Dedication

To our patients and their families,
who continue to teach and challenge us
to improve our treatment of epilepsy

Foreword

Whenever a child presents with a seizure, physician, family and patient wonder about recurrence and whether it is epilepsy. The seizure type and possible epilepsy syndrome is to be delineated by careful clinical assessment and probable ancillary testing. The exact clinical approach to each patient depends upon the situation in which a seizure or seizures occurred, the associated factors, description of the events, and the child's comorbid conditions. Whether an acute illness, underlying neurologic or mental handicap, or seemingly progressive deterioration was present will determine whether to evaluate the child emergently or in the more routine fashion. Treatment decisions follow in the hope of stopping all seizure recurrence, producing no deleterious effects, and allowing as normal development as possible.

This book is intended to give practical information regarding the diagnosis and management of children with epilepsy through a case-based approach. Following a section entitled "The Basics," the editors have assigned child neurology experts to discuss various seizure, epilepsy, and disease entities so that the readers can adequately evaluate and form a treatment plan for each patient type. An age-based approach allows the reader to consider the appropriate conditions possibly presenting in their patient, and each clinical vignette discusses the essential characteristics, incorporating the differential diagnosis that should be considered.

This case-based approach is, in fact, the way most clinicians best learn to differentiate and manage various medical conditions. Epilepsy is no different. Indeed, we are all "students," each day learning about the nuances of pediatric epilepsy, its similarities and differences. Newer techniques of imaging, biochemical and genetic testing, and potential therapies through medication, surgery, and diet are all evolving. Each of us will find these case descriptions and discussions informative while reminding the reader of a "clinical pearl" or remembering "that case I saw… ." Seasoned clinicians will appreciate important lessons while reading about new techniques, while the novice medical professional will incorporate both basics and advanced understanding of pediatric epilepsy to use regarding their current and future patients. These case examples allow the clinician to appreciate the importance of establishing the epilepsy syndrome.

Although many will not read this text from cover to cover, my conviction is that most will refer to it many times, as they review the clinical scenario which best fits their individual patient or while they look for a specific test or find a reference regarding an entity that they suspect in their patient. All of us have and will continue to learn through case presentation and example. The editors and authors have indeed provided a real service in *Pediatric Epilepsy Case Studies: From Infancy and Childhood through Adolescence.*

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Preface

Epilepsy encompasses a wide variety of clinical syndromes characterized by heterogeneous etiologies, presentations, and prognoses. Accurate diagnosis is critically important for the proper care of patients with epilepsy, especially since some forms of epilepsy have a benign course whereas others are associated with progressive neurocognitive decline. Advances in neuroimaging and genetics have improved our diagnostic abilities and our fundamental understanding of the epilepsies. In addition, newer medications have offered patients better tolerability than traditional agents, but unfortunately, no significant improvements in overall seizure control have been afforded. Many epileptic conditions remain intractable to currently available medications. However, other nonpharmacological treatment options (such as the ketogenic diet and vagus nerve stimulator) may provide some hope for improved seizure control in these patients with medically refractory epilepsy.

For the physician in training, grasping the complexity and nuances associated with various epileptic syndromes can be daunting. The goal of this book is to help students, residents, and healthcare professionals understand the different epilepsies encountered in clinical practice across the pediatric age range. The initial section provides an introduction to the fundamentals of epilepsy, and subsequent sections include succinct case presentations and clinically relevant discussions of the more common epilepsy syndromes affecting each age group. Suggested references are also provided to guide the reader toward more detailed studies of a specific topic of interest.

This book is the culmination of a group effort involving many of the leading physicians and researchers in the field of pediatric epilepsy. We believe that their individual contributions together constitute a concise and practical reference for health professionals in training. Research in the field of epilepsy continues at a rapid pace, with the ultimate hope of curing many intractable epilepsy patients. We hope that this book may spark the interest of residents, trainees, and other healthcare professionals in joining the international fight against epilepsy.

