilepsy. In this regard, PET has had application in lateralizing and localizing epileptogenic foci in potential epilepsy surgery candidates, particularly in cases where other diagnostic modalities, such as magnetic resonance imaging (MRI), electroencephalography (EEG), and clinical semiology are equivocal or discordant. PET can in some cases obviate the need for invasive electrophysiologic monitoring techniques such as intracranial grids or depth electrodes. Reimbursement for FDG-PET (FDG: 2-fluoro-2-deoxy-D-glucose) in the presurgical assessment of patients with intractable epilepsy has been approved by Medicare in the United States (6).

PRINCIPLES OF PET IMAGING

PET imaging is based on detection of photons resulting from the decay of radionuclides incorporated into compounds designed to target specific biochemical or physiologic processes. The radionuclide labels are typically produced in a cyclotron by bombardment of a stable element with protons, deuterons, or helium nuclei. The resulting isotopes have excess protons and decay by emission of positrons, which are beta+ particles having the same mass as an electron. After traveling a short distance from the source (on the order of millimeters), emitted positrons encounter electrons. An annihilation reaction ensues, producing two 511 keV photons that are given off in opposite directions. When emitted photons strike the PET scanner detectors, which are arrays of scintillation crystals coupled to photomultiplier tubes, the deposited energy is converted to visible light and recorded as projection data. Localization is achieved using so-called coincidence detection, based on the assumption that two photons detected simultaneously (actually, within a pre-set time interval on the order of 6 to 12 nanoseconds selected based on detector characteristics) at opposing detectors are from a single annihilation event. Thousands of detected coincident events per second are recorded over the imaging period to generate a tomographic image using standard reconstruction software (7).

The spatial resolution of PET imaging is determined by factors inherent in the positron annihilation process, as well as by factors related to the detection system. Factors related to the annihilation process include the distance that the positrons travel from their origin to the point of annihilation, which varies with the kinetic energy of the positron and the tissue density being traversed, and by the deviation from 180° between the paired photons resulting from individual annihilation events. Detector factors influencing resolution include the distance between detectors, the distance from the source to the detectors, and electronic response time (dead time). Although a smaller diameter scanner ring will decrease the magnitude of error due to variance of coincident photons from 180°, the trade-off is that more scattered and random coincidences will be recorded. Scattered events result from the absorption or deflection of photons within body tissues before their detection.
Random events are due to unrelated annihilation photons detected within the coincidence time window that are misinterpreted as being from a single coincidence event. The impact of scatter and random events can be corrected to some extent using hardware or mathematical modifications. Accounting for all contributions, PET images using current scanners have a reconstructed spatial resolution of approximately 4 mm (8).

For brain imaging, approximately 80% of photon pairs will be attenuated by tissue before reaching the detectors. To correct for this, a transmission scan using an external positron emitting source is performed, and a tissue attenuation factor calculated and applied (7).

**RADIOTRACERS FOR PET IMAGING**

As previously noted, the basis for PET imaging is detection of radioactivity emitted from radionuclide labels incorporated into compounds that are designed to target specific physiologic processes. The most common positron-emitting radionuclides used for PET imaging include isotopes of the basic biochemical building blocks carbon ($^{11}\text{C}$), nitrogen ($^{13}\text{N}$), and oxygen ($^{15}\text{O}$), as well as flourine-18 ($^{18}\text{F}$), which serves as an isoteric replacement for hydrogen (9). Table 1 summarizes the characteristics of these labels. Of these, $^{13}\text{N}$ and $^{15}\text{O}$ have short half lives (10 and 2 minutes, respectively) limiting their usefulness for the most part to blood flow and metabolism studies. The longer half lives of $^{11}\text{C}$ and $^{18}\text{F}$ (20 and 110 minutes, respectively) allow for more complicated syntheses of physiologically active compounds, and more flexibility in imaging protocols.

**Table 1**  
Selected Radiotracers Used in PET Epilepsy Imaging

<table>
<thead>
<tr>
<th>Radiopharmaceutical-labeled compound</th>
<th>Application</th>
<th>Half-life (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{15}\text{O}$</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>$^{15}\text{O}_2$</td>
<td>Cerebral oxygen extraction</td>
<td></td>
</tr>
<tr>
<td>$^{15}\text{H}_2$</td>
<td>Regional cerebral blood flow</td>
<td></td>
</tr>
<tr>
<td>$^{13}\text{N}$</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>$^{13}\text{H}_3$</td>
<td>Cerebral blood flow</td>
<td></td>
</tr>
<tr>
<td>$^{11}\text{C}$</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>$^{11}\text{C}_\text{O}$</td>
<td>Cerebral blood volume</td>
<td></td>
</tr>
<tr>
<td>Carfentanil</td>
<td>mu-opioid receptors</td>
<td></td>
</tr>
<tr>
<td>Methylaltrindole</td>
<td>delta-opioid receptors</td>
<td></td>
</tr>
<tr>
<td>Diphrenorphine</td>
<td>mu-, kappa-, delta-opioid receptors</td>
<td></td>
</tr>
<tr>
<td>Flumazenil</td>
<td>GABA$_A$ receptor complex</td>
<td></td>
</tr>
<tr>
<td>Methionine</td>
<td>Dysplastic cortex</td>
<td></td>
</tr>
<tr>
<td>AMT</td>
<td>Serotonergic system</td>
<td></td>
</tr>
<tr>
<td>$^{18}\text{F}$</td>
<td></td>
<td>110</td>
</tr>
<tr>
<td>FDG</td>
<td>Glucose metabolism</td>
<td></td>
</tr>
<tr>
<td>FMISO</td>
<td>Hypoxia</td>
<td></td>
</tr>
<tr>
<td>FLT</td>
<td>Cellular proliferation</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations:* AMT, alpha-$^{11}$C-methyl-l-tryptophan; FDG, fluorodeoxyglucose; FMISO, fluoromisonidazole; FLT, fluorothymidine.
At the present time, $^{18}$F labeled 2-fluoro-2-deoxy-D-glucose ($^{18}$F)FDG is the most common PET radiotracer in clinical use, not only in brain imaging, but in whole body imaging as well. FDG demonstrates increased uptake in tissues having increased metabolic activity. ($^{18}$F) FDG-PET has found particular application in oncology for staging disease and following response to treatment, in cardiology for assessing myocardial viability, and in neurology for imaging a variety of conditions, including brain tumors, cerebrovascular disease, movement disorders, dementia, other neurodegenerative disorders, and the subject of this book, epilepsy. The clinical use of ($^{18}$F) FDG-PET will be discussed in more detail in Section IID1a.

Other $^{18}$F radiopharmaceuticals under active investigation include, for example, ($^{18}$F) fluoromisonidazole for hypoxia; $^{3}$-deoxy-$^{3}$-[($^{18}$F)]fluorothymidine for cellular proliferation; and ($^{18}$F) fluoromethylcholine as a marker for biosynthesis of cell membranes (10–15). Although these tracers permit in vivo PET imaging of unique pathophysiological processes, many tracers are often of limited use for epilepsy imaging due to limited permeability across blood–brain barrier (BBB). Brain tumors that are associated with disrupted BBB have been imaged using these tracers.

Patterns of cerebral perfusion and metabolism can be relatively nonspecific, as both of these are ubiquitous processes that are elevated in normal metabolically active tissues. In patients with epilepsy, these patterns can be diffusely altered, not only in the epileptogenic region but elsewhere, confounding identification of a resectable focus. In an effort to improve the specificity for detecting pathologic loci, a major emphasis in development of radiotracers has been synthesis of compounds aimed at more discretely localized processes, sometimes referred to as “molecular imaging.”

Radiopharmaceuticals targeting components of a variety of neuroreceptor and enzyme systems have been developed, most incorporating $^{11}$C as the radionuclide label. Among these, $[^{11}$C$]fi$umaz$e$nil (FMZ) has found particular application in functional imaging for epilepsy. Because FMZ is a specific antagonist that binds to the benzodiazepine receptor site in the gamma-aminobutyric acid (GABA$_A$) receptor complex, the $^{11}$C-labeled compound can be used as a marker for GABA$_A$ receptor distribution. This tracer has been under investigation for over 15 years and is gaining acceptance in clinical assessment of patients with intractable epilepsy, being available for clinical use in some centers (16–21). This tracer is discussed in greater detail in Chapter V5.

Other agents that have been evaluated for receptor imaging include $[^{11}$C$]$car$-fent$an$il for mu-opioid receptors, $[^{14}$C$]$dipren$orph$ine for mu-, kappa-, and delta-opioid receptors, $[^{11}$C$]$methyl$ni$tr$ind$ole for delta-opioid receptors, $[^{11}$C$]$depr$en$yl as a tracer for monoamine oxidase B, (S)-$[^{N}$-methyl-$^{11}$C$]$ketamine for $N$-methyl-$\alpha$-aspartate (NMDA) receptors, and $[^{11}$C$]$car$b$ony$l WAY-100 635 for serotonin 5-HT1A receptors (22–27). Other agents include $[^{11}$C$]$methion$ine, which shows increased uptake in epileptogenic dysplastic cortex, and alpha-$[^{11}$C$]$methyl-l-tryptophan (AMT), which is converted in the brain to alpha-$[^{11}$C$]$-methyl-serotonin, a metabolite that is not degraded by monoamine oxidase, and therefore accumulates at serotonergic terminals (28). AMT-PET demonstrates focally increased uptake confined to the epileptogenic lesions in children with tuberous sclerosis, as well as in those of children with multifocal cortical dysplasias, where FDG-PET shows more side-spread, nonspecific patterns of hypometabolism and no clear localization of a resectable focus (29,30). A recent study demonstrated dysfunction in the serotonergic system in temporal lobe epilepsy patients that had normal hippocampal volumes (31).
FDG PET IMAGING FOR EPILEPSY

Under normal physiologic conditions, the great majority of the energy used by the brain is derived from glucose supplied by the blood, with only a minimal contribution from neuronal glycogen stores (32). Because of the close association of neuronal activity with glucose metabolism, alterations in neuronal activity, whether pathologic or physiologic, are reflected in altered patterns of glucose uptake. The use of $^{18}$F-FDG as a surrogate imaging agent for cerebral glucose metabolism is based on this premise, and was developed by Phelps et al. (1) from modifications of a model for C-14-deoxyglucose developed for autoradiography by Sokoloff et al. (33).

$^{18}$F-FDG is transported across the BBB via the same carrier that transports glucose. In the intracellular compartment, $^{18}$F-FDG competes with glucose for phosphorylation by hexokinase, but does not enter further enzymatic reactions. The phosphorylated compound, $^{18}$F-FDG-6-phosphate, remains trapped within cells, where it accumulates in proportion to intracellular glycolytic activity, with slow dephosphorylation by glucose-6-phosphatase. The competition of deoxyglucose with glucose for both blood–brain transport and as a substrate for hexokinase-catalyzed phosphorylation has been exploited to construct a model for determining the rate of glucose utilization (33,34). This model has facilitated quantitation of FDG uptake in PET studies.

Normal brain typically demonstrates elevated FDG uptake in the cerebral cortex, particularly the visual and auditory association cortices, and subcortical structures, including the basal ganglia, thalamus, cerebellum, and brainstem (35). In patients with seizure disorders, interictal FDG-PET scans demonstrate varying patterns of hypometabolism, reflected by decreased FDG uptake both locally at the site of the epileptogenic focus, and elsewhere in regions presumed to receive projections from the epileptogenic zone, or possibly reflecting additional pathology. In their seminal study of PET imaging of patients with partial epilepsy, Kuhl et al. (5) captured three prolonged ictal episodes in two patients, and compared the images with those performed during an interictal period. The ictal images demonstrated increased metabolism (by $^{18}$F-FDG) and perfusion (by $^{13}$N ammonia) in the cortical epileptogenic regions, which in the interictal state were hypometabolic and hypoperfused. In practice, for most patients ictal imaging is impractical, as will be discussed below. Nevertheless, the findings of Kuhl et al. (5) are suggestive of coupling of perfusion and metabolic activity in cerebral cortex.

FDG-PET Imaging—Practical Considerations

The detection of a transient alteration in cerebral function, for example, ictal activity, requires that it occur simultaneously with radiotracer fixation. Because FDG requires 10 to 20 minutes postinjection to be fixed in the brain, FDG-PET is not generally amenable to the imaging of the typical seconds- to minutes-long ictal event. In addition, the short half life of $^{18}$F (110 minutes) does not permit delayed imaging. In contrast, the agents used for imaging epilepsy with single photon emission computed tomography (SPECT), which reflect alterations in cerebral perfusion, are fixed in the brain nearly immediately postinjection, and due to the long half life of the Tc 99-m tracer (six hours), permit delayed imaging. These characteristics allow SPECT to be used for ictal imaging. Ictal SPECT images provide a similar degree of accuracy in identifying seizure foci in temporal lobe epilepsy.
patients as interictal PET, on the order of 85% (36,37). However, ictal SPECT studies require in most cases that the patient be admitted to an inpatient epilepsy monitoring unit having specially trained personnel available for near-immediate radiotracer injection at the time of seizure onset, as well as acquisition and analysis of two sets of images.

Guidelines for brain imaging have recently been published in Europe, and provide detailed recommendations for $^{18}$F-FDG-PET and SPECT procedures (38,39). Selected recommendations for $^{18}$F-FDG-PET are summarized below.

The recommendations for patient preparation include the following. To minimize the effect of increased serum glucose levels following a meal, patients should fast for at least four hours prior to FDG injection. Blood glucose should be checked prior to injection, as in hyperglycemia (blood glucose $>160$ mg/dl), FDG uptake is reduced due to increased competition with glucose, resulting in an increase in stochastic noise and decreased contrast between gray and white matter. To minimize cortical activation which would result in physiologically increased FDG uptake with the potential for confounding image interpretation, patients should be instructed to rest comfortably without speaking or reading in a quiet dimly lit room before and for at least the first 20 minutes after FDG administration.

Scalp EEG is recommended beginning ideally two hours before FDG administration and continuing for at least 15 minutes postinjection to exclude the possibility of subclinical seizures. Seizure activity is known to result in hypermetabolism in the region of the seizure focus, in contrast to the interictal finding of hypometabolism, as discussed above. For this reason, seizures would cause significant alterations in patterns of FDG uptake, compromising meaningful interpretation of PET images. It is recommended that interictal imaging studies should be delayed at least 24 hours following any clinically apparent seizure (38).

Careful, reproducible positioning of the patient’s head is important, as is the need to minimize movement. Attenuation correction is necessary for accurate interpretation of PET brain images, and is accomplished by applying data from transmission images acquired using an external source or by use of mathematical corrections.

Emission imaging should begin no earlier than 30 minutes following FDG injection. A standardized acquisition protocol with a fixed time post-injection for start of imaging (30 or 60 minutes) is recommended, so as to allow comparison of images of different patients or of repeat images for individual patients. The duration of emission imaging is related to the minimum number of counts, with the range typically being 15 to 30 minutes.

Although dynamic imaging is considered more accurate, most facilities use simplified protocols based on static imaging (39). Quantification is not generally recommended for epilepsy imaging studies.

Functional imaging findings should be correlated with relevant structural imaging studies (MRI, CT). Comparison of the individual image with a pre-existing image database using objective voxel-based statistical parametric methods can be helpful in interpretation of subtle findings.

PET IMAGING FOR SELECTED APPLICATIONS IN EPILEPSY

In primary generalized epilepsies, interictal FDG PET is generally normal and so is not of diagnostic value (40,41). For this reason, this discussion is limited to localization-related epilepsies.
Temporal Lobe Epilepsy

One of the earliest recognized applications of PET in brain imaging was the potential for identifying an epileptogenic focus amenable to resection in patients having medically intractable localization-related seizures (5). Interictal PET demonstrates decreased blood flow and glucose metabolism in the area of the seizure focus in many patients, most reliably in those with temporal lobe epilepsy (TLE) (Figs. 1 and 2). The accuracy of FDG-PET in identifying a seizure focus in TLE patients has been reported to be 80% to 100% (42–47). In most of these cases, particularly with the advent of high-resolution techniques in the past 10 years, a corresponding abnormality on MRI will be apparent, and unless ictal EEG is discordant or nonlateralizing, functional imaging provides little additional useful information (48). Nevertheless, a significant number of patients with partial seizures (in some estimates up to 20%) may have microscopic structural abnormalities not detectable on MRI. In these patients, as well as in those with EEG or clinical findings discordant with any MRI abnormalities, functional imaging can be of value in localizing or lateralizing a seizure focus. In addition, FDG-PET patterns of hypometabolism can be of prognostic value in determining which patients may or may not benefit from resection (49).

One recurrent observation in studies of patients with partial seizures is that the area of abnormality on PET is often larger than the actual structural or EEG-defined abnormality (50). This finding has been attributed to reduced synaptic inhibition or deafferentation of neurons adjacent to regions of aberrant electrical propagation (51). In addition, regions of hypometabolism can be quite widespread and can exhibit considerable individual variability in pattern (17). In temporal

Figure 1  Interictal FDG-PET images of left temporal lobe epilepsy. Decreased glucose metabolism is seen in the left mesiotemporal cortex and lateral temporal neocortex. Additional areas of hypometabolism are seen in the left thalamus, left insula, and left inferior frontal cortex. Multiple areas of hypometabolism are often seen in temporal lobe epilepsy patients, and the extent of remote abnormalities may predict surgical outcome of temporal lobectomy.
lobe epilepsy, in particular for patients having a lesion in the inferior mesial temporal lobe, regions of hypometabolism often extend to involve other areas of the temporal lobe, including the lateral neocortex (42,52,53). Extratemporal abnormalities have been identified in many patients, with regions of hypometabolism frequently observed in the ipsilateral frontal lobe, parietal lobe, basal ganglia, and thalamus as well as in the contralateral temporal lobe (17,53,54). These regions seldom exhibit epileptiform activity, although they appear to represent functional abnormalities related to the affected temporal lobe structures and can be involved in seizure propagation.

The use of PET as an adjunct diagnostic technique for identifying the epileptogenic focus in patients with intractable partial temporal lobe epilepsy is discussed in detail in Chapter VII-19a of this volume.

Extratemporal Epilepsy

The identification of potentially resectable lesions in patients having intractable seizures arising from extratemporal foci is usually less straightforward than for those with TLE. EEG and neuroimaging studies tend to be less reliable, and PET has a lower sensitivity than in TLE. As in TLE, patients with neocortical epilepsies can have widespread hypometabolism extending beyond the region of the lesion that can often include the ipsilateral mesial temporal lobe, thalamus, and basal ganglia. In these patients, the MRI is more often nondiagnostic; a common pathology in extratemporal epilepsy arising from the neocortex is microscopic cortical dysplasia, which is not detectable with MRI (55). Multifocal epilepsy presents a particular challenge. On PET imaging, nonepileptogenic areas may show abnormal FDG or FMZ uptake indistinguishable from that of epileptogenic zones, due to abnormal metaboli-
cytoarchitecture (30). In this regard, alpha-[11C]-AMT, which demonstrates interictal accumulation in seizure foci, may provide greater specificity in identifying epileptogenic foci (30).

The frontal lobe is the most common site of extratemporal seizures, and FDG-PET appears to offer somewhat better localization for seizures arising there than from other extratemporal areas of the brain (30). Da Silva et al. (56) found frontal lobe hypometabolism in up to 80% of children with normal structural imaging and a presumed frontal lobe focus, although others have reported sensitivities on the order of 45% to 60% (57,58). PET sensitivities for detecting seizure foci elsewhere (e.g., in the parietal and occipital lobes) is significantly less (59).

**Childhood Epilepsy Syndromes**

PET studies have been used to diagnostic advantage in some childhood epilepsy syndromes, including infantile spasms (West syndrome), Lennox–Gastaut syndrome, and Sturge–Weber syndrome (30). In addition to identifying focal resectable lesions that may not be apparent on structural imaging, a finding of diffuse symmetrical hypometabolism infers a nonlesional cause, prompting consideration of an alternate explanation for the seizures, such as a genetic or metabolic disorder. PET can also be useful in evaluating the functional integrity of the contralateral hemisphere in children who are candidates for hemispherectomy. PET imaging has, in addition, helped elucidate important aspects of the pathophysiology of these disorders.

**Activation Studies**

Activation studies involve having the patient perform a specific task, with injection of a radiotracer and PET scanning to image patterns of cerebral uptake associated with task performance. Tracers targeting a number of aspects of brain physiology, including metabolism, perfusion, oxygen utilization, and neurotransmitter function, have been used in an effort to gain insight into a wide variety of neurologic and psychiatric conditions, as well as to characterize normal brain activity. FDG-PET activation studies are useful when the tasks of interest cannot be performed with the subject in the scanner; the prolonged fixation time for FDG in the brain permits the task to be performed in the interval between FDG administration and the time of FDG-brain fixation (on the order of 10–20 minutes) (60).

In epilepsy, activation studies have found application as an alternative to invasive monitoring techniques for localizing eloquent cortex for surgical planning. Although FDG-PET has been used for this purpose, the prolonged time for fixation can be problematic in designing appropriate tasks. For this reason, and to eliminate unnecessary radiation exposure, FDG-PET has been largely replaced with functional MRI for this purpose.

**BRAIN MAPPING ANALYSIS**

Brain mapping analysis (Fig. 3) may improve the sensitivity of detection of subtle differences in radiotracer uptake in cerebral cortex, particularly when the abnormalities are extratemporal and/or multifocal. Techniques include statistical parametric mapping (SPM) and three-dimensional stereotactic surface projections (3D-SSP/NEUROSTAT).
SPM was first developed for brain PET activation studies by Friston et al. (61). In contrast to visual analysis or region-of-interest type analysis, the advantage of this approach is that each pixel of the scanned image is treated statistically in the analysis. Application of SPM involves anatomic normalization of the scanned image using the stereotactic atlas of Talairach and Tournoux followed by pixel-by-pixel statistical analysis comparing scan conditions (62). SPM was developed for cerebral blood flow images of normal brains, but gradually applied to pathologic brains.

With 3D-SSP, the individual patient’s PET scan is subtracted on a pixel-by-pixel basis from a normalized database of control subjects. This technique was initially developed for observer-independent evaluation of functional images of patients with Alzheimer’s disease (63), and was later applied to analysis of PET scans in patients with both temporal and extratemporal epilepsy by Drzezga et al. (64), with the finding of improved sensitivity of localization of the epileptogenic foci, particularly in patients with extratemporal epilepsy.

Frey (NEUROSTAT/3D-SSP) and Koepp (SPM) extended applications of intersubject group analyses to the quantification of cerebral benzodiazepine binding sites using [11C]FMZ (19,65). The technique is fully automated, permits pixel-by-pixel analyses of neurochemical parameters, allows group versus group or individual versus group analyses, and can be generalized to other PET ligands used in brain imaging. These methods became a standard for image analysis in a modern brain mapping research using PET radiotracer methods.
CURRENT AND FUTURE RESEARCH ISSUES IN PET IMAGING FOR EPILEPSY

Functional imaging has to date had a significant role in efforts to enhance the understanding of cerebral function, with epilepsy being a major area of research. The introduction and clinical validation of new molecular imaging markers offers promise that localization of epileptogenic foci can continue to be improved for purposes of identifying resectable lesions, as well as for identifying patients who may not benefit from surgery, for determining prognosis, as biomarkers for development of medications or other modulating interventions, and for evaluating the integrity of cerebral function outside of the epileptogenic region. Importantly, in addition, these markers offer the potential for continued insight into the pathophysiology of epilepsy and a better understanding of the neurochemical processes involved.

Several issues remain to be elucidated. The cause of widespread perfusion and metabolic abnormalities often observed in scans of patients with partial seizures, even in those having well-defined epileptogenic foci who have good postoperative outcomes, remains obscure. Whether these abnormalities result from repeated seizures or give rise to them is still uncertain. Gaillard et al. (66) are conducting a longitudinal prospective study of children with new-onset partial epilepsy in an effort to elucidate the natural history of metabolic disturbance in patients with localization-related epilepsy.

From a practical standpoint, the production of tracers having short half lives, for example $^{11}$C, $^{15}$O, and $^{13}$N, requires that a facility using these radionuclides have an on-site cyclotron and a staff of physicists and radiochemists. The longer half-life of $^{18}$F has allowed for centralized commercial production of compounds containing this label, contributing to the expansion of the clinical use of $^{18}$F-FDG-PET. Development and clinical validation of other radiopharmaceuticals labeled with $^{18}$F would be an advantage in expanding the available selection of molecular imaging agents and allowing for their practical clinical use.

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PET in Epilepsy and Epilepsy Surgery


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Chapter VII-19a: Review of Uses of PET in the Evaluation of Temporal Lobe Epilepsy

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INTRODUCTION

This chapter reviews the role of positron emission tomography (PET) in the evaluation of temporal lobe epilepsy (TLE). There is a general overview of PET in the preceding Chapter VII-19, and the use of flumazenil (FMZ) PET is further discussed in Chapter 50.

In focal epilepsies, PET may be used in the search for an epileptogenic focus during presurgical workup in medically refractory patients, or to increase the knowledge on pathophysiological mechanisms.

[18F]DG PET AND H2[15O] PET IN THE PRESURGICAL EVALUATION OF TLE

Interictally, epileptogenic foci are associated with areas of reduced glucose metabolism and reduced blood flow, which are usually considerably larger than the pathological abnormality (1–3). [18F]DG-PET ([18F]DG: 18F-labeled 2-fluoro-2-deoxy-d-glucose) provides higher resolution and greater reliability than interictal regional cerebral blood flow (rCBF) studies using single photon emission computed tomography (SPECT) or H2[15O]-PET (4,5). Ictal H2[15O] PET scans can only be obtained fortuitously because
of the 2-min half life of $[^{15}\text{O}]$. Ictal $[^{18}\text{F}]$DG-PET scans are difficult to interpret because of the prolonged uptake of $[^{18}\text{F}]$DG and the resulting image representing an amalgam of ictal and postictal conditions. In general, partial seizures are associated with an increase in regional cerebral glucose metabolism and rCBF in the region of the epileptogenic focus, and frequently a suppression elsewhere (6,7).

PET was available before magnetic resonance imaging (MRI). Some epilepsy surgery programs have relied extensively on $[^{18}\text{F}]$DG-PET for localizing the epileptogenic focus. The routine use of this technique, with a radiation exposure of approximately five millisieverts (mSv), needs to be reevaluated in the light of developments in MRI. The finding of a focal epileptogenic abnormality with MRI, in particular hippocampal sclerosis (HS), may render an $[^{18}\text{F}]$DG-PET scan superfluous (8,9).

Interictal hypometabolism has been shown using $[^{18}\text{F}]$DG-PET in the ipsilateral temporal lobe in 60% to 90% of adults and children with TLE in multiple studies (1,2,10–17). The sophistication of equipment and analysis has a major impact on the results obtained. For example, the full-width at half-maximum (FWHM) spatial resolution of PET systems has been improved by a factor of more than two over the last decade, and quantification of hypometabolism is more accurate than visual assessment (18). $[^{18}\text{F}]$DG-PET is more sensitive than MRI, i.e., may be abnormal in MRI negative TLE, but does not add clinically useful information when a definitive MRI abnormality is present (9). Hypometabolism is quite strongly correlated with hippocampal volume, as expected, but partial volume effect correction shows relative hypometabolism per unit gray matter in epileptogenic hippocampi (19). Studies correlating hippocampal neuronal loss with degree of hypometabolism have found conflicting results (19–22). These are most likely owing to methodological differences in the degree to which partial volume effects were accounted for, and biological differences in neuronal dysfunction as a response to hippocampal neuronal loss.

Most studies correlating outcome after temporal lobe surgery with hypometabolism on $[^{18}\text{F}]$DG-PET were performed before the widespread availability of high resolution and quantitative MRI to detect HS. Degree and extent of temporal lobe hypometabolism have been strongly correlated with seizure outcome (23,24). Asymmetry of lateral but not medial temporal glucose metabolism was greater in patients who became seizure free after surgery than those who did not, and patients with an asymmetry of at least 15% were more likely to become seizure free (18). In another study, $[^{18}\text{F}]$DG-PET was more sensitive than hippocampal volumetry but did not predict good postoperative outcome in the absence of asymmetrical hippocampal volumes (25). Multivariate analysis may improve the predictive value (26). Bilateral temporal hypometabolism is associated with a poor prognosis for seizure remission after surgery (27).

Lateral temporal hypometabolism on $[^{18}\text{F}]$DG-PET correlated with interictal temporal slow waves (28). Hypometabolism often extends beyond the temporal lobe (29,30). Therefore, $[^{18}\text{F}]$DG-PET is less reliable for precise localization of the epileptogenic zone than for lateralization, although some pattern differences exist between mesial and neocortical forms (31).

False lateralizations may occur and may be related to interictal epileptiform activity or a postictal state with ensuing hypermetabolism, or nonquantitative assessment of $[^{18}\text{F}]$DG-PET data, for example, with asymmetry indices, which are particularly vulnerable to unexpected hypermetabolism (32,33). Furthermore, the demonstration of an area of neuronal dysfunction does not equate with epileptogenicity, which must still be verified electrophysiologically. Preoperative abnormalities
may disappear after temporal lobe surgery although the opposite has been found in the temporal pole after selective amygdala-hippocampectomy (34,35).

In summary, $[^{18}\text{F}]$DG-PET may be useful in the presurgical evaluation of selected patients. The findings of $[^{18}\text{F}]$DG-PET are, however, nonspecific with regard to etiology, and abnormalities are usually larger than pathological lesions or the epileptogenic zone as defined by other means. The role of $[^{18}\text{F}]$DG-PET has been reduced by the advances made by MRI over the past decade, in particular the ability of MRI to sensitively and specifically predict HS.

**SPECIFIC LIGANDS**

PET studies with specific ligands in TLE aim to inform both about the nature of the underlying abnormality and about the localization of that abnormality, which is relevant for presurgical evaluation.

**Benzodiazepine Binding Site of GABA$_A$ Receptors**

The GABAergic system has been studied mainly with the neutral antagonist $[^{11}\text{C}]$ flumazenil (FMZ). FMZ binds at the benzodiazepine binding sites of GABA$_A$ receptors containing four of the six possible $\alpha$-subunits, $\alpha$-1, 2, 3, and 5. These four are the most prevalent and FMZ, therefore, acts as a good marker for the GABA$_A$ receptor (36). As most neurons express GABA$_A$ receptors, FMZ can also, to some extent, be regarded as a neuronal marker.

In TLE, the area of reduced $[^{11}\text{C}]$ FMZ binding is more restricted than the area of hypometabolism shown with $[^{18}\text{F}]$DG-PET (Fig. 1) (37–40). The first study applying the voxel-by-voxel analysis of statistical parametric mapping to $[^{11}\text{C}]$ FMZ-PET scans of patients with HS diagnosed on MRI found decreases of $[^{11}\text{C}]$ FMZ binding to be restricted to the sclerotic hippocampus, with no abnormalities elsewhere (41,42). While such voxel-based analyses are more objective than hand-drawn volumes of interest and allow the investigation of the entire brain volume, they do not lend
themselves to absolute quantification of PET data. This requires a correction for partial volume effects caused by the limited spatial resolution of PET, usually by comparison with higher-resolution MRI data (43–45). Partial volume effects are more prominent in smaller structures, leading to an artificial apparent decrease of tracer binding in smaller structures (46). If structural changes affect control and patient populations differently, as for example in HS, correction is mandatory for correct quantification.

Correction for partial volume effect increased the sensitivity of $[^{11}C]$ FMZ-PET in detection of unilateral HS from 65% to 100% in patients with MRI-defined HS (47). Further, $[^{11}C]$ FMZ-PET was more sensitive than MRI in the detection of contralateral abnormalities, which were found in one-third of patients with apparent unilateral HS on MRI and also showed that loss of FMZ binding was consistently over and above loss of hippocampal volume, indicating that the former was not simply due to hippocampal atrophy (48).

This concurs with other in vivo studies which have shown greater $[^{11}C]$ FMZ binding loss than hippocampal volume loss or have demonstrated abnormalities of $[^{11}C]$ FMZ binding even when hippocampal volumes were normal (38,49–53). In the largest of these series of MRI-negative TLE patients, potentially surgically relevant changes, i.e., focal reductions of hippocampal or extrahippocampal FMZ-Vd, were found in seven of 18 patients (53). Increased FMZ-Vd in white matter, representing an increased density of heterotopic white matter neurons (microdysgenesis), was found in 11 out of 18 individual patients. Microdysgenesis is not detectable on MRI, and this may represent the pathophysiological basis of a proportion of TLE cases with normal MRI (Fig. 2).

The underlying pathological basis of reduced $[^{11}C]$ FMZ binding in HS has been extensively investigated (54–58). Quantitative autoradiographic and neuropathological studies of surgically removed hippocampi, compared with autopsy controls, showed that the number of GABA_A receptors bearing benzodiazepine recognition sites was reduced over and above neuronal loss in the CA1 subregion, while the loss

![Figure 2](image)

**Figure 2** Group results in a large series of patients with cryptogenic (MRI-negative) TLE. Fifteen patients with unilateral TLE, compared with 21 controls, show decreases of FMZ-volume-of-distribution (in black) in the ipsilateral (left side of the image) hippocampus ($Z = 3.01$; arrow) extending into the amygdala, and in the contralateral (right side of the image) hippocampus ($Z = 2.56$). There are also ipsilateral ($Z = 3.71$) and contralateral ($Z = 3.11$) increases of FMZ-volume-of-distribution (in white) in the temporal lobe white matter. *Source:* Data from Ref. 53.
of receptors paralleled the loss of neurons in other subregions. Additionally, increases in affinity were noted in the subiculum, hilus, and dentate gyrus (57,58). In the white matter, \[^{11}C\] FMZ binding was tightly correlated with the number of heterotopic neurons, determined semiquantitatively ex vivo in resected specimens (59).

The clinical utility of these findings is not entirely clear. In HS, \[^{11}C\] FMZ-PET abnormalities are often more restricted than \[^{18}F\] FDG abnormalities. No additional benefit accrues from detecting localized abnormalities of \[^{11}C\] FMZ binding in TLE with MRI-detectable HS if standard anterior temporal lobe resections are carried out. A clinical series of 100 presurgical patients who underwent MRI, \[^{11}C\] FMZ-PET and \[^{18}F\] FDG-PET included 30 with MRI-defined HS. In these patients, the authors considered \[^{11}C\] FMZ-PET useful when abnormalities coincided with \[^{18}F\] FDG-PET abnormalities, as this indicated the precise position of the epileptogenic zone (51). \[^{11}C\] FMZ-PET also helped to confirm the bilateral origin of seizures in one-third of patients with bitemporal epilepsy and identified contralateral abnormalities in a number of cases. The same group later highlighted three patients in whom FMZ decreases were seen contralateral to the epileptogenic temporal lobe and varied on two studies (60). Such variations in the Bmax parameter, obtained with a partial saturation protocol, were later related to time since last seizure in TLE patients with normal MRI (61). While this had not been observed with another method of quantification (53), the issue deserves further study.

Newer studies demonstrate some clinical usefulness of FMZ-PET in lesional epilepsies, neocortical foci with and without MRI abnormalities, and TLE with normal MRI (Figs. 1 and 2) (3,49,50,53,62). Limitations to the clinical use of \[^{11}C\] FMZ-PET are the requirement for suitable infrastructure including \[^{11}C\] radiochemistry, suitable modeling, and the need for a valid control group.

**Opioid Receptors**

Diprenorphine (DPN) is a high-affinity opiate receptor ligand with similar in vivo affinities for the three main receptor subtypes: \(\mu\), \(\kappa\), and \(\lambda\) (63). There were no significant asymmetries in \[^{11}C\] DPN binding in patients with unilateral TLE in two studies, but higher binding of the \(\mu\) subtype selective agonist \[^{11}C\] carfentanyl was seen in lateral temporal neocortex on the side of the epileptogenic focus, while binding in the amygdala was decreased (64,65). The latter finding might be due to partial volume effect, but the finding of lateral neocortical increases confirmed an earlier study (66,67). The increases of \[^{11}C\] carfentanyl binding were in areas of hypometabolism seen on \[^{18}F\] FDG-PET. It has been speculated that an increase in \(\mu\)-receptors may be a manifestation of a tonic antiepileptic system that limits the spread of epileptic activity.

\[^{18}F\] cyclofoxy is a specific antagonist at both \(\mu\) and \(\kappa\), but not \(\delta\)-receptor subtypes. Increased binding was seen in the ipsilateral temporal lobe in some TLE patients studied, but there was no overall asymmetry in the group (68). This could be explained through decreased affinity or number of \(\kappa\) receptors and would also be consistent with decreased \(\kappa\) receptor availability through occupation by an endogenous ligand.

Binding of the \(\delta\)-receptor subtype selective antagonist \[^{11}C\] methylnaltrindole was increased in mid-inferior temporal cortex and the anterior aspect of the middle and superior temporal cortex (69). In the same patients, \(\mu\)-receptor binding was increased in the middle aspect of the inferior temporal cortex.

At present, PET opioid studies are confined to research in a few centers and are not used clinically.
Other Tracers

Serotoninergic Neurons

α-Methyl-L-tryptophan (AMT) is an analog of tryptophan, the precursor of the neurotransmitter serotonin (5-HT), and labels serotoninergic neurons; however, it has been suggested that increased binding may reflect increase of the kynurenine pathway of tryptophan metabolism (70–72).

Focal increases of [11C] AMT uptake have been found in patients with malformations of cortical development and in MRI-negative patients, including some with temporal lobe foci (73,74). This is a promising finding, particularly in the difficult-to-treat imaging negative group. A recent study showed increased [11C] AMT binding in the ipsilateral hippocampus in a group of seven unilateral TLE patients with normal hippocampal volumes, but not in a group of seven unilateral TLE patients with HS; the lack of correction for partial volume effects in this study means that hippocampal increases in the sclerotic hippocampus may have been overlooked (72). [11C] AMT-PET is currently used only for research studies, but may have a wider clinical application.

Serotonin Receptors

A single study of [18F] FCWAY, a selective 5HT1A antagonist, found decreased volume-of-distribution in the inferior medial and the inferior lateral temporal lobe ipsilateral to the epileptogenic focus in TLE patients (75). The asymmetry of [18F] FCWAY volume-of-distribution in the inferior temporal across the group of patients was higher than the asymmetry of glucose metabolism and the asymmetry of hippocampal volumes. Decreased binding was found in the two patients with normal MRI included in this series. Another study used the 5HT1A radioligand [18F] MPPF to investigate nine patients with TLE who had depth electrodes implanted, compared with 53 controls (76). Binding was reduced in epileptogenic areas, and [18F] MPPF PET correctly lateralised in all three patients with normal MRIs. Similarly, binding of the 5-HT1A tracer [carbonyl-11C] WAY-100635 was reduced ipsilaterally, but not restricted, to the epileptogenic hippocampus in a group of 14 patients with mTLE, including those six with normal MRI and mostly normal [18F]FDG-PET studies (77). PET studies of serotonin receptors appear promising for lateralizing temporal lobe foci when other imaging methods are inconclusive.

N-Methyl-D-Aspartate Receptors

[11C] (S)-[N-methyl]-ketamine ([11C] ketamine) binds to the excitatory N-methyl-D-aspartate (NMDA) ionotropic glutamate receptor and is thus of great interest in epilepsy. In a pilot study of eight TLE patients, six of whom had unilateral HS, an average reduction of binding of 14% was seen on the side of the EEG focus (78). This finding may be due to partial volume effect in the smaller hippocampus, and it is possible that if partial volume correction had been used, the apparent decrease would have turned out to be an effective increase per unit of gray matter. Further studies are required, and several potential tracers are in development.

Monoamine Oxidase Type B

Deprenyl binds to monoamine oxidase type B (MAO-B) which is mainly located in astrocytes. Autoradiographically, higher [9H]-l-deprenyl binding was found in epileptogenic human hippocampi, and binding correlated with neuronal loss (79). Increased N-[methyl-11C]-a,a-di-deutero-l-deprenyl ([11C]deuterium-deprenyl) binding correctly
lateralized TLE in six out of seven cases, but the increased uptake was not limited to the mesial temporal lobe (80). With simplified methodology, only three of eight patients with TLE showed convincing asymmetries (81). $[^{11}C]$deuterium-deprenyl volume-of-distribution was of equivalent use to $[^{18}F]$ FDG-PET in lateralizing TLE with HS (82). In the same study, nine patients with seizures of neocortical origin did not show side-to-side differences or differences compared with six healthy controls. Thus $[^{11}C]$deuterium-deprenyl does not seem to be a useful tracer in neocortical epilepsies.

**Peripheral Benzodiazepine Receptors/Activated Microglia**

$[^{11}C]$ PK11195 labels macrophages and activated microglia and can be used to image inflammatory responses or areas of synaptic reorganization in the brain. Binding was similar to that in normal brain in three patients with established HS (83–85).

**Cholinergic Receptors**

Muscarinic acetylcholine receptors have been implicated in the pathogenesis of TLE where their number or availability may be transiently decreased after seizures but are probably not decreased over and above hippocampal neuronal loss in autoradiographic studies (86). They can be investigated in vivo using $[^{11}C]$ N-methyl-4-piperidyl benzylate (NMPB). $[^{11}C]$ NMPB binding was decreased in the mesial temporal lobe ipsilateral to the epileptogenic hippocampus in one study (86). Most of the effect seen in vivo, however, is likely due to neuronal loss.

Preliminary studies of PET tracers for the nicotinic acetylcholine receptor are ongoing (87,88).

**CONCLUSIONS**

$[^{18}F]$ FDG-PET has a role in the presurgical evaluation of TLE if MRI is unremarkable, or data is discordant. In cases with clear-cut structural abnormalities and concordant other data, $[^{18}F]$ FDG-PET is superfluous.

$[^{11}C]$ FMZ-PET can act as a good marker for cortical integrity in hippocampus and neocortex and may act as a marker for malformations of cortical development. It can yield information that is complementary to the information provided by structural imaging. Its future clinical role is likely to be in the presurgical evaluation of patients with normal MRI studies and those with malformations.

Currently, opioid receptor PET tracers are not clinically used in the presurgical workup. As the various tracers seem to be displaceable by endogenous opioids, ictal/interictal comparisons are of great interest and in the future may aid localization.

Excitatory amino acid receptors are of high theoretical interest. Data to date are inconclusive, and more suitable tracers are awaited.

Of the other systems that can be probed with ligand PET, those that measure nonspecific changes that can be seen with MRI, for example, gliosis, are unlikely to be of clinical benefit due to the scarcity and cost of PET compared to MRI.

The 5HT$_{1A}$ tracers look promising in view of the magnitude of changes seen which exceeds those seen on either MRI or $[^{18}F]$ FDG-PET in individual patients, and correct lateralisation in cases with normal MRI.

$[^{11}C]$ AMT shows increased uptake in at least some epileptogenic areas and appears promising, although the exact interpretation of abnormalities is difficult and needs rigorous quantitative evaluation and correction for partial volume effects.
All functional imaging data need to be interpreted in the light of optimal structural data, and extra yield is gained with a detailed and rigorous quantitative analysis.

REFERENCES

Chapter VII-19b: PET Is Useful in the Presurgical Evaluation of Temporal Lobe Epilepsy

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Despite advances in magnetic resonance imaging (MRI), published studies continue to show that positron emission tomography (PET) provides valuable clinical information, even when MRI is normal.

Although ictal single photon emission computed tomography (SPECT) may have comparable diagnostic sensitivity, it has proved to be more difficult to perform, as seizures can rarely be predicted, and the value of the procedure is based on isotope injection within seconds after seizure onset (1). Moreover, PET can be performed with several isotopes, two of which, 18F-fluorodeoxyglucose (FDG), and 11C-flumazenil, have been shown to have clinical value.

FDG-PET can predict the outcome of temporal lobectomy, the most common surgical procedure, independently of structural MRI (2). Several studies have shown that FDG-PET consistently detects a greater proportion of mesial temporal foci than volumetric MRI, and often than ictal SPECT (3–6). The proportion of patients with normal structural MRI has been above 50% in several series (4,5,7).

PET using 11C-flumazenil to image benzodiazepine receptors may be even more useful than FDG-PET for mesial temporal foci, although the isotope is slightly more difficult to produce. It can detect focal abnormalities that correspond to epileptogenic zones when both structural MRI and FDG are negative (4,8).

In patients with extratemporal epileptic foci, some studies report superiority of FDG-PET over both ictal SPECT and structural MRI, while others do not (9,10). In comparison with invasive studies, flumazenil has been shown to localize epileptogenic cortex and predict surgical outcome (11).

In contrast, most investigators have found that cerebral blood flow studies using 15O-H2O do not reliably localize or lateralize temporal lobe epileptogenic zones, or predict surgical outcome, paralleling results using interictal SPECT (10).

Several steps can be taken to make the most of PET. EEG should be monitored during the procedure, to exclude any contribution of ictal activity to the overall pattern.
Quantitative, rather than purely visual, analytic techniques should be used. Region of interest approaches, particularly when used in concert with coregistration with structural MRI, may be as robust as more complex approaches such as statistical parametric mapping. It may be important to consider a patient’s recent seizure patterns, and particularly whether any “nonhabitual” episodes have occurred recently (12).

The potential future value of “functional” MRI techniques is unknown. MR spectroscopy (MRS) is not yet widely used; studies that compared it with FDG-PET differed in their results, showing either equality or inferiority (3,13). In a recent report, arterial spin labeling MRI cerebral blood flow measurement was superior to structural MRI in localizing temporal lobe foci; and equal to FDG-PET (14).

It is estimated that only a small proportion of the patients who could benefit from surgery for intractable epilepsy are offered the procedure (15). New image processing techniques will probably add incremental value to structural MRI, but there will continue to be patients with normal studies who appear to be surgical candidates on the basis of clinical and EEG findings. They should have FDG or flumazenil PET studies. It is even possible that the use of a combination of structural and functional imaging studies could obviate the need for ictal video-EEG monitoring, thus reducing the risk, discomfort and expense of presurgical evaluation, and potentially increasing its availability. Centers performing surgery for epilepsy should have access to PET.

REFERENCES

Chapter VII-19c: Positron Emission Tomography Need Not Be Used Routinely to Evaluate Patients for Temporal Lobe Surgery

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At many centers, positron emission tomography (PET) is used extensively to define the epileptogenic zone in patients undergoing seizure surgery. [18F]fluorodeoxyglucose-PET (FDG-PET) has been the mainstay of clinical PET imaging. Recently, imaging of benzodiazepine receptors with [11C]flumazenil-PET (FMZ-PET) has also been used. The use of these studies in the presurgical evaluation varies widely from center to center. The need for PET studies in the presurgical evaluation is controversial and clinicians’ attitudes are constantly evolving as other imaging techniques are developed.

A major limitation of PET (and perhaps a major contributing factor to the variability in usage) is that it is not readily available at many major medical centers. A cyclotron is required to manufacture positron-emitting isotopes. The expense involved in procuring the necessary equipment is likely to be prohibitive for all but the largest medical centers.

In part because of the limited availability of PET scanners, many well-trained radiologists are inexperienced at interpreting PET studies. Mistakes in over- or under-interpretation are common. Even at centers where PET scans are performed frequently and readers are very experienced, computerized quantification should be used to help readers avoid these mistakes (1).
FDG-PET has been consistently shown to be sensitive for detecting reduced glucose metabolism in the epileptogenic temporal lobe and it is more sensitive than magnetic resonance imaging (MRI) (2,3). As magnetic resonance imaging is readily available at all medical centers, however, the potential utility for PET needs to be considered in the context of all patients having ready access to both MRI and inpatient video EEG monitoring.

The majority of patients with TLE demonstrated by video EEG monitoring will have either a structural lesion or mesial temporal sclerosis (MTS) demonstrated by MRI (4). These patients have an excellent chance for amelioration of their condition with resection of the structural abnormality (5–7). When PET is performed in these patients, it almost always demonstrates abnormalities that include the region documented by MRI and EEG (8). Although PET may provide non-redundant information about metabolism in this region (9,10), there is no obvious clinical utility for this information (3). Given the excellent prognosis for these patients, it is unlikely that PET will further stratify the patients as to their chance for successful surgery. Given our current knowledge of the relationship of the EEG-defined temporal lobe epileptogenic zone to PET abnormalities (both FDG-PET and FMZ-PET), it is unlikely that these studies will be as useful in tailoring the extent of the resection as they are in babies with infantile spasms (8,11).

The minority of patients with TLE who do not have MRI abnormalities could certainly benefit from an adjunctive test that would confirm the ictal EEG localization. This group of patients has consistently been shown to have a poorer chance for seizure-free outcome following surgery (5–7). Adjunctive functional imaging could conceivably enable patients with suggestive but equivocal ictal scalp EEG recordings to proceed directly to surgical resection rather than to monitoring with invasive electrodes. At UCSF we use PET in this group of patients. On a precautionary note, however, PET is less sensitive in this group (8). We have encountered patients in whom subtle asymmetries in glucose metabolism resulted in incorrect visual interpretation such that the temporal lobe contralateral to the seizure focus was reported as abnormal. When absolute counts were considered, the number was reduced in the contralateral temporal lobe but not to an extent that would typically be considered definitive for identification of the seizure focus. The reason for these subtle asymmetries is unclear. It is possible that these patients (who often have neocortical epilepsy) are more likely to have frequent, subtle seizures during the study resulting in a confusing metabolic pattern. Concurrent EEG should be performed in this group of patients and studies should be interpreted conservatively.

A final group of patients that might benefit from PET is the group without well-localized seizures based on scalp EEG and clinical criteria. PET should be considered most strongly in these patients when there is a strong suspicion that seizures arise from temporal structures (based on clinical characteristics, interictal EEG, and ictal EEG pattern). If this condition is not met, interpretation of PET findings can be very difficult since both FDG-PET and FMZ-PET often show metabolic abnormalities remote from the seizure focus in patients with nonlesional extra-temporal epilepsy (12,13). Even the presence of a prominent PET abnormality should probably not be used to change the surgical strategy in these patients except, perhaps, to modify the placement of intracranial electrodes.

In conclusion, PET is a sensitive, specific, expensive, and labor-intensive component of the presurgical evaluation in patients with refractory temporal lobe epilepsy. The clinical utility of this technology will need to be reassessed as our ability
to detect the seizure focus and functional tissue with other procedures advances. For now, I suggest the following:

1. PET need not be used routinely to evaluate patients for temporal lobe epilepsy surgery.
2. PET may be useful in some patients without MRI abnormalities or in patients with poorly localized (by EEG) seizures (if there is a suspicion that the seizures arise from temporal structures).
3. PET studies for refractory epilepsy should be performed at referral centers where case volume is large, practitioners are experienced, and quantitative techniques are available.

REFERENCES

Chapter VII-20
Single Photon Emission Computed Tomography in Epilepsy

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Over the last decade and a half, ictal single photon emission computed tomography (SPECT) has emerged as a frequently used clinical tool in the management of patients with medically resistant focal epilepsy who are under evaluation for surgical treatment. The sensitivity for detection of the seizure focus is similar to or higher than that of structural imaging but unlike magnetic resonance imaging (MRI), it gives little indication of the underlying pathology. The clinical value of SPECT is enhanced by subtraction of masked and normalized interictal from ictal SPECT images with the resultant image displayed on coregistered MRI.

SPECT TECHNIQUE

SPECT is performed with a rotating gamma camera. Image quality is superior with multihead cameras (two or three heads) due to the improved geometric efficiency for detection of gamma rays emitted from the brain. More detected photons (counts) means better images by permitting the use of higher-resolution collimators and reconstruction algorithms. However, it is unclear if this is important for SPECT seizure focus localization as ictal blood flow changes usually cover an area that is much larger than the resolution limits of a SPECT camera. Early ictal SPECT papers using single head cameras reported similar if not higher sensitivity than many recent papers using multihead cameras.

RADIOPHARMACEUTICALS FOR CEREBRAL BLOOD FLOW IMAGING

Two radiopharmaceuticals suitable for ictal SPECT are available. HMPAO (Ceretec) was the first, widely available, tracer suitable for ictal SPECT but required mixing with pertechnetate (technetium-99m in solution) at the bedside immediately before
injection due to instability once mixed. ECD (Neurolyte) was later introduced and became popular because of its stability in solution. Tc-99m ECD could be made at the beginning of each day and delivered to the monitoring room ready for direct injection. This reduced the delay from seizure onset to injection by 30 seconds or more and reduced the chance of misadministration. Subsequently, stabilized Ceretec was developed and is available in Europe and North America but not in Australia.

The mechanism of retention of ECD differs from that for HMPAO and is more dependent on intact intracellular oxygen status and esterase activity. Consequently, ECD does not show the hyperperfusion seen with HMPAO in “luxury perfusion” of subacute stroke, brain tumors, or herpes simplex encephalitis (1–3). Both HMPAO and ECD suffer from a nonlinear relationship between uptake and cerebral blood flow (CBF) at high flow states, progressively underestimating the degree of hyperperfusion. There is some evidence that ECD suffers more from this problem than HMPAO (4). These observations may have implications for ictal CBF imaging.

There have been no randomized or direct comparisons in the same patients of stabilized HMPAO and ECD in ictal SPECT and the little comparison that has been done is inconclusive. One group has compared the accuracy of ictal SPECT with ECD to earlier experience with nonstabilized HMPAO and concluded that the faster injection time for ECD resulted in greater accuracy (5). However, the uptake at the focus relative to the rest of the brain was no greater despite the time from seizure onset to injection being reduced from a mean of 80 seconds (and 57% postictal injections) to 34 seconds (and 16% postictal injections). In contrast, another group has reported lower sensitivity with ECD in comparison to their experience with stabilized HMPAO, particularly in neocortical epilepsy (6). They found that ECD showed less than half the magnitude of change at the focus but studied only 14 patients with ECD. ECD has less scalp and facial uptake that is an advantage when coregistering SPECT to MRI or when performing subtraction of SPECT images.

OPTIMAL IMAGE PRESENTATION

The complete three-dimensional data set provided by SPECT enables selection of optimal image planes. The temporal lobes are best viewed by reconstructing transaxial slices parallel to the temporal lobe with coronal slices perpendicular to this plane (7). Interictal asymmetry can be readily quantified in this plane using symmetrical regions of interest placed over the anterior temporal lobes. Interictal asymmetry is normally less than 5%, while more than 10% is definitely abnormal. Region of interest quantification does not improve the sensitivity of seizure focus detection and is therefore usually only performed for research purposes (8). Background subtraction and color scales are useful to enhance the mild degrees of temporal lobe asymmetry typically seen with SPECT in temporal lobe epilepsy (TLE).

SISCOM

Subtraction of interictal from ictal SPECT with coregistration on MRI (SISCOM) is an elegant way to display ictal SPECT data. It has the advantage of anatomical correlation and may highlight an area of relative hyper- or hypoperfusion not readily apparent on visual inspection. The SISCOM method as introduced by the Mayo Clinic group requires image smoothing, normalization of the ictal and interictal
SPECT scans to mean cerebral pixel counts, application of a user-chosen threshold to isolate cerebral cortex voxels, ventricular filling using math morphology, and subtraction of only the nonzero pixels. The scans are aligned with Wood’s automated image registration (AIR) algorithm (9).

Small degrees of edge misalignment will result in large signals at gray–white matter junctions and the outer cortical edge. Experience and comparison back to the nonsubtracted images are needed to sort the noise from the areas of true ictal hyperperfusion and ictal/postictal hypoperfusion. Attempts have been made to reduce the noise in the subtraction images by compensating for the variation seen with paired interictal studies. The methods employed have used nonlinear intersubject registration to combine a group of subtraction images into standard anatomical space. The patient subtraction image was also nonlinearly registered to standard anatomical space and a voxel-by-voxel statistical comparison using statistical parametric mapping (SPM) or similar methods was performed. Although this has been reported to improve subtraction image quality, there are no data indicating that it improves the accuracy of seizure localization (10,11).

Some authors claim a dramatic improvement in accuracy of localization compared to side by side visual comparison of interictal and ictal SPECT images (9,12). However, in these papers the localization rates with side by side visual comparison were less than 50% even in the unilateral TLE patients. Furthermore, there was very poor correlation between the readers. These results are not consistent with the vast majority of papers on ictal SPECT (see below). It is the authors’ experience that SISCOM can improve confidence when interpreting subtle blood flow changes in extratemporal lobe epilepsy and can draw attention to areas overlooked on the initial visual inspection. However reliance on SISCOM images alone is not recommended as imprecise coregistration of images will generate misleading subtraction results (13).

SPM

SPM is an image analysis tool that assesses the significance of CBF changes on a voxel-by-voxel basis by automated statistical comparison to a group of normal subjects. SPM can be used to analyze ictal SPECT either by comparison to a normal control group or by comparison of a subtraction image to images of variation between repeated scans in normal subjects (11,14). While the feasibility has been demonstrated, there is as yet no evidence of improved accuracy for SPM analysis verses visual side by side or subtraction analysis.

REGIONAL CEREBRAL BLOOD FLOW IN PARTIAL SEIZURES

Interictal

Between seizures, the interictal period, CBF may be normal or reduced. A reduction in the epileptogenic temporal lobe is frequently present in patients with TLE, while interictal regional abnormalities are less common in other forms of epilepsy in the absence of a structural abnormality. The mechanism for reduced blood flow and metabolism is unexplained and its relationship to neuronal loss is unclear. The area of hypoperfusion may be more extensive than that of demonstrable abnormality in resected specimens.
Ictal Blood Flow

Regional CBF (rCBF) in the epileptic focus increases by up to 300% during a seizure (15,16). This phenomenon was first observed by Horsley in 1892 and has subsequently been documented in both humans and animal seizure models by a variety of techniques (17). In the immediate postictal period regional cerebral blood flow is reduced to a greater extent than in the interictal period. The exact onset and duration of the postictal period is not strictly defined as the electrical, behavioral, metabolic, and blood flow features of this phase vary greatly in duration between individuals.

SPECT IN TEMPORAL LOBE EPILEPSY (Fig. 1)

Interictal SPECT

Interictal hypoperfusion was first demonstrated with SPECT in 1982 using 123I iodoamphetamine and a dedicated single-slice SPECT device. Ictal hyperperfusion was also reported in the same study in several patients injected during seizures (18). Since then many reports from seizure surgery centers have compared the results of interictal SPECT to ictal EEG localization or surgical outcome in patients with refractory temporal lobe epilepsy. A meta-analysis of these reports found that SPECT showed temporal lobe hypoperfusion on the side of the seizure focus in 55% and contralateral hypoperfusion leading to incorrect lateralization was present in 10% (19). SPECT studies in pediatric populations suggest similar clinical utility to adult studies.

Interictal SPECT does not have the sensitivity or accuracy of 18F-fluorodeoxyglucose (FDG)-PET as interictal blood flow changes are less marked than metabolic changes. Several studies have confirmed superior results with FDG-PET over PET blood flow imaging in the same patients with the same PET camera (20).

Figure 1  Interictal, ictal, and postictal (four minutes postcompletion of seizure) in a patient with right temporal lobe epilepsy. Studies were performed on separate days with Tc-99m HMPAO. The interictal study shows very mild hypoperfusion in the right lateral temporal cortex. The ictal scan shows intense hyperperfusion in the anterior right temporal lobe with some shutdown in the adjacent cortex and contralateral temporal lobe. The postictal scans shows marked hyperperfusion in the right temporal lobe with a small area of persisting hyperperfusion in the anteromedial right temporal lobe.
Interictal Variability

An alternative explanation for the lower sensitivity of SPECT compared with FDG-PET is that interictal blood flow and metabolism may be quite labile. Up to 10% of patients demonstrate interictal hyperperfusion but interictal hypermetabolism has not been described. In most patients, interictal CBF findings are reproducible, but examples of interictal temporal lobe hyperperfusion on the first study and hypoperfusion in the same area on a subsequent SPECT study have been documented, suggesting that temporal lobe perfusion may be labile in some individuals. Improved localization can be obtained by repeating a SPECT study when the first result is negative or unexpected, further suggesting that interictal temporal lobe activity is variable (21).

Patterns of Hypoperfusion

The degree and extent of hypoperfusion, like that of FDG hypometabolism, varies greatly from one individual to another. It most commonly involves the anterior pole of the temporal lobe and medial temporal region, but involvement of lateral temporal cortex and ipsilateral frontal and parietal cortex is not uncommon. On occasion, hyperperfusion is observed. The degree of unilateral temporal lobe hypoperfusion correlates with the age at onset of seizures but not seizure frequency, patient age, or the likelihood of secondary generalization (8). The presence of left temporal lobe hypoperfusion reduces the risk of a postoperative decline in verbal short-term memory function after a left temporal lobectomy (22).

Interictal SPECT has limited clinical value relative to other imaging procedures that have greater sensitivity and specificity such as PET and MRI. There is less contrast between normal and abnormal areas with SPECT compared with PET and aggressive reading to improve sensitivity increases false localization. The main role for interictal SPECT is to aid interpretation of ictal SPECT studies by providing a baseline for visual comparison or image subtraction.

Ictal and Postictal SPECT

Ictal studies are obtained with injection during the electrical or clinical manifestation of a seizure. Postictal studies are obtained by injection after completion of a seizure. Some authors use the term “peri-ictal” to refer to the ictal and early postictal phase given the variability of this period. The high first-pass extraction of $^{99m}$Tc-exametazime (Ceretec) and $^{99m}$Tc-ECD (Neurolite) with prolonged retention makes imaging of ictal cerebral blood flow feasible with these agents. ECD and stabilized Ceretec do not require bedside reconstitution immediately prior to injection, permitting faster injections and less staff training. Those centers that have the shortest delay between seizure onset and injection of tracer have constant close observation of the patient by an EEG technologist or a nurse who gives the injection of tracer. Average injection delays of 20 to 30 seconds from seizure onset to injection are now achieved in many centers.

Sensitivity

Over 500 patients with unilateral temporal lobe epilepsy proven by ictal EEG, MRI, and other ancillary investigations or by seizure-free surgical outcome have been studied with ictal SPECT and the results published (14,21,23–31). Correct identification of the seizure focus was achieved in over 90%, with incorrect lateralization in
less than 5%. In a postictal series, with injection given on average four minutes after seizure onset, correct localization was achieved in 70%, with incorrect localization in less than 5% (32).

Patterns of Ictal CBF
Temporal lobe hyperperfusion will be seen with injection given during the seizure or up to 30 seconds after seizure completion (33). The area of hyperperfusion is variable but typically involves the anterior pole with a variable degree of medial and lateral temporal cortex. Hyperperfusion of the ipsilateral basal ganglia is common and correlates well with dystonic posturing of the contralateral arm during the seizure (34). Hyperperfusion of lesser extent may also be seen in the ipsilateral thalamus. Propagation of the seizure also frequently leads to a variable degree of hyperperfusion in the contralateral medial temporal lobe (35). This is usually less extensive and of less intensity than in the temporal lobe from which the seizure originates. Involvement of the ipsilateral insula cortex and basal frontal lobe is not infrequent. Secondarily generalized complex partial seizures will show unilateral blood flow increase if injection is given before generalization or if the seizure remains predominantly lateralized to one hemisphere. In such circumstances, hyperperfusion may be seen in the temporal lobe, ipsilateral motor cortex, basal ganglia, and thalamus and contralateral cerebellar cortex. Ictal hyperperfusion is seen both with mesial temporal sclerosis and seizures due to structural lesions such as low-grade temporal lobe tumors, although the distribution is sometimes unusual with the latter. One study found that foreign tissue lesions in the lateral temporal lobe were likely to show bilateral temporal lobe hyperperfusion, though greater on the side of the lesion (36). It is postulated that spread from the lateral cortex to the contralateral amygdala occurs through the anterior commissure. Posterolateral temporal lobe foci are also said to show more extensive hyperperfusion in the lateral cortex compared to medial temporal lobe foci (37). Involvement of the temporoparieto-occipital junction should raise the possibility of a posterior temporal focus.

Patterns of Postictal CBF
The area of ictal hyperperfusion is usually surrounded by hypoperfusion. The latter becomes the predominant feature in the postictal period and may extend widely to involve the entire ipsilateral hemisphere and the contralateral temporal lobe. Postictal hyperperfusion, if present, is usually restricted to the anteromedial temporal lobe and is rarely seen more than five minutes after seizure completion (32). The timing of the switch from an ictal to a postictal pattern of perfusion varies between individuals, as does the duration of the postictal change. Postictal changes are more frequently bilateral and this, plus rapid resolution in some individuals, accounts for the reduced sensitivity of postictal imaging compared with ictal injection. The earlier the injection, the greater is the chance of detecting useful blood flow changes. Injection more than five minutes from seizure completion will substantially reduce sensitivity.

Unilateral hyperperfusion has been reported in patients with independent bilateral temporal lobe foci. Bilateral temporal lobe ictal hyperperfusion in a patient with a unilateral focus is occasionally seen but less often than would be expected given the frequent spread of seizure activity to the contralateral temporal lobe on depth electrode recordings. In such cases, the side of greatest hyperperfusion usually correlates with the seizure focus.
SPECT IN EXTRATEMPORAL LOBE EPILEPSY (Figs. 2 and 3)

In the absence of a causative structural lesion on MRI, such as a tumor or focal area of cortical dysplasia, localization of an extratemporal seizure focus is difficult. Such patients require extensive intracranial monitoring with subdural electrode grids and intracerebral depth electrodes.

It is in this challenging environment that ictal SPECT may have its greatest value. Accurate coregistration with MRI may permit detection of subtle structural abnormalities such as an area of cortical dysplasia and subtraction of interictal from ictal SPECT images is often useful. Very early ictal injection is vital to minimize the confounding effects of seizure propagation.

Ictal SPECT studies may show focal hyperperfusion and are useful to differentiate temporal from extratemporal epilepsy, confirm the epileptogenicity of a structural lesion, and to guide intracranial electrode placement in nonlesional cases (24,30,38–41). In a report of 41 nonlesional neocortical epilepsy cases, PET identified the focus in 43% and ictal SPECT in 33% (42). In another report of 117 neocortical epilepsy cases, MRI found a relevant abnormality in 60%, PET in 78%, and ictal SPECT in 70% (43).

In frontal lobe epilepsy, ictal hyperperfusion has been demonstrated in various parts of the frontal lobes and is frequently accompanied by ipsilateral basal ganglia and contralateral cerebellar hyperperfusion. A correlation between the site of frontal lobe hyperperfusion and different ictal clinical features has been shown. In parietal lobe epilepsy, ictal SPECT may show anterior parietal hyperperfusion when the ictal clinical

Figure 2  Ictal SPECT scan in left occipital lobe epilepsy. Tc-99m HMPAO was injected within 30 seconds of seizure onset. The scan shows focal hyperperfusion in the medial left occipital lobe but also bitemporal hyperperfusion. Very early ictal injection is required to avoid falsely localizing the seizure onset to the temporal lobe in occipital epilepsy. Abbreviation: SPECT, single photon emission computed tomography.
features are characterized by sensorimotor manifestations and posterior parietal hyperperfusion when the seizures are psychoparetic in type (44).

In occipital lobe epilepsy, propagation of the seizure to one or both temporal lobes usually occurs. Very early ictal injection is required to find a focus in occipital lobe epilepsy and to avoid incorrect localization to the temporal lobe. A study of 17 occipital lobe cases found ictal SPECT showed focal hyperperfusion limited to the occipital region in only 29% but hyperperfusion in the relevant hemisphere in 76%, but predominantly in the temporal lobe (45).

Focal tonic seizures are thought to arise from the supplementary motor area. They are often of short duration so that true ictal SPECT is difficult to obtain. In one study of 15 patients with focal tonic seizures, ictal SPECT confirmed the location of the seizure focus in only 40% despite injection within 30 seconds of onset (46).

Subtraction of interictal from ictal SPECT images with the difference image coregistered to the patient’s MRI is important for detection of the seizure focus in extratemporal lobe seizures. Many centers have reported improved sensitivity using this technique compared to visual side by side comparison of interictal and ictal images (9,13,47). This technique has also been reported to identify cortical dysplasia associated with dysembryoplastic neuroepithelial tumors (DNETs) (48).

**FDG-PET AND ICTAL SPECT COMPARED**

Several reports have directly compared the performance of PET and ictal SPECT for seizure focus lateralization. In a study of 35 patients with TLE, ictal SPECT was
marginally more sensitive than FDG-PET for the lateralization of the focus, 89% versus 83% (49). In another report, FDG PET was marginally more sensitive than either ictal SPECT or MRI in 117 cases of neocortical epilepsy, with sensitivities of 78%, 70%, and 60%, respectively (43). In one study of 41 nonlesional neocortical epilepsy patients, FDG PET and ictal SPECT had the same sensitivity of 56% but were described as complimentary (42). Similar sensitivity was reported for both modalities in another report of 36 patients, although it defined the ictal SPECT seizure focus by focal hypoperfusion as well as hyperperfusion (28).

It therefore appears that interictal FDG PET and ictal SPECT have similar accuracy in seizure focus localization but may be complimentary as one modality may be positive in a particular patient when the other is not.

**ICTAL SPECT AND SURGICAL OUTCOME**

There are little data on the predictive value of ictal SPECT for seizure-free surgical outcome. A report of surgical outcome in 36 patients with extratemporal epilepsy found that concordance of SISCOM SPECT (subtraction of MRI coregistered interictal from ictal images) with the site of surgery had independent predictive value over MRI and scalp ictal EEG for excellent seizure control (50).

**OTHER SEIZURE DISORDERS**

**Intractable Neonatal and Early Infantile Seizures**

Ictal SPECT has been used to investigate infants with infantile spasms (West’s syndrome). While most showed diffuse changes, one-third showed focal cortical hyperperfusion (51). Hemispherectomy is employed in some patients with catastrophic seizures and contralateral hemiparesis. A favorable outcome is strongly predicted by abnormal blood flow or metabolic findings restricted to the side of surgery (52).

**Rasmussen’s Syndrome**

Rasmussen’s syndrome, also known as smoldering encephalitis, is a rare form of childhood epilepsy characterized by intractable partial seizures and progressive hemiparesis. The only effective treatment is hemispherectomy although some patients have responded to antiviral therapy. SPECT shows focal or regional hypoperfusion or hyperperfusion that may be useful in defining a site for biopsy to confirm the diagnosis (53).

**Gelastic Epilepsy and Hypothalamic Hamartoma**

Laughing seizures (gelastic epilepsy) is classically due to hypothalamic hamartoma. Removal of the hamartoma is surgically challenging but if resection is complete the seizures are usually cured. Ictal SPECT demonstrates hyperperfusion of the hamartoma confirming the etiology of the seizures (54), although in some cases, propagation to cortical areas may be misleading, particularly if very early ictal injection is not obtained.

**Unilateral Amytal Hemispheric Anesthesia (Wada Test)**

Much of the hippocampus is supplied by the posterior cerebral circulation and it is unclear if medial temporal structures are adequately anesthetized by intracarotid
injection of sodium amytal. Cross flow into the contralateral hemisphere may also complicate interpretation. Exametazine (HMPAO) injected through the arterial catheter clearly defines the distribution of amytal and has revealed cross flow not seen on angiography (55). Alternatively, it can be given intravenously shortly after the amytal to define the extent of cerebral suppression. Intravenous injection should be delayed for 30 seconds after the clinical effects of the amytal become apparent (56). A 25% or more reduction of regional brain activity is then seen and test results can be interpreted with knowledge of the location and extent of the amytal effect (56,57).

**Benzodiazepine Receptor SPECT Studies**

A focal reduction in benzodiazepine (BZD) receptors in temporal and extratemporal lobe foci has been demonstrated with PET and SPECT using the BZD receptor antagonist flumazenil labeled with C-11 or the iodinated derivative I-123 iomazenil (IMZ) (58). C-11 FMZ PET can detect the BZR density changes of hippocampal sclerosis and may be more sensitive than FDG-PET and MRI in detecting this pathology (59). In a study of postsurgical outcome after resection of neocortical seizure foci, the initial extent of reduced FMZ binding and the amount of residual FMZ abnormal cortex after resection were inversely correlated with success. The same was not true for FDG-PET (60).

IMZ allows imaging of these receptors with SPECT. A multicenter European study found a reduction in BZD receptor binding with this agent at the presumed seizure focus in 72% of 92 patients with a variety of seizure types (61). However, in a study comparing C-11 flumazenil PET, FDG-PET, and IMZ-SPECT, the latter performed poorly (62). Like C-11 flumazenil PET studies, IMZ-SPECT may be a useful way to distinguish lateral from medial temporal lobe foci (63).

**CONCLUSIONS**

Ictal SPECT is a logistical challenge but provides unique information in many patients, particularly when MRI is normal or inconclusive. The ideal tracer for ictal SPECT has not been found as both HMPAO and ECD underestimate the degree of ictal hyperperfusion. Further studies are required to (i) better appreciate the relative merits of HMPAO and ECD for ictal SPECT, and (ii) determine the prognostic value for surgical outcome of ictal SPECT, particularly when MRI is negative.

**REFERENCES**


Chapter VII-20a: The Role of Ictal SPECT in the Presurgical Evaluation of Extratemporal Epilepsy

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Accurate localization of the epileptogenic zone (EZ) in patients with extratemporal lobe epilepsy (ETLE), especially in the absence of an MRI-identified abnormality poses a major challenge. This group makes up about 20% to 30% of the patients considered for epilepsy surgery at major centers. Postoperative seizure freedom is considerably worse in patients with nonlesional ETLE and remains as low as 30% to 50% (1,2). Identification and removal of the entire EZ is required to achieve seizure freedom after resective surgery (3). Scalp interictal EEG, ictal video-EEG monitoring, magnetic resonance imaging (MRI), and positron emission tomography (PET) studies are among the standard techniques used successfully in presurgical assessment for temporal lobe epilepsy (TLE). Ictal scalp EEG recording is often poorly localizing in ETLE, and FDG-PET (FDG: 18F-fluorodeoxyglucose) appears to be much less sensitive (estimated 30%) in defining the extent of the EZ in ETLE (4). Neuroreceptor PET imaging is promising in intractable ETLE, but it remains a research procedure.

Ictal single photon emission computed tomography (SPECT) is an effective and reliable noninvasive tool to determine increased cerebral blood flow in an area affected by an epileptic discharge. The uptake properties of SPECT radiotracers allow image acquisition for up to four hours after the seizure onset, when the patient is calm and there is minimal motion artifact. Unlike PET, SPECT is available in most clinical centers, because of the moderate imaging cost and commercial availability of radioisotopes with relatively long half-lives (5).

Our group and others have demonstrated that the clinical utility of ictal SPECT is enhanced using computer-aided techniques to produce subtraction ictal SPECT imaging coregistered with MRI (SISCOM) (6–10). SISCOM provides higher sensitivity, higher inter- and intraobserver reliability and higher facility of interpretation than traditional side-by-side interpretation. This method was initially validated by O’Brien and colleagues at the Mayo Clinic and was recently revalidated in adults with reference to intracranial EEG (6,10). Ictal SPECT is the most sensitive noninvasive imaging technique in adults with TLE and its localizing value is now well established with sensitivity of 97% (11). True ictal examination and localization of the EZ in ETLE, especially frontal lobe epilepsy, is difficult to achieve because frontal seizures are often brief, hypermotor, and nocturnal, and they tend to spread more rapidly. Therefore, extratemporal lobe seizures result in a less focal and sustained increase in regional cerebral blood flow. For ETLE, the sensitivity of ictal SPECT remains low at 50%,
but could reach up to 92% using subtraction techniques (11–16). The recent development of a stable radiotracer, Tc-ECD or 99m Tc-bicistate (technetium-99m-ethyl cysteinate diethylester), facilitated earlier ictal injections and may help overcome some of the above limitations in extratemporal seizure localization (5). This agent is stable in vitro for six to eight hours and does not require mixing just before injections, which is the case with the commonly used isotope 99m Tc-HMPAO (technetium-99m-hexamethypropylene amine oxime) (5).

To test the feasibility of SISCOM in pediatric population, in whom most epilepsies are extratemporal in origin, Chiron et al. (13) studied 26 patients with intractable epilepsies who underwent ictal and interictal ECD-SPECT combined with video-EEG monitoring. The subtracted images allowed detection of a focus in 92% compared to 73% in visually compared ictal and interictal scans. Spencer reported a diagnostic sensitivity of 81%, with a specificity of 93% for ictal SPECT compared with EEG in cases with ETLE (4). Packard and colleagues at Children’s Hospital Boston performed ictal technetium-99m-bicistate study on 10 patients with nonlesional MRI and found focal perfusion abnormalities in all of their patients (14). Harvey used ictal HMPAO-SPECT in children with frontal lobe epilepsy and described unilateral frontal uptake in 91%, which was in accordance with the EEG in 95% (15). Ho and colleagues found focal areas of parietal hyperperfusion in all of their 14 patients with parietal lobe epilepsy, and five with nonlesional MRIs (16).

Lawson et al. (17) studied SISCOM in 65 pediatric patients with intractable epilepsies, including 24 with ETLE who underwent video-EEG monitoring. In the subset of patients with ETLE, 58% had concordant SPECT. When the MRI was normal, the SPECT was localizing in 59% of the patients. They concluded that in patients without lesions, ictal SPECT provides useful additional localization that may be used as a guide to intracranial implantation.

O’Brien and colleagues from the Mayo Clinic studied the localization value of SISCOM as a predictive outcome in 36 patients with intractable ETLE who underwent resective surgery (7). Twenty-four patients (66.7%) had localizing SISCOM, including 13 (76.5%) of those with nonlesional MRI. The concordance of the SISCOM focus with the site of surgery and the extent of the excision were predictive of an excellent postoperative outcome, independently of MRI or scalp ictal EEG findings ($P < 0.05$). These results confirm that the peri-ictal SPECT analyzed with the aid of SISCOM provides nonredundant localizing information compared to the more standard tests. These findings also apply to patients with nonlocalizing MRI and scalp EEG results (7).

A recent study by Kaminska et al. (18) used intracranial EEG recording and postsurgical outcome to validate the use of SISCOM in localization of the EZ in children with intractable epilepsy. Twenty patients were studied, 10 of whom had extratemporal epilepsy. They showed that the site of highest increased ictal perfusion (IPA) colocalized with the site of onset of discharge and that of the lower IPA with the area of seizure propagation ($P < 0.0001$, sensitivity 0.80 and specificity 0.70). Among the patients with a favorable surgical outcome, the highest IPA colocalized with the resected area in 70% of the cases. The risk of falsely localizing the seizure propagation area instead of the true EZ was in the same range as other series with extratemporal lobe epilepsy (20% compared to 19%) (19). Their study demonstrates that ictal SPECT plays an important role as a noninvasive presurgical method of investigation to optimize the placement of intracranial electrodes in children and to improve the postsurgery outcome (18).
Subtraction ictal SPECT is more accurate than any other noninvasive procedures for the localization of epileptogenic zone and significantly increases the sensitivity of ictal SPECT in both adults and children with ETLE (5–18). This procedure is invaluable to help determine the optimal site for intracranial electrode placement and to limit the need for invasive procedures (18). Localization of the extratemporal epilepsy with SISCOM is predictive of an excellent postsurgical outcome, independent of MRI or scalp ictal EEG findings (7). It may also be useful in guiding the extent of the resection required for successful postoperative seizure control (7). In addition, SISCOM may also contribute to our understanding of the pathophysiology of propagation pathways (18). We believe that the use of subtraction ictal SPECT plays a pivotal role in routine presurgical workup of patients with intractable extratemporal epilepsy.

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Part Three

Surgical Procedures
INTRODUCTION

Resective epilepsy surgery has always had as one criterion for case selection the ability to localize the site of focal onset of the seizures. In the early days, most of the resections were in the Rolandic cortex, with clinical semiology of the partial motor or sensory seizures providing localization of the site of onset (1–3). The advent of electroencephalography (EEG) provided the basis for expanding the scope of resective surgery to the temporal lobe (4). Subsequently, the temporal lobe has become the major site for resective epilepsy surgery, both because seizures arising there are more likely to be medically refractory and because of the relative ease in identifying focal epileptogenic zones there with EEG and modern imaging. This, in turn, has stimulated interest in the functional roles of the temporal lobe, and in the basic mechanisms involved in generation of epilepsy there.

As a basis for considering the practice, and the controversies that surround the current practice of resective temporal lobe surgery, this chapter reviews:

1. Surgical anatomy of the temporal lobe
2. Temporal lobe functions relevant to surgical therapy
3. The variety of approaches to resective temporal lobe epilepsy surgery.

ANATOMY

Anatomically, the temporal lobe is considered the most heterogeneous of the four lobes, having a typical six-layered isocortical mantle that hides a complex convolution of mesocortex and allocortex medially, known as the limbic core, consisting of the hippocampal and prepiriform cortex and the amygdala. On the lateral surface of the brain the isocortical margin is indistinct posteriorly, ending at an imaginary perpendicular drawn from the end of the sylvian fissure to a line joining the
parieto-occipital sulcus to the temporo-occipital notch. This lateral isocortical mantle is highly variable except for the superior temporal gyrus which is delineated by the sylvian fissure dorsally and the superior temporal sulcus ventrally. The superior temporal sulcus runs parallel to the sylvian fissure to the angular gyrus, is usually deep, and travels in an unbroken line. The middle and inferior temporal sulci show considerable variations, are usually shallow, and are often discontinuous. On the ventral surface the fusiform or temporo-occipital gyrus of the temporal lobe is demarcated by the inferior temporal sulcus laterally and the collateral sulcus medially. The collateral sulcus is invariant like the superior temporal sulcus, and separates the fusiform gyrus from the parahippocampal gyrus. Interhemispheric transfer of information between the temporal lobes occurs primarily through the anterior commissure and the corpus calosum.

The medial portions of the temporal lobe are considered part of the “limbic lobe.” This includes the hippocampus, dentate gyrus, amygdala, and parahippocampal gyrus, all structures lying medial to the (often continuous) rhinal and collateral sulci. There is considerable individual variability in these sulci (5). The parahippocampal gyrus is continuous with the cingulate gyrus providing one link with the extratemporal limbic lobe. All of the limbic temporal lobe is “allocortex,” in contrast to the “neocortex” of the remaining temporal lobe. There is a gradual transition in the parahippocampal region from six-layered “paleocortex” laterally to three-layered “archicortex” of the more medial subiculum, hippocampus, and dentate gyrus.

The anterior portion of the parahippocampal gyrus (sometimes called entorhinal cortex) appears to have a pivotal position interconnecting the hippocampal formation with the neocortex. The entorhinal cortex provides the majority of the input to the hippocampal formation, through the perforant and alvear pathways. Though the fornix is often considered the major efferent pathway from the hippocampus, the majority of output from the hippocampus and subiculum also pass directly to the entorhinal cortex. Several structures within the hippocampal formation have been particularly important in the pathophysiology of temporal lobe epilepsy. These include the pyramidal cell layer of the hippocampus, traditionally divided into CA1 to CA4 regions, and the granule cell layer of the dentate gyrus, linked by a trisynaptic circuit, entorhinal cortex to dentate gyrus to CA3 (via mossy fiber connections) to CA1 (via Shaffer collaterals) and back to the entorhinal cortex.

Based on the pathologic findings of mesial temporal sclerosis, it has been suggested that some or all of the loss of pyramidal neurons in CA1 and CA3,4 with dispersion of the granule cell layer and sprouting of the mossy fiber system are factors in the pathophysiology of most cases of “limbic” temporal lobe epilepsy, those with evidence for medial temporal onsets. However, the presence of cases with quite typical temporal lobe epilepsy of medial temporal onset, with either none of these changes or at most subtle loss of CA4 neurons, has raised questions about the importance of some or all of those factors in medial temporal epileptic mechanisms.

From the standpoint of surgical anatomy, the collateral sulcus, choroidal fissure, choroidal point (the anterior limit of the temporal horn choroid plexus), hippocampal sulcus and amygdala are particularly important landmarks. Although the role of the amygdala in temporal lobe epilepsy remains controversial, this nucleus, located in the anterior portion of the temporal stem, provides an important landmark in all techniques of temporal resection to avoid encroaching on the internal capsule, basal ganglia, or brain stem, by leaving a shell of this structure posteriorly and superiorly.
FUNCTION

In resective temporal lobe epilepsy surgery, the major functional issues involve vision, and for the language-dominant hemisphere, language and memory. Although bilateral lesions of the anterior temporal lobe in monkeys result in behavioral changes that include visual agnosia of the Kluver–Bucy syndrome, and ventral visual pathways have been followed to the temporal pole in those species, neither of these effects is very prominent in humans (6,7). The human temporal lobe is about 10 times larger than that of monkeys, while primary cortices such as the primary visual cortex are only about three to four times larger. This expansion of association areas of the temporal lobe in humans is reflected in the extra lateral temporal gyrus and seems to involve the anterior as well as lateral temporal lobe, with the functional homolog of the monkey ventral visual pathway confined to the posterior–basal human temporal cortex.

Vision

Most of the visual deficits after temporal lobe resections are related to the primary visual pathways, particularly Meyers loop of the optic radiations, which extends a variable distance forward in the temporal lobe (8). Most often, encroaching on the optic radiation results in a contralateral peripheral superior quadrant visual field defect that will not be noticed by the patient unless they acquire formal visual fields. Larger superior quadrantanopsias, extending into central vision, will be noticed, but are rarely very disabling. As the optic radiations are located on the roof of the temporal horn, restricting any ventricular opening to the lateral edge reduces the risk of visual field deficits. Hemianopic deficits are usually due to damage to the optic tract, or branches of the posterior cerebral artery.

Formal neuropsychologic testing has demonstrated subtle perceptual deficits of which the patient is generally unaware. These are usually after right, nondominant resections, and include deficits in memory for some, but not all, types of visuospatial materials after resection of medial temporal structures, and subtle deficits in perception of facial features after lateral temporal resection (9,10). A more obvious deficit in facial perception, prosopagnosia, usually requires bilateral lesion of the posterior inferior basal temporal cortex (11).

Language

Classically, temporal lobe language representation is Wernicke’s area in the posterior superior gyrus of the dominant hemisphere. And classically, damage to this area is associated with a receptive aphasia. But it has always been something of a puzzle that the temporal lesions associated with aphasia were not always in the classical area, and the deficits were often expressive except in the selected population of elderly stroke patients. Indeed, even the lateralization of language is variable, with about 15% of patients not having language exclusively in the left hemisphere. For the surgeon, the crucial issues are whether this is the dominant hemisphere, and if so where are the crucial areas for language. Classically, language lateralization has been based on handedness, but this association is known to be quite inexact (12). A rare right-handed patient will not be left hemisphere dominant, but a substantial proportion of left-handers will be left hemisphere dominant. Of particular concern are the small number of cases who are right-handed, have right language dominance and a right temporal epileptic focus. Intracarotid amobarbital perfusion testing (the Wada
test) is the standard technique for establishing language lateralization. Whether the proportion of right-handers who are not left dominant is large enough to justify the risks of this procedure in those patients is controversial. Some epilepsy centers restrict use of the Wada test to left-handers. Additionally, functional magnetic resonance imaging (fMRI) during language measures may be a noninvasive technique for establishing language lateralization, based on the asymmetry of frontal lobe language activation (13).

Language localization within the dominant temporal lobe is most often based on anatomic landmarks. Those portions of middle and inferior temporal gyri anterior to the line of the central sulcus, anterior to the vein of Labbe, or within 4–4.5 cm of the temporal tip have been considered a “safe” region where resections would not lead to permanent language deficits. Application of a high-frequency electrical current to the cortex during simple language measures such as object naming will interfere with the language task at some sites. Often this interference is confined to focal areas of 1–2 cm² of cortical surface. When a resection encroaches on lateral temporal sites where language interference has been evoked, a post resection language deficit is likely, in both epilepsy and tumor populations (14,15). Thus, this technique of electrical stimulation mapping provides a way to identify the “essential” sites for language in individual subjects. When the location of these sites is assessed across subjects, considerable variation in exact location is evident. In a series of 117 dominant hemisphere mappings, only 65% had essential language sites identified anywhere in the superior temporal gyrus, while 15% had essential sites in the “safe” region based on anatomic landmarks (16). Similar variability is evident in children (17). Stimulation mapping has also interfered with language at basal fusiform gyrus sites, from 3 to 7 cm posterior to the temporal tip, and language deficits have been reported after resection of these sites (18,19), though the frequency, severity, and persistence of these deficits seems to be less than that observed when a resection encroaches on lateral cortical language sites.

This variability in the location of the focal essential language sites has two important consequences for planning temporal resections. Sometimes essential language sites will be in the “safe” region. Whether this happens often enough to require language mapping during dominant anterior temporal resections is controversial. But sometimes essential language sites are not present in the classical Wernicke language region, so that resections there can be safely done. Nearly all surgeons use some technique for individual language localization for resections there. There are a number of important technical details in electrical stimulation mapping, particularly the selection of current level, to avoid evoking a seizure, but still have adequate current to avoid false negative findings. Whether mapping is best done intraoperatorically, with the patient awake under local anesthesia for a portion of the operation, or extraoperatorically with the extra morbidity of subdural grid placement is also controversial. When a variety of different language measures are assessed in the same subject, the sites of stimulation interference are often separate. This includes some separation of sites for object naming in different semantic categories (Corina and Ojemann, unpublished data), for nouns from verbs, for naming the same objects in two different languages, and for naming compared to word or sentence reading (20–24). As it is usually not possible to assess a wide range of language functions in an individual, preservation of a full range of language abilities requires providing a margin around a site essential for a simple language function such as naming. In one study, a 2 cm margin along a continuous gyrus was adequate to avoid a postoperative language deficit (14).
There has been considerable interest in using fMRI localization to plan resective surgery. However, when the same language measures are used for stimulation mapping and fMRI, there is poor correspondence between temporal lobe sites with fMRI changes and those with stimulation interference with the language task (25). Since the sites related to language by stimulation mapping have been shown to be predictors of the language effects of a resection, it appears that these fMRI effects are not predictors. However, when fMRI is assessed during complex language tasks, and this localization is compared to stimulation mapping with simple language tasks, there seems to be closer correspondence of fMRI positive and stimulation interference sites, although even this fMRI localization does not provide accurate enough language localization to plan a temporal resection (26). fMRI provides somewhat more accurate language localization in the frontal lobe.

**Memory**

The multiple facets of human memory are now known to be dependent on different anatomic substrates. Bilateral resection of the anterior–medial temporal lobe, including anterior portions of the hippocampus, has been associated with a loss of the ability to retain new explicit memories (sometimes referred to as declarative memory) over a distraction (27,28). These patients do not form new long-term memories for these explicit events, and have a variable degree of retrograde amnesia, which may involve several years prior to the temporal damage. However, their long-term memory for earlier events is relatively intact, recent explicit (working) memory remains intact until they are distracted, implicit (unconscious) memory mechanisms such as those reflected in priming are intact, and memory for motor skills (procedural memory) is relatively intact. Unilateral anterior–medial temporal damage has been associated with material-specific rather than global deficits in the same memory areas: verbal material with dominant lesions and memory for certain types of visuospatial material for nondominant. Memory deficits are more severe with more extensive medial removal, and there is some evidence that they are also more severe with larger lateral resections, but memory deficits have occurred in patients with resections confined to anterior 40–45 mm of the temporal lobe with little or no hippocampus resection (9,29). Recent evidence of the importance of the entorhinal cortex in the maintenance of human memory may account for such cases (30). Although formal neuropsychological assessment shows material-specific deficits after resection of either temporal lobe, patients usually complain of memory loss only after dominant resections. The most common complaint is an inability to remember people’s names.

These memory deficits after temporal lobe resections show less recovery over time than do any language deficits. Verbal memory deficits after dominant temporal resections remain the major cognitive complication of resective epilepsy surgery, and have been considered by some to contraindicate resective surgery in the dominant hemisphere (31).

The probability of having memory loss after a dominant temporal resection depends on multiple factors. It is more likely in patients with seizure onsets in later life [after five in some studies, 18 in others (32) (Dodrill, unpublished)], perhaps in older and female patients, definitely in those with relatively intact preoperative verbal memory, those who are not seizure-free postoperatively, and those who do not have imaging evidence of medial temporal damage such as medial temporal sclerosis. Many of these factors are interrelated. Memory performance during the intracarotid
amobarbital perfusion procedure (Wada test) has also been considered a predictor of postoperative memory performance, with little memory deficits when the carotid ipsilateral to the side of the planned resection is perfused, and major loss with contralateral perfusion considered favorable findings. However, the predictive power of this test has been questioned, particularly since different measures of memory give different findings (Chapter IV-11, 33).

**APPROACHES TO TEMPORAL LOBE RESECTIVE SURGERY FOR EPILEPSY**

Selection of patients for resective temporal lobe epilepsy surgery is based on a classic set of criteria: medical intractability, identification of an epileptogenic zone in the temporal lobe, and a relatively low risk of new deficits. Identification of the epileptogenic zone is based on convergence of findings from electrophysiology with those from imaging, augmented by clinical semiology and neuropsychology. In general, the highest proportions of seizure-free patients are those with exclusively unilateral interictal posterior frontal–anterior temporal epileptic discharges based on scalp EEG and imaging evidence of ipsilateral medial temporal structural abnormalities, particularly medial temporal sclerosis (MTS). Some centers consider this adequate identification of the epileptogenic zone in such patients, others will want scalp ictal recordings with onsets in the same region as the interictal focus (see Chapter V-15, 34). Selection of cases on imaging changes alone has been proposed, but cases where the imaging changes were misleading (including MTS changes) have been published (35). The more a patient’s findings deviate from this ideal, the less likely that seizures will be controlled by a resection. However, patients with unilateral anterior temporal interictal foci, with scalp EEG ictal onsets in the same region but no imaging changes have nearly as favorable an outcome after temporal lobe resections as those with similar electrophysiological findings and MTS. Moreover, in patients with anterior temporal foci, the tissue resected to achieve seizure control is similar with or without MTS, predominately involving medial temporal structures. This is one piece of evidence that the vast majority of patients with medically refractory temporal lobe epilepsy have onset in medial “limbic” structures, regardless of whether the classical pathologic finding of MTS is present or not; true “neocortical” temporal lobe epilepsy is rare and usually associated with a lateral temporal structural lesion (37). The value of ictal semiology in selecting patients for temporal lobe resective surgery remains controversial (Chapter V-16). Neuropsychological findings have some predictive role (Chapter IV-10, 38). Patients with bilateral interictal abnormalities, but unilateral ictal onsets on scalp seizure monitoring do relatively well, particularly with ipsilateral imaging changes. However, once there is evidence for bilateral ictal onsets, even with substantial preponderance to one side, or if EEG and imaging changes are not concordant, the outcome is substantially less favorable, and intracranial recording is usually necessary. A seizure-free outcome in cases with bilateral ictal onsets usually is seen only when there is some lateralized abnormality on the noninvasive workup: preponderance of interictal discharges, abnormality on imaging, or lateralized neuropsychological findings (39). What, if any, role there is for intracranial recording in evaluating less complex cases for resective surgery is quite controversial (40).

When intracranial recording is indicated, additional controversy surrounds the relative merits of depth electrodes compared to subdural strips and grids. The extensive coverage of the cortical surface of one hemisphere provided by subdural
grids seem uniquely suited for evaluating cases with multiple unilateral scalp EEG foci to determine which ones generate seizures or where the separation of the site of seizure onset from functionally important brain is an issue. On the other hand, if all that is needed is identification of functionally important cortex, this can also be done intraoperatively, with less morbidity. Bilaterally placed depth or subdural strip electrodes are useful for establishing lateralization of seizure onsets. Depth electrodes provide more precise and sensitive sampling of the amygdala and hippocampus than do strip electrodes placed on the adjacent parahippocampal gyrus, but depth electrodes probably are associated with a slightly higher morbidity (41). When compared, lateralization of onsets is very occasionally different between hippocampal depth electrode and parahippocampal strip electrode recordings, suggesting that initial spread from the hippocampus can occasionally be to the opposite parahippocampal gyrus before the ipsilateral one. However, there does not seem to be a great difference in outcomes with series managed with either technique, and a series with randomized evaluation has not been reported. Unlike scalp EEG signals, which average activity over a considerable volume of tissue, intracranial electrodes, whether depth or surface, predominately record only local EEG activity, so that whenever they are considered there must be specific hypotheses as to where the seizures arise based on the noninvasive evaluation, to guide electrode placement.

The extent of temporal lobe resections for epilepsy has been determined in two different ways. In one group of approaches, the extent is tailored to the individual patient’s pathophysiologic findings. This information may be derived intraoperatively or extraoperatively. Extraoperative techniques to tailor a resection include placing; subdural grid, strip, or depth electrodes in the region of the suspected epileptogenic zone. With these techniques, ictal onset data are usually obtained. These techniques are used by most surgeons for cases with suspected lateral temporal “neocortical” epileptogenic zones, and by some for those with medial temporal onsets. Intraoperative techniques for tailoring resections usually depend on interictal epileptic activity to identify tissue requiring resection. The value of interictal data in providing this information is quite controversial. Some of this controversy may be a result of the different conditions under which the interictal recordings were obtained. In some techniques this information is acquired with the patient awake under local anesthesia as well as during various degrees of pharmacologic sedation; with other techniques the interictal recordings are obtained under general anesthesia. There has been little comparison of the effect of these different approaches on the interictal data, even though it is known that different general anesthetic agents influence interictal activity (42). Having the patient awake under local anesthesia also allows detailed intraoperative functional mapping, including language mapping. When used, the intraoperative tailoring technique is most often applied in cases thought to have medial temporal onsets.

In a second group of approaches, the extent of the temporal resection is anatomically standardized. With this approach the preoperative evaluation must indicate that the epileptogenic zone is in the region included in the anatomically standard operation. Most often this approach has been applied to cases thought to have medial temporal onsets. Anatomically standardized operations include classical anterior temporal lobectomy, with resection of 4–4.5 cm of the dominant hemisphere anterior temporal lobe, as measured from the temporal tip, and 5–5.5 cm of the nondominant one (43). Classically these resections include medial and lateral structures back to this level, although the superior temporal gyrus is usually spared in the dominant hemisphere.
More recently, anatomically standard operations that include predominantly medial temporal structures have been widely performed, following the reports of Neimeyer and especially Weiser and Yasargil (44,45). These operations are often grouped under the heading amygdalohippocampectomy (Chapter VIII-24). However, there are quite a number of variations in the route used to access the medial temporal structures: through the superior temporal gyrus, after resection of the anterior 3 cm of the temporal cortex, through the middle temporal gyrus, or by way of the basal temporal cortex (45–48). Moreover, the extent of the medial resection is also quite variable, in some techniques including all hippocampal formation (hippocampus and underlying parahippocampal gyrus), and in others including only a portion of those structures, to the peduncle or further to the collicular cistern. The extent of amygdala resection has also been variable. Favorable outcomes have been reported in series where the hippocampus was resected but the amygdala spared, and in series with amygdala and adjacent extrahippocampal structures resected but little or no hippocampal resection (49,50). Additionally, favorable outcomes have been reported with an anatomically standard resection that included the anterior temporal lobe but little if any of the hippocampal formation (51). Moreover, perhaps surprisingly given the emphasis on the hippocampus as the primary source of seizure activity in medial temporal epilepsy, follow-up of the extensive series of amygdalohippocampectomies of Weiser and Yasargil indicated that it was the extent of resection of the parahippocampal gyrus that correlated with seizure outcome, and not the extent of resection of the amygdala or hippocampus (52). Nevertheless, most contemporary series use techniques that resect some or all of the hippocampal formation. Details of surgical technique also differ among these operations: some removing medial structures with subpial techniques, retaining medial pia as a barrier to brain stem and vascular structures, while others use an extrapial approach (45).

There is no currently convincing evidence of superiority of one of these approaches over another. Comparisons of cases managed by different approaches are often confounded by historical factors: cases managed with one approach representing earlier series than those managed with another (53). A randomized evaluation of these different techniques has not been done. However, reviewing reported results of temporal lobe resective surgery over the past 50 years suggests that a larger proportion of patients have become seizure-free with more recent surgical approaches that include resection of medial temporal structures (54,55), though this difference is partly confounded by improvements in case selection. One randomized study found a higher probability of seizure control with more extensive hippocampal resections (56).

Destruction of medial temporal structures with radiosurgery using the gamma knife has been recently proposed as an alternative approach to resective surgery for temporal lobe epilepsy (Chapter 52). Favorable results in patients with imaging evidence of MTS and an appropriate scalp EEG focus have been reported (57). Seizure relief usually occurred 12 to 18 months after treatment. This approach is currently the subject of ongoing studies to evaluate the safety (the radiation dose is quite high and local brain swelling has been reported) as well as efficacy. One suggestive preliminary finding is that patients treated this way with dominant hemisphere foci may have relatively less verbal memory loss, perhaps because the evolution of the gamma knife medial temporal lesion is similar to the effects of serial lesions rather than an acute lesion, though since these patients all have MTS, and memory loss is less in MTS patients than those without imaging changes, this finding will need confirmation.
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Chapter VIII-21
Language Mapping for Temporal Lobe Epilepsy

Chapter VIII-21a: Review of Language Mapping Procedures for Temporal Resections

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INTRODUCTION

Postoperative language deficits are distressing potential complications of dominant hemisphere epilepsy surgery. To minimize the risks of these complications, techniques have evolved to locate areas essential to language function. The locations of these areas are highly variable, and cannot be predicted on the basis of surface topography. Mapping techniques include cortical stimulation (intra- and extraoperative) and functional imaging. Electrophysiological methods offer superior spatial resolution and reliability. Functional imaging allows visualization of the entire brain but, as yet, is not reliable enough to guide surgical strategy. The optimal method and the need to identify language sites for dominant temporal lobe resections remain controversial. This chapter reviews the techniques of language mapping and introduces some of the controversies surrounding its use.
ELECTRICAL STIMULATION MAPPING

The most reliable method of localizing essential language areas is electrical cortical stimulation mapping (ESM). One of the first applications of stimulation mapping can be traced to the 1870 work of Gustav Theodor Fritsch and Edouard Hitzig. These investigators demonstrated the concept of cerebral localization of function by eliciting focal motor responses with electrical stimulation of the canine cortex (1). The Scottish neurosurgeon David Ferrier (2,3) extended this work to primates in an attempt to substantiate John Hughlings Jackson’s theories about the origins of partial motor seizures (4).

