Clifford R. Jack, Jr, MD

Epilepsy: Surgery and Imaging[1]

THE purpose of this article is to provide a review of the history, classification, epidemiology, imaging, and some aspects of surgical management of epilepsy. While epilepsy is sometimes viewed as simply an electrophysiologic disturbance, it actually can be defined in terms of a number of different neuroscientific parameters. In addition to those of electrophysiology, abnormalities in gross and microscopic anatomy, cell morphology, neuropharmacology, neurochemistry, molecular genetics, cerebral perfusion, and metabolism have all been identified. Many of these topics are not discussed in this article, which focuses on surgery and imaging.

HISTORY

The word *epilepsy* is derived from the Greek word *epilepsia,* meaning "to take hold of or seize." Recorded references to epilepsy date back about 7,000 years; however, epilepsy was not distinguished from psychiatric disease or other conditions producing a sudden loss of consciousness or odd behavior (1,2). The concept that epilepsy was due to a hereditary or acquired dysfunction of the brain surfaced in the ancient Greek culture (3). While the idea that epilepsy had a biologic basis was correct, treatments for epilepsy practiced at this time were ineffective. These included dietary change, phlebotomy, trephining, cauterization of the skull (to allow egress of pathologic humors), circumcision, and castration. In parallel with the notion of epilepsy as a disease of biologic origin, however, was the supernatural belief that epilepsy was caused by demonic possession. The latter view prevailed in the European culture of the Middle Ages.

The concept of epilepsy as a supernatural disease was gradually replaced by an awareness of its biologic origins during the 1800s in Europe (1). Against this background, the modern understanding of epilepsy began in the 1860s with the studies of John Hughlings Jackson (1835–1911) (4,5). Through a careful study of patients with partial seizures, he is credited with introducing the idea that seizures are due to an excessive, uncontrolled discharge originating within the cerebral gray matter. Furthermore, he postulated that seizures of focal onset were due to an abnormal electric discharge arising from localized areas of cortex and that the specific clinical manifestations of individual seizures depend on the site of origin and spread. Victor Horsely, a colleague of Hughlings Jackson, performed the first cortical resection for epilepsy in 1886 on a patient who suffered from focal motor seizures due to a posttraumatic cortical scar (6). Over the next 40 years, a number of surgeries for focal epilepsy were performed in Europe employing the following lesion-directed approach (7,8). The site of seizure onset was first roughly localized by using clinical signs and symptoms and, when available, imaging techniques such as plain skull radiography and pneumoencephalography. After a craniotomy was performed, detailed electric stimulation of the cortex was undertaken to define the epileptogenic zone (by reproducing the patient's aura) and also to define functionally eloquent cortex.

Surgery directed with electroencephalography (EEG) was developed in the 1930s and 1940s. This stands in contrast to lesion-directed procedures in the pre-EEG era. The invention of the human EEG by Hans Berger, a German psychiatrist, in 1924 (9) permitted a more profound understanding of the relationship between ictal seminology and underlying electric events. During the 1930s and 1940s the role of the temporal lobe in epileptogenesis was first appreciated (10–13), which in turn led to development of the procedure of anterior temporal lobectomy (14–17). Credit for recognizing complex partial seizure disorders as a major distinct epileptic syndrome most often arising from the temporal lobe is generally shared by Gibbs, Gibbs, Lennox, and Jasper (10–13). The most prominent figure in epilepsy surgery in this period (probably in this century) was Wilder Penfield (1891–1976), who established the Montreal Neurologic Institute in 1934 (18).

The development of cross-sectional neuroimaging techniques in the 1980s, particularly magnetic resonance (MR) imaging, ushered in the next phase in the surgical approach to epilepsy. In the pre–MR imaging era, the surgical target was defined by means of EEG criteria alone; the histologic substrate of epilepsy (the epileptogenic lesion) was often unknown until the surgical specimen was analyzed. Modern MR imaging, however, will demonstrate preoperatively nearly every epileptogenic lesion seen on a standard microscopic pathologic

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Abbreviations: EEG = electroencephalography, FDG = fluorodeoxyglucose, HMPAO = hexamethyl-propyleneamine oxime, MEG = magnetoencephalography, MST = mesial temporal sclerosis, PET = positron emission tomography, SE = spin echo, SPECT = single photon emission CT, SPGR = spoiled gradient echo, TE = echo time, TR = repetition time.

study. This correlation has led to increased reliance on MR imaging over the past 5 years both in determining the surgical target and in selecting patients for surgery (19).