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1 A Pediatric Epilepsy Primer

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CONTENTS

Epilepsy is a common, and commonly misunderstood, chronic medical condition of childhood. As frequently encountered as childhood asthma, convulsions occur in approximately 5% of all children in the United States, and 1% of children are diagnosed with epilepsy.[5,9,11,23] Appropriate diagnosis and management are crucial given the potential for lifelong consequences to the developing brain. Not all seizures need to be treated, as there are differences in the management of true epileptic conditions versus reactive or isolated seizures. An example of the former would be recognizing the clinical phenotype of infantile spasms, a particularly devastating type of developmental brain disorder. An illustration of the latter would be refraining from use of anticonvulsant medications for children with recurrent, brief febrile seizures. This common form of acute provoked seizure does not reflect an enduring epileptic condition, and daily preventative treatment is not warranted. Furthermore, there are many paroxysmal disorders affecting children, such as parasomnias and behavioral problems, which are frequently mistaken for epileptic phenomena. The epilepsies of childhood differ significantly both from each other as well as from those encountered in adulthood; the pediatric brain is not just a smaller adult brain. The key, then, is to understand what epilepsy is and what it is not, and to appreciate the unique age- and syndrome-dependent nature of epileptic conditions to guide proper diagnosis and management. In this introductory chapter, a few key points regarding pediatric epilepsy will be highlighted, and expanded upon in the remainder of this book.

PEDIATRIC EPILEPSY IS COMMON

Within the first two decades of life, approximately 5% of children will have experienced some form of convulsion. A significant majority of these seizures will be acute provoked events, often in the context of a febrile illness, and not the recurrent unprovoked seizures that are the hallmark of epilepsy. Among all children who have a single unprovoked seizure, only about 40% of them will ever have a second.[22] This rate of recurrence varies greatly depending on such factors as what type of seizure occurred and whether there is other evidence of neurological dysfunction. For example, a patient who, at baseline, has an abnormal neurological examination, abnormal electroencephalogram, and abnormal MRI may have a risk of recurrence of approximately 90%.[18] Of course, this does not indicate when a subsequent seizure might actually occur.

Approximately 20% of patients experiencing a convulsion of some type will later develop epilepsy: by 20 years of age, approximately 1% of the population will have been diagnosed with this condition.[11] Published studies of incidence vary greatly, which may be partly due to the inclusion of single unprovoked seizures as well as acute symptomatic seizures in some studies. With respect to age-specific incidence, it seems clear that the onset of epilepsy most frequently occurs at the two extremes of the lifespan. A number of studies have shown that the incidence of epilepsy is high in the first year of life, lowest in middle age, and rises again in the elderly. In a population of patients aged 70 years or more, the incidence is as high as 3%.[11] As one might imagine, the causes, types, and outcomes differ significantly between these two populations, although there is certainly some overlap.

PEDIATRIC EPILEPSY ENCOMPASSES A WIDE RANGE OF DISORDERS

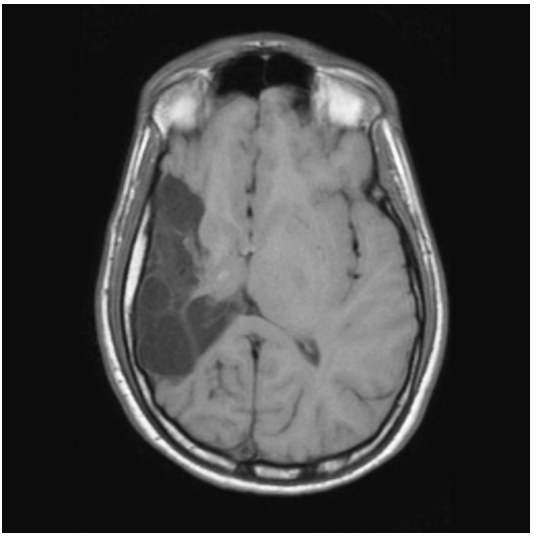
Imagine sitting in the waiting room of a pediatric epilepsy clinic and observing the variety of patients awaiting their turn to be evaluated. A 6-year-old child, initially referred for "staring spells," is now here for a follow-up appointment with well-controlled childhood absence epilepsy. In a wheelchair you see a 13-year-old child with spastic quadriparetic cerebral palsy, moderate mental retardation, and poorly controlled symptomatic localization-related epilepsy. She is here to have the settings on her vagus nerve stimulator adjusted in the hope that her secondarily generalized seizures might become less frequent. An 8-month-old infant has been worked into the schedule, with continued clusters of infantile spasms despite completing a trial of adrenocorticotropic hormone (ACTH). A new patient is here for a second opinion about whether or not his brief stereotyped events of generalized shaking with partial loss of consciousness are epileptic in nature. Finally, there is an 8-year-old for a 6-month postoperative follow-up visit after a focal neocortical resection to remove an area of cortical dysplasia, who happily remains seizure free. As different as these patients may be in age, clinical phenomenology, and response to therapy, they all have epilepsy. Clearly, this is a heterogeneous collection of distinct disorders, which may more appropriately be referred to as "the epilepsies." To understand this clinical

spectrum, one must be familiar with both what unifies these conditions and what makes each distinct.