Bartholow (5), in 1874, was the first to perform such experiments in the human, using needle electrodes to pierce the exposed dura of his house servant whose scalp cancer resulted in a skull defect. Horseley applied the technique during surgery to map the thumb area of the Rolandic cortex (6). Cushing (7) wrote on faradic stimulation to map the postcentral gyrus. Krause (8,9) and Foerster (10) published elaborate maps of the motor and sensory cortex based on ESM.

Penfield, who studied with Foerster, is credited with popularizing ESM (11–13). Penfield (12) was also the first to note differential effects of current application in the primary and association cortex. Conversely, stimulation in the lateral association cortex, such as temporal lobe language areas, interfered with ongoing verbal behavior, resulting in speech arrest. This phenomenon was employed by Penfield and Roberts (14) to map cortical representations of language during overt naming.

Using refinements of this technique, modern ESM identifies “essential” language regions where stimulation reproducibly produces anomia. These essential areas are approximately 1 cm², and typically occur in the perisylvian frontal operculum and in the temporoparietal cortex. The distance from the resection margin to the nearest essential language site is the most important variable in determining the duration of postoperative language deficits, and whether postoperative deficits were permanent (15). Over 90% of patients with resection margins less than 1 cm from an essential language site experience immediate postoperative language deficits and 28% experience permanent deficits (15). Conversely, if the resection margin is greater than 1 cm away, 36% experience immediate deficits and no patient experienced a permanent language deficit. Stimulation mapping has a high predictive value for language preservation.

The exact number and location of essential sites is highly variable and cannot be predicted on the basis of anatomical considerations alone (Fig. 1). This variability is seen in patients with early (16) and late acquired lesions (15), suggesting that language variability is a fundamental principle in language localization (17). Furthermore, separation of language sites is a function of the specific task employed (18–23), such as naming, reading, recent verbal memory or verb generation (24), differences in the semantic category of the objects to be named, and naming of the same object in two languages (25,26). The ability of ESM to reliably predict postoperative language deficits makes this technique clinically useful.

TECHNIQUES OF STIMULATION MAPPING

Stimulation mapping can be undertaken during surgery or postoperatively, following placement of electrode grids and/or strips as part of a two-stage procedure. Each of these techniques has relative advantages and limitations.
Intraoperative Stimulation Mapping

Intraoperative ESM provides real-time information, but is more demanding for the patient. Patient selection contributes significantly to outcome (27). As intraoperative ESM requires an awake, cooperative patient, younger children and patients with significant cognitive, psychiatric, or developmental disabilities must be excluded (19). Furthermore, baseline naming error rates must not exceed 25%. Medical co-morbidities, including obesity, sleep apnea, and pulmonary conditions, may hinder safe administration of neuroleptic anesthetic agents (28). Patients with large mass lesions must be excluded due to elevations in arterial $pCO_2$ during the neuroleptic anesthetic phase of the procedure. ESM also carries the potential risk of seizures, both spontaneous and stimulation induced. It is therefore imperative to assure therapeutic anticonvulsant levels prior to surgery.

Early seizures may be terminated with the administration of short-acting barbiturates or benzodiazepines along with cold irrigation solution applied directly to the cortical surface (29).

The technique of intraoperative language mapping has been described in detail (16,30). Briefly, under propofol sedation, a field block is achieved with local anesthesia instillation using a mixture of 0.25% bupivacaine, 0.5% lidocaine, and 1/200 epinephrine. A craniotomy is then fashioned to offer ample exposure of all cortical regions likely to be involved in temporal lobe language processing. The dura can be infiltrated with the local anesthetic mixture prior to allowing the patient to awaken fully.

Stimulation mapping proceeds, following placement of an array or grid of cortical electrodes (Fig. 2). Continuous electrocorticography (ECoG) permits determination of the afterdischarge threshold and surveillance of afterdischarges induced by cortical

Figure 1  Variability of language localization in 117 patients undergoing electrical stimulation mapping. Language sites could be found well beyond the typical Broca’s and Wernicke’s areas. Numbers within circles represent the percent of patients who possessed an essential naming site within the given cortical zone delineated. Numbers to the right of circles represent the number of patients stimulated in that cortical zone. Source: From Ref. 16.
stimulation. This is important since afterdischarges may portend a seizure or lead to mapping errors. In contrast to mapping the primary motor cortex, where one elicits muscle contraction, mapping the language cortex depends on the ability to block rather than elicit a function. The use of bipolar stimulation allows precise induction of a focal depolarization blockage localized between the electrode contacts (31). Typical bipolar stimulators are designed with two 2 mm spherical electrodes separated by 5 mm. Bipolar stimulation consists of one millisecond alternating biphasic square wave pulses at 60 Hz for a pulse train of three to four seconds. This current is increased in 1 to 2 mA increments until afterdischarges are noted on the ECoG. Determining the afterdischarge threshold establishes the maximum current that can be applied to the cortex without inducing a propagating wave of depolarization. Such current spread may produce seizures or result in false-positive ESM testing by blocking a language site remote from the actual site of stimulation.

Fifteen to 20 evenly spaced sampling sites are selected and labeled with sterile numbered paper tickets. When necessary, unexposed cortex can be accessed with strip electrodes (32). Patients are then shown a series of objects, which are named
aloud. During stimulation, current is applied throughout the object presentation. The surgeon recursively stimulates each site in pseudorandom fashion (accepting that no site is stimulated twice in succession) until all sites have been stimulated at least three or four times.

Intraoperative stimulation mapping has the advantage of requiring only one operation. Additionally, if the resection encroaches on an essential language site, the surgeon retains the ability to tailor the resection by repeatedly stimulating (or testing an awake patient) during the resection. Mapping during resection is particularly important in the presence of a lesion which has distorted the cortical surface but left the underlying white matter intact, such that ascending and descending fibers do not run perpendicular to the gyral crown.

Extraoperative Stimulation Mapping

Extraoperative stimulation mapping is necessary when patients do not qualify for awake surgery, or when chronic intracranial seizure monitoring is required. In addition, patients may benefit from input from the entire epilepsy team (neurologists, neuropsychologists, etc.), who cannot all be present in the operating room.

Extraoperative mapping carries several potential advantages over intraoperative methods. First, mapping may occur over several sessions, allowing multiple language functions to be explored and patient fatigue to be minimized by scheduling rest periods between sessions. Second, the surgeon is provided with a functional language map prior to entering the operating room to perform the resection, allowing the entire epilepsy team to participate in surgical decisions and permitting discussion with the patient and family, for improved informed consent.

Extraoperative mapping has limitations as well. These include the need for two operative procedures and the inherent risk of infection with in-dwelling foreign material. The electrode position may shift during the interval between surgeries, leading to inaccuracies in localization. The cortical region stimulated with grid electrodes is less precise because typical contacts are larger (4 mm) and are spaced farther apart (1 cm) than the bipolar stimulator. These contacts bear a fixed position relative to each other; therefore, there is no allowance for contacts overriding vessels or straddling sulci. Electrodes may stimulate the middle cranial fossa dura, producing painful sensations. Lastly, contacts must be stimulated in series of electrode pairs to triangulate essential areas, which occasionally produces ambiguous or inconclusive data.

Extraoperative mapping occurs in a quiet room equipped with the display screen for the naming paradigm (e.g., laptop or slide viewer), the stimulator (OCS-1, Radironics, Burlington, Massachusetts, U.S.A.) and an electroencephalogram (EEG) machine to monitor ECoG. Stimulus parameters include a 0.2 millisecond biphasic pulse of 2 mA current at 60 Hz applied for a pulse train of one to five seconds. With incrementally increased current, the appearance of afterdischarges establishes the maximum stimulus current.

Object naming then commences, with electrode pairs systematically tested at current intensities 1 to 2 mA below the afterdischarge threshold. Episodes of anomia produced by the depolarization blockade are documented. Sites are tested three to four times to ensure reliability. Particular attention is directed to the cortex near the planned resection area. With a functional language map in hand, the surgeon may devise an operative strategy that minimizes risk to essential language regions.

Although cortical mapping is an important tool, potential pitfalls must be recognized to utilize mapping safely. For instance, the inability to identify functional
cortex does not prove that one is not in functional cortex. It may indicate that there was a problem with mapping, not necessarily that resection is safe. Also, more than two essential language areas are not uncommon (16); therefore, the entire region to be resection should be mapped.

**ALTERNATIVES TO STIMULATION MAPPING**

**Wada Testing Alone**

The intracarotid sodium amobarbital test (33) has long been the gold standard for lateralizing language function. However, its utility to localize language within a hemisphere has not been convincingly demonstrated. This may be due to several factors. Wada test procedures are subject to variability and the scores themselves may be open to varying interpretation (34). The results may be difficult to interpret when there is significant vascular shunting, as with arteriovenous malformations and some tumors. Additionally, Wada testing is associated with a false negative rate. This is reflected by right-sided Wada results in patients who subsequently are found to have left hemisphere ESM sites (35). While left-sided Wada language lateralization is strong support for exclusively left-sided language function, right-sided Wada language lateralization does not exclude left-sided language. Patients with right or bilateral dominance on Wada testing should still have left hemisphere cortical stimulation for localization of language areas (35).

**Functional Imaging**

Functional magnetic resonance imaging (fMRI) has shown great promise in localizing function within primary cortices. For example, fMRI can distinguish somatotopic representations of specific body parts in response to isolated contralateral movements (36). fMRI also appears to be equivalent to Wada testing in determining language lateralization (37,38).

Comparisons between fMRI and Wada share a high, but not perfect, degree of concordance (39). On the basis of these reports, fMRI has been proposed as a non-invasive replacement for Wada testing (40).

The potential for fMRI to replace ESM for language localization has been recognized practically since fMRI’s inception. Before fMRI may be used to guide surgical decisions, it is necessary to first establish that essential language areas can reliably be localized. This requires a minimal occurrence of false-positive activation sites (sites of fMRI activation where no ESM sites are found) and false-negative sites (sites without fMRI activation but where ESM sites are present). In reality, this requirement has not yet been met (41). fMRI studies often demonstrate signal changes throughout the dominant hemisphere at locations remote from essential language areas as well as revealing signal change in the opposite hemisphere.

Several direct comparisons between fMRI and ESM have been attempted with mixed results. Whereas ESM delineates “essential” cortex, fMRI delineates “involved” cortex. This difference explains the primary shortcoming of utilizing fMRI to guide surgical strategy. Pouratian et al. (42) studied 10 patients with vascular malformations and found a high degree of colocalization with the use of a language battery fMRI paradigm. Few additional studies have met with similar success, however. Schlosser et al. (43) studied 33 patients who underwent preoperative fMRI and ESM. In roughly one-third of their cases, fMRI was unreliable due to head movement, computer error, or unexplained factors. Twelve of the remaining 14 patients demonstrated some degree of colocalization. Yet, the spatial extent of the fMRI activation and ESM did not
always correspond and findings contained both false-positives and false-negatives. Lurito et al. (44) focused on receptive language areas and found similar, but nonidentical, sites as well as false-negative regions.

In a series of 14 patients, Roux et al. (45) concluded that fMRI could not be used to make critical surgical decisions in the absence of direct brain mapping after noting colocalization in only 13 of 22 sites. Traditional ESM is in little jeopardy of being supplanted by fMRI with colocalization discrepancies of up to 2 cm and persistent false-positive and false-negative sites (46).

Confounding the interpretation of this literature is the variability of the testing paradigms within and across studies and the heterogeneous populations studied. Many fMRI paradigms involve passive listening tasks, whereas ESM typically employs overt language production (i.e., confrontational naming). Some language paradigms may be less reliable at producing consistent fMRI results than others (47). Furthermore, patients with widely varying diagnoses (e.g., tumors, epilepsy, congenital malformations) are considered together. While fMRI techniques may be applied to tumors (48), alterations in the regional activation and accuracy of fMRI have been reported (49). Despite these limitations, functional imaging will undoubtedly play an increasingly important role in preoperative planning of dominant hemisphere surgery.

CONCLUSION

While the final chapters in functional mapping remain to be written, electrophysiological methods currently provide the most useful clinical data. These methods are invasive and time-consuming, but they provide information that may be critical for surgical decision making. Functional imaging methods are noninvasive and visualize the entire brain in a few seconds, but discrepancies in language localization and false localization currently limits fMRI from guiding surgical decisions.

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Chapter VIII-21b: Language Mapping Is Necessary for Language-Dominant Temporal Resections

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There is currently little or no controversy about using language mapping in posterior temporal resections in the dominant hemisphere. Indeed with that technique it is often possible to resect an epileptogenic zone that, based solely on anatomic criteria, would be considered to be in Wernicke’s area and thus unresectable. The usefulness of language mapping depends on several factors. Sites where stimulation interferes with a language task such as naming are often localized to relatively focal areas in an individual patient (1). When resections encroach on those lateral cortical perisylvian sites, there is likely to be a language deficit, thus their location identifies where essential language cortex is located in that patient (2,3). Across a population of patients with medically refractory epilepsy there is substantial variability in the location of that cortex in the lateral temporal (and frontal) lobe (1). It is the combination of the focal nature of essential language cortex in an individual patient with the variability in the location of these areas across patients, so that anatomic landmarks do not reliably indicate what cannot be resected, that makes stimulation mapping of language a useful tool in posterior dominant temporal lobe resections.

Any controversy that exists with the use of language mapping in posterior temporal resections centers on whether the mapping should use intraoperative or extraoperative (chronic subdural grid electrode) techniques (4). It is the author’s view that this depends on the need for intracranial ictal recording; if that is needed to identify the epileptogenic zone (as it often is in the posterior temporal lobe) then the mapping should be extraoperative through those electrodes.

However, if all that is needed is language mapping, it can usually be accomplished with less risk and greater accuracy by intraoperative mapping in patients awake under local anesthesia, after the block and craniotomy have been placed under propofol (5). Indeed, if a posterior temporal resection is to be done close to essential language sites based on extraoperative mapping, the author will usually do that resection with the local/propofol technique, using intraoperative language testing to identify the essential language areas with a finer resolution that can be accomplished with extraoperative mapping, and to assess language during the resection.

It is in anterior temporal resections where there is controversy concerning the usefulness of any language mapping. Classically, dominant hemisphere anterior temporal cortex in middle and inferior temporal gyri is not considered essential for language. Exactly how far posterior one can safely go, in this classical view, varies: the line of the central fissure, or the vein of Labbe, or 4 to 4.5 cm from the temporal tip have been proposed as the posterior limit of the “safe” zone. However, stimulation mapping has identified sites where the current interferes with language within all of
these "safe" zones. Such sites were present in the early Penfield and Roberts (6) experience (though not commented on) and confirmed in later series (1). The Ojemann et al. (1) series of language mapping in 117 dominant hemisphere patients provided estimates of finding essential language sites in various zones of the temporal cortex. In the superior temporal gyrus, 15% of these patients had such sites anterior to the line of the central sulcus. In some patients these sites have been within 3 cm of the temporal tip. In the middle temporal gyrus, 5% of patients had essential language sites. These would be the patients at risk from an anterior temporal resection without language mapping.

Indeed, in a comparative study of mapped and not mapped anterior temporal resections that spared the superior temporal gyrus, this is about the proportion of patients with major postoperative language deficits, although with this small a proportion, with the numbers of patients in that study, there were no differences in postoperative language performance between the total populations of patients managed either way (7,8). Whether to use language mapping, then, depends on what risk of a postoperative language disturbance is considered acceptable. Modern "awake" neurosurgical techniques are so well tolerated by most adolescents and adults, however, that the author sees little reason to run the higher risk associated with a resection done without mapping.

Whether to map basal language sites is even more problematic. It has long been known that stimulation mapping will interfere with language tasks at sites in some brain regions where resection does not result in a permanent language deficit, most notably the supplementary motor area (6). That situation may also apply to basal language areas, as basal resections done without mapping have a much lower incidence of postoperative language disturbances that would be expected from the reported proportion of patients with basal language areas (9). It has not been the author’s practice to map basal language areas, but to map lateral cortical language and to tailor the lateral resection to avoid any lateral cortical language sites identified. At present, sites essential for language cannot be sufficiently reliably identified with functional magnetic resonance imaging (fMRI) to plan a resection, although further experience with fMRI changes with more extensive language measures may provide that information (10).

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Chapter VIII-21c: When Is Language Mapping Needed for Temporal Resections?

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Standard anatomic resections of the dominant temporal lobe for mesial temporal lobe epilepsy (MTLE) pose a potential risk to language function. Indeed, most but not all studies have reported language deficits, including verbal naming and verbal memory loss, following dominant anterior temporal lobectomy (1–7). The rationale for routine language mapping in dominant temporal resections is that performing a “tailored” resection that avoids identified language sites will minimize postoperative language deficits.

Using intraoperative cortical stimulation mapping (8), Ojemann and colleagues have found that while there is a wide degree of interindividual variability, language sites tend to cluster in the perisylvian regions, particularly in the posterior inferior frontal gyrus and middle and posterior superior temporal gyrus (9,10). The relative paucity of anterior temporal language sites has led to the adoption of “standard” anteromesial temporal resections for dominant-hemisphere MTLE without undue concern for postoperative aphasia. Typically, this involves removal of the anterior ~4 cm of middle and inferior temporal and fusiform gyri and radical resection of the medial structures (hippocampus, parahippocampal gyrus, and amygdala) (11). The controversy arises over whether intraoperative language mapping will help to identify and preserve essential language sites in the subpopulation of MTLE patients with anterior temporal language sites (8).

There are no studies demonstrating that tailored resection based on intraoperative language mapping leads to better language outcome. In contrast, a multicenter
study found no postoperative difference in visual naming between patients who were mapped with visual naming compared to those who underwent standard resections without mapping (12). Furthermore, there was no difference in visual naming between patients in whom the superior temporal gyrus was spared or removed (12). However, the exclusive language outcome measure in this and most studies was visual object naming, and potential language deficits resulting from auditory naming or comprehension sites were not studied.

While most studies have been done with language “sites” identified by stimulation-induced naming errors or speech arrest, other language tasks identify distinct sites (13). For example, recent studies using cortical stimulation mapping have identified an anatomic dissociation of auditory and visual naming in the lateral temporal cortex, with auditory naming sites located more anterior (14,15). In fact, nearly all sites identified in the most anterior 4 cm of temporal lobe were “auditory-only” sites not sensitive to visual naming (14). Thus, testing auditory rather than visual naming may be more appropriate in the pre- and postoperative evaluation of language functioning in MTLE patients undergoing standard anteromesial resection (16). In addition, these studies further call into question the utility of standard mapping based on visual object naming, as patients who undergo intraoperative mapping solely with visual naming tasks may decline postoperatively and experience “word-finding” deficits related to the auditory-naming sites.

Furthermore, there is evidence that resection of identified language sites may still not lead to persistent language deficits. For example, while electrical stimulation of the basal temporal language area leads to global aphasia, resection produces no long-lasting language changes (17,18). Thus, identification of a language site by electrical stimulation mapping does not necessarily imply that it is “essential” to language function. Finally, patients who have resection of only the mesial temporal lobes in selective amygdalohippocampectomy may have significant changes in verbal memory, calling into question whether mapping of the lateral temporal surface is sufficient in attempts to avoid these deficits (19).

Awake language mapping is clearly not appropriate in many cases. For example, it is poorly tolerated in patients younger than 10 years of age. In a multicenter study of 82 children under 17 years of age undergoing temporal lobectomy for unilateral TLE, the largest cognitive outcome study to date in the pediatric age group, only 10% (eight patients) experienced significant postoperative decline in verbal function (20). Interestingly, of these eight patients, three had undergone right temporal lobectomy. Therefore, this study offers little support for the use of awake language mapping in the pediatric population for dominant anteromesial temporal resections. Other patient populations in which language mapping is difficult or impossible include those with psychiatric problems or developmental delay. Awake mapping is also difficult in the setting of medical comorbidities such as obesity, sleep apnea, smoking, and other pulmonary problems. Having a patient awake during such procedures has theoretical increased risk, as patients may have seizures or move unexpectedly during a procedure.

Extraoperative mapping of language cortex may serve as a useful adjunct to or replace intraoperative mapping entirely (21). Subdural or epidural grid electrodes can be implanted over putative language cortex. Advantages of awake extraoperative mapping include that it allows for a more extensive mapping protocol, may be repeated on different days, and can be done with no sedating medications that might cloud the interpretation of results (21–23).

Disadvantages include infection risk, lower spatial resolution, and the requirement for an additional surgical procedure for electrode implantation.
Functional imaging methods may eventually be sufficient to map language functions noninvasively. Several studies have used positron emission tomography (PET) to compare areas activated during auditory and visual naming, and also to directly compare PET to cortical stimulation mapping (24). Functional magnetic resonance imaging (fMRI) has also been used to map language noninvasively and has been correlated to stimulation mapping (25–28). In general, the concordance between sites identified by cortical stimulation and fMRI has been good, with fMRI identifying many more additional sites (26) (but see Ref. 29). A recent important study provides the first evidence that fMRI can predict postoperative naming deficits following left anterior temporal lobectomy (30).

Thus, the available data indicate that in many patient populations, awake language mapping for standard anteromesial temporal resections for MTLE is not necessary. Whether it may be useful in a select subpopulation of patients to tailor resection and improve postoperative language outcome is still an unproven hypothesis. Newer neuropsychological and stimulation mapping data strongly suggest that if intraoperative mapping is employed, then auditory rather than visual naming may be more sensitive and specific in the identification of anterior temporal language sites. Modality-specific language testing before and after surgery combined with detailed language outcome studies will help elucidate the exact contribution of the anterior temporal lobe to language function. Preoperative evaluation with functional imaging may also prove of benefit in localization of language functions.

Ultimately, what matters most following anterior temporal lobectomy is its demonstrated beneficial effect in properly selected patients on seizure control and long-term psychosocial outcome, including return to work, functional independence, and quality of life (31–33).

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Chapter VIII-22
Intraoperative Electrocorticography in the Temporal Resection

Chapter VIII-22a: Description of the Electrocorticographic Technique for Tailored Mesial Temporal Epilepsy Surgery

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This form of electrocorticography (ECoG) was developed to support a tailored approach to epilepsy surgery of medically intractable epilepsy emanating from the mesial structures of the temporal lobe. The ECoG is used not only to identify epileptic activity, but also to determine afterdischarge thresholds to select an appropriate stimulating current for language or memory mapping in the awake patient. Two major changes in methods have occurred over the past 10 years. First, the use of propofol as an anesthetic and, second, the conversion from analog to digital electroencephalographic equipment. Propofol allows the anesthesiologist to awaken the patient relatively quickly for electrocorticographic recordings and to be able to cooperate fully with brain mapping. Digital recording allow the electroencephalogram to be viewed not only by the interpreting electroencephalographer, but utilizing a slave viewing screen the neurologic surgeon can simultaneously review the ECoG.

The ECoG sessions are divided into three distinct phases or sessions. The first is a preresection recording; the second is after the anterior inferior temporal structures are removed. This second stage gives direct access to the hippocampus via the temporal horn of the ventricular system and to the parahippocampal gyrus. This second recording allows tailoring of the amount of hippocampus to remove. The third and final session makes sure that no residual interictal epileptic activity remains in the unresected portion of the posterior hippocampus and parahippocampal gyrus.
STAGE I

After exposing the appropriate frontal-temporal region and using a local anesthetic four four-contact electrode strips are placed on the undersurface of the temporal and frontal lobes. Strip 1 is placed from lateral to medial under the anterior portion of the temporal lobe. The most distant contact (D) (strip 1) is medial and the most proximal contact (A) (strip 4) is lateral. Strip 2 is placed posterior to strip 1, but with the same orientation. Strip 3 is posterior to strip 2. Strip 4 is placed on the under surface of the frontal lobe with the same lateral to medial orientation. After the strip electrodes are placed, a series of carbon electrodes are placed in the following locations. Most commonly, three electrodes are placed from anterior to posterior on the middle temporal gyrus and three electrodes are placed from anterior to posterior on the superior temporal gyrus. Suprasylvian electrodes are placed anteriorly over the frontal lobe and posteriorly by an electrode placed approximately over the motor gyrus (Fig. 1). Neck electrodes are utilized for reference.

After all the electrodes are in place, the anesthetic propofol is stopped and the patient allowed to awaken. Propofol has been found to be a good anesthetic agent for this type of surgery as patients generally awaken quickly. Over the years, we have identified a definite pattern of ECoG change as the patient clears this drug. At the onset of this sequence, the ECoG shows a pattern of burst-suppression in virtually all areas being recorded. The burst-suppression activity is not synchronous in the various regions being recorded. As the patient lightens, the frontal and lateral temporal regions are the first to attain continuous activity. The posterior subtemporal cortex is the last to attain continuous activity. At times, patients have attained consciousness and continued to demonstrate an infratemporal burst-suppression pattern. During the transition from burst-suppression to a continuous awake pattern, care must be taken not to interpret spike components within the burst as epileptic in nature. There is a phase in the transition when the ECoG has just become

![Figure 1](image_url)  
**Figure 1** The location of the four-contact strip electrodes and the cortical electrodes used for stage I electrocorticography and determination of afterdischarge threshold.
continuous that interictal epileptiform activity is activated. The frequency of these discharges may reduce in frequency as the patient achieves full consciousness. Rhythmic sharply contoured activity in the posterior infratemporal region is not epileptic in nature and most often represents physiologic alpha activity. This can be confirmed by having the patient open and close their eyes. After collecting a representative sample of epileptic discharges, the patient then undergoes after discharge threshold determination. Utilizing a battery-operated Ojemann Bipolar Cortical Stimulator, which delivers a biphasic square wave with a duration of 100 milliseconds at 60 Hz and delivered through a bipolar stimulating electrode, a series of stimuli starting at 1–2 mA are delivered around a cortical electrode and gradually increased until an adequate level (6–8 mA) is reached. The next electrode is then analyzed, usually starting with a higher safe current (1–2 mA) lower than that selected on the first electrode. The afterdischarge threshold in remaining electrodes are then measured. An example of afterdischarge spikes is shown in Figure 2. After the stimulus intensity is selected, the patient undergoes language and/or memory mapping. The ECoG is run continuously during mapping to identify any significant runs of afterdischarge and to prevent the patient from developing a clinical seizure. After completion of the mapping the patient is anesthetized for the remainder of the surgery. The first stage resection is then carried out.

**STAGE II**

After removing the anterior inferior portion of the temporal lobe, leaving the parahippocampal gyrus intact the patient undergoes a second stage ECoG. A four-contact electrode strip is placed in the ventricle of the temporal horn abutting the hippocampus in an anterior–posterior orientation. Electrode contact D (1) is the
posterior contact. A second four-contact electrode strip is placed in an anterior–posterior orientation on the undersurface of the parahippocampal gyrus (Fig. 3). Electrode strip 3 is placed on the undersurface of the temporal lobe just posterior to the resection in a lateral–medial orientation. Electrode strip 4 is on the undersurface of the frontal lobe, again with a lateral–medial orientation. Cortical electrodes are placed on the unresected portion of the middle and superior temporal gyrus. After the recording starts, propofol is stopped and the patient allowed to

**Figure 3** Drawing to demonstrate the relationship of the hippocampal and parahippocampal strip electrodes during stage II recordings. Note the view is in proper relationship to the surgeon. *Source:* Drawing created by Mr. Hector Lettish, REEGT.

**Figure 4** Sample of interictal discharges isolated to the hippocampus only. There appear to be at least two separate generators for these discharges. The discharges are very restricted and include only the B and C contacts.
lighten. Three patterns of mesial temporal interictal epileptiform discharges tend to occur.

1. Both surface positive and negative spikes may be isolated to just the hippocampal electrode strip (Fig. 4). If the most posterior contact (D) shows interictal spike activity, the electrode strip is advanced until a clear zone is reached posteriorly.

2. The most common pattern is when the hippocampus demonstrates a surface positive spike discharge and the electrode strip on the under surface of the parahippocampus records a simultaneous surface negative spike (Fig. 5). This is a physiologic phase reversal suggesting the source is between the recording electrode strips.

3. Least frequent is when the discharges are isolated to the electrodes of the parahippocampal strip (Fig. 6). Using this information the surgery is tailored to the individual patient.

STAGE III

After the surgical removal of the appropriate mesial temporal structures a third recording session is accomplished. Electrode strip 1 is again placed in the ventricle on the unresected portion of the posterior hippocampus. Electrode strip 2 is placed on the undersurface of the unresected portion of the parahippocampus. Electrode strips 3 and 4 remain on the undersurface of the temporal lobe and frontal lobe as found in stage II. Cortical electrodes are again placed on the unresected portions of the superior and middle temporal gyrus. Propofol is stopped after the recording
The recording is continued until continuous activity is seen in all regions or until the patient begins to move. This last stage of ECoG recording is to confirm that no remaining epileptic activity remains in the unresected posterior hippocampus or parahippocampal gyrus.

**Figure 6**  Sample of interictal epileptic discharges originating in the parahippocampus gyrus only. Note, the ECoG continues to demonstrate a burst-suppression pattern, but these spikes occur during the interburst phase. The large spike associated with the burst in PARA B should be ignored. This is most likely part of the burst, related to the propofol and not related to the patient’s epileptic disorder.

begins. The recording is continued until continuous activity is seen in all regions or until the patient begins to move. This last stage of ECoG recording is to confirm that no remaining epileptic activity remains in the unresected posterior hippocampus or parahippocampal gyrus.

**Chapter VIII-22b: Intraoperative Electrocntoricography Is Useful in Temporal Resection**

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**INTRODUCTION**

Intraoperative electrocorticography (ECoG) as a technique for planning resective surgery for epilepsy was introduced over half a century ago, not long after the development of electroencephalography (EEG). Its use was part of the transition
of epilepsy surgery from lesion-based localization, usually a meningovascular cica-
trix, to electrophysiologically based localization, and resections from predominantly
in the sensory-motor cortex to the temporal lobe. Jasper and Penfield at the Mon-
treal Neurologic Institute were its best known advocates (1). Intraoperative record-
ings very rarely capture a seizure, so that interictal spikes are the information used to
identify the apparent epileptogenic zone requiring resection. The value of corticogra-
phy, then, is the value of interictal activity in providing this information.

In experimental models of partial seizures, the location of interictal spikes
and ictal onsets is commonly similar. However, early in the use of intraoperative
electrocorticography it was recognized that not all interictal spikes indicated the epi-
leptogenic zone, what Rasmussen called “red” and “green” spikes (2). Specifically,
interictal spikes recorded from the insula (2), and those that first appeared following
a resection, especially on the resection margins (1), were considered not to indicate
tissue requiring resection. The predictive value of lateral cortical interictal discharges
that persist after temporal resections has been controversial. Several studies found
higher rates of seizure-free patients when postresection recordings were free of spikes
(3–7), while others did not find any relation between presence or absence of lateral
or basal temporal cortical postresection spikes and outcome (8–19). The location
and timing of interictal spikes have also been considered to be of value in predic-
ting outcome. Posterior temporal spikes have been implicated as a predictor of poor
outcome (8), as was failure to include all areas of earliest appearing spikes in the
resection (20).

Over the past dozen years, the author has recorded interictal activity directly
from the hippocampus, from a strip electrode inserted in the temporal horn of the
lateral ventricle. The posterior extent of these discharges was found to vary, and
the medial extent of the resections were generally tailored to include only the portion
of hippocampus with discharges, with the exception of a few cases where memory
concerns indicated a smaller hippocampal resection. In the initial series of 140
patients, with this technique the outcome was similar in those with large or small hip-
pocampal resection (21). Moreover, there was a clear relation between the presence
or absence of interictal discharges in the residual hippocampus, with 73% of those
without discharges seizure-free, and only 29% of those with discharges in the residual
hippocampus. The relationships held for both the patients with and without mesial
temporal sclerosis in the resected hippocampus. Similar results were found in a sec-
ond series of 46 patients (22). The importance of limiting the medial resection in this
way to reduce the risk of memory loss in patients at high risk for that complication is
discussed in a separate commentary in this book. In both these series, the presence or
absence of interictal spikes after lateral cortical resections had no significant relation
to outcome.

The conditions of interictal ECoG recording also may be important in deter-
mining its value. The recordings in the two series showing that relation were obtained
under the combination of local anesthesia and propofol anesthesia. Interictal spiking
is influenced by levels of anesthesia and different anesthetic agents, factors that may
account for some of the differences in the literature. Thus the value of intraoperative
ECoG depends on where and how it is recorded.

The extent of interictal spikes in the hippocampal ECoG recorded under local/
propofol anesthesia provides the information needed to plan the extent of medial
resection needed to achieve seizure control with minimal neuropsychologic risk.
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Chapter VIII-22c: Intraoperative Electrocorticography Has a Limited Role in the Treatment of Nonlesional Medial Temporal Lobe Epilepsy

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Nonlesional medial temporal lobe epilepsy is a syndrome defined by several diagnostic criteria that can be determined prior to obtaining diagnostic tissue demonstrating mesial temporal sclerosis (MTS) (1). The most salient of these include clinical history characterized by an early childhood insult such as febrile seizures, complex partial seizure semiology with infrequent secondary generalization, video-electroencephalographic (EEG) localization, lateralizing intracarotid amobarbital procedure (IAP) and neuropsychological memory compromise, unilateral positron emission tomography (PET) hypometabolism, and hippocampal atrophy or increased signal on magnetic resonance imaging (MRI). Although each individual criterion by itself is insufficient to define the syndrome, few patients present to the clinician with all of the above criteria completely met. Hence, there is a spectrum of disease presentation defined on one end by a “classic” patient for whom there would be little disagreement as to the diagnosis and etiology of the epilepsy and on the other end by an ambiguous patient in whom the exact anatomic etiology of the seizures remains in question.

I argue in this essay that patients on the “classic” end of the spectrum are not only adequately, but optimally treated with a surgical procedure consisting of removal of the entire hippocampus and entorhinal cortex as well as a significant majority of the amygdala and parahippocampal gyrus. On the other hand, patients who present to the clinician with an ambiguous set of diagnostic results are best treated with chronic implantation of subdural electrode arrays to precisely define the region of epileptogenicity. Where in the spectrum of disease presentation each individual epilepsy center draws the line between performing a “standard” resection (by “standard” I mean the operation defined above, rather than the classic definition of the “standard” resection) and requiring an implant may vary. Nevertheless, there
is no obvious “gray” zone in the middle where electrocorticography (ECoG) plays a significant role in defining the epileptogenic substrate. I would add that if pre-operative diagnostic tests indicate a definite temporal neocortical onset (SISCOM or lesion on MRI), with no evidence of medial temporal lobe pathology such as asymmetric IAP results, then intraoperative ECoG may play a more significant role, particularly in lesional epilepsy (2–4).

What is the evidence that mesial temporal sclerosis is best treated with the surgery described above? First, the rate of surgical cure following selective amygdalohippocampectomy, whether approached via a transcortical or trans-sylvian incision is comparable to resections tailored with intraoperative ECoG (5–7). Hence, there is no gain in the number of patients cured following a more extensive neocortical resection as might be performed to chase neocortical spikes. Second, depth electrode studies in patients with MTS have documented ictal onsets from a variety of regions including the tail, body, and head of the hippocampus as well as the amygdala and entorhinal cortex (8–10). So, without knowing the precise onset zone in an individual patient, the surgeon is safest removing all of these structures if the morbidity of doing so is not excessive. This philosophy is supported by a randomized prospective study that demonstrated that removal of the entire hippocampus affords a higher cure rate than a subtotal resection (11). In addition, reoperation to remove residual mesial structures provides an additional ~30% cure for those patients who fail temporal lobectomy and subtotal hippocampal resection (12–14). Finally, the extent of resection of various medial temporal lobe structures has been correlated with outcome in patients with MTS, the extent of neocortical resection has not (15–18). The only argument for performing hippocampal ECoG is to preserve functional hippocampus, which might theoretically result in improved neuropsychological outcome. Not only has this assumption never been proven, but it makes little anatomic sense since hippocampus is deafferented once the entorhinal cortex is resected (19).

What is the evidence that patients who are not “classic” in presentation are best treated with an implantation of subdural electrodes? First, several studies demonstrate that there is no correlation between the frequency of either pre- or post-resection intraoperatively recorded neocortical spikes and outcome for patient with MTS (16,20–23). Hence, if the patient does have medial temporal lobe onsets, the results of the ECoG will be not only irrelevant but misleading and may provoke an unnecessarily extensive neocortical resection with an increase in the visual field deficit and removal of potential neocortical essential memory sites that may not be mapped if only language mapping is performed on the dominant side (24). If the patient ultimately is found to have temporal neocortical onsets, either as a result of dual pathology or in association with normal mesial structures, then the best predictor of successful outcome will be a complete resection of the epileptogenic zone as defined by chronic surface recordings (25,26). In addition, the advantages of extraoperative language mapping which can be performed over several hours in a relaxed setting include the ability to test multiple language functions and increased patient compliance in addition to a reduction in operating room time.

Future developments in the field of epilepsy, in particular noninvasive diagnostic techniques, will help reduce the number of patients who require implants by more clearly defining which patients have a mesial temporal onset and which are neocortical. For example, a patient with complex partial seizures and convincingly localized video-EEG, neuropsychological, and IAP data, but a normal MRI would require an implant in our center. However, ipsilateral mesial temporal hypometabolism on PET
scan might be sufficient data to triage the patient for a standard resection. Data are lacking in this area. Likewise, a SISCOM study in this same patient showing a focal neocortical onset would also push us to implant the patient unless the IAP and neuropsychological testing revealed no memory dysfunction, in which case one might be able to perform a limited neocortical resection guided by SISCOM coregistered with frameless stereotaxy and intraoperative ECoG.

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Intraoperative Electrocorticography


Chapter VIII-23
Is It Necessary to Include the Entorhinal Cortex in Temporal Resections?

Chapter VIII-23a: The Entorhinal Cortex in Human Temporal Lobe Epilepsy

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The human mesial temporal lobe is composed of the hippocampus, the amygdala, and the parahippocampal region. The parahippocampal region comprises several cortical regions grouped together on the basis of their unique laminar organization and connectivity (1). In its anterior portion the parahippocampal region includes the entorhinal cortex (EC) and the perirhinal cortex; its posterior portion is composed of the posterior parahippocampal cortex (areas TH and TF of von Bonin and Bailey) (2). While the EC is the major route through which cortical information enters the hippocampus, the perirhinal and posterior parahippocampal cortices are major sources of cortical input to the EC (3).

Temporal lobe epilepsy (TLE) is frequently associated with hippocampal neuronal loss and gliosis, particularly in the CA1 subfield and the dentate hilus (Ammon’s horn sclerosis) (4). The pathogenesis and functional significance of Ammon’s horn sclerosis are still poorly understood. For historical and practical reasons in both human and animal models of TLE, most attention has been dedicated to the hippocampus as playing a major role in the epileptogenesis at the expense of the remaining components of the mesial temporal lobe. In particular, the contribution of the parahippocampal region to the epileptogenic process in limbic seizures was underestimated.

Indeed, recent observations in humans with TLE and in animal models of this condition indicate that the epileptogenic zone is broad, and suggest that the
substrate for seizure generation is distributed over several limbic structures, widen
in particular the EC (5–7).

In animal models of TLE, the EC has been shown to contribute to the develop-
ment and maintenance of epileptiform activity in the temporal lobe (8,9). In acute
animal experiments, electrolytic lesions or electric stimulation and administration of
chemoconvulsants to this region can effectively induce seizures in the hippocampus
(8). Furthermore, in vitro studies of focal epileptogenesis in combined hippocampal–
entorhinal slices have demonstrated that the EC possesses an intrinsic capacity to
generate epileptiform discharges (10,11). On the other hand, damage to the EC
may contribute to long-lasting changes in its excitability, and may therefore play a
primary role in the genesis of temporal lobe seizures (11). After an extended seizure
period, irreversible neuronal damage appears in the EC within 48 hours, and is fol-
lowed by neuronal loss and gliosis in other areas such as the subiculum, CA1 subfield
of the hippocampus, and amygdala. Since EC neurons are heavily interconnected to
the subiculum and CA1 subfield of the hippocampus (12), it has been postulated that
entorhinal neurodegeneration may secondarily result in hippocampal hyperexcit-
ability and thus contribute to limbic seizures (13). There is also evidence that cell
damage in CA3 to CA1 areas of the hippocampus, by reducing hippocampal output
activity and abolishing the inhibitory control over the EC, releases EC network
hyperexcitability (14). Therefore, changes in the network interaction between the
hippocampus and the EC is believed to confer to the epileptic, damaged limbic
system the ability to produce recurrent limbic seizures.

Human electrophysiological data indicates that the EC is part of the epilepto-
genic network in TLE (15–18). Investigations with stereotactically implanted electro-
dodes have shown that seizures may originate not only in the amygdala and the
hippocampus but also in the EC (18). Some studies have suggested that potentials
recorded with scalp or depth electrodes may reflect seizure activity that begins in
the hippocampus or be is the result of hippocampal amplification of a signal from
the EC (18,19). It has also been shown that intraoperative stimulation of the EC
may induce a hippocampal response identical to interictal spikes (15,20).

Pathological changes of the parahippocampal region have not been extensively
studied in TLE mainly because of the inadequacy of the surgically resected speci-
mens usually used for routine examinations (21). However, there is evidence from
some early pathological studies (22,23) and more recent studies for variable degrees
of neuronal loss and gliosis in the EC (16) that seem to occur even in the absence of
hippocampal sclerosis (24).

In clinical practice, the investigation and treatment of patients with epilepsy
has been revolutionized by the advent of magnetic resonance imaging (MRI), which
has been demonstrated to be a reliable and accurate indicator of pathologic findings
underlying epilepsy. MRI benefits from the ability to vary image acquisition and
postprocessing parameters in order to study different types of anatomical properties
in the brain. Techniques such as the volumetric acquisition of thin contiguous slices
and three-dimensional reformatting have enhanced the ability of MRI to display
brain anatomy and to visualize epileptogenic brain lesions. Contrary to visual MRI
inspection, image processing provides quantitative MRI analysis, which is likely to
be of great aid in structural brain imaging. In the field of neuroimaging of TLE, most
MRI studies have assessed the hippocampus and little attention has been paid to
structural changes in extrahippocampal limbic structures.

One explanation for this arises from the fact that early MRI protocols included
thick slices which were adequate to evaluate the hippocampus, but were not of
sufficient resolution to properly identify and segment smaller mesial structures such as the EC. Advances in image acquisition and processing techniques combined with detailed descriptions of anatomy and cytoarchitectonic borders of parahippocampal structures on histologic sections (25) have created the basis for precise determination of the boundaries of these cortical areas on MRI.

To further elucidate the role of EC in human TLE and to determine if morphologic changes of the EC in TLE are apparent on MRI, we developed a standardized protocol to measure the EC in vivo. Detailed correlations between the cytoarchitecture and the gross anatomy of EC by Amaral and Insausti (26) and Insausti et al. (27) were used as the basis for the anatomical landmarks of this region on MRI. We studied patients with pharmacologically intractable TLE who were being evaluated for temporal lobe surgery. To determine if EC changes were specific for TLE, we also performed volumetric measurement of the EC in groups of patients with medically refractory nonlesional TLE, extratemporal lobe epilepsy, and idiopathic generalized epilepsy.

In agreement with neuropathological studies (22,23), our results confirmed that damage to the mesial temporal lobe involves not only the hippocampus and the amygdala, but also the parahippocampal region structures in patients with intractable TLE (28). Within the parahippocampal region, the EC was the most affected structure (29). EC atrophy seems to be specific to TLE, since we found no atrophy in other epilepsy groups. We showed that EC volumetry can provide correct lateralization of the seizure focus in 73% of TLE patients with hippocampal atrophy. We subsequently demonstrated that EC atrophy ipsilateral to the seizure focus can be the only MRI sign of mesial temporal damage in 64% of patients with normal hippocampal volumes (30).

In this group who constitute about 15% of patients with TLE, hippocampal volumes are normal—even though the majority of these individuals demonstrate histopathological evidence of hippocampal sclerosis in postoperative specimens (31). Due to the difficulty in seizure lateralization, many of these patients undergo intracranial recordings with depth electrodes. Volumetric measurement of the EC is therefore informative because it allows detection of structural abnormalities in the mesial temporal lobe that would have been missed by measuring volumes of the amygdala or the hippocampus alone. We have also found EC atrophy ipsilateral to the seizure focus in the majority of patients in whom both MRI volumetric measurements and histopathology of the hippocampus are normal (32). This finding again emphasizes the clinical usefulness of measurement of the EC in patients with TLE who are candidates for surgical treatment of their seizures.

In the group of TLE patients with hippocampal atrophy, we observed that the atrophy was more severe in the anterior portion of the mesial temporal lobe involving mostly the hippocampal head, body, and the EC (29). This pattern of atrophy characterized by an anteroposterior gradient of pathology may be explained by a disruption of entorhinal–hippocampal connections. Indeed it is known that the EC plays a pivotal role in the parahippocampal region because it receives most of its cortical inputs from the perirhinal and posterior parahippocampal cortices, and in turn, gives rise to most of the cortical input to the dentate gyrus, CA1 to CA3 fields, and the subiculum (33). The densest projection along the rostrocaudal axis of the hippocampus is located at the transition from the uncal hippocampus, which coincides with the transition of the hippocampal head to its body.

Therefore, it is conceivable that preferential anatomical connections between the hippocampus and the EC establish avenues of electrical spread that lead to a severe neuronal loss and atrophy in these structures. Aside from dense anatomical
connections between the EC and the hippocampus, it has been shown that the EC is remarkably hyperexcitable (11,34,35). This hyperexcitability could explain the more severe atrophy of the EC within the parahippocampal structures and our observation of EC atrophy in patients with normal hippocampal volumes (30). An alternative interpretation for more prominent atrophy of the anterior hippocampus and EC could lie in the distribution of neurotransmitters, gamma aminobutyric acid (GABA) in particular, in this region. Parvalbumin is among the calcium-binding proteins that react to GABA as a neurotransmitter (36). Immunohistochemical studies in humans have shown that the part of the EC projecting to the uncus contains fewer parvalbumin immunoreactive neurons and fibers than the part of the EC projecting to the body and tail of the hippocampus. Since a deficit of GABAergic inhibition may underlie some forms of epilepsy (37), one can speculate that a deficit of GABAergic neurons in the rostral EC, and consequently in the anterior hippocampus, may be responsible for the greater vulnerability of this region to injury.

It is now recognized that in temporal lobe epilepsy the disease is not confined to the hippocampus. Although the cause of TLE is still unknown, the importance of limbic network and as such the role of the EC as a major participant in epileptogenesis is being widely acknowledged, based on studies in both animal models and humans with this condition. We have demonstrated that EC atrophy is specific to patients with TLE. Volumetric analysis of the EC allows detection of atrophy ipsilateral to the seizure focus not only in patients with hippocampal atrophy, but also in those patients with normal hippocampal volumes. Based on our experience, we believe that volumetric measurement of the EC is a useful adjunct to the presurgical MRI evaluation of patients with pharmacologically intractable seizures. Since the EC plays a pivotal role in the epileptic network, it is also conceivable that its resection is important to achieve a favorable seizure outcome after temporal surgery (38). However, it is not known whether the excision of the EC alone would be sufficient to attain seizure freedom. Further studies are needed to assess the relationship between seizure freedom and the extent of resection of different mesial temporal structures.

REFERENCES

Chapter VIII-23b: It Is Necessary to Include the Entorhinal Cortex in the Temporal Resection

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ENTORHINAL CORTEX AND EPILEPTOGENESIS

The entorhinal cortex (ERC) is located in the region of the uncus and adjacent parahippocampal gyrus forming a shell around the medial surface and part of the inferior surface of the amygdala as far forward as its rostral pole. It extends ventrolaterally to the rhinal sulcus or collateral sulcus and posteriorly along the parahippocampal gyrus to the level of the body of the hippocampus. The ERC funnels
information from polymodal association areas of the frontal, temporal, parietal, and limbic cortices to the hippocampus and from there back to these association areas. It is ideally situated to function as a gateway for the flow of information between the hippocampus and neocortical and other allocortical areas.

Although the hippocampus is believed to play a primary role in temporal epileptogenesis, there is emerging evidence that the parahippocampal region and more specifically, the ERC may be important. In a model of limbic seizures in the rat, Bertram (1) found that simultaneous seizure onset could occur in the hippocampus, ERC, and perirhinal cortex. Other studies have shown that the ERC contributes to the development and maintenance of temporal epileptiform activity (2,3). In vitro studies with hippocampal–entorhinal slices have demonstrated that the ERC has the capacity to generate epileptiform discharges (4,5).

There are data to suggest ERC involvement in human temporal epileptogenesis. Invasive studies have shown interictal spikes occurring independently in the hippocampus and ERC, and spontaneous seizures arising from the hippocampus, ERC, or both simultaneously (6). ERC stimulation in vivo can produce widespread discharges in adjacent limbic structures (7).

MRI volumetric studies show concomitant decrease in ERC and hippocampal volumes ipsilateral to temporal lobe seizure onset with relative sparing of the adjacent parahippocampal structures (8–11). Neuropathological studies of resected temporal lobes show selective cell loss in superficial layers of the ERC, especially layer III, in addition to the usual hippocampal pathological findings (3).

SURGICAL RESECTIONS FOR TEMPORAL LOBE EPILEPSY

A number of surgical techniques are currently used for the treatment of intractable TLE, and there is no consensus regarding which structures should be resected and the extent of such resections necessary to produce satisfactory results. Surgical approaches include: neocorticectomy (12,13), corticoamygdalectomy with no or minimal hippocampal removal (14), corticoamygdalohippocampectomy with substantial hippocampal removal (15–17), neocortical and hippocampal resection sparing the amygdala (18), and selective amygdalohippocampectomy (19,20). These seemingly disparate surgical approaches appear to produce similar seizure outcomes. How can this be so?

Goldring et al. (18) suggested that the common denominator in all of these procedures was resection of the ERC. Surgical resections including the amygdala or anterior hippocampus would include the anterior parahippocampal region and at least the anterior uncus, therefore all or most of the ERC. On the other hand, neocorticectomy as described by Keogan et al. (13) was designed to spare the hippocampus and amygdala and, presumably the parahippocampal gyrus. Jones-Gotman et al. (21) compared postoperative MRI scans of patients who had undergone Keogan’s neocorticectomy with those who had anterior temporal lobectomy and selective amygdalohippocampectomy and found that the amount of parahippocampal gyrus that had been removed was comparable in all three groups, suggesting that a portion of the ERC was resected in the course of carrying out neocortical resection.

Siegel et al. (22) assessed postoperative MRI scans following selective amygdalohippocampectomy and found that better seizure outcome was obtained with more radical resection of the parahippocampal gyrus and subiculum. Although
they did not specifically look at ERC resection volume, the parasubicular area merges into the ERC along the medial aspect of the parahippocampal gyrus making it likely that resection of this area would correlate with resection of the subiculum.

At the London Health Sciences Centre, we performed stereotactic radio frequency ablations of the amygdala and hippocampus in 19 patients and demonstrated with volumetric postoperative imaging that the parahippocampal gyrus (including the ERC) was spared and that better seizure outcome was associated with a larger volume of hippocampal ablation (23). However, outcome in this group was never as good as would be seen following standard anterior temporal lobectomy, a finding we feel supports a significant role for the ERC in temporal epileptogenesis.

**SUMMARY**

There are data from animal studies and human electrophysiologic studies that support a role for the ERC in temporal epileptogenesis. An examination of the resective procedures currently used for the treatment of temporal lobe epilepsy suggests that the area of common resection in successful surgery is the ERC.

**REFERENCES**

Chapter VIII-24
The Selective Amygdalohippocampectomy

Chapter VIII-24a: Review of Selective Amygdalohippocampectomy Techniques

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HISTORY

The mesiobasal temporal structures have been known to play an important role in the pathogenesis of human epilepsy for some time. Animal studies conducted in the early 1950s demonstrated seizure activity from stimulation of “rhinencephalic” structures, including the hippocampus and amygdala. This experimental data was followed by the observations of Penfield, Jasper, and others (1) that the mesial temporal lobe played a significant role in the pathogenesis of epilepsy.

Since that time, remarkable advances have been made in both the diagnosis and treatment of epilepsy. In particular, improved electrodiagnostic tools have led to dramatic advances in the understanding of the electrophysiology of temporal lobe epilepsy. Refinements in the electrode arrays including intracranial depth electrodes and foramen ovale electrodes have proven critical in establishing the role of the mesial temporal structures as both primary and secondary generators of abnormal electrical activity. Concordantly, imaging modalities have provided a window to both intracranial anatomy and function. The development of high-resolution magnetic resonance imaging (MRI) has made the detection of subtle parenchymal abnormalities more straightforward. Both signal characteristic and volumetric analysis of the hippocampus correlate well with the structure’s role in the generation of seizure activity. Similarly, positron emission tomography (PET), single photon
emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) have allowed better understanding of normal and abnormal metabolic activity in the functioning brain. Time and again these tools have bolstered the evidence supporting the mesial temporal structures as the anatomic substrate in the majority of cases of temporal lobe epilepsy.

The ability to more accurately localize the area of the brain responsible for the initiation of an abnormal electrical signal has resulted in the resurgence of interest in the surgical treatment of epilepsy. In 1958, Niemeyer (2) suggested a more limited transcortical resection of the hippocampus in lieu of the more popular anterior temporal lobectomy (ATL). With the mounting diagnostic evidence implicating these structures as a primary locus, Yasargil and Wieser (3) revitalized the idea of a more selective operation. In their work, a trans-sylvian route to the mesial temporal lobe avoided damage to the lateral temporal cortex. In addition to the aesthetically appealing notion of resecting the seizure locus and sparing the uninvolved brain, they hoped to improve results with regard to verbal memory and language deficits that sometimes followed ATL. Around the same time, Olivier (1) and others at the Montreal Neurological Institute (MNI) refined Neimeyer’s technique and began to examine its effect on both seizure outcome and postoperative neuropsychological functioning.

With the advent of image-guided surgery, the amount of tissue removed in selective amygdalohippocampectomy (SAH) has been standardized. Many centers now routinely use neuronavigation based on preoperative MRI to ensure adequate resection. This approach is limited by the “not real time” nature of the navigation system, and some surgeons have been exploring the use of intraoperative MRI (iMRI) as a tool for defining the extent of resection. While these tools have proven valuable in maximizing outcome, they are clearly not a substitute for an intimate knowledge of the anatomy of the mesial temporal lobe. Indeed, the surgical treatment of epilepsy remains confined to centers where the labor-intensive presurgical evaluation and an experienced surgical team can coexist.

The issue of whether selective amygdalohippocampectomy is simply esthetically pleasing or whether it confers real benefit remains controversial. In this chapter, we examine the three main operative techniques for selective amygdalohippocampectomy: trans-sylvian, transcortical, and subtemporal. In addition, we briefly discuss the expanding role of various intraoperative image-guided systems.

INDICATIONS

In the classification of Wieser and Yasargil, SAH can be broadly grouped into two categories according to the ability of preoperative neurodiagnostic studies to define the epileptogenic focus (4,5). “Causal” SAH implies that the mesial structures have been identified as the initiator of the abnormal electrical activity and, therefore, the removal of these structures constitutes an attempt to abolish seizure activity. In a “palliative” SAH, electrical and imaging studies have either failed to localize a discrete focus or that focus is located in an eloquent area of the cortex. Further, the preoperative data implicates the mesial temporal lobe in the propagation of the abnormal electrical signal. Operative intervention, in these cases, is intended to diminish seizure severity and improve quality of life. Clearly, causal SAHs are likely to be more efficacious as they attack the root of the problem and this only further underscores the importance of exhaustive techniques to determine whether the mesial temporal structures initiate or simply facilitate the seizure syndrome.
Semiology

Temporal lobe seizures are classically time-limited events accompanied by psychosensory and psychoaffective symptoms with or without automatisms. Hippocampal seizure onset in particular is often associated with arrest (5).

As the discharges spread to involve the remaining mesolimbic structures, recollections, hallucinations, delusions, fear, and ecstasy can be observed. An especially strong component of fear often implicates the amygdala’s involvement in the seizure. Amygdalar involvement is further indicated by the presence of epigastric phenomena, nausea, and oral automatisms. Olfactory auras may also be observed.

Electrodiagnostic Studies

While seizure semiology and clinical observations are critical to diagnosis, spatially and temporally accurate localization of seizure activity relies increasingly on sophisticated electrodiagnostic testing. Preoperative interictal electroencephalogram (EEG) has been studied with regard to surgical outcome with mixed results (4). Many centers supplement routine ictal EEG and video monitoring with more invasive techniques designed to improve accuracy. Wieser and Yasargil strongly advocated the use of stereotactic depth electrode recording (5,6) during their group’s development of indications and technique associated with trans-sylvian SAH. This technique allows near pinpoint accuracy both anatomically and chronologically of the site of seizure onset. Depth electrode recordings clearly implicate the amygdala and hippocampus as the generator of seizure activity. In the Montreal Neurological Institute series, neocortical onset was unusual but rapid spread of electrical discharge from the limbic structures to the neocortex was frequently observed (7). Similarly, stimulation of the amygdala and hippocampus produced the clinical characteristics of temporal lobe epilepsy including aura, psychosensory phenomena, and automatisms (7,8). This causal role of the amygdala and hippocampus forms the basis of the argument for selective resection of the mesial temporal lobe. Further refinements in technology led Wieser’s Zurich group to use less invasive multicontact foramen ovale electrodes. Reporting on this technique in 1991, Wieser and Siegel (9) concluded that it was as efficacious as stereotactic depth electrodes in terms of both the quality of data obtained and correlation with outcome. Many centers prefer this somewhat less invasive technique of recording from the mesial limbic structures. These exhaustive electrodiagnostic efforts create a small and highly selective pool of operative candidates for which SAH offers a high probability of cure (10). The clarity with which electrical data points to the hippocampus or amygdala as the seizure generator in a particular patient defines the likelihood of success. “No seizures” or “rare seizures” rates in palliative cases are less than half that of causal SAH.

Imaging Analysis

Equally impressive advances in neuroimaging have matched the advances in electrodiagnostic capabilities. The development of new and sophisticated MRI techniques has greatly enhanced the noninvasive analysis of the mesial temporal lobe (Fig. 1). MRI is vastly superior to computed tomography (CT) in its ability to detect subtle abnormalities in brain tissue, including gliosis and migrational abnormalities. Gliosis, in particular, is indicated by signal characteristics associated with increased tissue free water. Taken independently, this signal abnormality, unfortunately, is among the least sensitive indicators of mesial temporal sclerosis (11). In the early 1990s,
MRI technology reached a level of sophistication that made morphometric studies of the brain possible. After initial validation confirming the consistency of MRI hippocampal volumetric measurements (12), Cascino and Jack correlated hippocampal volume loss on MRI with pathological changes in the hippocampus (13). The more atrophy observed radiographically in the hippocampi, the more severe is the histopathologic change. Lencz et al. confirmed a correlation between neuronal loss and MRI. Further, they correlated left hippocampal and temporal lobe volume loss with decreased performance on memory tests (14).

In a similar study, Trenerray et al. (15) found resection of MRI-measured atrophic left hippocampi was associated with an improvement in neuropsychological function. Conversely, resection of relatively non-atrophic hippocampi was associated with deterioration in both verbal and visual memory. Differences in right and left hippocampal volume measurements were 76% sensitive for lateralizing seizure onset (16). Similarly, Cook et al. (17) at Queen’s Square found hippocampal volumetry useful in distinguishing hippocampal from frontal pathologies. Several other studies continued to examine volumetric analysis to the point that MRI evidence of hippocampal volume loss and signal abnormalities serve as noninvasive surrogates of mesial temporal sclerosis (MTS) (11).

**Selective Amygdalohippocampectomy vs. Corticoamygdalohippocampectomy**

The question, why perform a selective resection in lieu of a more traditional neocortical and mesial resection, remains controversial. Corticoamygdalohippocampectomy continues to be a valid surgical technique for appropriately selected patients. In a study of 74 patients with various patterns of volume loss on MRI, Arruda et al. (18) concluded that selective amygdalohippocampectomy and corticoamygdalohippocampectomy were equally effective surgical treatments. Studies of postoperative memory performance failed to conclusively demonstrate the superiority of one technique. In some studies, postoperative PET (19) and MRI (20) have questioned the “selectivity” of SAH, citing evidence of persistent damage to the unresected temporal lobe. While these studies validly question changes in the ipsilateral temporal lobe, many patients do not progress to develop seizure foci in this region so as to

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**Figure 1** MRI images in a patient with mesial temporal sclerosis (MTS). (A) Coronal FLAIR image showing atrophy of the right hippocampus. (B) Magnified view of the FLAIR coronal image in the same patient.
warrant its prophylactic removal. As Olivier (1) eloquently states: “It remains that if the site of origin of the seizures resides in the damaged structures then these should be resected as radically and selectively as possible. The larger cortical removal in standard resection should not become, or remain, simply a method of exposing the limbic structures.” Indeed, the argument could be made: why not do a selective resection?

**TECHNIQUE**

**Choice of Approach**

Neimeyer (2) first suggested a transcortical transventricular approach to the mesial temporal lobe and selective resection in the mid-1950s. This particular approach, through the middle temporal (T2) gyrus was largely supplanted by the popular anterior temporal resection. Yasargil (21) developed a trans-sylvian approach in the 1980s and with Wieser, working in Zurich, promoted the concept that the selective resection in appropriately chosen patients is as effective and less radical (3,5). Since that time, selective amygdalohippocampectomy has experienced a dramatic resurgence in popularity. Approaches to the mesial temporal lobe can be broadly divided into three categories: the trans-sylvian approach developed by Yasargil, a cortisectomy in the lateral temporal cortex, and the subtemporal approach. The approach through the temporal cortex can be through the T1 gyrus, the T2 gyrus, or the T1-2 sulcus. With the exception of the subtemporal approach, all techniques involve entry into the temporal horn of the lateral ventricle. Of these three categories, the trans-sylvian and the transcortical are more commonly performed.

When Yasargil and Wieser proposed selective resection of the mesial temporal structures, they did so in distinction to the anterior temporal lobe resection. Anterior temporal lobectomy, in their view, produced unnecessary damage to the temporal neocortex in patients whose seizure could be localized to the amygdala and hippocampus. Yasargil (21) pointed out that the transcortical or trans-sulcal approaches would be plagued by these same issues. The trans-sylvian approach avoids the lateral temporal cortex and, therefore, was thought to be less disruptive. Indeed, Goncalves-Ferreira et al. (22) studied the exposure afforded by each technique and found that the trans-sylvian approach involved the least amount of tissue transected en route to the ventricle. The mean thickness of the temporal stem in that study was 1.5 cm. The disadvantage of this approach is the complexity of the vascular anatomy in the sylvian fissure and the attendant risk of injury to those structures. Upon entering the lateral ventricle, the amygdala, hippocampus, and parahippocampal gyrus are resected. Yasargil’s (21) extensive description of this technique involved opening the pia of the medial temporal lobe and identifying structures in the lateral carotid and anterior ambient cisterns.

The technique of Olivier and others at the Montreal Neurological Institute is representative of the transcortical route. We employ a similar route at Oregon Health & Science University (OHSU) depending on the anatomy of the cortical surface. Olivier describes an evolution of the approach now used at the MNI from one that places the cortisectomy in the T1 gyrus, then the sulcus, and finally the T2 gyrus (1). As Goncalves-Ferreira et al. (22) point out, the trans-T2 approach exposes the hippocampus transversely and requires a more extensive resection of neocortical tissue. The route to the lateral ventricle can be more difficult to define and many centers use image guidance to enhance precision and placement of the cortical
incision. The advantage of this technique is its directness and avoidance of vascular structures in the sylvian fissure. At OHSU, trans-sulcal vs. transcortical route is chosen at the time of surgery based on the shortest distance to the ventricle as measured by image-guidance software and cortical anatomy.

Hori et al. (23) refined the usual subtemporal approach to minimize retraction. This modification elevates the temporal lobe anterior to the vein of Labbe and places the surgeon at the patient’s side rather than the head to facilitate a better viewing angle. In their series, they did not experience significant complications from venous injury. This technique avoids the lateral temporal neocortex and, thus, adheres to the principle of preserving uninvolved cortex proposed by Wieser. The fusiform gyrus is entered but this has not caused injury in Hori et al.’s series. Still, many surgeons do not prefer this approach because the retraction, although reduced by the aforementioned modifications, is still greater than with other techniques.

No clinical study has been performed to demonstrate the superiority of one approach versus another. Goncalves-Ferriera et al. (22) studied 80 cadaveric specimens subjected to one of four routes, trans-sylvian, trans-T1, trans-T2, or through the T1-2 sulcus. They measured amount of nontarget tissue transected and the maximum exposure of the mesial structures. Their study found little difference in the exposure offered by each method. While the trans-sylvian approach demonstrated the least amount of damage to the lateral cortex, the depth of the cavity created by this approach angle was greater than that of a cortical approach. The subtemporal route was not performed in this study. From the standpoint of outcome, results from series using various methods are equivalent. During the development of the selective resection techniques, a comparison to the more popular anterior temporal resection was made and found to be similar in terms of outcome. As mentioned previously, some have questioned the use of the term “selective” as the amount of retraction and resection might be expected to have adverse effects on the function of the remaining temporal cortex. Dupont et al. (19) performed PET scanning on patients one year after selective amygdalohippocampectomy and continued to find significant alterations in metabolism in the ipsilateral temporal lobe. This same study found improvement in the metabolism of the contralateral hippocampus. It is unclear, however, which effects are a result of approach (trans-sylvian in this case) and which are the result of ipsilateral hippocampal resection by any route.

Neuronavigation

An interesting adjunct to intracranial microsurgery in the last decade has been the introduction of intraoperative neuronavigation. In SAH, the amount of tissue removed has been correlated with success and too limited a resection can result in higher failure rates (24). While preoperative MRI routinely aids in defining sulcal anatomy (25) and the site of cortisectomy (26), intraoperative neuronavigation allows more accurate use of preoperative imaging. Some surgeons hoped to standardize the technique of SAH, including the amount of hippocampus resected. Wurm et al. (27) found neuronavigation contributed both flexibility of entry point and completeness of resection through a minimal cortisectomy without inaccuracies related to brain shift. On the other hand, Van Roost et al. (28) studied the use of a frameless neuronavigation system and found it overestimated the extent of hippocampus resected. Not surprisingly, the discrepancy was related to the preoperative nature
of the images, brain shift, and cerebrospinal fluid (CSF) loss intraoperatively. At OHSU, we find the neuronavigation unit helpful and accurate.

To avoid problems associated with brain shift, Schwartz et al. (29) reported on their experience in a 0.12T intraoperative MRI environment. They found that an additional 4 to 8 mm of hippocampus remained after the surgeon felt a complete resection had been performed. The iMRI was then used to ensure a more complete resection could be accomplished. While this series was small and adequate conclusions regarding outcome are difficult to make, the iMRI provided useful information without hampering technique. Kaibara et al. (30) used a 1.5T in–out design in their series. The constraints of this system—moving the magnet in, draping, etc.,—did not significantly impact operative time and allowed rapid high-resolution image acquisition. Further resection of the mesial structures was performed in 50% of the cases after iMRI imaging showed incomplete resection. Thus, the use of image-guided surgical techniques contributes positively to the surgeon’s armamentarium in SAH.

**Technique at Oregon Health and Science University**

On the day of surgery, in the morning, the patient has frameless stereotactic fiduicials placed on the scalp. It has been our protocol to place these in a specified manner in order to standardize the way frameless stereotactic cases are processed at our institution. Following fiducial placement, a high-resolution MRI scan is obtained. The MRI sequence used depends on the presence or absence of lesional pathology on the diagnostic MRI taken during the preoperative workup. If a lesionectomy is to be performed in addition to SAH, the sequence that best demonstrates the lesion is chosen for planning. For straightforward SAH, we routinely use a standard T1 sequence as our neuronavigational-planning scan. The data are transferred to the neuronavigational station and modeled in the usual way. Using the trajectory and planning software, the T2 gyrus is identified and a route is plotted to the lateral ventricle. Care is taken to ensure that cortisectomy will allow easy access to the tip of the temporal horn of the lateral ventricle (Fig. 2).

Once under general anesthesia, the patient’s head is rigidly fixed and the intraoperative neuronavigation unit and probes are appropriately positioned and

![Figure 2](image-url) **Figure 2** Image guidance is used to directly navigate from a point on the middle temporal gyrus approximately 2.5–3.0 cm posterior to the temporal tip, to the most anterior aspect of the temporal horn of the lateral ventricle. The cross-hairs are positioned to indicate the planned posterior extent of the hippocampectomy, at the collicular plate on axial image. Images shown are from the StealthStation™ treatment guidance system (Medtronic Surgical Navigation Technologies, Minneapolis, Minnesota, U.S.A.) (A) sagittal, (B) axial, (C) coronal.
registered (Fig. 3). The incision extends from the zygoma 1 cm anterior to the tragus to the superior temporal line. A small craniotomy centered over the T2 gyrus is created with the high-speed drill. The neuronavigation software can be useful in helping to plan an adequate craniotomy. The dura is opened and reflected (Figs. 4 and 5).

Figure 3  Head fixation in the intraoperative neuronavigation unit. (A) Patient under general anesthesia, incision line marked. The curvilinear incision extends from the zygoma 1 cm anterior to the tragus to the superior temporal line. (B) Patient’s head is rigidly fixed and the intraoperative neuronavigation unit. (C) Probes are appropriately positioned and the fiducials are registered. (D) The projected cortical entry point is reconfirmed after prepping and draping.

Figure 4  Schematic of opening. (A) The incision is made from the zygoma to the superior temporal line. (B) The bony opening (solid line) over the projected middle temporal gyrus entry point.
The neuronavigation system aids in the identification of the T2 gyrus. The T1-2 sulcus is inspected. If the sulcus is essentially free of large veins, we have often used the "trans-sulcal" route as an alternative to a T2 cortisectomy. Regardless, a 1.5–2.0 cm opening in the lateral neocortex must be made on a trajectory to the anterior aspect of the temporal horn of the lateral ventricle (Fig. 6).

Upon entering the ventricle, the prominence of collateral sulcus on the floor of the ventricle is identified. Resection of the amygdala is initiated at the anterior medial aspect of the ventricle and the neuronavigation system is used as an aid to maximize the dorsal resection border. The uncus is then removed in a subpial manner. The choroidal fissure is identified and retractors are repositioned posteriorly to expose the length of the hippocampal formation. Using the neuronavigation setup, we resect the hippocampus posteriorly to the level of the quadrigeminal plate. The hippocampus is freed from its medial pial attachments. The parahippocampal gyrus is transected and the specimen is removed en bloc (Fig. 7).

We have found the use of bipolar cautery and suction sufficient to perform the resection. This allows for a more delicate touch and does not violate the medial pial boundary. Rarely, in cases of severe gliosis, the ultrasonic aspirator can be used for resection. The most severe complications of this approach are a result of damage to vascular structures in the ambient cistern medial to the hippocampus. These structures include the posterior cerebral artery (PCA), anterior choroidal artery (AchA), oculomotor nerve, and lateral brainstem. At all stages of the procedure, precise
knowledge of the local anatomy is indispensable. While the neuronavigation system is a useful tool to help gauge the posterior extent of resection, it does not represent intraoperative reality. Intraoperative brain shift and CSF loss can dramatically alter the anatomy such that navigation based on preoperative imaging should be approached with caution. In general, roughly 4 cm of hippocampus is removed and the structures in the cistern are easily identified through the pia.

Figures 8 and 9 depict typical immediate postoperative lateral skull X ray and axial unenhanced CT image, and a three-month follow-up MRI scan, respectively.

**OUTCOME**

Outcome, regardless of technique, is quite good. Wieser (6) updated previously published results in 1988. Outcome was reported using a standard scale: seizure-free, rare seizure, worthwhile improvement, and no worthwhile improvement. In that series, patients undergoing amygdalohippocampectomy (SAH) who did not have evidence of tumor on pathologic section were seizure-free or had rare seizures in 72% of cases. An additional 15% experienced worthwhile improvement postoperatively. In a previous report in 1986, this same group correlated hippocampal sclerosis, age of seizure onset, and postoperative EEG “spikes” with outcome (5). Patients with hippocampal sclerosis as indicated by preoperative studies did better than those without; 52% were seizure-free or had rare seizures versus 10%. Palliative operations
Figure 7  The resection includes: uncus (arrow 1), parahippocampal gyrus (shaded area = resection) (2), midbrain cerebral peduncle (arrow 3), posterior limit of hippocampal resection (collicular plate on axial MRI section) (dotted line 4), inferior temporal gyrus (arrow 5), occipitotemporal gyrus (arrow 6), and temporal pole (arrow 7).

Figure 8  (A) Immediate postoperative lateral skull X ray and (B) axial unenhanced CT scan.
for patients whose primary generator could not be localized or was in an unresectable location and in whom the mesial temporal lobe participated in epileptogenesis achieved a seizure-free/rare seizure rate of 16% as opposed to “causal” SAH at 45%. As mentioned earlier, the Zurich group has performed a number of studies correlating the predictive value of various diagnostic modalities and outcome (4,24,31).

Olivier at the Montreal Neurological Institute reported in 2000 on 150 patients with at least six months follow-up (1). At initial operation, 88% were either seizure-free or had only rare seizure. In this series, five patients underwent reoperation for further resection of the mesial structures secondary to persistent seizures. All of these patients were rendered seizure-free or with rare seizures at second operation. Hori et al. (23) report their results for a very small series of patients \( (n=4) \) operated via the subtemporal approach. All patients in their series were seizure-free or a 90% reduction of seizure frequency.

**Figure 9** T2 MRI images three months postoperative in the coronal (A–B) and axial (C–D) planes showing the extent of the resection. The web within the resection represents the remnant of the pial banks of the parahippocampal gyrus and hippocampal sulcus.
The reported complication rates for all approaches are quite low. Again, complications from selective resection usually result from injury to the structures in the ambient cistern. Thus, stroke causing hemiparesis, sensory disturbance, or ataxia are rarely seen.

Familiarity with regional anatomy, meticulous microsurgical technique, and efforts to maximize the amount of the mesial resection cannot be overemphasized. Selective amygdalohippocampectomy’s effect on verbal and visual memory remains controversial. Some studies have suggested that left SAH, in particular, leads to postoperative deterioration in memory at the same rate as corticoamygdalohippocampectomy (32,33). As expected the dominant left temporal lobe is more prone to postoperative memory disturbance. Right SAH did not significantly impair nonverbal memory in a study by Gleibner et al. (34). Other complications include visual field loss from damage to the optic radiation traveling in proximity to the temporal horn. In addition, Jones-Gotman et al. (35) showed impairment of odor identification postoperatively, regardless of approach. Overall, selective amygdalohippocampectomy remains a safe, effective technique in experienced hands.

CONCLUSIONS

Selective amygdalohippocampectomy has become a widely accepted procedure for medically intractable mesial temporal epilepsy. Three main approaches to the mesial temporal lobe are commonly utilized: transylvian, transcortical, and subtemporal. While each of these techniques has its benefits, no technique has been shown to be superior to others in terms of outcome. Neuronavigation, both frameless stereotactic and real-time iMRI, have become useful tools in ensuring an adequate resection of the mesial structures is accomplished.

REFERENCES


Chapter VIII-24b: Selective
Amygdalohippocampectomy
Has Major Advantages

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Selective amygdalohippocampectomy (SAH) with the trans-sylvian approach had been introduced in Zurich by Yasargil in 1975 (1,2) based on stereo-electroencephalographic (SEEG) findings. At this time we had found that the majority of psychomotor seizures with temporal lobe origin had their initial seizure onset in the hippocampal formation and the amygdala (3). We argued that the removal of the initial seizure onset zone should suffice to render the patients seizure-free and hoped that the postoperative neuropsychological outcome of this selective resective surgery for temporal lobe epilepsy (TLE) would be better compared to that of the classical anterior temporal lobectomy. Thus, SAH was designed for mesial temporal lobe epilepsy.
(MTLE) with the histological substrate of hippocampal sclerosis (HS) or circumscript lesions in these structures (SAH with curative indication). However, some neocortical temporal lobe epilepsies with secondary ictal involvement of the ipsilateral mesial temporal lobe structures were also operated on by SAH with a “palliative indication.” “Palliative SAH” was assigned to surgeries in patients when the seizure generating structures were not within, or exceeded the borders of the resection.

FREQUENCY OF SAH AND PRESURGICAL EVALUATION OF CANDIDATES FOR SAH IN THE ZURICH EPILEPSY SURGERY PROGRAM

From 1975 to November 2003, 478 patients have been operated on with SAH at our institution by two neurosurgeons (Profs. Gazi Yasargil and Yasuhiro Yonekawa). From 1975 on our epilepsy surgery data bank lists a total of 820 epilepsy surgeries in 810 patients (10 reoperations). Thus 59% of our epilepsy surgery patients had SAH. Since 1969 a total of 141 patients have had SEEG; since the end of 1984, 249 patients have had foramen ovale (FO) electrodes alone (n = 202), or in combination with subdural strips or grids (n = 32), or in combination with stereotactic depth electrodes (n = 15). A total of 117 Wada tests (98 selective temporal lobe Amytal tests) (4) and, since 1993, 279 electrocorticographies (ECoGs) have been performed.

At the time of our last comprehensive update (end of 1999) (5) 10% of 424 SAH patients had SEEG and 39% had presurgical evaluation with FO electrodes alone. Seventy-three percent of patients with selective Wada tests underwent SAH in Zurich, 19% had other surgeries than SAH in Zurich, 4% underwent temporal lobe (TL) surgery abroad, and 4% were not operated on, because they had failed the selective Wada testing.

With the introduction of modern diagnostic methods, the presurgical evaluation has become less invasive: in the pre-MRI era, 37% of SAH patients had preoperative SEEG, 3% had semi-invasive FO electrode seizure monitoring, and 60% had noninvasive preoperative seizure monitoring. From 2000 on, 1% of SAH had invasive, 15% had semi-invasive, and 84% had noninvasive presurgical evaluation.

DOES SAH RESULT IN BETTER SEIZURE OUTCOME?

In the presence of unilateral MTLE-HS the extent of mesial resection correlates positively with seizure outcome (6,7). However, the “extent” of mesial resection needs to be defined more precisely. Surgical series where only the anterior pes, or no hippocampus, was removed indicate less seizure control than when most of the hippocampal body along with the pes is removed. In a prospective, randomized, blinded clinical trial Wyler et al. (6) compared seizure outcome and neuropsychological outcome from anterior temporal lobectomies in two groups of patients. One group (n = 34) underwent hippocampal resection posteriorly only to the anterior edge of the cerebral peduncle (partial hippocampectomy). In the other group (n = 36), the hippocampus was removed further to the level of the superior colliculus (total hippocampectomy). The amount of lateral cortical resection was the same between the groups. At one year postoperatively, the total hippocampectomy group had a statistically superior seizure outcome compared with the partial hippocampectomy group (69% vs. 38% seizure-free), and examination of time to first seizure (survival analysis)
revealed significantly superior outcomes associated with total hippocampectomy. There was no increased neuropsychological morbidity associated with the more extensive hippocampal resection.

If there is evidence for the presence of HS, according to our experience, the anterior parahippocampal gyrus should be resected after careful evaluation of the remaining functions of the to-be-resected structures (8). The amount of amygdala that needs to be resected in MTLE with HS is unknown. Further studies will be necessary to resolve this question. In addition, it is unclear how often one sees “amygdala sclerosis” alone without HS. Most of the surgical techniques remove at least parts of the amygdala together with the anterior hippocampal formation (SAH) or the anterior temporal lobe with its polar region in addition to amygdala and anterior hippocampus. Results of stereotactic amygdalotomy suggest that removal or destruction of the amygdala alone is not sufficient to treat MTLE with HS successfully. The so-called amygdalar epilepsies, a very rare subtype, might be an exception. But even in such a rare condition resection of the hippocampus might become necessary in the long-term (9). In the presence of circumscribed foreign tissue lesioens, such as ganglioglioma, dysembryoplastic neuroectodermal tumor (DNET), and other low-grade tumors a lesionectomy might suffice in certain instances. If there is evidence for “secondary” HS or “dual pathology,” it is recommended that both the foreign tissue lesion and the gliotic hippocampus be resected.

There is controversy about the need to resect lateral temporal cortex in the presence of MTLE with HS. From the systematic review of McIntosh et al. (7) there is no indication that extent of lateral neocortical resections correlates with seizure outcome. However, up to the present, there are no convincing studies to show that more selective mesial resections are correlated with better neuropsychological outcomes, although this has been claimed. Also, there is controversy as to whether tailored resections using pre-/postintraoperative recording improves seizure outcome.

Besides the completeness of the removal of the epileptogenic lesion, the underlying histopathology of the resected structures is the major factor for seizure outcome. There is a positive association between the presence of MRI-HS, extent of mesial resection, and good seizure outcome. Seizure outcome in MRI-negative patients and in patients without histopathological abnormalities in the resected specimen is poor. Outcome may be good in MRI-negative patients with temporal hypometabolism on fluorodeoxyglucose-positron emission tomography (FDG-PET), who usually do show histopathologic abnormalities.

The actuarial analysis of Berkovic et al. (10) showed that outcome at postoperative year five is different for MTLE with HS compared to other forms of TLE: five years after surgery 21% with normal MRIs had no postoperative seizures versus 50% with hippocampal sclerosis, and 69% of patients with foreign tissue lesions. Similarly, an eventual seizure-free state of two years or more, whether the patient was seizure-free since surgery or not, was achieved by 36% of those with normal MRIs, versus 62% of those with HS, and 80% of patients with foreign tissue lesions.

**SEIZURE OUTCOME OF “CURATIVE SAH”**

In the Zurich SAH series, “curative” surgeries were performed on patients with electrophysiologically documented seizure origin in the resected mesial temporal lobe structures or with a lesion in these structures highly concordant with the seizure semiology and the noninvasive EEG, and MRI and PET findings. In our retrospective
long-term seizure outcome analysis after SAH in 369 patients operated on at our institution between 1975 and 1999 with a median follow-up of 7.1 years (minimum one year, maximum 24 years; in 125 patients, follow-up period was 10 years or more) we calculated last available and annual (year by year) seizure outcome using the classification of Engel I through IV (11,12) and the proposed new International League Against Epilepsy (ILAE) classification 1–6 (13). Results of this study have been described in detail (5). Table 1 lists the last available outcome with respect to various histopathological subgroups.

In general, in the last years seizure outcome following SAH has improved with 89% free of disabling seizures (Engel Class I) one year after SAH for the period from 2000 on, compared to 75% for the period 1993 to 1999, and 69% for the period 1975 to 1992.

SEIZURE OUTCOME OF “PALLIATIVE SAH”

In the Zurich SAH series, “palliative” SAH was performed in a small group of patients with seizure origins outside or exceeding the borders of the resection and with evidence that the resected mesial temporal lobe structures were of importance for the maintenance of the seizure (i.e., a secondary epileptogenic “pacemaker” or seizure sustaining substrate) (3). Many of these patients had posterior lateral neocortical TL seizure onset in or close to Wernicke’s area or showed bilateral mesial temporal epileptogenicity of various degrees. In the latter patients, long-term video-EEG monitoring revealed independent spiking in both mesial TLs and seizures originated in both mesial TLs in an alternating manner. As described by our group, in such patients we recorded a minimum of three and a maximum of 54 seizures (mean seven in the operated group) and calculated a laterality index \([\text{greater number of seizures originating in one TL/total number of seizures}] \times 100\) and a PET asymmetry index \([\text{[(left TL – right TL)/(left TL + right TL)]/200]}\) (14). Patients were considered candidates for palliative SAH if the seizure laterality index was above 66% and concordant with the PET asymmetry index and if the MRIs were either concordant or nonconclusive. Furthermore, all patients of this category had to pass a selective temporal lobe amytal memory test (4).

In the last comprehensive analysis of long-term seizure outcome 43 out of 400 (=11%) SAH patients have been operated with a “palliative indication” (5). In an earlier follow-up study (15), we reported that 12% of palliative SAH became free of disabling seizures (Engel Class I) for a follow-up of 55.7 ± 31.0 months. In the recent outcome study at postoperative year 10, 13.8% of 29 patients who had palliative SAH were in Engel Class I and 13.8 were outcome class ILAE1 (as opposed to 77.9% Engel I and 70.6% ILAE1 operated on with curative SAH).

Most enlightening is the year-by-year seizure outcome for ILAE Class 1a (completely seizure- and aura-free since surgery) insofar as from postoperative year nine on no patient remained in this outcome class, i.e., all patients with a palliative SAH had a relapse of seizures and or auras (Table 2). This is ample evidence that the careful selection of patients with a unilateral seizure generation in the hippocampal formation is a most important precondition for a successful SAH.

Antiepileptic drug (AED) treatment before and after SAH also has been studied in detail. During the year prior to surgery, in the HS group a mean of 2.3 ± 0.8 AEDs were taken. After SAH the percentage of patients without AEDs increases to 36% in the postoperative years 12 to 15 and is 40% to 43% in postoperative years 7 to 11 (16). Figure 1 depicts the proportion of patients with HS who are seizure-free and without AEDs.
Table 1  Last Available Seizure Outcome (Classified According to Engel’s Scale and ILAE Outcome Scale) Following SAH Correlated with Severity of Hippocampal Sclerosis (HS) and Presence and Type of Lesion \((n = 317)\)

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<th>Engel classes (%)</th>
<th>ILAE classes (%)</th>
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<tr>
<td></td>
<td>I</td>
<td>II</td>
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<tr>
<td>Severe HS ((n = 46))</td>
<td>86.9</td>
<td>4.3</td>
</tr>
<tr>
<td>Moderate HS ((n = 34))</td>
<td>76.5</td>
<td>8.8</td>
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<tr>
<td>Mild HS ((n = 51))</td>
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<tr>
<td>Vascular lesions ((n = 41))</td>
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</tbody>
</table>

From a total of 369 SAH patients with sufficient follow-up 18 patients are excluded, because the degree of HS was not exactly determined. Furthermore, tumors with WHO > II (mainly astrocytoma III) and other rare pathologies were excluded. “Without pathology” includes patients with insufficient tissue for histopathological examination.

*There were no entries in ILAE Class 6.

*Abbreviations: ILAE, International League Against Epilepsy; SAH, selective amygdalohippocampectomy; WHO, World Health Organization.*
Table 2  Annual and Last Available Seizure Outcome of Those Patients Who Remained Completely Seizure- and Aura-Free Since SAH (ILAE Class 1a) Differentiating Between “Lesional” and “Nonlesional” and Between “Curative” and “Palliative” Subgroups

<table>
<thead>
<tr>
<th>Years post-op</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>Last</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross vascular or foreign tissue lesion (n pts)</td>
<td>189</td>
<td>161</td>
<td>140</td>
<td>127</td>
<td>113</td>
<td>98</td>
<td>92</td>
<td>82</td>
<td>73</td>
<td>61</td>
<td>56</td>
<td>52</td>
<td>40</td>
<td>33</td>
<td>23</td>
<td>189</td>
</tr>
<tr>
<td>% ILAE1a</td>
<td>66.0</td>
<td>56.9</td>
<td>51.1</td>
<td>47.6</td>
<td>48.2</td>
<td>50.5</td>
<td>51.6</td>
<td>50.6</td>
<td>48.6</td>
<td>50.0</td>
<td>47.3</td>
<td>47.1</td>
<td>46.2</td>
<td>34.4</td>
<td>31.8</td>
<td>45.2</td>
</tr>
<tr>
<td>HS or no histopathology (n pts)</td>
<td>180</td>
<td>170</td>
<td>147</td>
<td>134</td>
<td>121</td>
<td>105</td>
<td>96</td>
<td>87</td>
<td>74</td>
<td>64</td>
<td>55</td>
<td>48</td>
<td>40</td>
<td>34</td>
<td>24</td>
<td>180</td>
</tr>
<tr>
<td>% ILAE1a</td>
<td>46.1</td>
<td>44.1</td>
<td>33.3</td>
<td>30.6</td>
<td>28.1</td>
<td>27.6</td>
<td>25.0</td>
<td>19.5</td>
<td>16.2</td>
<td>17.2</td>
<td>18.2</td>
<td>16.7</td>
<td>14.7</td>
<td>12.5</td>
<td>17.8</td>
<td></td>
</tr>
<tr>
<td>Curative SAH (n pts)</td>
<td>326</td>
<td>288</td>
<td>248</td>
<td>226</td>
<td>203</td>
<td>173</td>
<td>159</td>
<td>140</td>
<td>121</td>
<td>101</td>
<td>90</td>
<td>79</td>
<td>61</td>
<td>49</td>
<td>34</td>
<td>326</td>
</tr>
<tr>
<td>% ILAE1a</td>
<td>62.0</td>
<td>55.9</td>
<td>46.8</td>
<td>44.2</td>
<td>42.9</td>
<td>45.1</td>
<td>44.7</td>
<td>41.4</td>
<td>39.7</td>
<td>41.6</td>
<td>41.1</td>
<td>41.7</td>
<td>42.6</td>
<td>34.7</td>
<td>32.4</td>
<td>40.5</td>
</tr>
<tr>
<td>Palliative SAH (n pts)</td>
<td>43</td>
<td>43</td>
<td>39</td>
<td>35</td>
<td>31</td>
<td>30</td>
<td>29</td>
<td>29</td>
<td>26</td>
<td>24</td>
<td>21</td>
<td>21</td>
<td>19</td>
<td>18</td>
<td>13</td>
<td>43</td>
</tr>
<tr>
<td>% ILAE1a</td>
<td>14.0</td>
<td>14.0</td>
<td>12.8</td>
<td>5.7</td>
<td>6.5</td>
<td>3.3</td>
<td>3.4</td>
<td>3.4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>9.3</td>
</tr>
<tr>
<td>Total (n pts)</td>
<td>369</td>
<td>331</td>
<td>287</td>
<td>261</td>
<td>234</td>
<td>203</td>
<td>188</td>
<td>169</td>
<td>177</td>
<td>125</td>
<td>111</td>
<td>100</td>
<td>80</td>
<td>67</td>
<td>47</td>
<td>369</td>
</tr>
<tr>
<td>% ILAE1a</td>
<td>56.4</td>
<td>50.1</td>
<td>42.2</td>
<td>39.1</td>
<td>38.0</td>
<td>38.9</td>
<td>38.3</td>
<td>34.9</td>
<td>32.7</td>
<td>33.6</td>
<td>33.4</td>
<td>33.0</td>
<td>32.5</td>
<td>25.3</td>
<td>23.4</td>
<td>36.8</td>
</tr>
</tbody>
</table>

Follow-up years 16 and later are not given, but are included in the last available seizure outcome (under entry “Last”).

Abbreviations: SAH, selective amygdalohippocampectomy; ILAE, International League Against Epilepsy.
Thus, taken together seizure outcome and AED treatment following SAH, these outcome data corroborate our philosophy that surgical resection in MTLE should be limited to the structures responsible for seizure initiation, sparing as much of the “healthy” neocortical temporal lobe as possible.

The possible disadvantage of a limited resection is seizure recurrence. However, our detailed studies on relapse rate after SAH (5, 16) do not indicate a higher rate of relapse compared to data in the literature reported with anterior two-thirds resection. Nevertheless, a critical volume of resection, particularly of the parahippocampal gyrus, may be necessary to achieve good long-term seizure outcome results (8).

Thus, we conclude that with appropriate selection of candidates for SAH, long-term seizure outcome is at least as good as with standard two-thirds anterior TL resection (17). However, precondition for a successful SAH is seizure origin in the resected structures.

**DOES SAH RESULT IN A HIGHER RATE OF SURGICAL COMPLICATIONS?**

Defining surgery-related complications as unwanted, unexpected, and uncommon events, we differentiate into minor and major. Minor complications are complications that resolve within three months without sequel. A major complication affects activities of daily living and lasts longer than three months. Surgery-related complications were determined for all SAH patients \( n = 478 \) (Table 3). There was no surgery-related death. Twenty-eight complications occurred in 23 patients; five patients are listed with two concomitant complications. Seventeen patients (3.6%) experienced minor and six patients had major complications (1.26%); five of these six patients had lesions. Persistent hemiparesis (duration >3 months) due to stroke in the territory of the anterior choroidal artery in the knee or posterior part of the internal capsule was observed in four patients.

While SAH may be a more time-consuming and technically challenging operation, we show that with experienced neurosurgeons morbidity following SAH is similar to other surgical treatments of MTLE. Indeed, the limited resection
in SAH may account for the surprisingly low percentage of patients suffering postoperatively from severe global memory deficits or persistent dysphasia (0.21% compared to 1–5%).

Thus, we conclude that in the hands of experienced neurosurgeons SAH is not associated with higher mortality compared to other TL surgical procedures (18).

**DOES SAH RESULT IN BETTER NEUROPSYCHOLOGICAL AND PSYCHOSOCIAL OUTCOME?**

Some studies suggest postoperative neuropsychological outcome might be better in patients with SAH compared to patients with temporal lobectomy (19,20). There are, however, no prospective studies with pre- to postoperative analyses comparing the various surgical procedures. The study of Jones-Gotman et al. (21) compared the postoperative performance of 71 Dublin patients (and 40 controls) with anterior TL resection including amygdala and some hippocampus (MNI, \( n = 23 \)) with nominal temporal neocortical resections, (said to spare the hippocampus, although MRI revealed an encroachment upon medial structures in many individuals; \( n = 23 \)) and 25 Zurich SAH patients. This study revealed no particular advantage or disadvantage of one type of surgical excision over another with respect to the aspects of learning and memory tapped by the tasks that were used. However, no pre to postoperative analyses were done, but patients were only assessed postoperatively.

At the time of the introduction of SAH in Zurich we studied the neuropsychological outcome in 14 patients who were operated upon by the same neurosurgeon, had the same preoperative evaluation with comparable findings, but were operated on with different approaches: five patients had anterior two-thirds TL resection (two left, three right), three patients underwent right hippocampectomy and an

<table>
<thead>
<tr>
<th></th>
<th>SAH “lesional”</th>
<th>SAH “nonlesional”</th>
<th>Total</th>
<th>% Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute epidural</td>
<td>2(419)</td>
<td>2(322)</td>
<td>4</td>
<td>0.84</td>
</tr>
<tr>
<td>Acute subdural</td>
<td>2(419)</td>
<td></td>
<td>4</td>
<td>0.84</td>
</tr>
<tr>
<td>Delayed subdural</td>
<td></td>
<td>1</td>
<td>1</td>
<td>0.21</td>
</tr>
<tr>
<td>Cranial nerves injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III—oculomotor</td>
<td>1</td>
<td>5(320)</td>
<td>4</td>
<td>0.84</td>
</tr>
<tr>
<td>IV—trochlear</td>
<td>—</td>
<td>1</td>
<td>1</td>
<td>0.21</td>
</tr>
<tr>
<td>Homonymous hemianopia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral transient</td>
<td>2(419)</td>
<td>2(340)</td>
<td>4</td>
<td>0.84</td>
</tr>
<tr>
<td>Contralateral persistent</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>0.84</td>
</tr>
<tr>
<td>Transient dysphasia</td>
<td>—</td>
<td>1(340)</td>
<td>1</td>
<td>0.21</td>
</tr>
<tr>
<td>Persistent dysphasia</td>
<td>1</td>
<td></td>
<td>1</td>
<td>0.21</td>
</tr>
<tr>
<td>Disabling persistent memory deficit</td>
<td></td>
<td></td>
<td>1</td>
<td>0.21</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.42</td>
</tr>
<tr>
<td>Meningitis</td>
<td>—</td>
<td>1(320)</td>
<td>1</td>
<td>0.21</td>
</tr>
<tr>
<td>Deep leg vein thrombosis</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.42</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>15</td>
<td>28</td>
<td>5.86</td>
</tr>
</tbody>
</table>
anterior mesial temporal pole resection (Spencer type of resection), and six patients had SAH (three left, three right). Pre to postoperative neuropsychological performance changes ($\Delta T =$ deviation from individual median in $T$-values) were measured in several neuropsychological tests sensitive to right and left hemispheric functions (Fig. 2) (19).

Treyer (22) examined 93 consecutively operated SAH patients who underwent the same kind of neuropsychological pre and postoperative testing. Inclusion criteria were: (i) same pre- and postoperative test procedure, using parallel versions, of the following test battery: Rey Auditory Verbal Learning Test (AVLT), a modified Rey Visual Design Learning Test (VDLT), Rey-Osterrieth Complex Figure Test, Word Fluency Test, Five-Point Test, Stroop Test, Kramer Two-Group Test, Goldenberg Association Learning, and Tachistoscopic Lexical Decision Task; (ii) time of testing was within three months before, and three to four months after surgery. Excluded were patients with (a) “palliative” SAH, (b) semimalignant or malignant tumors, and (c) surgery-related complications. Her sample consisted of 45 females and 48 males. Forty-three SAH were left and 50 were right. Mean age at surgery

Figure 2  Pre to postoperative neuropsychological performance changes ($\Delta T =$ deviation from individual median in $T$-values) in several neuropsychological tests in TL patients operated on with various resections (two-thirds anterior TL-ectomy, Spencer type of resection, and SAH). **Abbreviations:** R, right; L, left. **Source:** From Ref. 19.
for this subgroup was 33.41 years (left vs. right SAH: n.s.). There were 13 left-handers. Sixty-one patients were “nonlesional—curative” (25 females, 36 males; 30 left, 31 right SAHs; age at surgery was not significantly different between left and right AHEs; six patients were left-handers).

Figure 3 displays the main group results for memory (Memory I–V) and for the Stroop Test (Executive Functions I) as well as for the Word Fluency and Five Point Test (Executive Functions II) of this sample. Data are shown comparing the changes pre- to postoperative. Left SAH patients have a slight to moderate decline of memory in the AVLT, which is more marked for lesional than for nonlesional patients. In all other modalities no significant pre to postoperative changes were detected in this selected subpopulation. Similar neuropsychological outcome data on AHE patients have been reported earlier by Regard et al. (23).

Kurmann-Bärlocher (25) studied the neuropsychological and psychosocial outcome in consecutive 90 SAH patients without gross lesions (Fig. 4). For this subpopulation neuropsychological test criteria were less stringent. We included patients with slightly differing test batteries preoperatively compared to postoperatively, and allowed for a larger time window postoperatively (up to nine months). Thirty-seven patients of this subpopulation had a left SAH and 53 had a right SAH. Concerning the frontal lobe functions 48 patients (53%) were postoperatively unchanged, 21 patients (23%) improved postoperatively (left SAH n = 10, right SAH n = 11), and 10 patients (11%) deteriorated (left SAH n = 6, right SAH n = 4). Thus, in the latter group left SAH were twice as often compared to right SAH (6/37=16% vs. 4/53=8%). With regard to verbal memory 22 patients (24%) were postoperatively better (left SAH n = 7, right SAH n = 15) and 20 patients (22%) were worse (left SAH n = 12, right SAH n = 8). With regard to figural memory 28 patients (31%) were postoperatively better (left SAH n = 13, right SAH n = 15), and 12 patients (13%) were worse (left SAH n = 6, right SAH n = 6).

The assessment of psychosocial outcome of these 90 “nonlesional” SAH patients is summarized in Table 4. Sixty-two patients (68.9%) reported to be seizure-free at the time of responding to the questionnaire, five patients (5.6%) indicated that they had less than three seizures per year, and seven patients (7.8%) reported a worthwhile improvement with a seizure reduction of 90% or more compared to preoperatively, i.e., 82.2% of these subset of patients claimed to experience a postoperative seizure-reduction of 90% or more.

A multivariate logistic regression analysis revealed that the presence of a postoperative psychiatric diagnosis has the highest impact on psychosocial outcome, followed by the seizure situation and side effects of AEDs. The duration of active epilepsy and neuropsychological deficits are also very important.

We conclude that neuropsychological outcome and related quality of life parameters after SAH are satisfactory. On the basis of our small study sample comparing different TL excisions pre- and postoperatively, it is likely that the more selective surgery causes fewer memory problems than standard two-thirds anterior TL-ectomy. However potential collateral cortical damage due to the approach must be considered a potential source of additional memory impairment in highly selective mesial resections.

Overall employment rate increased after SAH. Postoperative seizure freedom and absence of a psychiatric diagnosis and complications were the most important predictors for a good psychosocial outcome.

Generally, with epilepsy surgery, patients after SAH are either “double winners,” i.e., seizure-free and with improvement of quality of life, or “double losers,” not seizure-free and then frequently not profiting from surgery or even having some
Figure 3  Pre-/postoperative neuropsychological test performances [changes of memory (I–V) and executive functions] in a subpopulation of consecutive SAH patients. Source: From Ref. 24.
additional impairment. To minimize the latter risks careful selection of patients and the best safety that the intended surgery will not lead to unwanted side effects have to be strived for. At present in our institution the temporary inactivation of the to-be-resected structures with the so-called selective temporal lobe amytal memory test is performed in all patients at risk for postoperative memory problems.