CLASSIFICATION OF EPILEPTIC SEIZURES AND EPILEPTIC SYNDROMES

A seizure is a discrete clinical event. Epilepsy, on the other hand, is a condition characterized by recurrent unprovoked seizures. All patients with epilepsy have seizures; however, all individuals who experience a seizure do not necessarily have epilepsy. An important distinction is made between epileptic *syndromes* and epileptic *seizures*. Seizures that occur in short-term direct response to an acute event resulting in brain insult are termed "acute provoked seizures," and patients with such seizures are not considered to have epilepsy. Acute febrile convulsions in childhood are the most common example of acute provoked seizures; other examples are seizures that occur in response to acute head trauma, acute stroke, or alcohol withdrawal. Conversely, patients who experience recurrent seizures over months or years are considered to have epilepsy. Patients who experience a single (provoked or unprovoked) seizure are not classified as epileptics.

Epileptic Seizures

The modern classification of epileptic seizures was proposed in 1981 and adopted in 1984 (Fig 1) (20). It is based on both clinical and EEG findings. The clinical manifestations of a particular seizure depend on the site of origin of the discharge and the site or sites of spread. Seizures may be divided into two broad categories: partial seizures (synonyms are local, focal, or localization related), which begin with discharge of a circumscribed set of neurons, and primary generalized seizures, in which the onset of epileptic activity occurs simultaneously throughout the brain. Partial seizures are in turn divided into three broad categories. Simple partial seizures are those that do not result in impairment of consciousness. These most frequently begin in the sensorimotor, supplementary motor, or visual cortex. Complex partial seizures (previously called psychomotor seizures when originating in the temporal lobe) are those that have a focal onset and do result in impairment of consciousness. These may be accompanied by abnormal behaviors called automatisms. Complex partial seizures most frequently begin in the temporal lobe or less often the anterior or basal frontal lobe. Finally, a third category has been recognized under the general class of partial seizures, which is partial seizures evolving secondarily to generalized seizures.

- I. Partial (focal, local, localization related) seizures
  - A. Simple partial seizures
    - 1. With motor signs
    - 2. With somatosensory or special sensory symptoms
    - 3. With autonomic symptoms or signs
    - 4. With psychic symptoms
  - B. Complex partial seizures
    - 1. Simple partial onset followed by impairment of consciousness
    - 2. With impairment of consciousness at onset
  - C. Partial seizures evolving to secondarily generalized seizures
    - 1. Simple partial seizures evolving to generalized seizures
    - 2. Complex partial seizures evolving to generalized seizures
- II. Generalized seizures (convulsive or nonconvulsive)
  - A. Absence absences
    - 1. Typical absences
    - 2. Atypical absences
  - B. Myoclonic seizures
  - C. Clonic seizures
  - D. Tonic seizures
  - E. Tonic-clonic seizures
  - F. Atonic seizures (astatic seizures)
- III. Unclassified epileptic seizures

Figure 1. International classification system for epileptic seizures.

Generalized seizures have been subdivided into convulsive and nonconvulsive types, but the definition of these terms has been imprecise. The nonconvulsive forms include those seizure types characterized primarily by lapses of consciousness. Absence seizures (formerly known as petit mal seizures) are most typically seen in the pediatric age group. These are characterized by a sudden loss of awareness of the environment with staring. The convulsive generalized seizures are tonic-clonic (formerly called grand mal seizures), purely clonic, purely tonic, or atonic. Tonic refers to stiff extensor posturing of all the extremities. Clonic refers to rhythmic motions of the extremities. Myoclonic seizures are characterized by a brief muscular contraction or contractions of central nervous system origin.