The definition of epilepsy is deceptively simple: having two or more unprovoked seizures separated by more than 24 hours. Each component of that definition is important to bear in mind. Seizures are paroxysms of abnormally hyperexcitable and hypersynchronous cortical activity that result in a change in sensation, motor function, behavior, or the sensorium. If the seizure occurs immediately following a precipitating event, then it is referred to as an acutely provoked/reactive seizure or acute symptomatic seizure. As mentioned previously, a common example of such an event would be a febrile seizure: 2 to 4% of all children between the ages of 6 months and 5 years experience a generalized seizure lasting less than 15 minutes in association with a fever not caused by a central nervous system (CNS) infection. In this case, the acute provoking event—the fever—is immediately followed by the seizure. Other examples of acute symptomatic seizures would include those that occur at the time of trauma, in the context of hyponatremia, or in association with a withdrawal syndrome (e.g., alcohol). In contrast, with epilepsy, there is no immediate provoking event for the seizure. At times, the seizure may arise from an old injury such as from a prior stroke. Because the precipitating event precedes the seizure by weeks to years, such an event is considered unprovoked and is often referred to as a "remote symptomatic seizure." Finally, in order to meet the definition of epilepsy, two or more unprovoked seizures must be separated by more than 24 hours. The reason for this is that rapidly recurrent seizures occurring close together carry the same epidemiological risk of eventual recurrence as a single seizure.[12]

If a patient has two or more unprovoked seizures, then that patient may justifiably be labeled as having epilepsy. Given the broad nature of this definition, many different types of clinical phenotypes fall under the cover of this one large umbrella. It is a bit like stating that one lives in North America—helpful information but not very specific! Nowhere is this more evident than in the pediatric epilepsies in which cause, clinical phenomenology, and outcome vary greatly. As with the epilepsies that arise in adulthood, children may suffer seizures as a consequence of trauma, CNS infections, strokes, and other brain insults. A particular example of this would be children who suffer injuries in utero or during the process of birth. Largely unique to childhood are seizures that arise from developmental brain malformations such as disorders of neuronal migration leading to focal cortical dysplasias. It is interesting to note, however, that although the abnormally formed cortex is present from birth, an epileptic disorder may not develop for many years. The reasons for this remain unclear.

To bring some semblance of order to this landscape, the epilepsies have historically been categorized or classified on the basis of electroclinical features. Clinically, this is accomplished using a schema developed by the International League Against Epilepsy (ILAE), which utilizes etiology and seizure type.[4,6] If the patient's epilepsy arises from an evident cause, such as a remote symptomatic seizure due to an old brain injury, then the epilepsy is referred to as *symptomatic* (Figure 1.1). In general, the abnormal area of the brain will be evident on MRI or other imaging modality. Another example of a symptomatic epilepsy would be one arising from a focal cortical dysplasia. However, some epilepsies are caused not by a clear anatomic abnormality but are instead inherited—either as a single mutation or, more

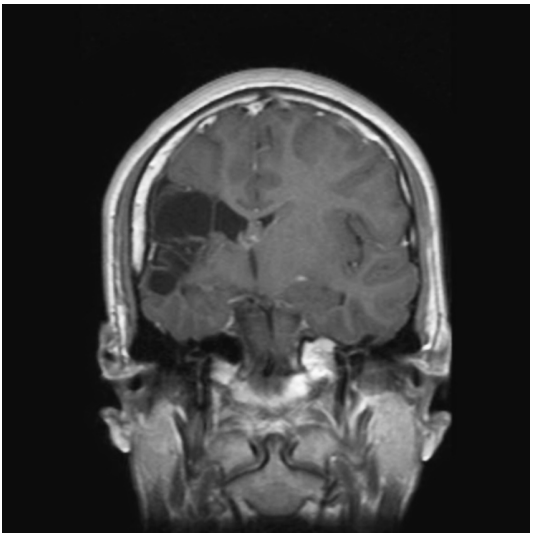


(A)