Table 4  Psychosocial Outcome After SAH

<table>
<thead>
<tr>
<th>Main category</th>
<th>Improved (%)</th>
<th>Unchanged (%)</th>
<th>Worse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall quality of life</td>
<td>Postoperatively, 68 patients rated it with good, 13 with moderate, 9 with poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td>43</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>Housing</td>
<td>30</td>
<td>48</td>
<td>22</td>
</tr>
<tr>
<td>Preoperatively, 32 patients were living with their parents, 24 with a partner, 23 with partner and children, and 11 alone. Postoperatively, the housing situation changed in 33 patients (37%): only 18 patients were living with their parents, but 23 patients alone; 49 patients were either married or lived with a partner (10 patients found a new partner and lived together, and 10 patients got one or more children since the surgery)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support by family and/or a partner</td>
<td>22</td>
<td>11</td>
<td>57</td>
</tr>
<tr>
<td>Social contacts</td>
<td>31</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td>Sexual life&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>Sport activities</td>
<td>10</td>
<td>22</td>
<td>64</td>
</tr>
<tr>
<td>Hobbies</td>
<td>23</td>
<td>18</td>
<td>52</td>
</tr>
<tr>
<td>Overall leisure time</td>
<td>37</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Depression</td>
<td>31</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>Anxiety</td>
<td>30</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>Self-confidence</td>
<td>36</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>Independence</td>
<td>26</td>
<td>21</td>
<td>48</td>
</tr>
</tbody>
</table>

<sup>a</sup>No response: 11%.

*Source: Dr. Kurmann-Bärlacher.*
In conclusion, we believe that our long-term seizure outcome results after SAH suggest that SAH has major advantages, if performed in a curative indication. Furthermore, we conclude that SAH, carried out by an experienced neurosurgeon, is a safe surgical procedure, with low rates of complications and morbidity. Seizure outcome following SAH is excellent both in patients with a distinct anatomical lesion (vascular anomaly or benign tumor), especially when the preoperative duration of disease is less than five years, and in patients with hippocampal sclerosis. The significant differences between “palliative” and “curative” SAHs in the Zurich outcome study is ample evidence for the importance of a careful presurgical evaluation, since these differences suggest that the preoperative evaluation is able to predict the existence of epileptogenic tissue outside the resected area. On the other hand, the less than good results with the “palliative” SAH raise the question of SAH in this subgroup. These patients might have been candidates for a tailored larger temporal resection including lateral neocortex.

ACKNOWLEDGMENTS

I am indebted to the neurosurgeons, Profs. Gazi Yasargil (Department of Neurosurgery, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, U.S.A.) and Yasuhiro Yonekawa who performed the surgeries, and to Prof. Adriano Aguzzi and Dr. Achim Gooss for neuropathological reevaluation of the HS tissue samples. Profs. Marianne Regard, Thedy Landis, and Dr. Bruno Weber are thanked for neuropsychological examination. Special thanks are due to all members of the epileptology and neurosurgery groups who contributed to the data bank, in particular to my colleagues PD Dr. Marketa Hayek, PD Dr. Adrian M. Siegel, Dr. Alain Witztum, Dr. Hans-Günter Frank, Dr. Dominik Zumsteg, Dr. Daniel Eschle, and Dr. Kaspar Schindler; furthermore to Gaby Körner, Simone Spring and Matthias Sitzler, and to many doctoral students, among them Valerie Treyer, Anita Kurman-Bärlocher, Marcos Ortega, and Adrian Häne.

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Chapter VIII-24c: Selective Amygdalohippocampectomy: Is Less Really Better?

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Every surgical decision that is made in the treatment of epilepsy patients is ultimately a careful risk–benefit analysis. The goals of surgery are to maximize the chance of seizure freedom while minimizing the risk of neurological decline as a result of the surgery. While simple in principle, the weighing of these factors to decide on a “best” surgical approach for a particular epilepsy subtype is, in reality, remarkably complex. The epilepsy subtype has to be clearly defined based on seizure semiology, electrophysiology, and imaging-based pathological substrate; the chance of seizure freedom based on surgical approach has to be considered; the baseline neurological status of the patient has to be assessed; and the chance of a new postoperative deficit that impacts a patient’s function must be analyzed.

For temporal lobe epilepsy (TLE), the question of whether a selective amygdalohippocampectomy (SAH) is superior to an anterior temporal lobe (ATL) resection remains valid. The basic premise of the selective SAH approach is that a more limited mesial temporal lobe resection, when properly applied to well-localized mesial onset TLE, can provide a similar seizure freedom to an ATL, while sparing functionally important lateral and basal temporal neocortex. The purpose of this chapter is to discuss concepts relevant to these surgical approaches and discuss the strength of recommendations that can currently be made in support of SAH or ATL.

Concept 1: SAH may be better than ATL, but it is not widely applied because of its technical difficulty.

Reality 1: As outlined in Chapters VIII-24a and VIII-24b, the trans-sylvian SAH surgical methodology was initially applied by Yasargil and Wieser in 1975. This is a technically demanding approach. Most epilepsy surgeons do not have Professor Yasargil’s vascular neurosurgery expertise and do not feel that a wide dissection of the sylvian fissure is necessary for the purpose of mesial temporal lobe epilepsy surgery. A trans-sylvian approach likely has a higher risk of vascular injury via retraction or direct injury, as well as a steeper learning curve. The low complication rates described by Professor Wieser in Chapter VIII-24b are a credit to the technical skills of Professor Yasargil and Professor Yonegawa. However, these numbers cannot be automatically generalized to the epilepsy surgery community.

The application of frameless stereotactic methodology together with the implementation of trans-cortical/trans-sulcal and subtemporal lateral approaches has greatly simplified the technical demands of the SAH procedure. Using MRI-based frameless stereotactic guidance to localize the ventricle as outlined in Chapter VIII-24a, most surgeons would argue that the SAH procedure is easier, faster, and more cosmetic than the ATL procedure. A straight linear incision can be used with
minimal bony drilling required in addition to the craniotomy. The temporalis muscle can be linearly divided rather than elevated off of the squamous temporal bone with the scalp flap. Once the ventricle is identified, the mesial temporal structures can be readily removed under microscopic visualization in subpial fashion.

**Concept 2**: There is great variation in the ATL surgical methodologies, while the SAH technique is a more standardized resection of solely the mesial structures.

**Reality 2**: There is considerable variability in how ATL resections are carried out. Some centers still carry out a large neocortical resection that is bigger on the nondominant side, while others use a minimal neocortical window through the middle or inferior temporal gyrus to access the basal temporal lobe and ventricle. There is variability in whether the superior temporal gyrus is included in the resection.

Tailored resections alter the amount of neocortical removal based on electrocorticography (ECoG). More recently, anterior temporal disconnective procedures have been proposed to spare tissue removal and possibly decrease complications (1).

Similarly, there are significant differences in the techniques used for SAH and their potential ramifications on temporal lobe function. The only truly selective approach to the mesial temporal lobe structures that does not violate a portion of the lateral neocortex/white matter or the temporal stem is the subtemporal approach used by Hori et al. (2,3). This approach may require spinal drainage or significant subtemporal retraction as the middle fossa deepens during cranial development from childhood to adulthood. As the hippocampus does not present to the basal or medial temporal lobe surface, access to the hippocampus is gained by entering the ventricle inferiorly or by removing the medial parahippocampal and basolateral amygdalar structures. The trans-sylvian approach requires entry through the temporal stem to access the mesial structures, while the lateral stereotactic approach uses entry through the middle temporal gyrus or the superior or middle temporal sulcus down to the ventricle. Most surgeons remove the parahippocampal gyrus as part of the SAH, an important consideration for both seizure freedom and postoperative neuropsychological function (see below). The degree and location of “collateral damage” differs between the SAH approaches and impacts neuropsychological outcome (4,5). For example, the trans-sylvian approach may alter verbal memory not just from mesial temporal resection, but possibly also from interruption of basal forebrain projection fibers (6). Neuropsychological outcomes were similar when the trans-sylvian and transcortical SAH approaches were compared at a single center (5).

**Concept 3**: The hippocampus is the pathological substrate in TLE, and removal of the hippocampus is the critical determinant in seizure outcome.

**Reality 3**: As delineated in other sections, there is growing evidence of the importance of the parahippocampus, in particular the entorhinal cortex, in the development and maintenance of the hippocampal sclerosis (HS) subtype of TLE (Chapters II-4c, II-4d, VIII-23a, and VIII23b). Despite extensive animal model and human work, the exact source of the seizure generator in HS is not clear. Various circuit reorganizations such as dentate mossy fiber sprouting, loss of hilar inhibitory interneurons, altered dentate granule cell “gating,” and aberrant neurogenesis are variably thought to be integral to the generation of seizures in HS TLE. However, in its severest form, the sclerotic human hippocampus has marked neuronal loss in the CA1 and CA3 subfields, hilus, and dentate gyrus. Exactly where the abnormally synchronized activity begins and how it spreads within the epileptic human mesial temporal lobe is not completely understood. As mentioned above, most selective
SAH approaches and all ATL approaches resect the parahippocampus in addition to the hippocampus and basolateral amygdala.

The SAH approach is most commonly applied to HS TLE. It is clear from multiple series of ATL resections with ongoing follow-up that: (i) excellent seizure outcome is achieved in this group by any surgical approach that involves extensive resection of the mesial structures; (ii) these patients are generally at low risk of functionally significant neuropsychological decline following either dominant or non-dominant resection, as the damage to the mesial temporal structures has “already been done”; and (iii) seizure-free outcomes worsen over time. It is well recognized that residual hippocampus, when present, can be the source of recurrent postoperative seizures. However, recurrent seizures can develop despite initially successful complete mesial temporal lobe resections (7). There is increasing recognition that a network of interconnected brain structures is involved in TLE beyond the mesial temporal structures (8).

It is possible that a larger resection of the anterior temporal network provided by an ATL may preserve seizure freedom in better fashion than SAH based resection. Long-term comparative outcome studies of HS TLE following ATL and SAH will be required to address this issue.

HS TLE is one of the most successfully treated epilepsy surgery pathologies, with success rates of upwards of 80% to 90% reported in both the SAH and ATL literature and little functionally important neuropsychological risk in most patients. In contrast, non-HS TLE patients with normal hippocampus on high-resolution MRI are a much more difficult group to treat, with a significantly worse seizure-free rate following epilepsy surgery (~60%). These patients are also the ones with higher baseline preoperative neuropsychological function and thus higher risk of postoperative decline. The balance between surgical resection to maximize seizure outcome and minimize neurological decline is particularly tenuous in this group.

For non-HS TLE cases, the discussion of ATL versus SAH may be too simplified. Various strategies have been adopted including ATL, SAH, tailored hippocampal resection, and hippocampal sparing resection. Tailored hippocampal resection (9) and hippocampal sparing (10) surgical approaches are further extensions of the logic behind SAH, namely that the epileptogenic zone can be identified and removed, with preservation of functionally important tissue. The phenotype of non-HS (magnetic resonance image normal) TLE patients is likely composed of multiple subgroups. They may be mesial or lateral temporal in onset, potentially with a wider epileptogenic network than the HS patients.

One subgroup of non-HS TLE patients can be identified by hypometabolism on PET scanning. A recent report of TLE patients without HS found lateralizing [¹⁸F]FDG-PET hypometabolism in the 26/30 individuals. Twenty of these patients underwent surgery, half via a hippocampal sparing ATL procedure and half via a standard ATL procedure. Seizure outcomes were similar in both groups, and equal to the results achieved in HS patients at the same center. Interestingly, the baseline neuropsychological preoperative evaluation in this non-HS subgroup was similar to that in patients with HS (10). In our center’s experience, another group of non-HS patients exists with considerably better baseline neuropsychological performance than HS patients, and thus more at risk from surgery. The FDG-PET area of hypometabolism is greater in non-HS than HS TLE. Extent of resection of the FDG-PET area of hypometabolism is a predictor of outcome following non-HS TLE surgery (11).

**Concept 4:** In comparison to ATL, SAH minimizes neuropsychological decline following TLE surgery, while achieving equal or better seizure control.
Reality: It is logical to hope that preserving anterior temporal lobe tissue via an SAH approach will result in better neuropsychological outcomes than following an ATL approach. Whether this is true remains to be conclusively determined. The human hippocampus and parahippocampus may subserve somewhat different memory functions, but both of these structures are removed in SAH surgery (12). It is unclear whether preserving basal and lateral temporal neocortex will minimize neuropsychological decline if the parahippocampus and hippocampus are removed downstream. In one study of 115 patients assessed 3 and 12 months postoperatively following SAH, one-third to one-half of dominant resection patients had sustained “clinically meaningful” postoperative verbal memory decline. Not surprisingly, the greatest predictor of decline was higher preoperative verbal memory function (13).

There is a scarcity of direct comparative data between the two approaches using similar selection criteria for the patients operated. Some of the available representative recent literature includes the following: 1) Within a larger series of sequential TLE resections from Bonn between 1988 and 1997, a large subgroup of ATL patients operated between 1988 and 1992 was compared to subsequent SAH patients operated in the later half of the study. Seizure outcomes were similar. In patients with good preoperative verbal memory and left-sided surgery, a postoperative verbal memory decline was more likely. Verbal memory deterioration was seen more frequently following ATL (36/83 = 43%) than SAH (39/126 = 30%) (14). 2) The King’s College Hospital epilepsy team compared 91 patients who underwent ATL with 15 SAH patients. They found no substantial postoperative changes in intelligence quotient or memory scores following either approach. ATL patients who failed the Wada test showed more deficits than those who failed the test and underwent SAH. The authors suggest that SAH may be preferred to ATL in patients who fail the Wada test (15). A recent abstract from Osaka, Japan compared 17 ATL patients to 19 SAH patients. Seizure freedom was similar (71% vs. 74%). Decline in verbal memory was seen postoperatively following left-sided surgeries by both approaches. Following right surgery, SAH patients’ nonverbal memory improved while ATL patients declined (16). Another recent series detailed 80 ATL patients in comparison with 81 SAH patients. Seizure freedom was similar between the groups (72.5% ATL vs. 71.6% SAH). The neuropsychological findings were not presented (17).

Selection bias and length of follow-up are very important factors to consider in comparing seizure freedom rates and neuropsychological outcomes following TLE surgery. For instance, in the Zurich series discussed in Chapter VIII-24b, the seizure-free rate at last year’s follow-up (Engel Class I) is 89% for patients operated by “curative” SAH from 2000 to 2004, 75% for 1993 to 1999, and 69% for 1975 to 1992. Some of these differences are likely due to recurrence of seizures over time following initially successful surgery. To what degree these differences reflect alterations in patient selection due to advances in EEG detection and neuroimaging is not clear. In comparing results from an SAH cohort such as the large Zurich group to an ATL cohort, it is critical that patients are matched for length of follow-up, surgical histopathology, and seizure outcome criteria. Such an analysis is very difficult to do, given the variability of presurgical evaluation and surgical resective techniques.

The only real way to address the issue of ATL versus SAH is a randomized controlled trial. To my knowledge there has been only one small randomized trial comparing ATL to SAH. The Cleveland Clinic randomized 28 patients with HS by MRI and ipsilaterally localized TLE to either ATL or SAH. Seizure outcomes were similar, with ATL resulting in 67% seizure freedom/87% Engel Class I outcome versus 69% seizure-free/92% Engel Class I for SAH. SAH did not prevent
postoperative decline in Boston Naming following dominant sided surgery, nor were differences detected between the two approaches for the Wechsler Memory Scale-Revised (WMS-R) Logical Memory and Visual Reproduction subtests. The only advantage for SAH over ATL was seen in recall on two of three variables of the Rey Auditory Verbal Learning Test (18).

Most data regarding the success of SAH have been reported in the adult epilepsy population. There is evidence that in pediatric TLE, SAH may be less effective than ATL. The Bonn group analyzed two successive large cohorts of pediatric epilepsy patients managed by ATL and then SAH, as the surgical focus of their epilepsy center shifted to a more anatomically refined resective approach. The first group of 35 included 28 patients operated by ATL for presumed mesial onset TLE. In the later cohort of 54 patients, the approach was tailored to the MRI and EEG localization of the epileptogenic focus. Twenty-seven patients had SAH procedures for mesial onset TLE. The ATL group achieved 94% seizure freedom versus 77% for the SAH patients. For left-sided surgeries, the difference was 85% seizure-free for ATL versus 58% for SAH. Most of the patients not rendered seizure-free following SAH had pathologies other than HS including tumors, dysplasia, gray/white matter demarcation loss, and normal histological features (19).

Concept 5: There is sufficient evidence to recommend one surgical approach over another for the treatment of TLE.

Reality: The strength of any treatment guideline must be based on the accumulated scientific evidence. The only abstract published Class I evidence (prospective, randomized, controlled trial) comparing ATL to SAH in HS TLE showed no difference in seizure outcome and minimal difference in neuropsychological outcome (18). There is no Class II evidence (nonrandomized, prospective, controlled trial, or observational study) comparing ATL to SAH. There is some Class III evidence in the form of retrospective case series suggesting that there may be neuropsychological benefit of SAH in comparison to ATL. On the basis of the available Class I evidence and the lack of Class II evidence, neither SAH nor ATL can be recommended over the other option as a standard or guideline in the surgical management of TLE. On the basis of Class III evidence, SAH is recommended as an option over ATL in patients with left-sided surgery and good preoperative verbal memory performance or Wada test failure. There will be no evidence-based standards or guidelines in this arena until a prospective controlled trial is carried out, with careful MRI and PET imaging based stratification of entry criteria and long-term postoperative follow-up.

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Chapter VIII-25
Is Surgery Ever Indicated in Bitemporal Epilepsy?

Chapter VIII-25a: Review: Why Worry About Bitemporal Epilepsy?

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The most pertinent reason to worry about bitemporal epilepsy is that the presence of bitemporal independent seizures can be a cause of failure in the surgical treatment of temporal lobe epilepsy. After resection of one temporal lobe, seizures are sometimes found to continue to arise from the other. There can be other problems. Patients with bilateral temporal dysfunction have more cognitive problems before surgery and may be at greater risk of neuropsychological deficits afterwards (1).

WHAT IS BITEMPORAL EPILEPSY?

From the earliest years of epilepsy surgery, when workers had to rely primarily on clinical semiology, the skull X ray, and interictal findings on scalp EEG, it had been obvious that patients with independent spikes or sharp waves over the temporal regions did not obtain as high a rate of complete seizure control after temporal lobe surgery, as compared to those who had a unilateral temporal lobe focus (2,3). The prognostic significance of unilateral temporal spikes in the scalp EEG as a predictor of outcome after temporal lobe surgery has been reinforced by several more recent studies. Even the presence of as little as 5% to 10% of overall spike count from the unoperated side can be a negative prognostic indicator (4,5). However, not all patients with bitemporal spikes fared poorly. As a group, approximately 50% can be expected to become seizure-free after surgery (5,6). Those with low grade tumors
in the temporal lobe and bitemporal spikes had excellent surgical outcome. Although not completely proven, it is generally assumed that patients with bitemporal spikes have a higher risk of bilateral independent seizures.

With the advent of long-term electroencephalographic (EEG) monitoring, the criterion for the definition of bitemporal disease shifted from interictal spikes to seizures. When scalp ictal recordings were poorly localized and lateralized, or showed bilateral independent onsets in these patients, further investigation depended on the intracranial EEG. This has become the most exacting definition of bitemporal epilepsy, namely independent seizures from each temporal lobe in intracranial EEG recordings.

There are additional measures of bitemporal disease. Autopsy material of chronically institutionalized patients with a clinical diagnosis of temporal lobe epilepsy provided a spectrum of bitemporal pathology, with evidence of some type of bilateral temporal pathology in as much as 80%, and bilateral hippocampal sclerosis in 50% (7,8). Volumetric study of the hippocampus and other mesial temporal structures revealed evidence of bitemporal atrophy in 9% to 18% of patients evaluated for temporal lobe epilepsy (9–11), using normative data in healthy individuals as control. Bitemporal abnormalities are also found in T2 relaxometry (12), a measure of the sclerotic hippocampi. Pathological alteration of the metabolic ratios in magnetic resonance spectroscopy had been reported in 30% to 54% of patients with temporal lobe epilepsy (13,14). Bitemporal hypometabolism can be also found in fluorodeoxyglucose-positron emission tomography (FDG-PET) studies (15,16). Neuropsychological studies often point to bilateral dysfunction in verbally and visually based memory tasks that are nonlateralized (17) and the intracarotid amobarbital (Wada) test can likewise reveal memory deficits in each hemisphere.

The presence of bitemporal dysfunction in each of these modalities of testing has been correlated with a poorer outcome for seizure control after surgery as compared to patients with unilateral findings alone (3,16,18,19). Although a logical assumption, it has never been proved that the reason for poor surgical outcome in patients with bilateral abnormalities in structural or functional tests is a result of bitemporal seizures.

Rather, there are several examples of patients with bilateral abnormality on PET and magnetic resonance imaging (MRI) who had only unilateral seizures and fared well after unilateral temporal resection (9,10,15). Thus there may be other reasons for surgical failure in patients with bitemporal abnormalities apart from the presence of bitemporal seizures. This could include changes in seizure circuitry or extent of the epileptogenic zone that make a localized resection less likely to arrest seizures.

We can add a few words of what is not true bitemporal epilepsy. These are patients with extratemporal epileptogenic zones with misleading clinical or EEG features falsely localizing to the temporal lobes. One or both temporal lobes can be affected. Bitemporal seizures are then the artifact of independent spread to each temporal lobe. The extratemporal epileptogenic zone had been found in all lobes, and also in patients with hypothalamic hamartomas. Most commonly, they are in areas that have well-known functional connections to the temporal lobes, such as the orbitofrontal cortex, cingulate gyrus, and association areas in parietal or occipital lobes.

PATHOPHYSIOLOGICAL IMPLICATIONS

There are a number of potential mechanisms for bilateral disease involving both temporal lobes. First, bilateral damage from a single causative insult. An example would be the damage that could follow herpes encephalitis. Second, independent
diseases of different causes affecting each temporal lobe. Third, a disease state or process derived from the pathologically affected temporal lobe that affects the other. The conceptual model here is secondary epileptogenesis. Fourth, progressive damage to contralateral and other brain regions as a consequence of chronic epilepsy. These mechanisms are not necessarily mutually exclusive, and may perhaps jointly contribute to bilateral disease in an individual.

The evidence for bilateral injury from a definable insult in patients with bitemporal epilepsy (bilateral independent seizures) is difficult to come by. Historical insults that can be accepted without controversy include adult onset encephalitis and hypoxic–ischemic encephalopathy. There is evidence from hippocampal volumetric analysis that a history of meningitis or encephalitis is correlated with bilateral hippocampal volume loss (20). Such insults probably account for a relatively small proportion (estimate 10% to 20%) of all patients with bitemporal seizures. Bilateral injury can also arise from independent processes affecting each temporal lobe (Fig. 1). It could be regarded as an extreme example of “dual pathology.” While the term has been much more commonly used to describe the concomitant finding of mesial temporal sclerosis with other pathologic diagnoses as cortical dysplasia or tumors in the same temporal lobe, bilateral hippocampal atrophy was found in 57% in one series of patients with temporal lobe cortical dysplasia (21). The contribution of such “dual pathology” is again likely to be small, as least based on imaging studies in life, since it is not feasible to subject both temporal lobes to microscopic examination other than at autopsy.

The contribution of secondary epileptogenesis (22), if any, in human bitemporal epilepsy remains controversial. The original experimental observations were based on the development of “mirror” spike foci then seizures in homologous structures of the

![Figure 1](image)  
**Figure 1** Patient with right neocortical temporal cavernous hemangioma and left hippocampal sclerosis. Early history of chickenpox encephalitis at age four. Scalp EEG showed unilateral left mesial temporal sharp waves and left temporal onset to seizures. Neuropsychometrics revealed bilateral memory deficits, while intracarotid amobarbital test showed right hemisphere speech and bilateral memory without lateralization. Combined depth and subdural strip EEG recording from both temporal lobes demonstrated two populations of seizures, with those of left medial limbic origin the more clinically disabling. The patient underwent a left anteromesial temporal resection with control of those seizures. Mild partial seizures of dizziness and brief amnesia of right temporal origin persist.
contralateral hemisphere after creation of an epileptic focus in submammalian species (23). Subsequently, independent seizures from the contralateral temporal lobe have been observed in mammalian species after induction of epileptic activity in one temporal lobe by intrahippocampal kainic acid or by kindling (24,25).

The finding of bitemporal spikes in almost a third of patients with small circumscribed low grade temporal lobe tumors, where there is no reason to anticipate bilateral pathology, is probably the best support to this hypothesis in human epilepsy (26). However, there are no convincing reports other than the cases presented by Morrell (22) to show that a patient with a nonprogressive unilateral temporal lesion ever develops seizures from the opposite side. Other indirect attempts to find clinical phenomena that may support the notion of secondary epileptogenesis in human epilepsy, such as correlating the duration and frequency of seizures with unilateral or bitemporal spikes or seizures have not yielded any consistent results (27,28). Maybe the best indication that one epileptogenic zone can be dependent on or be influenced by another is in patients with bitemporal independent seizures who become seizure-free after unilateral temporal resection. By some means, it appears that one focus facilitates the other, and the judicious removal of one can lead to the cessation of seizures in the other. Another supportive piece of data comes from the normalization of abnormal proton magnetic resonance spectra in the contralateral temporal lobe after successful temporal lobe surgery where they had been bilaterally abnormal before operation (29,30).

The evidence for a spectrum of bilateral disease in autopsy material, and MRI, magnetic resonance spectroscopy (MRS), PET, and EEG studies as already alluded to, is most applicable to human mesial temporal epilepsy with mesial temporal sclerosis as the pathological substrate. Some argue that mesial temporal sclerosis is by its very nature a bilateral process, based on the examination of pathology material of patients at autopsy. Thus bilateral disease may both be cause and effect or inherent in mesial temporal epilepsy. However, the picture is far from clear.

Patients with mesial temporal sclerosis frequently relate a history of some early cerebral insult before the age of five, most commonly febrile seizures. One might expect that whatever had been responsible for the genesis of mesial temporal sclerosis to be more overtly expressed in patients with bitemporal disease. However, when looked at, it turns out that a history of febrile seizures is actually less common in patients with bilateral independent spikes (27) or seizures (28), as compared to those with unilateral spikes or seizures. As to the concept of progressive damage to mesial temporal structures in chronic temporal lobe epilepsy, recent MRI studies have been supportive of this notion. However, as already alluded to, attempts to show that bitemporal spikes or seizures are correlated with disease duration, age at onset, or disease severity have been inconclusive.

This leads to two further concepts in looking at temporal lobe epilepsy, at least in mesial temporal epilepsy: (1) as a disease that can be unilateral or bilateral along a continuum, and (2) where there is bilateral disease, the possibility of a “dominant” focus, the removal of which can lead to seizure control. Whether these concepts apply to patients outside of mesial temporal epilepsy, is unknown.

RESULTS OF SURGERY IN PATIENTS WITH BITEMPORAL SEIZURES

There are now several series of patients who had a temporal resection after recording of bitemporal independent seizures verified by intracranial EEG (Table 1) (6,31–34).
Patients had been selected over the past three or more decades, encompassing significant changes in the technologies for presurgical evaluation. The study from the Montreal Neurological Institute was from an era before the widespread use of PET scans, and before hippocampal atrophy and sclerosis could be reliably determined on MRI (31). Subsequent studies included patients that underwent MRI examinations with incremental improvements in resolution and quantitative measures.

The results show that patients can be successfully selected for temporal resection with a reasonable outcome, but one that is somewhat less favorable (approximately 50% seizure-free) than that obtained by patients with unilateral disease. It is obvious that the more highly selected the patients, the better the likely outcome.

**WHAT ARE THE CRITICAL CRITERIA FOR THE SURGICAL SELECTION OF PATIENTS WITH BITEMPORAL EPILEPSY?**

The congruence of independent tests of localization is the key. The early series from Montreal almost entirely relied on depth EEG results alone in an era before PET and MRI imaging, and found that the only preoperative variables that correlated with a good outcome for seizure control were seizure predominance, namely a preponderance in excess of 70% to 80%, and a history of an early convulsion before the age of three years (usually febrile seizures). There was a trend for lateralized amobarbital test memory dysfunction to correlate with outcome although it did not reach significance (31). The value of ictal predominance was tempered by the recognition that the recording of seizures is subject to problems of statistical sampling. Once bitemporal seizures are found, in theory a very large number in the order of 11 or 17 would need to be recorded in order to have any statistical confidence that one has identified a predominant focus (36,37). This condition is rarely met in clinical practice, and thus the whole notion of predominance needs to be evaluated with the total number of seizures in mind. Two studies reported good results in operating on patients with bitemporal seizures who had at least 50% of seizures from the temporal lobe to be resected and adequate contralateral memory reserve on amobarbital testing (32,34). Furthermore, concordant hippocampal atrophy or amobarbital memory deficit were both associated with good outcomes. What should be noted in these two studies is that an almost equal number of patients with bitemporal epilepsy were not offered surgery.

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>No. operated/total</th>
<th>Engel Class I: seizure-free</th>
<th>Engel Class II: rare seizures</th>
<th>Engel Class III: 50–75% reduction</th>
<th>Engel Class IV: not improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>So et al. (31)</td>
<td>21/27</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td>5</td>
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<tr>
<td>Hirsch et al. (32)</td>
<td>11/23</td>
<td>9</td>
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<tr>
<td>Hufnagel et al. (33)</td>
<td>8/8</td>
<td>1</td>
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<td>4</td>
</tr>
<tr>
<td>Sirven et al. (34)</td>
<td>15/28</td>
<td>10</td>
<td>4</td>
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<tr>
<td>Holmes et al. (35)</td>
<td>19/19</td>
<td>6</td>
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<td>7</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>74/105</strong></td>
<td><strong>34 (46%)</strong></td>
<td><strong>6 (8%)</strong></td>
<td><strong>19 (26%)</strong></td>
<td><strong>15 (20%)</strong></td>
</tr>
</tbody>
</table>
The importance of concordant MRI abnormality, either changes of mesial temporal sclerosis or localized temporal lobe lesions, was confirmed by Holmes et al. (35), who also found that the degree of ictal predominance in intracranial EEG, a 75% predominance of surface interictal spikes, and lateralized dysfunction on neuropsychological tests to be important predictors. Of historical factors, the presence of a history of febrile seizures was found to be a favorable prognostic factor in two studies (31).

No doubt reflecting the relatively small number of patients with bitemporal independent seizures at each center, there have been limited to no data on the usefulness of other preoperative tests. In a study of deoxyglucose PET in patients investigated with depth EEG for lateralization of temporal lobe epilepsy, six of nine patients who had congruent lateralization by depth ictal onset predominance (>80%) and PET hypometabolism became seizure-free (15). A single patient in whom the PET scan and depth EEG lateralized to opposite side did not benefit after operation on the temporal lobe selected by EEG. However, three of four patients with nonlateralized bitemporal hypometabolism also became seizure-free. The contribution of additional imaging modalities to this problem is awaited. Flumazenil PET studies often reveal a more localized pattern of deficit in temporal lobe epilepsy and may be revealing in this regard. However, ictal single photon emission computed tomography (SPECT) studies are probably unlikely to resolve the matter, as the temporal structures showing hyperperfusion will likely follow the side of ictal onset, which means that independent left or right localizations could be possible in the same patient if enough seizures are sampled.

Thus, in patients with bitemporal independent seizures, the more there is congruence between intracranial ictal EEG and other test data, the greater the chance of a good outcome. Conversely, discordant test results are likely predictive of poor outcome.

It also appears that the degree of ictal predominance can be somewhat flexible provided other tests, in particular the MRI, are clearly lateralizing. But how should a patient with a close to 50:50 split of seizures be considered? Some would argue that if there are one or more other lateralized tests that are in agreement then a case can be made for operation, although not all will agree that the data support such a recommendation.

ARE THERE PATIENTS WITH BITEMPORAL EPILEPSY WHO SHOULD NOT BE CONSIDERED FOR SURGERY?

It is necessary to state that patients should not be rejected from surgical consideration because of scalp EEG data alone, whether these show nonlateralized bitemporal independent spikes or seizures. Some of these patients will turn out to have unilateral ictal onsets on intracranial EEG from unusual propagation patterns of seizures, starting in the mesial limbic structures of one side spreading to the opposite temporal neocortex. Others may turn out to have bitemporal independent seizures, but can be still a candidate for surgery because of presence of other lateralizing data.

The absence of lateralization in MRI signs of mesial temporal sclerosis (amygdala or hippocampal atrophy, or sclerosis), or in neuropsychological evidence of memory impairment (by conventional neuropsychometrics or by the amobarbital test) would reduce the likelihood of success, if intracranial EEG fails to show 100% unilateral predominance, but should not necessarily exclude patients from a planned intracranial EEG investigation, since some of these patients would turn out to have
unilateral seizures and do well from surgery. Patients with bilateral symmetric hippocampal atrophy have been rendered seizure-free when appropriately selected after depth EEG investigation (10).

Are there any patients who should not undergo an intracranial EEG investigation for a problem of bitemporal epilepsy? Maybe a small number with no prior history of febrile convulsions or other early insults, normal MRI, nonlateralized memory tests, and clear bilateral independent seizures on scalp ictal EEG with two distinct populations based on semiology: for instance, head version to the right with a left temporal onset pattern, and head version to the left with a right temporal onset pattern. There may also be a few patients with bitemporal spikes and seizures on scalp EEG and discordant noninvasive tests that may be spared an unnecessary intracranial EEG procedure, for instance, MRI finding of left hippocampal atrophy, but evidence of severe memory deficit on the right side by amobarbital test such that even if seizures were proved to come from the left side by intracranial EEG, surgery could not be safely pursued.

In the majority of patients with a problem of bitemporal epilepsy, intracranial EEG is needed before a final recommendation for or against surgery. Patients with no clear ictal predominance, and who also have nonlateralized or discordant imaging or memory tests should probably be advised against surgery. In such patients, surgery may produce more harm than good. Even minor auras from the nonoperated temporal lobe can produce disabling amnesia since this is now the only functional temporal limbic circuit. Patients with bilateral hippocampal dysfunction are also more likely to complain of greater memory problems after surgery, particularly when operated on the dominant temporal lobe (1).

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Surgery is possible in some patients with evidence of bitemporal epilepsy. The critical issue, of course, is identifying the best surgical candidates. Ideally, when faced with the problem of probable bitemporal epilepsy, clinicians should be able to recognize potential candidates before invasive monitoring is employed. There is reason to believe that such identification may be possible, an opinion that is based on some newly available data. One recent study examined the postsurgical outcome of 42 consecutive patients with medically refractory seizures and evidence of bitemporal epilepsy (1). Evidence of bitemporal epilepsy in this series was based on scalp electroencephalographic (EEG)-video monitor documentation of at least one clinical seizure arising independently from both right and left temporal regions. All subjects subsequently underwent bilateral, subdural EEG video monitoring, with strip electrodes placed over basal and lateral temporal regions. All operative decisions were based on the results of the intracranial EEG recordings.

Overall, 26 (62%) of the subjects were found to have seizures that originated from one side only, based on invasive recordings. Surgery was offered to 25 of these
subjects. With an average follow-up of four years after surgery (range 1–10 years), seizure freedom was documented in 16 (64%), and worthwhile improvement (more than 75% reduction in seizures) was found in three (12%). The most relevant finding in this study was that seizure freedom or worthwhile improvement only occurred when the noninvasive assessment, apart from the electrographic data, disclosed some lateralizing features to the side of resection ($p = 0.004$).

Specifically, a preponderance (>75%) of interictal scalp EEG discharges to one side, a focal temporal lobe lesion on magnetic resonance imaging (MRI), or lateralizing deficits on verbal or visual reproduction memory testing, were each found to be independently associated with good outcome. There were two other notable, and perhaps surprising, observations. First, outcomes were not related to the number of lateralizing factors present. Individuals with a single factor did as well as those with two or three. Second, outcome was not directly linked to the fact that intracranial EEG recordings in this group disclosed complete lateralization of seizures to one temporal lobe or the other. Rather, a seizure-free outcome only occurred when some other concordant, lateralizing feature was present on noninvasive studies.

In the same series, intracranial recordings disclosed that seizures arose independently from both temporal lobes in 16 (38%) of the subjects. Surgery was performed in seven, and was based on both a clear preponderance of seizures to one side and the presence of at least one other invasive measure [e.g., magnetic resonance image (MRI) lesion] concordant to the side of the majority of ictal onsets. Five of these subjects had at least a 75% reduction in seizures postoperatively.

From a pragmatic point of view, the clear implication of these findings is that identifying potential surgical candidates among subjects with likely bitemporal epilepsy can be made during the noninvasive evaluation. Proceeding with intracranial recordings appears justified only when some lateralizing feature is disclosed during that initial assessment. Even subjects with normal MRI may do well after surgery, provided the preoperative interictal scalp EEG or neuropsychological data shows lateralizing findings.

Much of the literature on patients with bitemporal epilepsy to a large degree concerns specific methods of intracranial recording, and discussions concerning the degree of lateralization of intracranial seizures that anticipate favorable outcomes (2–6). It is probable that neither the specific methods of intracranial recording nor the magnitude of preponderance of ictal onsets to one side are, by themselves, as important as the concordance of noninvasive factors with invasive electrographic findings in predicting outcome. This position is supported by the work of other investigators who find that evidence of unilateral hippocampal atrophy or memory failure with the intracarotid amobarbital procedure concordant with the side of surgery is generally associated with generally better postoperative outcomes, compared to situations where these factors do not hold (6).

For more than a decade, neuroimaging, particularly with high-resolution MRI, has played a crucial role in the preoperative evaluation of medical epilepsy. It is important to emphasize, however, that in considering subjects with bitemporal epilepsy for surgical therapy, other noninvasive functional measures may prove to be important in the decision-making process. Not every method has been adequately studied. In this regard, it is possible that lateralized findings on positron emission tomography (7), single photon emission tomography (8), or magnetic resonance spectroscopy (9) could prove to be as useful as the factors that have been previously reported by other investigators (1,6). Further research is needed, and could lead to other means of reliably, and safely, recognizing appropriate surgical candidates.
REFERENCES


Chapter VIII-25c: The Role of Surgery in Bitemporal Epilepsy

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Over the past three decades, various authors examined criteria for, and results of, surgical intervention in patients with bitemporal epilepsy, and generated somewhat conflicting conclusions (1–5). The entity of bitemporal epilepsy was, however, defined differently [sometimes using interictal, sometimes ictal electroencephalography (EEG)], and criteria for interpretation and consideration of ancillary studies of functional, electrical, and structural involvement varied considerably. An “80% rule” for lateralization of ictal onset was promulgated as a determining factor for selection of the temporal lobe for surgery (4). In my view, a consideration of the pathophysiology underlying refractory medial temporal lobe epilepsy clarifies the route to successful treatment, including surgery, and charts a somewhat different approach.

Pathological series found medial temporal lobe epilepsy to be a bilateral continuum with variable asymmetry (6–8). In “true” mesial temporal lobe epilepsy with hippocampal sclerosis, bilaterality of the pathological abnormality, including
hippocampal neuronal loss and gliosis, is found frequently; variable reports of the incidence range from 47% to 86% (7,8). Babb and Brown have written that over 90% of hippocampal sclerosis is bilateral (6). These findings suggest that unitemporal and bitemporal epilepsy are points along a continuum, and that this bilaterality is variably detected in clinical practice, depending on the degree of investigation, the sensitivity of the studies used, and the amount of asymmetry in a given individual.

These comments apply only to the syndrome of “true” mesial temporal epilepsy, with the characteristic historical, pathological, electrical, structural, and functional abnormalities previously described (9,10).

Indeed, it may be the bilaterality of this syndrome that makes it the most refractory partial epilepsy and hence the partial epilepsy syndrome most often considered for surgical treatment. Bilateral, but not unilateral, aluminum hydroxide implants in temporal lobes elicit recurrent psychomotor seizures in a monkey model of epilepsy (11). Some investigators suggested that mutual facilitation occurs between homotopic regions in epileptogenic temporal lobes, which renders the epilepsy so refractory (11).

Accordingly, resection of mesial temporal lobe structures on one side might be expected to diminish the refractory nature of the epilepsy, if not cure it altogether, despite its bilateral representation, and regardless of its degree. In other words, the percentage of ictal onsets from one or the other temporal lobe is not necessarily the best criterion to use in choosing the operative site, and theoretically may have no influence on surgical outcome. Rather, the goal of, and need for, invasive EEG localization relates in this situation to establishing true mesial temporal lobe seizure onset (unilateral or bilateral), without features that implicate extratemporal seizure origin with variable propagation, or multifocal epileptogenicity including but extending beyond the two temporal lobes (5). If true mesial temporal lobe epilepsy is established, bilaterality is almost sure, though it may not always be immediately apparent from initial evaluation. These observations lead to the conclusion that invasive EEG is not needed, when true mesial temporal lobe epilepsy can be established with non-invasive study. Predictably, bilateral independent interictal spikes arising in mesial temporal regions are also common in mesial temporal lobe epilepsy, although published literature differs regarding their implications or significance in surgical outcome prediction (12,13).

A decision regarding surgical treatment of mesial temporal lobe epilepsy should then rest on the degree of lateralized functional (mesial temporal) impairment, an adequate assessment of which emphasizes the need for extensive evaluation, including mechanical resonance imaging (MRI), positron emission tomography (PET), single-proton emission computerized tomography (SPECT), neuropsychological evaluation, sodium amytal testing, careful review of historical features, and video-EEG. Thus, the methods used to establish the localization of the epileptic syndrome (bitemporal/limbic vs. various neocortical localizations) can also be applied to a conclusion regarding the degree of lateralized functional impairment, in a manner similar to the assessment and decision for so-called unilateral medial temporal resection as treatment. Marked impairment of material-specific memory, as established by neuropsychological profile and intracarotid sodium amobarbital test, as well as profound hypometabolism referable to one temporal lobe, in the presence of normal/adequate mesial temporal function contralaterally, stand as excellent indicators for resection regardless of the degree of laterality of ictal onset. In most patients with medial temporal lobe epilepsy, the asymmetry of functional impairment parallels the asymmetry of pathologic involvement and seizure onset—so the
same temporal lobe is selected for resection using these concepts, or using the “80% rule.” But all situations will not fall neatly around these findings. The predicted pathophysiology should drive the final decision regarding surgical treatment. In my view, even equally distributed ictal onset on each side is compatible with cure of seizures in a patient with true medial temporal lobe epilepsy, selected for surgery with these methods, and we have shown this in our own series (5).

REFERENCES

Chapter VIII-26
Can Resection Ever Be Done in the Language-Dominant Hemisphere in Patients with Intact Memory?

Chapter VIII-26a: Resection Can Be Done in the Language-Dominant Hemisphere in Patients with Intact Memory, with the Correct Surgical Strategy

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Deficits in verbal memory represent the major morbidity of dominant hemisphere temporal lobe resections for medically refractory epilepsy. The risk of this deficit can be partly predicted by multiple interrelated presurgical patient characteristics. The risk is lower in the presence of mesial temporal sclerosis (MTS), low presurgical verbal memory performance, early life seizure onset (before five years in one study, 18 years in another), younger patients, and male gender. It may be lower in patients with little worsening of verbal memory performance with dominant hemisphere intracarotid amobarbital perfusion, and substantial worsening with nondominant perfusion, though the predictive power of this test has been questioned, and may depend on the measure used to assess verbal memory (1). The risk is less when the patient is seizure-free postoperatively, indicating that any strategy to reduce the risk to memory must not compromise the chance of seizure control. It is clearly a
problem restricted to dominant hemisphere resections. Thus, there are patients at
high and low risk for verbal memory loss after dominant temporal resections. One
strategy for reducing this risk is to limit dominant hemisphere operations to the
low-risk group. It is also important to stratify patients by these presurgical risk fac-
tors in any study of effects of temporal lobe resections on verbal memory.

The fundamental issue for the surgeon planning a dominant temporal resection
is whether there is any anatomic separation between temporal lobe structures gener-
ating the seizures, and those essential for verbal memory, particularly if resections
are to be done in high-risk patients.

Classically, the extent of memory loss after temporal resection has been related
to the extent of hippocampal removal. Patients with temporal lobe epilepsy (TLE)
have often been divided into those with hippocampal sclerosis on imaging, consid-
ered to have a “mesolimbic” epileptic focus, and imaging-normal patients with a
“neocortical” focus. Presumably the latter group would not require hippocampal
resection to achieve seizure control, and thus have little risk to memory. Such a
model is incorrect. As I have discussed elsewhere in this volume, most patients with
a temporal lobe epileptic focus require a medial temporal resection, including por-
tions of hippocampus, to achieve seizure control. Only a small proportion of cases
have a lateral temporal “neocortical” focus, and then usually with a lateral temporal
lesion demonstrated on imaging. And in a substantial proportion of those cases there
is also medial temporal involvement in the epileptogenic zone, the so-called “dual
pathology.” Thus most TLE patients, imaging-normal or not, will require some
degree of medial temporal resection if they are to be seizure-free.

However, the extent of medial temporal resection needed to achieve seizure
control varies among patients. As also discussed elsewhere in this volume, over
the past dozen years, we have recorded the extent of interictal epileptic activity in
the hippocampus, and tailored the medial extent of the resection to the posterior
extent of that activity. In a series of 140 temporal lobe resections for TLE tailored
in this way, the extent of hippocampal resection varied from 5 to 46 mm. Patients
with small resections were as likely to be seizure-free as those with large, so long
as no interictal activity remained in recordings from the residual hippocampus. This
effect was present for patients with MTS, and for those with pathologically normal
hippocampi (2).

In a separate series of 46 cases, we then evaluated whether tailoring the medial
resection in this way had any effect on postoperative verbal memory performance.
When the change in verbal memory performance on the Weschler Memory Scale
Form I from pre- to postoperative was assessed by combining changes in the
immediate and 30 minutes delayed logical memory test and the easy and hard paired
associates measures, a significant correlation with the medial extent of the 26 dominant
hemisphere resections was present. This correlation remained significant for the 15
cases with pathologically normal hippocampi (the cases at high risk for memory loss),
but not the remaining cases with MTS (3). This study indicates a strategy for minimiz-
ing memory loss in some high-risk cases, those that are likely to become seizure-free
with smaller hippocampal resections based on tailoring to the hippocampal interictal
epileptic activity. Using this technique to tailor resections, in the 15 patients of that
series at high risk for memory loss after dominant temporal resections, we achieved
a Class 1 outcome in seven with minimal (<10%) or no verbal memory loss. Thus, this
approach provides a technique for achieving seizure control with little or no verbal
memory loss in some patients with medically refractory TLE, dominant hemisphere
foci, and intact memory with a high risk for postoperative loss, although it does not
solve the problem of memory loss for those patients with interictal epileptic activity that involves most or all of the hippocampus.

Medial temporal structures are not the only ones that have been implicated in human verbal memory mechanisms. A lateral temporal cortical component has been identified in lesion, functional imaging, stimulation mapping, and neuronal recording studies. In an earlier study of cases most of which likely had MTS, we found a correlation between the lateral extent of dominant temporal resections and postoperative verbal memory loss (4).

In the aforementioned study, encroachment of the resection on sites related to verbal memory by stimulation mapping was particularly likely to be associated with memory loss. In several cases, tailoring the lateral resection to avoid such sites was associated with little memory loss. In a recent study there is a hint of the same effect for the group of patients with MTS, with a higher correlation in that group to the lateral, compared to medial extent of resection. Thus, it may be that reducing the chance of worsening memory in the low-risk group may involve tailoring any lateral resection to sites related to memory by stimulation. Unfortunately, restricting resection to mesial structures, as with amygdalohippocampectomy, has not prevented the verbal memory loss with dominant resections. Thus there are a number of techniques for performing dominant hemisphere temporal lobe resections that control seizures with little or no memory loss in patients with intact verbal memories. Somewhat different techniques may be needed to prevent further loss in those with poor presurgical memory.

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Chapter VIII-26b: Temporal Lobe Resection for Epilepsy in the Language-Dominant Hemisphere with Normal Recent Memory on Modified Wada Test

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The high rate of improvement after surgery for medial temporal lobe epilepsy (TLE) has led to enthusiasm for early surgery in drug-resistant TLE (1–7). An important question then arises—should surgery be done when recent memory is intact? Recent memory function has been pivotal in the surgical decision tree since the first report of “severe and lasting memory loss” after bilateral medial temporal lobe (TL) resection (8). Currently, surgery is offered when memory is impaired in the TL to be resected but intact contralaterally. When recent memory is intact in language-dominant TL, indications and contraindications for surgery are not as clearly defined.

To address these issues, we reviewed outcome of TL resections in language-dominant hemispheres of 42 patients whose recent verbal memory was shown by the modified Wada test to be normal bilaterally before surgery. We contrasted these 42 patients’ outcome with 17 patients whose impaired recent verbal memory was on the same side as epileptogenic zones. Both groups were followed up 1–17 years after surgery. All had intact recent memory in the spared TL. Patients were subdivided into pure medial, combined mediolateral, and pure lateral TLE based on epileptogenic ictal zones located by scalp/sphenoidal EEG, intracranial stereoelectroencephalography, or intracranial grid/strip recordings, and by signs of structural damage and sustained periodic spikes and sharp waves on interictal intraoperative electrocorticography (9).

Among patients with preserved recent verbal memory, more patients had pure lateral or combined lateral–medial TLE than pure medial TLE (29:13 or 2.2:1). In contrast, patients with impaired recent verbal memory were as likely to have pure medial TLE as lateral or combined lateral–medial TLE (8:9 or 0.9:1) ($\chi^2 = 2.5$, $P < 0.2$) (Table 1).

Pure medial TLE almost always had hippocampal sclerosis (10/13) while pure lateral TLE had neoplasm, traumatic encephalomalacia, cavernous angioma, or heterotopia. One case of pure lateral TLE had both hippocampal sclerosis and traumatic encephalomalacia. Combined lateral–medial TLE was most commonly
associated with traumatic encephalomalacia, neoplasms, or heterotopia (18/21). The increased frequency of hippocampal sclerosis in medial TLE versus lateral or combined lateral–medial TLE is statistically significant ($\chi^2 = 12.35, p = 0.01$).

When recent verbal memory was impaired in the left hemisphere on modified Wada testing, more patients had hippocampal sclerosis (11/17), and epileptogenic zones were often purely medial. Viewed the other way, pure medial TLE with impaired recent verbal memory almost always had hippocampal sclerosis (6/8). When recent verbal memory is impaired on the modified Wada test, pure lateral TLE can also be associated with hippocampal sclerosis (3/4) while combined lateral–medial TLE showed hippocampal sclerosis, encephalitis, and heterotopia on neuropathology (Table 2).

Thirty-eight of 42 patients (90%) who had intact recent verbal memory before surgery complained of and had worse recent verbal memory on formal

### Table 1 Subvarieties of TLE Among Patients with Normal or Impaired Recent Verbal Memory

<table>
<thead>
<tr>
<th>Subvariety of TLE</th>
<th>Recent memory, ascertained by mWada test</th>
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<tbody>
<tr>
<td></td>
<td>Intact bilaterally</td>
<td>Impaired on left, intact on right</td>
</tr>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
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<tr>
<td>Pure medial</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td>Combined mediolateral</td>
<td>21</td>
<td>47</td>
</tr>
<tr>
<td>Pure lateral</td>
<td>8</td>
<td>16</td>
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<tr>
<td>Total</td>
<td>42</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 2 Relation of Pathology to Temporal Lobe Epilepsy Subtype

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Recent memory as ascertained by mWada test</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Intact bilaterally</td>
</tr>
<tr>
<td></td>
<td>Pure medial</td>
</tr>
<tr>
<td>Hippocampal sclerosis</td>
<td>9 + 1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>0</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>0</td>
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<tr>
<td>Traumatic gliosis, encephalomalacia</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cavernous angioma</td>
<td>1 + 2&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heterotopia</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
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</table>

<sup>a</sup>Dual pathology with hippocampal sclerosis  
<sup>b</sup>Triple pathology of neuronal migration disorder, hippocampal sclerosis, and trauma  
<sup>c</sup>Resected portions of temporal lobe did not include epileptogenic zones in opercular perisylvian areas  
<sup>d</sup>Dual pathology with heterotopia and traumatic encephalomalacia/gliosis  
<sup>e</sup>Medial epileptogenic ictal zones and lateral cavernous angioma
psychometrics after surgery. However, most patients, including 19 professionals and students, were able to adapt to impaired recent verbal memory as demonstrated by return to work or school or acquisition of new employment (Table 3). Three patients did not experience any deterioration of recent verbal memory after surgery.

The first was a statistics student with gifted IQ who only had lateral temporal corticectomy and whose hippocampus was spared. Magnetic resonance imaging (MRI) verified resection of 3 cm of the hippocampus in the second patient. In a third patient, 1.5 cm of the hippocampus was resected.

Location of epileptogenic zones determined who became seizure-free after surgery ($\chi^2 = 16.55$, $P < 0.025$). All ten of ten patients with pure medial TLE and five of five patients with polar mediolateral and/or inferobasal TLE became seizure-free. Results were not as good when “posterior” mediolateral TLE had epileptogenic zones in the superior temporal gyrus more than 2.5 cm from the pole and more than 4.5 cm from the pole in the middle temporal gyrus. Only four of nine became seizure-free. When mediolateral epileptogenic zones were anterior to these boundaries, seven of nine became seizure-free. Three of four patients with pure lateral TLE were relieved of seizures. However, when epileptogenic zones were mediolateral or lateral plus suprasylvian or opercular, only one of five patients were seizure-free after surgery (Table 4).

On balance, 39 of 42 patients (93%) were satisfied with the results of surgery. Twenty-six of 42 improved their quality of life because they were seizure-free (50% or 21/42) or had rare seizures (5/42). They expressed satisfaction because they were employed or able to finish college or were living independently or driving (Table 3) (3,4,7).

Nine other patients among the 42 were unemployed but satisfied with results of surgery because they were free of seizures. Three other patients who had rare seizures but chose to remain unemployed were happy with results of surgery.

Four patients were unhappy with results of surgery. Seizures persisted and incapacitated three patients. Levetiracetam stopped seizures in one of these three patients. Of the two remaining patients with persistent seizures, one was a school teacher with lateral and medial epileptogenic zones in the posterior superior temporal–parietal regions and hippocampus.

Two separate attempts to resect all epileptogenic zones resulted in impaired recent verbal memory and language difficulties. Although she continued to teach, she described diminished capacity in comprehension and expression of spoken and written language. The other patient with persistent seizures had a venous angioma that bled in the lateral TL. Resection of epileptogenic zones was incomplete because fluent cortex in the superior temporal gyrus was spared. The fourth unhappy patient had rare seizures but was unable to adapt to loss of recent verbal memory and dropped out of school where he had been enrolled in an MBA program.

In summary, TLE surgery in language-dominant hemisphere with intact recent memory can completely relieve seizures in 71% (30 of 42) of patients. Pure medial, polar mediolateral, and/or inferobasal TLE have a high likelihood of becoming seizure-free. Although 90% of patients had worse recent verbal memory after surgery, most were able to go back to work or school. These results are partly supported by Wyllie et al. (10) who demonstrated a nonstatistically significant trend towards decline of recent verbal memory among those with intact (10/27) versus those with impaired (2/10) recent verbal memory prior to surgery.

Caution is advised when: (i) epileptogenic zones are in both superior temporal gyrus and frontal or parietal operculum, and (ii) resection of epileptogenic zones in both fluent temporal neocortex and hippocampus is required. In the latter setting,
### Table 3  Employment Among Patients with Preserved Recent Verbal Memory on Modified Wada Test

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<tr>
<th>Employment</th>
<th>Before surgery</th>
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<th>After surgery</th>
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<tbody>
<tr>
<td></td>
<td>Employed/college</td>
<td>Not employed</td>
<td>Employed/college</td>
<td>Occasional/rare seizures</td>
<td>Intractable seizures</td>
<td>Not employed</td>
<td>Occasional/rare seizures</td>
<td>Intractable seizures</td>
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<tr>
<td>Professional/businessman</td>
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<tr>
<td>Office worker/store supervisor/administrator</td>
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<td>2</td>
<td>3</td>
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<tr>
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<td>5</td>
<td>9</td>
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Resective Surgery for Temporal Lobe Epilepsy
highly functional professionals who require intact recent verbal memory and eloquent speech (i.e., lawyers and teachers) can develop occupational and functional difficulties after surgery.

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REFERENCES


INTRODUCTION

Unlike mesial temporal lobe epilepsy (MTLE), neocortical epilepsy comprises a variety of seizure types depending on the location of the epileptogenic cortex. Lateral temporal lobe epilepsy, medial and lateral frontal lobe epilepsy, and the more rare entity of parieto-occipital epilepsy, all fall within the category of neocortical epilepsy. Unlike MTLE, which involves a defined allocortical circuit, neocortical epilepsies can involve a variety of pathways and structures, and may involve or be in close proximity to eloquent cortex including motor, speech, and visual areas.

A characteristic semiology, electroencephalography (EEG) pattern, and pathologic findings define MTLE. Seizures typically consist of automatisms of the face and hand, speech disturbances, and sometimes secondary generalization (1). Interictal EEG shows anterior temporal discharges and ictal EEG is lateralized in 90% of cases. Magnetic resonance imaging (MRI) scan often reveals hippocampal atrophy, magnetic resonance (MR) spectroscopy shows abnormal creatine/N-acetylaspartate (NAA) ratio, $\text{[18}^F\text{]}$ fluoro-2-deoxyglucose-positron emission tomography (FDG-PET) shows hypometabolism in the ipsilateral temporal lobe, and ictal single-proton emission computerized tomography (SPECT) reveals a distinct pattern of hyperperfusion and hypoperfusion (2). Pathologic changes include marked neuronal loss in the CA1 and CA4 regions of the hippocampus, with sparing of the CA2 region (1). Thus, in contradistinction to neocortical epilepsy, MTLE is a well-defined clinical entity that is generally amenable to a unified surgical approach.

Neocortical epilepsy varies in seizure characteristics, ictal and interictal discharges, and may or may not be associated with a structural lesion. Neocortical temporal lobe epilepsies are more frequently associated with olfactory and gustatory auras, complex gestures, ictal speech, and secondary generalizations (3,4). Frontal lobe epilepsies tend to be briefer, more frequent, and may involve the supplementary motor area (SMA), motor strip, or consist of brief lapses of awareness ("pseudoabsences"), and the discharge can spread rapidly to other brain areas (5).
Parietal and occipital seizures classically begin with visual and somatosensory auras, and may arise within or close to eloquent cortex (6).

The etiologies of neocortical epilepsy are diverse. Mesial temporal sclerosis (MTS) underlies the majority of MTLEs and, although the inciting event of MTS is unclear, the pathologic endpoint is constant—namely, neuronal loss in the hippocampus, and less frequently the amygdala. Neocortical epilepsies do not share a unifying pathologic finding. Rather, epileptogenic foci in the neocortex may be associated with pathologically normal brain (idiopathic or cryptogenic) or with a lesion. Lesions can be classified as developmental abnormalities including heterotopias, hamartomas, cortical dysplasias, and gyral anomalies; tumors including gangliogliomas, gliomas, and dysembryoplastic neuroectodermal tumor (DNET) among others; vascular lesions including cavernous malformations and arteriovenous malformations; and encephalomalacia due to trauma or ischemia (Table 1). In a subset of neocortical epilepsy, particularly of the lateral temporal lobe, MTS is also present, presenting the clinician with a picture of dual pathology.

EEG findings vary in neocortical epilepsies. Lobar localization may not be possible based on scalp recordings alone, and secondary spread is common. MRI is useful in guiding the search for a structural lesion that may be associated with the epileptogenic focus. Adjunctive imaging, including interictal FDG-PET and ictal SPECT scanning, may help with localizing the seizure focus (7).

Although noninvasive measures can generally localize seizure foci, none can do so with perfect sensitivity and specificity. Hong et al. (8) compared ictal EEG, interictal FDG-PET, and ictal SPECT with invasive monitoring in 41 patients with intractable epilepsy and no visible lesion on MRI. Ictal EEG was most likely to correctly localize the seizure focus to the appropriate lobe, doing so in 67% of patients. FDG-PET localized the correct lobe in 43% of patients, and ictal SPECT localized correctly in 33% of patients. All modalities did best with neocortical temporal lobe

<table>
<thead>
<tr>
<th>Table 1 Classification of Lesions</th>
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<tbody>
<tr>
<td><strong>Developmental abnormalities:</strong></td>
</tr>
<tr>
<td>Cortical dysplasia</td>
</tr>
<tr>
<td>Heterotopias</td>
</tr>
<tr>
<td>Hamartomas</td>
</tr>
<tr>
<td>Gyral abnormalities</td>
</tr>
<tr>
<td><strong>Tumors:</strong></td>
</tr>
<tr>
<td>Grade I gliomas</td>
</tr>
<tr>
<td>Grade II gliomas</td>
</tr>
<tr>
<td><strong>Vascular lesions:</strong></td>
</tr>
<tr>
<td>AVMs</td>
</tr>
<tr>
<td>Cavernous malformations</td>
</tr>
<tr>
<td><strong>Encephalomalacia:</strong></td>
</tr>
<tr>
<td>Trauma (including scar)</td>
</tr>
<tr>
<td>Ischemia</td>
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<tr>
<td>Birth trauma</td>
</tr>
<tr>
<td><strong>Other:</strong></td>
</tr>
<tr>
<td>Gliosis</td>
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<tr>
<td>Granuloma</td>
</tr>
<tr>
<td>Unspecified</td>
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<tr>
<td>Normal brain (no lesion)</td>
</tr>
</tbody>
</table>

*Abbreviation: AVMs, arteriovenous malformations.*
epilepsy (NTLE), and all the methods falsely localized the lobe in at least one case.
Boon et al. (9) similarly examined patients with lesions on computed tomography
(CT) or MRI. Of 20 patients (including five with isolated MTS) this group found sei
zure semiology correlated with lesion location in 55%, interictal EEG lateralization
was correct in 85%, ictal EEG lateralized correctly in 70% and localized in 50%, and
interictal PET was congruent in 81%.

The epileptogenic focus of epileptic activity may not correlate precisely with the
imaging abnormality. Techniques for localizing the electrical abnormality include scalp
EEG, which often only gives lobar localization, invasive EEG monitoring (utilizing
surgically implanted electrode grids or strips on the cortical surface, or depth electrodes
placed within the brain matter), and intraoperative electrocorticography (ECoG). Inva
sive monitoring requires proper placement of surface or depth electrodes. Ictal recor
dings are most useful in localizing seizure onsets, but prolonged monitoring may be
required to record an ictal event. Intraoperative ECoG may vary depending on whether
ictal versus interictal recording is obtained, and the presence of anesthetic agents.

Surgical strategies include lesionectomy alone, lesionectomy with cortical
resection of epileptogenic cortex, resection of electrically abnormal tissue alone,
lobectomy, or strategies based on disconnecting the pathways of seizure spread.
Epileptogenic cortex can be defined by an abnormal spiking on ECoG (adjacent
or remote foci) or by ictal foci localized by invasive EEG monitoring. Often, a
combination of strategies is utilized.

This chapter deals with surgical planning for neocortical epilepsy, identified
either by imaging abnormality or by electrical abnormality. Surgical results for lesion
ectomy alone, or lesionectomy with resection of epileptogenic foci are compared.
Further, methods used for defining electrically abnormal brain, including extraopera
tive and intraoperative methods, are compared. Surgery is only considered for epi
lepsy uncontrolled by medications (intractable), or epilepsy associated with lesions
for which surgical treatment is indicated regardless of associated seizures as with
tumors and an teriovenous malformation. Outcomes after surgery can be classified
by the Engel system, with four main categories of seizure outcome (10). The categories
are I, seizure-free; II, rare seizures (two to three per year); III, worthwhile improve
ment in seizure frequency (> 90% reduction); and IV, no worthwhile improvement
in seizure frequency (< 90% reduction). Each category can be further subclassified.

**SURGICAL APPROACHES**

Lesionectomy is defined as standard surgical removal of the structural lesion alone.
In some cases, this may involve removal of adjacent structurally normal brain, or a
formal lobectomy. Treatment by this method implies tailoring surgery strictly for the
goal of removing the lesion, and not pursuing epileptogenic foci. However, electri
cally active foci may be removed incidentally if they are adjacent to the lesion.

A second approach is to remove the epileptogenic cortex alone. The rationale is
that the structural abnormality seen on imaging may be unrelated to the seizure syn
drome. Sometimes the lesion itself may not be resectable if it is located in inaccessible
or eloquent cortex. In general, if a lesion is present in some relation to the ictal
source, some attempt will be made at resection. Other strategies aim to transect
pathways along which seizures spread.

Seizure surgery aims to remove the structural lesion, if one is present, as well as
the epileptogenic cortex. The epileptic foci may be adjacent to or removed from any
lesion that is present. In some cases, more than one epileptogenic focus is found, and may be the mesial temporal lobe, especially in cases of NTLE. Whether these secondary foci arise from abnormal stimulation by the primary focus or independently is not known. Further, at what point the secondary focus is able to generate seizures autonomously is also unclear.

Localizing the electrical abnormality can be undertaken in many ways. Noninvasive studies include seizure semiology, ictal scalp EEG (video EEG), interictal EEG, interictal FDG-PET, and ictal SPECT. Invasive studies include implanted subdural grid and strip electrodes or depth electrodes for prolonged monitoring of both ictal and interictal discharges, as well as intraoperative ECoG.

Comparing outcomes for patients with different surgical strategies may be difficult. Outcomes may differ due to factors inherent in the disease such as the nature and location of the lesion. Lesions in eloquent areas are not as amenable to complete resection without subsequent neurologic deficits. The nature of the lesion (such as glioma vs. cortical dysplasia) may play a role in the patient’s outcome. Further, many studies include patients who underwent surgery prior to high-resolution MR. Such patients with undetected lesions may have been inadvertently classified as having idiopathic epilepsy.

A meta-analysis of simple excision versus seizure surgery was performed in 1993 (11). Included were studies with follow-up of at least two years, a majority of adult patients, study size greater than five patients, and outcome measures that could be classified using the Engel scheme. Twenty-one studies met this criteria for simple excision (dates 1940–1991) and 15 studies for seizure surgery (dates 1959–1993). In total, 771 patients were in the simple excision group, and 703 patients in the seizure surgery group. Seizure surgery was defined as resection of the lesion as well as electrically abnormal cortex. Seizure foci were defined by a variety of electrical studies including ECoG and invasive monitoring. All patients had lesions, but were not separated by location of the lesion. Some patients did not have intractable epilepsy (approximately 20% in seizure group, and 60% in simple excision group). A total of 56% of patients had persistent seizures after simple excision, and 33% after seizure surgery. This difference persisted when the lesions were separated by type: vascular lesion, arteriovenous malformation (AVM), meningioma, low-grade astrocytoma, and ganglioglioma, and the difference was statistically significant. The authors concluded that if a patient with a structural lesion had medically intractable seizures, seizure surgery had a better chance of rendering the patient seizure-free.

Neocortical Nonlesional Epilepsy

As imaging techniques improve, the number of cryptogenic epilepsies dwindles. In particular, high-resolution MR scanning has become increasingly sensitive at picking up subtle lesions, such as cortical dysplasia, that were not visible by older imaging modalities. Also, pathologic examination of tissue resected during nonlesional epilepsy surgery can reveal subtle lesions such as cortical dysplasia or gliotic “scars.” Histologic examination may also reveal generalized gliosis, which may be a cause or consequence of seizure activity.

Neocortical Epilepsy with Structural Lesion

When a structural lesion is present with intractable epilepsy, the surgical approach must take into consideration the treatment of the lesion alone. For example, surgery
may be indicated for gliomas or AVMs regardless of associated epileptogenic foci. Primary tumors account for 10% to 30% patients undergoing epilepsy surgery (12). Vascular malformations including AVMs and angiographically occult vascular malformations (such as cavernoma) make up about 3% of patients considered for epilepsy surgery (12). In these patients, definitive action for the lesion may be undertaken before seizures have become intractable. As with tumor surgery, this is not strictly epilepsy surgery; rather, it is undertaken to treat the primary disease. In such a patient with concomitant intractable seizures, care must be taken to identify the focus of the seizures, which may be adjacent to or removed from the lesion, as well as strategies for ideal treatment of the primary lesion. Developmental abnormalities are present in 4.3% to 25% of intractable epilepsy and may be focal, multifocal, or diffuse (12). Especially in multifocal and diffuse disease, care must be taken to correctly identify epileptogenic brain. The focus in this chapter is on focal dysplastic lesions rather than diffuse disease. Encephalomalacia can also be associated with intractable epilepsy, and may have developed after trauma, ischemia, or infection. Again, care must be taken to isolate the epileptogenic focus, which may be related to the obvious atrophic area, or to more subtle damage related to the initial insult.

Temporal Lobe Epilepsies

NTLE can be treated using a variety of surgical strategies, and may include resection of mesial structures (Table 2). Dual pathology, discussed below, can be associated with neocortical temporal lobe lesions. Differentiating NTLE from MTLE may prove difficult. Neglecting to distinguish between the two may impact surgical outcome. The difficulty in part arises from the close proximity and extensive connections between these structures (3). Pacia et al. (4) tried to distinguish features of NTLE from MTLE by selecting 21 patients with EEG-defined NTLE who became seizure-free after temporal lobectomy. Auras were common (71%). MRI showed lesions in 4 of 21 patients and mesial sclerosis in 3 of 21. When two of the MRI-documented cases of mesial sclerosis were examined pathologically, MTS was not found. Unlike MTLE, NTLE patients did not have a significant association with febrile seizures.

Reported outcomes vary widely in cases of temporal lobe lesions with intractable epilepsy. Treating temporal lobe lesions by any surgical modality resulted in seizure freedom (Engel Class I) in 7% to 91% of patients (13–20). Surgical strategies fell into three groups: those with the goal of resecting the lesion, those that resect both the lesion and the electrical abnormality, and those that resect the electrical abnormality alone. Lesion-based strategies included lesionectomy and temporal lobectomy (which may or may not imply complete lesionectomy) and may have included mesial structures. Electrical abnormalities were excised by corticectomy using ECoG guidance or long-term extraoperative invasive EEG monitoring. The few studies reporting excision of electrically abnormal tissue alone were usually in the setting of unresectable lesions.

If EEG recordings were abnormal in the vicinity of the lesion (concordant), lesionectomy alone resulted in high rates of seizure freedom, but outcomes were less favorable if the abnormal EEG findings were distant from the lesion (13,14). In some reports, worse results were found with corticectomy than with lesionectomy (13,14). Schramm et al. (13) found Class I results in 91% versus 76% (not significant) for lateral temporal resection versus lesionectomy with corticectomy guided by invasive EEG monitoring. Furthermore, they found patients who did not undergo invasive evaluation had a better outcome. However, patients who underwent corticectomies
<table>
<thead>
<tr>
<th>Study</th>
<th>Lesion type</th>
<th>n</th>
<th>Surgical technique</th>
<th>Engel I</th>
<th>Engel II</th>
<th>Engel III–IV</th>
</tr>
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<tbody>
<tr>
<td>Casazza (14)</td>
<td>Tumors: 30</td>
<td>40</td>
<td>Lesionectomy, 32 5 reops for persistent sz with 3 MSR Lesionectomy + MTR in 8</td>
<td>23 (58%)</td>
<td>8 (20%)</td>
<td>9 (22%)</td>
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<tr>
<td></td>
<td>Vascular: 10</td>
<td></td>
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<tr>
<td>Schramm (13)</td>
<td>Developmental: 7</td>
<td>58</td>
<td>Lat. Temp. resect: 11</td>
<td>46 (79%)</td>
<td>7 (12%)</td>
<td>5 (9%)</td>
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<tr>
<td></td>
<td>Tumors: 35</td>
<td>3</td>
<td>Cort + lesionectomy: 50</td>
<td>2 (67%)</td>
<td></td>
<td>1 (33%)</td>
</tr>
<tr>
<td></td>
<td>Vascular: 11</td>
<td></td>
<td>Invasive in 26, used for language mapping</td>
<td></td>
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<tr>
<td></td>
<td>Gliosis: 5</td>
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<tr>
<td></td>
<td>Normal: 3</td>
<td></td>
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<tr>
<td>Jooma (15)</td>
<td>Developmental: 3</td>
<td>30</td>
<td>Lesionectomy, 16</td>
<td>3 (19%)</td>
<td>2 (12%)</td>
<td>11 (69%)</td>
</tr>
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<td></td>
<td>Tumors: 24</td>
<td></td>
<td>Lesionectomy + ECoG,14</td>
<td>13 (93%)</td>
<td>1 (7%)</td>
<td></td>
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<tr>
<td></td>
<td>Vascular: 3</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Kirkpatrick (18)</td>
<td>Developmental: 1</td>
<td>31</td>
<td>Temporal lobectomy, including hippocampus.</td>
<td>25 (81%)</td>
<td>3 (10%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td></td>
<td>Tumor: 30</td>
<td></td>
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<td></td>
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<tr>
<td>Clusman (17)</td>
<td>Tumors: 74</td>
<td>13</td>
<td>Ant temp lobectomy or lat lesionectomy, +Invasive monitoring in some cases (not sorted)</td>
<td>62 (84%)</td>
<td>7 (9%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td></td>
<td>Other: 62</td>
<td>6</td>
<td></td>
<td>35 (56%)</td>
<td>6 (10%)</td>
<td>21 (34%)</td>
</tr>
<tr>
<td>Jorge (16)</td>
<td>Tumors: 10</td>
<td>10</td>
<td>Lesionectomy</td>
<td>8 (80%)</td>
<td>2 (20%)</td>
<td>II-IV</td>
</tr>
<tr>
<td>Fish (19)</td>
<td>Tumors: 8</td>
<td>14</td>
<td>4 with dual pathology ATL</td>
<td>1 (7%)</td>
<td>2 (14%)</td>
<td>11 (79%)</td>
</tr>
<tr>
<td></td>
<td>Vascular: 3</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Scar: 1</td>
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<td>Other: 2</td>
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<tr>
<td>Pilcher (20)</td>
<td>Tumor: 10</td>
<td>10</td>
<td>Lesionectomy+corticectomy (ECoG)</td>
<td>9 (90%)</td>
<td></td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Hong (8)</td>
<td>Normal MR,</td>
<td>11</td>
<td>Corticectomy: Invasive EEG, ECoG and mapping in some cases.</td>
<td>5 (45%)</td>
<td>3 (27%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td></td>
<td>unspecified pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edwards (42)</td>
<td>Developmental: 6</td>
<td>6</td>
<td>Lesionectomy, invasive monitoring in some</td>
<td>2 (33%)</td>
<td>3 (50%)</td>
<td>1 (17%)</td>
</tr>
</tbody>
</table>

Table 2  Temporal Neocortical Epilepsies
may have more complicated disease, necessitating more invasive monitoring and complex surgery, indicating that there was a selection bias in this study.

Clusman et al. (17) reported their experience with lesionectomy (gross total) and resection of the adjacent 5–10 mm of “epileptogenic cortex,” limited in some cases by eloquent cortex. Surgical procedures included anterior temporal lobectomy, lateral lesionectomy, and variable mesial temporal resection. Invasive monitoring was undertaken in some cases (not sorted) and ECoG in rare cases. Most localization of epileptogenic cortex was based on traditional scalp EEG and seizure semiology. Mesial structures were resected if epileptogenic tissue was felt to be present. They found no difference in outcome based on operative technique, including use of invasive EEG, and without the routine use of ECoG. However, others have found ECoG to improve outcomes (15). Jooma et al. (15) reported class I outcomes of 19% for lesionectomy alone versus 93% if ECoG was used to guide resections (statistically significant). Furthermore, in the 8 of 11 cases where lesionectomy alone failed (class III or IV), subsequent completion of the temporal lobectomy resulted in class I outcome in 62% (5/8). Kirkpatrick et al. (18) examined the utility of ECoG in 31 patients with low grade temporal lobe tumors who underwent temporal lobectomy. ECoG was performed, but was not used to guide resection. Incomplete resection of the lesion by pathological examination occurred in 22 of 31 (71%) and was not correlated with worse outcome. Postresection ECoG appeared to show a decline in spike frequency (defined as “improved”), but not necessarily absence of spike activity. Improvement of postresection ECoG recordings did not predict outcome, but data were not analyzed on presence versus absence of postresection activity. Pilcher et al. (20) found ECoG guidance useful in a series of 10 patients with temporal gangliogliomas. A total of 90% of patients became seizure-free with lesionectomy and resection of additional epileptogenic cortex defined by ECoG. The one patient with persistent seizures had residual electrically abnormal cortex that could not be resected due to the involvement of functional cortex.

Resection of electrically abnormal cortex alone, leaving the lesion intact, does not appear to have favorable results. Fish et al. (19) reported on 20 patients with inaccessible posterior temporal, parietal, or occipital lesion. All patients underwent preoperative EEG localization, including long-term monitoring in 2 of 20 patients. The temporal lobe involved in the seizures was resected, while leaving the lesion intact. ECoG was utilized in 19 of 20 patients, and postresection ECoG was performed in 16 of 20, 13 of whom had persistent posterior spiking after resection. Only 7% became Engel Class I after surgery. Similar poor results were found in patients with parietal and occipital lesion undergoing temporal lobectomy in this study and others (21).

Many studies report differential results based on pathology. In one series of 85 patients with NTLE, excluding MTLE, 74% had lesions (41% tumors, 14% vascular, and 27% developmental). Outcome after surgery did not depend on pathologic diagnosis (22). Casazza et al. (14) however, found patients with cavernous malformations had better rates of seizure freedom than those with tumors, particularly if the resection was incomplete. After further resection to completely remove the tumors, however, they reported seizure freedom in three of four patients. Other studies have found better outcomes with neoplastic lesions, with Class I outcomes in 81% to 89% of cases (13, 17). In some studies, ganglioglioma and DNET conferred better outcomes, but this was not always the case (16, 17). Clusman et al. (17) found patients with tumors did better than all other patients (81% vs. 58% Class I) regardless of surgical method. Including the MTLE patients, outcomes from operations on
patients with tumors were most successful (89.3% Class I or II) compared to dysplasias (72%), dual lesions (70%), or no structural abnormality (46%). Further multifactorial analysis found positive outcome was associated with ganglioglioma or DNET and absence of dysplasia. Other groups have reported better seizure-free outcome with low-grade than high-grade lesions (23).

Studies examining nonlesional lateral temporal lobe epilepsies are sparse. In general, patients with nonlesional temporal lobe epilepsy have less favorable outcomes than patients with a lesion. Reported Class I outcomes range from 45% to 67% of patients (8,17). Honget al. (8) operated on 11 patients with no lesion on MRI, but subsequent pathology examination found a range of abnormalities, most developmental. Surgery was based on noninvasive studies, invasive monitoring, and, when needed, ECoG and functional mapping, with seizure-free outcome in 45% of patients. Operative outcome was better when localization of the focus was concordant between modalities. Functional cortex limited resection in some of the patients with poor outcomes.

In summary, results for treatment of lesional temporal lobe epilepsy vary widely. Strategies include lesionectomy, temporal lobectomy, and intraoperative or chronic ECoG-guided corticectomies. Good results have been reported with lesionectomy alone in cases with clearly related electrical abnormalities on EEG. Incomplete lesionectomy and resection of electrically active cortex alone appear less successful, with subsequent lesionectomy often having a positive effect. Some authors report better success when pursuing spike activity on ECoG after resection of the lesion, while others find no improvement with this technique. However, the methods of applying and utilizing ECoG information vary widely (reduction in spike activity vs. absence of spike activity postresection). Furthermore, the pathology of the patient population studied also affects outcomes.

Frontal Lobe Epilepsies

Medically intractable frontal lobe epilepsy can be difficult to treat, and outcomes after surgical treatment are less favorable than those with temporal lobe epilepsy (Table 3) (24,25). This may be due to several factors, including the large size of the frontal lobe, rapid spread of seizures, and poorly delineated seizure syndromes. Intracranial monitoring may play a greater role in frontal lobe epilepsy to define the ictal origin. However, even with invasive monitoring, the ictal focus can be difficult to identify. Sampling error may occur due to the large size of the frontal lobe.

Some authors find subdural recording is mandatory in frontal lobe epilepsy (25,26). The frontal lobe lacks clearly defined anatomical markers associated with seizure patterns, and neurological morbidity can be high, particularly in the dominant hemisphere. Subdural recording allows recording around a known lesion as well as functional mapping. Depth electrodes can record from deep frontal lobe structures, but the sampled area is small. Surgical options are similar to those of the temporal lobe, and include lobectomy, corticectomy, and disconnection of pathways.

Class I outcomes after surgery for intractable frontal lobe epilepsies range from 31% to 76% (8,20,24,26–28). Most authors reported a variety of surgical strategies, performing ECoG and invasive monitoring in some cases, and partial or total lobectomies in others, making it difficult to compare strategies. Olivier (26) reported his experience with 88 patients with frontal lobe seizures, using ECoG as the primary means of localizing the epileptogenic focus, but adding
<table>
<thead>
<tr>
<th>Study</th>
<th>Lesion type</th>
<th>n</th>
<th>Surgical technique</th>
<th>Engel I</th>
<th>Engel II</th>
<th>Engel III-IV</th>
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<tbody>
<tr>
<td>Pilcher (20)</td>
<td>Tumor: 2</td>
<td>2</td>
<td>Lesionectomy + corticectomy (ECoG)</td>
<td>2 (100%)</td>
<td></td>
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<tr>
<td>Jobst (27)</td>
<td>Developmental: 10</td>
<td>25</td>
<td>Lesionectomy + corticectomy based on invasive EEG monitoring in 24</td>
<td>13 (65%)</td>
<td>3 (15%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td></td>
<td>Tumor: 7</td>
<td></td>
<td></td>
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<td></td>
<td>Vascular: 2</td>
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<td></td>
<td>Gliosis: 1</td>
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<tr>
<td></td>
<td>Normal: 5</td>
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<tr>
<td>Mosewich (28)</td>
<td>Tumor: 7</td>
<td>68</td>
<td>Frontal lobectomy: 48</td>
<td>40 (59%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Vascular: 5</td>
<td></td>
<td>Partial lobectomy: 3</td>
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</tr>
<tr>
<td></td>
<td>Developmental: 9</td>
<td></td>
<td>Lesionectomy: 17</td>
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<tr>
<td></td>
<td>Scar: 17</td>
<td></td>
<td>Invasive monitoring: 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olivier (26)</td>
<td>Lesions: 20</td>
<td>88</td>
<td>Frontal lobectomy: 4</td>
<td>30 (34%)</td>
<td>6 (6%)</td>
<td>52 (60%)</td>
</tr>
<tr>
<td></td>
<td>Normal: 68</td>
<td></td>
<td>Partial lobectomy: 64</td>
<td></td>
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<tr>
<td>Munari (24)</td>
<td>Developmental: 14</td>
<td>33</td>
<td>Lesionectomy: 4</td>
<td>25 (76%)</td>
<td>1 (3%)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td></td>
<td>Tumor: 4</td>
<td></td>
<td>Corticectomy: 15</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Vascular: 2</td>
<td></td>
<td>Both: 12</td>
<td></td>
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<tr>
<td></td>
<td>Gliosis: 3</td>
<td></td>
<td>Partial lesionectomy: 2</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Normal: 10</td>
<td></td>
<td>SEEG in 25/33</td>
<td></td>
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</tr>
<tr>
<td>Hong (8)</td>
<td>Normal MR, unspecified pathology</td>
<td>16</td>
<td>Corticectomy: Invasive EEG, ECoG, and mapping in some cases</td>
<td>5 (31%)</td>
<td>1 (6%)</td>
<td>10 (62%)</td>
</tr>
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</table>
invasive EEG monitoring if no lesion was present. Patients with a lesion had better outcomes (65% Class I) compared to the group as a whole, and outcome did not depend on which frontal lobe (dominant or nondominant) was affected.

Other authors utilized invasive EEG monitoring as the primary means of localizing the epileptic regions. Jobst et al. (27) performed invasive EEG monitoring in 24 or 25 patients with frontal lobe epilepsies, 20 of whom had lesions. Patients with lesions who underwent complete lesionectomy did better, and patients without lesions had similar outcomes to those with lesions. Munari et al. (24) reported 33 patients, 23 of whom had lesions. Twenty-five patients underwent mapping with implanted electrodes, and had slightly worse outcomes than those who did not (72% vs. 87%). Overall, 76% of patients were seizure-free. Failures included resections limited by functional cortex.

Mosewich et al. (28) examined 68 patients with frontal lobe epilepsy, performing maximal safe frontal lobectomy in 48, partial lobectomy in 3, and lesionectomy in 17, and based the extent of resection on ECoG and relation to functional cortex. Postresection ECoG activity was present in 19 of 66 cases, and had no effect on outcome. Patients with lesions had significantly better outcome than those who did not (seizure-free 43.5% vs. 24.1%).

Thus, no strategy has clear benefits in all cases of intractable frontal lobe epilepsies. Although not universal, patients with lesions tend to have better outcomes than those who do not. ECoG appears helpful in guiding resection, but postresection spikes do not have a definite relation to outcome. Subdural monitoring can be helpful in guiding resection, particularly in patients without lesions, but is limited by the size of the frontal lobe.

Parietal and Occipital Epilepsies

Seizures arising from the parietal and occipital lobes may be simple or complex, partial or general. Seizure patterns include paresthesias, visual hallucinations, motor activity, pain, aphasia, or dysphasia, with frequent spread to other regions. The lack of typical seizure characteristics and frequent spread make localizing these epilepsies difficult.

Scalp EEG can be misleading and, at best, may lateralize the seizure focus (29–32). EEG may show abnormalities not only in parietal and occipital lobes, but also in ipsilateral or contralateral temporal and frontal lobes. Neuroimaging is critical to define structural abnormalities and guide the hunt for the seizure focus. Functional mapping may play a key role in surgical planning to avoid or minimize neurologic deficits from injury to the somatosensory cortex, association cortex, language areas, and visual pathways.

Several case series have documented treatment of patients with parietal and occipital epilepsies. Surgical outcomes for parietal and occipital intractable epilepsy, regardless of surgical strategy, report seizure freedom in 32% to 91% of patients (summarized in Tables 4 and 5). Results vary widely depending on the presence and nature of a structural lesion as well as surgical strategy.

Parietal Lobe Epilepsies

Series describing intractable epilepsy originating from the parietal lobe primarily include patients with parietal lobe lesions (Table 4). Cascino et al. (29) reported seizure freedom in 9 of 10 patients (90%) who underwent lesionectomy alone for intractable parietal epilepsy. ECoG was used in eight patients, and showed interictal epileptiform discharges in six of eight patients in the region of lesion before
<table>
<thead>
<tr>
<th>Study</th>
<th>Lesion type</th>
<th>n</th>
<th>Surgical technique</th>
<th>Engel I (90%)</th>
<th>Engel II (10%)</th>
<th>Engel III-IV</th>
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</thead>
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<tr>
<td>Cascino (29)</td>
<td>Development: 1</td>
<td>10</td>
<td>Lesionectomy, ECoG 8/10, (spikes not pursued)</td>
<td>9</td>
<td>1</td>
<td></td>
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<tr>
<td></td>
<td>Tumors: 5</td>
<td></td>
<td></td>
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<td></td>
<td>Vascular: 3</td>
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<td></td>
<td>Other: 1</td>
<td></td>
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<tr>
<td>Salanova (35)</td>
<td>Developmental: 7</td>
<td>79</td>
<td>Lesionectomy, and ECoG based</td>
<td>36 (46%)</td>
<td>15 (19%)</td>
<td>28 (35%)</td>
</tr>
<tr>
<td></td>
<td>Vascular: 6</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Encephalomalacia: 19</td>
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<td></td>
<td>Other: 2</td>
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<td></td>
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<tr>
<td></td>
<td>Unknown: 9</td>
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<tr>
<td>Williamson (30)</td>
<td>Developmental: 2</td>
<td>11</td>
<td>Lesionectomy: 10, Invasive monitoring: 5</td>
<td>10 (91%)</td>
<td>1 (9%)</td>
<td>“poor”</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Vascular: 1</td>
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<tr>
<td></td>
<td>Gliosis: 1</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Fish (19)</td>
<td>Tumor: 1</td>
<td>4</td>
<td>2 with dual pathology. All underwent Atl + ECoG</td>
<td>1 (25%)</td>
<td>3 (75%)</td>
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<tr>
<td></td>
<td>Undefined: 3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Hong (8)</td>
<td>Normal MR, unspecified pathology</td>
<td>4</td>
<td>Corticectomy: Invasive EEG, ECoG, and mapping in some cases</td>
<td>2 (50%)</td>
<td>2 (50%)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Lesion type</td>
<td>n</td>
<td>Surgical technique</td>
<td>Engel I (%)</td>
<td>Engel II (%)</td>
<td>Engel III-IV (%)</td>
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<tr>
<td>Bidzinski (36)</td>
<td>Encephalomalacia: 9 Normal: 3</td>
<td>11</td>
<td>Occipital partial or full lobectomy guided by ECoG and abnormal tissue</td>
<td>10 (91%)</td>
<td>1 (9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lesionectomy or lobectomy, ECoG</td>
<td>16 (46%)</td>
<td>4 (11%)</td>
<td>15 (43%)</td>
</tr>
<tr>
<td>Aykut-Bingol (31)</td>
<td>Developmental: 14 Tumors: 13</td>
<td>35</td>
<td>(spikes not pursued) Invasive monitoring: 19</td>
<td>10 (77%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Tumors: 10 (77%) Tumor: 1 Tumor: 2</td>
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</tr>
<tr>
<td>Kuzniecky (33)</td>
<td>Developmental: 6</td>
<td>6</td>
<td>Partial or complete lobectomy Invasive monitoring: 5</td>
<td>3 (50%)</td>
<td>2 (33%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Blume (34)</td>
<td>Developmental: 5 Tumors: 4</td>
<td>19</td>
<td>Corticectomy, lesionectomy guided by ECoG Invasive monitoring: 5</td>
<td>6 (32%)</td>
<td></td>
<td>13 (68%)</td>
</tr>
<tr>
<td></td>
<td>Tumors: 4 Vascular: 3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Encephalomalacia: 5 Normal: 2</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Palmini (21)</td>
<td>Gliosis: 5</td>
<td>8</td>
<td>Temporal lobectomy</td>
<td>2 (25%)</td>
<td>5 (62%)</td>
<td></td>
</tr>
<tr>
<td>Salanova (35)</td>
<td>Variety</td>
<td>37</td>
<td>Partial or total occipital lobectomy, guided by ECoG: 32</td>
<td>17 (46%)</td>
<td>8 (22%)</td>
<td>12 (32%)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Temporal lobectomy: 5 Invasive monitoring: 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish (19)</td>
<td>Unspecified</td>
<td>2</td>
<td>All underwent Atl + ECoG, 1 with dual pathology</td>
<td></td>
<td>2 (100%)</td>
<td></td>
</tr>
<tr>
<td>Hong (8)</td>
<td>Normal MR, unspecified</td>
<td>7</td>
<td>Corticectomy: Invasive EEG, ECoG, and mapping in some cases</td>
<td>4 (57%)</td>
<td>2 (29%)</td>
<td>1 (14%)</td>
</tr>
</tbody>
</table>
resection. Postresection ECoG was performed in four patients, two of whom (50%) were found to have persistent spikes that were not pursued. Despite this, all patients postoperatively were in Engel Class I or II, leading to the conclusion that lesionectomy alone results in excellent seizure control, while avoiding neurologic morbidity associated with resection of abnormal spike activity.

Salanova et al. (32) examined 79 patients retrospectively. They resected the lesion, if present (65/79), electrically abnormal tissue by ECoG (63/79), and tissue that reproduced the patient's aura upon stimulation. Postresection ECoG showed 43% of patients had residual spiking, which was not resected. Patients with reduced or absent postresection spiking had a better chance of having a Class I or Class II outcome (77%) compared with those who had persistent spiking (39%). Patients in this study had an overall seizure-free rate of 46%, but this includes cases before the advent of long-term EEG monitoring or MRI.

Williamson et al. (30) used implanted subdural grids in six patients with known parietal lesions in whom seizure localization was difficult, but was only able to localize the focus in one. Despite this, lesion removal resulted in the cessation of seizures in all six patients. In three patients who underwent callosotomy or temporal lobectomy rather than lesionectomy, results were poor. Two of these patients underwent subsequent lesionectomy, and both patients became seizure-free. Thus, lesionectomy resulted in the best chance of seizure freedom (91% of cases).

Occipital Lobe Epilepsies

Several surgical techniques have been reported for patients with intractable epilepsy, with or without lesions, and an occipital focus. Most of these cases were associated with a lesion, often developmental. In some cases, the seizure origin was unclear, and invasive monitoring was pursued. Surgical strategies included partial or total occipital lobectomy, lesionectomy, and temporal lobectomy. The latter has been attempted in order to transect seizure pathways while preserving visual function. Overall seizure freedom rates ranged from 25% to 91% (Table 5).

Subdural monitoring has been reported by several investigators (21,31,33–35). Most of these describe patients who have structural lesions on neuroimaging but unclear seizure onset. Invasive recordings localized occipital ictal onsets in 38% to 100% of cases (21,31,34). In some patients, invasive monitoring localized occipital ictal onsets in cases when the EEG localization of the seizure focus was unclear (34). In other patients, invasive monitoring showed significant involvement of the temporal lobe at ictal onset (21,35), but pursuing temporal lobectomy alone in these patients resulted in few successes (20–25% seizure-free).

Lesionectomy or occipital lobectomy alone was reported in several studies. Outcome for these patients was fair, with seizure freedom in 47% to 67% (31,33,35). Aykut-Bingol et al. (31) found no difference in seizure outcome based on any factor except pathology. Tumor patients undergoing resection had a 77% chance of becoming seizure-free compared with 46% for all lesions. Other groups included electrically abnormal tissue in the resection in addition to any structurally abnormal tissue. Seizure freedom in these cases ranged from 32% to 91% (34,36). Salanova et al. (35) found that 67% of patients with lesionectomy, and 53% of patients with no residual ECoG spikes after resection, became seizure-free.

Thus, for parietal and occipital lobe intractable epilepsy, no clear surgical strategy emerges for all cases. Invasive monitoring was useful for localizing seizure onsets in some patients with unclear foci. Lesionectomy alone was often successful,
<table>
<thead>
<tr>
<th>Study</th>
<th>Lesion type</th>
<th>n</th>
<th>Surgical technique</th>
<th>Engel I</th>
<th>Engel II</th>
<th>Engel III-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirkpatrick (18)</td>
<td>Tumor: 5 temporal</td>
<td>5</td>
<td>Temporal lobectomy, including hippocampus</td>
<td>4 (80%)</td>
<td></td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Clusman (17)</td>
<td>Developmental: 7</td>
<td>27</td>
<td>Lesionectomy + mesial structures</td>
<td>19 (70%)</td>
<td>1 (4%)</td>
<td>7 (26%)</td>
</tr>
<tr>
<td></td>
<td>Tumors: 2</td>
<td></td>
<td></td>
<td>Class I</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Other: 18</td>
<td></td>
<td></td>
<td>and II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jorge (16)</td>
<td>Tumor: 2</td>
<td>2</td>
<td>Lesionectomy</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td></td>
</tr>
<tr>
<td>Fish (19)</td>
<td>Tumor: 1</td>
<td>7</td>
<td>All underwent Atl + ECoG</td>
<td>1 (14%)</td>
<td></td>
<td>6 (86%)</td>
</tr>
<tr>
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<td>Vascular: 2</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td>Alsaadi (41)</td>
<td>Developmental: 3</td>
<td>15</td>
<td>Temporal resection, Invasive EEG in 8/7</td>
<td>13 (81%)</td>
<td>2 (13%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular: 2</td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td>Other: 1</td>
<td></td>
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</tr>
<tr>
<td>Li (39)</td>
<td>Developmental: 15</td>
<td>41</td>
<td>Lesionectomy: 16</td>
<td>2 (12%), 2 (20%),</td>
<td>3 (19%), 1 (10%),</td>
<td>11 (69%)</td>
</tr>
<tr>
<td></td>
<td>Tumors: 10</td>
<td></td>
<td>Mesial resection: 10</td>
<td>12 (80%)</td>
<td>1 (7%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td></td>
<td>Vascular: 5</td>
<td></td>
<td>Lesionectomy + mesial resection: 15</td>
<td></td>
<td></td>
<td>2 (13%)</td>
</tr>
<tr>
<td></td>
<td>Encephalomalacia: 8</td>
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</table>
particularly for parietal lobe lesions and tumors. Patients who underwent ECoG generally had better outcomes if abnormal spiking was reduced or absent after the resection. Pursuing temporal lobectomy alone in patients with occipital foci generally yielded less favorable results.

Dual Pathology

Dual pathology is the syndrome of a lateral temporal or extratemporal lesion with concomitant MTS. MTS is usually ipsilateral to the lesion, especially with temporal lobe lesions, but may also occur contralateral to the abnormality. The lesion type is often developmental, or gliotic lesions (37–39). The causative relationship has not been established between lesions and MTS. In one series, the incidence of MTS in patients with temporal lesions was 38% (24/63) (22). Patients with atrophic lesions (encephalomalacia and cortical scars) were most likely to have dual pathology (9/11 patients). Berger et al. (40) found a mesial temporal focus in 26 of the 29 temporal lobe tumors they studied, with an additional lateral focus in 15. The tumor was resected as were any ECoG abnormalities, unless functional cortex was involved. The overall Class I outcome was 91% (unsorted, included tumors from frontal and parietal lobes with no mesial temporal involvement).

Surgical strategies include resection of the extramesial lesion alone, resecting the sclerotic mesial temporal lobe alone, or resecting both. Several studies address this issue, but differ on the diagnostic approach to the seizure focus. Some groups use invasive monitoring in all patients, while others reserve this for those who do not have characteristic mesial temporal lobe seizure semiology and EEG findings. Not surprisingly, results vary widely as well.

Resecting the mesial temporal lobe structures alone is one approach, with seizure-free outcome in 14% to 81% (Table 6) (18,19,39,40). Alsaadi et al. (41) reported 15 patients’ extratemporal lesions (nontumoral) and seizure semiology characteristic of MTL epilepsy. Nine patients had MRI findings of MTS. Anterior temporal lobectomy was performed in 14 and selective amygdalohippocampectomy in one patient. Eighty-seven percent (13/15) became Engel Class I. All had pathologic abnormalities of the mesial temporal lobe: eight had MTS, and seven exhibited gliosis but no neuronal loss. No resection was performed on the extratemporal lesions. Other groups report less favorable results when the lesion was not pursued. Li et al. (39) reviewed 38 patients who had undergone 41 operations in all lobes, and found Engel I outcome in 80% of patients who had undergone lesionectomy and hippocampal resection, versus 20% of those of hippocampal resection alone, and 12.5% of lesionectomy alone (significantly different).

CONCLUSION

In summary, no clear surgical strategy fits every case of neocortical epilepsy. Outcome depends on many factors, including the presence and pathology of a lesion, the location of the seizure focus, and the relationship to functional cortex. As neuroimaging techniques improve, the number of cryptogenic declines, and increasingly subtle lesions are identified. Strategies to improve outcomes include the use of ECoG and invasive monitoring to both identify the seizure focus as well as adjacent functional cortex. Although no single surgical strategy emerges from the literature as ideal for every patient, as imaging and recording techniques improve, more tools are available to the neurosurgeon to tailor the best strategy for each individual patient.
REFERENCES

Chapter IX-27
Are Multiple Subpial Transections Effective and Useful?

Chapter IX-27a: Multiple Subpial Transections: A Review and Arguments for Use

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Vertis Neuroscience Inc., Seattle, Washington, U.S.A.

HISTORY

In 1989, Morrell et al. (1) described the technique of multiple subpial transection (MST) for treating epilepsy arising from cortex considered nonresectable by virtue of the underlying neurological function served. Since that time the technique has been adopted by numerous surgeons worldwide with varying results. MST has also been applied to a non-epileptic disorder, Landau–Kleffner syndrome, with good results (2). It is now considered a surgical option for highly selective cases of medically refractory epilepsy for which no other option exists. How best to apply this technique and in what cases should this technique be considered are issues that remain controversial.

RATIONALE

The rationale for MST is based on the following facts and suppositions: (i) The basic cortical unit of data analysis is organized into groups of neurons with columnar orientation. By this, it is meant that the major input–output connections to this basic cortical unit are via axons projecting to and from subcortical structures, such as thalamus. (ii) Although the exact mechanisms responsible for cortical epileptogenicity are not completely understood, it is clear that a certain degree of synchrony must
exist between cortical neurons to trigger the transition from the interictal state to the ictal state. Based on data from the penicillin model of epilepsy, Morrell believed that much of this synchrony relies on lateral radiating cortical–cortical interneuronal projections and that 1 cm² of cortex represented the minimal critical mass necessary to sustain development of the hallmark of epilepsy, the electrocorticographic epileptic spike. Based on these two key observations, Morrell reasoned it should be theoretically possible to either abolish or severely weaken focal cortical epileptogenicity by severing these lateral fiber connections without damaging the actual input–output data flow to the basic cortical computational unit.

Morrell and Whisler developed a technique wherein a right-angled blunt dissector is inserted through a small pial hole at the side of the gyrus and slid perpendicular to the gyrus long axis across the gyrus crown for a depth of 5–7 mm (see illustration in Ref. 1). Parallel cuts at 5-mm intervals are then made along the long axis of the gyrus like rungs on a ladder. These cuts effectively disrupt all interneuronal connections flowing along the long axis of the gyrus crown while preserving cortical–subcortical connections. These cuts however, would not theoretically disrupt connections made via cortical “U” fibers. (The relative contribution of such U-fibers in the propagation of ictal activity is not known for certain.) Morrell named this technique “multiple subpial transection.” Since Morrell’s initial report, the studies of Sugiyama et al. (3) on laboratory animals demonstrated that the technique does, in fact, limit intracortical spread of interictal epileptogenic activity (4). The technique, however, may not disrupt side-to-side interneuronal connections that parallel the transections.

**SURGICAL TECHNIQUE**

Morrell and Whisler’s technique is to insert a right-angled blunt dissector through a small pial hole at the side of the gyrus and then slide the instrument across the crown of the gyrus perpendicular to its long axis for a depth of 5–7 mm until the edge of the transector abuts the opposite sulcal bank. In so doing, all the intraneuronal intracortical fibers crossing this path are severed. This process is repeated, making parallel cuts at 5-mm intervals along the long axis of the gyrus like rungs on a ladder. Morrell pointed the tip of the instrument toward the pial surface.

Morrell’s basic technique leaves behind a modest degree of cortical damage. To minimize this damage Wyler designed an instrument with a blade substituted for the rounded, blunt edge of a right-angled dissector (5). In addition, Wyler suggested that in direct contrast to Morrell’s technique of pointing the instrument tip toward the pial surface, the tip should be directed away from the pial surface, thus allowing the blunt edge of the dissector to be directly under the pia. This, he felt, was safer and resulted in less subpial tearing and small vessel hemorrhage. AD-Tech Inc. (Racine, Wisconsin, U.S.A.) now provides this tool to neurosurgeons. This modification to the technique is not only safer but makes instrument manipulation ergonomically easier.

**Literature**

Numerous small series have been published since Morrell’s first description of the technique and these can be found with a computer search of any of a number of databases. They will not be summarized in this chapter. For a variety of reasons stated in the next sections, an evaluation of this literature is problematic. Rather than systematically reviewing individual reports, it is best to summarize the published results with the retrospective analysis of Spencer et al. (6). She collected
data from six major epilepsy centers performing MST. A meta-analysis was carried out to help define the indications and outcome, and to assess the results of the procedure. Overall, data on 211 patients were received that covered preoperative evaluation, procedures, seizure types and frequencies before and after surgery, postoperative deficits, and demographic information. Fifty-three patients underwent MST without resection. The remaining 158 patients had a combination of MST plus some resection. In patients with MST plus resection, excellent outcome (>95% reduction in seizure frequency) was obtained in 87% of patients for generalized seizures, 68% for complex partial seizures, and 68% for simple partial seizures. For the patients who underwent MST without resection, the rate of excellent outcome was only slightly lower, at 71% for generalized, 62% for complex partial, and 63% for simple partial seizures. Electroencephalography (EEG) localization, age at epilepsy onset, duration of epilepsy, and location of MST were not significant predictors of outcome for any kinds of seizures after MST, with or without resection. New neurologic deficits were found in 47 patients overall, comparable in MST with resection (23%) or without (19%). These preliminary results suggest that MST has efficacy by itself, with minimal neurologic compromise, for cases in which resective surgery cannot be used to treat uncontrolled epilepsy. MST should be investigated as a stand-alone procedure to allow further development of criteria and predictive factors for outcome.

Thus, it appears that the efficacy of MST is no longer in question.

Result Variability

Success rates from various reports vary considerably and this inconsistency results, in part, to the MST technique not being standardized. Different surgeons perform the technique differently. Some differences are minor and probably contribute little to result differences between case series. However, other differences are substantial and influence outcome greatly. These technical differences have not been objectively compared to one another, thereby preventing the choice of any rational preference.

Intertransection Distance

The choice of spacing between transections (cuts) has varied between 2 and 5 mm intervals depending upon the surgeon. In addition, some surgeons tailor intertransection interval based on acute intraoperative electrocorticography (ECoG), making additional transections between 5-mm spaced cuts until spiking disappears from the area of concern (7).

Crown vs. Entire Gyrus

Whereas some surgeons follow Morrell’s original technique and transect only the superficial surface of the gyrus, others have extended the cuts down the sides to the depths of the sulcus.

Defining the MST Area

The extent and location of the “focus”—the boundaries of cortex thought to be involved in epileptogenesis, and hence the subject of MST—has been defined differently from surgeon to surgeon. The approach I have always taken is to implant a 64-channel subdural grid electrode centered over the area of suspected epileptogenicity for long-term (days) recording of spontaneous ictal events. The “focus” is then defined as that cortex from which seizures
appear to originate. The school of thought here is that recordings that document the regions from which ictal events arise are more accurate than interictal recordings—especially acute interictal ECoG recordings—for defining the actual regions of epileptogenesis. This presumption is based on the fact that interictal epileptiform spikes are projected events and therefore can be present over much larger cortical areas than are actually responsible for the initiation of seizures. Thus, if one surgically treats all cortex from which spikes can be recorded, one will treat more than is necessary, which may have negative effects when dealing with resection. More to the point, if one is treating areas to which spikes are projected, they may be ignoring the sites from which the epilepsy originates. Obviously, this controversy has not been settled.

In contrast, some surgeons prefer to “tailor” MST areas based on the presence of epileptiform spiking recorded during acute ECoG during a craniotomy localized solely on scalp recording. Such an approach may be fairly accurate if the suspected focus is correlative with a discrete magnetic resonance imaging (MRI)-defined anatomical lesion known to be potentially epileptogenic, but without a lesion to help locate the focus, interictal recordings alone can be misleading.

**Sylvian Fissure**

In this author’s experience, cortical areas most commonly subjected to MST are immediately adjacent to the sylvian fissure. This is especially true for cases of Landau–Kleffner syndrome. In many cases it is very likely that whatever process was responsible for creating the epileptogenicity of the affected cortex (often times focal ischemia) has included, to a varying extent, cortex within the sylvian fissure. Ignoring the possible contribution of sylvian cortex to the focus is likely to generate a poorer result. The problems, however, are obvious: identifying if and how much sylvian involvement is problematic. Even more problematic is applying MST to this cortex.

For patients with a high likelihood of the pathology extending into the sylvian fissure—such as cases of Landau–Kleffner syndrome—I have relied on magnetoencephalography (MEG) to identify dipoles extending into the depths of the fissure. If it appears that the spikes are originating within the fissure, I expand my area of MST into the corresponding gyri. The technique for applying MST to the fissure is difficult. I have attempted to split the fissure for exposure, but have ended up using the MST tool blindly, pushing it along the pial surface to a depth in the fissure of no more than 2 cm.

**Resection Plus MST**

A major confounding variable in estimating MST efficacy for treating focal epilepsy is that many series have combined cases of MST alone with cases of MST plus focal resection. The resulting problem is obvious: one does not know if a good result is due to the MST, the resection, or a combination of both. Likewise, a failure does not condemn MST as a technique.

**Indication for Surgery**

Very few series have comparable patient mixes since the indications for applying MST are not as clear, for example, as those for temporal lobectomy. This author had applied MST most often for cases of epilepsy with foci in the immediate suprasylvian areas, i.e., those areas serving primary motor and speech function. On the other extreme, Patil et al. (7) applied this technique bilaterally for patients with Lennox–Gastaut syndrome. Quite often MST has been used in addition to resection for tumor
near, but with epileptogenic zones intending into, primary speech and motor areas. As mentioned previously, MST has also been applied to Landau–Kleffner patients.

**SUMMARY**

MST is a surgical technique that has proven merit as an option for (i) patients with epileptic foci within regions of nonresectable cortex who otherwise are not considered candidates for traditional focal resection, and (ii) patients with Landau–Kleffner syndrome who have not responded to more conservative medical options. The problem with evaluating the MST literature is the lack of standardization of actual technique, indications for treatment, and delineating the confines of the cortical area to treat. It is, in part, because of these disparate results that some surgeons believe that the technique should not be considered as a surgical option (see Ojemann, Chapter IX-27b). On the other hand, a meta-analysis of several centers actively using MST has demonstrated a very convincing effect. Thus, before condemning MST, I believe several issues need to be considered.

Those patients for whom MST is the sole surgical option (i.e., with no resectable lesion) usually have epileptogenic foci in extratemporal neocortex (most often frontal and/or parietal lobe). Results of extratemporal neocortical nonlesional resection for epilepsy are poorer than those reported by Spencer et al. for MST alone. Therefore, unless one is prepared to condemn all extratemporal neocortical nonlesional resections, one should not condemn MST. In fact, the results reported by Spencer are fairly good when compared with all other nonmesial temporal lobe epilepsy surgery, particularly since they represent an average of all reporting centers, good or bad. Like any surgical procedure still in its infancy, the more we learn about it, the better we can apply the technique to optimize outcomes. One only needs to look at the literature surrounding temporal lobectomy in the 1970s to discover how much we have progressed since then. Not only can we now more accurately preoperatively identify patients likely to have a good surgical outcome, we can identify patients who should not be operated upon. The surgical workup of patients with MRI identified mesial temporal sclerosis has become much more standardized. This, in turn, has resulted in a standardization of the surgical approach and most surgeons now conduct anterior temporal lobectomy under general anesthesia. With this standardization has come an improvement in surgical outcome: fewer neurologic sequelae and improved seizure outcomes. One can only assume that the same phenomenon will occur if rationale improvements are made in the application of MST rather than rejecting the technique based on emotional distrust.

Some of the most impressive results are from those patients treated for Landau–Kleffner syndrome. Many such patients have shown dramatic improvements that were unlikely to have occurred had they not received surgery. Moreover, speech is a neurologic function extremely sensitive to surgical trauma. The return of speech from a previously dysfunctional region of cortex subjected to MST is very impressive and seems to confirm the basic rationale upon which this technique was founded.

I can think of no other surgical treatment for epilepsy that is as well suited to systematic study in the laboratory. To ignore this opportunity to perfect a technique (and in the process possibly learn something of the basic mechanisms of epileptogenic propagation) that may provide options to patients otherwise deemed inoperable with traditional surgery does not make much sense to me. It is akin to the overused expression of throwing the baby out with the bath water.
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Chapter IX-27b: Multiple Subpial Transections Are Not Effective or Useful

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It has now been 14 years since Morrell (1) presented epilepsy cases thought to have foci in functionally important cortex that were treated with his innovative technique of multiple subpial transections (MST). That function can often be preserved with MST has been reasonably well demonstrated. Unfortunately, the effectiveness of this procedure in controlling seizures in patients with medically refractory epilepsy has not been demonstrated. The recent meta-analysis of outcomes with this procedure cited by Wyler in Chapter IX-27a as evidence for efficacy, illustrates the problems (2). The analysis is based on 211 cases collected from six centers. It has all of the defects with such pooled data discussed in the chapter on outcomes with temporal resections (Section XIV), including uncertainty as to how the follow-up data was acquired, the follow-up duration, and use of an outcome measure that defines “excellent” as a 95% reduction in monthly seizure frequency, with no seizure-free category. Indeed, data are only presented by seizure type; no information on how many, if any,
patients are free of all seizures is presented. Yet seizure-free outcomes are the usual standard for resective epilepsy surgery, and seizure-free outcomes are closely related to significant impacts on quality of life.

In the meta-analysis, in 155 of the 211 cases, MST was combined with resections. What, if anything, the MST added to the effects of the resection is unknown. Resecting only a portion of a focus, or only sites of early spread can occasionally control seizures. For example, in a series of 15 cases with seizure onsets in Rolandic cortex based on subdural grid recording, resection of the sites of early spread in premotor or postcentral areas resulted in 40% seizure-free at a minimum of three years of follow-up (average four years) (3). This is a setting where MST is often applied to the Rolandic focus, in addition to pre- and postcentral resections. It is this kind of mixed case that represents most of the “MST” outcomes, where the contribution of MST cannot be determined. The meta-analysis also does not indicate the distribution of cases by pathophysiology, other than the comment that there was a “tendency for remarkably better response in patients with developmental, tumor, or perinatal etiologies.” What makes this issue important is the use of MST in the Landau–Kleffner syndrome. These are not patients with refractory seizures. However, this is one of the few situations where MST is regularly used alone. It is doubtful that any conclusions about efficacy of MST alone based on Landau–Kleffner cases can be generalized to patients with refractory partial epilepsy.

The use of MST without resections in patients with refractory partial epilepsies is a therapy that needs to be subjected to rigorous evaluation as to efficacy, preferably in a clearly defined population such as cases with seizure onsets in hand motor cortex, in a case-controlled or better yet, a randomized study. In the author’s view, resources for randomized studies of epilepsy surgery should be directed to therapies such as MST, rather than “proving” the efficacy of temporal lobe resective surgery. At present MST is not a substitute for resection, when that can be done with a low risk of functional deficit.

There are, in fact, only a very few areas that cannot be resected because of unacceptable functional deficits: hand and leg motor cortex in either hemisphere, face motor cortex in the dominant hemisphere, and perisylvian sites essential for language in that patient based on electrical stimulation mapping. Thus a focus in anatomically defined Broca or Wernicke area does not preclude resection, only if the focus involves the essential language sites for that individual as identified by mapping (4). Limited resections can even be done in hand and leg motor cortex, although there will be a postoperative deficit that takes some months to clear. Non-dominant face motor cortex can usually be resected without deficit (5). Whether MST, in the few areas that cannot be resected because of functional risk, is of benefit remains to be demonstrated.

REFERENCES


Chapter IX-28
What Is the Best Way to Resect Lesions?

Chapter IX-28a: Lesionectomy Is Often Adequate for Neocortical Epilepsy

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Computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET) have increased our diagnostic resolution, selecting more patients with focal lesions amenable to surgical therapy. Different resection strategies have been promoted for dealing with epileptogenic MRI positive lesions. Resection of the lesion and the surrounding epileptogenic cortex may be carried out by a conventional neurosurgical approach or by stereotactic extirpation of the lesion. The nature of the underlying pathology, the completeness of resection of the structural lesion, and the extent of the removal of the electrophysiologically defined associated epileptic tissue may affect the surgical outcome in lesional epilepsy surgery. The relative contributions of these factors and their interactions are difficult to delineate. Moreover, the outcome results from the published series are difficult to compare because of different methods of patient selection, pathological classification, surgical technique, and follow-up.

We have previously proposed a substrate classification (pathology plus anatomical localization) to provide a practical dissection of the localization related epilepsies (1). The primary categories include: (i) medial temporal sclerosis, (ii) neoplasms, (iii) developmental abnormalities, (iv) vascular disorders, and (v) nonspecific gliosis. The anatomical location of each of the above pathologies helps to define clinical semiology since the unique topography of the lesion in various cerebral compartments allows recruitment of special groups of neural networks involved in expression of the clinical seizures. Therefore, both pathology and location are critical in understanding the pathophysiology and design of an appropriate treatment.
The goal of neuro-oncological/epilepsy surgery is maximal resection of the tumor and seizure initiation zone while preserving function. If preoperative data are concordant, our approach has been to resect the tumor to histopathologically proven clear margins. If the tumor is adjacent to functional brain, adults often tolerate an awake craniotomy during which the tumor is again resected to clear margins. Awake craniotomy allows functional cortical stimulation mapping and continuous intraoperative neurological monitoring to safely maximize resection. If children and adults are unable to cooperate with an awake craniotomy, subdural grids may be placed followed by extraoperative studies to map seizure onset and functional cortex prior to resection during a second surgery. This approach also allows preservation of function during tumor resection and both operations may be carried out under general anesthesia. This approach has been summarized in Figure 1. In some instances when primary sensorimotor cortex is the functional

**Figure 1** Our approach in the surgical treatment of a patient with an epileptogenic mass lesion.
region to be preserved, intraoperative stimulation or evoked potentials under light general anesthesia may suffice.

NEOPLASMS

The most common space-occupying abnormalities found in patients with intractable epilepsy are gliomas and vascular lesions. Although most of the tumors have a low propensity for growth, malignant lesions may be found. The association between the tumor and its epileptogenic focus is complex and poorly understood (2–4). Various hypotheses have been developed to describe this association. The lesion may induce neuronal injury and neurotransmitter changes in the tumor-infiltrated tissue or the surrounding cortex promoting epileptogenesis (5). The dual pathology model proposes the existence of a second structural pathology such as medial temporal lobe sclerosis in addition to the lesion, with both contributing to the generation of epileptic network. The presence of dual pathology may explain failures following removal of the lesion alone.

Four main approaches have developed in resection of epileptogenic lesions: lesionectomy alone, variable resection of the lesion and surrounding presumed epileptogenic cortical tissue, resection of the lesion and a presumed distant seizure focus, and resection of an electrophysiologically abnormal region without resecting the lesion (6). Potential epileptogenicity of the cortex may be defined based on an intraoperative preresection or postresection electrocorticography (ECoG) mapping or an extraoperative intracranial study that records spontaneous seizures. Lesionectomy may be guided by various techniques including stereotactic imaging, visual inspection, or histopathological examination of the resection margins. There is no well-controlled studies to adequately compare the efficacy of the above techniques.

Retrospective studies have demonstrated that resection of the lesion alone is efficacious in providing seizure freedom in 60% to 80% of the patients (4,7,8). In this approach, the anatomical connections between the lesion and the surrounding cortex are disrupted. The results may be improved if the associated epileptogenic tissue is resected in patients with arteriovenous malformations where there may be broad ischemic or hemorrhagic injury (9). In a study by Tran et al. (10), 36 patients who underwent resection of their tumor only based on histopathologically clear margins were studied. In their study, spike distribution and discharge rate on preresection ECoG in the cortex around the tumor did not significantly correlate with seizure outcome. However, there was a trend toward a relationship between postresection spikes and seizure recurrence. In another study by Boon et al. (3), 83% of the patients who underwent resection to tumor-free margins were rendered seizure-free. Overall, there is compelling evidence to support efficacy of lesional resection to histopathologically clear margins in providing seizure freedom (2,4).

The significance of preresection ECoG abnormalities remains controversial. Some studies report efficacy of lesionectomy alone while others recommend additional tailored cortical excision based on ECoG (8,10–16). Other studies have demonstrated the efficacy of complete lesional excision regardless of the extent of cortical excision (2). Postresection ECoG findings may be misleading as surgical irritation of the neocortex may produce reactive postresection epileptogenic discharges adjacent to an intra-axial tumor even in the absence of preoperative seizures (17). Using intraoperative ECoG to guide surgery may lead to removing more functional brain than necessary or even incomplete tumor resection.
TEMPORAL LOBE TUMORS

In temporal lobe epilepsy, intracranial recordings are helpful in determining if the medial structures adjacent to a lesion should be resected as part of the lesionectomy to improve seizure outcome. We have employed the following paradigm to maximize preservation of functionally intact medial structures in the treatment of epileptogenic medial and lateral temporal lobe tumors. In the dominant hemisphere, if a tumor is separable on MRI from medial structures and verbal memory is intact with a normal size hippocampus, the tumor is resected while preserving the medial structures. If the verbal memory is decreased greater than two standard deviations on selective reminding tests and the tumor is adjacent to or infiltrating the medial structures, then hippocampus, amygdala, and parahippocampal gyrus are also resected. If the tumor infiltrates the medial structures with normal verbal memory, then resective surgery is not offered and close clinical and radiological follow-up is instituted or stereotactic biopsy may be performed if diagnosis or tumor grade is questioned. If the tumor is in the lateral temporal lobe and quite separable from a normal size hippocampus and other functional measures suggest medial seizure onset with borderline verbal memory, intracranial monitoring is pursued to accurately localize the epileptogenic tissue.

In the nondominant hemisphere, medial structures are removed despite a normal size hippocampus and intact visual/spatial memory if the tumor is adjacent to or infiltrating the hippocampus. Separable tumors from the hippocampus in patients with normal visual/spatial memory are resected to pathologically proven clear margins, leaving the medial structures intact. The medial structures are always removed in patients with decreased visual memory and hippocampal atrophy whose tumors are adjacent to the medial structures. Finally, for both dominant and nondominant temporal lobes, if the hippocampus is small and memory is borderline, but the tumor is lateral, an intracranial study may answer the question regarding the presence of dual pathology.

MALFORMATIONS OF CORTICAL DEVELOPMENT

If neuroimaging is unable to differentiate a developmental substrate from a neoplasm, a comprehensive epilepsy evaluation is once again completed. However, instead of planning a resection with concordant data, these patients undergo frameless stereotactic biopsy to establish the pathology. If a developmental substrate is confirmed, further intracranial monitoring is instituted prior to resection (Fig. 1). It has been our experience that patients with developmental abnormalities often have epileptogenic zones which may extend beyond the MRI abnormality. Resection of certain well-delineated developmental substrates to histopathologically clear margins may also be a reasonable approach to therapy. These may include grade III cortical dysplasia of Taylor focal cortical dysplasia (FCD) and hamartomas.

ECoG may be useful in tailoring resection for FCD due to continuous ictal-like interictal epileptiform discharges found on ECoG in the majority of patients harboring this abnormality (18–21). However, at least two studies have noted a lack of correlation between the extent of cortical resection, solely based on the presence of intraoperative ECoG spiking, and seizure control outcome in patients with different forms of focal neuronal migration disorders including FCD (21,22).
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Chapter IX-28b: Lesionectomies Should Be Tailored Based on Ictal Recording

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OVERVIEW

The goal of epilepsy surgery is to identify and resect (or disconnect) the epileptogenic zone in order to render the patient seizure-free. If the seizures are not medically intractable, epilepsy surgery is unnecessary. When intractable epilepsy is associated with a structural lesion [other than mesial temporal sclerosis (MTS)], epilepsy surgery improves the rate of seizure-free outcome. This has been well documented in several studies and was the subject of a meta-analysis as well (1). Furthermore, lesion-associated epilepsy (LAE) surgery tends to have better outcomes than does nonlesional epilepsy surgery, particularly when the epilepsy arises in neocortex (2). However, demonstration of a lesion does not prove that the patient has epilepsy or that the lesion is the cause of epilepsy. The location of the lesion does not necessarily delineate the location of the epileptogenic cortical zone. Epilepsy does not arise from the lesion; it arises from the brain. A lesion may irritate or injure cortex locally or at some distance from the margins of the lesion (i.e., “dual pathology”) (3,4).

Strategies for intractable LAE include lesionectomy alone, use of intraoperative electrocorticography (ECoG), and placement of intracranial electrodes for extracranial ECoG monitoring. Although intraoperative ECoG has been shown to have some value for defining the extent of allocortical (i.e., hippocampal) resection needed to eradicate seizures, the role of ECoG in neocortical epilepsy surgery is significantly more limited (5). In general, the more complete the resection of the epileptogenic cortex, the better the seizure outcome. Awad et al. (1) showed that 79% of patients evaluated were seizure-free after complete resection of the epileptogenic cortex, whereas only 52% were seizure-free after partial resection of this region.
Only one of these three available strategies permits localization of the cortical region where the seizures arise.

ADVANTAGES OF INTRACRANIAL ELECTRODE RECORDINGS

Anyone who has reviewed chronic scalp or intracranial electrode monitoring knows that spike populations shift over time and that the location of the interictal activity does not necessarily predict the location of the ictal onsets (6). Clearly, many patients (with or without lesions) have multiple spike populations with variable presence and prominence over time (7). In fact, many patients with focal epilepsy have bilateral interictal spikes. ECoG spikes are rarely limited solely to the region of the lesion. Levesque et al. (8) found that the site of the seizure onset corresponded with the site of the lesion in 10 of 44 patients studied. The most common site of “separated” epileptogenic cortex is the ipsilateral mesial temporal lobe (4,8–10). Therefore, a brief period of interictal recording, either in the operating room or at the bedside, can be tremendously misleading. To verify this sentiment, simply review the ECoG from a patient with intracranial electrodes in place on several different days. Then ask: If the surgical resection had been based on the interictal spike population observed over any given 10 to 20 minute epoch, would that resection be the same as the resection based on the ictal onsets?

Performing a craniotomy for electrode placement allows the surgeon to obtain tissue for histopathology. Relying on frozen section determination is notoriously inadequate. Lesions such as cortical dysplasia and low-grade gliomas cannot be discriminated with certainty without permanent histology with immunohistochemical verification. Therefore, when tissue is obtained at the first craniotomy, the surgeon can know whether or not the lesion needs to be removed (i.e., it is a tumor) in addition to knowing the precise location of the epileptogenic zone. Additionally, the surgeon can counsel the patient on the pathology (treatment options, prognosis, and impact of resection) prior to resection. The risks of the planned resection can be discussed with the patient prior to surgery, unlike intraoperative ECoG, which forces the surgeon to make the decisions without informed patient consent (because the specific resection plan is unknown prior to surgery).

When performing ECoG in the operating room, the electrocorticogram is altered by whatever anesthetics have been given (11). For awake cases, this is usually residual propofol; for cases performed under general anesthesia, there are many agents that impact the electrocorticogram. Intracranial electrodes allow chronic recording during sleep and waking periods, free of anesthetic influence. Furthermore, when cortical stimulation mapping is planned, this can be done with adequate anticonvulsant levels to help prevent seizures, and can be repeated if necessary. This is imperative for patients who are not good candidates for awake surgery (cognitively impaired, sleep apnea, airway problems, and large mass lesions).

CONCLUSIONS

Although intraoperative ECoG requires a single operation, rather than two (for electrode placement followed by electrode removal and resection), intracranial electrodes provide significantly better information regarding pathology and location
of epileptogenic cortex. Accurate knowledge of lesion pathology often alters the surgical plan. Knowing the risks of surgery (the location of the epileptogenic cortex in relation to important functional cortex, whether or not multiple subpial transections will be needed) and having the opportunity to include the patient and family in resection strategy decision making, with respect to risks, goals, and options, provide significant advantages for the patient, the surgeon, and the entire epilepsy team.

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Section X
Corpus Callosotomy: Indications, Surgical Procedures, and Outcomes

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INTRODUCTION

The corpus callosum consists of 180 million axons and is the largest and most significant neural commissure (1). Its broad-reaching interconnections afford epileptic discharges rapid access to the contralateral hemisphere, setting the stage for generalized seizures. Erickson was the first to demonstrate this principle, in 1940, by recording discharges induced by stimulating the contralateral cortex in the monkey (2). The physiological basis for dividing the callosum, therefore, lies in the opportunity to arrest the propagation of epileptic discharges from one hemisphere to the other. While Dandy (3) had described division of the callosum to gain access to third ventricular lesions in the early 1920s, surgical division of the corpus callosum for the treatment of seizures was first introduced by Van Wagenen and Herren (4), who trained under Harvey Cushing. Early attempts at commissurotomy were plagued by significant morbidity and mixed seizure outcome. Refinement of the surgical techniques and limitation in the number of structures divided has made this procedure safer and just as effective as multiple commissurotomies (5). With these advances, modern techniques boast improvement in seizure outcome in 60% to 100% of patients (6). This chapter provides a brief overview of the clinical indications, surgical techniques and outcomes of corpus callosotomy in the hope of stimulating future discussions on this controversial procedure.

INDICATIONS

General Considerations

Surgical division of the corpus callosum is a palliative procedure reserved for patients suffering from severe, medically intractable generalized seizures where akinetic seizures,
or “drop attacks,” are a predominant feature. It is generally accepted that primary generalized seizures, and those with rapid secondary generalization, will respond favorably to corpus callosum section. These generalized discharges include major motor seizures, such as tonic–clonic spells, as well as atomic “drop attacks” (4,5,7–17). Drop attacks are often characterized by repeated episodes of bodily injury, such as lacerations, fractures, and head trauma (28).

Neurological diseases characterized by mixed seizures or unilateral brain insult have been shown to respond favorably to callosotomy (29). Examples of these childhood diseases include infantile hemiplegia, Rasmussen’s syndrome, Lennox–Gastaux syndrome, frontal lobe epilepsy, multifocal epilepsy, and other conditions with diffuse primary brain dysmorphism or multifocal acquired pathologies. Infantile hemiplegia presents during early childhood with acute onset of hemiplegia. The etiology may be idiopathic or tied to an inciting event such as cerebrovascular disease, infection, brain injury, or cardiac disease (30). Forme-fruste infantile hemiplegia is similar to infantile hemiplegia, but without obvious hemiplegia, and may also respond well to callosotomy (29). Rasmussen’s syndrome, also known as progressive epileptic hemiplegic encephalopathy, presents in the first decade with progressive mental decline and hemiplegia. Rasmussen’s syndrome is distinguished by severe generalized seizures in concert with unilateral pathology mimicking encephalitis (31,32). Lennox–Gastaux syndrome presents with bilateral dependent and independent discharges with low frequency spike-and-wave complexes (33,34). Patients suffer from diminished mental capacity and sudden seizures occurring as frequently as 100 spells per day. Frontal lobe epilepsy presents with seizures that generalize rapidly, making localization, and even lateralization difficult. Focal or multifocal epilepsy may be an indication for callosotomy when no resectable lesion can be identified. Other uncommon hemispheric pathologies may benefit from callosotomy. For example, patients with large hemispheric lesions from Sturge–Weber syndrome or porencephalic cysts have experienced marked improvement following callosal section (17,18). Finally, patients who possess an atrophic hemisphere, but retain a functional contralateral hand, may be considered for callosotomy rather than hemispherectomy, as this procedure would not worsen any preexisting motor deficits (35).

**Contraindications**

While there are no absolute contraindications to callosotomy, the value of this intervention has been questioned for some patient groups. Patients who are candidates for lesionectomy or lobectomy are generally excluded from consideration because those procedures potentially could lead to becoming seizure-free, which is only infrequently seen following commissurotomy (36). Mental retardation remains a controversial relative contraindication. Poor results have been noted in patients with mental retardation, leading some to hypothesize that significant mental retardation reflects diffuse brain disease that responds poorly to any form of treatment, medical or surgical (8,23,26,29,37). Others have found no relationship between preoperative intelligence quotients and seizure outcome (38–41). Nevertheless, many agree that at the very least, patients should have neurological and intellectual capacity sufficient to allow a reasonable recovery. Finally, mixed or crossed cerebral dominance has been proffered as a relative contraindication. Worsened lateralized cerebral deficits have been noted in patients with crossed dominance, who have speech representation ipsilateral to the dominant hand (23,42).
SURGICAL PROCEDURES

Preoperative Evaluation

In many ways the preoperative evaluation of patients being considered for callosotomy is similar to that for other epilepsy surgeries, with a few special considerations. All patients undergo a thorough review of their seizure history, with emphasis on the medically intractable nature of their seizures despite therapeutic anticonvulsant levels. If present, multiple seizure types and their frequency should be noted. Thorough physical examinations should note any neurological deficits that suggest focal lesions.

Electroencephalography (EEG) plays a central role in preoperative planning. The EEG evaluation must exclude an identifiable, resectable focus as well as confirm generalized seizure activity. The EEG findings may be used to tailor the callosal section. A predominance of posterior epileptiform activity, for instance, may warrant a more extensive anterior partial callosotomy or a selective posterior callosotomy (35). Posterior-dominant discharges may portend a poor prognosis following anterior two-thirds callosotomy (43).

Imaging studies for callosotomy consist of skull radiographs and magnetic resonance imaging (MRI). MRI is essential for detecting structural lesions, and provides the surgeon with valuable preoperative information on the morphology of the callosum. Radiographs should include a true lateral skull film. The imaging studies are reviewed with special attention to the glabella–inion line. A vertical ray drawn perpendicular to, and bisecting, this line intersects the callosum at its two-thirds point (44,45). If frameless stereotactic navigation will be employed during surgery, the appropriate MR sequences will, of course, need to be obtained. Some surgeons advocate obtaining preoperative cerebral angiography to demonstrate prominent bridging veins along the planned approach (21,46). MR venogram, however, may be a sufficient alternative without subjecting the patient to additional invasive tests.

Intraoperative Techniques

A variety of techniques for callosal section have been described over the last 60 years. In their landmark work, Van Wagenen and Herren (4) performed multiple variations of commissurotomy, including partial and complete callosal section, both with and without division of the ipsilateral fornix, through a right frontoparietal craniotomy. Section of the anterior commissure and massa intermedia of the thalamus was also performed at times under the description of total commissurotomy. Bogen and Vogel (11) performed two craniotomies through a single scalp incision that allowed access to the anterior and posterior callosum for complete section. With experience, the number of commissures divided has declined. Modern techniques are limited to division of the corpus callosum, without attempts at sectioning the anterior commissure, massa intermedia of thalamus, or the fornices. Currently, most eligible patients are treated with anterior two-thirds of the callosotomy as described below (35).

Partial Anterior Callosotomy

While the extent of callosal section necessary to achieve adequate seizure control is a matter of continuing debate, partial anterior callosotomy has emerged as the operation of choice at many centers. Patients are maintained on full dose anticonvulsants
to minimize the risk of perioperative status epilepticus. Dexamethasone is administered along with prophylactic antibiotics at the start of the case. The patient may be positioned supine with the neck in neutral position, or in the lateral decubitus position depending on surgeon preference (35). The rationale for the latter maintains that gravity retraction of the dependent hemisphere eliminates the need for manual traction (28). In either instance, the head is positioned unturned in trivalent pin fixation. If the planned incision lies above the heart, Doppler and end-tidal CO₂ monitoring are indicated as venous embolism has resulted in death during callosotomy (28).

The particular skin incision and bone flap are also matters of surgeon preference. For anterior callosotomy, Roberts supports the use of a 9 cm horizontal linear incision made 2 cm anterior to the coronal suture and centered 1.5 cm to the right of midline (35). Through this incision, a 2-in trephination is performed that crosses midline to facilitate the interhemispheric approach. Others prefer larger craniotomies through curvilinear scalp incisions (18,45). This is particularly true if complete callosotomy is being performed (4,11,15,16,47,48). The periosteum is reflected and retracted with the scalp flap using fish hooks or self-retaining retractors. Burr holes may be placed on both sides of the sagittal sinus and connected with the craniotome to turn a free bone flap. Dural tack-up sutures are placed along the edges of the bone window. Brain relaxation is achieved prior to the dural opening with the use of osmotic diuresis, hyperventilation, or lumbar drainage (28,35).

The dura is then incised in a C-shaped fashion and reflected toward the sagittal sinus to be secured with retraction sutures. Dense subdural adhesions are frequently encountered in patients with a significant history of falls. Bridging veins may also be encountered, but with adequate craniotomy exposure, one may work around these without significant interference. Hemostasis is achieved with thrombin-soaked gelatin sponges, oxidized cellulose, gentle pressure, and bipolar electrocautery. Exposure down the right side of the falx is performed under the microscope employing standard microsurgical technique. When necessary, a Greenberg retractor aids in the interhemispheric exposure. Multiple arachnoid adhesions are encountered which require meticulous dissection and coagulation when separating the opposed cingulate gyri. The paired pericallosal arteries herald the arrival at the callosum. Division of the callosum is performed between these arteries using any combination of the irrigating bipolar forceps, ultrasonic aspirator, microsuction, and microdissectors. Callosal division begins at the junction of the posterior genu and anterior body. This allows the surgeon to open the callosum ventrally into the potential space of the cavum septum pellucidum (49). Entry into the ventricular system ensures that the full thickness of the callosum has been sectioned while permitting further cerebrospinal fluid drainage (45). Some surgeons prefer to remain extraventricular, hence, they preserve the bluish ependymal lining along the ventral limit of the callosum (35). The dissection is carried forward around the genu and through the rostrum. The anterior commissure is visualized between the columns of the fornix at the anterior limit of the dissection, but is left intact. Attention is then directed posteriorly, where the dissection is carried through the body of the callosum approximately to the level of the trigone of the lateral ventricle. The posterior limit of the resection is more difficult to estimate. Anatomical references which guide the dissection include the thinning of the posterior callosal body and the appearance of the fornices as they course superiorly, anteriorly, and medially. Intraoperative frameless navigational guidance is quite useful at this stage of the operation (50). Alternatively, a radiopaque clip may be applied along the posterior edge of the resection. In conjunction with an intraoperative lateral skull X ray, this clip will demonstrate whether the glabella–inion bisection ray has been reached, thus predicting that two-thirds of the callosum have been divided (45).
Once the resection is complete, the wound is copiously irrigated to confirm hemostasis. The retractors are withdrawn and the bridging veins are inspected for integrity. The dura is closed with a running 4–0 suture. A dural tack-up suture is brought up through the center of the bone flap to anchor the dura to the inner table. The bone flap is secured with 2–0 sutures or titanium plates and burr hole covers. The galea and scalp are then closed in the usual fashion.

Postoperative care follows standard postcraniotomy protocol. Patients are typically extubated in the operating room and monitored closely in the intensive care unit overnight. Following this, patients may be transferred to the neurosurgical ward where standard seizure precautions are maintained. Full antiepileptics are continued with routine drug level monitoring. A postoperative MRI is obtained to document the degree of callosal division prior to discharge.

**Partial Posterior Callosotomy**

The posterior portion of the callosal section may be performed several months to two years following anterior section for patients who do not experience significant improvement in seizure outcome following the initial procedure (5,25,45,51). This interval is chosen in an attempt to minimize the occurrence of acute disconnection syndrome (51).

Posterior callosotomy is similar to anterior section with some modifications. The patient is positioned supine with the neck flexed 20° to 40° in pin fixation. The head of the bed is elevated 30°, thus providing the surgeon a direct trajectory to the splenium. Roberts advocates a horizontal incision similar to his anterior approach, with this incision 5 cm posterior to the midpoint of the nasion–inion line (35). Others have described a curvilinear incision followed by a paramedian craniotomy extending four fingerbreadths above the lambdoid suture and one fingerbreadth below it (45). Either technique will offer a direct approach to the splenium. Exposure of the callosum itself is facilitated by the posterior falx which extends all the way to the callosum, thereby reducing the number of adhesions between the cingulate gyri. Toward the anterior aspect of this exposure, division of the full thickness of the callosum reveals the velum interpositum. Care must be taken toward the posterior aspect of the exposure, as division of the splenium exposes the arachnoid overlying the vein of Galen. In instances where the cavum vergae is present, the hippocampal commissure may be spared at the time of posterior sectioning, which some have suggested would lessen the adverse effects of callosal sectioning on memory (52,53). The closure and postoperative course are otherwise identical to anterior section.

**Complete Callosotomy**

Occasionally, complete callosal section is performed during a single operation (5,25,26). This has been the case for patients suffering severe, diffuse multifocal pathology who may have a diminished chance of adequate response following anterior section (35). Surgical techniques for complete callosal division combine the two techniques described above.

**New Approaches to Callosotomy**

Several reports have shown the utility of frameless stereotactic guidance to improve surgical accuracy and results for callosotomy as has been the case in other types of
neurosurgical procedures. Rutka et al. (50) have reported on image guidance in 17 patients undergoing partial or complete collosotomy with good results. They concluded that image guidance provided utility in the preoperative planning, e.g., determining side of craniotomy-based three-dimensional reconstruction of venous anatomy, as well as intraoperative determination of extent of resection.

Other techniques under development include use of endoscopy-assisted microsurgery, which may be promising as a minimally invasive technique coupled with image guidance. At the present time clinical studies and outcome data are not available. Another area that may potentially be important is radiosurgery. Presently, only a very small number of patients have been reported in the literature, though all with positive outcomes at 38 months. Future studies will be needed to fully evaluate the efficacy and risks of radiosurgery in these patients considered for callosotomy.

OUTCOMES

Seizure Outcome

Results from corpus callosotomy have been collected on hundreds of patients since its initial description. In Van Wagenen and Herren's original series, 9 of 10 patients experienced significant improvement in seizure outcome (4). Thirty years later, interest in callosotomy was revived by Luessenhop, who reported clinical improvement in three of four patients (15,16). Popularity for callosotomy as a potential treatment for generalized seizures grew as increasing numbers of surgeons gained experience in this procedure and reported their findings. Wilson (26,27) documented substantial improvement in 16 of 20 patients, Geoffroy (14) in six of nine, and Rayport (21) in seven of nine. Engel performed one of the largest seizure outcome analyses by collating data from multiple epilepsy surgery centers. In 563 patients who underwent callosotomy, he found that 7.6% (43 patients) were seizure-free, 60.9% (343 patients) were significantly improved, and 31.4% (177 patients) remained unchanged (36). The low number of seizure-free patients relative to those undergoing temporal lobectomy or lesionectomy underscored the fact that callosal section is a palliative treatment whose goal is not absolute seizure freedom, but reduction in the severity and frequency of devastating drop attacks.

Most patients being considered for callosal section suffer from multiple seizure types. Considering outcome as a function of seizure type, Roberts and Siegel (54) have summarized the Dartmouth experience of 83 patients on whom they collected 10-years of follow-up data. They compared the procedure's efficacy for atonic seizures, major motor seizures, focal motor seizures, and complex partial seizures. Atonic seizures responded most favorably with 72% of patients experiencing significant improvement. This consisted of 51% of patients who became seizure-free and another 21% who experienced greater than 50% reduction in seizure frequency. Spencer and colleagues reported similar findings for atonic seizures in their series of 330 patients undergoing callosotomy: over 70% experienced significant improvement (55). Considering patients with major motor seizures, 34% of Roberts' series were seizure-free and 24% experienced at least 50% reduction in seizure frequency (54). The effect of callosotomy on complex partial seizures was less favorable, but 42% of patients became seizure-free and 20% experienced at least 50% reduction in seizures. Indeed, others have noted some benefit of callosotomy on complex partial seizures (6,20). Focal motor seizures responded least favorably with only 21% of patients seizure-free and 17% with at least 50% reduction in seizure frequency.
Extent of callosal division may also be a variable in determining seizure outcome. Division of the anterior two-thirds of the callosum, for example, is more likely to be successful than division of the anterior one-half (38). Furthermore, an incremental improvement in seizure control follows total callosotomy in some patients who fail to receive significant benefit from anterior callosal section (54,55). In one series, 16 patients with atonic spells underwent a two-staged callosal division. Following anterior callosotomy, 6 of 16 patients (38%) achieved greater than 80% seizure reduction. Following completion of callosotomy, 13 of 16 (81%) achieved this level of seizure reduction (54). Yet, counterexamples are common. Fuiks and colleagues observed that none of their 10 patients who underwent completion of previous anterior callosotomy achieved substantial improvement in seizure outcome above what was seen following the first surgery (28). Completion of a partial callosotomy has greater neuropsychological consequence than partial section alone (56). Until more definitive data become available, a balance must be achieved between optimum seizure control and minimal long-term side effects. Controversy remains on the issue of how much of the callosum to divide.

Variables that apparently do not contribute to seizure outcome include age of seizure onset, mental retardation, episodes of status epilepticus, family histories of seizures, interictal EEG abnormalities, or known seizure etiologies (57).

**Neurological Effects**

Overall, 80% of patients’ families report satisfaction with the surgical result following callosotomy, and 70% report satisfaction with the family’s quality of life (58). But, callosal division is accompanied by neurological side effects. Acute disconnection syndrome, interhemispheric sensory dissociation, and subtle changes in attention and memory have all been described following callosotomy.

Acute disconnection syndrome occurs in the majority of patients in the immediate postoperative period. Characteristic features include transient reduction in spontaneity of speech (occasionally resulting in mutism), left-side apraxia or hemiparesis, bilateral grasp reflexes, bilateral extensor plantar responses, and urinary incontinence (51). The syndrome appears to be multifactorial. Operative retraction on the nondominant parasagittal cortex, including supplementary motor area, and brain edema have been implicated (28,45,59–62). Mutism may be due in part to disruption of commissural fibers originating from rostromedial cortical areas such as the anterior cingulated and supplementary motor area. Symptoms typically improve over several days to weeks leaving few long-lasting effects. It has been suggested that the incidence and severity of this syndrome has diminished since the adoption of the lateral decubitus position for anterior callosotomy (28).

Interhemispheric sensory dissociation invariably follows posterior callosal division (63). This permanent disconnection syndrome is characterized by failure of the ability of the two hemispheres to internally transmit visual or somesthetic information. Classically, this results in the patient’s inability to verbally report information which has been tachystoscopically presented to the visual field opposite the dominant hemisphere (64).

Some patients appear to suffer cognitive sequelae, such as learning and memory deficits. Patients may experience subtle deficits in recall or a more general attentional dysfunction (65,66). This has been attributed to disconnecting two damaged, but interdependent, hippocampal formations during division of the hippocampal commissure, which contains fibers from the presubiculum, entorhinal cortex, and medial parahippocampal gyrus (67).
CONCLUSIONS

Callosotomy has steadily gained recognition as an palliative option for certain generalized seizure disorders, particularly in cases in which a vagal nerve stimulator has been excluded as a treatment option. With a callosotomy atonic drop attacks and major motor seizures appear particularly likely to improve, although other seizure types may benefit. The neurological effects have been extensively studied, and generally do not result in significant long term effects. New approaches to callosotomy, such as endoscopically-assisted resection, may further reduce morbidity. Additionally, radiosurgery may one day have a role in treatment of these patients considered for resective callosotomy.

REFERENCES


Corpus Callosotomy

Corpus callosotomy is a palliative epilepsy treatment procedure that was developed by Van Wagenem and Herren (1) in Rochester, New York, 1940. Bogen and Vogel (2) picked up the procedure and published a series in 1962, as did Lussenhop et al. (3) in 1970. Most of these were small series until 1975 when D. H. Wilson et al. (4) adopted the procedure, refined it, and published the first Dartmouth series. The role of surgery was callosal division to prevent bilateral synchrony of epileptiform activity. Several subsequent series have been published since the original Dartmouth series and are included in Table 1.

Based upon this extensive body of clinical experience spanning almost 65 years, the most responsive epilepsy syndrome appears to be Lennox–Gastaut syndrome and the most responsive ictal pattern is the epileptiform fast electrodecremental. Complex partial, myoclonic, and atypical absence seizures do not have a clear response to the procedure that would suggest a primary indication (17).

To summarize the clinical outcome, 60% to 100% of drop seizures as a primary indication achieve a 50% or greater reduction (17). A total of 21% to 67% of tonic–clonic seizures as a primary indication have a greater than 50% reduction. However, if the tonic–clonic seizures are a secondary indication, i.e., the tonic seizures coexist, the improvement is very close to the drop seizure response rate. Seizure-free ranges are from 2% to 5%, supporting that this is indeed a palliative procedure and not a curative procedure (17).

Complications have been reported to be between 3% and 10% (17). These have included the “wicked hand” that has essentially disappeared with improved surgical technique. The wicked hand appeared to be a consequence of damage to the non-dominant circular gyrus in the frontal lobe due to retraction or vascular damage during the dissection to expose the callosum for dissection. Most patients respond to an anterior two-thirds division. Some do require a complete division, but it is preferred to do this as a two-stage procedure to improve rehabilitation time (17).

A fairly large series have shown a 75% to 80% successful outcome after anterior callosum division (18). Limiting the section to the anterior callosum is the most
### Table 1 Outcome After Corpus Callosotomy

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<th>Author(s) (Ref.)</th>
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*Seizure types are not specified/results are grouped. Satisfactory outcome, over 50% reduction of main seizure type.

**Abbreviations**: A, atonic; AB, absence; AC, anterior callosotomy; AK, akinetic; C, complete callosotomy; CC, corpus callosotomy; CP, complex partial; G, generalized; HEM, hemiclonic; MR, mental retardation; MY, myoclonic; SP, simple partial; T, tonic; TC, tonic–clonic; TS, two-staged callosotomy.
desirable approach, as there are significant neuropsychological consequences to the posterior division, such as after posterior callosotomy the nondominant hand is no longer able to communicate its recognition of objects to the dominant hemisphere, i.e., the disconnection syndrome.

Recent studies have demonstrated comparable results for vagus nerve stimulation (VNS) compared to corpus callosum division, especially for drop seizures. Figure 1 demonstrates the response rate to VNS at over 80% at six months for the majority of such patients treated (19). Given the results of these studies, corpus callosum division should probably be reserved for tonic or atonic seizure patients who have failed VNS.

Therefore, at this time, let us consider a unified theory of epilepsy surgery that would state: the surgical treatment of medically intractable epilepsy is designed to disrupt a dysfunctional system. However, rarely do these interventions, whether focal cortical resection, multiple subpial transection, corpus callosum division, or VNS completely remove or totally suppress the dysfunction. Patients with temporal lobectomies often have residual auras that are essentially partial seizures, and only 2% to 5% of patients subjected to corpus callosum division end up seizure-free. Therefore, our purpose in epilepsy surgery is to effect neuromodulation.

Focal resection happens to be our most successful technique for those patients fortunate enough to be candidates for such surgical interventions. Meaningful outcomes, as evidenced by seizure reduction and improvement of quality of life, can be had from corpus callosum division or VNS, as well.
REFERENCES

Corpus callosotomy (CC) is the section of the anterior three-quarters (preserving the splenium) or the complete disconnection of the callosal commissure for seizure control. This surgical procedure was first reported in 1940 by Van Wagenen and Herren (1).

Besides not being as effective as focal resections for the treatment of localization related epilepsy the CC also has an added disadvantage, namely the possibility of cognitive/behavioral complications typical to this surgical procedure. Because of these latter factors other options in the treatment of epilepsy such as two or three trials of proper antiepileptic drugs (AEDs), ketogenic diet, vagal nerve stimulation, and especially focal resection (when appropriate) should be contemplated before considering a patient for a CC. The vagal nerve stimulator placement is a much inferior procedure because it requires a craniotomy. Vagal nerve stimulation and the CC are used for the same range of seizure types but have different efficacies (see “Conclusion”) (2).

The main indication is the presence of intractable drop attack seizures (see discussion on seizure type in the following text) such as the ones seen in patients with the Lennox–Gastaut syndrome. Alternative indications are generalized tonic–clonic and partial seizures with frontal lobe onset without clear-cut lateralization.

Patients considered for CC have bilateral epileptiform discharges and onset of seizures, precluding focal resection as an option for the treatment of medically refractory epilepsy. At our institution, this is not an uncommon situation when dealing with patients who undergo a presurgical evaluation below the age of 21 years.

SEIZURE IMPROVEMENT AFTER CORPUS CALLOSOTOMY

As pointed out by others, the problems with methodology in reporting the seizure outcome after CC started with the very first report by Van Wagenen and Herren (1), which had a very short follow-up of the patients—only a few weeks (3). As it has been demonstrated in the outcome of focal resections for the therapy of medically refractory of partial seizures, the outcome with regard to seizure control after
CC may decline over time, especially during the first postoperative year (4,5). The lack of proper characterization of the preoperative seizures has plagued many of these reports leading to the use of names of seizures such as astatic or drop attacks as opposed to the clinical-electroencephalography (EEG) nomenclature tonic, atonic, myoclonic, myoclonic–atonic, and epileptic spasms.

There are many papers that have discussed seizure outcome after CC. The largest compilation of results includes 563 patients (6). In this series, during the postoperative period 61% of the patients were considered “improved” but only 7.6% were seizure-free, and 31.5% had no improvement or were worse. Some smaller series have had worse outcomes with less than 50% of the patients having a significant seizure reduction after a CC (7,8).

FACTORS INFLUENCING THE SEIZURE OUTCOME AFTER CC

Surgical Technique—Amount of Callosal Section

The procedure includes the section of variable amounts of the corpus callosum, massa intermedia, fornix, anterior, and hippocampal commissures (9–14). Ideally, one wants to have magnetic resonance imaging (MRI) documentation of the amount of callosal section. Other data, which allow the verification of surgical success, include clinical follow-up of at least two years, pre- and postoperative EEGs, and neuropsychological testing. The complete section of the corpus callosum appears to be twice as effective as the partial ones according to one study (77% vs. 35% elimination of secondary generalized seizures) (15). Gates et al. (16) also found that a complete callosotomy may be beneficial in patients who did not benefit from partial resection but it may produce more neuropsychological complications (see subsequent text). In support of the latter series is another one that found that smaller degrees of callosal section (<50%) are associated with worse seizure outcome (17).

Imaging and Neurological Abnormalities

Some authors have found that patients with preexisting hemiplegia/hemiparesis tend to do better after a CC (12,18). This finding was not corroborated in other studies (19,20). The presence of focal lesions on computed tomography (CT) has been found a good prognostic factor by some (15). One report mentioned good seizure control in one of two patients treated with a CC for subcortical laminar heterotopia (21). The seizures on the second individual were brought under control with the addition of lamotrigine.

Cognition and Age vs. CC

Patients with severe cognitive deficits are found to respond as well as the ones with normal intelligence whereas in another report worse outcome was noted in patients with mental retardation especially when the IQs were below 45 to 50 (7,8,15,18–20,22,23). The outcome for children and adults has been reported to be similar by Gates et al. (16) but more recently, Maehara and Shimizu (24) found that seizure outcome after CC is actually better in children. A pediatric long-term follow-up study found that 19 patients (47.5%) remained seizure-free while in another 11 cases (27.5%) the seizure frequency was less than three times per year (25). Age of onset, history of
infantile spasms or status epilepticus, family history of seizures, abnormal physical exam, and known etiology of seizures did not influence the outcome after CC in one large study (23).

**EEG and Outcome After CC**

Generalized discharges are often reduced but not eliminated after CC since diencephalic/mesencephalic structures can be a way for bilateral synchronization (26). At least two studies found that preoperative interictal EEG abnormalities did not bear any relationship with the prognosis after a CC (5,23). More recently, detailed analysis of the pre- and postoperative EEG uncovered some interesting findings (27,28). Anterior predominance of bilateral synchronous discharges on EEG predicts a slightly better seizure outcome after an anterior CC, but some patients with posterior predominant generalized spike and wave may still benefit from the procedure (28). The degree of interhemispheric synchrony is also a prognostic factor (27). This study shows that patients in whom most generalized discharges do not show a unilateral “lead” and the ones with less side-to-side amplitude difference (of the discharges) tend to have a better outcome after CC. Higher degrees of synchrony were better observed on the frontal and occipital leads and were less clear-cut on the mid-temporal ones (see Figs. 6 and 7 in Ref. 27).

The de novo appearance of more asymmetrical discharges with a unilateral lead and amplitude difference on the postoperative EEG correlated with a good seizure response (see Figs. 6–8 in Ref. 27). Further, the transformation of generalized spike and wave discharges into regional unilateral (usually fronto-central) was seen in many patients with good post-CC seizure control (Table 1) (27).

**Seizure Type/Localization and Outcome After CC**

A few series have documented the breakdown of the outcome after CC in relationship to the specific seizure types (5,15,20,24). This is especially important when trying to characterize the subtypes of “drop attacks.” Overall, drop attacks tend to respond well. Some of the variation on the seizure response after a CC is due to the range of “good response” or “improved” category. Even though not always well documented with video-EEG, the atonic seizures (drop-out of the electromyography (EMG) signal in association with an epileptic discharge) tend to respond well to CC but

<table>
<thead>
<tr>
<th>Prognostic factor</th>
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<tr>
<td>Hemiparesis</td>
<td>12,18</td>
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<tr>
<td>IQ normal or &gt;45</td>
<td>7,15,18</td>
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<tr>
<td>Focal CT lesions</td>
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<tr>
<td>Age &lt;18 yr</td>
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<td>Anterior 2/3 vs. total callosotomy</td>
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<td>Anterior predominance of bilateral discharges on EEG</td>
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<td>Symmetrical generalized discharges on the EEG</td>
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(Not Universally Accepted)
the range of response is wide, varying between 30% and 90% (5,29). Tonic seizures tend to respond well too, but again there is a wide range, from 32% to 86% (15,24). The good response of tonic and atonic seizures was confirmed by another survey of literature with some personal experience added to it (30).

Generalized tonic-clonic seizures have significant responses ranging from about one-third of the cases (31% in Ref. 24 and 33% in Ref. 20) to 76% (15). Myoclonic seizures find no mention in some studies while in others they appear to show good response in 60% to 80% of the cases (5,20). The same is true of atypical absences. It is not uncommon for patients with atonic and tonic seizures to have atypical absences but most reports do not mention this seizure type. In two reports, patients with atypical absences between one-third ($n = 8/24$) and two-thirds ($n = 9/15$) of the cases become free of such seizure type after a CC (5,31).

Some preliminary reports have shown some encouraging results with the use of CC in the treatment of frontal lobe seizures (32–34). In one study, four of five patients showed major seizure reduction on short-term follow-up (33). CC may also allow for EEG lateralization in cases in which frontal lobe seizures have bifrontal EEG discharges due to quick bilateral synchrony (Williamson P., personal communication 1994 and two of my personal cases). In one report, frontal lobe seizures seem to respond better than temporal lobe epilepsy (32). Nonetheless more long-term data are necessary to confirm this finding (Table 2).

### COMPLICATIONS

Serious complications of CC include epidural hematoma, intraparenchymal hemorrhage, cerebral edema, infection, hemispheric infarct/hemiplegia, and parasagittal infarct/
diparesis (7,36). Nonetheless, these serious complications are infrequent. An acute and usually transient syndrome has been described after callosotomies. This syndrome is characterized by speech problems such as mutism, difficulty initiating speech, or stuttering (36,37). Also transient are the left-sided neglect (sometimes described as paresis) or apraxia (8). Left-sided forced grasp and urgency incontinence have also been described. These symptoms may last from days to weeks and are thought to be the result of pressure on the nondominant medial frontal region including the supplementary motor and premotor regions. Spencer (32) described a few cases in which this syndrome was more prolonged and was thought to be a result of mixed dominance for speech.

Most patients do not show any neuropsychological complication from the corpus callosotomies on routine testing; on the contrary, some patients may show some improved scores in “intelligence testing,” which is probably due to decreased seizure activity or lower AED levels (16). On the other hand, more sophisticated testing may diagnose some problems in these patients. Sass et al. (38) showed that 18 patients with early-onset seizures and signs of severe unilateral central nervous system (CNS) dysfunction, who underwent partial or total corpus callosotomy, had some cognitive improvements. This study showed that all patients whose language-dominant hemisphere did not control their dominant hand had impairments in some aspect of speech and language function after callosotomy. These authors also observed unilateral deterioration of motor function in some patients. Postoperative deficits occurred with partial, as well as total callosotomy.

The disconnections seen after CC are of two main types: (i) visual disconnection (seen with posterior callosal section) consists of inability to report an object quickly (tachyscopically) to the nondominant visual hemifield (39); (ii) sensory disconnection, seen with anterior one-half callosal section, is characterized by the inability to describe objects presented tactiley on the nondominant side with the subject blindfolded.

CONCLUSION

Even though far from being a panacea for all types of seizures, CC remains an effective option for the palliative treatment of generalized epilepsies of refractory to pharmacotherapy. Tonic and atonic seizures are the main ones to be treated with CC. The efficacy of CC is probably somewhat smaller in the treatment of generalized tonic–clonic and myoclonic seizures. CC may also be efficacious against atypical absences and frontal lobe partial seizures but further studies are needed.

The risks of complications of CC are higher than with the ones seen with other commonly used options such as the ketogenic diet and vagus nerve stimulation (VNS). VNS and CC are efficacious against the same seizure types (2). VNS may have an efficacy comparable to CC for generalized seizures, especially tonic and atonic episodes, although the data on VNS are less extensive for tonic and atonic seizures (2). CC may well be less effective than VNS in the treatment of partial seizures (2,40). CC remains a viable option for patients with tonic, atonic, or even generalized tonic–clonic seizures who undergo VNS treatment without significant response after one to two years.

At this point no epilepsy center that deals with a large pediatric population can do without the use of CC because there is no effective and complete substitute. When used within its proper indications, CC is unique because it is a treatment option which can offer some improvement to patients who have not responded to any therapeutic modality known even in the 21st century.
REFERENCES

Section XI
Hemispherectomy: Historical Perspective and Current Surgical Overview

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Hemispherectomy, as a treatment for intractable epilepsy, and as a surgical procedure, has come a long way since its development in 1928 (1). In the 21st century, hemispherectomy still remains an attractive intellectual and surgical answer to patients whose hemispheric dysfunction renders them increasingly disabled. Despite disfavor following the discovery of long-term complications in the initial decades of its application, surgeons were unwilling to abandon the procedure on account of its remarkable rate of seizure control (2–5). Numerous technical modifications have been introduced to reduce these complications; at least eight have been described since 1992 (6–14). Due to the rapid development of the numerous modifications and the need to evaluate for possible long-term complications (up to 20 years postoperatively), no definitive conclusion has been made as to which approach will lead to the most acceptable and consistent outcome (15). It is the purpose of this chapter to provide a broad overview on hemispherectomy and to describe the background on its evolution from its inception to the most frequent currently cited surgical techniques.

HISTORY OF HEMISPHERECTOMY

Dandy and L’Hermitte independently introduced hemispherectomy as a drastic therapy for infiltrating gliomas of the nondominant hemisphere (1,16). Though the technique failed to provide sustainable long-term survival, postoperative survival from a known lethal tumor associated with limited functional recovery opened the doors for a more effective use of the hemispherectomy. Dandy would aptly conclude his study in 1928 with a statement that seems as appropriate today as it was 75 years ago. He wrote, “Although this is scarcely an operation to be advised, it nevertheless offers to those desirous of living under adverse conditions a much longer extension of life than is possible in any other form of treatment...” (1).

Just 10 years later McKenzie (17) used the procedure as a treatment for epilepsy. Krynauw’s 1950 report of hemispherectomy in 12 children with infantile
hemiplegia described improved seizure control, motor strength, personality, behavior, and mentation, thus further validating the technique (18).

Initial popularity of the procedure waned after reports of hemorrhagic complications surfaced in the 1960s (2). These complications included superficial cerebral hemosiderosis, hydrocephalus, and intracranial hematoma. Superficial cerebral hemosiderosis (SCH) led to neurological deterioration in up to 33% patients, 3 to 20 years postoperatively, and was attributed to recurrent intracranial bleeding in the resultant large surgical cavity secondary to minor head trauma or even normal physiological function (sneezing, coughing) (2,15).

Subsequently, a series of modifications were made to the original anatomical hemispherectomy to reduce and stabilize the brain/cranium interface in the postoperative cavity. Ignelzi and Bucy (5) created a procedure called hemidecortication, Wilson (19) used a modified anatomical hemispherectomy, Adams (4) suggested manipulation/plication of the dura, and Peacock et al. (20) advocated prophylactic cerebrospinal fluid (CSF) shunting.

Perhaps the most sustainable of these approaches was proposed by Rasmussen in 1983 (3). Observing that resection of two-thirds or three-quarters of a hemisphere had not resulted in long-term complications, Rasmussen created the “functional hemispherectomy.” He removed only a small portion of the diseased hemisphere, leaving the remainder disconnected but intact. His approach was successful both in terms of seizure outcome and elimination of long-term complications. In fact, few instances of SCH have been reported since functional hemispherectomy was established (21). Today functional hemispherectomy is one of the more successful epilepsy surgeries if viewed simply from terms of seizure control, with 60% to 94% patients experiencing complete or near complete seizure freedom (7,12,20,22–30). Equally important is the improvement or stabilization in cognitive and behavioral impairments that occur after hemispherectomy in children whose disease would otherwise dictate a fairly dismal natural history. The natural history of these children is best judged in a historical context when this surgical option did not exist. Secondary impairments such as epileptogenic encephalopathy and death from status epilepticus were commonplace and expected in children with unilateral hemispheric disease.

**INDICATIONS FOR HEMISPHERECTOMY**

Hemispherectomy is indicated for patients with pharmacologically refractory seizures originating from extensive or multiple regions of a single hemisphere where less extensive resections would be deemed inadequate (20,31). The seizure disorder is usually disabling and of varying semiology and frequency (several to 200 per day) (32). Signs of language and intellectual delay may be prevalent depending upon the age of onset and the extent of hemispheric damage (32). Most epilepsy centers employ a set of criteria for hemispherectomy that works in their particular referral population. At the University of Washington Epilepsy Center at Children’s Hospital and Regional Medical Center, patients who undergo hemispherectomy, in general, have (i) intractable seizures despite adequate therapeutic/pharmacologic trials, (ii) preoperative hemiparesis or hemiplegia, (iii) epilepsy arising from the hemisphere (and not just an isolated lobe) contralateral to the hemiparesis based on electroencephalogram (EEG) studies, (iv) a normal contralateral hemisphere based on magnetic resonance imaging (MRI), electrical, and functional studies, and lastly, (v) a family support system that could sustain and rehabilitate a patient with a significant postoperative deficit.
Subsequent complications and neurological impairment discussed with parents prior to surgery include death, infection, failure to improve seizure outcome, need for CSF diversion, need for transfusions, homonymous hemianopsia, aphasia/dysphasia, hemiplegia/hemiparesis, and sensory loss. We inform the parents that postoperatively, in most of our children who successfully undergo functional hemispherectomy, the hemiparetic hand functions as a helper hand with loss of some cortical function. The patients can lift their involved arm above the horizontal meridian and can hold a piece of paper, a ball, and most objects, but fine motor control of the fingers is significantly affected. Almost all children are eventually walking or running after surgery, albeit with a paretic gait. No child undergoes this operation without a resultant motor dysfunction and visual field cut and parents must be prepared accordingly.

The most appropriate indications for hemispherectomy at our center are unilateral hemispheric disorders. These disorders and diseases are often responsible for hemiparesis secondary to intractable seizures, which may be congenital or acquired in nature, and include hemimegalencephaly, migration disorder/cortical dysplasia, Sturge-Weber syndrome (SWS), Rasmussen’s encephalitis, cerebral infarct/porencephaly, neoplastic/traumatic/vascular disorders, and hemiplegia-hemiconvulsion-epilepsy syndrome (HHE) (23,33,34).

STURGE–WEBER SYNDROME

This neurocutaneous disorder of the phakomatoses family results from dysplasia of the vessels surrounding the brain wall, the membranous skull, and its integument during the sixth week of embryonic development. The syndrome is usually distinguishable from birth due to a port wine stain on the face and scalp, though the facial nevus may be undetectable in some cases. Other symptoms include partial motor seizures (though secondarily generalized seizures sometimes occur), developmental delay, hemiparesis, limb atrophy, and multiple optic problems stemming from the syndrome’s effect on the ophthalmic division of the trigeminal nerve territory (glaucoma, enophthalmos, exophthalmos, optic atrophy, and vascular malformation) (33,35).

The prognosis of SWS ranges from minimal to severe, depending largely on the extent of pial angiomatosis. In cases of localized SWS, seizures occur later in childhood and are responsive to antiepileptic drugs (AEDs); development is mostly unaffected aside from a visual field defect. In patients with diffuse SWS, symptoms typically arise during infancy and progress rapidly, ultimately causing intractable epilepsy, hemiplegia, and mental retardation. Hemispherectomy is the primary treatment for severe forms of SWS and should be considered soon after diagnosis (25,33).

Neuroimaging allows for noninvasive determination of the extent of hemispheric involvement. Characteristic results from imaging include “tram tracks” from skull X rays and intracranial calcification from the affected cortical regions, visualized on computed tomography (CT) scan. Angiography, magnetic resonance imaging/angiography (MRI/MRA), positron emission spectroscopy (PET), single photon emission computerized tomography (SPECT), and functional MRI have also been used to follow and map the progress of SWS. Prehemispherectomy mapping by subdural grid placement is utilized in selected patients for successful delineation of the epileptogenic cortex beyond areas of pial angiomatosis (33).
HEMIMEGALENCEPHALY

The characteristic enlarged hemisphere easily identifies this neuronal migration disorder. Patients have cortical lamination of only three or four layers, bizarre giant neurons, heterotopias, flat gyri and shallow sulci, abnormal white matter with poor differentiation between white and gray, and an enlarged ventricular system in the affected hemisphere (33,36). Hemimegalencephaly is sometimes associated with sebaceous nevus syndrome, hypomelanosis of Ito, or proteus syndrome (37–40). Dermatologic characteristics of these syndromes may aid in the diagnosis of hemimegalencephaly (25). Partial seizures with secondary generalization often arise during infancy and are pharmalogically intractable. Hemiparesis and mental retardation occur as a consequence, the extent of which varies with seizure severity. Hemispherectomy is indicated when severe seizures will lead to hemiparesis (25).

RASMUSSEN’S SYNDROME

Also known as chronic encephalitis, this acquired progressive syndrome is a confluently spreading cortical inflammation causing seizures (particularly *epilepsia partialis continua*), intellectual deterioration and relentlessly progressive hemiparesis (41,42). It becomes inactive in some patients, but because of the rapid nature of the disorder severe disability precludes cessation (43). The syndrome typically appears in children by the age of 15, though adult-onset variants have also been described (44–48). Imaging reveals atrophy of the cerebral hemisphere with enlarged ventricles (49). Misleading signs often necessitate a biopsy for diagnosis (25).

Though some epilepsy centers like ours advocate early surgery for Rasmussen’s to minimize intellectual impairment, no randomized trials have been conducted to show that hemispherectomy provides a better outcome than less-debilitating therapies (steroids, intravenous gammaglobulin, zidovudine, plasmapheresis) (25,28,33). Recent attempts to outline the etiology behind Rasmussen’s have led to an even greater number of possible therapies. Reports of Epstein–Barr virus and cytomegalovirus in several cases of Rasmussen’s suggest an antiviral therapeutic course, while the identification of autoantibodies to the glutamate receptor (GluR3) receptor have lead to immunosuppression therapy (45,50–54). The efficacy of these new therapies has yet to be demonstrated (see Chapter III-8).

PRESURGICAL ASSESSMENT

Presurgical assessment includes a thorough series of tests to confirm epileptiform discharges arising from diffuse regions of the damaged hemisphere and to ensure acceptable postoperative function of the contralateral hemisphere (33). A combination of classical cortical studies (electroencephalography, intracarotid amobarbital, neuropsychological tests) and recently developed neuroimaging techniques best determine if and where hemispherectomy should be performed. In addition, technology such as magnetoencephalography (MEG), magnetic resonance spectroscopy (MRS), neurotransmitter-specific PET, and SPECT may further the diagnostic acuity in a specific patient (33,55,56).
Electrophysiologic Tests

Surface electroencephalogram (EEG) confirms the containment of epileptogenic activity to multiple or extensive regions of a single hemisphere (32). Although bilateral activity appears in as many as 75% of patients, this activity is often secondary to epileptiform discharges of the diseased hemisphere and should not be used exclusively to rule out hemispherectomy (57). A Wada or intracarotid amobarbital test may be used to determine whether the epileptiform discharges from the contralateral hemisphere continue when disconnected from the diseased hemisphere (20).

Intracranial subdural electrocorticography (ECoG) is not uniformly performed but may be useful to confirm EEG recordings and is sometimes used for mapping of the cortex to further delineate epileptogenic foci beyond that which is seen on surface electrodes (32,33,58). This procedure may be used to determine if a hemispherectomy versus a lobectomy is required in a specific patient. Bilateral subdural strip/grid electrodes may be used to ensure that unilateral hemispheric disease is confirmed. ECoG performed prehemispherectomy, incurs the expense and risks of an additional craniotomy, but the benefits of performing the correct operation outweigh any potential risks (33).

Neuroimaging

CT and MRI reveal diffuse unilateral pathology, as in the pial angiomatosis of SWS or the rapidly progressing atrophy in Rasmussen’s encephalitis (59,60). Neuroimaging, including contrast enhanced studies, should also reveal a healthy contralateral hemisphere.

Functional imaging provides further insight into the condition of both hemispheres. PET identifies regions of abnormal blood flow and metabolism throughout the damaged hemisphere, confirming multifocal origins of epileptiform discharges. While PET is largely limited to the interictal period, SPECT identifies abnormalities both between and during seizures (33).

Timing of Surgery

The ideal timing of hemispherectomy remains undetermined, complicated by issues of sensorimotor transfer and progressive hemispheric damage. In the context of current practices and our knowledge of the natural history of many of the processes that require hemispherectomy, it would be somewhat challenging to randomize patients to early and late surgery. Left untreated, epileptiform discharges gradually damage the contralateral hemisphere resulting in severe intellectual impairment. Studies showing improved psychosocial and intellectual benefits after early surgery have caused many to advocate surgery soon after onset of seizures, even before maximal hemiparesis when etiology is progressive (28,61–63). The decreasing plasticity of the right hemisphere for language acquisition after the sixth to eighth year further supports the argument for early surgery. Certainly, advocates of early surgery suggest that it should be accomplished before the child is six to eight years old so that language and motor functions can successfully transfer hemispheres.

This perspective is contradicted by recent data that indicate improved motor function in patients who were not operated on until transfer of sensorimotor functions, which occurred in several stages (64–66). In balancing these factors in some
patients, it may seem more important to reduce crippling neurological damage than to save some fine and gross motor control (33). Until the critical operative period is established, early surgery prior to significant neurological deterioration must be weighed against the deficits that will result.

Some centers have been advocates of early surgery in children with Rasmussen’s syndrome. At Johns Hopkins Hospital, when the burden of seizures was deemed excessive and the natural history of the disease (i.e., Rasmussen’s) was uniformly poor, timing of the surgery included intervening even when the patient would be left with a worse motor deficit; thus, even patients with a mild motor deficit were selected for hemispherectomy (28). In children with cortical dysplasia, surgery would be performed in patients as young as three months when the seizures were unilateral, continuous, and incapacitating. Some of these children did not exhibit a hemiparesis preoperatively. The rationale for surgery, based on EEG and imaging which secured a diagnosis and inferred an irreversible natural history, was that the likelihood of significant seizure control by medications was low and the benefits of early surgery to prevent cognitive decline was therefore deemed justified. Furthermore, within the first years of life, hemiparesis may be difficult to detect because of the immaturity of the corticospinal tracts (31). However, in the Hopkins series, patients with vascular disorders had a dense hemiplegia prior to hemispherectomy. These patients often received operations late in life, specifically after the long-term deleterious effects of the seizures and medications became a burden (28).

**POSTOPERATIVE OUTCOME**

**Seizure Outcome**

Rates of complete or near complete seizure freedom vary between 60% and 94% (7,12,20,22–30). Recent data demonstrates that seizure outcome varies largely according to underlying pathology. At Johns Hopkins Hospital children with Rasmussen’s experienced the greatest postoperative outcome, with 89% having complete or near complete seizure freedom. Those with cortical dysplasias/hemimegalencephalies and congenital vascular problems/SWS had only 67% seizure freedom (28). The 2003 report from Great Ormond Street Hospital Oxford, U.K., showed similar variation. Seizure freedom, rare seizures, or greater than 70% seizure reduction was seen in 100% of patients with progressive pathology (Rasmussen’s and SWS), 91% of patients with acquired pathology (congenital middle cerebral infarct and others), and 88% of patients with developmental pathology (hemimegalencephaly and others) (27). From these data, it is evident that rates of seizure freedom culled from previous studies must be evaluated in the context of the percentage of patients with cortical dysplasia, Rasmussen’s, hemimegalencephaly, etc. These percentages are useful in tailoring outcome predictions for patients and their families.

**Cognitive Outcome**

Analysis of cognitive outcome from intelligence quotient/developmental quotient (IQ/DQ) and psychological tests indicate that hemispherectomy halts progressive intellectual deterioration. Preoperative deterioration was documented in a series from Great Ormond Street Hospital, Oxford, U.K., where 36% (12/33) of patients exhibited preoperative developmental regression, and at The Park Hospital, Oxford, U.K., where patients saw preoperative decline of 10 to 29 IQ points (27,61). Accordingly,
Hemispherectomy arrested developmental regression in the majority of these patients so that IQ remained the same for the majority of patients in the Great Ormond Street series and for nearly half (47%) of the Park Hospital series. In the two British series, improvements were seen in 12% (4/33) and 41% (7/17), respectively. In yet another study, IQ increased by 3 to 18 points for six of eight patients (15). Some series show that the arrest of cognitive regression allows improved postoperative cognition, usually when surgery is performed soon after seizure onset in children. Pediatric hemispherectomy series for SWS by Hoffmann et al. (67) and Falconer and Rushworth (68) reported a significant increase in postoperative intelligence. A comparison of intellectual function of patients with SWS showed greater intellect for those who had undergone hemispherectomy compared to those treated medically (69). It should be noted that cognitive progress is less likely to be seen in cases of widespread cortical dysplasia, and cognitive regression is found postoperatively in a few patients in most limited surgical series (27).

Language Outcome

As with cognitive outcome, reports of significant decreases in language outcome are rare, regardless of the side of hemispherectomy (20,27,28,70–72). Language was preserved in the case study of a nine-year-old patient undergoing hemispherectomy of the dominant hemisphere, leading the authors to conclude that enough language reorganization occurs in the nondominant hemisphere to permit basic communication. Similar findings were described in 12- and 13-year-olds at the Johns Hopkins Center and in 3.8- to 4.2-year-old patients at Great Ormond Street Hospital (27,28).

Behavioral Outcome

Behavioral problems have been reported in association with hemispherectomy candidates since Krynauw’s first series in 1950 (18). These have been described as unprovoked episodic outbursts of violent temper tantrums, behavior disorders with rages, screaming and poor attention, and “severe and unmanageable rage and aggression” (18,61,70). In studies describing this consequence of diffuse unilateral epilepsy, significant behavioral improvements were seen in the majority, if not entirety, of patients postoperatively (15,18,61,70). In only one recent series was deterioration of behavior (temper tantrums, mood swings, aggression) described in 5 of 33 patients; the authors suggest that these children were in a placid, inert state as a result of their epilepsy and surgery allowed them to behave like normal children (27).

Motor Outcome

For patients with a maximal hemiplegia and a preexisting hemianopsia, motor function typically remains unchanged after hemispherectomy (15,18,27,28,70). Most studies, however, report cases of gradual motor improvement after an initial hemiplegia, likely a result of seizure relief and transfer of motor function to the opposite hemisphere (27,70). In the progressive Rasmussen’s syndrome and SWS, surgery is often performed before maximal hemiplegia or hemianopsia. The premature hemiplegia induced by surgery is deemed a necessary sacrifice to prevent cognitive damage (32). Patients have been noted to improve and regain some motor function, albeit less in their hand, over the subsequent year.
COMPLICATIONS

Despite the apparent elimination of SCH since the introduction of new surgical techniques, hemispherectomy retains a relatively high mortality rate of approximately 1% to 3% as a consequence of other perioperative complications (21). Complications range from minor postoperative occurrences—fever, hypotonia, aseptic meningitis—to life-threatening problems like brain stem trauma, gross edema of the contralateral hemisphere, superior sagittal sinus occlusion, and hydrocephalus (21,23,73,74). Brian et al. (73) reported intraoperative complications of hypotension, hypocalcemia, coagulopathy, and hypothermia; larger excisions lead to longer operative time and result in a greater number of these intraoperative complications. Larger resections have also been tied to postoperative hydrocephalus, as they often require extensive removal of CSF absorbing subarachnoid space (23). The correlation between incision size and morbidity/mortality has sustained the development of shorter, less invasive surgical techniques.

SURGICAL APPROACH

There are many choices for the neurosurgeon deciding on a surgical approach to hemispherectomy. Seizure outcome is similar for all modern techniques, so different approaches must be compared in terms of incision size, operative time, blood loss, complications, technical difficulty, and applicability to different etiologies (23,28,75). All modern surgical techniques have benefited from the frameless stereotactic navigational devices and by compounding information from disparate studies (structural and functional neuroimaging, ECoG, cortical stimulation maps) (33). We currently use frameless stereotactic guidance and ultrasound in all our functional hemispherectomy patients to ensure our “disconnections” are anatomically complete.

An extensive review of all the technical variations of hemispherectomy is beyond the scope of this chapter. We have attempted to provide a broad overview of review those techniques that have had the most significant impact and that have comparable data. New techniques have followed the theme of Rassmussen’s functional hemispherectomy, leaving more disconnected brain matter in the hemispheric cavity (14). This evolution of operations has resulted in preservation of more subarachnoid space, required smaller craniotomies, has taken less time to complete and has resulted in improved recovery times. In 1992, Delalande et al. (6) used the term hemispherotomy to describe any variation of hemispherectomy in which disconnection predominates and resection is minimal. Deafferentation and the peri-insular techniques fall into this category. Because these modifications have only been recently introduced, conclusions about their long-term complications may be premature (9,14,76).

Anatomic analysis of the major hemispherotomy procedures has been beautifully delineated by Morino et al. in 2002. The authors provide a visualization of the overall anatomic result. The authors conclude that four surgical procedures must be incorporated into any hemispherotomy operation in order to achieve a successful outcome regardless of the type of technique employed. These four procedures include (i) interruption of the fibers of the internal capsule to the corona radiate, (ii) resection or disconnection of the medial temporal structures to include hippocampus and fimbria–fornix complex, (iii) corpus callosotomy from anterior commissure to splenium, and (iv) disruption of the frontal horizontal fibers (that include the occipitofrontal and uncinate fasciculus) (13).
Functional Hemispherectomy

Rasmussen noted that SCH did not occur in patients who had undergone multiple lobectomies or subtotal hemispherectomy. This observation inspired Rasmussen to perform the first functional hemispherectomy, where the central region and temporal lobe are resected and the remaining frontal and occipital lobes are disconnected from the rest of the brain. In 1983, Rasmussen reported an 84% complete or nearly complete reduction in seizure tendency in a series of eight functional hemispherectomies. The last available figures show that functional hemispherectomy or a subsequent modification is the most widely performed type of hemispherotomy, with 76% of epilepsy centers using a variation of the functional hemispherotomy technique (77). Because follow-up time has surpassed 20 years, most authors suggest that this technique does not appear to cause SCH (3,15).

The major advantages of functional hemispherectomy include shorter operative times, less extensive craniotomy with low reported rates of infection, blood loss, and hydrocephalus. The only obvious disadvantage to variations of functional hemispherectomy techniques is that each of the variations requires skill and extensive anatomical knowledge because failure to disconnect the potentially epileptogenic brain accounts for most surgical failures (3,24,76).

Hemicorticectomy

Winston modified Ignelzi and Bucy’s hemidecortication to create this technique; later Kanev used ultrasound to further modify the procedure (5,7,10). The entire cerebral cortex is removed, leaving the white matter intact around the ependyma. While this modification decreases the amount of resected matter and preserves an intact ventricular system, it has been criticized for failing to preserve pial blood supply to the disconnected hemisphere, for its technical difficulties, for carrying high risks of infections, and for only being applicable to patients without structural lesions (24,75,76).

Peri-insular Hemispherotomy

Villemure and Mascott created this second of four variations of functional hemispherotomy in which hemispheric disconnection is achieved through the ventricular system. A cortical resection called the suprainsular window is made approximately 5 mm above the sylvian fissure. The insular cortex and portions of the operculum are resected to reach the body of the lateral ventricle. The fibers of the internal capsule to the corona radiata are subsequently sacrificed. Once inside the body of the ventricle, a callosal section is performed. An infrasylvian window is made, thus entering the temporal horn. The medial temporal structures such as hippocampus, amygdala and insular cortex are removed through the infrasylvian window. Arteries and veins are preserved in order to keep viable the disconnected cortex (8,76). This approach requires only a medium-sized craniotomy, so operative time, blood loss, and incidence of aseptic meningitis and hydrocephalus are drastically reduced (29). The technique is ideal for cases with enlarged ventricles, and can also be useful for hemimegalencephaly associated with ventriculomegaly (14).

Modified Peri-insular Hemispherotomy

This is a technique described by Shimizu and Mauehara in 2000. The frontotemporaloparietal lobe is exposed and the sylvian fissure is split to expose the insular cortex.
The branches of the middle cerebral epilepsy (MCA) are then sacrificed as the insular, frontal, and parietal operculum are taken. Once the operculum is taken the body of the ventricle is entered. The fibers of the internal capsule to the corona radiata are then sectioned. The mesial temporal structures are taken through the temporal horn. A transventricular corpus callosal section is performed followed by sectioning of the horizontal fibers of the frontal lobe. In summary, this variation on the peri-insular hemispherotomy sacrifices all of the MCA branches on the surface of the insular as a strategy to control hemorrhage and achieve their result (11).

**Hemispheric Deafferentation**

This procedure was introduced by Schramm in 1995 and later redescribed with three distinct modifications. Schramm refers to his procedure as a deafferentation one because the cortical layers are disconnected from the deep structures. However, the term is synonymous, in effect, to the hemispherotomy procedures described above. The modifications include (i) removal of the superior temporal gyrus to access the mesial temporal structures, (ii) removal of the insular cortex and operculum through subpial dissection, and (iii) the trans-sylvanian keyhole functional hemispherectomy applied in patients with centrally placed cystic lesions (9,12). This deafferentation technique shares a similar transventricular callosal section with the peri-insular hemispherotomy techniques, but requires an even smaller craniotomy. The body of the lateral ventricle is entered through a C-shaped perisylvian cortical incision extending from the superior temporal gyrus to the inferior frontal gyrus. This incision makes a transventricular corpus callosal section possible and provides access for disconnection of the medial temporal structures such as the hippocampus and amygdala. The fibers of the internal capsule are likewise sectioned. A temporal lobectomy can be performed but MCA arteries and veins are preferably left intact. Like peri-insular hemispherectomy, deafferentation is appropriate when the ventricles are enlarged. Recent studies show a decrease in operative times and blood loss as compared to a standard functional hemispherectomy and the seizure control and outcome have been uniformly good (14).

**CONCLUSION**

The technique of hemispherectomy has undergone an amazing transformation since Dandy described it 75 years ago. The lure of high seizure control rates and improved neuropsychological outcome in patients with unilateral dysfunction who might otherwise rapidly deteriorate offset the acute motor deficits associated with this radical procedure. The most commonly employed procedure currently is one of the several variations of functional hemispherotomy. The essential four elements that make this operation with all its variations successful include disconnection/removal of the mesial temporal structures, section of the corpus callosum, interruption of the fibers of the internal capsule to the corona radiata, and disruption of the frontal horizontal fibers. The future of this technique is one of evolution as we gain greater understanding of cortical function and reorganization and the etiology of epilepsy in patients with structural lesions.

**REFERENCES**


Hemispherectomy 573
Chapter XI-31
Hemispherectomy: What Is the Best Surgical Approach?

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BACKGROUND

In 1996, our review of hemispherectomy cited 175 references dating from 1928 to 1995 (1). A current literature search found more than 185 reports published since 1995, a record that demonstrates the remarkable interest that has accrued in a brief time. In this paper, we focus on the continued evolution of surgical techniques, and efforts to evaluate long-term results.

Walter Dandy, who first described the hemispherectomy operation for glioma patients, noted that success was dependent on “painstaking care in hemostasis.” Despite his technological efforts, Dandy found that hemispherectomy could not, prevent recurrence of tumor and he abandoned it. Fortunately, K. G. McKenzie, who had trained under Cushing in Boston, recognized its potential for patients with intractable epilepsy. By the 1950s, Krynauw and others, building on McKenzie’s work, added important observations that would establish the basis for the operation in children today (1).

Awareness of the importance of the surgical approach and the need for long-term follow-up came together in the 1950s when several neurosurgeons noted potential late complications. Initial speculation focused on the possibility for “fatal brainstem shift” (2,3). Ulrich and coworkers correctly described superficial hemosiderosis in a patient. They concluded that repeated hemorrhages, fibrous meningitis (reducing phagocytosis of blood products), and reduction in the area of arachnoid membrane (limiting the possibility for absorption) aggravated hemosiderosis (4). Oppenheimer and Griffith confirmed these findings in 1996. Two factors contributed to efforts to continued use of the procedure (5). First, regardless of advances in antiepileptic pharmacology, hemispherectomy remained the only viable operation for medically intractable epilepsy. Second, qualified observers noted that once the problems of late complications were identified, they could be surgically managed.
By the 1970s, the operation was practiced on a limited scale, but by the 1980s, new case reports emerged, which signified an understanding of the long-term complications, and the need to continue to develop surgical approaches depending on the pathophysiology of the disease. Rasmussen published his experience with eight patients subjected to a "functionally complete but anatomically subtotal" procedure (6). Adams reported on four patients subjected to an "Oxford" modification (7). Briefly, Rasmussen and coworkers at the Montreal Neurological Institute, recognizing that subtotal resections were less effective for seizure control, designed a subtotal hemispherectomy (excision of the central region and temporal lobectomy) with additional sectioning of the white matter connections in the remaining parietal, occipital, and frontal lobes. The operation reduced the size of the subdural cavity and had an intended effect of "splinting" the brain against shock. This concept had been introduced earlier by Laine and Gros, Griffith, and Wilson (8–10). Adams' basic strategy also evolved from procedures described by earlier workers (1). After conventional hemispherectomy, the vault dura was stitched to the falx, tentorium, and skull base to create an extradural cavity. A further modification aimed at screening the ventricular system from blood products by obstructing the foramen of Monro by a plug of muscle (7). Winston et al. (11) described a "de-gloving" dissection around the lateral ventricle in 1992. The objective is to remove the entire cerebral cortex, leaving a layer of white matter around an intact ependyma. The cortex of the frontoparietal region is removed by creating a plane of dissection below the frontal opercular cortex and carrying it superiorly to the vertex, avoiding the frontal horn of the ventricle. No attempt is made to remove the insular cortex or the cortex in the "posterior inferior part of the frontal region." The cortex of the temporal and occipital lobes is removed by creating similar dissection planes around the temporal and occipital horns of the lateral ventricle, which an effort is made not to enter. Our group independently described a remarkably similar procedure in 1993, involving clipping the main branches of the three major arteries distal to the perforating arteries and removal of the entire cerebral cortex leaving white matter (corona radiata), the basal ganglia, and thalamus intact. The amygdala and hippocampus are removed in the Hopkins modification, which benefits from the additional measure of using a layer of gelfoam and fibrin to create a barrier between the intraventricular and subdural spaces (12,13).

SURGICAL OPTIONS

There is now a consensus that prolonged efforts to repeatedly subject patients to trials with one or more drugs is not the only, or even the best option for medically intractable epilepsy. Hemispherectomy is effective in controlling seizures and appears to be effective in significantly improving the long-term quality of life in most patients (14–17). One may categorize the surgical options into the anatomical and functional methods. Functional hemispherectomy, which is a modification of anatomical methods, continues to be modified by less invasive methods, which have been called hemispherotomy procedures.

Comparisons of hemispherotomy methods are difficult because reports generally involve small series from single institutions. Historical comparisons should be left to reviewers. Improvements in patient selection, operating room technology, imaging, and pediatric anesthesia procedures most probably will yield statistical gains in any series. Reports of significant improvements associated with decreased operative time or blood loss must be considered together with long-term outcomes,
which are not yet available. The newer functional procedures have been reviewed recently (16,18–20).

Comments at neurosurgical meetings suggest that mortality rates remain at about 2% for all procedures. Mortality has been associated with patients who had small ventricles, hemimegalencephalies, and coagulopathies. There are anecdotal reports of mortality associated with swelling secondary to excess surgical retraction in minimally invasive methods. Anatomical hemispherectomy, functional hemispherectomy, and less invasive hemispherotomy methods continue to evolve. The choice of surgical technique is, and will continue to be debated because it is difficult to see proximal opportunities for prospective, randomized trials. The debate has been clouded by comments and brief reviews that continue to associate anatomical hemispherectomy with early or late complications, such as hemosiderosis. We and others have never seen hemosiderosis in a modern anatomical series (21,22). The postoperative course of 102 anatomical procedures from the years 1975 to 2001 at our institution has been reported (22). Functional hemispherectomy methods are quicker and may involve less blood loss. Although reviews frequently describe the need for further resections following this procedure, the additional surgery may not diminish the long-term outcomes. No data suggest that functional hemispherectomies provide better seizure control, fewer complications, or that patients have improved outcomes compared to anatomical methods.

**FUTURE NEEDS**

Considerable evidence from studies of injury and stroke supports the idea for varying degrees of plasticity in the central nervous system. One challenge is to identify changes that mediate positive and negative responses. Mechanisms may be different qualitatively and quantitatively in adults and children, and in motor and sensory skills. The work described by several authors in this monograph is addressing these issues.

Studies with animal models continue to be of particular interest because of their potential to evaluate surgical resections as well as surgical restoration. A brief and incomplete list would note work by Machado and Marino in San Paulo on motor area maps after hemispherectomy in the rat, which suggests that each motor area has latent capacity for bilateral control and that such capacity is brought into function after removal of the opposite hemisphere (23). Other work from Montreal by Boire, Theoret, and Ptito has examined the effects of early hemispherectomy on the cytoarchitecture of the dorsal lateral geniculate nucleus and superior colliculus in a nonhuman primate model (24,25). Cat models continue to provide information about critical age periods and plasticity (26).

**SUMMARY**

Daniel and Villemure have noted that “when there is hypertrophic hemispheric disease, the surgeon’s experience and familiarity with the neuroanatomy of discon-nective procedures is the key to a successful operation” (18). To this we would add that it would be no surprise if outcomes from hemispherectomy followed the trend that has been documented with many outcome investigations: Morbidity (short- and long-term) and surgical experience are inversely related. Finally, it is essential to understand that even with superior technique, surgery itself is part of
a therapeutic strategy that starts with experienced pediatric neurologists and epilepsy specialists who select candidates, and who monitor the extensive occupational and physical therapy and support that patients and their families absolutely require over a multiyear period.

REFERENCES


INTRODUCTION

Over the past 75 years, hemispherectomy has evolved into an accepted procedure for medically intractable epilepsy in patients whose seizures arise in a nonfunctioning or minimally functioning hemisphere (1). The original surgical technique involved clipping of the major blood vessels at the skull base, followed by removal of the entire hemisphere en bloc. Problems with hydrocephalus and superficial cerebral hemosiderosis ensued in many cases, giving rise to modifications of the original technique (2). Newer techniques removed only portions of the hemisphere, while disconnecting the rest. All of these modifications share basic principles: only minimal brain is actually removed, the ipsilateral diencephalon is left undisturbed, and the pial blood supply to the un-resected brain remains intact.

The first major technical modification, and perhaps still the most common, was the functional hemispherectomy (3,4). One major advantage of this technique is that it is comprised of surgical techniques that are commonly used by most neurosurgeons. Therefore, special techniques do not have to be mastered, as with hemispheric deafferentation (5).

PATIENT SELECTION

Indications for surgical intervention are the same for each of these procedures. The patient’s epilepsy must be medically intractable, typically proving recalcitrant after at least three antiepileptic medication trials. All (or in rare instances, most) seizures must arise from one cerebral hemisphere. Because patients will have the epileptogenic hemisphere disconnected or removed, the hemisphere must not have significant function. These include patients with hemispherical syndromes such as: infantile hemiplegia hemiatrophy, Sturge–Weber syndrome, and hemimegalencephaly. Alternatively, a unilateral progressive loss of hemisphere dysfunction, such as with Rasmussen’s syndrome, is also an indication for hemispheral disconnection.
SURGICAL TECHNIQUE

Dexamethasone and antibiotics are administered prior to surgery. Surgery is performed under general anesthesia with the patient in a pin headrest (if the patient is old enough). The patient is placed in approximately 20° of reverse Trendelenberg and the head turned 30° away from the side of surgery. A large reverse question mark incision is made, extending from the zygomatic arch, extending anterior to the tragus, then superior and posterior to the ear, and then sweeping anteriorly, along the midline, to the hairline. A myocutaneous flap is then mobilized anteriorly.

The bone flap must permit each of the five surgical steps:

1. temporal lobectomy,
2. Rolandic topectomy,
3. complete callosotomy,
4. frontal lobe and parieto-occipital lobe disconnections, and
5. insular cortex resection (optional).

The dura is opened in a U-shaped fashion, based on the midline. Following the durotomy, a temporal lobectomy is performed. During this first step, the temporal horn of the lateral ventricle is opened, relaxing the brain and permitting more space for the ensuing steps. Although there are a number of temporal lobectomy techniques, the technique chosen must encompass removal of most of the anterior temporal lobe (approximately 5–7 cm), including the mesial structures, while leaving the blood vessels to the remainder of the brain uninjured.

The second step is a Rolandic topectomy. This is accomplished by aspiration of central cortex down to the underlying white matter. Functional mapping is not performed. If topography is unclear, the topectomy is simply extended to include all potential central cortex. This resection includes the paracentral lobule.

The third step is a corpus callosotomy, extending from the splenium to the anterior commissure. This step is facilitated by the first two steps, which decompress the brain (temporal horn entry) and provide a window to the midline structures (paracentral lobule topectomy). Some neurosurgeons have advocated leaving a ventriculostomy in place, for postoperative blood and debris removal. The efficacy of this maneuver remains unclear.

Disconnections of the frontal and parieto-occipital lobes are the next step. The frontal disconnection is accomplished by extending the anterior aspect of the Rolandic topectomy to the anterior skull base and the midline. Because blood vessels must be kept intact, this is performed in a subpial fashion. The parieto-occipital region is then disconnected by extending the posterior aspect of the Rolandic topectomy to the posterior skull base and midline in a subpial fashion. The inferior ramus of this disconnection extends into the temporal horn, which was opened in step one.

Not all neurosurgeons resect insular cortex with hemispherectomy. Whether or not this step adds to the rate of seizure-free outcome is unclear. This step is accomplished by removing enough of the frontal and parietal operculum to expose the entire circular sulcus. The insula can then be aspirated from the medial side, allowing subpial aspiration, leaving the middle cerebral artery vessels uninjured.

CONCLUSION

Results from the various hemispherectomy procedures appear to be the same (6,7). The choice of procedure must therefore be based on the surgeon’s experience. The
functional hemispherectomy provides the neurosurgeon with an option that is comprised of relatively common techniques, familiar to most epilepsy surgeons.

REFERENCES

Peri-insular hemispherotomy (PIH) is a relatively new technique introduced in 1993 by Villemure and Mascott (1–3). The PIH produces a functional hemispherectomy with minimal brain resection by disconnecting the hemisphere from within the lateral ventricle. The reported advantages of the PIH versus functional hemispherectomy have been reduced operative times, decreased blood loss, decreased recovery time, and improvements in the overall postoperative course including a reduced rate of postoperative aseptic meningitis (3–6). Since its introduction several authors have described the technique and minor variations have been introduced; however, the overall concept of creating a “radical hemispheric tractotomy” remains unchanged (3,5).

Peri-insular hemispherotomy is performed via a supra and infrasylvian cortical resection, which exposes the insula. After identifying the circular sulcus, an incision is made at the depth of the sulcus through the cortex and white matter and into the lateral ventricle. Using the suprasylvian window, an incision is made in the superomedial region of the body of the lateral ventricle to identify the pericallosal artery. The incision is then extended anteriorly and posteriorly along the pericallosal artery creating a parasagittal corpus callosotomy. The vessel is followed around the rostrum of the corpus callosum and down to the floor of the anterior fossa resulting in disconnection of the frontal lobe. The posterior end of the callosotomy is extended to the splenium of the corpus callosum then continued through the atrium ending at the choroidal fissure after transecting the fimbria of the fornix. The last portion of the procedure includes resection of the amygdala and hippocampus and removal of the cortex on the insula. At the conclusion of the procedure, the hemisphere is functionally isolated. The reader is directed to Villemure and Mascott’s original publication for a detailed description of the surgical technique and relevant anatomy (3).

In their initial publication, Villemure and Mascott reported their experience using PIH in 11 patients (3). Four patients were male and seven were female with ages ranging from 2 to 32 years of age. Epilepsy resulted from hemimegalencephaly in three patients, infantile hemiplegia in four, chronic encephalitis in two, meningitis in one, and cardiac embolus in one patient. Follow-up ranged from 0.3 to 3 years and results were excellent with 9 of 11 patients obtaining seizure freedom and two
patients obtaining a 95% reduction in seizure frequency. Perioperative complications were minimal with only mild symptoms related to aseptic meningitis and no complications related to hypovolemia.

Our group reported on 16 patients who had undergone either hemidecortication (HD) \((n = 5)\) or PIH \((n = 11)\) between 1993 and 1999 (4). Seven males and nine females ranging from 6 months to 15 years of age were included in the study. Five patients had cortical dysplasia, four had Rasmussen’s encephalitis, three had Sturge–Weber syndrome, two had hemimegalencephaly, one had pachygria, and one patient had a perinatal infarction leading to an extensive porencephalic cyst. Follow-up ranged from 3 months to 5.7 years (median 3.0 years). Fourteen of 16 patients were Engel Class I and two patients were Engel Class II. No patients had a decrease in ambulatory status following surgery and no patients demonstrated a decrement in speech function postoperatively.

The functional result of both hemidecortication and PIH were similar in our limited study with both groups attaining equivalent reductions in seizure frequency; however, an importance difference was noted in the perioperative course. Patients who underwent PIH had less blood loss, less intraoperative hypotension, fewer transfusions, fewer shunts, and an overall faster recovery. The postoperative recovery was protracted in the HD group with three of five patients experiencing the syndrome of aseptic meningitis. In comparison, only 1 of 11 patients in the PIH group developed the syndrome. It is thought that the syndrome of aseptic meningitis is caused by blood and debris introduced into cerebrospinal fluid during surgery (3). One advantage of PIH is limited tissue resection leading to reduced blood loss. These factors may lead to a reduced incidence of aseptic meningitis, which in turn promotes an expedited recovery. An additional benefit of PIH was a reduced rate of ventricular peritoneal (VP) shunting. No patients required VP shunting in the PIH group while two of five patients required a shunt in the HD group (Table 1).

Shimizu and Maehara reported 34 patients who underwent a modified PIH technique whereby the frontal operculum was resected before proceeding with the transventricular callosotomy (5). Shimizu suggested this minor variation facilitated intraventricular dissection especially in patients with small ventricles. In the study conducted between 1993 and 1999, 34 patients underwent modified PIH. The group included 21 males and 13 females ranging from 3 months to 30 years of age. Seizure etiology included cortical dysplasia in 14 patients, hemimegalencephaly in 12 patients, middle cerebral artery (MCA) occlusion in two patients, head trauma in two patients, infantile hemiplegia in two patients, and chronic encephalitis in one patient. Twenty-seven patients had at least one year of follow-up. Eighteen patients

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Perioperative Course with PIH and HD</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HD ((n = 5))</td>
</tr>
<tr>
<td>Estimated blood loss (cm³)</td>
<td>1300</td>
</tr>
<tr>
<td>Intraoperative hypotension</td>
<td>2/5</td>
</tr>
<tr>
<td>Transfusion required</td>
<td>5/5</td>
</tr>
<tr>
<td>Aseptic meningitis syndrome</td>
<td>3/5</td>
</tr>
<tr>
<td>VP shunt required</td>
<td>2/5</td>
</tr>
<tr>
<td>Avg. post-op hospital days</td>
<td>27</td>
</tr>
<tr>
<td>Rehabilitation care required</td>
<td>3/5</td>
</tr>
</tbody>
</table>

Source: From Ref. 4.
were Engel Class I (67%), two were Engel Class II (7%), six were Engel Class III (22%), and one was Engel Class IV (4%). One postoperative complication was noted that led to severe bilateral brain swelling and subsequent disability. Operative time was on average 6 hours 15 minutes, mean blood loss was 359 ml, and transfusions were needed in 79% of cases with a mean volume of 224 ml transfused. VP shunts were required postoperatively in five patients, all with hemimegalencephaly.