FIGURE 1.1 MRI images and EEG data from a teenager with symptomatic localization-related epilepsy. This 15-year-old right-handed boy had left-sided hemiplegic cerebral palsy and startle-induced complex partial seizures. Panels A and B are representative T1-weighted postcontrast MRI images (coronal and axial planes, respectively) demonstrating the damage caused by an in utero right middle cerebral artery territory infarction (the left side of the image corresponds to the right side of the brain). Panel C shows the patient's EEG immediately prior to and following an auditory startle as well as several seconds into his typical electrographic ictal discharge. Note the high-amplitude slow activity with superimposed faster frequencies in the leads labeled Fp2-F4, F4-C4, and C4-P4, indicating that the seizure is arising from the right frontocentral region (by convention, EEG leads with even numbers are on the right, and those with odd numbers are on the left; Fp = Frontal polar, F = frontal, C = central, and P = parietal). The patient underwent definitive surgical resection and remains seizure free off medication after more than 4 years.

commonly, as a collection of interacting mutations. Epileptologists refer to such epilepsies as *idiopathic*. Several common epilepsies of childhood, such as childhood absence epilepsy and benign Rolandic epilepsy, are considered idiopathic. Finally, some epilepsies occur in patients without an evident cause: the MRI is normal, there is no clear heritability, and no aspect of the workup reveals a potential etiology. These epilepsies are labeled *cryptogenic*—literally meaning that the cause is hidden. One of the primary goals of the epilepsy research community is to abolish the need for this category by increasing our understanding of what causes epilepsy as well as expanding our repertoire of tools available for diagnosis.

In addition to etiology, the present classification scheme utilizes seizure type as a criterion. Seizures that arise from a particular region of the brain are labeled *partial*, whereas seizures that involve both hemispheres from onset are referred to as *generalized*. Rather than using the term "partial" when categorizing the epilepsies, the ILAE scheme has adopted the term *localization related*. It should be noted