Daniel et al. (6) reported a series of six children undergoing PIH. Patients in this study consisted of five males and one female ranging from 7 to 15 years of age with the diagnosis of infantile hemiplegia in five and Rasmussen’s encephalitis in one patient. Follow-up ranged from 6 to 18 months with a mean of 13.7 months. Five of six patients were seizure-free; one patient had two seizures over nine months. All patients had their antiepileptic drug regimens reduced. Global cognitive functioning was reportedly improved in all six patients postoperatively.

Intractable epilepsy from diffuse hemispheric disorders responds well to hemispherectomy and the results obtained with PIH are similar to the results reported for functional hemispherectomy and hemidecortication (7–14). While the techniques produced similar rates of seizure control, PIH patients experienced less perioperative complications and less postoperative morbidity. Intraoperative advantages seen with PIH include reduced overall operative times, reduced blood loss, fewer episodes of hypotension, and a reduced need for transfusions. In the immediate postoperative period, our group and others have seen a reduction in the occurrence of aseptic meningitis, which has led to reduced recovery times (3,4). Villemure and Mascott suggest the reduced rates of aseptic meningitis are a direct result of reduced blood products and debris being introduced into the cerebral spinal fluid at the time of surgery (3). An additional benefit of PIH has been a reduced requirement for VP shunting. Evaluation of the patients reported in the Kestle and Shimizu studies demonstrated that only 5 out of 45 total patients required shunting (4,5). Villemure and Mascott suggest that the development of hydrocephalus may be reduced due to the preservation of a greater volume of subarachnoid space after PIH compared to other hemispherectomy techniques (3).

Objective criticisms of the PIH technique point to two technical challenges that could theoretically limit the utility of the procedure. The first issue relates to the technical feasibility of performing the procedure in patients with small ventricles. Villemure and Mascott noted that PIH is facilitated by enlarged ventricles; however, they subsequently noted that “after gaining experience with the technique, applying it in cases with minimally enlarged ventricles [was] more obvious” (3,5).

Shimizu and Maehara suggest that their modification using a frontal opercular resection facilitates access from the resection cavity to the ventricle when no ventricular dilation is present (5). They note that access from the suprasylvian window may be hampered when the lateral ventricle is small and/or positioned high. Our group has not encountered this difficulty possibly due to utilization of the operative microscope and we dispute the suggestion that small ventricular size is a contraindication for PIH.

A second criticism is concerned with the potential for marked cerebral edema following the sacrifice of perisylvian vasculature during exposure of the supra- and infra-sylvian windows. Our initial strategy was similar to Villemure whereby all the vessels around the sylvian fissure were sacrificed as the supra, and infra-sylvian windows were created (3,4). More recently, our strategy has been to preserve as many of the larger vessels as is feasible leaving them to bridge across the window portals. Shimizu and Maehara also note the preservation of large posterior draining veins
to reduce postoperative venous congestion (5). While a theoretical concern, clinically relevant postoperative edema has only been reported in one patient following PIH (5).

PIH is a relatively new technique for obtaining hemispheric isolation without extensive cortical resection. While relatively few reports have come forth in support of the technique, those patients reported in the literature have benefited from decreased operative times, decreased blood loss, equivalent seizure control rates, and reduced postoperative rates of aseptic meningitis. PIH patients have experienced shorter recovery times and there is a trend toward a reduced need for postoperative VP shunting. Overall, PIH seems to have many benefits compared to functional hemispherectomy or hemidecortication; however, given the limited number of patients who have undergone the procedure, more experience is needed to make definitive conclusions regarding the efficacy of the technique.

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Chapter XI-34
Hemispherical Deafferentation via the Trans-sylvian Keyhole

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Functional hemispherectomy procedures obviously are used more frequently in recent years, judged by the number of articles with results of clinical series and surgical modifications. In light of this increased interest and increasing numbers of epilepsy surgery centers considering taking up this kind of procedure, a discussion of the arguments that speak for the use of hemispherical deafferentation (or hemispherotomy) as opposed to other approaches will be the topic of this chapter. We will try to frankly review advantages and disadvantages of this procedure trying to offer information for those who want to take up this procedure and for more experienced surgeons to consider changing to this procedure.

Whereas hemispherectomy means the removal of a brain hemisphere, hemispherotomy describes various procedures that have the disconnection of the cortical layer of one hemisphere in common. A number of hemispherotomy procedures have been described recently, sometimes with little, sometimes with more brain resection (1–6). First ideas for these disconnective procedures which are justifiably called hemispherotomy procedures were mentioned in abstracts from three groups (5,7). The hemispherectomies grouped together here represent more disconnective than resective approaches. They comprise the older technique of peri-insular transcortical deafferentation, the trans-sylvian keyhole, the peri-insular hemispherotomy, the Delalande’s transcortical subinsular hemispherotomy, and the Japanese peri-insular modification (1–3,5–8). A functional hemispherectomy is not equivalent to an anatomical hemispherectomy but to a procedure that is functionally equivalent to hemispheric removal, but larger parts of the hemisphere such as the frontal lobe may just be disconnected and left behind. The prototype of functional hemispherectomy is represented by Rasmussen’s technique. The term “hemispherical deafferentation” avoids the impression in the non-neurosurgeon that large parts of the brain are removed. The procedures depicted in Figure 1 all have in common the principle of relatively small brain tissue resection combined with a transventricular disconnection of the hemisphere from its cortical layer and the long tracts down to the basal ganglia.
A review of the steps necessary for the different procedures has recently been published, apart from an anatomical study, which outlines the important steps that the procedures all have in common to achieve satisfying seizure freeness (9,10). For this group the reasons to go from the transcortical perisylvian approach to the trans-sylvian approach are well illustrated by the figures for surgical time and blood replacement (Table 1) (1,2). Not only was the trans-sylvian keyhole approach necessitating blood replacement in lower volumes but also in a much lower number of patients compared to the first used transcortical technique, but it was considerably more advantageous in this respect compared to the old Rasmussen technique. Whereas in Rasmussen's functional resection technique all cases needed blood replacement with a mean replaced blood volume of 835 ml, our older transcortical technique necessitated blood replacement in 58% of the cases with a mean volume of 315 ml. The newer trans-sylvian keyhole deafferentation technique using the transventricular approach necessitated blood replacement in only 15% of the cases and the average amount of

Figure 1  Schematic drawing of disconnections on coronal hemispheric cuts for four disconnection hemispherotomy types. (A) Trans-sylvian transcortical transventricular keyhole (2). (B) Perisylvian transcortical window (3). (C) Japanese modified perisylvian window (6). (D) Dorsal parasagittal transcortical transventricular technique (5,8).
Deafferentation via the Trans-sylvian Keyhole

Table 1  Blood Replacement and Surgery Times for Own 20 Cases of Transventricular Keyhole Procedures

<table>
<thead>
<tr>
<th>Surgery type</th>
<th>Rasmussen’s resectionᵃ (n = 17)</th>
<th>Perisylvian deafferentationᵇ (n = 12)</th>
<th>Trans-sylvian keyhole (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (hr)</td>
<td>6.3 (3.25–8.75)</td>
<td>4.9 (3.25–8.6)</td>
<td>3.6 (2.1–5.0)</td>
</tr>
<tr>
<td>Extubation within (hr)</td>
<td>6.2 (1–68)</td>
<td>5.6 (1–30)</td>
<td>5.0 (1–18)</td>
</tr>
<tr>
<td>Intraoperative blood replacement (ml) (only transfused patients)</td>
<td>835 (270–2200)</td>
<td>315 (150–600)</td>
<td>266 (200–400)</td>
</tr>
<tr>
<td>Intraoperative blood replacement (ml) (whole group)</td>
<td>835 (270–2200)</td>
<td>184 (0–600)</td>
<td>40 (0–400)</td>
</tr>
<tr>
<td>Number and percentage of patients with blood replacement</td>
<td>17/100%</td>
<td>7/58%</td>
<td>3/15%</td>
</tr>
</tbody>
</table>

ᵃData from Bonn series, partly mentioned before (2).
ᵇThe perisylvian group (n=12) originally published contained one keyhole case, which is now in the keyhole group.

Source: From Ref. 9.

transfused blood was 266 ml. Another group was able to confirm these lower numbers for required transfusions as compared to hemidecortication, plus a zero incidence of intraoperative hypotension, as well as a significantly decreased blood loss for a related hemispherotomy technique, the peri-insular window technique (11). A reduction of blood loss from a mean of 1300–452 ml could be demonstrated by going from a hemidecortication procedure to a disconnective procedure. A similar reduction in amount of blood replacement was found by Shimizu and Maehara to a mean of 422 ml with 79% of their cases needing blood replacement, but they had a high proportion of dysplastic cases known to increase blood loss. Another group also found decrease in blood loss with a disconnective procedure in two patients (12).

If one tries to weigh the advantage of the trans-sylvian hemispherotomy (or trans-sylvian disconnection procedure) toward the more voluminous resection types (hemidecortication, Rasmussen’s technique, or Adam’s modification) it appears that the advantages of the much smaller exposure and shorter operation time speak for themselves.

Whether Delalande’s technique or the perisylvian window techniques of Villemure and Mascott differ much from our own technique regarding operating room time and blood replacement cannot be judged upon, since no good figures are available for operation time, blood loss, and long-term complications (3,5,8). The latter technique and the related technique described by Shimizu and Maehara differ from our own in that they remove a certain part of the frontal operculum or the frontal operculum plus the underlying white matter down to the ventricle (6). This brings with it the problem of handling the candelabra-like major branches of the middle cerebral artery that first run underneath the operculum, then come on top of it and run over its surface towards the midline. These can be occluded, facilitating the opercular resection, but then a risk of space occupying infarction arises. In the cases of hemimegalencephaly where we use opercular resection we always try to preserve some of these candelabra-like branches. Undoubtedly the removal of a larger block of tissue makes more manipulation necessary, but whether this is a deciding disadvantage remains open.
Some discussion is needed concerning some true or perceived uncertainties about the trans-sylvian keyhole disconnection procedure (or the related procedures of Villemure, Shimizu, and Maehara). In meetings one can still hear that it has not been demonstrated that these disconnective or hemispherotomy procedures produce a higher rate of seizure-freedom than the anatomical or the decortication procedures. Another group was skeptical concerning the completeness of the disconnection and believed that the seizure-freedom rate would be lower. This question, however, can be answered as discussed in our article by referring to the extensive review of 328 patients from 11 centers published in a congress volume by Holthausen et al. (2,13). In these cases compiled from several centers \((n = 56)\) the hemispherotomy procedures as a group had a better seizure outcome (85.7% Class I) than the Rasmussen technique (66.1% Class I), or Adam’s technique (78.3% Class I), or the hemidecortication techniques (60.7% Class I). Whereas in the aforementioned series the seizure-freedom rate for all the hemispherotomy cases was 85.7%, in a large hemidecortication series it was lower (65%) with 58 and later 106 cases (14–16). So the facts demonstrate achievement of a reliable seizure-freedom rate with the disconnection procedure. In our own series of 20 keyhole technique cases, the seizure-freedom rate was 88% with a mean follow-up of 46 months (9).

Since the trans-sylvian/transventricular keyhole approach (and the related procedures) implies a total opening of the lateral ventricle from frontal horn to temporal horn and a lengthy intraventricular manipulation, a principal matter of concern is hydrocephalus that may be seen after any intraventricular procedure. At the time of publishing our first 20 cases there had been no case of hydrocephalus among the 20 first patients. At this time, having done 51 trans-sylvian keyhole disconnection cases, we have seen two cases of hydrocephalus. Since hydrocephalus may develop much later this is not necessarily the final figure to be observed in that series.

It has to be mentioned that related hemispherotomy techniques with a similar transventricular approach had a certain shunt rate: 10 shunts for 53 cases for the Delalande technique, 5 shunts for 32 cases with Shimizu’s and Maehara’s technique, and 5 out of 63 cases with the perisylvian window technique of Villemure et al. (6,8). It can therefore not be denied that the disconnection procedures that use the transventricular route will have a certain incidence of shunting, which may not yet have reached its full extent, since this type of surgery was not started until about 10 years ago. One should not forget that in long-term follow-up total anatomic hemispherectomy led to shunt rates of up to 50% (52% in the Montreal series). Other authors have reported relatively high rates of hydrocephalus for the decortication techniques: 20% and 33% (17,18). It appears that the hydrocephalus rate compared to the classic anatomic resection is lower with Adam’s technique but not lower than with the disconnection techniques (4). The hydrocephalus rate for a series of 54 Rasmussen technique cases was only 7% (4). In summary, although the disconnective procedures also have a certain shunt rate, it appears lower than in anatomical hemispherectomy.

Another possible disadvantage is the possibility for incomplete disconnection. Small numbers of cases with incomplete disconnection with the disconnection type of surgery have been reported necessitating reoperation (6,8). In our own series we have not seen such a case so far. One case with suspect incomplete disconnection was revised but found to be completely disconnected. We have, however, seen cases where the frontobasal disconnection line was not placed ideally posterior, i.e., close to the anterior cerebral artery (9). These experiences have to be weighted against the fact that incomplete disconnections may also occur in the Rasmussen type of surgery. In a large series Peacock et al. (19) had to do several reoperations for completion of disconnection.
Some hemidecortication procedures do not try to completely remove all areas of cortex; for example, the posterior frontobasal cortex is not entirely removed. A limitation of the trans-sylvian/transventricular hemispherotomy procedure is the fact that it is not the easiest procedure for hemimegalencephaly (HME). For HME cases it should only be used in combination with the resection of the frontal operculum or the resection of the temporal lobe, to have easier orientation and to leave some space for postoperative swelling. For HME cases we prefer the resection of the frontal operculum (very similar to Villemure) because in these enlarged brains this makes access to the lateral ventricle easier. It should be stressed that the trans-sylvian/transventricular procedure is ideal for very atrophic hemispheres and for all cases with porencephalic cysts, since in these cases the intradural part of the surgery can be finished within 1.5 to 2 hours.

In summary, it can be said that the trans-sylvian keyhole hemispherotomy (or trans-sylvian/transventricular disconnection) has undisputed short-term advantages (short operation time, low amount of transfused blood, and low number of transfused patients). Since follow-up times are no longer than 10 years, certain types of complications which may appear later or much later after surgery can not yet be fully judged upon, e.g., hydrocephalus. It appears safe to conclude that the seizure-freedom rate is likely to be better and certainly not systematically worse with the disconnection procedures compared to more resective procedures, such as anatomic resection, Rasmussen’s technique, or hemidecortication.

A final assessment of the advantages and disadvantages of these connective procedures (very similar to the procedures described by Delalande, Villemure, and Shimizu) will only be possible after another 10 to 15 years when larger numbers of cases have been followed up for well over 20 years.

REFERENCES

Hemicorticectomy, or hemidecortication procedures, were developed as an alternative to the anatomic hemispherectomy. The rationale behind the procedure is to remove the cortex, where seizures arise, while leaving the structural support of white matter and subcortical structures behind. Series that have employed this procedure have demonstrated good results and avoided some of the more morbid complications associated with anatomical hemispherectomy.

As discussed in other reviews, care must be taken when comparing surgical approaches when modern series have taken advantage of the advances in microscopic techniques that were unavailable to the pioneers of these procedures. In modern series, the hemidecortication does not appear to have the rates of morbidity and mortality previously associated with large resections (e.g., anatomic hemispherectomy). Functional disconnections do appear to be associated with quicker surgery and less blood loss than the decortications, but this again may be dependent on surgeon experience with a given procedure.

In the hemidecortication procedure, the depth of the convexity gray matter is entered and then a surgical plane developed within the white matter, deep to the sulci, removing the frontal and parietal cortex. A similar “degloving” is performed for the occipital and temporal lobes (1). The theoretical disadvantages include leaving behind posterior inferior frontal lobe, insular cortex (true of many of the disconnection procedures as well), and possibly portions of temporal lobe (1). The latter is avoided by incorporating a mesial temporal resection in some versions of decortication (2–4). Aside from a mesial temporal resection, the decortication procedure does not involve widely opening the ventricle. This may reduce the risks of postoperative hydrocephalus, and other wound complications related to cerebrospinal fluid collections. Aseptic meningitis appears to remain a problem despite avoiding large ventricular entry (3).

The results of decortication are comparable to other techniques, albeit based on small, single institution series for any given procedure (3–5). The largest series, from Johns Hopkins, reports outcomes comparable to other techniques (4). The indications for decortication are the same as for any hemispherectomy procedure (6). Depending
on pathology, hemidecortication resulted in long-term seizure freedom in 50% (migrational disorders) to over 80% for seizures secondary to congenital vascular injury. Even in the poorest outcome case of hemimegalencephaly, hemidecortication resulted in significant improvement in most patients and hemispherectomy should be strongly considered in patients with hemimegalencephaly and severe seizure disorder (4,7,8).

REFERENCES

Section XII
Vagus Nerve Stimulation: History and Overview

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BRIEF HISTORY

In 1985, Zabara (1) postulated that if vagus nerve stimulation (VNS) could desynchronize electroencephalographic activities, epileptic seizures might be attenuated. Earlier studies of VNS in animals had provided a good basis for Zabara’s hypothesis. In 1938, Bailey and Bremer (2) had elicited desynchronized orbital cortex activity using VNS in a feline model. In 1952, Zanchetti et al. (3) published their findings that intermittent VNS reduced or eliminated interictal epileptic effects chemically induced in focal cortex of cats. In 1980, Radna and MacLean (4) showed that VNS in the monkey caused marked single-unit effects on basal limbic structures. Zabara found support for his hypothesis in his subsequent animal studies, which led to the earliest human epilepsy trials.

Data from McLachlan’s studies, in which focal penicillin, cortical injection, and then pentylenetetrazol were used to trigger secondarily generalized seizures in rats, indicated that VNS has acute abortive effects when applied after seizures begin (5). Takaya et al. (6) demonstrated that VNS exerts a persistent anticonvulsant effect when administered immediately before induced seizures. Seizures were less severe in rats that had received VNS than in control rats. The greatest seizure-reducing effects occurred after 60 minutes of continuous VNS. Intermittent VNS was less effective than continuous VNS but more effective than when VNS was applied for only one minute before seizure induction. Effectiveness decreased with time after discontinuation of VNS, thus establishing its acute, prophylactic effects.

Lockard et al. (7) reported a prophylactic effect when VNS was administered over a period of two to six weeks in an alumina gel monkey model. These animal studies offered a foundation for future mechanism-of-action studies with VNS therapy.
in humans and contribute to a better understanding of how VNS therapy achieves anticonvulsant effects.

In 1988, Penry and others began treatment of the first human with VNS therapy delivered by the commercial VNS Therapy System (Cyberonics, Houston, Texas, U.S.A.). This pilot study demonstrated that VNS therapy was safe, and its efficacy in treating epileptic seizures warranted additional studies (8). A total of five clinical trials of VNS therapy for the treatment of epilepsy were conducted, with the final one being completed in 1996.

CLINICAL TRIALS

In 1999, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology noted the “sufficient evidence exists to rank VNS for epilepsy as effective and safe, based on a preponderance of Class I evidence.” This statement followed the committee’s evaluation of the second randomized, controlled, multicenter trial, known as E05. In both of the parallel clinical trials, E03 and E05, subjects with intractable partial seizures were randomized to either high or low stimulation for a period of three months, and raters were blinded to the subject’s stimulation parameters. The average reduction in seizure frequency was about 25% to 30% as compared with baseline, and 310 subjects completed the trials (9). The European Community approved VNS therapy for epilepsy in 1994, and, in 1997, the U.S. Food and Drug Administration (FDA) approved VNS therapy “for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial-onset seizures which are refractory to antiepileptic medications” (10). Two longitudinal pilot studies, E01 and E02, provided efficacy analyses for a total of 15 subjects. An open-label, compassionate-use study, known as E04, provided efficacy results for 116 subjects and included subjects younger than 12 years and those with generalized seizures (10). Since completion of the clinical trials, more than 32,000 epilepsy patients in over 24 countries have accumulated over 100,000 patient years of experience using VNS therapy (data on file at Cyberonics).

SIDE EFFECTS

The most frequently noted side effects during the clinical trials were hoarseness and occasional shortness of breath (9). In our clinical experience, voice alteration, cough, pain, and dypsnea are the most commonly reported side effects. Most patients are not bothered by the voice alteration. Some patients place the magnet over the generator to temporarily stop stimulation while they are speaking or singing. Generally speaking, side effects associated with VNS therapy are mild and patients usually become accustomed to them over time. Side effects may be ameliorated by altering parameter settings. For example, reduction in the pulse width or signal frequency (without changes in output current) may be effective in eliminating side effects. If these measures fail, only a slight reduction in output current is all that is usually necessary to produce the desired effect.

LONG-TERM RESULTS

The manufacturer of the VNS therapy device undertook a long-term outcome registry that compiled information about patients receiving VNS therapy for
Physicians who chose to participate in the registry submitted data describing their patients’ baseline status and progress with VNS therapy over time, with a maximal follow-up of 24 months. The first visit date recorded was November 7, 1997, and the registry closed on April 1, 2003. Follow-up data are not available for every patient at every interval. Median seizure reductions were 46% \((n=4448)\) after three months of VNS therapy, 57% \((n=2696)\) after 12 months, and 63% \((n=1114)\) after 24 months. Ages ranged from 1 to 83 years at each interval. Although new data are no longer being accepted into this original VNS therapy registry, physicians can consult it to obtain outcome data of patients with characteristics similar to those of potential VNS therapy patients. In addition, this registry has provided data for articles discussing the earlier use of VNS therapy (11), outcomes in pediatric patients, quality of life, patients with mental retardation and developmental disabilities, antiepileptic drugs, VNS therapy after epilepsy surgery, and Lennox–Gastaut syndrome (12–18).

Two recently published retrospective case series discussed the long-term outcome of patients receiving VNS therapy. A series reporting five-year or greater outcomes of 26 patients from the University of Wisconsin noted that the median frequency of seizures reported after one year of VNS therapy was decreased from baseline (–28%), but had decreased even more by the long-term follow-up (–72%). Six of the patients had not experienced a reduction in the frequency of seizures after one year of VNS therapy, but four of them had experienced reductions by the long-term follow-up. The authors recommended that clinicians not rush the decision to discontinue VNS therapy for patients who have not yet experienced a response (19). In another retrospective report, Uthman et al. (20) discussed outcomes of 48 patients treated with VNS therapy up to 12 years. The authors reported changes in seizure frequency with both declining \(n\) and last visit carried forward analyses. Similar to the Spanaki et al. (19) study, reductions in seizure frequency increased with time, e.g., at six months reductions were 22\% \((n=47, \text{both declining } n \text{ and last visit carried forward analyses})\) and at 12 years they were 82\% \((n=2, \text{declining } n \text{ analysis})\) and 52\% \((n=7, \text{last visit carried forward analysis})\). The effectiveness of VNS therapy was sustained, and patients did not develop a tolerance to it over time.

QUALITY OF LIFE

During the earliest trials for VNS therapy, investigators noted marked changes in alertness and improved quality of life for subjects receiving VNS therapy. Improvements in quality of life have been documented among patients enrolled in the VNS registry and completing the Quality of Life in Epilepsy Inventory (QOLIE) 10, a 10-question assessment of quality of life for patients with epilepsy (14). In the long-term Spanaki et al. (19) study, patients without reductions in the frequency of seizures after one year of VNS therapy nevertheless elected to continue the treatment because they felt it was helping to improve their quality of life through shorter seizures, reduced postictal confusion, and use of the magnet to interrupt or diminish seizures. On July 15, 2005, the FDA approved VNS therapy for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments (21). This additional benefit of VNS therapy may bear consideration by physicians who treat epilepsy patients with comorbid depression.
MECHANISM OF ACTION

When the FDA approved VNS therapy, the mechanism of action was not well understood, but subsequent research has suggested that the antiseizure effect of VNS therapy is the result of multiple actions. The widespread, bilateral, multisystem, polysynaptic projections of the left vagus nerve account for the multiple therapeutic mechanisms of VNS therapy (22). Additional studies will reveal more information about the mechanism of action of VNS therapy.

VNS THERAPY AND INTERMITTENT HYPOCAPNIA

Holmes et al. (23) explored the idea that VNS therapy might help control seizures through its effects on the neuronal microenvironment. Their study supposed that the preictal state could be affected by a small change in carbon dioxide levels. They monitored end-tidal carbon dioxide (EtCO₂) levels of 13 adult patients receiving VNS therapy during daytime sleep. The frequency or amplitude of respiration was altered in 10 of the 13 patients. In five patients, the increased respiratory rate was accompanied by a significant decrease in EtCO₂. Changes in EtCO₂ during VNS were occasional for an additional three patients and not clearly discerned for two other patients. Although the study did not directly show the effect of hypocapnic episodes on the frequency or occurrence of seizures, it did provide a basis for further exploration of the role of VNS-induced hypocapnia on the changes between the preictal and interictal states.

SURGICAL PROCEDURE

The VNS therapy system consists of an implantable pulse generator and bipolar lead, as well as an external programming system, which is used to adjust stimulation settings. The pulse generator transmits electrical signals through the bipolar lead to the vagus nerve. The surgery to implant the pulse generator and attach the electrodes to the vagus nerve generally takes < 2 hours and is performed usually while the patient is under general anesthesia, although local anesthesia is an option. Two incisions are usually required, one for placing the pulse generator in the patient’s left upper chest, below the clavicle, and the other for attaching the electrodes to the vagus nerve in the neck. The surgeon uses a specially designed tunneling tool to form a subcutaneous tract between the two incisions. After intraoperative testing of the lead, the incisions are closed, and the device is set as inactive for a two-week recovery period (24). Surgical complications include infections that occur postoperatively in about 3% to 6% of patients and rare instances of transient paralysis of the left vocal cord. The infections are usually treated with oral antibiotics and rarely require removal of the pulse generator or electrodes (25). Some infrequent incidents of bradycardia with or without asystole have occurred during the intraoperative lead test. Clinicians should be prepared to follow the guidelines of Advanced Cardiac Life Support if, during the lead test or when stimulation is initiated, a patient experiences severe bradycardia (heart rate < 40 beats/min) or a clinically significant heart rate change (10).

The left vagus nerve was selected for placement of the VNS therapy electrodes because the parasympathetic fibers of the left vagus nerve less densely innervate the ventricles than those of the right vagus nerve that more densely innervate the cardiac atria. Given this difference, VNS therapy is applied to the left, rather than right, vagus nerve in an effort to avoid cardiac effects (22).
INITIATING STIMULATION

Although physicians at some centers initiate stimulation at the conclusion of the implantation procedure or before the patient is discharged from the hospital, the manufacturer recommends a two-week recovery period to allow for healing before stimulation is begun. If, during the intraoperative lead test, a patient experienced asystole, severe bradycardia, or a clinically significant change in heart rate, the patient should be placed on a cardiac monitor while stimulation is initiated (10).

Suggested initial programming settings are 0.25 mA output current, 20–30 Hz frequency, 250–500 μsec pulse width, on for 30 seconds, and off for five minutes. Most physicians slowly titrated the output current from 0.50 to 1.50 mA over a period of about one month. The physician should monitor the patient’s ability to tolerate the output current and make adjustments for the patient’s comfort by first reducing the pulse width, then frequency, then, as a last resort, output current one level. Once pulse width and frequency have been reduced, reduction of the output current may not be required. If needed, the pulse width can be reduced from 500 to 250 μsec, then the output current can be increased while the pulse width is reduced. Patients should be monitored to make sure that they can tolerate the parameter settings before they depart the physician’s office. If symptoms of shortness of breath, throat tightness or discomfort, excessive hoarseness, or difficulty with swallowing are present, reducing the output current or duty cycle can alleviate these complaints (26).

VNS MAGNET THERAPY

Being able to use the VNS therapy magnet is not a requirement for a patient with epilepsy to be a candidate for VNS therapy. However, many patients and their caregivers do derive benefits from using the magnet. VNS therapy patients with epilepsy receive a magnet that can be swiped over the implanted pulse generator to deliver on-demand stimulation when the patient or caregiver senses an impending seizure. Patients who experience hoarseness during VNS may wish to stop stimulation while they are speaking or singing. Holding the magnet over the implanted pulse generator will stop the stimulation cycle until the magnet is removed. Because some patients become accustomed to VNS therapy and hardly notice the stimulation, the manufacturer recommends that patients apply the magnet daily to ensure that the device is working and the battery is not depleted.

The VNS therapy magnet is the only abortive therapy available without sedative side effects. Swiping the magnet over the chest area where the pulse generator is implanted will trigger the on-demand stimulation. Because the window of opportunity for applying the magnet to abort a seizure is of quite short duration, the manufacturer supplies the magnet in two forms so that it is readily available: worn on the wrist, similar to a wristwatch, and at the waist, similar to a cellular telephone. In our clinical experience, some patients or their caregivers are able to swipe the magnet and abort an impending seizure. In other instances, swiping the magnet lessens the duration or severity of the seizure. Many patients are unable to use the magnet, either because they do not have auras that signal impending seizures or they are physically unable to swipe it over the implanted pulse generator. However, even for these patients, a caregiver may be able to swipe the magnet and lessen the seizure. Some patients with epilepsy, especially pediatric patients, experience periods during which they are at greater risk of experiencing seizures. Again in our
clinical experience, prophylactic use of the magnet during these periods has reduced the use of “rescue benzodiazepines” by many of these same patients. Such results warrant further investigation of prophylactic use of the VNS therapy magnet.

BATTERY END OF SERVICE

Early models of the VNS therapy generator had relatively short battery lives, but the pulse generators currently being implanted (Models 102 and 102R) typically last about eight years, depending on the parameter settings and the extent of magnet use. During the battery’s end of service period, the pulse generator may deliver unscheduled stimulation that may be above or below the output programmed by the physician. When the battery is depleted, the pulse generator will not deliver VNS therapy, the patient will not feel the stimulation, and the programming wand will not be able to communicate with the device. In addition, the patient may experience increased seizure frequency, intensity, or duration. Pulse generators currently being implanted have an elective replacement indicator (ERI) that warns of the impending depletion of the battery when the physician interrogates the device during an office visit. The interval between the appearance of the ERI and the depletion of the battery depends on the device settings (10). To ensure uninterrupted treatment, most physicians recommend replacing the pulse generator before it is depleted.

PULSE GENERATOR REPLACEMENT

Replacing the pulse generator does not necessarily entail replacement of the lead, unless the physician suspects that the lead is fractured. For most patients, replacing the pulse generator requires dissection to the pulse generator with avoidance of damaging or cutting the lead. The surgical procedure usually requires one hour or less. In the Uthman et al. (20) long-term report, one patient had undergone seven replacements of the pulse generator, to include two revisions of the electrodes. Espinosa et al. (27) have described the surgical technique of electrode revision and noted the lack of gross changes to the vagus nerve after they had removed the electrodes. The decision to replace or remove the leads and electrodes, because VNS therapy is not effective, must be considered in light of the patient’s wishes, status of health, and the risks inherent in the surgery. When patients decide to discontinue VNS therapy, most physicians advise that the device be turned off and left in place for some time to allow time for a final decision before removal. When the decision is made to permanently discontinue VNS therapy, some patients choose to have the pulse generator removed. In most cases, the leads and electrodes are left in place.

PRECAUTIONS

Several precautions must be observed when treating patients implanted with the VNS therapy device. Shortwave diathermy, microwave diathermy, or therapeutic ultrasound diathermy cannot be used on patients implanted with the VNS therapy device. This contraindication does not include diagnostic ultrasound. The energy delivered by diathermy can concentrate in the device and cause heating which may damage tissue.
In addition, patients may require special positioning for mammography procedures. Most routine diagnostic procedures, such as fluoroscopy and radiography, are not expected to affect the system. Therapeutic radiation, external defibrillation, or electro-surgery may damage the pulse generator. Magnetic resonance imaging (MRI) should not be performed with the MR body coil in the transmit mode. Only a transmit-and-receive type of head coil should be used if an MRI is required, and the pulse generator output current should be programmed to 0 mA for the procedure. Additional instructions regarding MRIs are included in the VNS Therapy Physician’s Manual (10). In our clinical experience with use of the head coil, MRI can be routinely performed on patients with the VNS therapy device. Extracorporeal shockwave lithotripsy may damage the pulse generator, as may therapeutic ultrasound. If a patient requires a medical treatment involving electric current being passed through the body [such as a transcutaneous electro-nerve stimulator (TENS) unit], the output current should be set to 0 mA or else the function of the pulse generator should be monitored.

COST–BENEFIT ANALYSES

Several studies have discussed the cost–benefit profile of VNS therapy. During 1999, Boon et al. (28,29) of Belgium published two cost–benefit studies. One study featured results of 15 patients and reported that epilepsy-related direct medical costs per patient decreased from yearly pre-implantation estimates of $8830 to $4215 during the 12 months after implantation. In addition, the average number of days of hospitalization decreased from 21 to 8 days per year (28). The other cost–benefit study published by Boon et al. during 1999 featured 20 patients and reported that mean epilepsy-related direct medical costs per patient decreased from $6682 to $3635 per year. In addition, the average number of days of hospitalization decreased from 16 to 4 days per year (29). A study conducted in the Netherlands and published in 2001 considered both direct and indirect costs six months before and six months after implantation of the VNS therapy device in 16 patients with Lennox–Gastaut syndrome. During the six months after implantation, average direct and indirect costs were 2876.06 Euros less than during the six months before implantation (30). In 2002, Boon et al. (31) published a study comparing costs of 84 patients with refractory epilepsy who were treated with antiepileptic drug polytherapy ($n = 24$), epilepsy surgery ($n = 35$), and VNS therapy ($n = 25$). Average epilepsy-related direct medical costs decreased in all three groups: from $2525 to $2421 for patients who received antiepileptic polytherapy, from $1465 to $1186 for patients who underwent epilepsy surgery, and from $4826 to $2496 for patients who received VNS therapy. A study from Sweden, which was published in 2002, compared hospital costs 18 months before with those 18 months after implantation of the VNS therapy device in 43 patients and found an average annual cost savings of about $3000 per patient (32). A study from the United Kingdom, which was published in 2003, developed an economic model that attempted to measure increases in quality-adjusted years of life gained with VNS therapy. The authors concluded that the decision to implant a patient with the VNS therapy device should be on a clinical or efficacy basis because the economic model did not present a strong argument against implantation (33). Studies by Boon et al. (28,29), Majoie et al. (30), and Ben-Menachem et al. (32) provided data that showed cost savings over the battery life of the VNS therapy device could equal or exceed the costs associated with the implantation of the device.
VNS THERAPY IN THE EPILEPSY TREATMENT SEQUENCE

Physicians differ in their opinions about when it is appropriate to begin discussing the possibility of VNS therapy with a patient. The seizures of up to 40% of the patients with epilepsy may be pharmacoresistant (34). Clinicians may disagree whether polytherapy is appropriate after two trials of monotherapy have failed, but most agree that patients with localization-related seizures should be evaluated for epilepsy surgery if the third drug trial fails to control the seizures (35). In the authors’ personal clinical practices, we follow a treatment progression as shown in Figure 1. If the third round of antiepileptic drugs (either monotherapy or polytherapy) does not control a patient’s seizures, we recommend that the patient be evaluated for epilepsy surgery. This evaluation allows us to confirm our diagnosis regarding the epilepsy syndrome and type of seizure. It also helps to reduce the likelihood of implanting the VNS therapy device in a patient with psychogenic seizures. Furthermore, defining the syndrome and diagnosis positions us as clinicians to provide better-informed advice and options during future discussions of treatment.

Once the patient has been evaluated for surgery, the epilepsy syndrome defined, and the location of the seizures identified, we can then discuss treatment options with the patient and the patient’s family. If a patient with pharmacoresistant seizures is a suitable candidate, we recommend epilepsy surgery. We recommend VNS therapy for patients who are not suitable candidates for epilepsy surgery, those who are reluctant to undergo epilepsy surgery, those who cannot tolerate antiepileptic drugs and are not good candidates for epilepsy surgery, and those for whom epilepsy surgery is not successful in controlling their seizures. In addition, we prescribe antiepileptic drugs to patients who have undergone epilepsy surgery or implantation of the VNS therapy device according to their clinical needs. Introducing the concept of epilepsy surgery or VNS therapy after the failure of the third antiepileptic drug provides a wider range of options earlier in the course of the disease than was previously available.

CONTRIBUTING AUTHORS

This section includes chapters that discuss various aspects of VNS therapy and compares it with more traditional treatments for seizures. Thomas R. Henry of Emory University discusses the mechanism of action unique to VNS therapy. Martin C. Salinsky of the Oregon Health and Sciences University Epilepsy Center compares the efficacy of VNS therapy with other medical and surgical treatments and reminds the reader that each patient should be considered individually. Dieter Schmidt of the Epilepsy Research Group in Berlin conducted a review of the literature describing outcomes comparing the results of corpus callosotomy with VNS therapy. His conclusions echo those of Salinsky, that VNS therapy is less invasive, reversible, and has fewer side effects than corpus callosotomy and should be considered first for patients with pharmacoresistant Lennox–Gastaut syndrome or partial epilepsy when resective surgery is not appropriate. Considering a population for whom epilepsy surgery is not usually an option, Mark D. Holmes of the University of Washington reviews reports of VNS therapy among patients with generalized seizures. His report includes a summary of the results of 16 patients with generalized seizures whose medications remained stable throughout the trial, so the overall median seizure frequency reduction of 43.3% could be attributed solely to VNS therapy. Each of these authors brings his experience and knowledge to share his distinctive perspective of VNS therapy.
Figure 1  Epilepsy treatment sequence. Ketogenic diet is an age-specific treatment. *Abbreviation:* AEDs, antiepileptic drugs. *Source:* From Refs. 13, 35.
CONCLUSION

During the eight years since the FDA approved VNS therapy, it has become a mainstay in the comprehensive treatment of epilepsy. Although the FDA approved it for partial-onset seizures for persons aged 12 years and older, clinical experience has shown VNS therapy’s usefulness in treating a broad spectrum of epilepsy disorders. With few or no side effects, VNS therapy is complementary to antiepileptic drugs, and serves as a reasonable option for patients with pharmacoresistant epilepsy who are not good candidates for epilepsy surgery.

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Chapter XII-36
The Efficacy of Vagus Nerve Stimulation Relative to Other Medical and Surgical Treatments

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Vagus nerve stimulation (VNS) has been shown to be an effective treatment for epileptic seizures. As the first medical device approved for the treatment of epilepsy, its unique role in treatment is still being examined. Decisions regarding when to use VNS are best made in light of objective data. The next paragraphs review the efficacy of VNS relative to antiepileptic drugs (AEDs) and epilepsy surgery.

VNS EFFICACY

VNS efficacy was established in two randomized, controlled, double-blind trials, of nearly identical design (Class I evidence) (1,2). Patients with medically refractory partial seizures were implanted with vagal stimulators, and then randomized to receive “high” stimulation (presumed effective dose based on preliminary studies) or “low” stimulation (presumed ineffective dose). Seizure counts during 12 weeks of VNS were compared to counts during a 12-week pre-implantation baseline. AEDs were held constant. A total of 310 patients were enrolled. Results of the two studies were similar. Percentage reduction in seizure frequency (from baseline) was significantly greater with “high” stimulation (24.5% and 27.9% for the two trials) compared to low stimulation (6.1% and 15.2%). A significantly greater percentage of patients in the “high” stimulation group had at least a 50% reduction in seizure frequency (50% responder rate), as compared to the “low” stimulation group. These pivotal results led to Food and Drug Administration (FDA) approval of VNS as an adjunctive treatment for medically refractory partial seizures (1997). These remain the only randomized, controlled trials of VNS efficacy. Open-label long-term follow-up studies have reported that overall VNS efficacy remains stable or possibly improves over periods of one to three years (3–5).

Subsequent open-label reports of VNS efficacy in partial seizures have shown 50% responder rates as high as 60% (Class III evidence) (6–9). Open-label reports of
VNS in medically refractory generalized seizures have been encouraging, with a responder rate of 46% in one series (Class III evidence) (10,11). No randomized, controlled studies have been reported.

**VNS VS. AED**

There have been no direct comparisons of the efficacy of VNS and AEDs. Therefore any comparison must be made across clinical trials, despite the drawbacks of this type of meta-analysis. The two randomized, controlled VNS trials studied patients with medically refractory partial seizures, using a 12-week add-on design. A comparison of VNS and AED efficacy would best utilize similar data from randomized, controlled AED add-on trials, in similar populations. Fortunately, the efficacy of all of the newer AEDs has been studied in this manner (Class I data), permitting comparison to VNS. There are no VNS monotherapy trials, so there is no basis to compare VNS with AED monotherapy. In any case, the clinical question of most interest is: Given a patient with partial seizures who has failed several AEDs, would VNS or further AED trials be more effective?

Responder rates have been used for a gross comparison of efficacy across AED trials. Marson et al (12) have summarized 50% responder rates for several of the newer AEDs, based on data from randomized, controlled trials. Figure 1 summarizes their data, presented as odds ratios derived from logistic regression. A ratio of 1.0 indicates no treatment response versus placebo. We calculated the responder rate odds ratio for VNS using data from the two randomized, controlled trials, and charted this in Figure 1. The VNS odds ratio of 2.1 (vs. active control rather than placebo) is similar to that of lamotrigine and gabapentin, and less than that of

![Figure 1](image) **Figure 1** Odds ratios (●) and associated 95% confidence intervals for at least a 50% decrease in seizure frequency in response to gabapentin, lamotrigine, topiramate, tiagabine, zonisamide, and VNS. All data are from randomized, controlled trials in patients with medically refractory partial seizures. Calculations are based on response to active therapy as opposed to placebo (active control in the case of VNS). Source: From Refs. 12, 27.
zonisamide, tiagabine, or particularly topiramate. The overlap of the 95% confidence intervals for all six therapies questions the significance of any differences when this type of gross comparison is used. Therefore, the best available comparison of efficacy between VNS and several of the newer AEDs suggests overall equivalency when treating patients with medically refractory partial seizures, using similar trial designs. Very few patients became seizure-free during these pivotal AED trials, and the same was true for the VNS trials (one of 148 patients randomized to “high” stimulation).

It is tempting to believe that VNS, a very different mode of therapy, would have a better chance of reducing seizure frequency in a patient who has previously failed several AEDs, than would yet another AED. While this hypothesis is attractive (and deserves testing) there exists no controlled data to support it. The comparison of 50% responder rates suggests that medically refractory patients are overall as likely to respond to another AED as they are to VNS.

Efficacy is only part of the equation when selecting therapy for medically refractory patients. Toxicity, particularly neurotoxicity, is often a major concern. Many of our patients have chosen to try VNS prior to an additional AED because they are tired or intolerant of AED side effects. VNS may also be attractive due to its automatic operation, and due to the patient’s ability to self-activate the device during an aura. This latter feature provides a sense of control novel among antiseizure therapies. A majority of patients perceive this to be useful, though there are as yet no convincing data to support this perception (13). For these reasons VNS has met with widespread patient acceptance. Seventy percent of patients exiting the controlled trials chose to have a new device implanted after battery failure (despite a 50% responder rate of only 32%).

VNS VS. EPILEPSY SURGERY

Resective Surgery

The goal of any antiseizure therapy is freedom from seizures. Seizure-free patients will generally have a better quality of life, greater employability, and lower mortality as compared to patients with persistent seizures (14–18). VNS is a palliative therapy whereas resective epilepsy surgery often results in patients becoming seizure-free. Therefore, resection should be preferred to VNS in situations where surgery has a reasonably high likelihood of resulting in seizure freedom, and a reasonably low risk of serious complications. The decision making becomes more complex when a patient is a less than ideal surgical candidate, and when the risks of surgery increase.

Patients with medically refractory partial seizures and surgically remediable epilepsy syndromes have little to gain from a trial of VNS. Ideal candidates for epilepsy surgery include patients with discrete, magnetic resonance imaging (MRI) visible, structural lesions. These include (but are not limited to) patients with mesial temporal sclerosis, cavernomas, and tumors such as gangliogliomas and dysembryoplastic neuroepithelial tumor (DNET). A seizure-free or nearly seizure-free outcome (Engel Class I–II) can be expected in >65% of these patients (18–21). In contrast, only 1% of patients with medically refractory partial seizures treated with VNS in controlled trials became seizure-free. The use of palliative VNS in patients with surgically remediable syndromes would be expected to have a relatively small effect on disability as compared to curative epilepsy surgery (14,15).
Many patients with medically refractory partial seizures are not ideal candidates for epilepsy surgery, due to a higher than average risk of surgical complications and postoperative deficit, lower likelihood of success, or both. As the benefit/risk ratio declines there is a reasonable tendency to continue conservative therapies longer. In these situations a VNS trial (and/or additional AED trials) may be appropriate, with surgery reserved for therapeutic failures. This is a heterogeneous patient group and therefore a blanket statement regarding the utility of VNS is not possible. The decision must be individualized for each patient.

Callosotomy

VNS may be considered as an alternative to corpus callosotomy in the treatment of generalized or multifocal seizure disorders. Again, no formal efficacy comparison has been performed. Callosotomy, like VNS, is a palliative therapy, therefore comparison with VNS is more consistent than a comparison of VNS and resective epilepsy surgery. There are no controlled callosotomy trials. VNS trials in similar populations are also uncontrolled.

Reported 50% responder rates for callosotomy have varied from 48% to 79%, in part due to different patient populations, surgical procedures, and reporting methods (22–25). Patients with drop attacks and generalized tonic–clonic seizures appear to have greatest benefit. Reutens et al. (22) reported a ≥50% reduction in drop attacks in 60% of 45 patients followed for a mean of 29 months, results similar to those of Oguni et al. (24). These results are most appropriately compared to open-label VNS experience in patients with Lennox–Gastaut syndrome (LGS). The largest reported series included 50 LGS patients from six centers (Class III data) (26). At one month follow-up 43% of patients had a ≥50% reduction in overall seizure frequency, rising to 56% after three months (n = 43). None were seizure-free. Drop attacks decreased by 55% during the first three months of VNS. There were no significant complications. Given the difficulties in assessing the efficacy of LGS therapies, these encouraging open-label results should be interpreted cautiously.

The above studies suggest that both procedures are palliative and that VNS is nearly as effective as callosotomy in the treatment of seizures in LGS, particularly drop attacks. The operative morbidity, potential neurological complications, and cost of callosotomy are significantly greater than those of VNS. Therefore it is most reasonable to try VNS first, reserving callosotomy for VNS failures.

CONCLUSION

VNS is approved for the treatment of medically refractory partial seizures. In this population, the overall effectiveness of VNS is similar to that of several recently approved AEDs. There is no evidence indicating that VNS is more (or less) likely to be effective than additional AED trials in patients who have failed several AEDs. Patients with medically refractory seizures and surgically remediable epilepsy syndromes have little to gain from a trial of VNS as resective surgery results in seizure-free outcomes for a majority of patients, and VNS rarely does so. Those patients who are less than optimal candidates for resective surgery may benefit from a VNS trial, depending on the individual’s risk/benefit ratio for resective surgery. VNS can be recommended prior to corpus callosotomy in patients with LGS, given that both procedures are palliative and that callosotomy is associated with considerably greater complications.
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Chapter XII-37
Should VNS Be Considered Before Corpus Callosotomy?

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INTRODUCTION

In about 30% of all patients with epilepsy, seizures cannot be sufficiently controlled by treatment with current antiepileptic drugs (AEDs) (1). Fortunately, about 60% of patients with pharmacoresistant temporal lobe epilepsy are becoming seizure-free or almost seizure-free after focal resection while continuing their AEDs (2,3). Moreover, a long-term cure with seizure freedom off AEDs after temporal lobe surgery can be proven in 27% of patients undergoing surgery, but a larger percentage may, in fact, have experienced a cure, although they have chosen not to withdraw AEDs (Chapter XIII-41). However, a focal resection is not appropriate for a number of patients with pharmacoresistant epilepsy. Palliative surgical options for patients with pharmacoresistant epilepsy who are ineligible for cortical resection or have not responded to resective focal surgery include callosal section [corpus callosum transection (CC)] and vagus nerve stimulation (VNS). A number of recent extensive reviews are available for both VNS (4,5) and CC (6,7). In this chapter I briefly review reports comparing CC and VNS with particular attention on the evidence to place VNS first before recommending CC.

METHODS

A literature search (Medline, Bios, Embase) was undertaken to include all publications in English language since 1990 with the descriptors: VNS and CC or corpus callosum transection. In addition, the reference section of articles was perused. The search yielded 192 publications, 173 were excluded because they contained no seizure outcome data of CC or VNS in at least five patients and 10 review publications were added, resulting in 29 publications. The results of this literature survey are briefly summarized.
RESULTS

Corpus Callosotomy

No Class I evidence with randomized controlled trials are available on the efficacy and safety of CC. Class IV evidence (clinical observations) for efficacy and safety for treatment of symptomatic generalized epilepsies, e.g., Lennox–Gastaut syndrome (LGS) or syndromes with seizures that cause falls, indicates that 3% to 11% become completely seizure-free with Class I outcome (6,8,9), and 60% to 80% have a seizure reduction of more than 50% (6). Improvement is mostly seen in atonic or drop attacks; other seizure types respond less well (7,10). The neuropsychological sequelae of callosal section can be quite detrimental to some patients (11), as can the exacerbation of partial seizures (12). In one series all patients whose language-dominant hemisphere did not control their dominant hand had impairments in some aspect of speech and language function after callosotomy. In some patients, unilateral deterioration of motor function was observed and was associated with mild to moderate dysfunction in the contralateral hemisphere (i.e., memory impairment or preexisting hemiparesis). Postoperative deficits occurred with partial, as well as total, section (11). Depending on the extent of section and frontal lobe retraction, acute complications include venous thrombosis and transient paresis. Overall, the risk of death at callosotomy seems to be between 0% and 6% (cause of death including air embolism and seizure in intensive care unit) (6). Permanent neurological deficit occurs in <5%, and transient deficit is seen in up to 20% of patients undergoing CC (7). In addition, cognitive complications include impaired speech production and a posterior disconnection syndrome which, however, is less common when the operation is staged (7).

Vagus Nerve Stimulation

Vagus nerve stimulation usually refers to intermittent retrograde stimulation of the left vagus nerve using a commercial device. The implantation of the generator in the chest wall (just like a cardiac pacemaker), the subcutaneous lead, and the cervical implantation are done in one surgical session usually lasting no more than one hour. The efficacy of VNS is established with two randomized, active controlled trials (EO3 and EO5) for partial and secondarily generalized tonic–clonic seizures. There is also Class IV evidence with clinical observations (open-label studies) indicating efficacy in other seizure types including tonic or atonic seizures that cause falls. Drop attacks were reduced at three months by 55% and at six months by 88%. In five patients with prior callosotomy, seizures were reduced after VNS by 73% at three months and 69% at six months (13). At six months of follow-up, 3 of 13 patients with LGS between the ages of 4 and 44 years (mean, 16.7 years) had a >90% reduction in seizures, two had a >75% reduction, one had a >50% reduction, and six had at least a 25% reduction. One patient did not improve. No patient worsened after initial improvement. Side effects, including hoarseness, coughing, and pain in the throat, were transient, and tolerable. No patient discontinued VNS. The authors conclude that VNS could be an effective and safe adjunct therapy for the treatment of LGS (14). Other smaller studies have reported similar results (15,16). However, <10% of patients become completely seizure-free with Class I outcome (8). A group of European epilepsy experts recently concluded that based on controlled trials in partial epilepsy and clinical observations in refractory LGS, VNS is a palliative surgical procedure similar in efficacy to the newer AEDs for patients who cannot be treated sufficiently with existing anticonvulsants or resective epilepsy surgery (17). Overall more than
7000 patients have been treated with VNS. Several authors found VNS a helpful adjunct in treating patients in whom an initial surgical intervention has failed. This applies to focal resection as well as to CC (9,18,19). In one series of 19 children with refractory epilepsy, all three children with unsuccessful CC had improvement after implantation of the stimulator, and five of six children with LGS had a 90% reduction of seizures (20).

Complications of the surgical VNS implantation are altogether rare and include, in declining incidence, infection (1.5%), vocal cord paresis (1%), unilateral facial weakness (1%), and, during the early days and since corrected, lead breakage. Perioperative adverse events reported by at least 10% of patients in the E03 trial (11) and E05 trial (12) were pain (29%), coughing (14%), voice changes (13%), chest pain (12%), and nausea (10%). Although a number of stimulation-related adverse events were reported during the treatment with VNS during the E03 and E05 trials, the only adverse events that occurred significantly more often in the treatment group were dyspnea and voice alteration. Adverse events were judged to be mild and transient in almost all patients. No death and cognitive, sedative, visual, affective, or neurological or neuropsychological deficits were reported (21).

**Comparative Studies and Considerations: Pharmacoresistant LGS**

Vagus nerve stimulation and CC are surgical options for selected children with drug-resistant LGS. With palliative procedures such as callosotomy and VNS, approximately half of the patients will significantly improve after surgery (22). In one study five patients with LGS with unsuccessful prior callosotomy seizures were reduced after VNS by 73% at three months and 69% at six months. Drop attacks decreased by 88% after six months following VNS (13). After reviewing his own data and results of the literature and the VNS Patient Registry, Karceski (9) concluded that VNS appears equally as effective as callosotomy. Because VNS has a lower potential for adverse events, these results suggest in his view and that of others that VNS should be considered first in appropriately selected patients.

There is, however, no complete agreement in the literature to first consider VNS in a child or a young adult with drop attacks. In the Dutch Collaborative epilepsy surgery program, 10 patients with severe drop attacks were treated with callosotomy and six patients with VNS (23). After a minimum follow-up of one year, Class I or Class II results [in accordance with the University of California in Los Angeles classification (UCLA) where Class I = seizure-free and Class II ≤ 3 seizures per year] were obtained in 10% of patients who underwent anterior callosotomy. In five of these patients an improvement in their behavior occurred. Of the six patients who underwent VNS only one experienced a beneficial seizure reduction (UCLA Class III). Although in patients with tonic or atonic seizures in a series from Philadelphia, at least 50% seizure reduction was seen in 12 of 13 CC patients and in three of five VNS patients (24). In patients with additional refractory generalized tonic-clonic seizures, the proportion of patients with at least 50% reduction was significantly higher after CC than after VNS (40/49 vs. 6/18, \( p = 0.002 \)). Furthermore, Class I or II outcome was noted in 12 of 49 patients (24%) but in none of the 18 patients undergoing VNS stimulation. Complications were seen in 5 of 66 patients after CC (one each: death, disconnection syndrome, osteomyelitis, mild sensory loss right hand, gait difficulties) and in 2 of 27 patients after VNS with one infection, and one defective battery (24). In their conclusion, CC is more efficacious than VNS for patients with refractory generalized epilepsy with generalized tonic-clonic plus atonic and tonic seizures, and
than more experience is needed to fully assess and compare these procedures for tonic and atonic seizures. Severe complications were, however, more frequent with CC and with VNS (24). In the experience of Trevathan (25), properly selected patients with LGS tend to have a more dramatic reduction in drop attacks than those implanted with VNS. In his view, the decision of whether to place a vagus nerve stimulator or perform a CC in a child or young adult with LGS should consider the following issues: (i) whether the seizures that result in falls are clearly primarily generalized (by careful video electroencephalography (EEG) monitoring), in which case the CC may be more effective in reducing or eliminating the drop attacks, (ii) the general medical condition and size of the child, which influences anesthesia and operative risks, and (iii) other factors that influence the perceived benefit of each procedure.

Comparative Studies and Considerations: Pharmacoresistant Partial Epilepsy

Furthermore, palliative cortical resection, anterior callosotomy, and vagus nerve stimulator placement are options for medically intractable, localization-related epilepsy with normal magnetic resonance imaging (MRI) and multifocal origin (26). In addition, placement of a VNS unit may be considered for patients in whom the initial operation fails to decrease seizure frequency: in a recent series, six patients underwent intentionally palliative second surgery (CC or placement of a vagus nerve stimulator). Five of the six (83%) intentionally palliative second operations resulted in more than a 50% decrease in seizure frequency (18).

DISCUSSION

Based on the available evidence which is limited to clinical observations and thus unprotected against selection bias, CC and VNS are both effective tools to reduce seizure severity and frequency in children and young adults who are not candidates for resective surgery. Although unproven, CC may possibly be more effective than VNS in some patients. Nevertheless, based largely on the degree of invasiveness and risks, many, but not all, authors agree that VNS appears to be a reasonable first-line treatment, whereas CC should be considered second-line (9,27). In fact, most pediatric neurologists and neurosurgeons also agree that VNS should be offered to patients before consideration of a callosotomy as VNS is less invasive and seems to have good efficacy in this patient group (4). If adequate drug treatment and VNS provide insufficient seizure control, partial callosotomy may be an option for the treatment of frequent, intractable and disabling drop attacks (28). Others disagree and prefer CC to VNS for treatment of drop attacks in selected cases for better efficacy or conclude that it is too early to make any recommendation (24,25).

CONCLUSIONS

Corpus callosotomy and VNS are effective palliative procedures to reduce seizure severity and frequency in pediatric and adult patients who are not candidates for resective surgery. In the absence of direct comparative data, the available evidence suggests broadly similar palliative efficacy although some opine that within the constraints of a palliative procedure, CC may be moderately more effective in their
hands. However, VNS is certainly less invasive, reversible, and associated with fewer serious complications. These features result in a better overall safety and risk–benefit balance of VNS compared with CC. Currently, decisions regarding whether to perform a CC or to place a vagus nerve stimulator will have to be based on preliminary and often subjective data until and unless a proper comparative trial is performed. Nevertheless, the conclusion by many is that VNS should be considered before more invasive CC in patients with pharmaco-resistant LGS and with partial epilepsy when resective surgery is not appropriate or has failed to control seizures.

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Chapter XII-38
Is Vagus Nerve Stimulation Therapy Effective for Generalized Epilepsy?

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Although vagus nerve stimulation (VNS) therapy was approved in 1997 by the U.S. Food and Drug Administration (FDA) “for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial-onset seizures that are refractory to antiepileptic medications,” some clinicians have noted reductions in seizure frequency and severity among patients with generalized seizures (1). Several studies have documented improvements among patients with generalized seizure syndromes as well as those with syndromes characterized by generalized seizures, such as Lennox–Gastaut syndrome (LGS) and cryptogenic epileptic encephalopathy.

CLINICAL TRIALS OF VNS THERAPY

Subjects enrolled in the randomized, controlled trials of VNS therapy (E03 and E05) had partial-onset seizures, but the open-label, compassionate-use trial (E04) enrolled some subjects with generalized seizure syndromes. The randomized, controlled E03 trial enrolled subjects with epilepsy syndromes associated with partial seizures. The subjects had pharmacoresistant seizures, predominantly partial seizure types (simple, complex, or secondarily generalized). During the 12-week acute phase, median seizure reduction was 24.5% for the 54 subjects in the treatment group (2). The prospective, open-label E04 trial included 24 subjects with generalized epilepsy syndromes: 13 males and 11 females. Of the 24 subjects, seven had idiopathic epilepsy and 17 had symptomatic epilepsy. After 12 weeks of stimulation, the median change in seizure frequency of all subjects was −46% (range, −85% to +130%) when compared with baseline. Seizures were reduced by more than 30% for 16 of the 24 subjects and by more than 50% for 11 subjects. By syndrome, median changes in seizure frequency were −40% (range, −85% to +130%) for subjects with symptomatic epilepsy and −60% (range, −84% to +60%) for those with idiopathic epilepsy (3). After 12 weeks
of stimulation, subjects in the treatment group of the E05 study experienced an average 27.9% reduction in seizure frequency as compared with baseline (4). As with the E03 trial, these subjects had partial-onset seizures. The subjects with generalized epilepsy syndromes in the E04 trial experienced a greater overall reduction in seizure frequency than the subjects in the treatment group of either the E03 or E05 trial, both of which enrolled patients with partial-onset seizures.

**SINGLE- AND MULTICENTER STUDIES**

Several studies retrospectively describe the results of VNS therapy among patients with epilepsy syndromes characterized by generalized seizures and receiving care at epilepsy centers. One such study by Ben-Menachem et al. (5) describes the experience with 64 pharmacoresistant patients who received VNS therapy and were observed for up to five years at a university-based center in Sweden. Of the 64 patients, eight patients had primary generalized seizures. Five of those eight patients had seizure frequency reductions exceeding 50% and were classified as responders. The five responders had absence epilepsy, and the three nonresponders had unclassified idiopathic generalized epilepsy. Four of the eight patients, whose seizure frequency reductions exceeded 75%, had marked reductions in absence and generalized tonic–clonic convulsions (GTCs). Eight of the 64 patients described in the Ben-Menachem et al. study had LGS, and five of those eight patients were responders. Among the patients with LGS, seizure types with the greatest reductions in frequency were GTCs and absence.

In another single-center study, Labar et al. (6) observed five subjects with pharmacoresistant mixed symptomatic generalized seizure disorders who participated in the E04 study at their center. All of the patients had previously been diagnosed with LGS. After three months of VNS therapy, the median reduction in seizure frequency was 41% (range, 36–80%), after nine months, median reduction was 41% (range, 40–85%), and during the last three months of the nine-month study, median reduction was 48% (range, 28–93%).

Results of VNS therapy among patients with cryptogenic epileptic encephalopathy, whose epilepsy is characterized by generalized syndromes, have been presented in a report and follow-up letter to the editor from a single center. Results of VNS therapy among 15 children with cryptogenic epileptic encephalopathy, seven of them with LGS, three with de novo LGS, four with myoclonic epilepsy of infancy, and two with myoclonic atactic epilepsy, were more impressive after two years than one year. Through the first six months, median reduction in seizure frequency was 19%, between 6 and 12 months, it was 17%, and after two years, it was 43%. During the first year of VNS therapy, seizure frequency increased for several children, but seizure frequency had returned to that at baseline by the end of the second year. In addition, one child reported no seizures, five reported seizure reductions exceeding 60%, and an other three children reported reductions of more than 40%, as compared with baseline. During the second year of the study, antiepileptic drugs (AEDs) were changed for five patients: AED additions for three patients did not affect seizure frequency and two patients responding to VNS therapy each had one AED withdrawn (7). In the follow-up letter to the editor, the author reported results for 11 of the 15 children after three years of VNS therapy, but seizure frequency had not improved from baseline during the third year. The author noted that the children in the study were among patients with the most severe epileptic encephalopathies (8).
Patients with LGS and receiving VNS therapy have been described in several studies. A single-center study described 12 patients with LGS and mean follow-up of 31.7 months. Of the 12 patients, six achieved seizure reductions of 50% or more (9). A multicenter retrospective study of patients with LGS listed seizure-median seizure reductions of 42% for 46 patients after one month of VNS therapy, 58.2% for 43 patients after three months, and 57.9% for 24 patients after six months. The declining number of patients at later time points reflects the point at which data were collected, not the attrition of patients receiving VNS therapy (10).

INVESTIGATIONAL DEVICE EXEMPTION STUDY

All of the previously discussed trials, studies, and publications described subjects and patients who were identified within larger studies or reported retrospectively from epilepsy centers and private practice. The success of VNS therapy among patients with generalized seizures prompted the filing of an Investigational Device Exemption with the FDA by investigators at the University of Washington. The FDA- and University of Washington Human Subjects Review Committee–approved study included 16 subjects with pharmacoresistant generalized epilepsy syndromes, both symptomatic and idiopathic. Before enrollment in the study, all of the subjects were carefully screened with long-term video-electroencephalogram (EEG) monitoring to confirm the generalized seizure syndrome diagnosis. Seizure frequency data were collected from patient diaries. To help ensure the accuracy of diary entries, caregivers viewed videotapes of the subjects having various types of seizures before the study began. The subjects received VNS therapy and were evaluated for changes in both seizure frequency and seizure type. Follow-up ranged from 12 to 21 months. Because AED regimens were held stable throughout the evaluation, changes in seizure frequency and changes in seizure types to those considered less severe could be attributed solely to VNS therapy. At follow-up, the overall median seizure frequency

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The difference in seizure frequency reductions was not statistically significant between the two epilepsy syndromes (p = 0.958, Wilcoxon rank-sum test).

* *p < 0.05.

Abbreviations: IGE, idiopathic generalized epilepsy; SGE, symptomatic generalized epilepsy; GTC, generalized tonic-clonic.
reduction was 43.3\% (p = 0.002, Wilcoxon signed rank test) (Table 1). In addition, reductions were noted in the tallies of the types of seizures that may involve a fall or collapse with decreases in myoclonic, tonic, atonic, and clonic seizures (11).

**SUMMARY**

Epilepsy surgery is not usually an option for patients with pharmacoresistant generalized epilepsy syndromes, but VNS therapy, with its strong safety profile and limited side effects, offers the potential of helping to reduce the frequency of seizures in this population (2,4). The studies of VNS therapy summarized in this chapter report reduced frequency of seizures for generalized seizure syndromes consistent with or sometimes better than those reported for partial-onset seizures. Such evidence builds a compelling case for the consideration of VNS therapy for the treatment of patients with pharmacoresistant generalized seizure syndromes.

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Chapter XII-39
The Antiseizure Effect of VNS Is Mediated by Ascending Pathways

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VAGAL NEUROANATOMY

Therapeutic vagus nerve stimulation (VNS) stimulates only the left cervical vagus nerve, but known anatomical pathways support polysynaptic access to widespread subcortical and cortical sites bilaterally. Afferents compose about 80% of the fibers in the cervical portion of the vagus (1). These are mainly special and general visceral afferents, which carry gustatory, visceral sensory, and other information of the autonomic nervous system (2). Vagal afferents traverse the brainstem in the solitary tract, terminating with synapses mainly located in nuclei of the dorsal medullary complex of the vagus [nucleus of the Tractus solitarius (NTS), nucleus of the spinal tract of the trigeminal nerve, medial reticular formation of the medulla, area postrema, dorsal motor nucleus of the vagus, and nucleus ambiguus] (3,4). Among these structures, the NTS receives the greatest number of vagal afferent synapses, and each vagus nerve synapses bilaterally on the NTS.

The NTS projects most densely to the parabrachial nucleus of the pons, and also projects monosynaptically to all of the other nuclei of the dorsal medullary complex, to the parabrachial nucleus and other pontine nuclei, to the vermis and inferior portions of the cerebellar hemispheres, and to the periaqueductal gray (5). Vagal afferents project polysynaptically to the noradrenergic and serotonergic neuromodulatory systems of the brain and spinal cord, via the NTS (6). The locus coeruleus, a pontine nucleus, provides widespread noradrenergic innervation of the entire cortex, diencephalon, and many other brain structures. The raphe nuclei provide widespread serotonergic innervation of the entire cortex, diencephalon, and other brain structures. Vagal-locus coeruleus and vagal-raphe interactions are potentially relevant to VNS mechanisms, as norepinephrine, epinephrine, and serotonin exert antiseizure effects, among other actions (7). The vagus nerve afferents have some disynaptic projections
to the thalamus and hypothalamus (via the NTS and the spinal trigeminal nucleus). The spinal trigeminal nucleus projects unilaterally to somatosensory thalamic neurons, which project to the inferior postcentral gyrus and inferior parietal lobule (5). Complex polysynaptic pathways provide vagal afferents with access to multiple cortical sites, mainly via NTS and parabrachial nuclei, with the most prominent projections to the amygdala, anterior insula, infralimbic cortex, lateral prefrontal cortex, and inferior frontal cortex. A recent review of central vagal pathways provides further neuroanatomical information, and also relates altered vocalization, cervical paresthesias and other symptoms of VNS to functional localization along these vagal pathways (8). It can be concluded that the cervical vagus nerve and its connections are structured in ways that support polysynaptic effects of VNS in the autonomic, reticular, and limbic systems of the brainstem, cerebellum, diencephalon, and cortex.

ANTISEIZURE AND ANTIEPILEPTOGENIC MECHANISMS OF VAGUS NERVE STIMULATION IN EXPERIMENTAL MODELS OF EPILEPSY

Experiments in acute and chronic animal models of epilepsy demonstrate four temporal profiles of VNS effects, of relevance to epilepsy therapy. First, acute abortive antiseizure effects were observed by Zabara, who terminated pentylenetetrazol-induced convulsions in dogs by applying VNS during seizures (9). Second, acute prophylactic antiseizure effects were first demonstrated by Takaya et al. (10). Rats received pentylenetetrazol at variable periods after a train of VNS ended. Significantly fewer convulsions were induced, when VNS had been applied within about 10 minutes before pentylenetetrazol (10). This critical experiment showed that continuous stimulation of the vagus nerve was not necessary, but that trains of stimulation can be applied intermittently, in order to reduce overall seizure frequency. Third, chronic progressive prophylactic antiseizure effects occurred in some monkeys rendered chronically epileptic by alumina gel instillation on the cortex, in that declines in seizure frequency actually increased over weeks and months of ongoing, intermittent VNS (11). Fourth, antiepileptogenic effects of VNS were reported in the feline amygdalar kindling model (12).

Mechanistic experiments have interfered with VNS antiseizure effects so as to elucidate structures or processes that mediate, or do not mediate, these effects. Destruction of noradrenergic locus coeruleus neurons attenuates the antiseizure effects of VNS in the maximal electroshock model (13). Notably, VNS antiseizure effects are not terminated by physically or chemically ablating the nerve distal to the point of stimulation, in the pentylenetetrazol and maximal electroshock models (9,14). Thus, in animal models it is clear that central processing exerts the antiepileptic effects of VNS, without participation of the vagal periphery.

HUMAN ELECTROPHYSIOLOGY AND MECHANISMS OF VAGUS NERVE STIMULATION

Zabara initially theorized that the hypersynchronous states of partial and generalized seizures might be antagonized by VNS, based in part on early
observations that high-frequency vagus stimulation caused desynchronization of the electroencephalogram (EEG) in anesthetized cats (15). Detailed comparisons of baseline EEG and post-VNS EEG, in adults with partial epilepsies, showed no changes in spike frequency or in waking background activities, on qualitative or quantified frequency analyses, however. One study found that VNS increased the power of slow waves during stage 3 to 4 sleep, although magnitude of slow-wave power was not studied in relation to therapeutic effect (16–18). Another study, which included mainly children with symptomatic generalized epilepsies, found progressive reduction in generalized spike-wave discharges over many months of VNS (19). Electrophysiological studies have contributed little to our understanding of VNS mechanisms, but studies using nonlinear dynamical EEG analyses have yet to be reported.

A magneto-electrophysiological measure of interneuronal excitability suggested that VNS enhances inhibition in cortical circuits during repetitive excitation, but not during single depolarizing events (20). In this recent report, transcranial magnetic stimulation (TMS) was applied in single pulses and in paired pulses, and thresholds for evoked movement were determined. During pulses of VNS it was more difficult to evoke a second movement to the second of paired pulses, but no more difficult to evoke a motor response to the first pulse, than was observed in the absence of VNS. While TMS does not replicate the electrophysiology of spontaneous seizures, relevance to the sustained repetitive firing of neurons during seizures is suggested by the observation that antiepileptic drugs (AEDs) also demonstrate inhibition in this paired pulse paradigm (20).

HUMAN NEUROCHEMISTRY AND MECHANISMS OF VAGUS NERVE STIMULATION

Concentrations of cerebrospinal fluid (CSF) gamma-aminobutyric acid (GABA) and other diffusible neurochemicals can be sampled by lumbar puncture, and CSF concentrations reflect whole-brain concentrations of these neurochemicals. Serial measurements of a large set of neurochemicals found many changes after three and nine months of ongoing VNS, compared with baseline pre-VNS levels in CSF (21). Only one of many assayed neurochemical changes showed significant correlation with antiseizure effects, in patients who experienced useful seizure reductions during VNS (responders) versus patients who did not (non-responders). Significant CSF increases in the cell membrane phospholipid precursor ethanolamine were greatest in the VNS responders (at three and nine months). The investigators suggested that increased CSF ethanolamine levels may be a sign of increased turnover of neuronal membrane components (21). It remains unclear how increased neuronal membrane synthesis might be involved in processes by which VNS improves seizure control.

Hypocapnia occurred during VNS, related to increased ventilation during each train of stimulation, during stage 1 to 2 sleep in 5 of 13 patients studied with polysomnography (22). While intermittent hypocapnia might well alter cerebral function, antiseizure efficacy was not compared with hypocapnic effects in this study.
HUMAN FUNCTIONAL IMAGING AND MECHANISMS OF VAGUS NERVE STIMULATION

Anatomical sites of VNS-induced activation and deactivation of synaptic activity, which occur along recognized central vagal pathways, can be measured and mapped using functional imaging techniques. In general, rapid increases (or decreases) in regional cerebral blood flow (CBF) are the result of rapid activation (or deactivation) of synaptic information processing at the site, in the absence of seizures, ischemia, and state changes. Positron emission tomography (PET) with $[^{15}\text{O}]\text{H}_2\text{O}$, single photon emission computed tomography (SPECT) with CBF agents, and functional magnetic resonance imaging (fMRI) have been used to study VNS effects on CBF in epilepsy patients.

Acute VNS-activation PET studies (performed within the first 24 hours after VNS therapy began) found synaptic activations in the dorsal medullary complex of the vagus, the central pons and midbrain, inferior cerebellum, hypothalami, and thalami, and also showed a combination of activations and deactivations in amygdalae, hippocampi, insulae, and other neocortical sites bilaterally (23). Somatosensory system responses to VNS were unilateral, as might be expected in patients experiencing exclusively left-sided cervical paresthesias during VNS. Chronic VNS-activation PET studies (performed after three months of ongoing VNS therapy) showed synaptic activations in the same brainstem, cerebellar and diencephalic sites as were observed acutely, but cortical effects were markedly reduced on chronic as compared with acute CBF imaging (24). Acute VNS-activation PET findings were compared with response to seizures during three months of VNS, without AED changes (25). Patients who had greater bilateral thalamic activation went on to experience significantly greater seizure reduction during VNS, compared with those who had little or no thalamic activation. In this study other sites of acute VNS-induced CBF changes also tended to occur more often in VNS responders, but these trends did not achieve statistical significance. Chronic VNS-activation PET studies also showed that bilateral thalamic activation was significantly associated with greater seizure reduction.

Later fMRI investigations found highly similar results to those of acute and chronic CBF PET studies, with regard to sites of VNS-induced synaptic activation (26–28). In contrast, SPECT studies mainly found regional deactivations during VNS, which were located in the same areas that had activations on PET and fMRI measurements (29–31). Differences in the direction of VNS-induced CBF alteration, on SPECT versus PET and fMRI studies, may be caused by differing temporal resolutions of these imaging modalities, and by different timing of the onset of image acquisition with regard to the onset of trains of VNS. Image acquisition exclusively during stimulation in reported PET and fMRI studies, versus early poststimulation CBF measurement with SPECT, could account for the fact that the similar sets of regions had VNS-induced CBF increases on PET and fMRI, versus CBF decreases on SPECT studies. In depressed, non-epileptic patients receiving VNS, changes in pulse width caused changes in fMRI-determined regional CBF increases and decreases (32). Two fMRI-based studies found greater seizure reduction in patients who had greater thalamic CBF activation during VNS (26,27). The PET and fMRI studies suggest that VNS acutely and chronically alters thalamic processing in some way so as to antagonize partial-onset seizures.
CONCLUSION

Therapeutic VNS probably antagonizes epileptic seizures through multiple mechanisms of altered brain function, without participation of vagal efferent activities. Antiseizure effects of VNS are not reduced after physical or chemical destruction of vagal fibers distal to the site of cervical vagus stimulation, in experimental epilepsy models. Rapidly conducting afferent fibers predominate in the cervical portion of the vagus nerve, supporting polysynaptic access of the left vagus to autonomic, reticular, and limbic systems of the brainstem, cerebellum, diencephalon and cortex. Experimental and human studies suggest that antiseizure VNS effects involve altered noradrenergic neuromodulation, altered neuronal membrane phospholipid incorporation, and altered intrathalamic processing. Therapeutic VNS mechanisms are not fully elucidated at this time, but it appears that multiple central mechanisms likely operate in parallel, without participation of the vagal periphery.

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Part Four

Outcomes of Epilepsy Surgery
Section XIII
What Is the Best Way to Measure Outcome?

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There has been little consensus on the best approach for characterizing outcome after surgery. Although it is entirely fair to argue that the ultimate goal of surgery is to eliminate the burdens on the individual caused by epilepsy and hence measures of quality of life should ultimately be used to reflect the success of surgery, surgery itself is specifically directed at the elimination of seizures. For this reason, we contend that the primary assessment of surgery should be based on seizure outcome. Multiple schemes for classifying seizure outcome have been proposed and used in the past (1). The best known of these was described by Engel et al. (2) and has been a reference point for many studies (Table 1).

Each of the various classification systems proposed has its merits; however, each also has potential problems as categories are often overlapping or not objectively or absolutely defined. For example, designations of “worthwhile” improvement are highly subjective. Percent reduction in seizure frequency can place patients who, after surgery, have one or two seizures per year in the same category as those who have one or two seizures per week.

A recent Commission on Neurosurgery of the International League Against Epilepsy report proposed a seizure outcome classification that could be used to classify all types of seizure outcomes from various surgical procedures (curative and palliative) and provided categories that would facilitate comparisons with classifications typically used in randomized drug trials (e.g., 50% reduction in seizure frequency) (3). Emphasis was placed on objectively defined categories with measurement only of seizures and not whether the change in seizure frequency was “worthwhile.” The proposed approach also recommended classification of outcome at each year after surgery rather than at a single, unspecified point in time (Table 1).

As an overall approach and one that facilitates comparisons across broad ranges of treatments and surgeries, this is a well thought-out and appreciated effort. We
would argue, however, that for studies of specific forms of surgery, resective surgery in particular, we should focus on the most biologically relevant outcomes that reflect the immediate goals of the surgery in order to evaluate the success of surgery and to identify factors that aid in selection and counseling of patients for surgery.

The new International League Against Epilepsy (ILAE) proposal has a category for completely seizure-free since surgery as well as a designation of seizure-free during any given year; however, even these do not fully capture the range and extent of seizure outcomes that may be most biologically relevant. In addition, the other categories, although seemingly reasonable, do not necessarily represent the outcomes that have the greatest impact on individual patients. We will consider each of these issues in turn.

**SEIZURE FREEDOM**

Although an apparently simple concept, seizure freedom still must be operationalized. Factors to consider include the minimum duration of time seizure-free before

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**Table 1** Significant Seizure Outcome Classification Schemes

<table>
<thead>
<tr>
<th>Engel et al. (2)</th>
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<tbody>
<tr>
<td>Class I. Free of disabling seizures</td>
</tr>
<tr>
<td>Completely seizure-free since surgery</td>
</tr>
<tr>
<td>Nondisabling simple partial seizures only since surgery</td>
</tr>
<tr>
<td>Some disabling seizures after surgery but seizure-free for ≥2 yr</td>
</tr>
<tr>
<td>Generalized convulsions with AED discontinuation only</td>
</tr>
</tbody>
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| Class II. Rare disabling seizures, almost seizure-free |
| Initially free of disabling seizures, has rare seizures now |
| Rare disabling seizures since surgery |
| More than rare disabling seizures since surgery but rare seizures for past 2 yr |
| Nocturnal seizures only |

| Class III. Worthwhile improvement |
| Worthwhile seizure reduction |
| Prolonged seizure-free intervals amounting to greater than half the follow-up period and not <2 yr |

| Class IV. No worthwhile improvement |
| Significant seizure reduction |
| No appreciable change |
| Seizure worsened |

<table>
<thead>
<tr>
<th>Wieser et al. (3)</th>
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<tbody>
<tr>
<td>Seizure status during a 1-yr period</td>
</tr>
<tr>
<td>Completely seizure-free, no auras</td>
</tr>
<tr>
<td>Auras only, no seizures</td>
</tr>
<tr>
<td>One to three seizures per year, ±auras</td>
</tr>
<tr>
<td>Four seizure days per year to 50% reduction of baseline seizure days, ±auras</td>
</tr>
<tr>
<td>&lt;50% reduction of baseline seizure days, ±auras</td>
</tr>
<tr>
<td>&gt;100% increase of baseline seizure days, ±auras</td>
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<table>
<thead>
<tr>
<th>Vickrey et al. (1)</th>
</tr>
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<tbody>
<tr>
<td>Seizure status during a 1-yr period</td>
</tr>
<tr>
<td>Seizure-free</td>
</tr>
<tr>
<td>Auras ± one seizure</td>
</tr>
<tr>
<td>2–12 seizures</td>
</tr>
<tr>
<td>&gt;12 seizures</td>
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</tbody>
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*Abbreviation:* AED, antiepileptic drug.
someone can be considered in remission, whether persistent auras should preclude the
designation of remission, when the remission occurs, and whether it endures.

Duration
Although not rooted in some physiological reality, a one year period has come to be
a significant landmark in epilepsy treatment, is implicitly used in the Commission’s
proposed classification scheme, and is commonly used in studies of seizure outcome—
surgical or otherwise. This is largely because of the convenience of anniversaries and
is reinforced by administrative factors, particularly driving regulations which, until
relatively recently, often required a one year seizure-free period before a person with
seizures could drive. Thus, unless a rationale for a different minimum duration
becomes evident, we will continue to recommend that a minimum definition of good
surgical outcome should be based on at least one year seizure-free. Ultimately, the
goal should be permanent seizure freedom.

Auras
Generally, auras have been considered a relatively minor phenomenon and not
sufficiently severe to preclude a designation of good seizure outcome. The analysis
of Vickrey et al. (1) of different seizure outcome classification systems (discussed later
in this chapter), however, suggested that being completely seizure- and aura-free was
superior to being seizure-free with continued auras. This study was based upon
patients studied cross-sectionally and not longitudinally so there is still the lingering
question of whether a change from seizures and auras to just auras produces a lesser
benefit to the individual than a complete elimination of all seizures and auras. For
now, investigators studying seizure outcome after resective surgery should be explicit
about the handling of auras.

Timing
The recent Commission reports state that seizure outcome should be classified during
each year after follow-up. Wieser has retrospectively classified the seizure outcomes in
a large cohort of resective surgical patients followed up to 25 years (median ~7) after
surgery (4). He used the new ILAE classification of seizure outcomes (3). The propor-
tion completely seizure- and aura-free since surgery starts off at about 45% one year
after surgery and drops to about 15% at 15 years, after surgery as initially seizure-
free patients relapsed. By contrast, the proportion seizure-free without auras
each year after surgery stays relatively constant at about 50%. This group contains
individuals who have had seizures since surgery but are currently seizure-free. In fact,
seizure outcome—remission or otherwise—can fluctuate for an individual from year
to year (5).

The ILAE approach approximates the more formal Markov model used by
Rougier et al. (6). They too reported that a relatively constant proportion of the
cohort was seizure-free at any given point in time; however, the specific individuals
in the seizure-free group changed as patients relapsed and remitted.

The Markov approach has some advantages for summarizing the state of the
overall group at a given point in time. It does not, however, readily translate into
a long-term prognosis for an individual patient. Modifications to the approach
can be developed; however, at the present time, means of implementing these models
are not readily accessible and their results must be interpreted carefully. A more
clinically useful and individually meaningful approach asks each question as it arises: Given someone has just had surgery, what is the probability he will become seizure-free and when? Given someone has just become seizure-free, what is the probability he will relapse and when? The simple actuarial approach provides a nonparametric and visual analysis of the probability of ever having achieved remission at any time after the initial point of entry into observation (surgery in this case) (7). For example, Figure 1A represents remission data from the National Institute of Health (NIH)-funded Multicenter Study of Epilepsy Surgery (7). A one-year remission does not necessarily occur immediately after surgery, and a proportion of patients continue to have seizures during the first year or two before attaining remission. This approach can be applied to subsequent conditional outcomes, such as relapse after achieving the initial remission and subsequent remission after relapse.

Relapse in patients who have undergone temporal lobectomy occurs in a substantial proportion (about 30%) of those who attain a one year remission (Fig. 1B) (7). The reason for relapse is critical to characterizing outcome as well. In postsurgical patients, relapses after remission may occur for a number of reasons. One of the most important of these may be planned reduction or discontinuation of antiepileptic drugs (AEDs). There is a large amount of literature in nonsurgical patients on the risk of relapse after stopping AEDs (8). Little information is available on the risk and predictors of relapse in postsurgical patients who have achieved remission. What is available suggests that perhaps a third will relapse after discontinuation of AEDs; however, deliberate prospective studies are greatly needed in this area (9).

Other reasons for relapse include but are not limited to seizures following noncompliance, seizures in the context of severe illness, and unprovoked spontaneous relapses. This last group may reflect an evolving aspect of the natural history of refractory partial epilepsy, particularly temporal lobe epilepsy, which has not been systematically explored. To examine this properly would require deliberate and prolonged follow-up.
OTHER CRITERIA FOR CLASSIFYING SEIZURE OUTCOME

Outcomes that represent partial success may be important to consider as well. The concept of Health-Related Quality of Life (HRQOL) provides an approach for assessing the sum total of the effects of epilepsy (or other conditions) and related factors on the individual (10,11). Standardized, validated measures of HRQOL facilitate research into the often subjective and highly individual but nonetheless very important effects an intervention, such as epilepsy surgery, may have. In cross-sectional studies, there appears to be a continuum of HRQOL outcome associated with a continuum of seizure outcome. Completely seizure-free is optimal in that HRQOL scores are highest in this group. HRQOL generally drops with increasing frequency of seizures (12,13). An approach to defining seizure outcome based on HRQOL was pioneered by Vickrey et al. (1) who developed a seizure classification that maximized HRQOL differences among patients in different categories of seizure outcome measured cross-sectionally.

Ultimately evidence of change in HRQOL with change in seizure frequency is needed. In a study of patients with refractory partial epilepsy measured before and after receiving new AEDs, only those who became completely seizure-free experienced a significant improvement in HRQOL (14). A significant reduction in seizure number without complete remission resulted in minimal, nonsignificant changes in HRQOL.

As seizure outcomes do not remain static over time, a longitudinal approach that goes beyond a simple before–after measure is ultimately needed. Recently, Spencer et al. (7) found continued improvements in some aspects of HRQOL over time (from 3 to 12–24 months) in the patients who were completely seizure-free since surgery. Thus the time dimension is an important aspect of outcome.

CONCLUSION

Seizure outcome after resective surgery should focus on complete remission from seizures as this is the ultimate goal. Evidence to date also demonstrates that it is the outcome that maximizes patients’ quality of life. The phenomenon of continued auras needs further study. Complete remission should be defined as a minimum of one year seizure-free and should be studied as an event that occurs in time. It may or may not be enduring, and appropriate statistical techniques should be used to capture this variation in seizure outcome over time. Long-term studies into the reasons for relapse and outcomes after relapse from remission as well as the benefits of partial success (i.e., reduction in seizure frequency and severity without enduring remission) are needed to round out our understanding of the full efficacy of surgical treatment of refractory partial epilepsy.

ACKNOWLEDGMENT

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INTRODUCTION

Epilepsy is a chronic illness with complex effects on many aspects of the health of affected persons. Although seizure frequency and the status of complete seizure cessation are necessary outcome measures, the complexity of the long-term effects of chronic epilepsy, which include common comorbid disorders such as depression and memory dysfunction, requires more comprehensive assessment in addition to seizures. During the past decade advances in the technology and methodology for reliable and valid assessment of subjective health status after epilepsy surgery have allowed dramatic increases in our understanding these multifarious effects (1). For example, even occasional seizures that transiently impair awareness have a similar magnitude of impact on social function, emotional well-being, and overall quality of life as does congestive heart failure or recent myocardial infarction (Fig. 1) (2). Recent investigations of health outcomes in epilepsy respond to challenges from facets of the clinical scientific community to provide patient-oriented data, such as Clancy and Eisenberg’s (3) statement in Science that “outcomes research—the study of the end results of care that takes patients’ experiences, preferences, and values into account—is intended to provide scientific evidence relating to decisions made by all who participate in health care.” Although much work remains to be done in clinical research in epilepsy, substantial evidence is now available to allow assessment of the overall impact of epilepsy surgery on health status (4,5).

This chapter reviews the theoretical basis and results of health outcomes research in epilepsy, and selected studies of patient-oriented outcomes from surgical interventions.
THEORETICAL BASIS FOR HEALTH OUTCOMES RESEARCH IN EPILEPSY

In 1946 the World Health Organization began a campaign to extend the traditional models of illness, redefining health as a "state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." After more than two decades of treating patients with epilepsy surgery, in 1955 Penfield and Paine (6) eloquently proposed that:

"It is not enough to know whether a radical surgical procedure has stopped attacks or not. We must know its effect upon the patient's ability to work, to hold a job, to study; the effect on physical and mental function; the effect on behaviour and on the happiness of the patient and friends. When all the features of his life are considered, it still remains for the physician to ask the final question: In the opinion of the patient and of those who love him, was the operation a success or failure?"

Many clinical investigators responded to this challenge for patient-oriented research in chronic illness during subsequent decades, yielding informative qualitative studies (7–11). Advances in knowledge of the requirements for reliability and validity of instruments used to measure subjective health, analogous to methods utilized in

Figure 1  Subjective health status of epilepsy surgery patients compared to outpatients with hypertension, diabetes, heart disease, and/or depressive symptoms. Source: From Ref. 2.
molecular and cellular laboratory investigations, fostered development of more accurate techniques (12). For example, the SF-36 evolved from the Medical Outcomes Study that defined the broad subjective health effects of chronic illnesses such as hypertension, diabetes mellitus, and heart disease (13).

In 1992 Vickrey et al. (14) developed an instrument to evaluate subjective health status in patients after epilepsy surgery, called the Epilepsy Surgery Inventory (ESI)-55, which included the SF-36 as a generic core (13). An outgrowth of this project evolved into the Quality of Life in Epilepsy Inventory (QOLIE)-89 (15) for use in adult patients with epilepsy. These instruments have utilized quality of life as the core construct to assess the well-being and function of patients with epilepsy. Drs. Baker and Jacoby (16) from the Liverpool group have employed a battery of individual instruments to assess quality of life, while O’Donoghue et al. (17) used the construct of “handicap” to evaluate patient functional status. Gilliam et al. (18) utilized a method of direct patient assessment to evaluate assumptions regarding the relative importance of domains of quality of life from the patients’ perspective, as shown in Figure 2.

Each of these approaches has specific merits and limitations. For example, more general assessments of quality of life may be less sensitive to changes in the effects of recurrent seizures than more epilepsy-specific instruments, whereas assessments more focused on epilepsy-related disability may have less generalizability and limit comparisons with other disease states (19).

CONTRIBUTIONS TO RESEARCH IN SUBJECTIVE HEALTH STATUS IN EPILEPSY

Various study designs have been used in the application of valid and reliable instruments to the investigation of health outcomes in epilepsy, including observational, comparative, and randomized trials. Baker et al. (20) performed the largest observational study that included >5000 patients recruited from epilepsy support groups in 15 European countries. Although the results may not reflect the “typical” patient who may not participate in support groups, the findings in this study do offer important insights into the experience of epilepsy that are applicable to our general

**Figure 2** Concerns listed by more than one-third of patients who have had one or more seizures in the past six months. *Source:* From Ref. 18.
understanding of the effects of epilepsy and medications on subjective health status. Approximately 50% of the sample had been seizure-free during the previous year, and 25% were having less than one seizure per month, suggesting a reasonably similar distribution of seizure control to the entire population of epilepsy based on outcome from prior studies on newly diagnosed patients (21–23). Approximately 25% were unemployed or unemployable. Twenty-seven percent reported a head injury, 13% reported dental injury, and 8% described burns or scalds within the past year. Of patients receiving monotherapy carbamazepine, valproate, or phenytoin, >50% reported tiredness, >40% reported difficulty concentrating, >30% described sleepiness, and >30% reported difficulty thinking clearly. Similar to the findings in the Vickrey et al. (2) paper mentioned above, most areas of perceived health status were worse in patients with epilepsy than patients with other chronic illnesses. Patients who were seizure-free, or having less than one seizure per month, had better SF-36 scores than patients with higher seizure rates. Moreover, patients with multiple seizure types had poorer subjective health status than patients with either only tonic-clonic or partial seizures.

Additional studies have further evaluated the association of seizure frequency and severity with subjective health status. Leidy et al. (24) reported significant differences in most QOLIE-89 scale scores between groups of patients who were either seizure-free, having one to five seizures per month, or having six or more seizures per month. It seems clear from these and other data that being seizure-free allows improved overall health, but the relative effect of seizures within the “average” range of people with uncontrolled epilepsy is not established (25). For example, it is not definitely established that a person experiencing two seizures per month has better perceived health than a person having eight seizures per month. Furthermore, evidence suggests that self-reported seizure rates are relatively inaccurate (26). The association of seizure severity with health and quality of life is also uncertain. After a study of 340 patients using the National Hospital Seizure Severity Scale and the QOLIE-89, Vickrey et al. (27) concluded that “this seizure severity measure assesses constructs that are generally distinct from health-related quality of life (HRQOL), except for moderate and broad associations between HRQOL and patients’ perceptions of the average duration of recovery time after seizures.”

Prior studies have demonstrated that mood dysfunction is associated with subjective health status, and this relationship appears to be of particular importance in patients with epilepsy (13). Perrine et al. (28) found that mood assessments explained 47% of the variance in QOLIE-89 scores of 257 patients from 25 centers, and recommended that HRQOL measures be interpreted in conjunction with assessments of mood and cognition. Hermann et al. (29) recently found that scores on the Symptom Checklist Revised-90 correlated QOLIE-89 scores across all scales; they recommended that “quality of life research should devote greater attention to the potential impact of comorbid psychiatric distress.” Gilliam et al. also reported that the Profile of Mood States summary score had the strongest correlation with Epilepsy Surgery Inventory-55 composite scale scores compared with other clinical outcome variables in 125 patients after temporal lobe resection (Table 1).

**EPILEPSY INTERVENTION OUTCOMES**

Several studies have evaluated outcome from epilepsy surgery using reliable and valid instruments (30–34). McLachlan et al. (32) reported that five of 10 subscales
and the overall scale were significantly better at 24 months follow-up after temporal lobe resection, than patients who continued antiepileptic medications after they were determined not to be candidates for surgery. In a similar prospective but nonrandomized study, Markand et al. (33) found that 10 of 17 QOLIE-89 scales were significantly better in 53 patients after temporal lobectomy compared with 37 nonsurgical controls. They also reported that the improvement in the surgical group “was related to achieving entirely seizure-free status (i.e., no seizures or auras postoperatively).” The only randomized controlled trial of surgery in temporal lobe epilepsy demonstrated improved QOLIE-89 global scale scores after one year in 40 patients treated surgically compared with 40 treated with optimal medical management after poor initial control (34). However, it is interesting to note that both treatment groups significantly improved between baseline assessment and the final assessment at one year.

Gilliam et al. (18,31) compared the scores of the Epilepsy Foundation of America (EFA) Concerns Index in 125 patients more than one year after anterior temporal resection to 71 patients who were waiting for the same procedure after selection using similar magnetic resonance imaging (MRI) and electroencephalogram (EEG) criteria. Sixteen of the 20 items were significantly better in the postoperative group, as shown in Figure 3. The magnitude of the better scores on the EFA Concerns Index compared with the QOLIE-89 subscales suggested greater sensitivity to epilepsy-related improvement after seizure reduction; however, this requires further study. This study also found better Profile of Mood States summary scores and decreased medication toxicity as measured by the Adverse Events Profile (Table 2). More than twice as many patients were driving in the postoperative group, and 30% fewer patients were taking an antiepileptic drug (AED). Interestingly, in the postoperative group mood status was a stronger predictor of physical health and role function than was seizure-free status, as shown in Table 1.

Although most studies of outcome from AED treatment have not included reliable and valid assessment of subjective health status, several recent trials have

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Mental health</th>
<th>Physical health</th>
<th>Role function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profile of mood states summary score</td>
<td>-0.762&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.528&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.532&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Employment</td>
<td>0.273&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.373&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.410&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Driving</td>
<td>0.290&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.381&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.349&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>AED-free</td>
<td>0.214&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.277&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.300&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Seizure-free</td>
<td>0.188</td>
<td>0.193&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.262&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.079</td>
<td>0.022</td>
<td>-0.002</td>
</tr>
<tr>
<td>Gender</td>
<td>0.018</td>
<td>-0.024</td>
<td>-0.066</td>
</tr>
<tr>
<td>Postoperative performance IQ&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.105</td>
<td>0.181</td>
<td>0.137</td>
</tr>
<tr>
<td>Postoperative verbal IQ&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.097</td>
<td>0.148</td>
<td>0.147</td>
</tr>
</tbody>
</table>

Significance (two-tailed):
<sup>a</sup><i>p < 0.01</i>
<sup>b</sup><i>p < 0.05</i>
<sup>c</sup>Continuous variables evaluated with the Pearson r correlation; all other clinical variables are dichotomous and were evaluated with the Pearson point-biserial correlation.

Source: From Ref. 31.
used instruments such as the QOLIEs. Cramer et al. (35) reported results of a randomized, blinded trial comparing add-on placebo, levetiracetam 1000 mg, and levetiracetam 3000 mg. A significant difference was found among groups in the Seizure Worry, Overall Quality of Life, Cognitive Functioning, and Total scale scores at the end of the 18-week treatment period. Patients who had a >50% reduction in seizure frequency had a significant improvement in all areas, except Medication Effects, compared with nonresponders.

Table 2 Comparison of Assessments of 71 Patients Awaiting Anterior Temporal Lobe (ATL) Resection and 125 Patients More Than One Year After ATL

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Awaiting ATL (n = 71)</th>
<th>Post-ATL (n = 25)</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure-free</td>
<td>N/A</td>
<td>81 (65)</td>
<td>–</td>
</tr>
<tr>
<td>Driving</td>
<td>19 (27)</td>
<td>75 (60)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Taking AEDs</td>
<td>71 (100)</td>
<td>88 (70)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adverse events</td>
<td>47 (10.8)</td>
<td>35 (10.6)</td>
<td>&lt; 0.001b</td>
</tr>
<tr>
<td>Profile, mean total scorec (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profile of mood states</td>
<td>52 (35.4)</td>
<td>33 (36.5)</td>
<td>&lt; 0.001b</td>
</tr>
<tr>
<td>Employed or in school full-time</td>
<td>45 (61)</td>
<td>78 (62)</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Values are presented as n (%).

aChi-square analysis: df (1).

bIndependent t-tests.

cHigher scores indicate greater medication side effects or worse mood status.

Source: From Ref. 31.

Figure 3 Sixteen of 20 items on the EFA Concerns Index were significantly better in patients >1 year after anterior temporal lobe (ATL) resection than those waiting for ATL. Source: From Ref. 31.
Similar to AEDs, few studies of vagal nerve stimulation have used a reliable and valid instrument for subjective health measurement. Cramer (36) described the outcome of 136 patients included in the voluntary prospective registry. All adult patients as of January 2001 who could complete the QOLIE-10 and had adequate baseline and three months postimplantation data were included. Although six of the 10 items were significantly changed over time in the entire group (interestingly “downheartedness” was significant in the opposite direction from the other items), only energy level was improved in responders with >50% seizure reduction compared with nonresponders. Most of the changes for the entire group were <15%, indicating minimal if any clinical significant improvement, and the “trouble with driving” item did not significantly change. These results are difficult to interpret (seven possible explanations of the results were offered), but generally support a limited effect on HRQOL as shown in an earlier controlled trial.

DISCUSSION

For most patients, epilepsy is a chronic disorder with complex effects on social, vocational, and psychological function. Although epilepsy is defined by the occurrence of seizures, and seizure cessation is the primary goal of pharmacological and surgical treatment, outcome from any intervention appears to require additional dimensions (37,38). The evolution of methods for health outcomes research in chronic illnesses, and specifically for epilepsy, during the past decade offers the opportunity to define the results of an intervention from the broad perspective of the patient. Use of an external standard such as HRQOL yields important information regarding the relative importance of different seizure rates on patients’ function and well-being, as demonstrated by Vickrey et al. (25). Comprehensively, patient-oriented outcomes assessment after epilepsy surgery complements assessment of the seizure rates, and allows more complete understanding of the effects of surgery in optimizing the presurgical informed consent process.

ACKNOWLEDGMENT

This work was supported by National Institutes of Health grant NS01794-01 and a grant from the Epilepsy Foundation of America.

REFERENCES


Chapter XIII-41
How Often Does Surgery “Cure” Drug-Resistant Epilepsy in Adults?

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INTRODUCTION

The ultimate aim of epilepsy surgery is to cure epilepsy. A reasonable definition for cure of epilepsy after surgery is having no seizures of any type for several years without taking antiepileptic drugs (AEDs) (Table 1). Surgical resection of epileptogenic tissue will control drug-resistant partial seizures in 64% to 70% of patients with temporal lobe epilepsy with continued AED treatment (3–5). Current definitions of complete seizure control after surgery allow for patients in Class I to have postoperative seizures such as simple partial seizures (auras), “nondisabling” seizures, or tonic-clonic seizures associated with drug withdrawal (Table 1).

THE CONCEPT OF CURE AFTER EPILEPSY SURGERY

The proportion of patients cured by surgery with respect to seizures will depend on how many patients are rendered seizure-free after surgery without a subsequent seizure recurrence (Fig. 1). Seizure recurrence has been reported after planned discontinuation of AEDs, during partial withdrawal, because of poor drug compliance and in patients staying on their medication (Fig. 1). In this brief chapter, pharmacological factors impacting on the outcome of surgery with respect to seizure recurrence are discussed starting with seizure recurrence after planned discontinuation of AEDs.