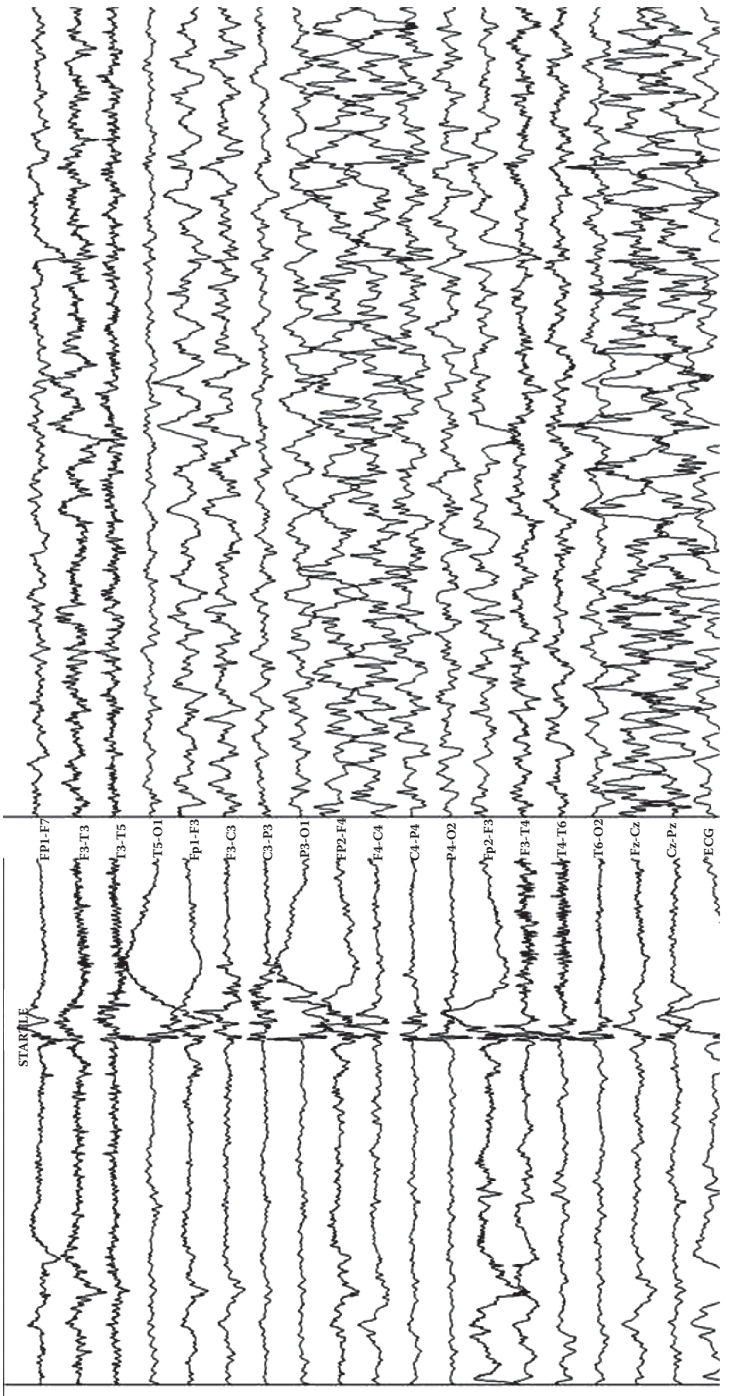


(B)

FIGURE 1.1 (continued)

that seizures may begin focally (as a partial seizure) and then spread to involve the other hemisphere. Such a seizure is said to be *secondarily generalized*. Although not utilized in the classification scheme, partial seizures are further divided into *simple partial seizures* if they do not affect consciousness, and *complex partial seizures* if consciousness is in any manner impaired. Putting the etiologic and phenomenological criteria together yields the appropriate classification. For example, epilepsies may be *symptomatic localization related* (a clear anatomic cause affecting just one part of the brain), *idiopathic generalized* (an inherited epilepsy producing seizures that affect both hemispheres at the outset, such as childhood absence epilepsy), *cryptogenic localization related* (epilepsy with no clear etiology, which arises from a restricted focus), or any other combination of terms. As will become clear in the chapters to follow, utilizing this scheme is helpful in determining an appropriate evaluation and management strategy.

Another peculiarity of pediatric epilepsy is the concept of an epilepsy syndrome: a constellation of a particular type of seizure (or seizures), EEG features, and other clinical phenomenon often associated with a particular age of onset. For example, West syndrome represents the combination of infantile spasms (a particular type of seizure), an interictal EEG pattern called hypsarrhythmia, and developmental arrest or regression with a peak age of onset between 3 and 7 months of age.[15] Although still clinically diverse, epilepsy syndromes seem to represent a more homogeneous clinical population than is afforded by the ILAE classification scheme. For example, childhood absence and juvenile myoclonic epilepsy are both categorized as idiopathic generalized epilepsies, but they differ significantly in their age of onset, predominant seizure type, and rate of remission.



(C)

FIGURE 1.1 (continued)

PEDIATRIC EPILEPSY VIEWED FROM A DEVELOPMENTAL CONTEXT

The CNS is unique in that its development extends from early embryonic life, throughout childhood, and even into early adulthood. This has implications for both the causes and consequences of pediatric epilepsy as well as its treatment. An important determinant of the effects of a developmental insult is the ontogenetic stage at which it occurs. For example, failure of the anterior neuropore to close in the fourth embryonic week would cause anencephaly, whereas an insult in the second trimester might cause a focal cortical dysplasia.[21] For reasons that remain incompletely understood, the immature nervous system seems to be uniquely susceptible to developing seizures. Another way to state this is that the "seizure threshold" of the developing nervous system seems to be lower than that of the adult nervous system. At least part of this susceptibility may be secondary to the ongoing ontogenetic processes of the immature brain.[3,24]

One possible contributor to the decreased seizure threshold of the immature nervous system is a physiological imbalance of excitation and inhibition. In general, excitatory synaptic connections develop before inhibitory ones. Further, very early in development, it appears that inhibitory neurotransmission is actually depolarizing and therefore possibly excitatory. This appears to be due to the developmental expression of a particular type of cation chloride cotransporter that produces a more positive (depolarized) chloride reversal potential than what is found in the mature nervous system.[7] This is a potentially clinically relevant physiological phenomenon because most first-line anticonvulsants used to treat neonatal seizures—barbiturates and benzodiazepines—act by increasing inhibition. Maturation of the GABA-ergic system also involves expression of different receptor isoforms as well as unique modulatory neuropeptides (such as somatostatin). Overall, relatively late emergence of functional inhibition may increase the propensity of the CNS toward excessive excitation, which increases the likelihood of seizures.

The process of synaptogenesis involves abundant synapse formation followed by activity-dependent pruning of ineffective, aberrant, or unnecessary connections. Such developmental plasticity requires the developing nervous system to be uniquely responsive to environmental effects. Because of this, insults can have pervasive and persistent effects. Excessive activity during critical periods of development may strengthen neuronal pathways that subsequently form a seizure focus or become pathways of seizure propagation. Indeed, this may be one important component of the process of developmental epileptogenesis. Relative immaturity of cortical connections is also important for the clinical appearance of seizures. For example, neonates, who physiologically lack extensive well-formed intercortical and interhemispheric connectivity, do not exhibit generalized seizures.

Formation of the cerebral cortex is an intricate and remarkable process that begins with cells becoming neurons near the ventricles, followed by migration of these new neurons to their appropriate location in the cortex.[16] Interestingly, this process proceeds in an "inside-out" fashion—with the most recently generated neurons migrating through cells forming the more inner cortical layers. This choreographed relocation of cells involves glial cells, called radial glia, upon which the neurons migrate, as well as morphological cues to guide their entrance to and exit from this

pathway. As might be expected, given the inherent complexity of this process, not all cells successfully reach their designated location. Such "heterotopic" neurons are likely of little consequence if found in isolation, as they are a common incidental finding in the brains of normal individuals without epilepsy. However, in some patients, a collection of neurons fails to completely migrate and may become a focal cortical dysplasia.[20] The extent of dysplastic cortex can range from quite restricted to very extensive. For reasons that are incompletely understood, such foci of an abnormally formed cortex are often highly epileptogenic and are commonly found in children with localization-related epilepsy.

In addition to the developmental causes of epilepsy, clinicians caring for children with epilepsy must always be mindful of the potential developmental consequences of our treatments.[13] Antiepileptic medications, in general, act by increasing inhibition or decreasing excitation. Such therapeutic manipulations interact with the ongoing process of synaptogenesis and may alter cognitive processes. This is one important reason to be judicious in the use of medical therapy because it can carry its own set of potential morbidities.

A WIDE RANGE OF TREATMENT OPTIONS IS AVAILABLE

Once the diagnosis of epilepsy has been made, consideration turns to appropriate treatment. Some forms of childhood epilepsy may not require any intervention other than education and reassurance. For example, benign Rolandic epilepsy is a common idiopathic localization-related epilepsy of childhood that spontaneously resolves by the age of 20.[8] Benign Rolandic epilepsy is also referred to as "benign epilepsy with centro-temporal spikes" (BECTS). Approximately 60% of patients with this condition experience very few seizures. When seizures do occur under such circumstances, an abortive therapeutic option—such as a rectally administered form of diazepam—is often prescribed in lieu of daily medical therapy. For those children with recurrent unprovoked seizures that are sufficiently frequent to require intervention, there are at least 16 different medications from which to choose. Factors such as type of epilepsy, age of the patient, and comorbidities are important considerations in deciding which medication to use. Perhaps the single most important factor in medication choice is the specific side-effect profile of the drug and its suitability for a particular patient. Overall, approximately 60% of patients will become seizure free with one of the first two anticonvulsants prescribed.[17] Unfortunately, for those whose epilepsy does not respond, the chance of treatment success with subsequent medication trials is much less. For this reason, patients who do not respond to one of the first two or three medications are referred to as "medically refractory."

Fortunately, there is an ever-increasing range of options for patients with medically refractory epilepsy. One possibility is the use of the ketogenic diet: a high-fat and low-carbohydrate protocol, which results in ketone body production and which produces improved seizure control.[10] For certain carefully selected patients, the best option is epilepsy surgery: for example, neurosurgical removal of the focus of the epileptogenic cortex. Examples of such procedures range from focal neocortical resection for patients with an area of cortical dysplasia to removal of the anterior temporal lobe in patients with temporal lobe epilepsy to hemispherectomy in patients with