Seizure Recurrence After Planned Discontinuation of AEDs in Seizure-Free Patients After Surgery

It is not well known how many seizure-free patients with Class I outcome will experience a seizure recurrence after discontinuation of AEDs under medical supervision. There is also little information concerning when and how to perform AED withdrawal following a postoperative seizure-free interval (6).
Risk factors for seizure recurrence with discontinuation of medication in this situation have not been determined adequately. While some Class I patients may wish to discontinue AEDs, others are reluctant to do so. In fact, many adult seizure-free patients prefer to remain on medication when they are told that they cannot drive for six months while undergoing drug withdrawal. The following questions are addressed: (i) How many patients suffer a seizure relapse after planned discontinuation of AEDs? (ii) How long should patients be seizure-free after surgery before AEDs can be safely discontinued? (iii) When do seizures recur after discontinuation? and (iv) Do patients with seizure recurrence regain seizure control with reinstitution of AEDs?

A literature review, described in detail elsewhere, showed that no randomized controlled trials on AED withdrawal had been done in patients rendered seizure-free by surgery (7). From the retrospective clinical observations found, two large representative studies are discussed here (Table 2). Following planned discontinuation of AEDs in adult patients rendered seizure-free after epilepsy surgery, most often various forms of temporal lobe surgery, the mean recurrence rate in adults was 32% (Table 2). In a postoperative group of 103 patients, 39 were completely withdrawn from AEDs after being seizure-free for one or more years (9). The likelihood of removing AEDs and remaining seizure-free after medication withdrawal was 77% for year one, 72% for year two and 66% for year three. In another large retrospective study of 493 patients undergoing surgery between 1989 and 1993, AEDs were discontinued in 84 of 210 consecutive seizure-free surgical patients with mostly (90%) temporal lobe epilepsy. The seizure recurrence rate two and five years after complete AED withdrawal was 14% and 36%. Most recurrences occurred in the three years following discontinuation. In contrast, only 3% and 7% of the 30 patients who did not alter AED treatment after surgery had recurrent seizures two and five years later (8). Reinstitution of AED treatment resulted in seizure control in 20 of 22 patients who had recurrent seizures (8). The remaining two patients (10%) developed medically refractory partial seizures despite the reinstitution of medication. In adult patients seizure recurrence appeared to be unaffected by the duration of postoperative AED treatment (8). As a consequence delaying discontinuation beyond one to two years of complete postoperative seizure control seems to have no added benefit. Other risk factors were not found except that a longer duration of epilepsy prior to surgery increased the recurrence risk suggesting that earlier surgery may carry an extra benefit (9). Given the retrospective nature of these studies these risk factors and the reported absence of risk factors cannot be considered robust, however. Furthermore, partial withdrawal or taper of AEDs, poor drug compliance, and seizure recurrence while continuing AEDs (8) may further reduce the number of patients cured after surgery (Fig. 1) (10).
Seizure Recurrence Following Partial Withdrawal, Unplanned Discontinuation of AEDs, and in Seizure-Free Patients Staying on Medication After Surgery

Although the finding that over 60% of adult Class I patients undergoing AED discontinuation remain seizure-free is reassuring, seizure recurrence may not only occur after planned discontinuation of AEDs. In addition, evaluation of long-term seizure control off AEDs needs to include patients who never become seizure-free after surgery (Class II–IV), and formerly seizure-free patients with seizure recurrence while on AEDs, following unplanned discontinuation or poor drug compliance, after partial AED withdrawal.
The large number of seizure-free patients who prefer to stay on medication is a confounding factor because they may or may not, in fact, be cured (Table 2).

Taking into consideration, however, that seizure recurrence has been noted on average in 32% of seizure-free patients following complete discontinuation during a mean follow-up of five years as summarized above, the estimated average percentage of seizure-free patients off AEDs five years after surgery could be estimated to be in the range of 44% = 65% minus 21% (32% of 65%). However, the extrapolated figure of 44% does not yet include patients with seizure recurrence during partial withdrawal or taper of medication and during continued AED treatment. Data on seizure recurrence during partial withdrawal are particularly difficult to obtain. In one study, seizure recurrence following taper or complete discontinuation of AEDs was 30%, and with unchanged medication 17% (11). In two retrospective observations, seizure recurrence following a partial withdrawal varied widely ranging from 14% (8) to 89.5% in a second, smaller study (9). The findings are not robust, however, because of the retrospective nature of these observations, differences in rate of withdrawal and the type of medication withdrawn. In addition, seizure recurrence has been reported in seizure-free patients with continued AED treatment in 17% during a follow-up of one year and in 7% after five years (8,10). If one further subtracts 14% (for seizure recurrence during taper) and 7% (for seizure recurrence while on AEDs) from 65% (Class I outcome), the extrapolated proportion of patients cured by surgery could possibly be as low as 23% [65% – (21% + 14% + 7%)]. Our estimate was recently confirmed (10). Five years after temporal lobe surgery, 21% of patients were seizure-free without AEDs (10). After 30 years, 29% were seizure-free off AEDs (10). These tentative figures from different studies have to be confirmed in an extensive literature review and ultimately need to be tested in a controlled trial. Unless and until a long-term randomized controlled trial on AED discontinuation is performed in seizure-free patients with an open long-term extension it will be difficult to know precisely how many patients are cured by epilepsy surgery.

CONCLUSIONS

Surgical resection of epileptogenic tissue has become a standard treatment to control drug-resistant partial seizures in 64% to 70% of patients with anteromesial temporal lobe epilepsy with continued AED treatment. Seizure recurrence has been noted on average in 32% of seizure-free patients following planned complete discontinuation after surgery during a follow-up of five years. Although risk factors for seizure recurrence have not been well established, it appears that discontinuation can begin after one to two years of seizure control while on continued AED treatment after surgery.
The finding that a significant minority of patients rendered seizure-free by focal resection will have seizure recurrences when AEDs are withdrawn suggests either that the focus could not be fully removed in these patients or alternatively, that at least in those with seizure recurrence after surgery, drug-resistant temporal lobe epilepsy may involve a more widespread network of epileptogenic disturbances which exceed the site of resection and thus escape focal surgical treatment. The finding of a seizure recurrence in one of three patients is useful for counselling on the risk of AED withdrawal in patients rendered seizure-free by surgery.

Although cure is the ultimate aim of epilepsy surgery, the percentage of patients cured by surgery cannot be well defined at the moment. The proportion of seizure-free patients off AEDs five years after surgery could possibly be as low as approximately one in four adult patients undergoing surgery. A major methodological obstacle to finding out how many patients are cured after surgery is that the majority of seizure-free adults after surgery prefer to stay on medication, so it remains uncertain if they are cured. Unless and until a long-term, randomized controlled trial on AED discontinuation is performed in seizure-free patients followed by long-term open extension it will be difficult to know precisely how many patients are cured by epilepsy surgery.

REFERENCES

Chapter XIII-42
Altered Ictal Semiology as an Outcome of Temporal Resection

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GENERAL CONSIDERATIONS

Temporal resection controls complex partial (CP) and secondarily generalized seizures in the majority of patients who have strong evidence of unilateral temporal lobe epilepsy (TLE), although many patients require continuing antiepileptic drug (AED) therapy to remain seizure-free (1–14). Surgical cure, in which seizures cease entirely in the absence of AED use, can be distinguished from noncurative surgical success, in which preoperatively refractory seizures cease only in the presence of tolerable AED therapy. Even some surgical “failures” represent useful surgical interventions, in that overall seizure frequency is markedly reduced following resection. Other types of surgical “failure” might be useful to individual patients; for example, generalized tonic–clonic (GTC) seizures incur greater potential for cerebral and somatic injury than do CP seizures and auras, and GTC seizures might cease even when the overall seizure frequency is not significantly reduced postoperatively. While total postoperative seizure counts are standardly analyzed in evaluation of seizure outcome, alterations in ictal semiology are rarely considered in assessment of epilepsy surgery.

Postoperative seizure classification systems are commonly used to inspect and summarize surgical outcome data. These data summaries facilitate comparison of surgical outcomes with specific patient characteristics within one center, and comparison of surgical outcomes across centers. Most such classification systems eliminate detailed information concerning many aspects of pre- and postoperative seizures, in order to provide an overview of outcomes that does not include too much information for the observer to comprehend. Further, a seizure outcome classification system must not require information that is not routinely available, if it is to be used to compare data generated at many different sites. When one has available both pre- and postoperative counts of seizures classified by type, a more complete classification system such as the Seizure Type–Frequency Differential Scoring (STFDS) System (Table 1)
can be applied. The STFDS compares pre- and postoperative seizure frequencies, and fully distinguishes among isolated auras, and CP and GTC seizures (8).

Acute postoperative seizures, those occurring within the first week following temporal resection, are not considered in the following discussion. Most studies suggest that acute postoperative seizures have little or no predictive value for long-term postoperative seizure outcome (10,15,16). It appears that acute postoperative seizures have little to do with chronic, habitual postoperative seizures. It therefore seems reasonable to exclude acute postoperative seizures, when examining alterations between ictal semiology and postictal states of chronic pre- and postoperative periods.

Alterations in ictal semiology after temporal resection have received little attention, but are important in individual patient outcomes. Studies of surgically altered ictal semiologies also contribute to our understanding of pathophysiology and therapeutic mechanisms in localization-related epilepsies. These phenomena can occur in several ways. First, some alterations consist of change in relative distributions of seizure types occurring after surgery compared with preoperative periods. For example, the ratio of GTC seizures to CP seizures increases postoperatively compared with preoperative GTC-to-CP ratios, even though the total numbers of seizures fall postoperatively, among patients who are not seizure-free after temporal lobe resection. Second, other alterations may consist of changes in semiology within one type of seizure. An example of this is urinary incontinence during CP seizures, occurring after but not before resection. Third, the intensity, duration, and specific characteristics of postictal cerebral dysfunctions may be altered by temporal resection.

### ALTERATION IN THE DISTRIBUTION OF SEMIOLOGIC SEIZURE TYPES

**Increased Secondary Generalization of Partial Seizures**

The occurrence of GTC seizures after temporal resection has been reported in several surgical series, but rarely has been analyzed in detail (1–3). Seizure frequency by

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**Table 1** The Seizure Type–Frequency Differential Scoring System

<table>
<thead>
<tr>
<th>Descriptor: $S_S - C_C - G_G$</th>
</tr>
</thead>
<tbody>
<tr>
<td>The descriptor is completed with seizure occurrence values ($x$) for each seizure type, for pre- and postoperative intervals that must be specified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Seizure types</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S$ = Isolated aura or simple partial seizure</td>
</tr>
<tr>
<td>$C$ = Complex partial seizure, not secondarily generalized</td>
</tr>
<tr>
<td>$G$ = Generalized tonic–clonic seizure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Seizure occurrence values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0$ = Did not occur before or after surgery</td>
</tr>
<tr>
<td>$1$ = Occurred before surgery, but not after surgery</td>
</tr>
<tr>
<td>$2$ = Occurred before surgery; occurred once after surgery</td>
</tr>
<tr>
<td>$3$ = Occurred before surgery; occurred more than once after surgery with $&gt;90%$ reduction in frequency after surgery</td>
</tr>
<tr>
<td>$4$ = Occurred before surgery; $51$–$90%$ reduction in frequency after surgery</td>
</tr>
<tr>
<td>$5$ = Occurred before surgery; $0$–$50%$ reduction in frequency after surgery</td>
</tr>
<tr>
<td>$6$ = Occurred before surgery; increased frequency after surgery</td>
</tr>
<tr>
<td>$7$ = Did not occur before surgery, but did occur after surgery</td>
</tr>
</tbody>
</table>

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seizure type was analyzed for two-year periods before and after temporal resection, in a series of patients who did not significantly change AED regimens for two years following surgery (8). Over the cohort of 60 patients, 20 had postoperative CP or GTC seizures, and among the 20 patients, the ratio of GTC-to-CP seizures was significantly greater after surgery than it was before surgery (8). Overall, the 20 patients experienced considerable reduction in total frequency of CP and GTC seizures after surgery compared with presurgical seizure rates. Each of the 20 patients had AED levels determined at the time of the first postoperative CP or GTC seizures; on comparison of these levels with AED levels obtained on interictal days while using the same AED regimen, it was apparent that unexpectedly low AED levels were no more likely to occur on the day of a postoperative GTC seizure than on the day of a postoperative CP seizure. Among patients in this series who had both CP and GTC seizures before surgery, the relative reductions in postoperative seizure frequency were greater for CP than for GTC seizures. Many patients never experience GTC seizures during the course of TLE, but five patients in this series experienced their first GTC seizure only after temporal resection (8,17). These results suggest that increased rates of secondary generalization after temporal resection are probably due to the resection, and not to unrelated effects of the natural history of TLE, nor to effects of altered AED regimens or AED withdrawal.

A simple concept of the “epileptic focus,” which initiates partial-onset seizures and which can be resected to abolish partial seizures, cannot account for increased generalization of postoperative seizures. Further, in patients who become free of CP and GTC seizures following temporal resection, habitual preoperative epileptic auras often persist as isolated auras after surgery, as discussed below (7,14). Perhaps an epileptogenic hippocampal formation (or hippocampal–amygdalar–dentate–entorhinal cortical loop) amplifies and propagates seizures within the limbic forebrain, producing the full clinical state of CP seizures, even though the seizure-initiating, aura-generating, ictal discharges began in some other site. In experimental epilepsies the conversion of partial seizures to generalized convulsions requires propagation of ictal discharges from the forebrain into the pons and mesencephalon (18). Seizures of TLE may begin in a site that is not ablated by anterior temporal lobectomy (ATL), and after surgery this site may generate simple partial seizures without propagation (manifested as isolated auras), or with propagation to convolution-generating brainstem sites. These sites might include the deep rostral piriform cortex (area tempestas), the insula, and the septal nuclei, all of which have dense projections into the hippocampus–amygdala–entorhinal cortex, and also have pathways projecting to pontomesencephalic sites without traversing areas resected at ATL (19,20). The substantia nigra, and anterior and midline thalamus probably regulate propagation of limbic partial seizures to pontomesencephalic convolution generators, but in themselves are unlikely to initiate partial seizures (21–24). The dentate gyrus may function to maintain and propagate CP seizures within other temporal lobe sites and also may antagonize seizure activities in extratemporal sites (25).

With increased knowledge of the neuronal assemblies which promote ictal initiation, propagation, and maintenance, and of those which antagonize seizure onset and spread in human epilepsies, temporal lobe ablation might be modified to eliminate surgically induced promotion of secondary generalization, while retaining or increasing efficacy in treating CP seizures. Perhaps certain characteristics of postresection seizures might be used to determine the therapy that will render the patient seizure-free (or therapies that should be avoided because of high likelihood of inefficacy) when applied after temporal resection, based on more
complete pathophysiologic studies. Patients who have exclusively GTC seizures after temporal resection may be less likely to benefit from a second resective procedure than would patients who have only auras and CP seizures after temporal resection. This hypothesis has not as yet been empirically established. Currently it is reasonable to warn patients that a postoperative seizure may be a GTC seizure, even if GTC seizures did not occur before temporal lobe resection, and that full compliance with recommended postoperative AED regimens may reduce the risk of postoperative CP and GTC seizures.

Persistence of Isolated Auras with Cessation of CP and GTC Seizures

Many patients cease to experience CP and GTC seizures after temporal resection, but continue to experience isolated auras, which are not associated with impaired awareness (7,8,14,26–28). In one surgical series, isolated auras occurred postoperatively in approximately one-fifth of patients who were rendered free of CP and GTC seizures after resection of a sclerotic hippocampus (7). In another series it was observed that isolated auras occurred postoperatively in approximately one-third of patients who had isolated auras before surgery; among patients who did not have isolated auras before surgery, none had isolated auras after temporal resection (8). While it might seem that the occurrence of purely subjective symptoms in the form of isolated auras is quite benign; in fact patients with postoperative isolated auras (in the absence of CP and GTC seizures) report significantly lower quality of life than do patients who are free of all paroxysmal phenomena after surgery (14,26).

Given that isolated auras probably represent electrographic seizures of limited propagation, it might be expected that AED effects are acting to restrict spread of aura-associated ictal discharges. Removing these AED effects might permit generation of CP and GTC seizures that would not otherwise occur. It seems reasonable to hypothesize that patients who have isolated auras (only), and who have continuously used AEDs postoperatively, would be more likely to have CP or GTC seizures after discontinuing AEDs, than would patients who have no paroxysmal phenomena while using AEDs postoperatively. This concept has not actually been tested in randomized, prospective fashion. In the future a randomized, prospective study of AED discontinuation after epilepsy surgery, as has been proposed, might well analyze the importance of isolated auras in prognostication of the outcome of postoperative AED reduction or discontinuation (29).

Currently it is not clear whether aggressive efforts to abolish isolated auras with AED therapies are justified in patients whose CP and GTC seizures were controlled with temporal resection. Given that isolated auras probably represent electrographic seizures of limited propagation, it is possible that ongoing AED adjustments might fully control isolated auras postoperatively. Isolated auras are bothersome to many patients, and might subtly impair cognition and other cerebral functions. It might be speculated that repeated auras can contribute to epileptogenic processes, such as development of new pathways of preferential seizure propagation, possibly leading to late recurrence of CP or GTC seizures. On the contrary, adverse effects due to increasing doses and numbers of AEDs may not be trivial. While many patients may elect small AED dose increases if auras are subsequently controlled, the importance and urgency of abolishing isolated auras is not established at this time.
ALTERATION IN ICTAL SEMIOLOGY AND POSTICTAL DYSFUNCTIONS WITHIN SEIZURE TYPES

Auras, Automatisms, and “Intensity” of CP Seizures

Subjective ictal symptoms and objective behavioral manifestations of auras and CP seizures often change across time in TLE, with or without temporal resection. Individual patients may report lesser (or greater) impairment of awareness during seizures, or reduced (or increased) duration of seizures, on comparing postoperative CP seizures with the preoperative seizures. Available reports do not suggest a trend for temporal resection to intensify or de-intensify auras or CP seizures, but the question has not been addressed in detail. The author has observed several patients who began to experience falling during postoperative CP seizures, and several others to experience urinary incontinence during postoperative CP seizures, among patients who did not experience these ictal phenomena preoperatively. While these patients attributed the negative alteration in ictal automatisms to surgical effects, the temporal association with surgery does not exclude itself in the evolution of ictal semiology due to unknown factors underlying epilepsy.

Some patients postoperatively “lose” their premonitory auras in their reportedly predictable sequence of CP seizure occurrence, among patients who had auras preceding CP seizures preoperatively and who continue to have CP seizures postoperatively. Such patients often find this change undesirable, due to inability to sit down or to make other safety-enhancing (or embarrassment-limiting) preparations for impending unconsciousness. Clearly loss of premonitory auras also can occur in temporal relationship with AED changes, among patients who do not have epilepsy surgery. Specific associations between temporal resection and altered semiologies within specific seizure types have not been established in prospective studies.

Altered Postictal Dysfunctions

Durations, intensities, and specific characteristics of postictal states may be altered in a consistent fashion by temporal resection. As for alterations in postoperative seizures compared with preoperative seizures, variability in the natural history of TLE and changes in AED regimen also must be considered before attributing such alterations to surgical effects. The author has noted that many of his own patients have felt that duration and intensity of postictal states have been reduced following surgery, but that specific dysfunctions were unchanged, comparing pre- and postoperative seizures of the same types. Anecdotally, one trend in subjective reports seems fairly consistent across patients: among patients who experience new or increased naming impairment or delayed recall impairment as persisting interictal dysfunctions postoperatively, postictal dysfunctions are more likely to transiently exacerbate the new (or increased) impairment, when CP or GTC seizures occur after surgery.

CONCLUSION

ALTERATION IN ICTAL SEMIOLOGY AND POSTICTAL DYSFUNCTIONS WITHIN SEIZURE TYPES

Auras, Automatisms, and “Intensity” of CP Seizures

Subjective ictal symptoms and objective behavioral manifestations of auras and CP seizures often change across time in TLE, with or without temporal resection. Individual patients may report lesser (or greater) impairment of awareness during seizures, or reduced (or increased) duration of seizures, on comparing postoperative CP seizures with the preoperative seizures. Available reports do not suggest a trend for temporal resection to intensify or de-intensify auras or CP seizures, but the question has not been addressed in detail. The author has observed several patients who began to experience falling during postoperative CP seizures, and several others to experience urinary incontinence during postoperative CP seizures, among patients who did not experience these ictal phenomena preoperatively. While these patients attributed the negative alteration in ictal automatisms to surgical effects, the temporal association with surgery does not exclude itself in the evolution of ictal semiology due to unknown factors underlying epilepsy.

Some patients postoperatively “lose” their premonitory auras in their reportedly predictable sequence of CP seizure occurrence, among patients who had auras preceding CP seizures preoperatively and who continue to have CP seizures postoperatively. Such patients often find this change undesirable, due to inability to sit down or to make other safety-enhancing (or embarrassment-limiting) preparations for impending unconsciousness. Clearly loss of premonitory auras also can occur in temporal relationship with AED changes, among patients who do not have epilepsy surgery. Specific associations between temporal resection and altered semiologies within specific seizure types have not been established in prospective studies.

Altered Postictal Dysfunctions

Durations, intensities, and specific characteristics of postictal states may be altered in a consistent fashion by temporal resection. As for alterations in postoperative seizures compared with preoperative seizures, variability in the natural history of TLE and changes in AED regimen also must be considered before attributing such alterations to surgical effects. The author has noted that many of his own patients have felt that duration and intensity of postictal states have been reduced following surgery, but that specific dysfunctions were unchanged, comparing pre- and postoperative seizures of the same types. Anecdotally, one trend in subjective reports seems fairly consistent across patients: among patients who experience new or increased naming impairment or delayed recall impairment as persisting interictal dysfunctions postoperatively, postictal dysfunctions are more likely to transiently exacerbate the new (or increased) impairment, when CP or GTC seizures occur after surgery.

CONCLUSION

Alterations in ictal semiology after temporal resection have received little attention. These alterations are important in individual patient outcomes, and in the understanding of pathophysiology and therapeutic mechanisms in localization-related epilepsies. These phenomena can occur as change in relative distributions of seizure
types, and as changes in semiology within one type of seizure, or in the intensity, duration and specific characteristics of postictal cerebral dysfunctions, after surgery compared with preoperative periods. Alternatively, the evolving natural history of an individual’s epilepsy, or alterations in medication regimens, may cause changes in the relative distribution of semiologic seizure types, and in specific features of ictal semiology and postictal dysfunctions within seizure types, unrelated to epilepsy surgery. Extensive descriptive studies should offer greater attention to details of ictal semiology over prolonged periods, and not merely to seizure frequency, in evaluation of epilepsy surgery and other therapies.

REFERENCES

Section XIV
Outcomes of Temporal Lobe Epilepsy Surgery

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Since Horsley’s 1886 case report of epilepsy surgery (1), a substantial amount of literature has developed on the outcome of epilepsy surgery. Many case series (2–6) demonstrated that epilepsy surgery could make some patients seizure-free and tried to identify predictors of this outcome. It was assumed that without surgery these patients would have continued with uncontrolled seizures, but subsequently, series of matched medical and surgical cases have been reported (7–10). It was not until 2001 that a randomized, prospective study of the efficacy of epilepsy surgery was reported (11, Chapter XIV-43).

HOW TO REPORT OUTCOMES

Before reviewing this literature, several issues related to assessing outcome need to be addressed (see also Section XIII). The first is how to classify changes in seizure frequency after surgery. There is relatively little problem with a patient who has neither overt seizures nor auras, though many series do not report such “cured” patients separately. But once the patient has events, subjectivity in classification enters in. Is it an “aura,” presumably a brief simple partial subjective seizure, or a “real” simple partial seizure? Are the auras bothersome or nonbothersome? The classification problems increase if seizures interfering with consciousness occur. Are seizures during antiepileptic drug (AED) tapering as significant as those occurring on stable drug therapy, or off of AEDs? How should one count exclusively nocturnal seizures? What level of seizure reduction should be considered “worthwhile improvement?” Would an episode of status epilepticus, a cluster of seizures, or multiple seizures in a day be counted as one seizure or as multiple seizures? Additionally, postictal deficits, which impair quality of life (QOL) in a variable fashion, are ignored in current outcome classifications.
Classifications

The 1993 Engel classification system (Appendix) is most widely used to assess seizure outcome after surgery (12). In his Class I “free of disabling seizures,” the patient is seizure-free (IA), but may have auras or nondisabling simple partial seizures (IB), may have had disabling seizures but not for the last two years (IC), or may have generalized tonic–clonic seizures with medication taper (ID). Therefore a “Class I” outcome includes patients who have had seizures with loss of consciousness. Moreover, what constitutes a “disabling” seizure can be very subjective. In the earlier, 1987 version of this classification, a 90% seizure reduction is worthwhile (Class III), though going from 100 to 10 seizures daily may be less beneficial than going from 10 to one seizure yearly (13). The most recent, 1993 version is more subjective, requiring that “worthwhile improvement” be determined by “quantitative analysis of…seizure reduction, cognitive status, and QOL.” While this classification is ultimately most related to QOL, a classification related to the biological outcome is also needed.

An earlier report of outcomes of temporal lobectomies reported outcome by seizure types, only noting reduction of major convulsions and psychomotor seizures (3). This neglects the important groups of patients who are free of seizures or only having rare ones. In this report, Bailey (3) also used a qualitative outcome classification system, indicating degree of reduction of attacks: greatly improved, and not improved. This is really similar to current classifications and about as accurate as one can be, considering the complexity and incertitude in assessing seizure occurrence. Indeed, the “not improved” category appears to be the most universally consistent at around 20% to 30% in most series. The recent randomized controlled study by Wiebe et al. (11) used a different classification: Class A—no seizures or aura of any kind, and Class B—no seizures that interfered with consciousness. This study illustrates how the outcome classification system can alter results, with a 20% difference in favorable outcome by one measure compared with the other.

Another approach is to assign weights to the different seizure types (6). Generalized tonic–clonic seizures are assigned greater weight than complex partial seizures, with simple partial seizures having the least weight. Such a system could provide a single metric reflecting both frequency and severity, but it is cumbersome and has not been widely adopted. Additionally, outcome is sometimes classified by whether the patient is on or off AEDs, though the decision to withdraw all AEDs in a seizure-free patient is often most reflective of patient and physician preference.

An International League Against Epilepsy (ILAE) committee has recently addressed issues related to outcome measures (14). That report reflects many of the concerns about the current measures discussed above, and recommended that outcome be assessed by number of seizure-free days after surgery. This outcome measure could be expressed as a ratio of days of follow-up to days seizure-free, and is similar to the outcome measure used by Van Buren et al. (6). A limitation is that this approach lumps together days with a single seizure with those with multiple seizures and status epilepticus. It would be useful to include a seizure severity rating scale, and to report days of loss of function due to seizures, which could then account for status epilepticus, seizure clusters, and multiple seizures, and also prolonged postictal deficits. Van Buren et al. (6) proposed a year-by-year score for each patient, but the ILAE reports the year-by-year group experience. This loses information on the long-term outcome of individual patients, who might shift from one class to another over time.
Method of Follow-Up

The second issue is the follow-up method. Direct patient–observer interview with chart review is probably the most reliable approach. However, this still depends on patient reports, which are subject to underreporting, so that the patient can drive, or over-reporting, to maintain disability status. In a study comparing direct interviewing by two professionals, there was a 14% disagreement in outcomes [University of Washington (UW) Study]. Indeed, in that study, chart review alone without additional patient and companion interview and other medical records would have found a much higher percentage seizure-free and significantly improved patients. Telephone or postal interviews are likely even less reliable.

Duration of Follow-Up

A third issue is the duration of follow-up, and how that is reported. Seizure outcome after surgical resections is usually ascertained by statistically manipulating data on patients with a variable follow-up period, sometimes with a minimum time as short as six months (15). Falconer and Serafetinides (4) concluded that long-term and short-term results are similar, though a few patients who were seizure-free during the first year later developed seizures, and some patients who had no seizures in the first year later became seizure-free. Van Buren et al. (6), on the other hand, found that while more than 60% of patients who had a total excision of a temporal lobe were seizure-free one year after surgery, only 33% remained so at five years. Delayed recurrences after a period of 10 years have previously also been reported (7).

The common practice of reporting a mean follow-up period can be misleading if very short follow-ups are included (5). Another practice is to report seizure-free rates by each year of follow-up, rather than the cumulative rate of being seizure-free. Year-by-year reports of percentage of patients seizure-free in that year obscure the outcome of individuals, as they may move into and out of the seizure-free group. In contrast, the Kaplan–Meier (KM) event-free plot (16) documents continuous seizure freedom, but ignores the substantial benefits to those patients who have only one or two seizures in a year, a common occurrence. Van Buren et al.’s older classification system remains the most informative (6).

Outcomes Reported Depending on the Location and Nature of the Epileptogenic Zone

Outcomes vary considerably depending on the location of the epileptogenic zone. Some series lump all cases together as “epilepsy surgery” (7). In that situation, outcome may depend primarily on case mix, with potentially substantial differences between epileptogenic zones in different regions obscured. Outcome also depends on etiology, and on the mix of cases with very focal or multifocal epileptogenic zones (17).

When surgical outcomes are to be compared with another group, as in case-matched and randomized studies, there must be stratification for factors that influence surgical outcome. Besides having similar duration of seizures and number of AED trials, and having scalp electroencephalographic (EEG) interictal and ictal findings that make them potential surgical candidates, surgical outcome is influenced by the presence of structural brain lesions, not only tumors and vascular malformations, but imaging evidence of mesial temporal sclerosis (MTS) and
dysplasia, or the presence of previous head injury or encephalitis, as well as the presence of “active” generalized tonic-clonic seizures. All of these factors ideally require stratification.

Assessing Outcome with Neuropsychologic, Quality of Life, and Vocational Measures

Neuropsychologic, QOL, and vocational outcome measures are also of great importance. There has been much less emphasis on these measures than seizure frequency. Standard neuropsychologic and QOL measures adapted to the epilepsy population are commonly used. For vocational assessment, age at surgery and previous work history are important variables requiring stratification for comparative groups.

COMPLICATIONS

Surgical complications are an aspect of outcome, but are generally reflected only in QOL measures and are not integrated in any way into outcome. A drug study by Mattson et al. (18) applied a weight to toxicity that could be included in an overall outcome measure; a similar approach could be applied to surgical outcomes. In case-matched and randomized studies, of course, complications and toxicity in the medical arm also need to be assessed, as illustrated by the single death in the medical arm of the randomized surgical outcome study (11). Thus it is desirable to have two outcome reports: one report of QOL reflecting the overall effectiveness of the procedure, and another assessing seizure frequency with complications listed, reflecting the biologic result.

CRITERIA FOR CONSIDERING RESECTIVE SURGERY FOR EPILEPSY

The classical criteria for considering resective surgery for epilepsy include medical intractability (Section I) as well as an identifiable focus usually not in eloquent brain. Postsurgical QOL studies have shown that to become seizure-free is the essential goal of therapy (19). This is the criterion usually used to establish surgical success. Complete seizure control is attained medically in about 60% to 70% of patients with complex partial seizures (CPS) (20,21). Patients with long-standing persisting complex partial seizures rarely become seizure-free with additional aggressive medical management after failure of two appropriate AEDs (Section I) (22,23). Thus, potential candidates for surgical therapy can be identified early, often within a year of diagnosis. Further attempts at medical management are likely to gain little and lead to additional loss of educational and developmental progress.

REPORTED OUTCOMES

The literature on epilepsy surgery outcomes includes a variety of different presurgical evaluations and operative techniques, confounding attempts to pool outcome data (24). Therefore, in this chapter, we have concentrated on series managed in a defined way usually by a single center, where factors influencing outcome reporting can be ascertained. Tables 1 through 5 present methodology and results of selected studies covering...
different surgical eras where cases were selected early on by clinical data and interictal EEG, then later on ictal EEG criteria, followed by the addition of modern imaging.

**UNIVERSITY OF WASHINGTON CASE-MATCHED STUDY**

One of the authors (LMO) and her colleagues conducted a retrospective review of a consecutive series of surgically treated patients with nonlesional temporal lobe epilepsy (TLE) \((n = 92)\) who had been followed for at least five years and a subset \((n = 26)\) followed for at least 10 years (Table 1). The patients were operated on from 1977 to 1986, the era before magnetic resonance imaging (MRI), and identified through a Regional Epilepsy Center database. A unique case-matched group of 81 patients who received aggressive medical treatment with AEDs drawn from the same clinic were used as a nonsurgical control group. Preliminary reports have previously been published (9,10).

**Surgical Group**

This represents all living, contactable patients who had anterior temporal lobectomies and a complete presurgical workup including EEGs and Computed Tomography (CT) scans, some with standard MRIs and neuropsychologic and psychosocial evaluations. All were at least 16 years of age at the time of surgery and had four or more partial seizures per year in the prior two years. The resections were performed by Arthur Ward, Alan Wyler, or George Ojemann and were tailored to remove interictal epileptiform abnormalities on electrocorticography and spare eloquent cortex mapped by electrical stimulation (25).

**Medical Group**

These patients were managed by neurologists who, at the time, were not enthusiastic about surgery for epilepsy. It was not until the 1990 National Institutes of Health (NIH) consensus conference (26) that referrals for surgical therapy rose markedly. Criteria for entry into this group included partial seizures with or without secondary generalization as demonstrated by focal EEG abnormalities (10). All were 16 years or older and had at least four partial seizures per year in the two years prior to the initial assessment. In about two-thirds, AED treatment was managed at the Regional Epilepsy Center, the rest in the community. All patients were followed for five years, 36 were followed 10 years. Matching with the surgical group was based on clinical and EEG features indicating a temporal lobe focus.

Follow-up for the medical and surgical groups was obtained from interviews of patients and companions, reviews of seizure calendars, medical records, from the Epilepsy Center, outside physician records and laboratory reports of AEDs by one of us (LMO).

**Outcome**

For the surgical patients \((n=92)\) followed for five years, 45 patients (48%) were seizure-free in the fourth and fifth follow-up years (class 1, Appendix). In contrast, for the medically treated group of patients \((n = 81)\) followed for five years, only three (3.7%) were seizure-free in the fourth and fifth follow-up year (chi sq = 41.4, \(p < 0.0001\)). Eighty-nine percent in the surgical and 10% in the medical group

*(text continues on page 680)*
<table>
<thead>
<tr>
<th>Study</th>
<th>Wieser (33)</th>
<th>Yoon (17)</th>
<th>UW (9,10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year published</strong></td>
<td>2003</td>
<td>2003</td>
<td>1992</td>
</tr>
<tr>
<td><strong>Duration of follow-up years</strong></td>
<td>Up to 24, median 7.2</td>
<td>At least 3, mean = 8.4 (3.1–20.0)</td>
<td>5 yrs and 10 yrs</td>
</tr>
<tr>
<td><strong>Method of follow-up</strong></td>
<td>Review of clinic visit records</td>
<td>Chart and telephone calls</td>
<td>Patient and significant other interview and medical records, and seizure calendars (when available)</td>
</tr>
<tr>
<td><strong>Number of patients in study</strong></td>
<td>(369–430) 218 “lesional,” 182 “nonlesional”</td>
<td>371 pts</td>
<td>92 surgical, 81 medical</td>
</tr>
<tr>
<td><strong>Method of surgery</strong></td>
<td>Sel AH</td>
<td>80% temp lobectomy (standard resections), 20% extratemporal resections</td>
<td>Tailored resection</td>
</tr>
<tr>
<td><strong>Classification of outcome</strong></td>
<td>Engel and ILAE</td>
<td>Time to first seizure (for those seizure-free yr 1) Kaplan–Meier curve Included AED withdrawal seizures; included pts with seizures during post-op hospitalizations</td>
<td>UW classification</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Engel classification: Lesional I: 59.4%–73.3% 2: 9.8%–16.0% 3: 10.1%–20.8% 4: 2.0%–7.8%</td>
<td>Out of 371 pts, 51% (189) seizure-free in first year Of 175 available for follow-up 110 pts (63%) no relapse Of 65 who relapsed, 63 had reliable seizure frequency recorded</td>
<td>Surgical outcome, 92pts yrs 4 and 5 1: 48% (44 pts) 2: 14% (13 pts) 3a: 6% (6 pts) 3b: 9% (8 pts) 4: 22% (20 pts) 5: 1% (1 pt)</td>
</tr>
</tbody>
</table>
Nonlesional
I: 48.4%–88.7%
II: 3.8%–12.9%
III: 3.8%–19.4%
IV: 3.8%–19.4%

49% (31 pts) had more than 1 sz/yr
16% (10 pts) had more than 1 sz/mo

Curative group = Unilateral TLE (30 pts)
Outcome 1 = 19 pts (63%)
Outcome 2 = 4 pts (13.3%)
Outcome 3a = 3 pts (10%)
Outcome 3b = 2 pts (6.6%)
Outcome 4 = 2 pts (6.6%)

Palliative group = Unilateral, multifocal, and bilateral TLE (50 pts)
Outcome 1 = 15 pts (30%)
Outcome 2 = 9 pts (18%)
Outcome 3a = 4 pts (8%)
Outcome 3b = 4 pts (8%)
Outcome 4 = 17 pts (34%)
Outcome 5 = 1 pt (2%)

EEG reports were available for review in 80 of the 92 patients
Medical outcome, 81 pts yrs 4 and 5
Outcome 1 = 3 pts (4%)
Outcome 2 = 1 pt (1%)
Outcome 3a = 3 pts (4%)
Outcome 3b = 13 pts (16%)
Outcome 4 = 58 pts (72%)
Outcome 5 = 3 pts (4%)

(Continued)
Table 1  Reported Outcomes of Selected Studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Wieser (33)</th>
<th>Yoon (17)</th>
<th>UW (9,10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical outcome</td>
<td>26 pts yrs 9 and 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 1</td>
<td>16 pts (61.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 2</td>
<td>1 pt (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 3a</td>
<td>1 pt (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 3b</td>
<td>2 pt (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 1–3b</td>
<td>20 (77%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 4 and 5</td>
<td>6 (23%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical outcome</td>
<td>36 pts yrs 9 and 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 1</td>
<td>2 pts (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 3a</td>
<td>4 pts (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 3b</td>
<td>8 pts (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 1–3b</td>
<td>14 pts (39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome 4 and 5</td>
<td>22 (61%)</td>
<td></td>
<td></td>
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</tbody>
</table>

Etiology

<table>
<thead>
<tr>
<th>Lesional 248 pts</th>
<th>Lesional and nonlesional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular malformations and vascular tumors</td>
<td>1) Developmental lesions that included cortical dysplasia, heterotopic neurons, tuberous sclerosis, and hamartoma.</td>
</tr>
<tr>
<td>Benign tumors</td>
<td>2) Tumor (25% of patients)</td>
</tr>
<tr>
<td>Semi-benign tumors, semi-malignant, and malignant tumors</td>
<td>3) Mesial temporal sclerosis (45% of patients)</td>
</tr>
<tr>
<td>Others</td>
<td>4) Vascular malformation</td>
</tr>
<tr>
<td>Nonlesional 182 pts</td>
<td>5) Normal or gliosis w/o other findings (13% of patients)</td>
</tr>
<tr>
<td>Includes varying degree of HS: 151 pts (83%)</td>
<td>6) Other (including infection and trauma)</td>
</tr>
<tr>
<td>And no disease found: 31 pts (17%)</td>
<td></td>
</tr>
</tbody>
</table>

Nontumoral: Encephalitis, birth related, trauma, febrile Sz, malformations, meningitis, encephalitis
<table>
<thead>
<tr>
<th>Criteria for operation</th>
<th>Medically intractable MTLE</th>
<th>Medically intractable epilepsy</th>
<th>Medically intractable TLE pre-op/eval neuropsych exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard scalp EEG</td>
<td>Yes</td>
<td>Not stated</td>
<td>Yes</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>Yes</td>
<td>Not stated</td>
<td>Some</td>
</tr>
<tr>
<td>Subdural brain recording</td>
<td>Some</td>
<td>Not stated</td>
<td>Some</td>
</tr>
<tr>
<td>Depth electrode</td>
<td>Some</td>
<td>Not stated</td>
<td>No</td>
</tr>
<tr>
<td>Angio/Wada</td>
<td>Some</td>
<td>Not stated</td>
<td>Yes</td>
</tr>
<tr>
<td>Psychometrics</td>
<td>Yes</td>
<td>Not stated</td>
<td>All</td>
</tr>
<tr>
<td>CT</td>
<td>Yes</td>
<td>Not stated</td>
<td>Yes</td>
</tr>
<tr>
<td>MRI</td>
<td>Some</td>
<td>Not stated</td>
<td>Some</td>
</tr>
<tr>
<td>Hi-res MRI</td>
<td>Some</td>
<td>Not stated</td>
<td>No</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Some</td>
<td>Not stated</td>
<td>No</td>
</tr>
<tr>
<td>SPECT</td>
<td>Some</td>
<td>Not stated</td>
<td>No</td>
</tr>
<tr>
<td>Receptor PET</td>
<td>No</td>
<td>Not stated</td>
<td>No</td>
</tr>
<tr>
<td>Comments</td>
<td>Depending on the particular analysis, different numbers of patients were included.</td>
<td>The KM curve does not show those who became seizure-free after year one, or those who had years with no seizures. It describes the probability of developing seizure recurrences related to time from surgery to relapse.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td>(Continued)</td>
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</tbody>
</table>

Outcomes of Temporal Lobe Epilepsy Surgery 669
### Table 1  Reported Outcomes of Selected Studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Wieser (33)</th>
<th>Yoon (17)</th>
<th>UW (9,10)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The lesional group did significantly better than the nonlesional group.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The curative group did significantly better than the palliative group.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>In the nonlesional group, those with the most severe HS did better than those with the mildest or no HS.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table 2</td>
<td>Reported Outcomes of Selected Studies</td>
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<tr>
<td>----------</td>
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<td></td>
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</tr>
<tr>
<td>Study</td>
<td>Penfield (2)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Rasmussen (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Van Buren (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year published</td>
<td>1950</td>
<td>1983</td>
<td>1975</td>
</tr>
<tr>
<td>Duration of follow-up years</td>
<td>1–11</td>
<td>2–44 (median 12)</td>
<td>3–16</td>
</tr>
<tr>
<td>Method of follow-up</td>
<td>Patient correspondence</td>
<td>Patient medical records</td>
<td>124</td>
</tr>
<tr>
<td>Number of patients in study</td>
<td>51</td>
<td>894 non-tumoral cases with follow-up data for 2 or more years</td>
<td></td>
</tr>
<tr>
<td>Method of surgery</td>
<td>Tailored resection</td>
<td>Tailored resection</td>
<td>Tailored resection</td>
</tr>
<tr>
<td>Classification of outcome</td>
<td>4 = Seizure-free since discharge</td>
<td>(Auras not counted.) Seizure-free since discharge. Became seizure-free after some early attacks.</td>
<td>Seizure-free 3 or more years then rare or occasional attacks. Marked reduction in seizure tendency.</td>
</tr>
<tr>
<td></td>
<td>3 and 4 = “Success”</td>
<td>Seizure-free 3 or more years then rare or occasional attacks. Marked reduction in seizure tendency.</td>
<td>Moderate or less reduction in seizure tendency.</td>
</tr>
<tr>
<td></td>
<td>2 = at least 50% improved “worthwhile”</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 = 25% improved</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 = no improvement or more frequent than pre-op sz frequency</td>
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<tr>
<td></td>
<td>0 and 1 = “Failure”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>4 = 27.4%</td>
<td>Cumulative for 894 pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 = 25.5%</td>
<td>2–44 years f/u</td>
<td>1 seizure-free = 26 pts, 21%</td>
</tr>
<tr>
<td></td>
<td>3 and 4 = 52.9% “success”</td>
<td>Seizure-free since discharge</td>
<td>2 no improvement = 41 pts, 33%</td>
</tr>
<tr>
<td></td>
<td>2 = 25.4% “worthwhile”</td>
<td>194 pts (22%)</td>
<td>Anatomically “total” resections (76 pts)</td>
</tr>
<tr>
<td></td>
<td>1 = 7.8%</td>
<td>Became seizure-free after some early attacks</td>
<td>1 seizure-free = 24 pts, (31.6%)</td>
</tr>
<tr>
<td></td>
<td>0 = 13.7%</td>
<td></td>
<td>2 no improvement = 15 pts, 19.7%</td>
</tr>
<tr>
<td></td>
<td>0 and 1 = 21.5% “failure”</td>
<td>138 pts (15%)</td>
<td>Anatomically “partial” resections (48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Free 3 or more years then rare or occasional attacks, 119 pts (13%)</td>
<td>1 seizure-free = 2 pts, 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marked reduction in seizure tendency, 117 pts (13%)</td>
<td>2 no improvement = 26 pts, 54%</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Penfield (2)</th>
<th>Rasmussen (5)</th>
<th>Van Buren (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology/Pathology</strong></td>
<td>Non-tumor, atrophy, scars from trauma or abscess, microgyria, hemangioma, uncategorized, no abnormality found</td>
<td>Non-tumor, Trauma, post-inflammation, febrile convulsions, congenital malformations, vascular malformations, multiple potential causes, miscellaneous lesions</td>
<td>Febrile seizures, trauma, CNS infections, 5 unsuspected tumors, microangiomas</td>
</tr>
<tr>
<td><strong>Criteria for operation</strong></td>
<td>Medically intractable TLE</td>
<td>Medically intractable TLE</td>
<td>Medically intractable TLE</td>
</tr>
<tr>
<td><strong>Standard scalp EEG</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Ictal EEG</strong></td>
<td>No</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td><strong>Subdural brain recording</strong></td>
<td>No</td>
<td>Some</td>
<td>Infrequent</td>
</tr>
<tr>
<td><strong>Depth electrode</strong></td>
<td>No</td>
<td>Some</td>
<td>Infrequent</td>
</tr>
<tr>
<td><strong>Angio/Wada</strong></td>
<td>No</td>
<td>Some</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Psychometric</strong></td>
<td>No</td>
<td>Some</td>
<td>Not mentioned</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>No</td>
<td>Some</td>
<td>No</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hi-res MRI</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>FDG-PET</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>SPECT</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Receptor PET</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Plain X ray and pneumoencephalography</td>
<td>Year by year outcomes and patient “bad year phenomenon.”</td>
<td>Shows late recurrences</td>
</tr>
</tbody>
</table>

An additional 7 patients underwent exploratory operation only, and either the extent of focus was too great or the source of seizures was not found. None of the 6 patients followed became seizure-free.
<table>
<thead>
<tr>
<th>Study</th>
<th>Bailey (3)</th>
<th>Keogan (34)</th>
<th>Bien (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year published</td>
<td>1961</td>
<td>1992</td>
<td>2001</td>
</tr>
<tr>
<td>Duration of follow-up yrs</td>
<td>5</td>
<td>3–15</td>
<td>2–10 (4.8 avg) post-op compared to 1 yr pre-op/evaluation</td>
</tr>
<tr>
<td>Method of follow-up</td>
<td>Patient, observer, and physician reports</td>
<td>Patient interview</td>
<td>Two clinic visits:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Visit 1: Baseline: calculate monthly seizure frequency previous 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Visit 2: Rate outcome depending on monthly seizure frequency since visit 1.</td>
</tr>
<tr>
<td>Number of patients in study</td>
<td>60</td>
<td>50</td>
<td>148 surgical; 94 medical</td>
</tr>
<tr>
<td>Method of surgery</td>
<td>Standard en bloc; 2 standard ways and some with removal of opposite temporal pole</td>
<td>Corticectomy temporal neocortex</td>
<td>Temporal lobectomy, amygdalohippocampectomy, lesionectomy</td>
</tr>
<tr>
<td>Classification of outcome</td>
<td>A: Greatly improved</td>
<td>Modified Crandall</td>
<td>A) Continuously seizure-free including auras</td>
</tr>
<tr>
<td></td>
<td>B: Improved</td>
<td>1a = no seizures</td>
<td>B) Sz-free for ≥1 year, but not permanently seizure-free</td>
</tr>
<tr>
<td></td>
<td>C: Not improved</td>
<td>1b = auras and no CPS</td>
<td>C) Sz during previous 12 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1c = few post-op seizures but none for 2 or more years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>II = rare seizures, 1 sz/yr or long period seizure-free, or nocturnal seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>III = worthwhile improvement, 1 sz/mo, &gt;50% reduction in seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV = no worthwhile improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>V = deterioration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good outcome = Class 1 &amp; II</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not consider nocturnal seizures or seizures with AED withdrawal</td>
<td></td>
</tr>
</tbody>
</table>
Table 3  Reported Outcomes of Selected Studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Bailey (3)</th>
<th>Keogan (34)</th>
<th>Bien (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Psychomotor attacks:</td>
<td></td>
<td>Surgical:</td>
</tr>
<tr>
<td></td>
<td>A = 18 (30.0%)</td>
<td>1a = 24%</td>
<td>A 44.6%; B 17.6%; C 37.8%</td>
</tr>
<tr>
<td></td>
<td>B = 23 (38.3%)</td>
<td>1b = 22%</td>
<td>Mean number of AEDs = 1.34, 8% no AEDs</td>
</tr>
<tr>
<td></td>
<td>C = 19 (31.7%)</td>
<td>1c = 4%</td>
<td></td>
</tr>
<tr>
<td>Major Convulsions:</td>
<td></td>
<td>II = 10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A = 28 (56.0%)</td>
<td>III = 12%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B = 5 (10.0%)</td>
<td>IV–V = 28%</td>
<td>A 4.3%; B 3.2%; C 92.5%</td>
</tr>
<tr>
<td></td>
<td>C = 17 (34.0%)</td>
<td></td>
<td>Mean number of AEDs = 2.33, none on no AEDs</td>
</tr>
<tr>
<td>Never had any = 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psych. symptoms:</td>
<td></td>
<td>Overall (I + II = 62%) good outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A = 2 (5.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B = 17 (30.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C = 34 (64.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never = 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEG:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A = 15 (25.0%)</td>
<td></td>
<td>Surgical Group:</td>
</tr>
<tr>
<td></td>
<td>B = 21 (40.0%)</td>
<td></td>
<td>Hippocampal sclerosis (40%); low-grade</td>
</tr>
<tr>
<td></td>
<td>C = 21 (35.0%)</td>
<td></td>
<td>tumor (30%); normal (9%); neur.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>migration/developmental disorder,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>vascular malformations, and other (21%)</td>
</tr>
<tr>
<td>Etiology/pathology</td>
<td>Not stated</td>
<td>No lesions/febrile seizures, meningitis, trauma, and family history</td>
<td></td>
</tr>
<tr>
<td>Criteria for operation</td>
<td>Medically intractable TLE</td>
<td>Medically intractable TLE</td>
<td>Medically intractable TLE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Note: Medical group were not surgical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>candidates due to: epileptic region not well</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>localized, neurologic or psychiatric risk,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>multifocal EEG, patient preference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>Medical</td>
<td>Surgical</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------</td>
<td>----------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Standard scalp EEG</td>
<td>Yes</td>
<td>Yes</td>
<td>All medical and surgical</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>No</td>
<td>No</td>
<td>Some medical and surgical</td>
</tr>
<tr>
<td>Subdural brain recording</td>
<td>No</td>
<td>No</td>
<td>Some medical and surgical</td>
</tr>
<tr>
<td>Depth electrode</td>
<td>No</td>
<td>No</td>
<td>Some medical and surgical</td>
</tr>
<tr>
<td>Angio/Wada</td>
<td>Yes</td>
<td>Yes</td>
<td>All medical and surgical</td>
</tr>
<tr>
<td>Psychometrics</td>
<td>Yes</td>
<td>Yes</td>
<td>Some medical and surgical</td>
</tr>
<tr>
<td>CT</td>
<td>Yes</td>
<td>Yes</td>
<td>Most medical and surgical</td>
</tr>
<tr>
<td>MRI</td>
<td>Yes</td>
<td>Yes</td>
<td>Some medical and surgical</td>
</tr>
<tr>
<td>Hi-res MRI</td>
<td>No</td>
<td>No</td>
<td>Some medical and surgical</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>No</td>
<td>No</td>
<td>Some medical and surgical</td>
</tr>
<tr>
<td>SPECT</td>
<td>No</td>
<td>No</td>
<td>Some medical and surgical</td>
</tr>
<tr>
<td>Receptor PET</td>
<td>No</td>
<td>No</td>
<td>Some medical and surgical</td>
</tr>
<tr>
<td>Comments</td>
<td></td>
<td></td>
<td>It is not clear how many patients in each category and whether or not any are free of all seizures at any time. States “It is now quite obvious that the best results are obtained on patients with a sharply localized focus in one temporal lobe.”</td>
</tr>
<tr>
<td>Surgery based on clinical picture and interictal EEG</td>
<td></td>
<td></td>
<td>Surgery based on clinical picture and interictal EEG</td>
</tr>
<tr>
<td>Fewer AEDs used in the surgical group than in the medical group.</td>
<td></td>
<td></td>
<td>Fewer AEDs used in the surgical group than in the medical group.</td>
</tr>
</tbody>
</table>
**Table 4  Reported Outcomes of Selected Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Wiebe (11)</th>
<th>Jutila (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year published</td>
<td>2001</td>
<td>2002</td>
</tr>
<tr>
<td>Duration of follow-up years</td>
<td>1</td>
<td>(0.25–10.5) Mean = 5.4 yr</td>
</tr>
<tr>
<td>Method of follow-up</td>
<td>Clinic visit</td>
<td>Medical records</td>
</tr>
<tr>
<td>Number of patients in study</td>
<td>40 (36) surgical, 40 medical</td>
<td>140</td>
</tr>
<tr>
<td>Method of surgery</td>
<td>Mainly standard en bloc; one selected AH</td>
<td>Tailored ATL and AH (113) Tailored ATL + AH + lesionectomy (9), selective AH (18)</td>
</tr>
<tr>
<td>One large resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classification of outcome</td>
<td>A = Free of sz with impaired consciousness</td>
<td>Adapted from Engel</td>
</tr>
<tr>
<td>B = Free of all sz including auras</td>
<td>Ia = Sz-free</td>
<td></td>
</tr>
<tr>
<td>C = 1–4 sz/month</td>
<td>Ib = Sz-free and auras only</td>
<td></td>
</tr>
<tr>
<td>D = 5 or more sz a month</td>
<td>II = Rare sz</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III = Worthwhile improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV = Not helped</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excluded first mo post-op</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Curative unilateral TLE (103 pts), f/u 5 yr (.25–10.5 yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ia, 46% seizure-free</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ib, 10% auras only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II, 15% rare sz</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III, 14% worthwhile improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV, 17% not helped</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Palliative group (37 pts), f/u 4.4 yr (1.0–9.0 yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I, 35% seizure-free</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II, 5% rare sz</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III, 22% worthwhile improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV, 38% not helped</td>
<td></td>
</tr>
</tbody>
</table>
Etiology/Pathology  
No brain lesions  
"Probable symptomatic" or "symptomatic"  
Included in the symptomatic: hippocampal atrophy,  
"asphyxia," "central nervous system infection," "tumor  
or cystic lesion," dysplasia, contusion, miscellaneous.  
Febrile seizures, family history of epilepsy.  

Criteria for operation  
Unilateral EEG temp focus or most unilateral  
EEG temp focus by ictal or interictal.  
IQ > 70  
No ET spikes  

Medically intractable TLE  
Mostly nonlesional  
Curative: unilateral  
Palliative: Bilateral or multifocal, incomplete removal, or  
structural lesion non-concordant EEG.  

<table>
<thead>
<tr>
<th>Test</th>
<th>Temporal Lobe Epilepsy Surgery</th>
<th>Outcomes of Temporal Lobe Epilepsy Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard scalp EEG</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Subdural brain recording</td>
<td>Some</td>
<td>Some</td>
</tr>
<tr>
<td>Depth electrode</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Angio/Wada</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Psychometrics</td>
<td>Yes</td>
<td>Yes, also psychiatric exams</td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hi-res MRI</td>
<td>No</td>
<td>Second group</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>SPECT</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Receptor PET</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Comments</td>
<td>No classification for rare sz, i.e., &lt;12 sz/yr</td>
<td></td>
</tr>
</tbody>
</table>
Table 5  Reported Outcomes of Selected Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Clusmann (32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year published</td>
<td>2002</td>
</tr>
<tr>
<td>Duration of study</td>
<td>1989–1997</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>Mean of 38 mo (12–108 mo) 86% had f/u of &gt; 2 yrs</td>
</tr>
<tr>
<td>Method of follow-up</td>
<td>Last outpatient clinic visit and telephone interviews</td>
</tr>
<tr>
<td>Number of patients in</td>
<td>321 total number of patients</td>
</tr>
<tr>
<td>study</td>
<td></td>
</tr>
<tr>
<td>Method of surgery</td>
<td>85 patients lesionectomy</td>
</tr>
<tr>
<td></td>
<td>138 patients AH</td>
</tr>
<tr>
<td></td>
<td>98 patients ATL</td>
</tr>
<tr>
<td>Classification of outcome</td>
<td>Engel’s Classification</td>
</tr>
<tr>
<td></td>
<td>‘‘Good’’ outcome = Engel Class I-II</td>
</tr>
<tr>
<td></td>
<td>‘‘Unsatisfactory’’ outcome = Engel Class III-IV</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TLE (236 pts)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts.</td>
</tr>
<tr>
<td>1989–1992</td>
<td>74</td>
</tr>
<tr>
<td>1993–1994</td>
<td>13</td>
</tr>
<tr>
<td>1995–1997</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>98</td>
</tr>
<tr>
<td>Outcome all 321 patients</td>
<td>Class I (seizure-free) = 227 pts (70.7%); Class II (rare and non-disabling sz) = 36 pts (11.2%) (Satisfactory = Class I &amp; II = 263 pts) (81.9%); Class III = 24 pts (7.5%); Class IV (no worthwhile improvement) = 34 pts (10.6%) (Unsatisfactory = Class III &amp; IV = 58 pts) (18.1%)</td>
</tr>
</tbody>
</table>

<p>| Etiology              | Febrile convulsions, trauma, infection, familial seizures, dysplasia, and neoplasia |
| Criteria for operation | Well-documented chronic and medically intractable TLE &gt; 1 yr duration, as well as adequate trials on at least 2 AEDs and having a pre-op MRI |
| Standard scalp EEG    | Yes with sphenoidal electrodes |</p>
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ictal EEG</td>
<td>Yes</td>
</tr>
<tr>
<td>Subdural brain recording</td>
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</tr>
<tr>
<td>Depth electrode</td>
<td>Some</td>
</tr>
<tr>
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</tr>
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<td>CT</td>
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<td>Hi-res MRI</td>
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<tr>
<td>FDG-PET</td>
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<tr>
<td>SPECT</td>
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<tr>
<td>Receptor PET</td>
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</tr>
<tr>
<td>Comments</td>
<td>Those with lesions had a higher percentage of good outcomes. Structural abnormality 84.5% good outcome. No abnormality 53% good outcome.</td>
</tr>
</tbody>
</table>
were in UW Class 1-3a for the fourth and fifth follow-up year (chi sq = 63, \( p = < 0.001 \)). Worthwhile improvement (UW Class 1–3b see Appendix) was seen in 78% of the surgical group and 28% of the control group (chi sq = 46, \( p = < 0.001 \)). Twenty-two percent of the surgical group and 72% of the control group showed no improvement in the same follow-up period (chi sq = 10.3, \( p = < 0.01 \)).

In the 10-year groups, 61% in the surgical group (\( n = 26 \)) were seizure-free in the ninth and tenth years of follow-up compared with 6% in the medical group (\( n = 36 \)) (chi sq = 23, \( p = < 0.01 \)). Sixty-nine percent in the surgical and 17% in the medical group were in UW Class 1–3a for the ninth and tenth years (chi sq = 18, \( p = < 0.001 \)). Worthwhile improvement (UW Class 1–3b) was seen in 77% of the surgical and 39% of the control group (chi sq = 8.8, \( p = < 0.01 \)). The differences between these two groups were highly significant.

In any given year 51% to 58% of the surgically treated patients were seizure-free. For all five years, 32% of the 92 patients were seizure-free. Of the 26 patients followed for 10 years, 31% were seizure-free all 10 years. One additional patient in that group was seizure-free all but year eight when she had a single seizure. Patients with only complex partial and no other seizure types did well—75% of these patients were seizure-free (chi sq = 5.7, \( p = < 0.025 \)) and 94% were helped by surgery (UW Class 1–3b or better). Generalized tonic–clonic seizure within the two years preceding surgery was a negative factor, where only 37.5% become seizure-free.

Outcome was also related to the presurgical interictal EEG. Of the 30 patients with unilateral anterior or mid-temporal interictal spikes, 19 were seizure-free (63%) (chi sq = 8.5, \( p = < 0.01 \)) and only two (7%) had no worthwhile improvement. Of the 50 patients with bilateral or extratemporal discharges, 15 (30%) were seizure-free and 18 (36%) had no worthwhile improvement (chi sq = 8.6, \( p = < 0.01 \)). Although this series antedates modern imaging techniques, the outcome in patients with unilateral anterior temporal interictal discharges is similar to that in modern series with concordant temporal lobe EEG and imaging abnormalities (17).

**Psychosocial Function**

In this study, at five years follow-up, the surgical group had significantly better overall psychosocial functioning and vocational and emotional adjustment (27). Those who were students at study entry and completed schooling at follow-up had a particularly favorable vocational outcome after surgery, with 90% of the surgical patients working part or full time, compared with 47% of the medical group (\( P < 0.001 \)) (27).

On neuropsychological assessment at five years, five of the twenty variables were significantly improved relative to study initiation in the surgical groups. This improvement included the Wechsler Adult Intelligence Scale Full, Verbal and Performance IQs, as were the proportion of abnormal tests and the impairment index. On the contrary, verbal memory performance after dominant temporal resections showed a decline postoperatively, even in those seizure-free but especially in those not seizure-free (Dodrill, unpublished data). Repeat neuropsychologic assessment at 10 years postoperative did not provide any evidence of late decline in neuropsychologic performance (28).

**COMMENTS ON OTHER STUDIES**

Horsley in 1886 (1) reported on three operations for seizures arising from the frontal lobe with one to several months follow-up. His classification consists of “cured.”
Penfield and Flanigan (2) reported success as seizure-free or few seizures before cessation (Table 2). Bailey (3) reported outcome by seizure type rather than by patient (Table 3). Preoperative criteria were clinical seizures and standard EEG data with a temporal lobe focus.

Van Buren et al. (6) reported outcome as a chronological display for individual patients (Table 2). For each year a score of 1–2 is given; a score of 1 indicates no seizures at all, 1.01–1.39 (very rare seizures), 1.40–1.79 (rare seizures), 1.80–1.99 (moderate improvement), and 2 (no improvement). He also stratifies patients by the completeness of the resection. In his report, he states “…33% of the patients with ‘total’ excision became totally seizure-free and only 20% can be considered therapeutic failures, whereas among the cases with ‘partial’ excision, the failures amount to over 50% and total successes decrease to less than 5%” (p. 169). He suggests surgical success tends to be higher in short follow-up. He states, “These same data would seem to suggest not only that short periods of postoperative follow-up three years or less are rather meaningless for a reliable assessment of surgical results, but that, actually, even with longer follow-ups, one may seldom be able to state with complete certainty that the treatment has indeed been fully successful” (p. 169) and later states, “…it seems safe to state that of those patients who have been seizure-free for five continuous years, at least 90% have a very high probability to remain seizure-free permanently” (p. 171). This classification, even though more comprehensive than others, still does not take into account days lost due to postictal deficits or to losses due to operative complications.

Rasmussen (5) reported on 894 patients followed for 2 to 44 years (median 12 years), 22% were seizure-free (auras are not considered), and 15% became seizure-free after early attacks (Table 2). One cannot tell how many “seizure-free” years patients experienced.

**RANDOMIZED STUDY**

The recent study of Wiebe et al. (11) is the only formal randomized study testing outcome of temporal resective surgery (Table 4). Randomization actually occurred before the EEG monitoring need to establish if the patient were a surgical candidate. Thus, it is actually a randomized study of the intent to treat with surgery. This led to inclusion of four patients who did not meet the criteria for surgery and did not have surgery in the group of 40 “surgical” patients. Despite this, for the year of follow-up, the surgical group had significantly fewer seizures, overall, than the medical group, as well as fewer seizures that interfered with awareness.

**PROGNOSIS WITH PERSISTENCE OR RECURRENCE OF SEIZURES**

Yoon et al. (16) retrospectively ascertained long-term outcome in a series of 375 patients (Table 1). Of these, 189 patients (51%) were seizure-free the first year postoperatively and 175 were available for follow-up (80% of whom underwent temporal lobectomies). Sixty-three percent (110 patients) had no relapses for a minimum of three years follow-up (mean 8.7 years). That is, 30% of the original cohort was seizure-free for three consecutive years. Almost half had more than one seizure per year, and 16% more than one seizure per month, in contrast to the UW study where three-quarters of the recurrences were single seizures per year. Normal pathology and longer preoperative seizure disorder were associated with increased risk of
relapse. A late recurrence, often of only one or two seizures in a single year, was also noted by Van Buren et al. (6). This series consisted of 80% temporal lobe resections.

**RECURRENCE OF SEIZURES IN THE UW STUDY**

The patterns of seizure recurrence varied. Some patients experienced a single seizure or rare seizure clusters early in their postoperative course or as isolated events long after their surgeries. Others had recurrences, but had decrease in seizure frequency compared with the preoperative period. Of the 92 patients in the operated group, 48 were completely seizure-free (UW 1) in the first postoperative year, and 29 remained seizure-free all five years. Of the 19 patients who developed seizures after being seizure-free for the first postoperative year, 12 recurred in year two. Thus a two-year follow-up included most recurrences. Seven of 19 patients with recurrences had only a single seizure in the year of recurrence and were seizure-free in all subsequent years. In only one did seizures recur with a frequency considered to indicate no surgical benefit.

After two years seizure-free, seven of 36 had recurrences. However, in four, this involved only one year of the subsequent three years of follow-up, and in three there was only a single seizure in that year. Of the 44 patients who had seizures in the first year, six were seizure-free the remainder of the five years. Five of these were among the 11 patients with only one or two seizures in the first postoperative year. Four additional patients had only one additional year with seizures during the five-year follow-up; for three there was a single seizure in that year. This indicates that patients with seizures in the first year after surgery have some chance of becoming seizure-free, especially if there were only one or two seizures in that year. If seizures then persist into the second year, there is only a very small chance of a seizure-free outcome.

**STUDIES COMPARING DIFFERENT CASE SELECTION AND SURGICAL TECHNIQUES**

**Outcome by Site of Origin of Seizures**

The study by Jutila et al. (17) highlights the difference in outcome between cases where the resection is likely to encompass the epileptogenic zone (‘‘curative’’ operations) and those where some of the epileptogenic zone is likely left behind (‘‘palliative’’ operations) (Table 4). Jutila et al. (17) distinguish between ‘‘curative,’’ unilateral TLE with unilateral EEG focus, and ‘‘palliative,’’ those with bilateral and extratemporal EEG foci. Fifty-six percent of the curative group was seizure-free whereas only 35% of the palliative group attained this status. This difference is also evident in the UW study. When selection criteria are based on EEG focus, an outcome of Class I is more likely with a unilateral anterior temporal lobe focus than with bilateral foci. In the Jutila study, using the same three-year follow-ups for the early nonimaging and later imaging series, the proportion of ‘‘curative’’ cases seizure-free improves from 51% to 59%.

Although there is a statistical difference when looked at by epochs before and after modern imaging, this comparison is confounded with all the unknown subtle changes in technique and selection that occur over time. In the curative group, in the ‘‘pre-MRI’’ period, with a longer follow-up—7.7 years (1–10.5 years)—51% were seizure-free (39% seizure-free without auras and 12% auras only) and 18% not helped. In the ‘‘post-MRI’’ period, with a much shorter follow-up—3.8 years (three months to 6.5 years)—59% were seizure-free (52% seizure-free without auras and 7% auras only) and 15% were
not helped. When structural lesions are found concordant with the EEG focus in unilateral TLE, surgical outcomes are improved (UW, unpublished data) (29).

Although there are a variety of surgical approaches to temporal resections, ranging from neocorticectomy to anterior temporal resections that spare hippocampus and associated entorhinal cortex, to selective amygdalohippocampectomies, outcomes of series managed with one technique or another have been similar, when case selection criteria have been comparable.

**Amygdalohippocampectomies**

Niemeyer (30) pioneered amygdalohippocampectomy (AH) in the 1950s, and interest was renewed by Wieser and Yasargil (31) in the 1980s. Comparison of anterior temporal lobectomy (ATL) and AH in the Palm Desert conference pooled data showed no outcome differences (24). In addition, Clusmann et al. (32) reported similar outcomes with a “good” outcome in 83.3% (115 patients) managed with AHs and 79.6% (78 patients) with anterior temporal resections (Table 5). Most of the anterior temporal resections were done in an earlier era and the majority of the AHs were done later. Wieser et al. (33) reported favorable outcomes for AHs: in nontumoral cases, 48.4% to 88.7% seizure-free and 3.8% to 19.4% not helped (Table 1). Depending on degree of hippocampal sclerosis (HS), seizure-free rate was 88.7% for severe HS, 59.6% in mild HS, and 48.4% when no disease found.

Bien et al. (8) reported the outcome of 94 non-surgical candidates with TLE to that of 148 surgically treated patients with TLE, by temporal lobectomy, AH, or lesionectomy (Table 3). After a mean of 4.8 years, 44.6% of the surgical patients and 4.3% of the medically treated patients were continuously seizure-free. Those in the surgical group, even those with ongoing seizures, were on fewer AEDS than those in the non-surgical group.

**Neocorticectomy**

Results with neocorticectomy are remarkably similar to ATL. Keogan et al. (34), using the preoperative interictal surface EEG, without ictal EEG and without MRI as criteria for surgery, reported long-term follow-up (3–15 years) with removal of temporal neocortex with preservation of deeper limbic structures (Table 3). They found 46% or 50% seizure-free depending on follow-up (no seizures 24%, auras and no complex partial seizures 22%), few postoperative seizures but none for two or more years (4%), and 26% not helped (18% no worthwhile improvement with 8% worse).

Again, in this series, those with unilateral anterior temporal anterior mid-temporal spikes had better outcome than those with bilateral or extratemporal spikes, a 91% versus 26% chance of experiencing a cure or almost cure—an outcome of “Modified Crandall” I or II. In addition to a clear anterior mid-temporal EEG focus, factors predicting favorable outcome were: a stereotypical onset of temporal lobe seizure and a greater volume of tissue removed.

**OPERATIVE COMPLICATIONS**

Operative complications of temporal lobe resections for seizures are low. A review by Pilcher and Rusyniak (35) indicate that death is rare (<1%). Transient (4%) and permanent (2%) hemiparesis were thought to be due to impingement on nearby vascular structures. Mesial temporal lobe resections are often associated with mild contralateral
superior quadrantanopia (>50%), usually not recognized by the affected patient. Occasional symptomatic field cuts occur (8%), and are judged disabling in 2% to 4%. Resection of the temporal lobe in the dominant hemisphere very rarely results in a permanent dysphasia (1–3%) but more frequently produces transient dysphasia, which usually resolves in several days. Global memory deficits occur rarely (1%), however verbal memory deficits after dominant hemisphere resections remain a problem. These occur even with seizure control, but are more severe if seizures persist. Memory deficits are more likely to be noted in intellectually highly functioning individuals. Reports of surgical outcome have not usually included neuropsychologic outcomes.

Transitory psychosis and depression are reported in 2% to 20%. There is controversy concerning the incidence of permanent psychosis (36). Bailey (3) and Falconer and Serafetinides (4) reported that psychosis appeared not to be caused nor alleviated by surgery, but the improvement in patient’s adjustment was noted with seizure relief (37). Rayport and Ferguson (38) pointed out that interictal psychosis must be differentiated from ictal psychosis. Psychosis also occurs in medically treated patients (39). There is no control-matched series of surgical versus medically treated patients to settle this ambiguous issue.

QUALITY OF LIFE

There is disagreement in reports of effects of surgery on QOL and vocational outcomes. Studies comparing a surgical group to a nonsurgical group have reported no difference in QOL or employment (7,40). In 1991, Guldvog et al. (7) reported on 185 medically and 201 surgically treated patients. The surgical group claimed improved working ability, but this was not reflected in the working situation. Those who were more likely to enjoy improved vocational outcome had been regular students or working before surgery. This is in accordance with the UW results that those who had been gainfully employed or were students preoperatively were more likely to be employed at a higher level of compensation postoperatively. Vickrey et al. (40), in a study of 202 surgically treated compared with 46 medically treated patients, reported improved QOL in the surgically treated group, but not in the nonsurgical group; there was no difference in vocational status.

Both these studies (7,40) compared a surgical group with a medically treated group which included patients who were not surgical candidates and therefore not with a comparable disease. Wiebe et al. (11) reported that the surgical group compared with a randomly selected medically treated group showed significant improvement in QOL, but not vocational outcome. There was a trend for the surgical group to be more frequently employed or attending school at one year.

In contrast, Jones et al. (41) reported that the 61 patients in the surgical group enjoyed both a better QOL and vocational status compared to the 23 patients in the medical group. Again, this is not a matched group. The medical group either failed to fulfill the criteria for surgical treatment or declined surgery. In the seizure-free patients compared with those still with seizures, no statistical difference was found for psychosocial outcomes or employment status.

With regard to relation of vocational outcome and degree of seizure control, this is different from the findings of Sperling et al. (19). In Sperling et al.’s group of 86 patients treated with ATL followed for 3.5 to 8 years after surgery, vocational status was correlated to the degrees of seizure freedom. Seizure-free patients did
better than patients with occasional seizures. Ongoing studies are addressing the issue of QOL following temporal lobotomies (42).

CONCLUSION

The studies are convincing that surgical treatment of TLE in properly selected patients with pharmacoresistant seizures is superior to that of continued medical treatment (8–11). Further double-blind, prospective studies addressing this issue are unnecessary and would divert valuable resources from other research. The question of when seizures become intractable is less well established, but studies are in agreement that seizures are likely to become refractory when they do not respond early to AED treatment (20,21).

Issues of relevance at this time appear to be:

1. Outcomes have not improved much over time: the failure rates remain approximately 15% and 30% regardless of technique.
2. Patient selection appears to be the determining factor for quality of outcome. EEG criteria appears to be the most important determining factor; a clear anterior temporal interictal epileptic focus and a concordant structural lesion augurs the likelihood of the best outcome. Selection criteria, especially EEG data, should be noted when reporting outcomes. Classifications should be stratified as curative and palliative based on EEG, and classifications should be stratified as lesional versus nonlesional, and further pathological conditions reported separately as they appear to respond differently to surgical therapy.
3. The classification should include not only the number of seizures, but also the severity of seizures and include the effect of the postictal state (e.g., ILAE classification).
4. Two classifications of outcome are desirable, one to reflect the biological/physiological effect of the surgery which reports the effect on the seizure frequency, and another classification which reflects the effect on the QOL and does not necessarily report the exact seizure count.
5. A minimum of two years follow-up is likely prognostic of long-term outcome. Late recurrences do occur but are likely to be single seizures and usually not recurrence of intractable epilepsy.
6. Follow-up periods should be clearly identified and reported on a year-by-year basis as per Van Buren et al. (6) as well as by a KM curve rather than a group experience at a point in time. In addition, note should be made of those not seizure-free who became seizure-free later (not accounted for in the KM curve), as per Van Buren et al. (6). Note should be made of those with just one or more years with seizures and to what degree of seizure control they had that year (6).
7. Complications of surgery should be included, ideally as is toxicity in AED studies, as in Mattson et al. (18). However, the outcome classification has already become so complex and cumbersome that such an addition may be prohibitive, and complications may have to be reported separately as has been and mainly would be reflected in the QOL classification.
8. The relationship of psychosis to TLE as well as the relationship to TLE surgery is not clearly reported (38). Structured and uniform psychiatric evaluations should be performed in all pre- and postsurgical patients.
Furthermore, any relationship of psychosis to surgery needs to be studied in a control-matched series of surgical versus medically treated patients. As it is established that surgery for TLE is an effective treatment, it is now important to find more effective ways to establish the epileptic foci and to determine better ways to target those foci more discretely avoiding nearby normal tissue. In addition to novel EEG techniques, some of those tools may now include modern imaging, such as high-resolution MRI and fluorodeoxyglucose (FDG) Positron emission tomography (PET). There is little experience with promising tools such as flumazenil (FMZ) PET. PET receptor studies of other specific ligands also deserve further study, such as [1C]Carfentanil, a mu opioid agonist, [1C]Deprenyl, which binds to monoamine oxidase type B (MAO-B) receptor, [11C](S)-N-Methylketamine, which binds to the N-methyl-D-asparate (NMDA) receptor, and [α-11C]Methyl-L-tryptophan (AMT) which is a marker for serotonin synthesis (43). Whereas the FMZ PET identifies the areas of diminished gamma aminobutyric acid (GABA) receptors, the AMT PET appears to identify those receptors that are epileptogenic as opposed to those areas in which there is cell death as the cause of decreased GABA-receptors. Receptor binding studies are likely to prove useful in identifying the epileptogenic focus in those with mesial temporal lobe epilepsy (MTLE) and normal MRI. This is especially important as a seizure-free outcome is more likely in those with MTLE and mesial temporal sclerosis on MRI than in those with a normal MRI, there is a likelihood of seizure-free outcome in 55%. The EEG is still the gold standard; receptor imaging may increase the yield, helping to identify the focus mainly by directing the placement of electrodes when proceeding with direct brain recording.

**APPENDIX**

**UW Classification**

<table>
<thead>
<tr>
<th>Class</th>
<th>Number of seizuresa</th>
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<tr>
<td>Class 1</td>
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<tr>
<td>Class 2</td>
<td>Rare seizure (&lt;1/yr)</td>
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<td>Class 3a</td>
<td>75% reduction (&lt;5/yr)</td>
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<tr>
<td>Class 3b</td>
<td>75% reduction (≥5/yr)</td>
</tr>
<tr>
<td>Class 4a</td>
<td>Better than preoperative, &lt;75% reduction</td>
</tr>
<tr>
<td>Class 4b</td>
<td>No change</td>
</tr>
<tr>
<td>Class 4c</td>
<td>Worse than preoperative</td>
</tr>
<tr>
<td>Class 4d</td>
<td>Exact number of seizures unknown</td>
</tr>
<tr>
<td>Class 5</td>
<td>Unknown</td>
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</table>

**Engel Classification of Postoperative Outcome (12)**

Class I: Free of disabling seizuresa

A. Completely seizure-free since surgery
B. Nondisabling simple partial seizures only since surgery

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a Excludes early postoperative seizures (first few weeks).
C. Some disabling seizures after surgery, but free of disabling seizures for at least two years
D. Generalized convulsions with antiepileptic drug withdrawal only

Class II: Rare disabling seizures (almost seizure-free)
A. Initially free of disabling seizures, but with rare seizures now
B. Rare disabling seizures since surgery
C. More than rare disabling seizures after surgery, but rare seizures for at least two years
D. Nocturnal seizures only

Class III: Worthwhile improvement
A. Worthwhile seizure reduction
B. Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not < two years

Class IV: No worthwhile improvement
A. Significant seizure reduction
B. No appreciable change
C. Seizures worse

ILAE Classification of Postoperative Outcome
1. Completely seizure-free, no auras
2. Only auras; no other seizures
3. One to three seizure days per year; plus or minus auras
4. Four seizure days per year to 50% reduction of baseline seizure days; plus or minus auras
5. Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; plus or minus auras
6. More than 100% increase of baseline seizure days; plus or minus auras

Van Buren Clinical Scoring for Outcomes
Global score = yearly score (above) added and divided by number of years
1. seizure-free
1.0–1.39, very rare seizures
1.40–1.79, rare seizures
1.80–1.99, moderate improvement
≥2.0, no improvement

REFERENCES

b Determination of “worthwhile improvement” requires quantitative analyses of additional data such as percent seizure reduction, cognitive function, and QOL.
Chapter XIV-43
Are Prospective, Randomized Trials Necessary? Review: The Role of Randomized, Controlled Trials in Epilepsy Surgery

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Brain surgery for epilepsy is a time-honored therapy that has been used for more than a century in thousands of patients. Accordingly, publications on epilepsy surgery (ES) have exploded. The National Library of Medicine contains over 4400 articles focusing on ES. Of these, nearly 75% were published after 1990. Yet, when looking for answers about the efficacy and safety of ES, we need to focus on the most scientifically rigorous studies, because they are most likely to provide valid answers that are closest to the truth.

The design and conduct of a study determine its scientific validity, and the optimum study design depends on the clinical question being asked. Different study designs are needed to answer clinical questions about diagnosis, prognosis, treatment, epidemiology, cost-effectiveness, and so forth.

OPTIMUM STUDY DESIGNS FOR QUESTIONS ABOUT THERAPY

To be useful, results of studies about therapy must be valid, i.e., unbiased, and applicable to common clinical situations. Bias, a process at any stage of research, which tends to produce results that differ systematically from the truth, occurs when known or unknown prognostic variables are distributed unequally in the intervention and comparison groups. Bias can be introduced in the selection of patients, application of interventions, assessment of outcomes, follow-up, and data analysis.
Controls and Randomization

Researchers have wrestled with bias for a long time. It is well known that studies without controls are the most likely to provide biased results. The best way to assure “positive” study results is to have no controls. For example, bloodletting and leeches were a panacea in the medical armamentarium for centuries. George Washington’s fatal pneumonia was aggressively treated in this manner. It was not until the 18th century that this therapy fell out of favor, thanks to Pierre Louis’s systematic observation that febrile patients who were not bled fared better than those who were bled. The simple but revolutionary inclusion of controls dramatically influenced the design of future studies about therapy.

Random Assignment to Interventions

The method of assigning patients to treatment and control groups has proven just as important as having controls. An analysis of 408 studies found that results of studies with historical controls are significantly more variable than those with concurrent controls (1). Researchers have used a variety of methods to assign patients to treatment groups, including matching based on known prognostic factors, or alternation between treatment groups based on predefined sequences, birth date, address, chart number, etc. Although superior to historical controls, all of these methods have a fatal flaw, i.e., the assignment to treatment groups is not truly experimental or chance-determined. This has two immediate, deleterious consequences. First, it does not address imbalances of unknown prognostic variables. Namely, one may inadvertently and systematically select patients with better—or worse—unknown prognostic factors for one of the treatment groups. Second, unconcealed assignment schedules introduce selection bias. That is, by knowing the next patient’s assigned treatment, research personnel may decide to skip randomization in the next patient, based on beliefs and expectations about that particular patient. The optimum remedy for these biases is random assignment to treatment groups, i.e., randomized, controlled trials (RCTs). In RCTs, each patient has an equal, chance-determined opportunity of being assigned to a treatment group, resulting in groups with balanced known and unknown prognostic variables. Because of their scientific rigor and unique ability to balance confounders, RCTs are the gold standard for assessing the effect of therapies.

In a recent analysis of current evidence for resective ES, Engel et al. (2) found that prior to the publication of the only RCT of medical versus surgical epilepsy therapy, only one of 415 potentially useful studies used controls (3,4). However, these were patients who declined or were not candidates for surgery, therefore non-equivalent to surgical patients. This illustrates the prevailing methodological inertia in clinical studies of ES.

Concealed Randomization

Patient enrolers must not know which treatment group the next patient will be assigned to. The importance of concealing the randomization schedule from those enrolling patients was demonstrated in an analysis of 250 RCTs (5). When study personnel knew the randomization schedule studies overestimated the benefit of interventions by an astounding 41%. This is particularly important in surgical RCTs, where study personnel and patients often have strong views about which treatment arm they prefer.
Randomization Is Not Everything

As crucial as concealed randomization is, the label of “RCT” does not guarantee valid study results. Consider some of the reasons for obtaining “positive” results in a controlled study:

- The treatment actually works.
- Treated and control patients are different to start with (in prognostic variables, definition of disease, referral base, etc.).
- The result is due to chance.
- Clinicians and patients are more committed to one treatment than another.
- Co-interventions other than the experimental intervention differ between groups.
- The experimental environment differs between groups.
- Outcomes are assessed differently in each group (different outcome definition and assessment, data collection quality, and follow-up).

Notice that random allocation only addresses dissimilarities between treatment groups. Chance results are dealt with by adequate sample size calculation and precision of measurement. To deal with other issues one requires high quality, prospective, parallel comparisons with pre-established protocols for patient recruitment, treatment, outcome assessment, and analysis.

Blinding

Blinding protects against outcome assessment bias and it is particularly important in studies evaluating “soft” outcomes, e.g., outcomes other than death or permanent loss of function or body parts. RCTs without blinding overestimate the benefit of interventions by about 20% (5). Blinding is important in ES because the typical outcomes (patient-reported seizures and health-related quality of life) are not particularly “hard.” Direct blinding is impossible in ES without sham surgery. Nonetheless, a panel of blinded, independent adjudicators who determine whether each patient-logged event is a seizure achieves unbiased outcome assessment, as shown in the RCT of temporal lobe ES (3). No other resective ES studies have used blinded outcome assessment (2).

RCTs OF EPILEPSY SURGERY

Despite calls for RCTs of ES dating back to 1963, very few have been conducted (6). The main reasons are unfeasibility, as illustrated by a failed RCT attempt, or a strong notion that “surgery works” and RCTs are unnecessary or even unethical (7,8). These hurdles are common to surgical RCTs, in which timing of the RCT is fundamental. If the RCT is done early, when the intervention is still evolving, few centers can participate, the technique is imperfect, the results are poorer, and they rapidly become obsolete. If done later, when the procedure has been adopted as “standard practice,” the RCT may be considered unethical. However, it is important to stress that in the absence of RCTs, notions about the magnitude of therapeutic effects are often incorrect. Extreme examples include interventions considered as beneficial in non-RCTs, but subsequently proven ineffective or deleterious in RCTs, e.g., intracranial–extracranial bypass surgery for stroke prevention, or mammary artery ligation for angina pectoris (9,10). On the contrary, even when RCTs confirm the usefulness of surgical interventions, such as in carotid endarterectomy for stroke prevention, the true
magnitude of the treatment effect can only be assessed through RCTs, which often yield a lower therapeutic effect than uncontrolled studies of the same interventions (11). Finally, very few interventions in medicine have such clear-cut beneficial results that assessment in RCTs is redundant, e.g., insulin for diabetes. Even appendectomy was recently compared to IV antibiotics in an RCT, which found that acutely, antibiotics were as effective as surgery (12).

Other hurdles to ES RCTs include poor compliance with the randomization protocol (crossover), difficulties in standardizing the surgical procedure, differences in postoperative and ancillary care, blinding and the use of placebo surgery, and strong patients’ and clinicians’ preferences for noninvasive procedures. All of these factors explain why only seven RCTs involving 535 patients have assessed surgical procedures or devices in epilepsy (3,13–18). Three compared low versus high intensity vagus nerve stimulation in medically refractory epilepsy, one assessed rapid versus low cycling of vagus nerve stimulation, one compared partial versus complete hippocampectomy in temporal lobe epilepsy, one assessed the impact on language of resecting the superior temporal gyrus, and one compared surgical versus medical therapy of temporal lobe epilepsy (Table 1) (3,13–18). Currently underway are a National Institute of Health (NIH) funded, multicenter RCT comparing early surgery versus medical therapy in mesial temporal lobe epilepsy, and some RCTs of chronic brain stimulation (19).

The collective experience with RCTs in ES pales in comparison with that of other neurosurgical interventions. For instance, in ischemic stroke, the Cochrane collaboration alone contains at least eight meta-analyses involving more than 10,000 patients participating in more than 30 RCTs of surgical interventions (20). Fortunately, the tide seems to be turning in ES, with the advent of recent RCTs and the planning of new trials.

RCTs AND NON-RCTs OF EPILEPSY SURGERY

It is useful to compare the results of the existing RCT of temporal lobe ES with selected non-RCTs that fulfill minimum scientific criteria. The non-RCTs derive from the evidence base for a practice parameter of resective ES (2). All 24 non-RCTs were series of cases, and only one had a control group.

In an intention to treat analysis of the RCT, 58% of patients remained seizure-free for one year with surgery, in comparison with 8% with medical therapy (3). In a per-protocol analysis, 64% of patients remained seizure-free with surgery (3). The pooled proportion of seizure-free patients in the meta-analysis of non-RCTs was 67.2%, which is nearly identical to the per-protocol results of the RCT (64%) (Fig. 1). This confirms clinicians’ long-standing notions about the efficacy of this procedure. However, it is instructive to assess the distribution of results of non-RCTs (Fig. 1). The spread of seizure-free rates is substantial, ranging from 29% to 80%. The proportion of seizure-free patients was higher in 17 (71%) of the non-RCTs than in the RCT, and the point estimate of eight non-RCTs was higher than the upper 95% confidence interval limit (72%) of the RCT. This illustrates several points. First, non-RCTs exhibit substantial variability. Second, non-RCTs tend to overestimate the benefit of interventions. Third, it is difficult to interpret the results of non-RCTs in the absence of controls. Finally, it should be noted that the meta-analysis of non-RCTs excluded studies of preselected lesional cases, which often report even higher seizure-free rates.
<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Interventions</th>
<th>Main outcomes</th>
<th>n</th>
<th>Follow-up</th>
<th>Centers</th>
<th>Concealed randomized</th>
<th>Blind</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Vagus nerve stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salinsky (13)</td>
<td>Low vs. high intensity</td>
<td>Seizures</td>
<td>114</td>
<td>3 mo</td>
<td>Multi</td>
<td>Yes</td>
<td>D</td>
<td>Positive</td>
</tr>
<tr>
<td>Handforth et al. (15)</td>
<td>Low vs. high intensity</td>
<td>Seizures</td>
<td>196</td>
<td>3 mo</td>
<td>Multi</td>
<td>Yes</td>
<td>D</td>
<td>Positive</td>
</tr>
<tr>
<td>Amar et al. (17)</td>
<td>Low vs. high intensity</td>
<td>Seizures</td>
<td>17</td>
<td>3 mo</td>
<td>Single</td>
<td>?</td>
<td>D</td>
<td>Positive</td>
</tr>
<tr>
<td>Scherrmann et al. (16)</td>
<td>Rapid vs. slow cycling</td>
<td>Seizures</td>
<td>28</td>
<td>Unknown</td>
<td>Single</td>
<td>?</td>
<td>No</td>
<td>Negative</td>
</tr>
<tr>
<td>Two surgical techniques</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wyler et al. (14)</td>
<td>Small vs. large hippocampal resection</td>
<td>Seizures</td>
<td>70</td>
<td>1 yr</td>
<td>Single</td>
<td>?</td>
<td>S</td>
<td>Positive</td>
</tr>
<tr>
<td>Hermann et al. (18)</td>
<td>Sparing vs. resecting the superior temporal gyrus</td>
<td>Language</td>
<td>30</td>
<td>8 mo</td>
<td>Single</td>
<td>?</td>
<td>S</td>
<td>Negative</td>
</tr>
<tr>
<td>Surgery vs. medical therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiebe et al. (3)</td>
<td>Temporal antero-mesial resection vs. optimum drugs</td>
<td>Seizures and QOL</td>
<td>80</td>
<td>1 yr</td>
<td>Single</td>
<td>Yes</td>
<td>S</td>
<td>Positive</td>
</tr>
<tr>
<td>Engel (ongoing)</td>
<td>Early temporal antero-mesial resection vs. optimum drugs</td>
<td>Seizures and QOL</td>
<td>200a</td>
<td>2 yrsa</td>
<td>Multi</td>
<td>Yes</td>
<td>S</td>
<td>Pending</td>
</tr>
</tbody>
</table>

Positive and negative results denote differences between the interventions.

*Planned.

*Abbreviations: n, number of patients; QOL, quality of life; D, double; S, single.
*Source: From Ref. 8a.
Figure 1  Proportion of patients with temporal lobe epilepsy who became seizure-free in 24 uncontrolled series of cases (■), their overall estimate (▲ and dotted line), and in the RCT (▲).
Admittedly, some conditions or procedures are too rare or too deeply ingrained in practice to permit assessment in RCTs. In these circumstances, systematic, well-conducted non-RCTs can provide useful information. To illustrate, Benson and Hartz (21) and Concato et al. (22) independently showed that top-quality non-RCTs can yield results that are very similar to those of RCTs of the same therapies. Therefore, scientific quality determines the validity and usefulness of RCTs and non-RCTs alike. In ES, quality indicators of non-RCTs include a prospective design, nonhistorical controls, systematic patient selection, uniform interventions and co-interventions, systematic and independent outcome assessment, complete follow-up, and analysis of prognostic variables.

CONCLUSIONS

Although high-quality non-RCTs can provide useful information about therapy, they are susceptible to biases that only high-quality RCTs—the gold standard for assessing the efficacy of interventions—can address. RCTs are relatively new and their methodology is evolving. The first RCT was done in 1948, when researchers in the United Kingdom randomly assigned patients with tuberculosis to placebo or streptomycin (23). Since then, methodological standards for RCTs have been widely adopted, as illustrated by the consolidated standards for reporting trials (CONSORT) statement on quality of RCT reports, to which most medical journals adhere (24).

No antiseizure drug is licensed without evidence from well-conducted RCTs. By contrast, RCTs of ES are only starting to be implemented. The generation of robust scientific evidence supporting ES has important implications. First, it can help the larger medical community to view ES as a safe and effective procedure, rather than as a last resort for the most intractable patients. Second, it can help alleviate the well-known underutilization of ES in industrialized countries and its virtual non-existence in the developing world. The increasing awareness of scientific standards in surgical research among the ES community, and the advent of RCTs and high-quality non-RCTs can only bode well for the care of epilepsy sufferers.

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Chapter XIV-44
Prospective, Controlled, Randomized Trials of Epilepsy Surgery Are Necessary

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Since modern epilepsy surgery began about 125 years ago, our ability to accurately localize the epileptogenic region for surgical resection has been greatly enhanced by the advent of electroencephalography and neuroimaging (1–7). Two international conferences on epilepsy surgery documented a worldwide tripling in the number of epilepsy surgery centers and surgical procedures performed to treat epilepsy between 1985 and 1990, and an increase in seizure freedom after temporal lobe epilepsy from 56% to 68% (8–11). Nevertheless, epilepsy surgery remains, arguably, the most underutilized of all proven-effective therapies in the entire field of medicine.

Of 100,000 to 200,000 potential epilepsy surgery candidates in the United States, only 2000 therapeutic procedures were performed in 1990, and perhaps no more than 3000 annually at present (10). The same degree of underutilization exists in virtually every industrialized country in the world, and only recently has epilepsy surgery become available in a few developing countries (12). Furthermore, when patients do undergo epilepsy surgery, it is performed an average of 20 to 22 years after onset of seizures, too late to reverse disabling social and psychological consequences, so that postoperative freedom from seizures does not permit rehabilitation to a normal, independent lifestyle (13,14). This represents not only an unnecessary cost in human terms, but also an unnecessary cost to society, given that 80% of money spent on epilepsy is accounted for by patients whose seizures are not controlled (15).

The reasons for such egregious failure to identify and refer potential surgical candidates are difficult to understand. Although brain surgery can be a frightening concept, the risk of death and disability is greater with continuing epileptic seizures (16). Despite recent recognition of surgically remediable syndromes, most physicians who refer patients for surgery still consider this treatment to be a last resort, and adequate trials of all the new antiepileptic drugs can take a lifetime (17). Newer diagnostic technologies have greatly reduced the cost of epilepsy surgery, which is, in any event, considerably less than the cost of a lifetime of disability. The medical community has been well informed about advances in epilepsy surgery from...
hundreds of papers and over 20 books published in the past two decades. An over-
riding issue appears to be continued distrust of the data reported from epilepsy
surgery centers and, until recently, the lack of a randomized controlled trial (RCT),
the gold standard for assessing therapeutic intervention. It was only because of the
RCT comparing surgery with continued medical treatment for temporal lobe epilepsy
(18) that the American Academy of Neurology (AAN) finally consented to publish for-
mal practice parameters recommending surgical treatment for temporal lobe epilepsy,
but refused to recommend surgery for focal neocortical epilepsy because there is, as yet,
no RCT (19). Furthermore, although the AAN now recommends surgery for temporal
lobe epilepsy, there are no data to establish guidelines on when to consider surgical
intervention. As recommended by the AAN, a multicenter RCT, Early Randomized
Surgical Epilepsy Trial (ERSET), is in progress to address this question (20). Clearly,
if the neurological community will not recommend early surgical treatment for
temporal lobe epilepsy without appropriate RCTs, then the medical community as a
whole will not support attempts to overcome the appalling underutilization of this safe
and effective alternative therapy until more RCTs are completed and published.

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When Are Prospective, Controlled, Randomized Outcome Trials of Epilepsy Surgery Really Justified?

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With the emphasis on evidence-based medicine and the establishment of an evidence classification system that gives primacy only to randomized studies, the assumption has developed that all therapies must be evaluated by randomized prospective trials to be valid. That assumption is challenged by several factors. The vast majority of current medical therapies are not based on randomized prospective trials including some that are overwhelmingly effective, such as penicillin use for certain infections, or aspirin as an analgesic. Moreover, randomized, prospective studies utilize substantial resources, and there are insufficient resources to evaluate every potential therapy in this way. Some therapies, indeed most, will have to be based on “lesser” data. Requiring that a therapy be evaluated with a prospective randomized study should not be undertaken lightly. It should require that there be “equipoise,” that is, no overwhelming albeit lesser evidence that one therapy is better than the other with which it will be compared in the study. Equipoise is necessary both ethically, so that one patient group will not be denied an effective therapy, and practically, so that the limited resources for prospective randomized studies will be channeled to areas where there is real doubt about efficacy. Additionally, randomized prospective studies must be designed so that if a statistically significant difference is present, it also represents a clinically important difference.

What then is the status of resective temporal lobe surgery for epilepsy in regard to equipoise, when compared with continued medical management? For the “ideal” surgical candidate, a patient with persisting seizures who has had trials of at least three antiepileptic drugs (AEDs) at appropriate levels and has a unilateral electrographic epileptic focus and concordant imaging changes of mesial temporal sclerosis, the probability that another AED will control seizures is <5%, while the probability that a surgical resection will control seizures is well over an order of magnitude greater, 70% to 80% or better. Even though these probabilities are based on less than Class I data, the difference is so great that this comparison does not represent...
equipoise, at least when effects on seizure frequency are the primary outcome measure. The effort by Weibe et al. (1) at a randomized prospective study of surgical therapy in these patients illustrates the problem. The study has the expected outcome, resective surgery was significantly more effective than continued medical management. But because of the lack of equipoise, the follow-up period was only one year, considered by most epileptologists to be too short a period to establish the persisting effectiveness of surgical therapy. Moreover, the study design could be ethically justified only by the inefficiencies in the health care system under which it was done, that commonly delayed surgery for a year or more. And the only way the treating physicians would accept randomization was if it were done before complete evaluation for surgery. That had the odd effect of including several patients who did not meet criteria for resections, so did not have them, in the “surgical” group. Of course, if the treating physician thought there really was equipoise between surgical and medical therapy, they would have accepted randomization of those who met the criteria for surgery after the evaluation was completed. While we may now all feel good that a randomized, prospective study has “proven” the efficacy of surgery, the reality is that the follow-up is too short to establish that, so we are back to relying on what we already knew from “lesser” data.

Are there aspects of surgical therapy of epilepsy that should be evaluated by randomized prospective studies? I believe so. There is controversy as to the effectiveness of resective surgery in patients with less clear indications: evidence for bilateral onsets but predominance on one side for example. Evaluating the role of resections in imaging normal temporal lobe epilepsy (TLE) is a more complicated issue. The seizure-free rate is high enough in those with electrophysiologically delineated unilateral temporal epileptogenic zones that equipoise may not be present in those patients (2). If such a study were to be done, a long follow-up period would be needed to address issues of late recurrence (3). Controversy exists over the value of resective surgery in altering some aspects of quality of life, especially vocational outcome. Randomized, prospective studies with this as the primary outcome measure would be of interest. It is here that early surgical intervention seems to be important and will need to be part of such a study. On the contrary, there seems to be a limited or no role for randomized studies in evaluating timing of surgery with effect on seizures as the main outcome measure, for it is well established that persisting major seizures are associated with an increased risk to life, with patients dying while awaiting surgery (1). Thus there is little justification for delaying surgical evaluation and surgery if indicated, once it is established that a patient is medically refractory. Randomized evaluations of AEDs have shown that adding a third drug has a very low probability of controlling seizures, when the initial AEDs have been assessed at adequate dosage, providing a criterion for medical intractability. Alternatives to resective surgery as therapy of TLE patients, such as gamma knife therapy and various stimulation approaches, definitely require randomized prospective evaluation. It is in these controversial areas that resources for randomized prospective studies of surgical therapy should be directed, rather than “proving” what we already know.

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Section XV
Outcomes of Extratemporal Epilepsy Surgery

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Surgery for medically intractable epilepsy can provide dramatic benefits, both in elimination of seizures and reduction of medication-related toxicity. The last few decades have brought technological advances that facilitate noninvasive identification of appropriate surgical candidates, and a wealth of experience to guide such surgery. However, many advances are for temporal lobectomies, with seizure-free outcomes of 60% to 90%, compared with about 50% for neocortical resections (1,2). Epileptic foci outside the temporal lobe remain challenging for several reasons. Localization may be more difficult, as seizure semiology and electroencephalographic (EEG) patterns are more varied and the areas to be surveyed much larger and often less accessible than in temporal lobe epilepsy. Motor, sensory, and language areas may lie in or near the epileptogenic zone, raising the potential risks of resection. Current rates of seizure freedom in extratemporal resections remain disappointing but many patients benefit.

This chapter reviews extratemporal surgery outcomes. We focus on seizure control as well as complications. We also briefly examine the prognostic value of preoperative tests. When available, outcome data are reported using Engel’s classification (3). Our focus is on seizure-free rates, as the definition of “worthwhile outcome” not only varies in different reports but is sometimes not even quantified. Reports vary in the duration of follow-up. Studies were included if extratemporal cases and the proportion seizure-free could be clearly identified, with an emphasis on series including 10 or more patients. There are no randomized, controlled trials of surgery in extratemporal epilepsy, and all reports are prospective or retrospective case series (2).
SEIZURE OUTCOMES

Frontal Lobe Resections

The frontal lobes occupy about 40% of the cerebral cortex, and are the second most common location for focal epilepsy after the temporal lobe (4). Frontal lobe surgery remains problematic. Different seizure semiology occurs with foci in different regions. Although clinical features such as focal clonic, asymmetric tonic or hyperactive automatic activities support a frontal lobe origin, the semiology does not localize at a sublobar level and medial parietal seizures can spread anteriorly to produce this “frontal” semiology (5). Interictal spikes and ictal patterns may spread rapidly, making localization and even lateralization difficult (6). Epileptogenic zones may be widespread, requiring extensive resection (4). Eloquent areas such as Broca’s area and the primary motor area may limit the resection. Cortical and vascular anatomy create technical problems that may impede investigation and resection of deeper areas such as the mesial frontal and perisylvian regions (4,7). The sheer size of the frontal lobe makes it more difficult to cover adequately with invasive EEG electrodes. Table 1 lists outcomes of frontal lobe series.

The extent and location of a frontal resection may influence outcome. Rasmussen (8) found 26% of 257 nontumoral patients were seizure-free after frontal resection: 47% in anterior frontal resections, 35% convexity only, and 32% with maximal frontal lobectomy, but only 18% in parasagittal and 10% in frontal plus adjacent central or temporal tissue. A similar effect of sublobar anatomy was reported by Smith et al. (9), with seizure freedom in 9 of 12 (75%) lateral frontal resections, 2 of 13 (15%) mesial resections, and 7 of 12 (58%) lobectomies. Bleasel (10) reviewed nine series of mesial frontal epilepsy surgery, and found among 93 patients, 38% overall became seizure-free, and 71% had a “good outcome” (Engel Class I–III). Bass et al. (11) reported seizure freedom or “worthwhile improvement” in five of six children with supplementary sensorimotor area resection.

Postoperative seizure control may change over time, for better or worse. Ficker et al. (12) found changes in seizure control in the first postoperative year in 15% of 214 temporal lobectomies (5% improved, 10% worsened), and in 20% of 59 frontal resections (15% improved, 5% worsened). The frontal group’s greater improvement over time may simply reflect their poor initial outcome (i.e., leaving a greater chance for improvement).

Parieto-Occipital Resections

The parietal and occipital lobes are the rarest locations for epileptic foci, accounting for only 1% of resections in some series (13). They are often considered together because their anatomical boundaries are less well defined than those of the frontal and temporal lobes. Many critical functions are served by these lobes, limiting surgical approaches. Primary visual and somatosensory cortices and their unimodal association cortices take up much of this region (14). Praxis and posterior language cortex are found in the left parietal lobe. Resections sparing language cortex can cause alexia without agraphia. Resection of parietal or posterior temporal white matter can create a visual field defect. The percentage of lesional cases is higher in series of parieto-occipital surgeries compared with temporal or frontal locations, likely because of these functional issues (13,15). Table 2 lists outcomes of parieto-occipital series.

Localization to this region can be problematic, as seizure symptomatology and even EEG patterns may only be evident when the seizure spreads to other regions
<table>
<thead>
<tr>
<th>References</th>
<th>No. of patients</th>
<th>Seizure-free (%)</th>
<th>Other outcomes (if available)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(89)</td>
<td>330</td>
<td>41.2</td>
<td>12.8% rare seizures, 20% with &gt;90% reduction, 19.1% no improvement</td>
<td>Global survey of 1980–1990 experience</td>
</tr>
<tr>
<td>(90)</td>
<td>287</td>
<td>11</td>
<td>26% seizure-free after early attacks, 13% with rare attacks, 17% marked decrease, 44% moderate or less reduction</td>
<td>Four operative deaths</td>
</tr>
<tr>
<td>(91)</td>
<td>100</td>
<td>11</td>
<td>55% “practically cured,” 76% w/75% reduction</td>
<td></td>
</tr>
<tr>
<td>(10)</td>
<td>93</td>
<td>38</td>
<td>71% “good outcome” (Engel I–III)</td>
<td>Review of nine series</td>
</tr>
<tr>
<td>(48)</td>
<td>68</td>
<td>54</td>
<td>19% class II, 15% class III, 12% class IV</td>
<td>All lesional cases</td>
</tr>
<tr>
<td>(35)</td>
<td>68</td>
<td>58.8</td>
<td>72% seizure-free in lesional cases versus 41% in nonlesional cases</td>
<td></td>
</tr>
<tr>
<td>(73)</td>
<td>61</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(92)</td>
<td>54</td>
<td>52</td>
<td></td>
<td>70% of cases lesional</td>
</tr>
<tr>
<td>(92)</td>
<td>54</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(22)</td>
<td>33</td>
<td>87 (w/o stereo-EEG), 72 (w/stereo-EEG)</td>
<td>W/o stereo-EEG: class III 13%, class IV 0%; w/stereo-EEG: class III 8%, class IV 16%</td>
<td>Children and adolescents</td>
</tr>
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<td>(93)</td>
<td>32</td>
<td>86 (tailored resection in 22), 20 (lobectomy in 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5)</td>
<td>26</td>
<td>80% “favorable outcome” (Engel class I or II)</td>
<td>All lesional cases</td>
<td></td>
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<tr>
<td>(87)</td>
<td>22</td>
<td>60</td>
<td>20% class III, 20% class IV</td>
<td>“Pure frontal” group</td>
</tr>
<tr>
<td>(23)</td>
<td>19</td>
<td>60</td>
<td>All had &gt;75% reduction</td>
<td>All cases with encephalomalacia</td>
</tr>
<tr>
<td>(74)</td>
<td>17</td>
<td>70</td>
<td></td>
<td>Anterior callosotomy included in seven, callosotomy only in two</td>
</tr>
<tr>
<td>(94)</td>
<td>16</td>
<td>67</td>
<td>7% II, 27% III/IV</td>
<td>Peri-Rolandic lesions</td>
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<td>(45)</td>
<td>14</td>
<td>78</td>
<td></td>
<td>Dorsolateral or frontocentral resections</td>
</tr>
<tr>
<td>(95)</td>
<td>10</td>
<td>20</td>
<td>70% “significant reduction,” 10% “no change”</td>
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Table 2 Outcomes of Parieto-Occipital Surgeries

<table>
<thead>
<tr>
<th>References</th>
<th>No. of patients</th>
<th>Seizure-free (%)</th>
<th>Other outcomes (if available)</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>(20,41)</td>
<td>8 (occipital, temporal)</td>
<td>25</td>
<td></td>
<td>All nonlesional</td>
</tr>
<tr>
<td>(41)</td>
<td>79 (parietal)</td>
<td>65</td>
<td></td>
<td>Operated between 1929 and 1988</td>
</tr>
<tr>
<td>(96)</td>
<td>6 (occipital)</td>
<td>50</td>
<td></td>
<td>Cortical developmental abnormalities</td>
</tr>
<tr>
<td>(97)</td>
<td>42 (occipital)</td>
<td>46</td>
<td>21% “significant reduction”</td>
<td>23 had occipital resections, five had only temporal resections, 14 had multi-lobar resections</td>
</tr>
<tr>
<td>(15)</td>
<td>39 (parietal), 30 (occipital)</td>
<td>52 parietal, 71 occipital</td>
<td>35% seizure-free w/lesionectomy, 60% seizure-free w/lobectomy</td>
<td></td>
</tr>
<tr>
<td>(98)</td>
<td>35 (occipital)</td>
<td>46 overall</td>
<td></td>
<td>34 lesional, one nonlesional</td>
</tr>
<tr>
<td>(41)</td>
<td>28 (parietal)</td>
<td>75</td>
<td></td>
<td>All had tumors</td>
</tr>
<tr>
<td>(21)</td>
<td>24 (occipital)</td>
<td>14/16 (88%) w/lesionectomy, 0/6 w/temporal lobectomy, 0/2 w/callosootomy</td>
<td></td>
<td>All lesional</td>
</tr>
<tr>
<td>(42)</td>
<td>19</td>
<td>32</td>
<td>74% “significant reduction”</td>
<td>Included parietal, occipital, and posterior temporal cortex</td>
</tr>
<tr>
<td>(99)</td>
<td>186</td>
<td>34</td>
<td>23% “marked reduction”</td>
<td></td>
</tr>
<tr>
<td>(100)</td>
<td>12 (occipital)</td>
<td></td>
<td></td>
<td>11/12 “very good,” 1/12 “good”</td>
</tr>
<tr>
<td>(17)</td>
<td>11 (parietal)</td>
<td>91</td>
<td></td>
<td>All nonlesional</td>
</tr>
<tr>
<td>(18)</td>
<td>10 (parietal)</td>
<td>90</td>
<td></td>
<td>All lesionectomy cases</td>
</tr>
</tbody>
</table>
such as the temporal lobe (16–18). Boesebeck et al. (19) found that lateralizing seizure semiology can be helpful in surgical prognosis for posterior cortex surgery. In this group of 42 patients with lesions, seizure freedom was found in 57% of those with versus 28% without lateralizing auras, and in 57% of those with versus 17% of those without lateralizing ictal semiology. Temporal lobectomy is not effective for parieto-occipital foci with prominent seizures spread to the temporal lobe (20,21).

**Multilobar Resections and Other Reports**

Some patients have extensive epileptogenic zones that extend beyond the border of a given lobe. Attempts to resect as much tissue as possible from the involved lobes have been less than satisfactory. Munari et al. (22) compared their series of frontal lobe resections to those with multilobar (including frontal lobe) surgeries. They found a significantly worse outcome in those with multiple lobes resected (28% of 49 patients seizure-free) compared with frontal resections (76% of 33 patients). Swartz et al. (23) examined 37 patients diagnosed with frontal lobe epilepsy. They found 19 had pure frontal lobe epilepsy (60% seizure-free), and 12 had frontal plus extrafrontal epileptogenic zones (10% seizure-free).

Some reports describe results of extratemporal surgery, but breakdown of outcome by lobe is not specified. These are summarized in Table 3.

**Multiple Subpial Transection**

The overlap of the epileptogenic zone with an area of critical function typically limits the extent of resection and the benefits. Morrell et al. (24) developed multiple subpial transection (MST) to extend surgery safely to these regions. MST was performed in motor, sensory, and language areas. In a series of 32 cases, they found no clinically significant behavioral deficits, and 11 of 20 (55%) patients with adequate follow-up had complete seizure control (24). Spencer et al. (25) performed a meta-analysis of published MST outcomes, as most reports include few patients. They analyzed 211 patients, of whom 55 had MST only and 156 had MST plus resection. They found similar results in both groups (excellent outcome in 68% with resection and 63% without). New neurological deficits appeared in 22%, with similar rates for both resected and nonresected cases (see Chapter IX-27 in this volume).

**Table 3** Outcomes of Extratemporal Surgeries Not Further Specified

<table>
<thead>
<tr>
<th>References</th>
<th>No. of patients</th>
<th>Seizure-free (%)</th>
<th>Other outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(101)</td>
<td>48</td>
<td>79</td>
<td>15% class II, 2% class III, 4% class IV</td>
<td>Pediatric series</td>
</tr>
<tr>
<td>(102)</td>
<td>35</td>
<td>63</td>
<td></td>
<td>Pediatric series, no invasive EEG used</td>
</tr>
<tr>
<td>(103)</td>
<td>16</td>
<td>81</td>
<td>19% had 90% or greater seizure reduction</td>
<td></td>
</tr>
<tr>
<td>(43)</td>
<td>15</td>
<td>40</td>
<td>7% almost seizure-free, 40% “worthwhile improvement”</td>
<td>All lesional</td>
</tr>
</tbody>
</table>
Reoperations

While surgical failures are disappointing, they help us understand the limits of surgery and where to change our approaches. Some cases have undergone repeat surgery to achieve a better outcome. Munari et al. (26) analyzed their series of 344 first operations. Of these, patients became seizure-free in 73% of temporal surgeries, 57% of extratemporal unilobar resections, and only 37% of multilobar resections. They found a difference in the results of reoperation depending on whether the first surgery was performed at another center (68.4% seizure-free) versus their center (30.5% seizure-free). They attributed failure of the first operation to intentional limitation of resection because of functional reasons in 56%, unintentional incomplete resection in 16.4%, incomplete definition of the epileptogenic zone in six cases, and could not find a cause of failure in three cases. Thus, most failures were predictable at the time of surgery, an important point in advising patients.

Awad et al. (27) analyzed 15 patients who were reoperated. In three (all extratemporal), ictal onset was remote from the area of previous resection, and two had recurrence in the area of previous extratemporal resection associated with residual structural lesions. Repeat surgery led to seizure freedom in 47%.

Salanova et al. (28) reoperated 39 (14%) of 284 patients who had initial frontal resections between 1929 and 1980. Further frontal resection was undertaken in 26, and 13 had temporal lobe resection as well. Of the 35 with follow-up data, 20% were seizure-free and 31% had significant reduction. None of the patients with temporal resection became seizure-free, a result similar to others (22).

In 21 reoperations, Holmes et al. (29) found no difference in outcome between temporal and extratemporal locations.

Temporal vs. Extratemporal Outcomes

The disparity in outcomes between temporal and extratemporal surgeries raises important questions about the factors contributing to success. Reports from different centers at different times, using different approaches and technologies, make it hard to compare studies. However, many centers have reported their results of both temporal and extratemporal surgeries together, allowing a fairer comparison. Table 4 outlines such series. Most series show striking differences, with 60% to 80% seizure-free after temporal lobe surgery, but only 25% to 64% after extratemporal surgery. These results suggest that the difference is because of the anatomy and disease affecting outcome, not factors such as personnel and technology.

Lesional vs. Nonlesional Extratemporal Outcomes

The presence of a focal lesion is a positive prognostic factor in almost all studies. However, it is difficult to determine the relative effectiveness of surgery in lesional versus nonlesional epilepsy, because many series are retrospective and lesions may bias toward surgery. In addition, different pathologies may carry different prognoses.

Zentner et al. (30) reviewed 60 consecutive cases of extratemporal surgery. Overall, 54% were seizure-free. Seizure-free rates were 80% in 15 patients with neoplasia, 52% of 31 patients with nonneoplastic focal lesions, and 20% of 10 without imaging or histopathologic abnormalities. Among 49 patients with frontal lobe epilepsy, Smith et al. (9) found seizure freedom in 5 of 17 (29%) nonlesional cases versus 21 of 32 (66%) with lesions. Eight of 10 tumor cases (80%) were seizure-free versus 13 of 22 (59%) nontumor lesions. Wyllie et al. (31) reported 136 pediatric
and adolescent resections, and found 82% seizure freedom among the lesional cases and 52% with cortical dysplasia. Another study examined 35 children and adults with malformations of cortical development, and found 49% seizure-free, with no statistically significant prognostic factors [although complete resection of a malformation had a better seizure-free rate (58%) than incomplete resection (27%)] (32). Eriksson et al. (33) found seizure freedom in 76.9% with vascular malformations versus 39.4% with microdysgenesis. Smith et al. (34) had much better seizure-free rates in lesional (70%) compared with nonlesional (37%) extratemporal cases in a group of 158. Mosewich et al. (35) found excellent outcome (seizure-free or nondisabling seizures) in 72% of lesional frontal lobe cases compared to 41% without a lesion.

**COMPLICATIONS OF EPILEPSY SURGERY**

Surgical complications are often unpredictable and can result from the surgical procedure, especially with invasive electrodes, or from resection of functional tissue. There may be new or worsened neurological deficits that may be predictable with preoperative testing. The following discussion focuses on large case series which reported complication rates.

Wass et al. (36) reviewed 291 consecutive patients operated at Mayo Clinic from 1972 to 1985 (27% were extratemporal and 73% were temporal lobe cases). Sensory or motor deficits occurred in 4%, related to Rolandic surgery. Surgical intervention was required for hemorrhage in 2% and cerebrospinal fluid (CSF) leakage in 1%. Infections developed in 10% (only 3% were at the surgical site). Anemia was common (22%). There were single cases of myocardial infarction, viral hepatitis and drug-induced hepatitis, and a single death occurred because of herniation from acute third ventricular obstruction from a tumor.

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**Table 4** Comparison of Temporal and Extratemporal Resections in the Same Series

<table>
<thead>
<tr>
<th>References</th>
<th>Temporal lobe</th>
<th>Extratemporal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(104)</td>
<td>76 (68)</td>
<td>23 (42)</td>
<td>Outcome at 5 yr postoperative</td>
</tr>
<tr>
<td>(105)</td>
<td>73 (59)</td>
<td>45 (29)</td>
<td>All children</td>
</tr>
<tr>
<td>(31)</td>
<td>72 (78)</td>
<td>48 (54)</td>
<td>Children and adolescents</td>
</tr>
<tr>
<td>(106)</td>
<td>667 (43)</td>
<td>229 (25)</td>
<td>Montreal series up to 1972, prior to modern neuroimaging</td>
</tr>
<tr>
<td>(107)</td>
<td>51 (78)</td>
<td>79 (64)</td>
<td>Neocortical temporal lobe versus frontal lobe</td>
</tr>
<tr>
<td>(34)</td>
<td>311 (67 of nonlesional, 78 of lesional)</td>
<td>158 (37 of nonlesional, 70 of lesional)</td>
<td>Children and adults</td>
</tr>
<tr>
<td>(108)</td>
<td>30 (70)</td>
<td>6 (33)</td>
<td>Pediatric series</td>
</tr>
<tr>
<td>(109)</td>
<td>29 (66)</td>
<td>37 (62)</td>
<td>All with gangliogiroma</td>
</tr>
<tr>
<td>(110)</td>
<td>27 (81)</td>
<td>9 (44)</td>
<td>All children or adolescents</td>
</tr>
<tr>
<td>(111)</td>
<td>14 (71)</td>
<td>23 (28)</td>
<td></td>
</tr>
<tr>
<td>(36)</td>
<td>212 (43 since surgery, 61% in 3 yr prior to survey)</td>
<td>79 (37 since surgery, 49 in 3 yr prior to survey)</td>
<td></td>
</tr>
</tbody>
</table>
Behrens et al. (37) described the complications of 708 epilepsy surgery procedures in 429 patients (84 extratemporal surgeries included in this group). There was no mortality, and a total rate of neurological complications of 5.4%, with 3.03% transient and 2.33% permanent morbidity. Thirty-three surgical complications occurred, including wound infection and hydrocephalus.

Rydenhag and Silander (38) performed a multicenter study of all epilepsy surgery complications in Sweden. Of 654 procedures, 205 were invasive EEG and 449 were therapeutic. Only minor complications (resolving in <3 months) occurred in 6.3% of invasive EEG cases. In the therapeutic group, minor complications occurred in 8.9% and major complications (lasting >3 months or affecting activities of daily living) in 3.1%. All but one complication occurred in patients over age 35, suggesting better safety in younger patients.

Wyllie (39) described complications in 136 pediatric patients from 1990 to 1996. Four (2.9%) had wound infections and two (1.3%) died peroperatively.

In a series of 37 patients with frontal resections, eight developed hemiparesis, one monoplegia, one a buzzing sensation in the left ear, and two dysphasias (40). Eight developed fever, with four requiring removal of the bone flap and cranioplasty. One had a CSF leak requiring surgery.

In a series of 82 parietal lobe resections, Salanova et al. (41) found sensory deficits only when the resection included the postcentral gyrus, and disturbance of body image associated with extensive resections of the nondominant inferior parietal lobe. Blume et al. (42) reported 19 patients with resections of the “posterior cortex” (parietal, occipital, and posterior temporal). A new or increased visual field deficit occurred in 43%.

Davies and Weeks (43) found one case of increased hemiparesis and three postoperative infections among 15 extratemporal resections.

Functional reorganization may occur in eloquent areas with tumors or other lesions, reducing the risk of resection. Devaux et al. (44) found persistent mild facial or arm deficits in only two of six patients operated for tumors in the central region. Sandok and Cascino (45) also evaluated patients undergoing perirolandic surgery and found only 1 of 14 with increased monoparesis after surgery.

Shaver et al. (46) found significant motor and language deficits in three of 20 children who had multilobar reoperation, whereas none occurred in patients with lobectomy or corticectomy.

Kloss et al. (47) reported 68 children operated for focal cortical dysplasia, of whom five developed subdural hygroma and two had increased motor deficits.

Schramm et al. (48) reported 68 adults with frontal lobe surgery, of whom three had surgical complications, 10 with transient neurological deficits, and one with permanent neurological deficit.

Bleasel et al. (49) studied the effects of mesial frontal lobe resection in detail in 10 patients. Five had acute reduction in spontaneous movements, worse contralaterally, which varied in severity and recovered to baseline from two days up to two months, typically lasting one to two weeks. There was also a reduction in speech output (even mutism), with preserved comprehension. On late follow-up (six months to seven years), they found a “striking” absence of motor deficits given the severity of immediate postoperative findings. Krainik et al. (50) also found about 50% of mesial frontal resections caused speech disturbances with good long-term prognosis. Zentner et al. (51) found a higher 89% rate of deficits in 28 patients after supplementary motor area resection, but all had complete recovery.

Hamer et al. (52) reviewed the complication rates of subdural grid electrodes in 187 patients undergoing a total of 198 monitoring sessions from 1980 to 1997. The
overall complication rate was 26.3%, which included infections, transient neurologic
deficits, epidural hematoma, increased intracranial pressure, infarction and a single
death. However, there was improvement over time, with only a 13.5% rate in the
most recent three-year period. Complication rates were statistically correlated with
>60 electrodes implanted, duration of monitoring >10 days, older patient age,
left-sided insertion, and use of burr holes in addition to craniotomy. Lee et al. (53)
also looked at complication rates with subdural grid electrodes. In 50 cases, they
had 7.8% with subdural hematoma requiring evacuation, 3.9% with infection, 2%
with epidural hematoma, and 2% with cerebral edema. Subdural hematomata were
eliminated by the use of a subdural drain. Stephan et al. (54) found inflammatory
responses more common in subdural compared with depth electrodes, and clinically
silent hematomata in a histopathological study of invasive EEG.

Simon et al. (55) and Onal et al. (56) reported complications of invasive EEG in
children. CSF leakage was common (21/67 and 5/35, respectively). Infections were
uncommon (<10%) however, and consisted of osteomyelitis and wound infections
rather than meningitis. Hemorrhages were found subdurally in 5 of 35 and intracere-
brally in 3 of 35 by Onal et al., but none were seen by Simon et al. Both concluded
that invasive EEG could be performed in children with acceptable risks.

Electrical cortical stimulation using subdural grids appears to be safe. Gordon et al. (57)
found no histopathologic abnormalities related to stimulation
in resected specimens.

Lesionectomy may carry less morbidity than more extensive cortical resection.
Cascino et al. (58) found 13 of 29 patients undergoing extratemporal corticectomy
had at least one adverse event, with four requiring a corrective surgical procedure.
Persistent neurologic deficits occurred in 3 of 29 with corticectomy and 1 of 21 with
lesionectomy. Lesionectomy cases spent less postoperative time intubated, in the
intensive care unit and in the hospital.

More subtle complications of epilepsy surgery involving cognitive and beha-
vioral changes can occur and are likely underreported in the literature. Lendt et al.
(59) found that preexisting behavior disorders improved in children undergoing
epilepsy surgery (11/24 cases were extratemporal), with a good seizure outcome being
the main predictive factor. Gilliam et al. (60) performed neuropsychological testing
on 21 of 33 consecutive children after epilepsy surgery; six (29%) had improvement
of >10 points in Verbal or Performance IQ, and one (4%) had a decrease of >10
points in Verbal IQ. Quality-of-life measures tend to correlate with postoperative
seizure freedom (61). In a series of seven children with perirolandic surgery,
two had exacerbation of preexisting attention deficits, and none had permanent
sensorimotor deficits (62). Mood disturbances may be seen after epilepsy surgery,
with risk factors being preoperative depression and right hemisphere surgery (63).

Detailed neuropsychological testing can reveal a variety of postoperative defi-
cits. Frontal lobe surgery may affect motor planning, associative learning, olfactory
discrimination, handgrip strength, memory for temporal order, and generation of
conditional responses (64–69). There may also be increased impulsivity (70).
Helmstaedter et al. (71) compared the neuropsychological results of 33 frontal
versus 45 temporal lobe surgeries. Postoperatively, patients with temporal resection
had improved frontal functions, while patients with frontal resection had mild dete-
rioration. However, short-term memory improved in seizure-free frontal patients.
Motor and language deficits were seen in frontal resections involving the premotor
or precentral/central regions. A study of 70 patients (54 temporal lobe, 12 frontal lobe)
found overall cognitive stability after surgery (72).
STRATEGIES FOR PREOPERATIVE EVALUATION

Noninvasive Testing

The definition of the epileptogenic zone begins with analysis of seizure semiology and electrographic patterns on video-EEG testing. While scalp EEG can be notoriously unhelpful, some features predict surgical outcome. Janszky et al. (73) found in 61 frontal lobe resections that poor outcome was predicted by generalized EEG abnormalities, a somatosensory aura, secondarily generalized seizures, and normal magnetic resonance imaging (MRI). However, Ferrier et al. (40) did not confirm the significance of the generalized EEG abnormalities in a series of 37 frontal lobe resections. Kazemi et al. (74) found that a focal beta discharge on scalp EEG predicted a good outcome after resection of frontal lobe encephalomalacia. Holmes et al. (75) found that in patients with extratemporal surgery interictal spikes in 26 of 126 patients were strictly unifocal, all of which agreed with ictal onsets. This group had a 77% seizure-free rate, compared with 34% in those with other patterns.

MRI is critical for defining structural abnormalities in epilepsy surgery candidates, but is often unrevealing. A study of 37 patients with frontal lobe epilepsy found 32% with a focal frontal abnormality, 13% with large lesions extending beyond the frontal lobe, and 54% with normal imaging (76). A separate patient group in the same report had only 25% seizure freedom in those with frontal resections and normal MRI, versus 67% with abnormalities only in the resected frontal lobe. The presence of an extratemporal MRI lesion can even be misleading, as Alsaadi et al. (77) found in 15 patients who had temporal lobe resections with good results despite extratemporal lesions. However, Fish et al. (78) found poorer results with only two of 20 patients seizure-free after temporal lobectomy in the presence of extratemporal lesions. Functional MRI can map cortical function based on blood flow changes, and can noninvasively guide resection, but no studies have reported outcome on seizure control. Magnetic resonance spectroscopy (MRS) is an MRI-based technique that can show metabolic abnormalities in an epileptogenic zone. MRS may help define an abnormal area in a patient with normal structural imaging and guide invasive recordings (79).

Positron emission tomography (PET) using fluorodeoxyglucose (FDG) may show focal hypometabolism in extratemporal cases (64% in one study) but less frequently than in temporal lobe epilepsy (80). PET scanning with flumazenil has been studied. Juhasz et al. (81) used both flumazenil and FDG in 15 children undergoing epilepsy surgery (five frontal, seven multilobar, and three temporal), and found better outcomes when the area of flumazenil PET abnormality was smaller and included in the ultimate resection. In contrast, the extent of the FDG abnormality, if any, was not correlated with outcome.

Single photon emission tomography is less sensitive than PET in interictal localization, but sensitivity is significantly improved by subtracting the interictal blood flow image from an ictal study, and co-registering the findings onto the MRI scan subtraction peri-ictal SPECT (single photon emmission computed tomography) co-registered to MRI. O’Brien et al. (82) used this method to study 36 extratemporal patients. Overall, SISCOM was localizing in 66.7% (of note, 76.5% of these had no MRI lesion). Excellent outcomes occurred in 11 of 19 (57.9%) with localized SISCOM findings concordant to the final resection, but only 3 of 17 (17.6%) with nonlocalizing or nonconcordant SISCOM.
Invasive EEG

Difficulties localizing extratemporal foci and the need to map functional areas often lead to invasive EEG in this population. Several studies have examined the prognostic value of extraoperative (chronic) intracranial EEG patterns. Lee et al. (83) and Park et al. (84) found that low-voltage fast activity correlated with better seizure outcome compared with other ictal patterns. Kutsy (85) looked at a variety of ictal patterns, and found that slow spread to contiguous areas carried the best prognosis (5/8 seizure-free), whereas noncontiguous spread fared the worst (4/5 with no significant improvement).

Wennberg et al. (86) studied 60 consecutive nontumoral frontal lobe resections with intraoperative electrocorticography (ECG). The best outcomes were in cases with epileptiform activity restricted to one or two gyri and absent after excision. They found similar results in another study of lesion-related frontal lobe surgery (87). However, Ferrier et al. (88) did not find any relationship between postresection ECG spiking and outcome.

CONCLUSIONS

Extratemporal epilepsy surgery can significantly improve seizure control, although the benefits are inferior to temporal lobe surgery. Extensive investigation is often required to localize the focus because of anatomic and physiologic factors. Invasive EEG is often required to better define the epileptogenic zone and determine areas of eloquent cortex.

Some factors appear to be prognostic in extratemporal surgery. Lesional epilepsy fares better than nonlesional, with tumors and vascular malformations having better seizure-free rates than cortical dysplasia. The more restricted the focus and concordant the noninvasive and invasive data, and the more complete the resection, the better the outcome. Location may play a role, as mesial frontal resections seem to fare worse than lateral resections. Multilobar resections have much lower seizure-free rates and higher complication rates, and such surgery might be considered essentially palliative. Certain EEG patterns, such as more focal scalp interictal and ictal patterns, a low-voltage fast ictal onset on invasive EEG, and slow spread from the focus are predictive of better outcome. Unfortunately it may require invasive EEG to provide the best prognostic information, but this data can be used to counsel the patient prior to resection of any tissue.

Overall complication rates after epilepsy surgery are significant, although most problems are treatable and resolve. Neurological deficit rates may be lower in lesional epilepsy because of functional reorganization, and even dramatic deficits can resolve in mesial frontal surgery. Visual and language deficits are most to be feared in parieto-occipital surgery, while cognitive and behavioral changes are most disabling but difficult to predict in prefrontal surgeries.

REFERENCES


Outcomes of Extratemporal Epilepsy Surgery

Chapter XV-46
Neurosurgical Treatment Is Important for Nonlesional Extratemporal Epilepsy

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INTRODUCTION

For patients who have an identifiable lesion, epilepsy surgery is effective and well accepted. What is the outlook for the patients without magnetic resonance imaging (MRI) lesions? Are the success rates good enough to justify the risks of surgery? Extratemporal epilepsies represent a heterogeneous group of epilepsies arising in epileptogenic regions with different locations, sizes, margins, and pathologies. These heterogeneities become even more complex in the literature as different centers take different approaches and use different measures for surgical success or morbidity.

This chapter is presented in two parts. The first part discusses the qualitative aspects of nonlesional (MRI-negative) epilepsy emphasizing the factors producing the heterogeneity of the disease and the reported outcomes. We argue that in most patients surgical treatment needs to be considered and pursued but the risks and outcomes are patient-specific. In the second part, we look at the specific challenges of nonlesional extratemporal epilepsies and strategies to overcome these challenges.

While the number of patients with nonlesional extratemporal epilepsy is relatively small, the issues raised here have broader implications to all localization-related refractory epilepsies. Some mesial temporal lobe epilepsy patients have a second nonlesional extra-hippocampal focus. There are also patients whose identifiable MRI lesions are not the focus of their seizures (1). Moreover, surgery is sometimes performed in the setting of multiple pathological areas on imaging, for example, tuberous sclerosis. These examples demonstrate the challenge of functionally identifying the epileptogenic areas independently from the MRI imaging results. The techniques discussed in this chapter are, therefore, relevant to many other localization-related epilepsies.
PART I: PATIENTS AND OUTCOMES

The Natural History of Nonlesional Extratemporal Epilepsy

Pathological examinations from nonlesional cases mostly show nonspecific benign changes such as gliosis or microdysgenesis, if any changes are observed at all (2,3). Pathology might predict the course of a patient’s epilepsy. Nevertheless, pathology cannot predict the course of epilepsy after it has become refractory. Different studies define refractoriness differently, presenting patients who have failed different numbers of drugs for different durations of follow-up. This makes it more difficult to compare the clinical course of nonlesional epilepsies among these studies.

There are no long-term studies looking at medically refractory extratemporal nonlesional epilepsies as a distinct entity. Among the broader category of surgical candidates with localization-related epilepsy, the long-term outcomes without surgery seem to be poor, but some of the results are mixed. One study (4) reported that in 39 patients with medically refractory epilepsy who refused surgery, no one had become seizure-free after several years of follow-up. In contrast, in a more recent study, 21% of 34 patients were seizure-free for 2.5 years after definitive surgery was declined (5). These comparisons are complicated by the fact that in this latter study, many patients had undergone invasive monitoring before declining resective surgery and the effects of this invasive intervention are unclear. Nonetheless, there is every indication that once refractory, nonlesional extratemporal lobe epilepsy patients have little chance of seizure freedom without surgery. The readers are well familiar with broad aspects of continuing seizures on quality of life, and the risks associated with these seizures. What matters, however, is each individual’s chance of seizure freedom and risk for surgery.

Is the Risk of Surgical Morbidity Acceptably Low?

Many eloquent cortical areas are extratemporal. Therefore, variable size and lack of clear boundaries of nonlesional epileptogenic regions pose a special surgical challenge. The documentation of pre- and postoperative deficits is not standardized, so reported surgical morbidity rates must be evaluated cautiously. While focal paresis is easy to document, more subtle neurological deficits may be missed. Visual field defects, for example, occur frequently with occipital or temporal lesions but may be missed unless specifically evaluated. This is in contrast to medial temporal lobe epilepsies where pre- and postoperative deficits related to memory are better known and documented. In addition, the course of epilepsy without surgery is not static, making selection of control groups important. Is the appropriate comparison group for a nonrandomized study intractable patients who do not undergo surgery, or patients with imaging proven lesions in the same areas?

It is not surprising then, that the reported surgical morbidity has been quite variable. Some possible complications from invasive diagnostic procedures and surgical resections in various anatomical locations have been reviewed by Pilcher et al. (6). Earlier case series have reported as many as 37% of patients with persistent deficits (7), but recent reports note only small complication rates (8–10), often comparable with temporal lobe surgery complication rates. Mortality is rare. These low rates could be the result of several possibilities: (i) overall current morbidity and mortality may be truly low with improved modern surgical techniques, (ii) appropriate measures of morbidity are not performed (see above), (iii) only institutions with low complications report their results, creating reporting biases, and (iv) case selection biases
with retrospective case series may inherently undercount complications occurring before definitive surgery. For example, complications as a result of grid placement that preclude patients from undergoing surgery may not be counted in the complication rates in some of the examples above. The true incidence of surgical morbidity may be under measured.

**What Are the Surgical Success Rates?**

Surgical success rates for nonlesional extratemporal epilepsies have varied from 40% to more recent rates as high as 80%, but definitions of “success” varies from $>70\%$ seizure reductions to seizure freedom (3,8,11). These differences likely also reflect case selection, reporting biases, different follow-up periods, and the heterogeneity of epilepsy location and etiology.

Perhaps it is most important to compare the qualitative results of resection with the alternatives of medications or vagal nerve stimulation. Introduction of a new drug may reduce seizure frequency but only rarely provides complete seizure freedom. In contrast, in a significant fraction of patients the surgical result is complete seizure freedom that has a far greater impact on the patient’s quality of life (such as ability to live independently or drive). The goal of surgical success is therefore qualitatively different than the usual definition of a successful medication or vagal nerve stimulator trial.

**PART II: THE CHALLENGE OF A NONLESIONAL MRI AND HOW TO OVERCOME IT**

**What Does It Mean When the MRI Is Nonlesional?**

The first question a negative MRI should raise is whether the study was technically sufficient. One should not discount the value of updated MRI examinations or experienced readers in identifying lesions, with sensitivities for detecting lesions ranging from 39% (for nonexpert readers) to 91% (for expert readers using dedicated epilepsy MRI protocols) (12). Overall, 85% of patients in one study initially said to have nonlesional MRIs had identifiable imaging abnormalities (12). Additional clinical clues [such as electroencephalographic (EEG) abnormalities] can also be used to focus imaging attention on suspected brain areas increasing yields. In children, maturational changes may reveal MRI pathologies on repeated scans that were not visible in younger patients.

Despite these efforts, MRI may still fail to identify a lesion. This means MRI will neither help locate the epileptogenic focus, nor define the anatomical boundaries of the disease area. Poorly defined margins affect the efficacy and morbidity of surgical procedure because proximity of disease margins to eloquent cortical areas become ill defined. When surgical resections fail, many times the residual seizures emanate from the previous resection bed, reflecting a suboptimal marginal resection (13). The surgical evaluation needs to overcome both of these challenges—localizing the focus and defining its boundaries.

**What Are the Strategies to Identify the Epileptogenic Zone?**

The techniques used to evaluate nonlesional epilepsy differ in availability and risk, and many centers lack experience with some tools [e.g., positron emission tomography...
(PET) and magnetoencephalography (MEG)]. Ultimately the techniques used in each case reflect the unique clinical aspects of the patient and where they are evaluated. We, therefore, focus on the relative clinically relevant advantages of different methods in defining both the ictal onset zone, and the resectable margins.

**Clinical Evaluations (Including History/Semiology/Clinical Examination/Neuropsychological Examination)**

Focal stereotyped ictal semiology that at least initially remains localized has some localizing value, but reflects brain regions involved in the path of seizure propagation, and not necessarily the exact nidus. In addition, semiology provides little information on the anatomical boundaries of the epileptogenic zone. Semiology can highlight the proximity of the focus to eloquent cortex and provide a proxy for surgical risk. Clinical examination and neuropsychological testing are helpful in defining the extent of diseased cortical areas when present. They identify neither the epileptic focus nor the epileptogenic zone, but may provide lateralizing clues. As a whole these simple clinical methods provide us with initial clues, which we can use to guide other investigations.

**Scalp and Video-EEG**

Surgical success rates are greater if interictal spikes are confined to a single locus, or if ictal focal beta discharges are present (14,15). These findings provide only proximate measures of the epileptogenic focus because of limited spatial resolution of routine EEG. For both focal beta discharges and unifocal interictal spikes, good reported outcomes were achieved when these features guided additional investigation such as grid placements.

**Magnetoencephalography and Dense-Array EEG**

Magnetoencephalography looks at the magnetic fields generated by cortical electrical activity (Chapter 49). Dense-array scalp EEG is obtained by more closely spaced scalp EEG detectors (usually 128–256 electrodes) that may have a broader signal bandwidth as well (Fig. 1). Neither technique has been widely assessed in specific epilepsy syndromes, or is widely available. They have not been compared with each other, but both hold promise for greater spatial resolution for localization of spikes (16,17). However, both of these technologies are most sensitive to the most superficial cortical signals. MEG, despite its higher spatial and temporal resolutions, has yields similar to scalp EEG in identifying spikes (16). Dense-array EEG yields have not been widely reported. MEG has the advantage of less signal loss in the higher frequency part of the signal spectrum as the skull does not attenuate magnetic signals as much as electrical signals, but this advantage has not been used to study high-frequency epileptiform cortical rhythms. Both techniques have been limited to brief recordings lasting an hour or less and are most useful for assessing interictal spikes. Instead of obviating the need for more invasive procedures, these techniques provide ancillary information that can be used to guide further localization of the pathological region using dedicated imaging or invasive monitoring with grids.

**Flumazenil PET**

[11C] flumazenil-PET appears to be a promising technique for nonlesional neocortical epilepsy (18). Flumazenil binds to the gamma-aminobutyric acid (GABA-A) receptors
that may be reduced in regions of epileptic foci (19, Chapter 50). This method identifies the region of abnormalities with a higher sensitivity and specificity than fluoro deoxyglucose (FDG)-PET—resection of flumazenil abnormalities was associated with good outcome in one series (20). Because of highly specialized cyclotron requirements, it is used primarily in investigational protocols and not in clinical practice.

SPECT and SISCOM
Single photon emission computed tomography (SPECT) and more recently SISCOM (subtraction peri-ictal SPECT co-registered to MRI) have been used functionally and noninvasively to identify epileptogenic areas by measuring relative regional increases in blood perfusion immediately after a seizure (Fig. 2; Chapter VII-20). Resection of epileptogenic areas identified with this method reportedly correlates with good outcomes (21). Its main disadvantage is the need for the specialized facilities and trained staff to make timely injections of the contrast material. In addition, if a seizure spreads rapidly, the abnormal SPECT regions may include wider cortical areas often highlighting the involved hemisphere without precisely locating the focus. The regions of SPECT abnormality seem to be larger than FDG-PET. Nevertheless, in individual cases SISCOM may provide the only localizing clue allowing the workup to proceed to invasive investigation with subdural grids.

Specialized MRI Sequences
Use of higher strength magnets (including 3 and 7 T magnets), surface coils, diffusion tensor imaging, and multimodality imaging protocols in various small case series have been able to identify lesions, where previous MRI scans were nondiagnostic (22).
Postictal diffusion MRI looks at relative changes of water diffusion (presumably from cellular dysfunction) immediately after a seizure. In one small study this was shown to identify the epileptogenic region in nonlesional extratemporal epilepsies after a single seizure (23). Its role, sensitivity and specificity remain unclear. Magnetic transfer imaging is a technique for assessing the relative integrity of macromolecular structures (e.g. myelin) by their relative ability to exchange magnetization with free electrons in bulk water. The relative magnitude of this exchange is represented by the magnetic transfer value that can be shown as an image. In a very small number of conventional MRI-negative patients, these images have been able to demonstrate areas of abnormality (24).

**Functional MRI with EEG Co-registration**

Recently, it has become possible to acquire EEG signals in an MRI scanner, allowing analysis of regional blood flow changes reflected on functional MRI (fMRI) during interictal epileptiform discharges (25). Unfortunately, even more than MEG and dense-array EEG, scan time limits this tool to observation of events that can be captured in a brief recording. In addition, the selected images are often limited to one plane to allow better averaging of the spike occurrences. For these reasons, for the near future, this will remain an investigational tool.

**Invasive Electrocorticography with Grid Electrodes**

Many of the studies mentioned here have used electrocorticography as the final confirmatory test in localization of the epileptogenic focus, after an initial localization
with another modality. Therefore, assessing the utility of electrocorticography in isolation is hard. Overall, some of the best surgical outcome rates have been reported in a series where grids were placed widely and liberally (8). Electrocorticography offers the advantages of high spatial and temporal resolution. As an additional benefit the same electrodes can be used to map the eloquent cortical areas to reduce morbidity. Seizures from medial structures are poorly localized by scalp EEG and may be seen from subdural electrodes over these regions.

The disadvantages are many. Because of their invasiveness, there is a higher risk of infection and other morbidity. Further, only a small area of the cortex can be covered at a time, making accurate placement of electrodes essential. This is why so many other techniques are used to roughly estimate the epileptogenic zone before grids are placed. Finally, the definition of the exact epileptogenic zone is subjective and liable to investigator and/or institutional bias.

What Are the Prospects for Our Patients?

In the discussion up to this point, we have focused our attention on unifocal, localization-related epilepsies. Multifocal epilepsies do not benefit from surgery to the same degree (3). Unfortunately, multifocal cases are often not identified until after invasive investigations have started. Even then, additional epileptogenic foci may be missed if additional epileptogenic regions are not covered by electrodes, or are inactive during the monitoring period. Obviously, identifying multifocal epilepsies earlier in the course of evaluation will improve the effectiveness of surgery.

As mentioned previously, nonlesional extratemporal epilepsies are diverse. These patients should not categorically be rushed into surgery or, alternatively, never assessed for a chance for a cure. Nevertheless, given the poor natural history of refractory epilepsies without surgical intervention, surgery may be the best hope for many.

The overall strategy in all cases will be the same: identify patients with probably unifocal disease, and then locate the most likely responsible region and define its resection margins. As one of the last steps, most patients will need invasive studies with grids. While in most cases noninvasive localization will not be definitive, these data are useful in guiding grid placement.

We have discussed several techniques available for the noninvasive identification of the epileptogenic region. These methods differ in their availability, cost, and practicality, but overlap in their role so their use will ultimately be a center and patient-specific matter. Patients with frequent interictal discharges can benefit from several newer techniques with high spatial resolution such as MEG, dense-array EEG, and fMRI with EEG co-registration. These patients, however, represent a small fraction of all candidates. Other methods are useful for defining the disease regions. These include flumazenil-PET, and magnetic transfer MRI. SPECT images and perhaps diffusion MRI can define the epileptogenic area when practical.

Should patients be referred for surgical assessment in the face of a normal MRI? The answer should often be yes. The outcomes can be good and liberating. We can provide good information for each patient to make his or her own decision for a chance for definitive cure but at a real risk. Over time, as MRI capabilities improve there will likely be fewer patients in this category, yet the challenges presented here will continue as we try to reconcile which one of multiple foci is responsible for a patient’s epilepsy.
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Chapter XV-47
The Limited Role of Resective Surgery in Nonlesional Neocortical Epilepsy

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INTRODUCTION

It is well documented that the surgical outcomes in nonlesional [normal magnetic resonance imaging (MRI)] neocortical or extra-mesial temporal epilepsy cases (XMT) are not comparable to outcomes of cases with MRI-documented mesial temporal sclerosis (MTS) who undergo anterior temporal lobectomy (ATL) or amygdalohippocampectomy (1). In MTS cases, seizure-free outcomes occur in about two-thirds of cases, and in nonlesional XMT cases, seizure-free outcomes occur in about 45% (1). Fortunately, nonlesional XMT cases make up a small percentage of epilepsy surgery series. A review of 144 of our cases done between 1997 and 2001 [with the aid of fluid attenuated inversion recovery (FLAIR) MRI for detection of MTS] revealed 78 (54%) had MTS, 15 (10.5%) were lesional anteromesial temporal cases, 26 (18%) were lesional XMT cases, and 25 (17%) were nonlesional XMT cases. Of 48 XMT cases with normal MRI operated between 1988 and 1999, 22 (46%) were seizure-free at one year postoperative, and 14 (29%) had a <90% decrease in seizure frequency. Reasons for the limited success of nonlesional XMT cases may include: (i) a widespread epileptogenic area, (ii) misleading scalp electroencephalographic (EEG) data because of dipole orientation, sulcal location of epileptogenic tissue, or a mesial or basal epileptogenic zone, or (iii) involvement of nonresectable elo-quent cortex (2). The relatively limited effectiveness of nonlesional XMT resections raises the question of whether (i) specific ictal electrographic patterns, (ii) interictal epileptiform magnetoencephalographic (MEG) findings, (iii) results of additional imaging studies [positron emission tomography (PET), single photon emission computed tomography (SPECT), MRI], (iv) age at surgery, or (v) seizure semiology might better identify a subpopulation of nonlesional XMT cases more likely to have seizure-free outcomes.
FACTORS AFFECTING SURGICAL OUTCOME OF NONLESIONAL XMT EPILEPSY

Electrographic Studies

Noninvasive Electrographic Studies
There are very few ictal scalp EEG studies of nonlesional XMT cases. In one study of nonlesional frontal epilepsy, focal ictal EEG beta frequency onsets correlated highly with seizure-free outcomes (3). In this study, all four cases with localized ictal beta frequency onsets were seizure-free postoperative, but only two of 12 cases without beta frequency onsets were seizure-free. This communication pointed out that beta frequency onsets occurred in only about 25% of cases. The study also pointed out that lateralized ictal EEG onsets were not associated with seizure-free outcomes (3). Another study, including both lesional and nonlesional XMT cases, showed that, although ictal scalp EEG could provide localizing or lateralizing data in up to two-thirds of nonlesional frontal, 80% of lateral temporal, and a very high percentage of occipital cases, only 24% of frontal, 15% of lateral temporal and 53% of occipital ictal scalp onsets were in the beta frequency (4). Such focal ictal scalp EEG onsets are usually not seen with mesial frontal and orbital frontal foci because of their deep location (4). The same would presumably be true for other mesial and basal epileptic foci.

Invasive Electrographic Studies
The number of studies of invasive ictal electrographic findings in nonlesional XMT cases is also limited. Features of invasive EEG monitoring in nonlesional XMT cases that have correlated with seizure freedom or significant improvement include a reproducible ictal onset zone with persisting discharges within that zone, and low-voltage fast or high amplitude beta ictal activity (5). Rhythmic spikes or sinusoidal waveforms in the alpha to delta range were more often associated with unfavorable (Class IV) outcomes, with rhythmic round theta–delta activity thought to be unique to distant propagated sites (5,6). Good outcomes also seem to depend not only on resection of the ictal zone but also the associated surrounding irritative zone (7).

Magnetoencephalographic Studies
Magnetoencephalography, also referred to as magnetic source imaging (MSI) may play a significant role in guiding nonlesional XMT epilepsy surgery. One study has reported that 10 (83%) of 12 cases undergoing resection of at least two-thirds of the MEG XMT interictal epileptiform focus were seizure-free at one year postoperative (the other two had rare seizures). Only one of 11 (9%) in which no more than 50% of the focus was removed was seizure-free, and eight had Class IV outcomes (7). All of the 11 seizure-free cases had convexity foci with the exception of one mesial frontal case which underwent extensive resection of the MEG epileptiform focus. Two orbitofrontal cases in the same report had no detectable epileptiform MSI dipoles, emphasizing the difficulty of localization of deep epileptiform foci with MEG.

Imaging Studies

MRI
Volumetric MRI may have a role in imaging of nonlesional XMT cases. A study of nonlesional frontal and temporal cases found seizure-free outcomes in four of seven
(57%) frontal and five of nine (56%) temporal cases with significant ipsilateral temporal lobe volume decrease (8).

PET
One study has shown that when an interictal hypometabolic PET focus defined with flumazenil [FMZ—which measures gamma aminobutyric acid (GABA-A) receptor activity] is completely or nearly completely resected there is a high likelihood of a seizure-free outcome. Leaving a residual volume of the area of decreased FMZ uptake reduces the likelihood of seizure-free outcome (9). Of nine cases with normal MRI, seven (78%) were seizure-free. Four had all of the area of decreased FMZ activity resected, and the other three had 75% to 90% resected.

The other two cases were-Class III outcomes, which had 77% and 62% of the FMZ areas resected. Areas of decreased FMZ activity were usually smaller than the related areas of fluorodeoxyglucose hypometabolism. Not resecting portions of the latter areas did not correlate with worse outcomes. Unfortunately, FMZ PET is not readily available.

SISCOM
Extent of resection of cortical areas of increased isotope uptake in subtraction ictal SPECT co-registered to MRI (SISCOM) studies has been correlated with outcome of nonlesional XMT cases (10). In one study, 12 of 17 (71%) cases with nonlocalizing MRI had SISCOM and EEG and/or intracranial EEG localization. Six of 12 were seizure-free or had nondisabling seizures. The three cases with complete resection of the SISCOM focus were seizure-free or had nondisabling seizures.

Age at Surgery
Of the 48 XMT cases with normal MRI operated at our institution between 1988 and 2001, 11 of 19 (58%) who were 18 years old or younger were seizure-free at one-year follow-up. Of 29 nonlesional XMT cases older than 18, 11 (38%) were seizure-free.

Seizure Semiology
Little information is available on the association of seizure semiology with outcome in nonlesional XMT cases. One study found that localizable auras may be more often associated with favorable (Class I–III) outcomes (5). However, the epileptogenic area may be remote from the symptomatogenic zone (11). Therefore, seizure semiology alone, although sometimes helpful in lateralizing or even localizing a seizure focus, probably should not be relied on for seizure focus localization.

CONCLUSION
The above-mentioned studies suggest that the following factors may have an influence on outcome of nonlesional XMT cases:

1. Presence of a beta frequency ictal focus on surface EEG,
2. Presence of a low-voltage fast or high amplitude beta frequency ictal onset on intracranial EEG confined to a discrete area that is anatomically reproducible in all seizures,
3. Resection of at least two-thirds of any interictal epileptiform MEG focus,
4. Presence of significant ipsilateral temporal lobe atrophy in nonlesional
   temporal and frontal seizure cases,
5. Complete resection of an area of decreased FMZ PET activity or an area of
   increased isotope uptake in a SISCOM study that is concordant with
   electrographic data, and
6. Early surgery (18 years old or younger).

A relatively small number of nonlesional XMT cases will probably meet the
majority of the above criteria. In our experience, cases with poor scalp EEG locali-
zation are unlikely to have good MEG localizing data, and are probably not good
candidates for invasive monitoring. However, if there are concordant lateralizing
scalp EEG, SISCOM (and, if available, FMZ PET), and clinical data suggesting
an XMT focus, invasive monitoring may be considered.

Some patients may benefit from nonresective surgery. In cases with an epilepti-
form focus located entirely or partially within functional cortex, multiple subpial trans-
section has produced at least a Class III outcome in half of the cases. However, only
about 20% were seizure-free. Depending on seizure semiology, patients with poor elec-
trographic localization may be candidates for anterior callosotomy or vagal nerve stimu-
lation, with about 50% having a >90% or >50% decrease in seizures, respectively.

Currently, it would seem that only a limited number of nonlesional XMT cases
can be expected to have seizure-free outcomes. Strong consideration should be given
to invasive monitoring in only those cases with normal MRI whose noninvasive
electrographic (and/or MEG) data and SISCOM/PET data suggest a well localized
epileptogenic focus.

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Although epilepsy surgery has been conducted for more than 100 years, with an increasing frequency both nationally and internationally during the last half of the 20th century, the attention to psychosocial and functional outcome postsurgery has been chiefly recent, occurring primarily during the last 15 years. Some of this emphasis has evolved from the established medical success of these operations to an effort to look beyond basic surgical seizure outcome and assess other functional impact of the operation. Another reason for this latter emphasis is the concern of allied health groups that have been assembled in order to assess and aid in the transition of the patient pre-and postoperatively. There is no question that as medical surgical procedures continue to be refined, there remains a continuing need for attention to improve vocational and important psychosocial transitions. Otherwise, surgery’s full benefit to the patient and the operation’s cost-effectiveness to society are simply not being maximized. This chapter reviews findings related to vocational and psychosocial variables around epilepsy surgery, describe trends in the assessment of outcome, and make recommendations not only in relation to assessment, but also the actual intervention process.

**VOCATIONAL OUTCOME FINDINGS**

There have now been several studies and actually reviews around epilepsy surgery related to vocational outcome. In the review by Dodrill et al. (1), the authors noted improved employment status relating to epilepsy surgery, chiefly linked to a seizure-free status. Findings from a number of studies emphasize that employment outcome needs to be examined very carefully and as an ongoing process (2–5). Although underemployment can decrease relatively quickly postsurgery, it may take some time for actual unemployment rates to drop due to a variety of variables (e.g., physical
and emotional recovery from the operation, access to vocational or retraining services, gaining an understanding of the world of work, social maturation, etc.). Sperling et al. (6) noted that unemployment rates declined in their series postsurgery (3.5–8 years after surgery), with 25% unemployed before surgery (n = 18) and 11% unemployed after surgery (n = 8). Seizure-free patients fared better than patients with inconsistent seizure-free years, for whom a high unemployment level persisted. Patients with seizures in each year during the follow-up fared worst relative to the ability for work. These researchers noted that the presurgery unemployed patients took up to six years to obtain work after surgery and that of the 13 who were students at the time of surgery, 11 graduated and nine were employed. Approximately half of the sample took more than two years to find a job. It is also of note that one variable, age, significantly differentiated between patients who remained unemployed (x age at surgery = 42 years) versus those who became employed (x age at surgery = 31 years).

Findings from the University of Washington Regional Epilepsy Center group as reported by Fraser and Thorbecke (2) indicate that the surgery patients as compared to a medication-only comparison group, at 5 and 10 years postsurgery, gained both in the number of weeks worked during the last two years preceding follow-up and in hourly salary. Of note was the fact that the medical comparison group actually lost ground relative to number of weeks worked from presurgery baseline while the surgery group was increasing in weeks of work engagement and also moving ahead relative to rated improvement in job performance (i.e., indications of promotion, wage increase exceeding the customary, increased range of job responsibility, etc.). Again, as in the Sperling et al. (6) study, 90% of the individuals who were students at the time of surgery were working versus 47% of the student medical comparison group.

A recent study was conducted at the University of Wisconsin-Madison by Jones et al. (7) which involved 61 patients who had undergone anterior temporal lobectomies and 23 individuals who did not undergo surgery and served as a medical comparison group at follow-up. Surgery patients were two to nine years postsurgery, with a mean of 5.8 years. There was a significant difference between the groups in employment outcome with significantly more in the surgery group (69%) versus the medical comparison group (39%) working more than 35 hours a week for wages at minimum or higher. In the surgery group, only 25% were unemployed at follow-up compared to a marked 52% in the medical comparison group. Moreover, in the surgical group, 80% were financially independent versus only 52% in the medical comparison group. In this study, as in prior ones, it must be emphasized that it may take three or more years postsurgery in order to see the differential impact of the surgical intervention. It is also of note in the Jones et al. (7) study that there was a 13% increase in the ability to work full-time in the surgical group versus a loss of ability to work full-time in the medical comparison group from 48% to 39% at follow-up. This parallels the findings as reported by Fraser and Thorbecke (2) from the University of Washington series with the “medication-only” patients, not receiving the surgery intervention, tending to lose work engagement. To date, freedom from seizures and age appeared to be discriminators relative to outcome in the study by Sperling et al. (6) while in the work from the University of Washington Regional Epilepsy Center (2) freedom from seizures coupled with higher educational level had a significant impact on successful outcome. Mediating variables, other than seizure-free status (e.g., aura-free status, neuropsychological functioning, etc.), undoubtedly continue to deserve further attention.

The fact that younger patients (viz., students at the time of surgery) seem to do substantially better vocationally at follow-up, as compared to medication comparison groups, deserves continuing emphasis. The above data need to be carefully reviewed
by surgery-eligible patients and their significant others as part of the epilepsy surgery decision process. Increased productivity and economic self-sufficiency are very positive trends. Parents of youth eligible for the surgery also need to consider the above benefits. Younger students at the time of surgery can also have a more normal developmental life, which is a positive interactive component in successful career planning.

**PSYCHOSOCIAL OUTCOME FINDINGS**

As with the vocational outcome, there has been an increased emphasis over the last 15 years on psychiatric and other psychosocial outcomes postsurgery such as independent living, and social and recreational functioning. Glosser et al. (8) indicate that 65% of epilepsy surgery patients, either before or after epilepsy surgery, had an Axis I diagnosis such as depression, anxiety, and organic mood disorder. The Glosser group indicates that the onset of new psychiatric problems in the months directly following surgery may be as high as 31%. However, at six months follow-up, the severity of psychiatric symptoms was much lower than before the operation. A complex symptom entity, involving mixed features of anxiety, irritability, and depression, seems to occur in episodic cycles around the operation. A continuing seizure status seems to be confirming and predictive of psychiatric and psychosocial adjustment, but there was also a slight trend for individuals that were seizure-free to develop early, but transient, psychiatric worsening. This could relate to the organic impact of the operation itself, but also may relate to other variables such as “the burden of normality,” which will be discussed later in this section. Glosser et al. (8) stress that elements of anxiety and depression are quite common, even for those with no psychopathology, in the initial weeks postsurgery. Ring et al. (9) indicate that the anxiety tends to remit at three months while depression may be more resistant. Although these symptoms generally resolve, some individuals will feel some continuing anxiety and depression (particularly those with poorer seizure outcomes).

Koch-Stoecker (10) at the Bethel Center in Germany indicates a strong relationship between freedom from seizure involvement and lack of an Axis I or Axis II diagnosis (89%) while only 43% of those with a consistent Axis I or Axis II disorder reach seizure-free status. She notes that postoperative mood disorders can be predictable and related to preoperative dysthymic disorders, which can exacerbate into major depressive episodes and somatoform disorders. Even these exacerbations will generally remit within a year with antidepressants. On an overview, reduced anxiety and increased self-esteem were among the most important changes noted after surgery. Koch-Stoecker (10) also noted that individuals with organic personality disorders seemed to have the worst outcome and can require careful consideration in relation to surgery. They tend to have both continuing seizure difficulties and, postoperatively, some complex psychiatric reactiveness. Derry et al. (11) indicate that elevation on the emotional adjustment scale of the Washington Psychosocial Seizure Inventory (WPSI) was highly correlated with persistent depression two years after surgery. This correlation was even higher for patients who were older, experiencing generalized seizures and preoperative neurological deficits, and/or had a history of psychiatric illness or a genetic history of seizures within the family. The WPSI Emotional Adjustment Scale remained the best predictor of depression level even within the context of seizure-free status. This WPSI emotional scale was superior to the Center for Epidemiological Studies Depression Scale and other WPSI
scales as a predictor of postoperative depression. These authors make a case that early and successful epilepsy surgery may be preventative of chronic psychological maladjustment into which these chronic seizure patients can transition as adults.

Blumer et al. (12) emphasize that individuals with preexisting mood disorders can certainly be treated preoperatively by one or more antidepressants. Continuation of psychotropic medication after surgery is recommended. Blumer et al. (12) recommend that patients who are seizure-free and remain abstinent of depressive symptoms are considered stable within a range of 6 to 18 months postsurgery. Reutens et al. (13) reviewed five cases of patients with dual diagnosis of medical refractory epilepsy and chronic psychosis who underwent temporal lobe resection. Seizure outcome was excellent for all without influence on the nature and evolution of their psychosis. These patients did actually function better in activities of daily living and integration within the psychiatric treatment facilities postsurgery. They conclude that “with appropriate psychiatric intervention, patients with chronic psychosis and refractory epilepsy can participate in presurgical investigation successfully and can undergo surgery uneventfully” (13, p. 1935).

Another promising area of research relates to patient personal characteristics, expectations, and satisfaction related to surgery. Wheelock et al. (14) underscored that satisfaction with surgery was largely a function of presurgical expectations and directly related to expectations for seizure elimination. In this study, postsurgery patients in the seizure-free group showed improvements on the psychosocial measures at two months and one year, whereas patients with continuing seizures showed improvement at the two months follow-up (possibly a halo effect having the operation) and then a decline to baseline or worse at one year follow-up. As reported by Hermann et al. (15) reduction of seizure frequency of even 75% may not result in improvement on measures of psychosocial functioning.

One emphasis in examining the impact of epilepsy surgery has been the use of quality of life instruments. Wiebe and Derry (16) single out the Liverpool Battery (17), the epilepsy surgery inventory (ESI)-55 (18), and the quality of life in epilepsy inventory (QOLIE)-89 (19) as having sufficient responsivity in order to measure within patient improvement over time. One of the critiques of quality of life measures is that they can be a bit global and of not major utility relative to specific psychosocial planning efforts. Hermann et al. (15) indicate that much of the variance in these measures can be affected by mood. Taylor et al. (20) and Fraser and Thorbecke (2) encourage specific evaluation of patient aims via interview and goal scaling in evaluating the operation’s psychosocial outcome in a linear manner relating to success to the level of patient’s aims achieved. In review of the aims of 69 patients by Taylor et al. (20), the most frequently cited aims were to be working or working better, driving a motor vehicle (21), being independent and free from supervision (20), socializing (19), and relief from seizure medication (14). Two-hundred and four stated aims were made across the 69 patients relating to the epilepsy surgery event. Thorbecke (2) has patients scale expected postoperative functioning across a number of life domains such as independent living, school functioning, social functioning, interpersonal relationships, etc., on a scale of 1 to 10. This provides a simple and graphic format in which patients’ expectations can be reviewed and planning/action steps undertaken from presurgery forward. In this manner, we move beyond the establishing of the patient’s general state of well-being at a given point in time and are more able to grasp concrete stages in the process of patient adjustment across multiple domains as endorsed by Wilson et al. (22).
Some significant emphasis has been placed on predictions of surgical success and outcome. As with vocational outcome, seizure status can account for a significant part of outcome variance. In the study by Wilson et al. (23), seizure outcome accounted for 33% of the variance in relation to patients’ ratings of surgical success while affective feelings of depression and anxiety postoperatively accounted for 9%, and preoperative expectations and plans accounted for an additional 7%. It should be noted that the freedom from seizure status is not always consistent across all studies in relation to perception of surgical success. Gilliam et al. (24) indicated that mood status, employment functioning, driving capacity, and anticonvulsant cessation were more important predictors of patient health-related quality of life than actual seizure freedom.

**PSYCHOSOCIAL ADJUSTMENT MODELING IN EPILEPSY SURGERY**

More recently, there has been an emphasis on model building relating to positive psychological and psychosocial outcome postsurgery apart from the more linear seizure relief interest. Derry and Wiebe (25), based upon their review of the literature, indicate that preoperative positive psychological adjustment, good perceived quality of life, low neuroticism, a tendency toward learned resourcefulness (or coping), and available social support all increase the possibility of positive postsurgical outcomes. Less favorable prognostic signs involved considerable presurgical psychological distress, anxiety and neuroticism, a helpless attitude toward medical self-management, rigidly unrealistic expectations, and poor interpersonal interactions with the physician. In relation to model building, Wilson et al. (22) have added the construct of the “burden of normality” or the ability of the patient to discard the sick role. These authors and McLachlan et al. (26) also emphasize the concept of lag time in postsurgical adjustment as assessed at different points in time. McLachlan et al. (26) show that there was only one of 11 subscale significant changes on the ESI-55 at six months, two of the subscales at 12 months, and six of the subscales at 24 months. Both groups emphasized that cross-sectional evaluation of quality of life at standardly timed anchor points through two or more years postsurgery may provide a better perspective on psychosocial outcome.

The benefit of the psychosocial adjustment model as proposed by Wilson et al. (22) is that they take into account preoperative patient perceptions of illness, disablement, and opportunity for dramatic cure and track “burden of normality” characteristics across the psychological, behavioral, affective, and sociological domains of functioning during the postoperative period. Examples of “burden of normality” concerns in these domains would include: sociological—new vocational horizons, behavioral—excessive or manic activity, psychological—potential grieving over life’s “lost years,” and affective—increased anxiety. This model moves beyond the more global assessment of quality of life and involves detailed and intensive interviewing within potentially challenging domains of life functioning. Wilson et al. (21) later tested this model and mapped through patient interviews over a period of two years postsurgery-specific symptoms of the “burden of normality.” Findings from the study at 24 months indicate that patients who had been seizure-free or experienced auras only within the previous 18 months were significantly more likely to report “burden of normality” and adjustment symptoms compared to patients who had continued to experience complex partial and/or generalized tonic–clonic seizures ($p = 0.03$). Across salient domains of psychosocial functioning, the data from this study support...
the clinical existence of the “burden of normality” arising across a time-dependent context—as time passed, patients appear to become increasingly aware of new expectations and the real demands of postoperative life as affecting their behavior. Patients whose surgery had minimal affects on their seizures did not report these symptoms. The symptoms, however, were reliably detected, appeared at different points in time, and were still increasing in occurrence two years postsurgery. Wilson et al. (21) suggest that identity reintegration from that of chronically disabled person to wellness is time dependent and contingent upon the patient’s perception of surgical outcome. The authors emphasized that like this “burden of normality,” those who experience loss of hope relative to postoperative improvement will experience an alternate set of psychosocial sequelae or burden which has received little assessment to date.

Bladin et al. (27) offer a different perspective in presenting postoperative adjustment using data on 70 patients. In this study, they examined four domains of adjustment: special physical, general physical, psychological, and social behavioral, and issues of basic postoperative adjustment, and then problems related to the burden of normality, viz., problems generated by surgery’s success itself, within each domain. They also examined these concerns broken out for the seizure-free and the group that had only a modicum of success relative to seizure freedom or some continuing seizure frequency. These authors (28, p. 317) offer the observation that “a seizure surgery program must possess an effective postoperative follow-up and rehabilitation program, with repeated patient interview built into it, in order to detect postoperative adjustment problems early enough to offer assistance.” They also emphasize that the follow-up program must be of sufficient length to allow for problem identification. Wilson et al. (21) indicate that this could be up to 10 years postsurgery. This full perspective on structured follow-up for two years or more across specific domains of functioning and burden of normality or worsening adjustment challenges within these domains of life functioning might be considered an ideal paradigm for optimizing outcome.

CONCLUSION

On an overview, there are now a number of consistent findings in the research literature relating to vocational and psychosocial outcomes for individuals undergoing epilepsy surgery. People with successful seizure freedom appear to be doing better on both quality of life measures (although perhaps largely influenced by mood) and in specific vocational and other domains of psychological and social adjustment. It would appear that many individuals who are seizure-free can do exceedingly well and it is not optimal to delay the surgery, particularly for youth during the school years. It is to be noted that in assessing outcome, the element of timing is important and many individuals will take two or more years for the benefits of surgery to be concretely established relative to psychosocial outcome.

In relation to preexisting psychopathology, many individuals may benefit from the operation—although as established by Koch-Stoecker (10) those with Axis I or Axis II disorders do less well and those with organic personality disorders seem to have the worst outcome medically. It seems that individuals with chronic personality disorders, organically mediated or otherwise, tend to have poorer outcome both psychosocially and medically.

It is very encouraging to see model building relative to prognostic characteristics that enable individuals to do well medically and psychosocially and conversely
those prognostic signs “that” appear to relate to poor outcomes. This is not in order to deny individuals access to the operation, but hopefully to better target those who may require considerable assistance in postsurgical psychosocial services. Given limited resources, allied health teams may be more successful if they not only target these individuals for services, but do so relatively early presurgery.

Of considerable interest is the focus upon model building relative to psychosocial adjustment which relates not only to predisposing characteristics relative to positive or negative psychosocial outcome, but also in the optimal tracking of achievement across specific vocational, behavioral, psychological/affective, and sociological domains of functioning postsurgery. Taking this a step further would be the tracking at fixed points in time of both the individuals who are seizure-free and meeting new challenges under “burdens or normality” in specific domains of functioning and also those with less than optimal seizure outcome across the same domains. This obviously takes additional effort to go beyond administration of quality of life instruments to more discrete evaluations of functional gains.

It must be recognized that comprehensive intervention around the epilepsy surgical event is carried on in several countries outside the United States, such as Holland or Germany, due to significant support from national governments or established nonprofit foundations. Currently, this has not occurred in any standardized or comprehensive way within the United States. Not every epilepsy surgical center in the United States necessarily has even a fully dedicated social worker. Work by Bell et al. (28) in the United States relating to scheduled telephone follow-up for individuals experiencing traumatic brain injury details a cost-effective method of scheduled telephone follow-up, problem identification, and triage resulting in improved functional outcome. Within the United States and other countries in which psychosocial services are less available around epilepsy surgery, new avenues need to be explored to not only discretely improve psychosocial adjustment, but also to do so in a timely manner. Scheduled telephone assessment using structured protocols and referral mechanisms appears to be a cost-effective option that needs further exploration. To date, it is the lack of standardized pre-and postsurgical assessments and intervention capacity around the surgical event that has been sorely lacking in the United States and in many other industrialized countries while the operation itself may border on becoming commonplace. Unless new cost-effective psychosocial assessment and intervention options are developed, the benefits of the surgery will not be optimized for both the seizure-free (e.g., now dealing with the “burden of normality”) and those not helped or even worsened (although a small group) due to surgery outcome.

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Part Five

Investigational Procedures and Treatments
Chapter 48
Use of Full-Band EEG for Noninvasive Ictal Localization

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BACKGROUND

Determination of the epileptogenic zone is typically attempted by ictal video electroencephalographic (EEG) recordings with scalp electrodes, correlated with other noninvasive studies, particularly neuroimaging. However, conventional scalp EEG gives often equivocal information about the location of seizure origin, or it is incongruent with other tests, leading to the requirement for invasive recordings (1–4). The spatial resolution of the conventional scalp EEG can be enhanced with existing, but clinically unexploited, source localization techniques (5). However, there remains an obvious need for better noninvasive detection of seizure-related signals that arise in brain structures (e.g., deep temporal lobe and neocortex) typically involved in seizure initiation. It is evident from our recent work that detection of such signals is greatly improved with an extended EEG bandwidth (6). While conventional EEG has a limited bandwidth (typically 0.5–70 Hz), distorting or ignoring slow EEG events, a full-band EEG (FbEEG) that detects all physiological frequencies can be obtained using a DC-coupled (direct current coupled) amplifier and proper electrode–skin interface. This
chapter describes the use of very slow (infraslow; see Ref. 7), ictal EEG events to locate the epileptogenic zone.

A large number of animal experiments, as well as early invasive recordings on humans, have established that seizures are associated with very slow EEG responses often referred to as DC shifts (7a–11). However, until our recent work, there have been no noninvasive studies recording focal seizures with DC amplifiers (6). Other recent studies have used conventional EEG amplifiers together with Ag/AgCl scalp electrodes or metal subdural electrodes. Even with this technical limitation (see section “Technical Requirements and Practical Aspects”), these studies have observed ictal low-frequency fluctuations that were congruent with but more localized than the fast ictal EEG activity (12–14). Thus, both the earlier animal work, as well as the recent clinical recordings, demonstrate the advantage of studying very slow ictal EEG changes and the need to develop practical methods to achieve true FbEEG recordings at the bedside (15,16).

ORIGINS OF SLOW EEG EVENTS

Generation of slow ictal EEG responses likely includes several mechanisms in addition to the intracortical neuronal current loops implicated in the generation of higher frequency oscillations. There is evidence that glial cells may be an important generator of slow DC shifts, which may arise even in gliotic human hippocampus (i.e., with Ammon’s horn sclerosis) (17–21). Several studies have also provided evidence supporting the presence of intracranial, non-neural (i.e., not neurons or glia) generation of slow DC shifts, especially those arising at the blood–brain barrier (22–27). Taken together, it seems likely that the ictal slow DC shifts arise from multiple cellular structures and mechanisms. Since these mechanisms are presumably confined to the volume of brain engaged in the ictus, three-dimensional source localization of the ictal DC shifts may, indeed, have analogies with several neuroimaging modalities [e.g., positron emission tomography (PET) or single photon emission computed tomography (SPECT)].

TECHNICAL REQUIREMENTS AND PRACTICAL ASPECTS

Reliable recording of slow EEG events requires (Fig. 1) a genuine DC-coupled amplifier with sufficiently high input impedance and DC stability as well as a wide enough dynamic range (preferably ±200 mV or higher). Amplifiers with an automatic input offset compensation have been used to extend the dynamic range and to avoid amplifier saturation due to possible artifactual changes or drift of the baseline. The first commercial DC-coupled amplifiers suitable for clinical use have recently become available. Also the electrode–gel and skin–gel interfaces must be DC coupled and sufficiently stable. The electrodes must be nonpolarizable, since all polarizable electrode materials (such as gold, tin, platinum, or steel) are coupled in a mainly capacitive manner to their external environment, which leads to high-pass filtering at the electrode–gel interface (28,29). Among the currently available electrodes only those based on Ag/AgCl are adequate (29), and the sintered contact elements used in our work have proved to be both maintenance-free and very stable in recordings lasting up to several days (6,22,23,29,30). Chloride is required in the gel for stable operation of Ag/AgCl electrodes, hence precluding the use of electrolyte-free gels (29). A stable skin–gel contact requires prevention of gel drying, good attachment of the electrode to the skin, as well as short-circuiting of skin-borne signals [caused by movements and
galvanic skin response (GSR) by penetration of the epithelium through the basal lamina at the recording site (22,31–33).

Implementation of FbEEG recordings into routine clinical practice could be remarkably easy. DC-coupled amplifiers are not more expensive than the current clinical amplifiers, suitable electrode material (Ag/AgCl) is sterilizable and has been in clinical use for decades, attachment of the electrodes on skin is practically as quick as with the conventional electrode types, and finally, sufficient scratching of the skin is so painless that we have successfully done that even with sleeping neonates (30).

The lack of scalp FbEEG recordings of focal seizures in the literature is mostly due to the technical difficulties in the early pioneering work in the 1960s (34–36). In our experience, this technique is reliable and readily applicable to bedside recordings once the basic technical requirements are met (16,29,37,38). The limitations of the FbEEG technique are mostly similar to those of the conventional EEG. When comparing FbEEG and conventional EEG, the visual appearance of slow artifacts (e.g., eye and tongue movements) are somewhat different due to the lack of high-pass filtering in the former, and hence some experience is needed for their proper identification (6,39,40). Distinguishing between artifacts and seizure-related DC shifts is, however, easy because artifacts have their characteristic waveforms with a typically faster time course (only up to a few seconds) and usually a particular global distribution. Many artifacts can be very efficiently eliminated by using median filters or spatial filters readily available in pertinent analysis softwares (41,42). Skin potentials (“sweat artifacts”) do not cause problems in FbEEG recordings of the present kind because they have been excluded by short-circuiting (see above). Movement artifacts just before and during seizure onset may occasionally make the evaluation of DC shifts difficult. However, most of the movement artifacts can be avoided by firm attachment of the electrodes to the skin (e.g., with collodion), and by using appropriate placing of the reference electrode (e.g., vertex).

FbEEG RECORDINGS OF FOCAL SEIZURES

We have recently conducted FbEEG recordings on epilepsy patients undergoing presurgical evaluation (6). Our results have clearly demonstrated that focal seizures are associated with DC shifts confined to the seizure focus (Fig. 2). The ictal DC shifts begin within seconds of electrographic seizure initiation, and they continue throughout
the seizure with the amplitude fluctuating slowly between few tens of microvolts to over a hundred microvolts (Fig. 2). The polarity of the DC shift is typically negative above the ictal focus, and the spatial extent of the shift may ultimately cover several brain regions upon spread of the seizure activity. The relatively large spatial distribution of the ictal DC shifts call for particular attention to how offline re-referencing is performed, and often a computerized source localization (Fig. 3E) may help in getting an unbiased signal location. An examination of a series of temporal lobe epilepsy cases with data from simultaneous intracranial recordings showed that the onset of the scalp-recorded DC shift discloses the side of seizure initiation, and the extent of the DC shift reflects spreading of the seizure activity (Fig. 3). As yet unpublished data based on three-dimensional source analysis have shown that focal DC shifts may appear already before the seizure activity becomes obvious in the conventional EEG (Fig. 3B, C). The geometry of the ictal brain areas is often complex (e.g., in mesial temporal lobe onset seizures), and the polarity of the DC shift in a given derivation may change during the spread of seizure activity (Fig. 3B). Hence, in an attempt to identify and locate DC shifts originating from the seizure initiation focus, DC shifts of either polarity should be sought at and before the electrographic seizure onset.

**CONCLUSIONS**

Our recent methodological, physiological, and clinical studies have shown that FbEEG is relatively easy and practical at bedside. Ictal DC shifts are consistently seen in scalp recordings, and the DC shifts give information that agrees with seizure lateralization as defined by the other established criteria. Hence, very slow EEG signals may provide invaluable information in noninvasive determination of the side of seizure origin.

Finally, it is notable here that FbEEG records all EEG frequencies. Its wider bandwidth covering low frequencies does not lead to any compromise in recording of fast or even ultrafast events (16,43). In addition to this, DC-coupled amplifiers have superior artifact tolerance, which per se will likely make them penetrate clinical EEG markets in the near future. Once this new EEG amplifier generation is implemented in the clinic, the actual recording bandwidth will be determined only by the low-frequency compatibility of the skin–electrode interface. Thus, the use
Figure 3  (A–E) FbEEG recording during a left-side onset, complex partial seizure, with simultaneous recording from subdural strip electrodes. Traces in (A)–(C) are all in the same time scale [amplitude bar 200\,\mu V for (A) and (C), 30\,\mu V for (B)], and from the same signal: (A) shows the seizure with FbEEG recording, (B) shows the slow component subtraction of a highpassed [as in (C)] signal from the FbEEG only, whereas (C) demonstrates the signal with conventional settings (i.e., high-pass filtered at 0.5 Hz). Traces in the bottom (D) are selected channels from an intracranial recording, which has been stretched slightly to better illustrate the changes in fast activity. Seizure onset (mesial) and spread (to lateral) in the intracranial EEG are shown with respective arrows, and seizure spread to right mesial TL is shown with an asterisk. Note the prominent positive DC shift in the left temporal derivations after mesial TL activation, and the negative DC shift later after neocortical spread. Three-dimensional analysis (E) of the DC shifts before the onset of fast spiking demonstrates a prominent activity in scalp potential distribution (top figure), as well as in the cortical current source density (middle and bottom; minimum-norm estimate). All derivations in FbEEG are referred to a linked Cz+Pz. Lateral eye movement artifacts before the seizure [marked with \( \mathbb{V} \) in trace (A)] have been removed offline in trace (B) before (A)–(C) subtraction in order to improve the visual clarity of the later occurring DC shift. \textit{Abbreviations:} RST, right mesial TL; RLT, right lateral temporal lobe; LST, left mesial TL; LLT, left lateral temporal lobe. \textit{Source:} From Ref. 6.
of proper electrodes and electrode–skin contacts (see above and Ref. 29) will permit recordings of all physiologically and clinically relevant EEG frequencies, and FbEEG will most likely become a new clinical standard.

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Chapter 49
Magnetoencephalography (MEG)

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INTRODUCTION

Magnetoencephalography (MEG) is a technique that utilizes superconducting quantum interference devices (SQUIDs) to measure the extracranial magnetic fields generated by intraneuronal electric currents (1,2). The extracranial magnetic fields result from intracranial tangential neuronal currents in the fissural cortex which makes up two-thirds of the surface of the human brain (3). Using MEG analysis one can localize an equivalent current dipole (ECD) model as a source of intracranial electrical activity by analysis of extracranial magnetic fields. The MEG source localizations are then overlaid onto magnetic resonance (MR) images of corresponding areas of the brain, thus generating a magnetic source image (MSI). This chapter reviews the current clinical applications of MEG for epilepsy surgery.

MEG DATA ACQUISITION

The urban environmental magnetic noise is 1,000,000 times larger than the magnetic activity of epileptiform spikes, which are only 2000 to 5000 femtotesla (fT) in magnitude (1 fT = 10\(^{-15}\) T). Hence the device used for measuring neuromagnetic signals, a biomagnetometer, is typically housed in a room magnetically shielded with high-permeability metals to reduce external magnetic noise.

Zimmerman et al. (1) developed the point-contact SQUID to detect the weak magnetic signals emitted by the brain. The detector array is mounted within a container, known as a Dewar, which keeps the detector coils cooled at −269°C in liquid helium. Current biomagnetometer systems have between 140 and 300 detector channels, which are configured in a helmet-shaped array to sample the magnetic field pattern around the entire head.

Magnetic field signals are recorded as waveforms similar to electroencephalography (EEG), and have spatial patterns over the scalp that can be used to localize the
sources of the intracranial activity. The source localization has to solve the inverse problem that calculates the three-dimensional (3D) intracranial location, orientation, and strength of the neuronal sources backwards from a measured magnetic field pattern. The accuracy of a solution of the inverse problem depends on numerous factors including the forward problem. The forward problem uses an iterative algorithm to determine the location, orientation, and strength of the ECD that best accounts for the measured magnetic field pattern. The accuracy of the forward problem is critically determined by the shape and conductivity of the volume conductor of the head model. MEG forward solution is more robust than that of EEG because of homogeneous conductivity in magnetic field.

In order to correlate the locations of MEG sources with the anatomy of the patient, source data derived from MEG are co-registered with high spatial resolution structural MR images, “to create an” MSI (4–6).

**BASIC PHYSIOLOGY AND SCIENTIFIC JUSTIFICATION**

Neural currents that give rise to both MEG and EEG signals are caused by a flow of ions through postsynaptic dendritic membranes ($10^{-14}$ nA m). The intracellular current flow within an individual neuron is quite small, with a proportionately small magnetic field. Approximate one million synchronously activated neurons can produce a magnetic signal which is detectable extracranially (7). It has been suggested that a typical dipole moment of 5 nA m of sensory evoked responses on MEG would correspond to the signals simultaneously arising from 100 to 250 mm$^2$ of the cerebral cortex (8,9). In addition, the current flows must be parallel to the surface of the skull in order for the magnetic field to penetrate the skull and be detected by sensors oriented perpendicular to the scalp.

Therefore, the MEG is relatively more sensitive than the EEG to sources whose current flows are tangential to the surface of the scalp, but current flows in the gyral crest that are perpendicular to the scalp are only minimally detected by MEG (10,11).

Studies using simultaneous MEG and subdural EEG recordings have shown that a finite area of synchronized epileptic activity is necessary to produce a detectable MEG signal (12–15). When epileptic spikes in the convex cortical surface of the brain extend over 3 cm$^2$ across the fissure, MEG spikes can be detected with a probability >50% and their localization correlate with the spatial extent and amplitude of spikes recorded simultaneously by electrocorticography (ECoG) (14). In contrast to MEG, simultaneous intracranial electrodes and scalp EEG recording studies indicate that larger areas of 6–10 cm$^2$ of spiking cortex are necessary in order to generate a measurable scalp-EEG spike (16,17).

An important advantage that MEG has over EEG is that, unlike electrical fields, magnetic fields are not attenuated or distorted by intervening brain, dura, cerebrospinal fluid, bone, and skin (18,19). Therefore, the problem of false localization or lateralization, which may be encountered with EEG, is rarely seen in MEG. However, EEG has the advantage of long-term recordings that can facilitate extensive sampling across various situations of sleep, awake, preictal, ictal, and postictal periods. Table 1 summarizes dipole source localizations and recording data of MEG and EEG for patients who are undergoing epilepsy surgery.

The single ECD method is ideal to localize a simplified neuronal current at a single time point. It is well known that ECD provides only an abstraction or a center of gravity in the epileptic areas (20–22). However, epileptic discharges often rapidly propagate...
within the complicated epileptic networks to generate asynchronous interictal discharges (23,24). When many different sources simultaneously activate and affect each other, the single ECD method cannot explain all of the exciting epileptic activities. Multiple signal classification (MUSIC), synthetic apparatus magnetoencephalography (SAM) and minimum current estimation (MCE) methods have been developed to improve the clinical application of MEG in the analysis of these complicated neuronal networks that are involved in epileptogenesis (25–29).

**Clinical Applications of MEG for Epilepsy Surgery**

*Mapping of the Epileptogenic Zone in the Presurgical Evaluation of Patients Who Are Candidates for Epilepsy Surgery*

In patients with localization-related epilepsy undergoing evaluation for epilepsy surgery, if the clinical, neuropsychological, EEG, and radiological data are all concordant and point to the same area of epileptogenicity in the brain, cortical excision of the primary epileptic zone is undertaken. However, if the data are discordant or the epileptic zone resides wholly or in part within eloquent cortex, intracranial EEG is required to localize the areas of epileptogenesis (30–33). The localization of interictal MEG spike sources has been reported to correlate with the localization of the epileptogenic zone as determined by conventional noninvasive and invasive localizing modalities in adult patients with refractory seizures who have undergone epilepsy surgery (5,6,34–36). As well, MSI has been shown to be an accurate, noninvasive diagnostic modality for localizing the origin of the epileptogenic zone in children with extratemporal epilepsy (37–42).

**Use of MEG in Extratemporal Epilepsy**

In patients with extratemporal epilepsy, treatment is complicated because the variety in patterns of epileptiform discharges and their propagation, and the complexities of

<table>
<thead>
<tr>
<th>Source generators</th>
<th>MEG</th>
<th>EEG</th>
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<tbody>
<tr>
<td>Intracellular currents generate magnetic fields</td>
<td>Extracellular currents generate electrical fields</td>
<td></td>
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<tr>
<td>Tangential in fissural cortex</td>
<td>Radial in gyral crest and tangential in fissural cortex</td>
<td></td>
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<tr>
<td>Less influenced by tissues</td>
<td>Influenced by heterogeneous conductivities; scalp, skull, CSF, brain</td>
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| Spatial resolution | 2–3 mm | 7–10 mm |
| Recording time     | 2–4 hr | 30 min to 14 days, with time-locked digital video monitoring |

| Interictal spikes | Limited number of interictal spikes | Large number of interictal spikes in different stages: awake, sleep, preictal, and postictal |
| Ictal discharges   | Rare spontaneous or induced seizures | Prolonged video-EEGs capture spontaneous and habitual seizures |
seizure semiology all conspire to make the epileptogenic zone much more difficult to localize than in temporal lobe epilepsy. In extratemporal epilepsy, both the interictal zone and the ictal onset zone on scalp-EEG are usually widespread or ill-defined due to rapid propagation of epileptic activity among extensive intra- and interlobar epileptic networks (43). Therefore, intracranial EEG studies are still necessary to localize the epileptogenic zone in most patients. However, prolonged scalp-video EEG may provide inadequate data for the accurate placement of the subdural grid electrodes such that they completely cover the putative epileptogenic zone (44). In addition, since the extratemporal epileptic zone is not infrequently located adjacent to eloquent cortex, accurate functional mapping also is essential for surgical planning (39,41,45–47). For these reasons, the surgical outcome for extratemporal epilepsy is worse than that for temporal lobe epilepsy (48).

MEG has proven exceptionally valuable in localizing the epileptogenic zone in surgical candidates with complex extratemporal localization-related epilepsy. A number of MEG studies have shown excellent agreement between interictal MEG spike source localizations and the localization of the epileptogenic zone as demonstrated by ictal intracranial EEG recordings in this group of patients (6,34,35,37,39–42,47,49–57).

Recently, a cluster of MEG spike sources, defined as more than six spike sources with 4 mm distance between spike sources, was shown to co-localize to the epileptogenic zone in patients with extratemporal localization-related epilepsy (57). Hence, the presence of clustered MEG spike sources on MSI will improve the chances of the correct placement of intracranial electrodes significantly.

**Use of MEG in Lesional Epilepsy**

Successful surgical treatment of lesional epilepsy requires that the lesion be removed and that the epileptogenic tissue be removed or disconnected (58). For greater precision, either intra- or extraoperative subdural ECoG recordings may be used to guide surgical resection of both the lesion and epileptogenic zone (59–61).

MSI provides spatial anatomic data relative to the anatomic localization of the lesion, the epileptogenic zone, and eloquent cortex in patients with lesional extratemporal epilepsy (62). For example, in lesional epilepsy secondary to brain tumor, the MEG spike sources have been shown to be asymmetrically localized to the lesion as delineated on MSI (42). The complete resection of both tumor and marginal extrinsic epileptic discharges resulted in a favorable outcome in patients regardless of residual postexcisional extramarginal spikes (42,59).

In contrast to brain tumors, cortical dysplasias (CDs) show intrinsic clusters of MEG spike sources both within and extending from the lesion as demonstrated on MRI (42,63). CD with balloon cells (BC) demonstrated high signal intensity of fluid-attenuated inversion recovery (FLAIR) MRI (64). However, the ictal onset came mainly from cortical areas of CD without BC, and none of seizures originated from the neocortical areas of CD with BC (65). The brain region containing BC was less epileptogenic than adjacent dysplastic regions without BC. In order to control the seizures in patients with CDs, therefore, it is necessary to define and resect the epileptogenic area in CD. Further studies are needed to understand the epileptic network in CD. Such studies will have to take into account characteristics of the MEG spike sources, the MRI features of the CD, the localization and morphology of intracranial EEG discharges, the histopathology of the CD, and the surgical outcome.
Use of MEG in Temporal Lobe Epilepsy

MEG is not as accurate in the delineation of the precise anatomic localization of interictal discharges in mesial temporal lobe epilepsy as it is in extratemporal epilepsy. The reason is the decreased magnetic field in the temporal lobe, the spiral shape of the hippocampus, and the closed circuitry of the hippocampus and parahippocampal gyrus, all of which make it difficult to detect an aberrant magnetic field from deep and mesial temporal structures by recording from MEG sensors that are located at the lateral temporal convexity. However, in spite of this limitation, MEG can differentiate between mesial, lateral, and diffusely involved temporal lobe onsets in mesial temporal lobe epilepsy (66–68).

In temporal lobe epilepsy there are three MEG dipole patterns that correlate with the localization of the ictal onset zone as defined by intracranial EEG recordings (66–68).

The anterior temporal horizontal dipole is associated with hippocampal atrophy and mesial temporal lobe seizure onsets and appears to be generated by activation of the cortex of the temporal tip (Fig. 1A).

The anterior temporal vertical dipole is correlated with anterior and perhaps mesial temporal lobe seizure onsets and is activated by cortex of the anterior superior temporal plane (Fig. 1B).

The posterior temporal vertical dipole corresponds to a lateral localized or nonlocalized seizure onset and is activated by cortex of the posterior superior temporal plane.

MEG has been demonstrated to be predictive of surgical outcome in mesial temporal epilepsy. MEG was performed before and after anterior temporal lobectomy with amygdal hippocampectomy in patients with hippocampal sclerosis (69). Anterior temporal MEG spike localization was defined as more than 70% of spikes localized to the anterior temporal lobe. Following surgery, all patients with anterior temporal MEG spike localization became seizure-free and postoperative MEG spike free. In those patients with nonanterior temporal MEG spike localization, the surgical outcome was less favorable and inconsistent residual postoperative MEG spike sources were noted to occur. Nonanterior MEG spike localization has been defined as either nonmesial temporal lobe or spike propagation to the posterior and extratemporal

![Figure 1](https://example.com/figure1)

Figure 1 Three types of MEG spike sources in temporal lobe epilepsy. (A) Anterior temporal horizontal dipoles. (B) Anterior temporal vertical dipoles. (C) Basal temporal vertical dipoles.
regions. However, in lesional neocortical temporal lobe epilepsy, MEG spike sources accurately localize to the margin of the lesion.

Basal temporal vertical dipoles have been localized precisely in the absence of hippocampal involvement (14,70). In the basal temporal region, the orientation of cortical neurons is tangential to the scalp surface (Fig. 1C). Therefore, epileptic discharges in the fusiform and inferior temporal gyri provide accurate MEG spike source localization which has been confirmed by simultaneous intracranial EEG recordings.

The localization of low-frequency magnetic activity (LFMA) of the abnormal temporal lobe slow waves with frequency lower than 7 Hz has been compared to MEG spike source localization in mesial temporal lobe epilepsy (71). The lateralization of LFMA and MEG spike waves was concordant to the resected epileptogenic mesial temporal site in 58% of 29 patients. Therefore, concomitant analysis of interictal LFMA and MEG spike sources improves the diagnostic utility of MEG in mesial temporal lobe epilepsy.

Use of MEG in Children with Complex Epilepsy Syndromes

In contrast to adults where the most common cause of refractory seizures is mesial temporal lobe epilepsy, refractory seizure disorders in children are more often associated with extratemporal localization-related epilepsy (33,72). Therefore, in children with extratemporal epilepsy with all of its complex semiological and electrographic manifestations, MEG is particularly promising in the anatomic localization of both the primary epileptic zone and eloquent cortex prior to epilepsy surgery (41,42).

The logistics of performing an MEG in a child can be daunting and require experienced EEG technologists to obtain a successful study. At the Hospital for Sick Children MEG facility, parents are allowed to remain in the magnetically shielded room with their child for the MEG study, but are instructed to restrict movements and noise during testing. Instructions are given to the child to lie very still and to minimize eye movements (73). Children who are unable to cooperate because of age and/or limited cognitive ability are intubated and sedated with low-dose propofol and remifentanil for MEG and following MRI. Patients are carefully monitored from outside the shielded room by the anesthesiologist. Another problem in pediatric MEG is the small head size of the patient which results in a space between the scalp and the sensor coils. The result can be spatial localization errors because of declining magnetic fields. This error will be present to a greater degree in infants where a special effort should be made to shift the head closer to the recording site.

MEG has proven useful in the diagnosis of children with complex epilepsy syndromes and the selection of candidates with those syndromes for epilepsy surgery. For example, periorbital-sylvian epileptic syndromes are commonly seen in children where MEG may provide valuable spike source localizations to differentiate them.

**MEG IN BENIGN ROLANDIC EPILEPSY**

Benign Rolandic epilepsy (BRE) is characterized by infrequent nocturnal seizures, normal intelligence, and centrotemporal spikes seen on EEG (74). However, some (75,76) have reported the occurrence of frequent seizures and neurological deficits, while others (77) have found that patients with Rolandic spikes had more neuropsychological,
intellectual, and behavioral difficulties than age-matched control subjects. The symptoms of BRE patients with speech disturbance have been shown to strongly resemble Landau–Kleffner syndrome (LKS) (78). BRE and LKS are both characterized by epileptiform activity in the centrotemporal region. MEG study of patients with BRE showed consistent MEG spike sources in the anterior and posterior banks of inferior Rolandic fissure close to the somatosensory evoked responses (Fig. 2A) (79).

MEG IN LANDAU–KLEFFNER SYNDROME

Children with LKS initially develop normally, but at some time after age three years there is a rapid loss of receptive and expressive language that is manifested as a verbal auditory agnosia (80,81). A defining feature of LKS is that the EEG during slow wave sleep shows a nearly continuous spike-and-wave epileptiform pattern in the absence of clinical seizures. When ECoG abnormalities were observed in the posterior temporal region of Heschl gyrus, the patients improved language after multiple subpial transections over that area (82). MEG spike sources in children with LKS have been localized to the intra- and perisylvian regions, including the primary and associative auditory areas (Fig. 2B) (82–84). The propagation of epileptiform ECDs in LKS appears to be parallel to the sylvian fissure (85).

MEG IN MALIGNANT ROLANDIC-SYLVIAN EPILEPSY

BRE and LKS are forms of childhood epilepsy that share certain characteristics and can be sometimes controlled by medication. However, a subgroup of patients who manifest some of their characteristics do not fit the definitions of either of these two epilepsy syndromes and have been designated “atypical BRE” (86) and “LKS variant.” Using MEG we have defined seven patients with malignant Rolandic-sylvian epilepsy (MRSE), whose clinical, cognitive, and neurophysiological features
were malignant enough to suggest that they needed special attention to localize the epileptogenic zone and more aggressive management. In this group of children with MRSE, the MEG localized clustered and extensive MEG spike sources around the Rolandic-sylvian fissures and distinguished them from the localized spike sources found in BRE or LKS (Fig. 2C) (41).

Ictal MEG Recording

While prolonged scalp video-EEG and intracranial video-EEG studies are useful in localizing the ictal onset zone, short recording MEG studies also have been applied to the capture of focal ictal epileptiform discharges in a limited number of patients with epilepsy (70,87). There have been a few reports describing good agreement between ictal MEG spike source localization and ictal onset zone on intracranial EEG recording (36,70,88–90). The ictal epileptiform discharges provided the superior MEG spike source localization in patients who were selected with frequent or predictable seizures (56,91,92).

Ictal MEG recording would appear to represent the ultimate in the localization of the epileptogenic zone using whole head MEG sensors. However, there are at least two practical problems that put significant constraints on one’s ability to obtain appropriate ictal MEG data. First, the patient must have seizures frequently enough such that at least one event is captured in the magnetically shielded room during the MEG recording. Second, in order to obviate movement artifact, the seizure semiology cannot be characterized by too vigorous a movement and the patient’s head must stay in a fixed position over the ictal period (56,91–93).

Use of MEG for Functional Mapping

The successful outcome from epilepsy surgery is generally defined as a seizure-free state with no imposition of neurological deficit. In order to achieve these twin goals two criteria must be fulfilled. First, precise localization of the epileptogenic zone in the brain is necessary. Second, one must determine the anatomic localization of eloquent cortex that subserves sensory, motor, language, and memory function (33). Therefore the neurosurgeon requires the precise anatomic correlation between the epileptogenic zone and eloquent cortex before surgery. Noninvasive MEG studies are now used routinely in some centers (33) to localize eloquent cortex in patients undergoing epilepsy surgery.

The somatosensory evoked magnetic field (SEF) for median nerve stimulation is now widely accepted as a most reliable method for identifying the primary somatosensory cortex and localization of the central sulcus (94–96). Since the N20m component of SEF reflects the direct neuronal activity of primary sensory cortex, the SEF is generated from the posterior bank of the central sulcus. MEG has been used to define the somatotopic organization of the sensory cortex with identification of each digit, lip and foot (97–100).

The auditory evoked magnetic field (AEF) is used to identify the primary auditory cortex. The prominent components of N100 m around 100 msec after contralateral audio stimulation represents the AEF in the Heschl gyrus in the planum temporale (73,101). Similarly, the visual evoked magnetic field (VEF) is used to localize the primary visual cortex. P100 m at around 100 msec after visual stimulation produces VEFs in the mesial occipital region (102).
MEG can also be used to identify motor cortex. Movement-related cerebral magnetic fields following voluntary finger movement have demonstrated a unique area of motor control (103–107). In addition, desynchronization of MEG rhythm (108) and coherence between MEG and electromyography (EMG) (109) during execution of motor activities, have localized the primary motor cortex.

MEG has been reported to be useful in the lateralization and localization of language in seizure patients (110–113). During MEG recordings patients engaged in a word recognition task have been shown to activate language areas. Excellent agreement has been reported between MEG data and those obtained from Wada testing (114). In addition, there is good correlation between MEG and intraoperative direct cortical mapping in terms of localization of receptive language areas (110–113).

Use of MEG for Neuronavigation Systems

MEG data may be displayed intraoperatively by their integration into neurosurgical guidance systems (105,115–117). The resultant MEG neuronavigation system can provide neurosurgeons with 3D MSI localization, of both the epileptic zone and eloquent cortex, co-registered to the exposed brain surface in the operating room (Fig. 3). The use of the MEG neuronavigation system allows for the intraoperative anatomic identification of the central sulcus by SEF on 3D MSI, a particularly valuable technique in those patients who are possessed of a lesion around the central sulcus (105,115,116). Similarly, MEG spike sources overlaid onto images of the lesion on 3D MSI may direct and demarcate the margins of the epileptogenic zone to be removed (117). The MEG neuronavigation system also has been reported to be

Figure 3  Intraoperative MEG neuronavigation system. (A) Axial T1-weighted MRI demonstrate cyst and MEG spike sources in the left parietal region in a child with partial onset seizures. The cross point of the orthogonal white lines indicate the pointer of the neuronavigation system at the anterior margin of MEG spike sources (closed triangles with tails). (B) Three-dimensional reconstructed MSI synchronous to (A) shows the white bar of the navigation pointer targeting the anterior margin of the cluster of MEG spike sources that are remote from the precentral cortex (dark shaded) which was delineated by SEF on MEG. Numbers indicate electrode numbers on the intraoperative ECoG recording.
useful in the guide placement of intracranial electrodes in order to better completely cover the putative epileptogenic zone, where many MEG spike sources are tightly clustered (57).

CONCLUSION

MEG provides an excellent spatiotemporal resolution of intracranial epileptic and functional activities. MEG and EEG appear to complement each other in the detection and localization of interictal epileptiform discharges, because some spikes can be recorded only on MEG but not on EEG and vice versa (118–120). The combined analysis of whole-head MEG and multichannel EEG with advanced source localization methodology promises to provide both highly accurate localization of the epileptogenic zone and a more precise characterization of epileptic networks. The end result of this noninvasive technology will be a better outcome for all patients, adults and children, who are undergoing epilepsy surgery.

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Chapter 50
Flumazenil PET

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FLUMAZENIL PET—SCIENTIFIC BASIS AND METHODOLOGY

Radiolabeled ligands can be used for the in vivo assessment of neurotransmitter synthesis, density, and transport, as well as neuroreceptor binding in the epileptic brain. Among several neurotransmitter systems that play a role in the pathological mechanism of human epilepsy, the gamma-aminobutyric acid (GABA) system has gained the most attention in positron emission tomography (PET) studies. GABA is the major inhibitory neurotransmitter in the brain, and its action is mediated by GABA_A and GABA_B receptors. The PET tracer [11C]flumazenil (FMZ) (previously known as RO 15–1788, a benzodiazepine antagonist which binds reversibly to the α subunit of GABA_A receptors) can be used to image GABA_A receptor binding (1). As these receptors are primarily expressed on the basal dendrites of most neurons, GABA_A receptor binding is affected (i) by altered neuronal number (e.g., decreased binding in neuronal loss), (ii) as a result of change in receptor density on existing neurons, and/or (iii) by changes in receptor subunit composition leading to altered receptor affinity. In any case, in vivo imaging of GABA_A receptors can be used to investigate altered GABAergic inhibition in human epilepsy, and can localize epileptogenic brain regions more specifically than other methods such as glucose metabolism PET.

FMZ is an excellent PET tracer since it has a high affinity for GABA_A receptors, is not metabolized in the brain, and has low nonspecific binding. In tracer concentrations used for PET scanning, FMZ has no pharmacological effects. However, patients undergoing FMZ PET should not take drugs (such as benzodiazepines) that directly interact with GABA_A receptors. The effects of drugs that result in allosteric interactions with GABA_A receptors have not been well studied. Chronic vigabatrin treatment was associated with decreased cortical and cerebellar GABA_A receptor binding in young children with intractable partial seizures or
infantile spasms (2), but no similar effects were reported in adults (3). Drugs used for sedation during PET scanning (often unavoidable in young children) may also interfere with FMZ binding. However, among commonly used sedatives, pentobarbital was reported to have no significant effects on in vitro FMZ binding (4), while chloral hydrate was found to cause a negligible increase of in vivo FMZ binding in the whole brain of adults with partial epilepsy (5).

In order to obtain absolute measures of brain GABA<sub>A</sub> receptor binding, quantification of FMZ PET images can be performed using a three-compartmental or a simpler two-compartmental model (6,7). Quantification yields parametric images of the volume of distribution (VD) of the tracer in tissue and the ligand influx rate constant (K<sub>i</sub>). VD is a macroparameter incorporating both receptor density (B<sub>max</sub>) and receptor affinity (K<sub>D</sub>), and represents B<sub>max</sub>/K<sub>D</sub>. Direct comparisons of in vivo FMZ binding (VD) using PET with ex vivo binding measured in resected epileptic tissues using [3H]FMZ autoradiography showed that, after correction for partial volume effects, the degree of in vivo FMZ binding correlated well with ex vivo measurements of GABA<sub>A</sub> receptor binding in the epileptogenic hippocampi of patients with medial temporal lobe epilepsy (TLE) (8). However, studies in epileptic neocortex (obtained from resected temporal lobes) showed that decreased in vivo FMZ binding is not necessarily due to decreased GABA<sub>A</sub> receptor density, but may be due to complex changes that include both B<sub>max</sub> and K<sub>D</sub> in different cortical layers. In fact, [3H]FMZ autoradiography studies showed increased B<sub>max</sub> in cortical layers V–VI of spiking cortex, but decreased receptor affinity, which outweighed the increased receptor density such that the net effect was a decrease in VD shown as an area of decreased FMZ uptake on the PET images (9). Thus, altered FMZ binding on PET may be the result of spatial summation of multiple changes in GABA<sub>A</sub> receptor function.

Absolute quantification yielding FMZ VD images requires arterial blood sampling to provide the input function to the brain. However, arterial blood sampling is invasive and eliminating this aspect of the methodology can facilitate more widespread clinical application of FMZ PET scanning, particularly in children. For clinical purposes, reliable identification of focal cortical and subcortical abnormalities can be achieved using FMZ “activity images” that do not require arterial blood sampling. Comparison of focal FMZ abnormalities in patients with cortical epileptic foci showed that summed FMZ activity images obtained between 10 and 20 minutes after tracer injection are in excellent agreement with FMZ VD images, as compared to activity images obtained from earlier (5–10 minutes) or later (15–30 minutes) time frames (10). Thus, FMZ activity images obtained without arterial blood sampling can be used clinically for epilepsy surgery purposes to identify patterns of abnormal FMZ binding.

DECREASED FMZ BINDING AND THE EPILEPTIC FOCUS

Clinical application of FMZ PET in human epilepsy was first introduced in the late 1980s, when focal decreases of FMZ binding were reported in epileptogenic regions of 10 adult patients with partial epilepsy (11). Since then, clinical use of FMZ PET has been explored in temporal, extratemporal, and primary generalized epilepsies. Most of the FMZ PET studies were done in the setting of presurgical evaluation, and have relied on a region of interest (ROI) analytic approach or applied asymmetry measures explicitly addressing focal decreases of FMZ binding.
FMZ PET in Temporal Lobe Epilepsy

Several studies demonstrated that decreased FMZ binding is very common in the sclerotic hippocampus of patients with medial TLE (12–17). One of the important clinical issues is whether FMZ PET is superior to fluorodeoxyglucose (FDG) PET in accurately localizing the temporal epileptic focus. However, direct comparisons to address this issue have been surprisingly scarce. One study concluded that neither of these two methods is superb, but the number of patients with intracranial electroencephalographic (EEG) comparisons and surgical outcome (the gold standards of epilepsy surgery) was limited (16). In contrast, other studies agreed that FMZ PET abnormalities are usually more confined to the electrophysiologically abnormal regions than areas with abnormal FDG uptake; thus, FMZ PET scanning may be helpful when glucose hypometabolism is extensive and goes beyond the presumed temporal epileptic focus (12,17,18).

The question remained whether localized FMZ binding decreases in the temporal lobe represent purely neuronal loss or may also indicate dysfunctional epileptic areas with abnormal GABA_A receptor function. The findings have been somewhat controversial in this regard. Burdette et al. (19) reported a high correlation between FMZ binding decreases and neuronal loss. In contrast, Koepp et al. (15) demonstrated that, after applying correction for partial volume effects, the degree of decreased FMZ binding did not correlate and was over and above the severity of the hippocampal cell loss. This latter finding suggested that FMZ PET may be useful in patients where magnetic resonance imaging (MRI) volumetry does not show obvious hippocampal atrophy, but electroclinical findings suggest TLE (Fig. 1A). Subsequent studies of patients with TLE but normal hippocampal volumes, however, have demonstrated conflicting results. For example, transient and falsely lateralizing FMZ PET asymmetries have been reported in three patients with normal hippocampal MRI (20). A subsequent study reported abnormally decreased temporal FMZ binding in five of seven TLE patients with normal hippocampal MRI volumetry; the FMZ abnormalities occurred ipsilateral to the seizure focus in three of these cases (21). Histological examination verified the presence of hippocampal damage in these unilateral cases suggesting that FMZ PET can be useful to lateralize the epileptic temporal lobe in some (but not all) TLE patients with normal MRI. Using a more complex analytic method [by combining voxel-by-voxel statistical comparison using statistical parametric mapping (SPM) (22) and an MRI-based volume-of-interest approach with partial volume correction] in a similar group of MRI-negative TLE patients, Koepp et al. (23) found focal abnormalities of FMZ binding in 80% of the cases. However, these abnormalities did not consistently localize the epileptic focus. Altogether, these studies demonstrated a high prevalence of focal FMZ binding abnormalities in TLE patients with normal MRI, but at this point it remains unclear how these PET changes contribute to the presurgical localization of temporal lobe epileptic foci when MRI is normal.

Since decreased FMZ binding in pure medial TLE is largely (although not completely) confined to the affected temporal lobe, FMZ PET can be helpful in patients where a temporal lobe focus is suspected but other imaging modalities (e.g., FDG PET) raise the possibility of extratemporal involvement (Fig. 1B). If extratemporal decreases coexist on FMZ PET, they may indicate an independent seizure focus, a remote cortical abnormality (e.g., microdysgenesis) with or without epileptogenicity, or even a functional abnormality of GABA_A receptors that has the potential to normalize after the primary seizure focus is eliminated. This latter option has been supported by a small study that reported normalization of decreased FMZ
binding in remote cortical areas following successful temporal lobectomy in four patients (24). These findings, however, are yet to be replicated.

FMZ PET can be a useful imaging method when a potentially epileptogenic cortical lesion is suspected to be associated with hippocampal sclerosis, a phenomenon referred to as dual pathology. In such cases, if the hippocampal abnormality is mild, it could be overlooked by MRI or even FDG PET. Unrevealed dual pathology is a potential source of failed epilepsy surgery since the optimal surgical approach is to remove both the cortical lesion and the sclerotic hippocampus in these patients (25). FMZ PET can be particularly useful in such patients since it is highly sensitive in detection of subtle hippocampal abnormalities in addition to detecting the cortical epileptogenic lesion as well as perilesional epileptogenic cortex (26,27). In some cases, FMZ PET can detect multiple areas of decreased binding including both the hippocampus and neocortical areas that do not show any obvious lesion on MRI. Such findings may warrant intracranial EEG recording to determine whether both the hippocampal and neocortical areas are epileptogenic.

Figure 1  FMZ PET (A) in a 21-year-old woman with right temporal lobe epilepsy and normal MRI. Hippocampal and amygdala volumetry as well as fluid-attenuated recovery (FLAIR) images were all normal. Scalp-recorded EEG showed nonlateralizing seizure onset but postictal slowing occurred in the right temporal region consistently. Interictal EEG and seizure semiology also suggested a right temporal lobe focus. The FMZ PET scan showed a marked decrease of FMZ binding in the right medial temporal structures as well as a mild decrease in the right thalamus (arrows). FDG PET (B) also lateralized the focus to the right side but showed a considerably larger area of decreased glucose metabolism involving the right inferior and superior temporal cortex as well as the right frontal lobe. The patient underwent right temporal lobectomy and became seizure-free.
Decreased FMZ Binding in Neocortical Epilepsy

As current surgical results remain suboptimal in extratemporal (neocortical) epilepsies, there has been a great deal of interest in applying FMZ PET in the presurgical evaluation of such patients. To determine the electrophysiological significance of abnormal FMZ binding, findings from intracranial EEG electrodes were compared to those from FMZ PET. In such comparisons, FMZ PET appears to have 57% to 100% sensitivity in detecting neocortical epileptic foci (17,28–30). This large variation may be attributed to the heterogeneous patient populations and application of different analytic approaches. In a detailed comparison of objectively defined, surface-rendered FDG, and FMZ PET abnormalities (using an asymmetry-based approach) and intracranial EEG data, Muzik et al. (30) found areas of decreased FMZ binding to be significantly more sensitive for detecting zones of seizure onset and frequent interictal spiking than areas of glucose hypometabolism.

A close spatial relationship between seizure onset zones and the area showing reduced FMZ binding also has been reported in two patients with frontal lobe epilepsy associated with cortical dysplasia (31). Although these findings are based on a limited number of patients, they nevertheless suggest that FMZ PET is a useful clinical tool which can potentially further delineate epileptogenic neocortex to guide subdural electrode coverage for intracranial EEG monitoring. This concept has been also supported by a subsequent study demonstrating that complete resection of cortex with preoperative FMZ PET abnormalities is associated with excellent surgical outcome even in the absence of a structural lesion on MRI (32).

It has been increasingly recognized that areas of decreased FMZ binding often occur in cortical and subcortical regions remote from the primary epileptic focus. Comparisons of FMZ PET findings with outcome data have indicated that resection of such remote cortical FMZ abnormalities is not always necessary to achieve long-term seizure freedom (provided that the primary seizure focus has been removed), although many of these areas appear to be targeted by rapid seizure spread as shown by intracranial ictal EEG recordings (29). Furthermore, in patients with lesional epilepsy, many of these remote cortical areas with decreased FMZ binding were located in ipsilateral synaptically connected regions, and were associated with seizure onset early in life and long duration of intractable epilepsy (27). Altogether, these data suggest that cortical areas with decreased FMZ binding, particularly if located in projection areas targeted by seizure propagation, may be related to repeated seizures over a relatively long period, and might represent potential areas of secondary epileptogenesis. This, however, remains to be a controversial issue that requires further studies (see also section “Future Directions” below). In patients with neocortical epilepsy associated with a brain lesion, decreased FMZ binding commonly extends to the perilesional cortex (27,31,33). Perilesional FMZ PET abnormalities are often eccentric, and show a good correspondence with epileptiform activity on intracranial EEG. Thus, FMZ PET may assist tailored resection if an epileptogenic lesion is located close to motor or language cortex.

POTENTIAL SIGNIFICANCE OF INCREASED FMZ BINDING
AND WHITE MATTER ABNORMALITIES

Most FMZ PET studies that have applied a ROI based analysis approach or relied on asymmetry measurements did not address potential focal increases or white...
matter changes of GABA<sub>A</sub> receptor binding. Asymmetry-based analyses also would not be able to detect symmetrical bilateral changes. In contrast, application of a voxel-by-voxel approach using SPM has allowed objective identification of both focal decreases and increases of FMZ binding in patients with epilepsy. Using this approach, Richardson et al. (34) reported increases (in addition to decreases) of FMZ VD in two-thirds of patients with cortical dysgenesis detected by MRI. The FMZ abnormalities were often more extensive than corresponding structural lesions seen on MRI. In subsequent voxel-by-voxel FMZ PET studies, researchers from the same group reported variable increases of FMZ VD in the neocortex and hippocampus, as well as in the temporal and frontal lobe white matter of patients with temporal lobe epilepsy and normal MRI (23,35). Since GABA<sub>A</sub> receptor density of the normal white matter is low, increased neuronal number in white matter may have accounted for the increased FMZ binding. Thus, FMZ PET may be considered to be an in vivo neuronal marker. Indeed, increased FMZ binding in white matter was found both ipsilateral and contralateral to the presumed epileptic focus or, in some cases, even bilaterally. The authors showed histological evidence of increased neuronal number in the white matter of resected brain tissue, which had shown increased binding on FMZ PET, thus supporting the potential basis for increased GABA<sub>A</sub> receptor density and binding.

In a more recent study, white matter increases of FMZ VD were reported in more than one-third of patients with neocortical epilepsy and normal MRI (36). These increases were often distributed in the periventricular region, suggesting microscopic neuronal migrational disturbances. However, the EEG and clinical correlates of such abnormalities in white matter remain unclear. For example, it is not known whether such increases can potentially affect surgical selection or might predict an unfavorable outcome from epilepsy surgery.

CURRENT ROLE OF FMZ PET IN THE PRESURGICAL EVALUATION OF INTRACTABLE EPILEPSY

On the basis of the findings summarized above, FMZ PET is currently limited to certain subgroups of patients with intractable partial epilepsy who are undergoing presurgical evaluation. In patients with TLE, the use of FMZ PET should be considered on an individual basis. In patients with hippocampal sclerosis, wide availability of advanced MRI techniques has made PET scanning unwarranted in the overwhelming majority of subjects. However, FMZ PET may be helpful and can provide complementary information in TLE patients under some circumstances, for example, when dual pathology is suspected in patients with a potentially epileptogenic lesion, or when the ictal EEG in patients with a presumed medial temporal seizure focus suggests potential involvement of extratemporal structures, or when the FDG PET scan shows abnormalities of glucose metabolism extending beyond the medial and anterior temporal regions. In such cases, presence of decreased FMZ binding in extratemporal regions may support the need for careful evaluation of these neocortical areas as independent epileptic foci. In patients with suspected TLE but normal MRI (including normal hippocampal volumes), FMZ PET can be occasionally helpful by showing decreased binding in lateral or medial temporal lobe regions, but these findings should be carefully integrated with other localizing information, including ictal and interictal EEG findings, seizure semiology, and neuropsychological findings.
Nevertheless, since hippocampal FMZ binding is relatively high in normal individuals, even mild hippocampal asymmetries can be more obvious on FMZ than on FDG PET. Presence of unilaterally decreased thalamic FMZ binding is a strong indicator of an ipsilateral temporal lobe focus (37).

FMZ PET in neocortical epilepsy is mostly reserved for patients with normal MRI in whom seizure semiology and EEG findings do not provide adequate localizing data. In such cases, FDG PET (or, depending on availability, ictal single photon emission computed tomography (SPECT)) is typically performed before FMZ PET is considered. FMZ PET scanning can yield additional localizing information if FDG PET does not delineate a discrete cortical metabolic focus. If FDG PET shows multilobar hypometabolism, FMZ PET will typically show a more circumscribed cortical area that can be reasonably well covered by subdural grid electrodes. Occasionally, FMZ PET may also show areas of abnormality not detected by FDG PET. Therefore, with appropriate selection of patients, FMZ PET deserves to be included among the imaging options in patients with intractable epilepsy.

FUTURE DIRECTIONS

With increasing availability of FMZ PET worldwide, several unresolved issues should be addressed by future studies. In general, more FMZ PET correlations with the gold standard of intracranial ictal EEG findings, and with surgical outcome, are needed. It will be also important to further assess which analytic methods are reliable and most feasible in the clinical setting (Fig. 2). Specifically, the following issues deserve more detailed analysis in future studies.

Relationship Between Decreased FMZ Binding and Intracranial Ictal EEG

Although preliminary studies have shown good sensitivity and specificity of decreased cortical FMZ binding in localization of seizure onset and frequent interictal spiking in neocortical epilepsy, these findings have to be confirmed and extended to a considerably larger patient sample. It remains unclear whether nonepileptiform EEG abnormalities (e.g., focal slowing or background attenuation) are associated with decreased GABA_A receptor binding. It would also be useful to clarify how the relationship between GABA_A receptor abnormalities and epileptiform EEG changes is related to the underlying etiology (e.g., cortical developmental malformations versus acquired lesions).

Significance of FMZ PET Abnormalities Remote from the Primary Epileptic Focus

The clinical and electrophysiological significance of decreased FMZ binding at locations remote from the seizure focus needs to be further clarified. It is not clear whether these areas of decreased FMZ binding can be differentiated from those occurring in and around the epileptic focus. Perhaps combination of FMZ PET with other imaging modalities [e.g., magnetic resonance spectroscopy (MRS) to measure biochemical abnormalities in cortex with decreased FMZ binding] may address this issue. Postoperative FMZ PET scanning in patients who have undergone neocortical resection may determine whether nonresected cortex with preoperative FMZ PET
abnormalities remote from the seizure focus shows recovery of GABA_A receptor binding. It would also be clinically relevant to determine whether such remote abnormalities might be predictive of poor surgical outcome. On the basis of the preliminary data, we suspect that some of these remote FMZ binding abnormalities may be reversible and others may persist after removal of the primary seizure focus. The clinical circumstances related to each of these possibilities should be studied further.

**Significance of Increased Cortical FMZ Binding**

Although the presence of focal increased cortical and white matter FMZ binding has been reported, their electrophysiological correlates and clinical significance in terms of surgery outcome should be established. It is unclear whether presence of bilateral white matter increases (presumably indicating increased number of heterotopic neurons) can predict poor seizure control following unilateral surgical resection.

**Significance of Normal FMZ PET in Patients with Neocortical Epilepsy**

The reason why some patients with intractable partial epilepsy show completely normal FMZ binding while the majority of epileptic foci are associated with decreased GABA_A receptor binding is unclear. Yet, epilepsy is known to occur due to multiple etiologies affecting various mechanisms of neurotransmission. To further address this...
question, it would be worthwhile evaluating whether other, emerging receptor imaging modalities show focal abnormalities in patients with partial epilepsy and normal FMZ PET. Our preliminary studies demonstrated that PET scanning with \( \text{L-\[11C\]} \text{methyl-L-tryptophan (AMT, a tracer for tryptophan metabolism to serotonin or the alternative kynurenine pathway)} \) can show focal neocortical increases of uptake in some patients with extratemporal epilepsy and normal FMZ PET, while others can have decreased cortical FMZ binding and normal AMT PET (38). In other words, either FMZ PET or AMT PET could be abnormal, but it is rare that both modalities show focal abnormalities (FMZ decreases together with AMT increases) in the same epileptic brain. This study, however, included a limited number of patients, and requires further confirmation. Similar studies can be done using other neuroreceptor and transmitter imaging modalities to better understand which of these approaches are best suited for localization of epileptic foci in various epilepsy syndromes.

**Value of FMZ PET in Temporal Lobe Epilepsy and Normal MRI**

As discussed above, the currently available data are controversial regarding the clinical value of FMZ PET in TLE patients who have normal quantitative MRI. Since such patients are not uncommon in adult epilepsy surgery centers, further studies are warranted to determine whether these patients might benefit from FMZ PET as part of their presurgical evaluation and whether removal of regions with FMZ binding abnormalities is related to surgical outcome.

**Comparisons of FMZ PET Findings with Other Neuroimaging and In Vitro Tissue Findings**

Further comparisons of FMZ PET data with information from various other functional imaging modalities, such as functional MRI, magnetic resonance spectroscopy using high magnetic field (to measure GABA or glutamate peaks), or magnetic source imaging may help to further understand the significance of in vivo GABA\textsubscript{A} receptor abnormalities in the pathophysiology of human partial epilepsy. Finally, more detailed comparisons of in vivo findings with in vitro data from resected epileptic tissues may help to better understand the pathophysiological basis of decreased and increased GABA\textsubscript{A} receptor binding in and around the epileptic focus.

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Flumazenil PET


Chapter 51
Optical Imaging of Human Neocortical Epilepsy

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INTRODUCTION

Approximately two million people in the United States have epilepsy, and 20% to 30% of this population is refractory to all forms of medical treatment (1). The best viable treatment for patients suffering from medically intractable epilepsy, which allows the possibility of becoming seizure-free, is the surgical resection of the epileptogenic tissue. The surgical outcomes of patients suffering from neocortical epilepsy are not as successful as the surgical outcomes from resections of mesial temporal sclerosis (most common in adults). The main difficulty in the treatment of neocortical epilepsy is in the localization of the tissue responsible for the generation and spread of seizure activity with current technology. Increasing the accuracy of the localization of epileptogenic tissue in the human neocortex will require new methods, and we have applied a new optical imaging method for the intraoperative mapping of neocortical epileptic tissue in patients undergoing surgical treatment.

The optical scattering and absorption properties of brain tissue are dynamic, and vary as a function of neuronal activity (2,3). These activity-evoked optical changes are known as “intrinsic optical signals” (IOS), and can provide high-resolution maps of functional and pathological brain areas in humans (4–6). The IOS in brain tissue is thought to be generated in large part by changes in blood volume and blood oxygenation (7,8). Our preliminary data suggest that by selecting the appropriate optical wavelengths, IOS-imaging (IIOS) is capable of monitoring each of these physiological components (i.e., blood volume vs. blood oxygenation) independently. Compared to other brain-mapping modalities, IIOS is inexpensive, can provide significantly greater spatial and temporal resolutions, and is capable of on-line intraoperative imaging. Consequently, IIOS has the potential to become a
powerful and widely applicable tool for the intraoperative surgical treatment of neocortical epilepsy. However, IIOS techniques have remained of limited clinical use since there has been no significant effort to determine how well IIOS data correlate with standard methods used to localize epileptogenic foci and their pathways of propagation. The intraoperative optical imaging findings will also be of significant value beyond the specific findings, in that they will contribute to the interpretation of data acquired by other modalities (positron emission tomography, PET; single photon emission computed tomography, SPECT; and blood oxygen level dependent functional magnetic resonance imaging, BOLD fMRI) that rely upon hemodynamic and metabolic measurements in their attempts to diagnose and localize epileptiform activity (9).

IIOS IN THE NEOCORTEX

Our previous human study showed that intraoperative IIOS was able to provide dynamic maps of functional and epileptiform activity in neocortex, with micron-level spatial resolution, but with poor temporal resolution (1–4 sec/image) (4). Recent advances in charge coupled device (CCD) camera and computer technology, and advances in algorithms for improved data analysis [developed by Data Warehouse (DWH)] has made it possible to assemble an IIOS system that provides dramatically greater sensitivity and temporal resolution. Our preliminary in vivo studies from rat, monkey, and human somatosensory cortices show that, by using updated technology and improved data analysis algorithms, it is possible to reliably measure activity-related light scattering changes that have a magnitude of $<0.01\%$ at a rate of 100 to 200 msec/image (10).

Subsequent to our 1992 human IIOS publication, there has been relatively little published work on using IIOS to study normal activity in primates and humans, and none on using IIOS for studying epileptiform activity in humans (11–15). One of the major problems presently limiting the use of in vivo IIOS is the difficulty in interpreting the data acquired with this technique. For example, it is known that changes in blood oxygenation and blood volume contribute to activity-evoked changes in the optical properties of neuronal tissue (3,7). This is consistent with PET and fMRI data suggesting that there are dramatic changes in these hemodynamic parameters associated with cortical activation (8,16). In order to understand how these issues are related to the interpretation of IIOS data, it is necessary to consider the optical absorbance spectra of deoxygenated hemoglobin (Hb) and oxygenated hemoglobin (HbO$_2$) shown in Figure 1.

The graph on the left 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 wavelength), and since they are plotted logarithmically, subtle features are difficult to distinguish. By replotting these data on the right as a single graph of the absolute differences between Hb and HbO$_2$ optical absorbance, several features of these spectra are emphasized. First, there are several “isobestic points”—wavelengths at which the absorbance of both Hb and HbO$_2$ are indistinguishable (e.g., 535 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 a consequence of the Beer–Lambert law), isobestic points represent ideal wavelengths at which 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 right-hand graph touches the x-axis). Second, there are wavelengths at which Hb and HbO\textsubscript{2} are maximally distinguishable (660 and \textgreater 3900 nm). Consequently, these “oxygen-sensitive” wavelengths are ideal for optically monitoring changes in blood oxygenation. These oxygen-sensitive wavelengths are represented in the right-hand plot as points having a maximal value.

**ACTIVITY-EVOKED CHANGES IN CORTICAL HEMODYNAMICS AND CORRELATIVE IIOs CHANGES**

Two major hemodynamic changes are evoked by increases in neuronal activity: (i) localized increases in blood volume and (ii) increases in blood oxygenation in the veins draining regions of activated cortex (8,16,17). The cascade of events leading to these activity-evoked hemodynamic changes is thought to be as follows: (a) firing of action potentials induce a release of signaling molecules that cause small surface arterioles to dilate, (b) the dilation of arterioles is strictly localized over areas of increased neuronal activity and underlies the focal increases in blood volume, (c) blood flow increases dramatically, since flow is related to the fourth power of vessel diameter (18), and (d) large increases in blood oxygenation occur in the veins draining activated tissue since the transit time of hemoglobin in the tissue is dramatically reduced by the increased flow (17,19,20). The activity-induced changes in cerebral flow are facilitated by dilation of the terminal ramifications of the smallest pial arterioles lying on the cortical surface; the larger arterioles and veins do not dilate and hence do not play a role in the regulation of activity-evoked changes in cerebral flow (17,19,20). Therefore, changes in blood volume are highly localized in both space and time to areas of firing neurons.

The optical and physiological considerations presented above show the direct optical approach for dissociation of blood volume from blood oxygenation changes. The preceding explanations suggest that activity-evoked optical changes at specific
wavelengths are generated by and localized to distinct vascular compartments. IIOS data acquired at the isobestic points (535 nm) described above should be sensitive to blood volume changes and relatively independent from blood oxygenation changes. Since the small pial arterioles are the only vascular compartments that dilate during neuronal activity, optical changes should be restricted to these microscopic vessels. In contrast, blood oxygen changes should be predominant at oxygen-sensitive wavelengths (660 nm), and be restricted to the venous network draining the activated tissue. Indeed, these vascular-specific hemodynamic changes have been confirmed in our recent studies on the physiological mechanisms responsible for generating optical changes in neocortex (21,22).

One obvious limitation of the IIOS technique is that it only provides information about the cortical surface (more accurately, it can be said that IIOS integrates changes occurring throughout the entire gray matter; see Ref. 7). Given the major role that the pial arterioles lying on the cortical surface play in regulating cerebral flow, and the organization of neuronal cell bodies within the cortex, we believe that this is not a serious limitation of IIOS for mapping seizure foci and hemodynamic changes associated with neocortical epileptiform activity (23). Our technical improvements to the IIOS technique have allowed us to gain precise information regarding the changes in blood volume and blood oxygenation within specific vascular compartments with high temporal resolution (10). Here we apply these improvements to the problem of accurately mapping neocortical seizures.

OUTLINE OF METHODS OF OPTICAL IMAGING OF INTRINSIC SIGNALS AT TWO DIFFERENT WAVELENGTHS

For illumination of the cortical surface, four fiber optic lights regulated by a stable DC power supply are filtered with bandpass filters (±10 nm) at the following wavelengths: 530 nm (specific for blood volume changes) and 660 nm (specific for blood oxygenation changes) (22). Images were acquired with a high-quality, cooled, digital CCD camera (Roper Scientific’s PentaMax) with a dynamic range of 12 bits. The cortex was stabilized with a glass footplate (4). Images were acquired at a rate of 5 to 10 images/sec, allowing for an integration time of 100 to 200 msec/image. The camera and data acquisition were controlled with MetaMorph (Universal Imaging Corporation) and WinView (Princeton Instruments) software. Data analysis was performed using commercial software packages and specialized software written by DWH.

OPTICAL IMAGING OF INTERICTAL AND ICTAL ACTIVITY

Activity-evoked blood oxygenation changes and blood volume changes can be identified with optical imaging (21–23). We have done preliminary studies of IIOS changes in comparison to the changes in neuronal activity in nonhuman primates, since “detailed” correlative electrophysiological measurements (i.e., single unit and field recordings) are not possible to acquire in human patients. These studies have allowed us to perform a careful correlation between neuronal activity and the optical signals, where correlative single unit microelectrode recordings could simultaneously be obtained (21,22).

In this single example, a patient with focal motor seizures experienced intermittent seizure activity from the mouth/tongue area. The onset and cessation of each
seizure episode was identified by direct observation of tongue movement in this patient during an awake craniotomy. Each seizure episode lasted 20 to 30 seconds and then became quiescent for another one to two minutes. Stimulation mapping showed the exact location of the tongue motor and sensory cortex (Fig. 2A). During the focal motor seizure activity, we were able to perform IIOS of both the blood volume (Fig. 2B) and blood oxygenation changes (Fig. 2C). The IIOS of blood volume showed the largest changes highly localized at precisely the tongue motor cortex and the site of the seizure focus. The blood oxygenation changes were more diffuse and preferentially found in the surrounding draining veins (23).

**RATIONALE BEHIND THE INTRAOPERATIVE USE OF OPTICAL IMAGING FOR NEOCORTICAL EPILEPSY**

One of the only available treatments for patients suffering from medically intractable epilepsy is surgical resection of the epileptogenic tissue. It is estimated that currently 500,000 patients with intractable epilepsy are surgical candidates in the United States and 5000 to 10,000 new surgical candidates are added each year. However, due to limited resources and the costs and difficulties associated with surgical treatment, only 1000 to 2000 surgical resections are performed each year (1). In particular, neocortical epilepsy is one of the most difficult, as well as most resource intensive, epilepsy disorders to treat surgically (24–26). The main difficulty in the treatment of neocortical epilepsy is the localization of tissue responsible for the generation and spread of the seizure. This includes the identification of the epileptogenic focus, the pathways of spread across the neocortex, and the amount of neocortical tissue that needs to be surgically removed to cure the patient’s epilepsy (24–26). Even when...
all existing mapping technologies (i.e., PET, SPECT, MRI) are used to identify neocortical epilepsy, the outcomes are only half as good as the surgical outcomes from resections of mesial temporal sclerosis (33% seizure-free vs. 67–85% seizure-free, respectively) (24–26). A recent multicenter study showed an improved neocortical resection seizure-free rate of 56% at one year, but this was still far behind the 77% seizure-free rate for mesial temporal lobe resections (27).

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 (25,26). Ideally, the neurosurgeon would like to accurately map areas of cortex committed to 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 (28). Over one-third 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 (28).

CURRENT STATE OF THE ART FOR MAPPING EPILEPTIFORM ACTIVITY

Present techniques that provide partial information for the localization of seizure foci include electroencephalography (EEG), MRI, PET, and SPECT (29,30). However, because of their limited spatial or temporal resolutions, all of these methods are limited in their ability to “pinpoint” epileptogenic tissue interictally. EEG is useful mostly for diagnostic purposes, and in most cases, intracranial EEG is the gold standard for providing lateralization and localization information in patients with neocortical epilepsy (31). Although EEG techniques provide good temporal resolution, even intracranial EEG is of limited spatial resolution and can provide misleading information regarding seizure localization if the epileptogenic zone is not properly covered with recording electrodes. For example, epileptiform activity might be initiated at a distance away from the recording site and spread rapidly to the EEG electrodes, thus falsely appearing to originate at the EEG electrode. In some cases, PET and SPECT can provide approximate localization information. The slow temporal resolutions of PET and SPECT further reduce their spatial accuracies; during interictal and ictal activity, sites where the epileptiform activity is initiated are averaged together with the paths of propagation, thus “smearing” spatial information (8,30,32,33).

Current treatment for intractable neocortical epilepsy usually involves two surgeries: the first for the implantation of a subdural electrode array, and after one week of extraoperative monitoring of the implanted electrode array for localization of the ictal onset zone and pathways of seizure propagation, a second surgery for removal of the grid array and the definitive resection of the putative epileptic focus. The extraoperative monitoring is prolonged, for 7 to 10 days the patient tied to the bed by the recording electrodes; costly, accounting for one-third the total cost of the whole surgical treatment; time consuming, one week or more with a family member present nearly 24 hours a day; and introduces the risk of serious complications such as infection, up to a 10% chance, with the potential loss of the bone flap. The goal of applying optical imaging for intraoperative mapping is the potential to entirely eliminate the need for monitoring with subdural electrode arrays, thus
eliminating the need for two surgical procedures since only one would be necessary; all mapping could be accomplished at the time of a single surgical procedure. A second benefit potential of intraoperative optical imaging would be the dramatic reduction in the amount of cortical tissue removed during the surgical resection. It is currently typical to remove approximately 10 to 16 cm² area of neocortex and sometimes much more. Our preliminary optical imaging data suggests that seizure foci can be localized to areas often <1 cm² (see Fig. 2B). By correlating the intraoperative optical imaging maps with the areas of surgically resected tissue and patient outcome, we might determine that it is sufficient to remove smaller areas of tissue to treat patients with intractable neocortical epilepsy.

**Potential New Imaging Technique for Intraoperative Localization of Neocortical Epileptic Focus**

In conclusion, there are several steps in the surgical treatment of intractable neocortical epilepsy that could be eliminated, or whose time could be dramatically reduced. First, the need to map sites of seizure onset with subdural electrode arrays could be eliminated. This would eliminate both the need to perform the two surgical craniotomies, and the need for prolonged inpatient monitoring and its inherent risks. Second, the intraoperative time for EEG monitoring during the “only” single surgical procedure could be dramatically reduced. Finally, the amount of the neocortex removed during the resection could be significantly reduced, if as our preliminary data suggest, optical mapping provides considerably more accurate localization of the epileptogenic focus and the pathways of seizure propagation.

**REFERENCES**

Chapter 52
Radiosurgery for Intractable Epilepsy

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INTRODUCTION

There is a growing interest in the use of radiosurgery in epilepsy. Our clinical experience (106 patients), accumulated over the last 10 years, mainly includes treatment of mesial temporal lobe epilepsy without space occupying lesions (62 patients) and hypothalamic hamartomas (38 patients). The analysis of our material, as well as other clinical and experimental data, suggests that the use of radiosurgery is beneficial only to those patients in whom strict preoperative definition of the extent of the epileptogenic zone (or network) has been achieved, and where strict rules of dose planning have been followed. As soon as these principles are not observed, the risk of treatment failure and/or side effects increases dramatically. At present, the long-term results after functional radiosurgery procedures remain to be documented. The current indications for radiosurgical treatment of epilepsy and expected outcomes are discussed.

RATIONALE

There are convincing arguments for investigating the potential role of radiosurgery in epilepsy surgery. We know that:

1. Radiosurgery (since its introduction in the 1950s) has been demonstrated to have advantages in terms of safety and efficacy, for the treatment of numerous small, deeply seated intracerebral lesions.
2. Radiosurgical treatment of small cortico-subcortical lesions associated with epilepsy has been demonstrated to lead to seizure cessation in a high percentage (58-80% in arteriovenous malformation) of cases, long before the expected treatment of the lesion and sometimes even in spite of failing to cure the lesion itself.
3. Radiotherapeutic treatment of epilepsies with or without space occupying lesions can lead to a reduction in seizure frequency and/or severity.
4. Experimental models of epilepsies treated with radiation therapy have demonstrated a dose-dependent positive effect of radiation on the frequency and severity of the seizures, and on the extent of discharge propagation.

Leksell (1,2) conceived gamma knife (GK) radiosurgery as a tool for functional neurosurgery. Accordingly, he used GK in movement disorders and trigeminal neuralgia and other pain syndromes, but not for epilepsy surgery (3). The first radiosurgical treatments for epilepsy surgery were performed by Talairach et al. (4) in the 1950s. Unlike Leksell, he had specific involvement in epilepsy surgery and led one of the first large comprehensive programs for epilepsy surgery. As early as 1974, he reported on the use of radioactive Yttrium implants in patients with mesial temporal lobe epilepsy (MTLE) without space occupying lesions, and showed a high rate of seizure control in patients with epilepsies confined to the mesial structures of the temporal lobe (5). In 1980, Elomaa (6), apparently ignoring the pioneer work of Talairach, promoted the idea of the use of focal irradiation for the treatment of temporal lobe epilepsy, based on the preliminary reports of Tracy, Von Wieser and Baudouin (7,8). Furthermore, clinical experience of the use of GK- and Linac-based radiosurgery in arteriovenous malformations (AVMs) and cortico-subcortical tumors (mostly metastases and low-grade glial tumors) revealed an antiepileptic effect of radiosurgery in the absence of necrotizing effect (9–11). A series of experimental studies in small animals confirmed this effect and has emphasized its relationship to the dose delivered (12–17). Barcia Salorio et al. (18), and later Lindquist et al. (19–21), reported small and heterogeneous groups of patients treated with the aim of seizure cessation, but results were poor, and these data were never published in peer-reviewed papers (18–21).

The two major fields of expertise of the Department of Stereotactic and Functional Surgery in Marseille are epilepsy surgery and radiosurgery, which has facilitated investigation and development of GK radiosurgery in the treatment of intractable epilepsy. Since 1993, we have performed 106 cases of epilepsy surgery using GK radiosurgery. The majority of these patients presented with MTLE (62 patients) or hypothalamic hamartoma (HH) (38 patients). The rest suffered from severe epilepsy associated with small benign lesions (one ganglioglioma, three dysplasia, one periventricular heterotopia, one cavernous angioma), for which an epileptic zone was considered to be confined to the surrounding cortex (22). In HH, GK radiosurgery offers very low morbidity, with similar efficacy compared with microsurgical alternatives (23,24). This has led us to consider radiosurgery systematically as the first-line treatment in patients with small HH of type I, II, III and possibly type IV (24). In MTLE, on the other hand, in spite of a good short- and middle-term safety–efficacy ratio, the use of GK is still regarded as being an experimental technique, given the well-established long-term safety and efficacy of the microsurgical resection in the temporal lobe (25,26). Since 1994, we have promoted the idea that seizure cessation may be generated by a specific neuromodulatory effect of radiosurgery, without induction of a significant amount of histological necrosis (27–33). The selection of the appropriate technical parameters (dose, volume target, etc.) to accurately obtain the desired functional effect without histological damage, remains an important challenge.

HYPOTHALAMIC HAMARTOMAS

Hypothalamic hamartomas may be asymptomatic, associated with precocious puberty or with neurological disorders (including epilepsy, behavior disturbances,
and cognitive impairment), or both. Usually seizures begin early in life and are often particularly drug-resistant from the outset. The evolution is unfavorable in the majority of the patients because of behavioral symptoms (particularly aggressive behavior) and mental decline, which occur as a direct effect of the seizures, due to an epileptic encephalopathy (34). Interestingly, in our experience, the reversal of this encephalopathy after radiosurgery seems to start even before complete cessation of the seizures and seems to be correlated to the improvement in background electroencephalographic (EEG) activity. It is the authors’ speculation that these continuous discharges lead to the disorganization of several systems, including the limbic system, and that their disappearance accounts for the improvement seen in attention, memory, cognitive performance, and impulsive behavior, etc. Here, the goal of radiosurgery is the reversal of the epileptic encephalopathy more than seizure cessation. Consequently, we consider it to be essential to operate on these young patients as early as possible, whatever the surgical approach considered (resection or radiosurgery).

The intrinsic epileptogenicity of HH has been demonstrated even though the mechanisms of the epilepsy associated with HH are still debatable (35,36). The boundary of the target zone of treatment is that of the lesion visualized on magnetic resonance (MR) imaging. This contrasts greatly with cases of MTLE where there is no such clear delineation of an epileptogenic zone on the images used for planning radiosurgical intervention.

We retrospectively analyzed radiosurgery in a series of 10 patients collected from centers around the world (23). The very good safety–efficacy ratio (all improved, 50% cured and no adverse effects except one case of poikilothermia) led us to organize a prospective multicenter trial. Fifty patients have been included prospectively. Preliminary results so far confirm those of the more limited retrospective study (24). A minimum of two years follow-up after radiosurgical treatment is mandatory before considering a different treatment approach. Data for a more precise model of the relationship between the marginal dose, and the psychiatric, cognitive, hormonal, memory, and seizure outcomes, are also lacking. Since October 1999, 30 patients have already been included in this study, but two more years of follow-up are needed before any final conclusions can be drawn. Because of the very critical location of these lesions, we always try to tailor the dose plan for each patient, based on the use of a single run of shots with the 4 mm collimator. We pay special attention to the dose delivered to the mamillary body and to the fornix.

Patient selection is based essentially on the anatomical classification of the lesion. The classifications of Valdueza (37a) and Arita (37b) are proving rather too simplistic and not sufficiently adapted to the pleomorphism of the lesions, and the clinical and therapeutic consequences of these variations. As underlined by Palmini et al. (38) the exact location of the lesion in relation to the interpeduncular fossa and the walls of the third ventricle correlates with the extent of excision required, the seizure control, and the complication rate. This rationale led us to classify HH more precisely according to topology, relying on the pertinent features correlating with clinical semiology, prognosis, and surgical strategies. Although it may be an exceptional observation, type V (pedunculated) tend not to have neurological symptoms (no epilepsy, no cognitive deterioration, and no behavioral disturbances). They may present with precocious puberty or be symptom-free (39). Types I, II, III, and IV may cause seizures in many cases, as well as mental retardation, behavioral abnormalities, and precocious puberty. Type VI HH are frequently found in patients with especially severe clinical presentations. In our experience,
the indications for treatment are better refined on the basis of such a topological classification. We have found that partial treatment (of the superior part of the lesion) or low-dose treatment always results in a negative outcome. We consider radiosurgery as a first-line treatment for small type I, II, III, or IV HH. In large type IV HH, a combined approach, with initial surgery for section or resection via a pterional approach, followed by radiosurgical treatment of the upper part, is recommended. In type II, an endoscopic approach or a transcallosal interferneal approach may also be considered as an alternative to radiosurgery. These upper approaches are restricted by the difficulty of identifying the boundary between the HH and the hypothalamus, mamillary body, and fornix, yielding a significant rate of post-treatment short-term memory deficit and hormonal disturbances (Fig. 1) (24).

Two major questions remain. First, we know that complete treatment or resection of the lesion is not always mandatory, but we do not know how to predict in an individual patient the amount (and mapping) of the HH that must be treated in order to obtain a complete antiepileptic effect (40–42). Secondly, we know that these patients frequently present with an electroclinical semiology suggesting involvement of the temporal or frontal lobe and which can mimic a secondary epileptogenesis phenomenon (36,43). In our experience, some of these patients can be completely cured by the isolated treatment of the HH, while in others, a partial result is obtained, with residual seizures despite a significant overall psychiatric and cognitive improvement. In this second group, it is tempting to propose that such a secondary epileptogenic area accounts for the partial failure.

Our initial results indicate that GK surgery (GKS) is as effective as microsurgical resection and much safer. GKS also avoids the vascular risk related to radiofrequency lesioning or stimulation. The disadvantage of radiosurgery is its delayed action. Longer follow-up is mandatory for proper evaluation of the role of GKS. Results are faster and more complete in patients with smaller lesions inside the III ventricle (type II). The early effect on subclinical EEG discharges appears to play a major role in the dramatic benefit to sleep quality, behavior, and cognitive-developmental improvement. GKS can safely lead to the reversal of the epileptic encephalopathy.
Because of the very poor clinical prognosis of the majority of these patients with HH and the invasiveness of microsurgical resection, GK can now be considered the first-line intervention for small- to middle-size HH associated with epilepsy, as it can lead to dramatic improvements in the future of these young patients. The role of secondary epileptogenesis or of widespread cortical dysgenesis in these patients needs to be better evaluated and understood, in order to optimize patient selection and define the best treatment period.

MESIAL TEMPORAL LOBE EPILEPSY

The first GKS operations for MTLE were performed in Marseille in March 1993. As far as no similar experience was available at this time in the literature, we based our technical choices on hypothesis and experience of radiosurgery for other pathological conditions. Four patients were treated with different technical strategies (dose, volume, target definition). The delayed huge radiological changes observed some months after radiosurgery led us to stop such treatment and follow these first four patients (29). Because of the clinical safety of the procedure in these patients and the gradual disappearance of the acute MR changes after some months, we treated several new series of patients under strict prospective controlled trial conditions (with ethical committee approval). The treatment for the following 17 patients was based upon that of the first patient who had a successful outcome (as opposed to the three others who had partial or no effect). This “classic planning” was based on the use of two 18-mm shots, covering a volume of around 7 cm³ at the 50% isodose (24 Gy), and has turned out to produce a high rate of seizure cessation (25,26). For epileptological reasons, as well as for safety reasons, the targeting was very much centered on the parahippocampal cortex and spared a significant part of the amygdaloid complex and hippocampus. The refinement of the GKS technique, and the desire to find a dose which would create less transient acute MR changes, led us to reduce the dose from 24 Gy to 20 Gy and 18 Gy at the margin. However, this brought about a significant decrease in the rate of seizure cessation.

The timetable of events after radiosurgery and the follow-up is quite standardized. Patients are informed that delayed efficacy of radiosurgery is its main drawback. Typically, the frequency of the seizures is not modified significantly for the first few months. Thereafter, there is a rapid and dramatic increase in auras for some days or weeks and then the seizures disappear. Usually the peak in seizure cessation is observed around the 8th to 18th month with a clear variability in the delay in onset. In one patient, this occurred 26 months after GK radiosurgery. We usually consider a delay of two years as a minimum for postradiosurgery follow-up. In the absence of initial radiological changes or clinical benefit, the recommendation is to wait for the onset of the MR imaging changes and their subsequent disappearance. All our patients had the same pattern of MR changes whatever marginal dose (18–24 Gy) and volume of treatment (5–8.5 mm³) were used. However, the degree of these changes and their delay of onset varied according to the dose delivered to the margin, the volume treated, and the individual patient. In order to allow an optimal evaluation, we recommend that subsequent microsurgery not be considered before the third year after radiosurgery. Similarly, we believe that a patient who undergoes a cortectomy before the onset of the MR changes has occurred cannot be assumed to have failed radiosurgical treatment. Of course, before consideration of any further surgery, the question of the reason for the failure needs to be
addressed. After reviewing files of patients treated for MTLE with radiosurgery, it was sometimes possible to identify likely causes of failure, such as:

1. poor patient selection (e.g., epilepsy involving more than the MTL structures),
2. patients with the diagnosis of “treatment failure” (<3 years) who had been operated upon too early after radiosurgery (44),
3. targeting of the amygdala and hippocampus (which is not in our opinion the optimal target in terms of safety and efficacy) instead of parahippocampal cortex (45), and
4. insufficient dosage (44–46).

Our current strategy of treatment is based on our first series of MTLE patients who were strictly selected and treated systematically with a very simple but very reproducible dose planning strategy (25,28). The identification of putative improvements in the methodology requires a systematic analysis of the influence of the technical data from our experience and from the literature on the outcome of those patients.

The “Technical” Questions

The Dose Issue

The first targets used in functional GK radiosurgery (capsulotomy, thalamotomy of ventrointermediate (VIM) or the centromedianum, pallidotomy) were treated using high dose (150–300 Gy) delivered in very small volumes (3–5 mm in diameter) (3). The goal was to destroy a predefined very small anatomical structure with stereotactic precision. Quite a significant variability in the delay and amplitude of the MR changes has been reported with a fixed regimen of doses (47,48). Barcia Salorio et al. (49) have presented a small and heterogeneous group of patients treated with different devices and dosage regimens. Apparently some of those patients had no expanding lesion and were treated with very large volumes and very low dosage (around 10 Gy). On the basis of this experience, several teams have made the assumption that very low doses, as low as 10 to 20 Gy at the margin, should be as effective as the 24-Gy protocol (at the margin) that we used for our first series of patients with MTLE (25,26). A cautious examination of the last proceeding of Barcia Salorio et al. (49) shows that the individual information concerning the dose at the margin, the volume, and the topography of the epileptogenic zone are not provided. Moreover, among the 11 patients reported, the real rate of seizure cessation is apparently only 36% (4/11), which is much lower than what we would expect with resection in MTLE (18). In a heterogeneous group of 176 patients, Yang et al. (46) confirmed that only a very low rate of seizure control is achieved when low doses (from 9 to 13 Gy at the margin) are used.

The experience of the radiosurgical treatment of HH indicates that 18 Gy at the margin appears to be a threshold in terms of probability of seizure cessation (23). In this group of patients (36 cases), only one showed MR changes. The majority of the AVM cases with worsening of the epilepsy were treated with a range of doses between 15 and 18 Gy. Similarly, poor results have been reported by Cmelak et al. (44) in one case of MTLE treated with Linac-based radiosurgery, with 15 Gy at the 60% isodose line, who underwent surgical resection one year later. In this case, the authors first observed slight improvement followed by an obvious worsening. A recent de-escalation study
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has allowed us to demonstrate poorer results in patients receiving doses of 18 or 20 Gy at the margin as compared to 24 Gy (50,51). Because of the rate of seizure cessation that is achievable by conventional resection, a radiosurgical strategy associated with a much lower rate of seizure cessation appears unacceptable. Fractionated stereotactically guided radiotherapy has been demonstrated to fail systematically in controlling seizures. Among 12 patients treated by Grabenbauer et al. (52,53) none have achieved seizure cessation; only seizure reduction was obtained in this series.

Experimental studies on small animals have demonstrated the antiepileptic effect of radiosurgery, the dose dependence of this effect, and the possibility of obtaining clear antiepileptic effect without macroscopic necrosis using certain doses (12–16,54). Of course the rat models of epilepsy are far from being good models of human MTLE. However, taking into account the huge difference in volume of the target, it is intriguing to notice that according to our clinical experience in humans, a similar maximum dose range of 40 to 50 Gy is currently the range of dose providing the optimal safety–efficacy ratio.

The Target Definition

When the target is a lesion that is precisely defined radiologically, the question of the selection of the marginal dose can be quite easily addressed by correlating safety–efficacy individual outcome to the marginal dose. This can be refined based upon stratification according to volume, location, age, etc. However, in patients presenting with MTLE, this process is invalid for two reasons. First, there is no consensus regarding the requirement for extent of mesial temporal lobe resection. Secondly, the concept of MTLE syndrome with a stable extent of the epileptogenic zone and surgical target is increasingly the topic of debate (Fig. 2) (55,56).

The volume (in association with marginal dose) is well known to be a major determinant of the tissue effect, as shown in integrated risk/dose volume formulae (57). In the first series of patients that we treated, this marginal isodose volume (or prescription isodose volume) was approximately 7 cm³ (range 5–8.5).

An attempt to correlate dose/volume and the effect on seizures and on the MR changes (as evaluated by volume of the contrast enhancement ring, extent of the high T2 signal, and the importance of the mass effect) has been published recently (50). In this study, we found, not surprisingly, that the higher the dose and the volume, the higher the risk of having more severe MR changes, but also the higher the chance of achieving seizure cessation. However, these data have limited value. Hence, more precise identification of those structures of the mesial temporal lobe which needs to be “covered” by the radiosurgical treatment may allow more selective, but just as efficacious, dose planning strategies, in spite of smaller prescription isodose volumes.

There is growing evidence to support the organization of the epileptogenic zone in networks, meaning that several different and possibly distant structures are discharging simultaneously at the onset of the electroclinical seizure. This kind of organization explains why the risk of failure is so high when a simple topectomy (without preoperative investigations) is performed in severe drug-resistant epilepsies associated with a benign lesion (58). This has also been reported in MTLE (55,56). Certain nuclei of the amygdaloid complex, of the head, body, and tail of the hippocampus, and of the perirhinal, entorhinal (EC), and parahippocampal cortices may be associated with genesis of the seizures. The role of the EC cortex in epilepsy is supported by experimental studies in animals (59,60). The EC is considered to be the amplifier of the “amygdalohippocampal epileptic system.”
The pattern of the associated structures, including that of the structure playing the leader role, can vary significantly from one patient to another (55,56). There is a subgroup of patients who have clonic discharges and the involvement of the EC, amygdala, and head of the hippocampus, with a clear leader role of the EC. Wieser et al. (61) have analyzed the postoperative MR images of patients operated by Yasargil (amygdalohippocampectomy) and were able to correlate the quality of the resection of each substructure of the mesial temporal lobe area and the outcome with respect to seizures. Only the quality of the removal of the anterior parahippocampal cortex was correlated strongly with a higher chance of seizure cessation (61). We tried to perform a similar study in patients treated with GK radiosurgery (50). We defined and manually drew the limits of subregions on the stereotactic images of all these patients. The amygdala, the head, the body, and the tail of the hippocampus were first delineated. The white matter, the parahippocampal cortex, and the cortex of the anterior wall of the collateral fissure were then separately drawn and divided into four sectors in the rostro-caudal
axis, corresponding to the amygdala, the head, the body, and the tail of the hippocampus (50).

**Patient Selection**

Whang and Kwon (62) (without having first performed specific preoperative epileptological workup) treated patients with epilepsy associated with slowly growing lesions and observed seizure cessation in only 38% (12/31) of the patients. This kind of observation emphasizes the importance of preoperative definition of the extent of the epileptic zone and of its relationship with the lesion (58,63). In our institution, the philosophy is to adapt the investigations for each individual case. In some patients, the electroclinical data, the structural and functional imaging, and the neuropsychological examination are sufficiently concordant for surgery of the temporal lobe to be proposed without depth electrode recording. In other cases, the level of evidence for MTLE is judged insufficient, and a stereoelectroencephalographic (SEEG) study is performed. The strategy of SEEG implantation is based on the primary hypothesis (mesial epileptogenic zone) and alternative hypotheses (early involvement of the temporal pole, lateral cortex, basal cortex, insular cortex, or other cortical areas). The goal of these studies is to record the patient’s habitual seizures, in order to establish the temporo-spatial pattern of involvement of the cortical structures during these seizures. Clearly in these patients, the high resolution of depth electrode recording allows fine tailoring of surgical resection, according to the precise temporo-spatial course of the seizures. The main limitation of radiosurgery is that of size of the target (prescription isodose volume). The radiosurgical treatment of MTLE is certainly the most selective surgical therapy for this group of patients. The requirements for precision and accuracy in the definition of the epileptogenic zone is consequently higher. Furthermore, if depth electrode investigation enables demonstration of a particular subtype of MTLE, this can lead to tailoring of the treatment volume and frequently allows this to be reduced.

**The Potential Concerns**

The risk of long-term complications must always be cautiously scrutinized in functional neurosurgery. Radiotherapy is most frequently used in the brain for short-term, life-threatening pathologies. The use of radiotherapy in young patients with benign disease, such as pituitary adenomas or craniopharyngiomas, has been associated with a significant rate of cognitive decline and tumor genesis, including some carcinogenesis (64–67). If the risk of radiation-induced tumor was similar with radiosurgery we should have by now already observed numerous cases. However, such reported cases are extremely rare and frequently fail to meet the classical criteria by which tumors are deemed to be “radiation-induced” (68–72). In fact it is considered that, if this risk exists, it is likely to be far lower than the mortality risk associated with temporal lobectomy.

Epilepsy is a life-threatening condition. The risk of sudden unexplained death in epileptic patients is higher than in the general population (73,74). This risk is higher in patients treated with more than two antiepileptic drugs and IQ lower than 70 (as independent factors). Because seizure cessation after surgery reduces the mortality risk to that of the general population, microsurgical resection of the epileptogenic zone may confer a benefit in terms of the possibility of immediate seizure cessation and therefore reduced mortality risk, as compared to the more delayed benefits of
radiosurgical treatment (74). Our patients are systematically informed about this disadvantage of radiosurgery.

WHAT ARE THE CURRENT INDICATIONS?

We still consider the use of radiosurgery for MTLE to be experimental. The demonstrated advantages of radiosurgery are the comfort of the procedure, the absence of general anesthesia, the absence of surgical complications and mortality, the very short hospital stay, and the immediate return to the previous level of functioning and employment. Potential sparing of memory function is still a matter of debate and needs to be established using comparative studies. There is also a requirement for further demonstration of long-term efficacy and safety of radiosurgery. Worldwide, microsurgical cortectomies for MTLE are proving to be very satisfactory due to the rarity of surgical complications and a high rate of seizure freedom. In our experience, the most important selection parameters are the demonstration of the purely mesial location of the epileptogenic zone, as well as clear understanding by the patient of the advantages, disadvantages, and limitations. One other very good indication in our experience is that of patients with proven MTLE but previous failure of microsurgery, supposedly due to insufficient posterior extent of the resection.

CONCLUSIONS

The field of epilepsy surgery is a new and promising one for radiosurgery. However, determination of the extent of the epileptogenic zone requires specific expertise, which is crucial in order to achieve a reasonable rate of seizure cessation. In addition, the huge impact of fine technical detail on the efficacy and eventual toxicity of the procedure means that, at present, its use for these indications remains under evaluation, and further prospective work is absolutely required. It is difficult to know whether we really are at the dawning of a broader indication for the use of radiosurgery…in forthcoming years, our ability to identify the correct technical strategies should determine whether this is so!

REFERENCES

Brain stimulation for epilepsy is a potentially attractive modality of therapy. It can be reversed, does not invoke medication side effects, and usually is well-tolerated. Nevertheless, many uncertainties and controversies persist about this therapy. To an extent unusual in Neurology and Neurosurgery, brain stimulation has proceeded along clinical lines with relatively little prior animal laboratory research. In the 1960s, Dr. Irving Cooper of New York (1) implanted cerebellar stimulators into several patients with epilepsy and several with cerebral palsy. The rationale involved awareness that cerebellar cortical outflow was inhibitory to the deep cerebellar nuclei, and the outflow of the deep nuclei positively influenced manifestations of motor behavior. Cooper also implanted the anterior thalamus in several patients based upon the concept of the anterior thalamus as the rostral end of the reticular activating system (2,3). Laboratory underpinnings for this work followed the initial pilot human trials, and are ongoing.

Cerebellar stimulation for epilepsy appeared to have a beneficial outcome in all 11 initial studies (4). However, the two blinded control studies, one by Van Buren et al. (5), and the other by Wright et al. (6), failed to show clear benefit of stimulation. It should be noted that the two controlled studies comprised a total of only 19 patients. Failure of the controlled studies to show benefit led to discontinuation of cerebellar implantation for epilepsy, except by a few who continued to believe that the therapy was effective in selected instances (7).

In 1987, Velasco et al. (8) in Mexico City reported an open-label study of stimulation of the centromedian thalamic nucleus in five patients with a variety of uncontrolled partial and secondarily generalized seizures. Initial results were promising. Several subsequent papers followed their original observations, but none were controlled studies (9–11). Fisher et al. (12) performed a controlled study of centromedian stimulation, using a double-blind, crossover design to stimulate with either 0 or 5 V, 65 pulses/sec, 90 μsec pulse duration, on for one minute of each five minutes for two
hours per day each side. Seven patients with partial and secondarily generalized seizures were treated either with sham stimulation or active stimulation for the first three months, and then were given a three-month “wash-out,” followed by the opposite treatment to that which they received in the first three months. Comparison of stimulated versus unstimulated outcome for secondarily generalized seizures demonstrated a 30% reduction during the interval of active stimulation, but this result was not statistically significant. Only six patients could be analyzed. The seventh patient had a marked reduction in seizure frequency during the three months of active stimulation and would not permit alteration of the therapy; the patient therefore could not be included in data analysis. Given the relatively modest benefit of stimulation, coupled with risk for complications of depth electrode implantation (see below), the decision was made to return to laboratory studies to better define the possible candidates, targets, and stimulation parameters.

LABORATORY BACKGROUND

The fundamental physiology of brain stimulation is rather poorly understood. Stimulation will activate cell bodies and axons in passage. Pulses at frequencies around 10–20 Hz typically activate neuronal systems via synaptic pathways. At frequencies of 1 Hz or less there is an inhibitory effect. At higher frequencies, such as 100 Hz, effects of stimulation become more intense. Immediately in the vicinity of the stimulating electrode, neurons depolarize. This produces initial stimulation, followed by inhibition. Two theories have been suggested to explain the inhibition. First is the suggestion that the depolarization reduces the membrane potential to a level at which sodium channels no longer open, and the neurons stop discharging. The second hypothesizes that the stimulation selectively activates inhibitory circuits. Independent of pathophysiological theory, stimulation may produce excitation in neurons distant from the electrodes, if those neurons are only mildly depolarized.

Computer modeling using finite elements has been performed to portray the spatial extent of the effects of stimulation (13). Such effects depend upon the resistance of the brain; tissue interfaces between the brain, cerebrospinal fluid, and bone, and characteristics of the stimuli. Increasing stimulation intensity increases the volume of brain tissue being stimulated in a complex way. Inadvertent effects can emerge from activation of nuclei close to those being stimulated. In addition to frequency and intensity, effects of stimulation also depend upon electrode placement. If the cathode and anode are within a few millimeters of each other, stimulation will generate lines of current flow between the electrodes. If the distance between electrodes is more than a centimeter, modeling suggests that a separate current source and sink will develop around each stimulating electrode, without necessarily stimulating tissue between the two electrodes (13). Effects of stimulation also depend upon the task normally mediated by the part of the brain being stimulated. Motor cortex, when stimulated even at a relatively high frequency of 50 Hz, generates muscle tetany. No such positive elicitation of function occurs with stimulation in regions of brain mediating higher cortical functions, such as speech or reading. These higher functions are inhibited by stimulation. Because of our inability to predict the effects of electrical stimulation from primary principles, work with electrical stimulation has been based on empirical and incomplete rules.

Laboratory experiments have evaluated the upper limit of what is safe for tissue adjacent to electrical stimulation: approximately 30 μCoulombs per square centimeter of electrode surface per pulse (14). Stimulation frequency has usually been
chosen to be 50 Hz or higher; however, some researchers are attempting to exploit the inhibitory effects of stimulation at \( \leq 1 \) Hz. Inhibitory effects of high-frequency stimulation are best demonstrated with stimulation of ventral intermediate thalamus or subthalamus. Stimulation at frequencies of 130 Hz inhibits tremor. In the movement disorder field, stimulation traditionally is continuous. Epileptologists are accustomed to provide stimulation intermittently, after the example of the vagus nerve stimulator which was tested at 30 seconds on and five minutes off in the pivotal trials. If an effect is known to persist with intermittent stimulation, then such intermittent stimulation will preserve battery life, and might be less irritating to surrounding tissues.

Animal experimentation relevant to brain stimulation began in the 1930s, with demonstration that stimulation of the mesencephalic reticular formation and non-specific thalamus could desynchronize the electroencephalography (EEG). Work by Jasper and Droogleever-Fortuyn, along with others, indicated the importance of thalamus in mediation of certain types of primary and secondarily generalized epilepsy. Stimulation of thalamus at three per second in kittens can produce cortical spike-waves (15). Structures involved in generation and spread of seizures can be investigated by metabolic mapping. Mirski and Ferrendelli (16) used autoradiography in guinea-pig brain tissue to investigate active areas during pentylenetetrazol-induced seizures. The mammillary bodies and anterior thalamus, linked by the mammillothalamic tract, are prominent as active sites during such seizures. Lesions of the mammillothalamic tract increased the seizure threshold. Mirski and Fisher (17) explored whether electrical stimulation of the mammillary nuclei in rats at frequencies of 50–100 Hz could inhibit pentylenetetrazol-induced seizures. Such stimulation doubled the amount of pentylenetetrazol required to induce clonic seizures.

Posterior hypothalamus is a possible, but difficult clinical target because of the risk for Wernicke encephalopathy in case of hemorrhage or damage to critical vessels at the base of the brain. The next experiments therefore focused on the anterior nucleus of the thalamus, the rostral link of the mammillothalamic connection. This was the original target of Dr. Irving Cooper in his pioneering clinical trials. Stimulation of the anterior thalamic nucleus at high frequency in rats had a beneficial effect against cortical EEG spiking produced by pentylenetetrazol. The magnitude of the effect was similar to that produced by stimulation of the posterior hypothalamus. Effects of high-frequency stimulation were inhibitory to the anterior thalamus. Support for this view was gained by showing that the gamma-aminobutyric acid (GABA) agonist, muscimol, produced effects similar to that of stimulation (18). Electrical stimulation of the anterior thalamic nucleus in rats also inhibited seizures produced by systemically administered kainic acid (19). The anterior thalamus projects to the superior frontal region of the brain and, via the cingulate, to the entorhinal cortex and hippocampus. Therefore, stimulation of the anterior nucleus might be expected to have an impact against superior frontal seizures and temporal-limbic seizures.

PILOT CLINICAL TRIALS

With laboratory success in stimulating anterior thalamus for inhibition of pentylenetetrazol-induced seizures, human clinical trials were begun, which built upon previous work by Cooper and his associates (2,20). At the time of this writing, 22 patients have received anterior thalamic stimulators for intractable partial and secondarily generalized seizures, not amenable to other therapies. This number does not include the original patients implanted by Cooper, as his sample size is not
available in published literature. Patients have been implanted at several different institutions. Not all patients were implanted in accord with a unified protocol. Generally beneficial results were seen with reduction of seizures able to result in falls of 68% in three patients followed for a year (Fisher, unpublished data). One group saw a 54% reduction in total seizures (21). They argued that the benefit appeared to result from micro-lesioning by electrode placement itself, or perhaps placebo effect, as improvement during times of stimulation on versus off cycles was not evident. This point highlights our lack of knowledge about the duration, if any, of the effect of stimulation after the stimulation is stopped. One patient worsened when the stimulator malfunctioned, and improved when it was repaired. Another patient had a serious complication from hemorrhage secondary to the electrode placement. This parallels the approximate 5% incidence of hemorrhage with placement of deep brain electrodes for movement disorders.

In this pilot trial, electrodes were implanted using magnetic resonance imaging (MRI) and stereotactic guidance. Unit responses from the tip of the electrode were recorded while inserting the electrodes. With a superior-lateral approach, electrodes approached the anterior thalamus through the ventricle, so appearance of units marked arrival at the anterior thalamus. Equipment was provided by Medtronic. The Medtronic model 3387 deep brain leads have four contacts, spaced 2 mm apart. Contacts for stimulation were chosen based upon a combination of MRI evaluation of placement anatomy and the recording of an EEG recruiting response. A recruiting response resulted from eight per second stimulation at 5 to 10 V, resulting in a waxing–waning surface-negative 8/sec EEG response. Elicitation of such a response documented the ability of the electrical stimulation to affect widespread regions of frontal brain rhythms. A few patients underwent recording from anterior thalamus electrodes prior to internalizing the wires. Such recording demonstrated participation of the anterior nucleus in epileptiform activity during interictal spikes and seizures.

Conclusions from the pilot trials are as follows:

1. Stimulation of anterior nucleus of thalamus is feasible. Patients do not perceive the stimulation at the parameters used.
2. MRI localization and EEG recording of the recruiting response can be used to help localize placement of the stimulating electrodes into the anterior thalamus.
3. Initial results suggest possible efficacy, particularly with secondarily generalized seizures, but controlled studies are required to support this impression.
4. Serious complications occurred at 5% in this small sample, similar to prior experience with other types of brain electrode implantations.

Planning for a double-blind, controlled trial of anterior nucleus stimulation for epilepsy is now underway.

SUBTHALAMIC NUCLEUS STIMULATION

The subthalamic nucleus (STN) is the target for stimulation of patients with certain types of movement disorders, such as tremor and Parkinson’s disease. Stimulation for movement disorders was pioneered by Benabid et al. in Grenoble, France. Electrical stimulation of the thalamus and subthalamus is now approved by the U.S. Food and Drug Administration (FDA) for tremor and Parkinson’s disease. Based
upon the fact that pharmacologic or electrical inhibition of the STN is effective in treating animal models of epilepsy, Benabid et al. (22) began using high-frequency stimulation of STN to treat patients with medically intractable epilepsy (Table 1). These investigators used a frequency of 130 Hz, pulse width of 90 μsec, and voltage progressively increased from 0.8 V up to a maximum of 5.2 V. Four patients with localization-related epilepsy showed a significant improvement. One subject with autosomal dominant nocturnal frontal lobe epilepsy had no significant change in seizure frequency (22).

A second group in Cleveland has treated four patients with medically intractable localization-related epilepsy with STN stimulation. These investigators used 90 to 150 Hz, pulse width of 120 to 185 μsec, and 0.5 to 3.5 V constant stimulation, later changed to intermittent stimulation (30 seconds “on” followed by 4 minutes “off”). Two patients improved significantly with stimulation, one had no change in seizure frequency, and one became worse with STN stimulation (23).

Future studies will be required to compare continuous versus intermittent stimulation and stimulation of the STN versus stimulation of the substantia nigra pars reticulata, as well as other stimulation parameters. Both groups are planning blinded trials.

**HIPPOCAMPAL STIMULATION**

Successful reduction in seizure frequency by hippocampal stimulation was first reported in two patients by Sramka et al. (24). More recently Velasco et al. (25) have stimulated human hippocampus during chronic recordings done to map limbic seizure foci. Initially 10 patients underwent subacute electrical stimulation of the
hippocampal formation or gyrus (SAHCS) prior to anterior temporal lobectomy (ATL). The SAHCS was applied for two to three weeks, following the discontinuation of antiepileptic drugs (AEDs). Continuous stimulation was performed except for one hour per day while recordings were taken. Frequency was 130 Hz, amplitude was 200 to 400 μA. The later was adjusted for threshold in eliciting electropositive DC shifts just posterior to the stimulation sites. Seven of the subjects showed complete abolition of seizures by day seven. Those subjects with the fastest responses also showed a prominent, persistent monomorphic delta activity in the middle parahippocampal region. Preliminary results on a smaller number of patients reported by Velasco indicate that the antiseizure effect may persist for at least 90 days if stimulation is continued.

Single proton emission computed tomography (SPECT) studies on a single subject showed hippocampal hypoperfusion after both SAHCS and ATL, and increased perfusion in the left and right basofrontal and dorsolateral temporal cortices after SAHCS, but not after ATL. Following ATL no histopathological differences were found between stimulated and nonstimulated tissue by routine studies. Benzodiazepine receptor binding was studied in a single patient who had received SAHCS. The findings indicated a receptor density intermediate between the large amount in the normal hippocampus and the sparse amount in the hippocampus of a patient with epilepsy who had not been treated with SAHCS. These preliminary studies have laid the groundwork for planned blinded studies.

SAFETY

The long-term safety of implanted electrodes for treating epilepsy is unknown. Experience has been gained from deep brain electrodes implanted to treat pain and movement disorders. Electrical cardioversion could cause the stimulator to malfunction. Additionally, a large current potentially could be conducted into the brain, causing tissue damage.

There have been two cases where patients with implanted deep brain stimulators (DBS) received shortwave treatment. In both cases, the treatment interacted with the implanted DBS and caused severe and permanent brain damage leading to death. Patient harm or damage can occur during these treatments whether the DBS are turned “on” or “off.” These devices can also damage parts of the DBS. Further surgery may then be required to remove or replace parts of the implanted DBS, resulting in a temporary loss of therapy. Implanted patients must not be exposed to any shortwave, ultrasound, or microwave treatments anywhere on their body.

The risk of hemorrhage is about 5%. This includes potential intraparenchymal hemorrhage along the course of the wire, as well as possible postoperative subdural hematoma. There is also at least a 1% chance of infection, which may require removal of hardware.

Using current protocols, MRI has proven to be safe in patients with DBS implants so far. However, theoretical problems include heating of the implanted electrode, especially if there were to be a short-circuit present. Other problems could include rapid on–off cycling of the device, due to toggling of the magnetic switch in the stimulator, breakage of the device, and movement of the wires. There is little if any experience about the safety of these devices in MRI machines over 1.5 Tesla.

Electrical kindling in animals raises the concern that stimulation could make seizures worse, in terms of frequency, duration, intensity, or types of seizures. It is unknown whether the risk of status epilepticus is altered by DBS. If seizures were
to worsen, it is not known if the seizures would or would not improve after stimulation is stopped. Animal research has also shown immunological consequences from hippocampal stimulation (26).

Less serious risks include headache, local pain or discomfort at the equipment sites, worsening of sinus conditions, fullness or ringing in the ears, tingling or uncomfortable sensations on the face or body when stimulation comes on, or changes in mood, memory, thinking, and energy level.

In addition to any specific dangers of this device there are the risks of any brain operation and those of general anesthesia. The effects of brain stimulation during pregnancy are unknown.

**CONTROVERSIES**

Every aspect of brain stimulation is controversial. The key issue is whether deep brain stimulation is effective as a treatment for epilepsy. Given the risk for hemorrhage around the electrode and the risk for infection, stimulation will have to be more effective than is stimulation of the vagus nerve. We believe that stimulation must result in at least a 50% reduction of seizures capable of causing injury, in order for the risk to be justified. A companion question to that of efficacy relates to candidate selection. Who is most likely to benefit from electrical stimulation of the thalamus? We cannot predict this currently for vagus nerve stimulation. Importance of prediction will be even greater for brain stimulation because of the higher risk. Potential candidates presently seem to be those with either superior frontal or temporal seizures, seizures not controlled by an adequate trial of medications, seizures not susceptible to cure by resective surgery, and seizures capable of causing injury or major disruption in quality of life.
The best target remains controversial. Some investigators favor the STN and others the anterior nucleus of the thalamus. The STN is more difficult to test in a controlled trial, because subjects are more likely to perceive stimulation than they are during stimulation of the anterior thalamic nucleus. Many epileptologists are more comfortable with a concept of the thalamic nucleus, rather than the subthalamic region, having a significant role in epilepsy, but experimentation may not support this opinion. Direct stimulation of hippocampus is an attractive approach, but needs confirmation. Other targets, such as cerebellum, caudate, and brainstem have advocates, but each would require demonstration of efficacy in a controlled trial before they achieved widespread acceptance.

Parameters of stimulation engender controversy. Should stimulation be continuous or intermittent? Should it be referential or bipolar? Should the frequency of stimulation be 1, 50, 100, 130, 200 Hz or something else? How high a voltage should be used for stimulation? Should we use constant-current or constant-voltage stimulation? Should stimulation run on a programmed schedule, or be linked to seizure detection, seizure prediction, or an event push button? Each of these questions is unanswerable in light of current knowledge.

FUTURE DIRECTIONS

The most immediate need is for a properly controlled, randomized clinical trial to document efficacy and safety of brain stimulation for intractable epilepsy. On balance, the most promising target appears to be the anterior thalamus. A pilot trial of 20 patients was approved by the National Institutes of Health (NIH) and the FDA, but has not proceeded because of the need to obtain proper indemnification, which is not supplied by NIH. At the time of this writing, a large randomized trial is being planned by Medtronic. Studies of predictive factors for success also should be a high priority. Studies of closed-loop stimulation linked to seizure detection, seizure prediction, or patient push buttons will be of value. Possibilities are open to explore novel types of electrical stimulation other than rectified square waves or sine waves. The next several years should determine whether brain stimulation will step out of the shadows as a useful new therapy for intractable epilepsy.

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Chapter 54
Prospects for Developing Electrical Stimulation of the Cortex for Treatment of Intractable Seizures

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INTRODUCTION
Brain stimulation is not a new treatment for epilepsy. Electrical stimulation (with electricity from the torpedo fish) was used in the first century to treat epilepsy and depression (1). In the 18th century, Benjamin Franklin used electricity, delivered from a Leyden jar, to treat a girl with seizures (2). Over the past half-century, cerebellar, thalamic, subthalamic, hippocampal, vagal, transcranial magnetic, and closed loop stimulation all have been explored as seizure treatments, with varying results (3–19).

The idea that stimulation could treat seizures has received more attention recently in part because of the U.S. Food and Drug Administration approval of an “indirect” means of brain stimulation, vagal nerve stimulation, for this purpose. However, there are several lines of evidence to suggest that direct cortical stimulation could stop seizures (12,20–26).

Coupled with the efforts to optimize direct cortical stimulation paradigm is the research to predict seizures prior to their onset, so that an acute seizure prevention treatment could then be administered (27). Different methods have been used to analyze dynamic changes preceding spontaneous seizures in order to predict seizure occurrence (28–32).
SEIZURE GENERATION AND TERMINATION

Seizures are characterized by abnormal hypersynchronous oscillatory activity of neuronal populations (26,33). Once this has been activated, there are two additional components. First, the activity must propagate from a region of origin so that a larger population of cells participates in the epileptiform activity, a population sufficient to result in a clinical seizure. Second, the propagated activity must be synchronous among the activated cells.

PROPAGATION

For seizure activity to become synchronous over a wider area it must propagate, either through synaptic activity or via axo-axonal gap junctions (34). Propagation patterns have been reported to be stable in cortical slices treated with bicuculline (35,36). However, there are data showing both spatial and directional variations in propagation patterns, most likely reflecting underlying inhomogeneities in neuronal distribution and in the distribution of neuronal connections, especially excitatory ones, and also reflecting barriers to propagation across the boundaries of cerebral microregions, e.g., columns (35,37). Patterns of directional propagation of paroxysmal field potentials also are influenced by the time needed to excite a local population of neurons, the total number of synapses activating a paroxysmal field potential within the neuronal population, and the duration of the absolute refractory period (which eliminates backward propagation) (35,38). It is not only propagation that varies; there are data suggesting that the precise site of seizure onset within an epileptogenic region might vary from event to event (39–41). When stimulating neocortex during clinical localization testing, we have observed that there can be considerable plasticity in the distribution of afterdischarges (ADs) from event to event, even though the sites of stimulation remain unchanged (42). This implies that propagation patterns can vary over short periods of time.

SYNCHRONY

Experimental and theoretical work have established that the brain can manifest oscillatory activity within different frequency bands at the level of single units, multiple units, local fields, and larger neuronal populations (41,43–47). This activity results not only from the intrinsic property of individual neurons but also from emergent properties of networks of neurons, and changes as a result of changes in the underlying neurons, circuits, and networks. The word synchrony, applied to electroencephalography (EEG) implies that specific EEG waveform patterns are occurring concurrently at two (or more) locations in the brain. Spatially and temporally specific changes of EEG synchrony accompany cognitive, attentional, and motor tasks (48–50).

We have considerable data regarding local synchrony during seizures. The degree of epileptogenicity is correlated with the extent of synchronous neuronal burst discharges (51). Bilateral in vivo recordings from hippocampal neurons in patients with epilepsy have shown synchronized firing between neurons in the epileptic hippocampus (52). A simulation study of an array of pyramidal neurons and interneurons revealed that excitatory postsynaptic currents had to be precisely timed in order for synchrony to occur between two sites (53). There may be varying neuronal
mechanisms that modulate synchrony among brain sites. Knockout mice with diminished interneuron alpha-amino-3-hydroxy-5-methyl-4-isobenzole propionic acid (AMPA)-modulated excitatory postsynaptic potential (EPSPs) demonstrate intact local gamma frequency oscillations, but disrupted synchrony between pairs of spatially separated sites. Therefore, both excitatory and inhibitory mechanisms may modulate synchrony, as different mechanisms could underlie the occurrence of cortical oscillations at different frequencies (54,55).

Clinical studies of synchrony have measured activity between pairs of subdural or depth electrodes in patients who are candidates for resective seizure surgery. Franaszczuk and Bergey (56) found that synchronization increased during the ictus. Bartolomei et al. (57) found increased coherence both between electrodes relatively near to, and between electrodes more distant from, each other in the course of seizures. However, these researchers subsequently reported decorrelation between distant electrodes (58). In addition, Bullock et al. (59), using fast Fourier transform, found that coherence during the ongoing EEG could be high for adjacent electrodes but would decline markedly as separation increased further. They found that coherence increased during seizures, except in the 5 to 8 Hz band, and occasionally in the 8 to 13 or 35 to 50 Hz bands. Le Van Quyen et al. (60), using a nonlinear method, found that synchrony was low interictally but increased ictally although it varied during the seizure. Cranstoun et al. (61) assessed a channel of EEG containing four seizures and found that the average duration of stationary periods decreased in the preseizure period.

Netoff and Schiff (62) have suggested an alternate possibility, however. They recorded ictal and interictal firing patterns at pairs of electrodes. They showed that “seizure-like events,” but not interictal bursts, using the 4-aminopyridine model were manifested by firing that was asynchronous between the pair of sites. As they noted, this finding is consistent with theoretical work indicating that sustained activity is maintained by asynchronous firing and disrupted by synchronous firing (63). They thus proposed that asynchrony, rather than synchrony, might be a necessary condition underlying ictal activity. They also proposed that treatments that promoted synchronization of activity might be useful in controlling seizures. In summary, there are differences in the literature regarding whether the ictus is characterized by increased or decreased synchronisation.

METHODS OF STIMULATING THE BRAIN TO PREVENT OR TERMINATE SEIZURES

Similar differences exist regarding stimulation. It has been suggested that acute stimulation might abort seizures by causing desynchronization of a firing network (25,26,64). Conversely, a decrease in synchronization might underlie seizure maintenance, and an increase, seizure termination (62). Using uniform field direct current, an anode (positive) electrode placed near the basal dendritic tree hyperpolarizes the neuronal membrane and suppresses epileptiform activity (65,66). Localized fields, however, exert their effect independent of the orientation of the neurons in the induced field. Localized fields applied through point source electriodes can be more effective than uniform fields as they can produce large transmembrane currents (67). This method, through anodic current injection, has been successfully used in high-potassium and low-calcium in vitro epilepsy models (68,69). Similar effects have been shown in multiple in vitro models using alternate current (AC) stimulation applied through monopolar electrodes (70). However, application of
single or train of biphasic current(s) through a monopolar electrode in a 4-aminopyridine in vitro epilepsy model has been ineffective (71). The inhibition evoked by single pulse stimulation in synchronously firing epileptic neurons is significantly longer than that evoked by stimulating nonsynchronously firing neurons (52). This effect is present even in the absence of prior excitation, so that after-burst hyperpolarization is unlikely. However, longer periods of inhibition can follow synchronous firing of epileptic neurons, which suggests recruitment of more recurrent inhibitory circuits.

A better “timing” and optimization of electrical stimulation would be achieved if propagation and interaction of epileptic discharges during seizures were completely known. It is not clear if a single or multiple neuronal networks are needed to generate seizures, if these networks link together in re-entrant loops, and if these are identical with the circuits that generate interictal spikes. However, networks are known to act like a neuronal oscillator. In the tetanus toxin chronic epilepsy model, seizures can show bilateral and multifocal onsets with individual bursts propagating on either side and in either direction (72). Finnerty and Jefferys argue against unilateral driving focus as the side leading each burst switches frequently during the first 20 seconds of a seizure. Their tetanus model suggests that the critical neuronal mass that is needed for seizure generation includes several spatially distributed neuronal networks and the increased output synchrony (population spike firing) of these networks during the early part of seizures contributes to seizure generation and propagation. These findings, while in general supportive of the notion of using cortical stimulation to interrupt early seizure generation, are suggestive of a less critical role for exact localization of the stimulus application.

Several groups have been using nonlinear analysis tools based upon chaos theory to “time” delivery of single pulse or alternating current stimulation, so as to abort or desynchronize seizures and other oscillatory behavior (9,25,26,73). However, stimulation, or direct current (DC) delivery, at the time of event occurrence, also can be effective in reducing epileptogenic activity, as can periodic pacing (9,26,68,69,74–76). Therefore, nonlinear tools appear to be very useful, but may not be essential, for determining when to stimulate the brain to abort or prevent seizures.

In addition to overall timing, the efficacy of stimulation may depend upon AD morphology at the time of stimulation onset, and upon the location of stimulation with respect to the epileptogenic focus. For example, using subdural electrode recordings in humans (Figs. 1 and 2) we found that brief pulses of electrical stimulation (BPS) applied at peak voltage negativity of the AD waveform was more likely to abort ADs than were BPS applied at peak positivity. The sooner the BPS was applied the more likely it was to terminate the ADs. It was also more likely to terminate an AD at directly stimulated sites than at adjacent sites. These effects were not influenced by anticonvulsant levels (21). We found that BPS was more successful when ADs did not begin immediately after the end of the initial localizing stimulation.

The mechanisms underlying the anticonvulsant effects of stimulation are unknown. Possibilities include neurotransmitter build-up, activation of inhibition, loss of information transfer, disruption of feedback within neuronal networks, and depolarization block because of alterations in calcium channels, gamma-amino butyric acid (GABA) receptors, and extracellular potassium (25,26,77–80). For example, an excessive increase in extracellular potassium could abort rapid neuronal discharges. During an AD, the intensely discharging neurons lose potassium, and this in turn could trigger propagating waves of depolarization in the astrocytic network.
The astrocytes would release additional potassium, which in turn induces a depolarization block of spike generation in neurons or axonal conduction, hence aborting epileptiform discharges (79–84). However, others have suggested that extracellular potassium could be epileptogenic, and that glial buffering or sodium channel pump activity might buffer this potassium so as to stop seizures (85–87).

**Figure 1** Afterdischarges (ADs) induced by electrical stimulation via subdural electrodes in patients with intractable epilepsy who are candidates for surgical excisions. The location of subdural grid electrodes is dictated by the clinical situation. We test the cortex underlying the grid electrodes for language, motor, or sensory function. Simultaneous Video-EEG monitoring continuously displays both the patient and the EEG. Patients are normally taken off of their antiepileptic drugs (AEDs), or are on tapered doses prior to and during admission to the epilepsy monitoring unit. The electrodes we use are 2.3-mm-diameter platinum–iridium electrodes embedded in a plastic sheet with 1 cm center-to-center distances (Ad-Tech, Racine, Wisconsin, U.S.A.). We stimulate using 0.3-millisecond, 50-Hz alternating polarity square wave pulse pairs. The duration of stimulation is typically three to five seconds. We stimulate one electrode pair at a given time. Each targeted electrode pair is initially stimulated at a low intensity (1–2 mA) that is increased by 0.5–1.0 mA at a time until either a functional change occurs, a maximum current of 15 or 17.5 mA is reached, or ADs develop (20,21). When using this method of gradual increase in stimulation intensity, ADs usually do not occur. When they occur, they may be self-limited, or may evolve into clinical seizures (90). We found that brief pulses of electrical stimulation (duration 0.2–1.6 sec, mean 0.78) could terminate these ADs (21). In the figure, electrical stimulation induces ADs at the directly stimulated electrodes (*primary sites; LFC12 and 13*). There are less prominent ADs recorded in the neighboring electrodes (*secondary sites; LFC11 and 14*). A brief pulse of stimulation (BPS) immediately aborts the ongoing ADs at all sites. Both the initial stimulation and BPS were applied through the same (directly stimulated) pair of electrodes using the same stimulation parameters except that the duration of BPS was shorter than the duration of the initial stimulation. *Source:* Courtesy of Johns Hopkins University, 2004.
SAFETY

We investigated the safety of using electrical stimulation via subdural electrodes in humans (88). We found no histologic abnormalities attributable to the electrical stimulation. Chronic stimulation through depth leads for treatment of movement disorders has similarly been found safe, and is used clinically (4,89). Therefore, at least some parameters of stimulation in humans appear to be safe, and appear not to cause structural damage.

In order to develop a viable implantable cortical stimulator, epilepsy research will need to focus on both seizure prediction and termination. Both clinical studies and experiments in animal models of epilepsy will be needed to optimize the stimulation paradigms. Such studies will also increase our understanding of the mechanisms involved in epileptogenesis.

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Electrical Stimulation of the Cortex

Chapter 55
Focal Cortical Cooling

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BACKGROUND

Much of the information already presented in the preceding chapters in this book detail the rationale for epilepsy surgery and describe the complex problems associated with the planning and execution of epilepsy surgery. These problems can be simplistically reduced to decisions about which parts of the brain need to be removed to eliminate seizures and to predictions about the functional consequences of removing these regions. In some situations, especially with epilepsy arising from the medial temporal lobes, current surgical outcomes justify resection, and there is already substantial literature that permits some prediction of the consequences of epilepsy surgery (1). However, the situation with epilepsy arising from the neocortex is not so clear-cut. Even with the most up-to-date electrophysiological and neuroradiological mapping techniques, the prognosis after resection for neocortical epilepsy is disappointing, with long-term, seizure-free outcomes in the range of 50% (2).

These relatively disappointing results with present surgical techniques have led experimental epileptologists to consider alternative, but still scientifically based approaches to the therapy of focal epilepsy. These include application of external electrical fields, focal stimulation with implanted electrodes, and local administration of inhibitory agents into the epileptogenic zone (3–5). Local cooling, which has substantial physiological precedent as a suppressor of synaptic transmission, appears to be an attractive additional option to enhance the surgical management of neocortical epilepsy.

NEUROPHYSIOLOGICAL EFFECTS OF FOCAL COOLING

The original studies that demonstrated reversible inactivation of specific brain regions by local cooling were carried out independently by Stefani and Trendelenburg over a century ago and were summarized in a review by Brooks (6). More recent research reports and reviews confirm the ability of local cooling to reversibly deactivate cortex in vivo (7–9). Cooling appears to exert some of its effects through blocking of
voltage-gated ion channels (10). There is also evidence from the frog neuromuscular
junction that cooling inhibits vesicular transmitter release. Using mammalian brain
slices and modern imaging techniques that allow direct visualization of transmitter exo-
cytosis, we have recently observed a temperature-dependent reduction of presynaptic
function (11).

Physicians have recognized a relationship between seizures and temperature for
centuries, and modern accounts document the termination of human seizures by
brain cooling (12,13). Local application of cold saline can abort both induced and
spontaneous epileptiform activity observed during intraoperative mapping (14). Animal
experiments over 25 years ago showed diminished interictal bursting in
several epilepsy models during slow cortical cooling, but no attempt was made to
acutely stop seizures in any of these experiments (15). There are now several different
laboratories that have begun to utilize brain slice preparations to re-examine the
therapeutic potential of cooling for epilepsy. Smith et al. (16) used the convulsant
and potassium channel blocker 4-aminopyridine to induce spontaneous bursting in
rat hippocampal slices. They found that slowly cooling to 24°C reduced burst fre-
quency by over 90% and burst amplitudes. Javedan et al. (17) recently reported that
slowly cooling hippocampal slices from 34 to 20°C reversibly abolished paroxysmal
40 Hz gamma oscillations evoked by a burst of tetanic stimulation. Interestingly,
evoked excitatory synaptic potentials were preserved when the slice was cooled to 20°C.

RAPID COOLING IN EXPERIMENTAL MODELS OF EPILEPSY

The recent development of small thermoelectric (Peltier) cooling devices, initially
designed for the computer industry, suggested the possibility of utilizing cooling
technology as a therapy for certain types of intractable, focal epilepsy. These devices
are fabricated from a matrix of crystalline semiconductors each of which generate a
temperature differential when electrically polarized. The individual semiconductors
are arranged in parallel, but connected in electrical series. They are then sandwiched
between metallized ceramic plates to create a wafer (Fig. 1).

Figure 1 Photograph of small, commercially available thermoelectric (Peltier) devices. The
individual semiconductors are visible in the device on the left (arrow). The device on the right
has been sealed with epoxy to keep the semiconductor protected from the extracellular fluid.
When current flows, one plate cools almost instantly, and the other heats. In order to maintain effective cooling of one side of the wafer, heat needs to be continually removed from the “hot side,” by connecting it to a heat sink or heat pipe. The former is a reservoir for excess heat and the latter is an efficient conduit from heat source to heat sink. Thermoelectric devices as small as 3 mm wide and 2.5 mm thick are commercially available. There is substantial pressure from computer manufacturers to improve the design of thermoelectric heat pumps and heat pipes, because they are also used to cool computer microprocessors (18).

Hill et al. (19) first investigated the ability of thermoelectric devices to abort 4-aminopyridine–induced ictal activity in rodent hippocampal slices. They implanted a small thermoelectric device into the base of a plexiglass perfusion chamber, so that the cool surface was flush with the plexiglass, and placed the slice directly on the wafer. If cooling was activated at burst onset, seizures terminated within a few seconds. Seizures in slices cooled to as low as 21°C stopped within eight seconds, while control ictal events lasted for 35 seconds. Activation of the thermoelectric device only terminated seizures when it was in direct physical contact with the slice, making it unlikely that seizure termination was a result of the electrical field generated by the thermoelectric unit.

The same group proceeded to investigate the effect of rapid cooling on seizures in anesthetized rats (20,21). A frontal bone window was removed and focal seizures were produced by microinjecting 4-aminopyridine at a depth of 0.5 mm into the motor cortex. Within about 15 minutes of convulsant injection, discrete ictal events lasting 80 to 100 seconds were detected with standard bipolar electroencephalographic (EEG)
recording (Fig. 2A). Normal background EEG activity recovered between these events. A small thermoelectric device was then placed in direct contact with the dura overlying the site of drug injection. If the device was activated at seizure onset, seizures were abolished within 10 seconds (Fig. 2C). If the thermoelectric device was not in direct contact with the cortex, it had no effect on seizure duration (Fig. 2B). The cortical surface was never cooled below 20°C in these experiments, but had to be cooled below 26°C to have any effect on seizure duration (Fig. 3).

Although severe cooling can definitely damage the cortex, no injury was seen in any of these experiments and the cortical surface temperature returned to baseline within seconds of thermoelectric inactivation. In subsequent experiments, a thermocouple mounted in a 33-gauge needle mapped the temperature gradient immediately beneath the thermoelectric device. The temperature fell off rapidly and was no different from core brain temperature beyond 4 mm, suggesting that this method produces extremely restricted cooling.

More recent experiments have demonstrated that intermittent cooling either prior to 4-aminopyridine injection, or at regular intervals after injection, influences seizure development (22). When the cortex was cooled either way, the subsequent seizure activity was significantly briefer and less intense.

**FOCAL COOLING AND CLINICAL EPILEPSY**

Our success with local cortical cooling using Peltier devices, in a fairly severe model of focal epilepsy, has encouraged us to consider situations where these devices
might improve the therapy for human epilepsy. We believe that there are at least three situations where focal cooling using Peltier devices might improve the therapy of patients with intractable focal seizures. First, it could become an important ancillary mapping tool during focal cortical resections. If preoperative video-EEG monitoring or intraoperative electrocorticography suggested a restricted cortical site for seizure origin, specific site could be cooled to determine whether paroxysmal activity disappeared. During mapping in awake patients, a region suspected of being responsible for generating focal seizures could be temporarily inactivated, making it possible to anticipate potential functional consequences prior to an irreversible cortical resection. While microelectrodes have been used for years to focally stimulate and inactivate, focal cooling would likely provide more accurate functional localization in this situation.

Second, it should be possible to add thermoelectric devices to the recording grids presently used for invasive monitoring. These arrays of regularly spaced recording electrodes are implanted in the subdural space and typically kept in place for several days to provide accurate localization of a patient’s spontaneous seizures (23). These grids are routinely used in children, who are unable to cooperate for intraoperative localization under local anesthesia. If these grids had an array of thermoelectric devices, as well as electrodes, they could be used to cool the specific neocortical region from which seizures appear to arise to determine whether the seizures were aborted. This would enable the neurosurgeon to pinpoint the region which is needed to be resected, to prevent or abort a patient’s spontaneous seizures. Potential areas for resection could also be cooled to identify the possible consequences of reversible inactivation.

A third, and most ambitious objective, is to develop an implantable cooling device that could be activated on demand by a seizure detection or prediction algorithm (24–28). This alternative approach to neocortical resection would be an extremely attractive option in some patients, because it would avoid the neurological deficits associated with permanent cortical resections. Focal cooling might even make it possible to specifically target seizures arising in primary motor cortex and language areas, regions that have traditionally been out of bounds for epilepsy surgery. Transient loss of motor or language functions produced by cooling might be preferable to an uncontrolled seizure.

POTENTIAL PROBLEMS WITH FOCAL BRAIN COOLING

Despite the obvious appeal of cooling, there are technical hurdles that need to be overcome before focal brain cooling can be employed as a diagnostic and therapeutic tool for focal epilepsies, especially those arising from the neocortex. First, it is necessary to address a physical limitation associated with all thermoelectric devices—heat dissipation from the warm side of the wafer. In refrigeration devices and computers, heat is removed with fans or large metal heat sinks, which will not be available for thermoelectric devices implanted in the cranium. However, there have been significant advances in the fabrication of thin, bendable, and flexible heat pipes, some <0.5 mm thick, that could be attached to the warm side of our Peltier wafers. These heat pipes could efficiently transfer heat to the highly vascular dura, skull, or scalp, where blood flow would rapidly dissipate it through the body. These heat pipes could be made thin enough for insertion into a cortical sulcus, thereby allowing cooling of epileptic cortex partially buried within a sulcus. It is conceivable that thin, bendable
heat pipes could even be configured to cool the medial temporal lobe and provide an alternative to temporal lobe resections in that subtype of focal epilepsy.

Heat transfer will not be an issue for hand-held thermoelectric devices used for intraoperative mapping. The device we have already developed for use in rodents has a copper rod, which serves as both a handle and heat sink, attached to the thermoelectric device (20).

Second, the extent, if any, of cortical injury induced by cooling needs to be determined. While it is conceivable that direct contact with a thermoelectric device could damage cortex, even if the temperature is kept above 20°C, we have not observed damage several days after cooling for focal seizures (20). More recent experiments utilizing standard histological techniques have failed to reveal cortical damage after cooling to 5°C. When brain slices obtained from animals expressing the green fluorescent protein were cooled between 5 and 10°C, reversible dendritic swelling and spine loss were observed after 30 minutes (Yang and Rothman, unpublished data). Even more encouraging, basic neuroscience experiments have revealed no anatomic or electrophysiological evidence of neocortical damage after 1 and 2.5 years of daily cortical cooling to below 20°C for 1.5 hours, in the monkey and cat, respectively (7,8 and personal communication from Dr. Stephen Lomber). Nonetheless, it is possible that an implanted cooling device could damage the brain if left for years.

Third, the optimal temperature for cooling human epileptic cortex has not yet been determined. While we have found that we need to go below 26°C to abort seizures in the rodent 4-aminopyridine model, we need to recognize that this is a fairly severe experimental model, triggering seizures every one to two minutes for over two hours. It is reasonable to expect that more modest temperature reductions will be effective in preventing or terminating human focal seizures.

Fourth, practical development of an implantable cooling device will go much more quickly when algorithms that reliably detect or anticipate human seizures have been perfected. Much work has already been done on prototype programs, and while there are no unequivocally validated programs presently available, there are some encouraging preliminary results (24–29).

The technology required to make focal cooling for epilepsy a clinical reality, while not presently in hand, is within reach. Several mathematically sophisticated epilepsy research groups have made seizure detection and anticipation a major focus, and they have already had considerable success. Furthermore, the necessity for controlling microprocessor temperature in personal computers is driving research on thermoelectric devices and heat pipes at a rapid pace. A hand-held cooling device, applicable for intraoperative cortical mapping, could be available by the middle of the decade. This could pave the way for an implantable device by 2010, the centennial of Trendelenburg’s first reports on the functional effects of cooling the mammalian brain.

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