Epileptic Syndromes

The most widely accepted classification of epileptic syndromes is that proposed in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy (21). This classification scheme is based on three features: whether the seizures that characterize the epileptic disorder are partial or generalized, whether the disorder is idiopathic or symptomatic (the term idiopathic is used to indicate epileptic syndromes with no apparent cause; the term symptomatic is used to indicate syndromes in which an obvious cause—tumor, remote stroke, etc—is known or suspected), and the age of onset of recurrent unprovoked seizures. Certain epileptic syndromes are characterized by a specific window of onset and, in some cases, by spontaneous remission. For example, West syndrome (infantile spasms) always manifests before the age of 1 year; Lennox-Gastaut syndrome, in children age 1–8 years; and juvenile absence epilepsy, around puberty.

EPIDEMIOLOGY

Incidences for epilepsy of all types are on the order of 30–50 new cases per 100,000 person-years and are bimodal, with the greatest incidence in the very young and the elderly (22–24). This trend holds true across population studies from different countries. The incidence of epilepsy by seizure type also varies with age. Myoclonic seizures are the most common type during the 1st year of life but diminish in incidence afterward. Absence seizures, common in the young, diminish in incidence over the first 2 decades of life and are extremely rare in children older than 14 years. The incidence of both generalized tonic or clonic and partial seizures is fairly flat until age 60–65 years, at which point the incidence

increases, particularly for partial seizures. The incidence of epilepsy is slightly higher in men than women at all ages and for all seizure types with the exception of absence epilepsy, which has twice the incidence in girls as in boys. The cause-specific incidence of symptomatic epileptic syndromes varies with age, as well. The most common known underlying cause of epilepsy in the 0–4-year age group is related to developmental anomalies or postnatal insults. Remote head trauma is the most common cause of epilepsy in the 15–24-year age group. Cerebral vascular disease becomes the most common cause in the over 45 year age group and accounts for the vast majority of new-onset seizure disorders in adults older than 65 years. The increasing incidence of cerebral vascular disease with age is the major factor for the sharp rise in epilepsy incidence after age 65 years. It should be noted, however, that a specific antecedent cause of epilepsy is identified in only approximately 30% of cases.

Both incidence and remission rates must also be considered in order to appreciate the impact of epilepsy on a population. Contrary to popular belief, epilepsy is not necessarily a lifelong condition. It is estimated that 60%–70% of patients with epilepsy will attain complete seizure control with medication alone, and in 40%–90% of these, seizure medication may ultimately be withdrawn without seizure recurrence.

Approximately 5%–10% of all new cases of epilepsy (from a total of 10,000 new cases annually in the United States) will ultimately become medically intractable. In these patients, seizures occur with sufficient frequency despite optimal drug therapy to warrant consideration of surgery for seizure relief. The proportion of patients with "intractable disease" varies with seizure type. The majority of adults with medically intractable epilepsy have complex partial seizures with the site of origin in the temporal lobe. The standard surgical approach to epilepsy (focal cortical resection) is applicable only for those with a seizure disorder of focal onset. It is estimated that approximately 3,000–5,000 new people per year in the United States are candidates for surgical resection for medically intractable epilepsy (25). Furthermore, there may be an existing pool of up to 150,000 people in the United States whose seizures are inadequately controlled with medication and may be surgical candidates.

EPILEPSY SURGERY

Selection of Surgical Candidates

To be considered a candidate for a standard surgical procedure (focal cortical resection), a patient must have disabling seizures that are refractory to maximum-tolerated antiepileptic medications and a localized site of seizure onset the resection of which will not produce a significant functional deficit. Generally, a period of at least 2 years of intense medical therapy is necessary before medical failure is conceded. Factors that indicate a high likelihood of intractability are abnormal neurologic status, presence of a structural lesion on MR images, secondary generalization of partial onset seizures, frequent or clustered seizures, and seizure onset at an early age.

Preoperative Evaluation

The "epileptogenic zone" is the surgical target. It is a theoretical concept (which in practice may be elusive) defined as that area of cortex that must be totally resected to eliminate the patient's seizures (26). Each of the following "zones" are defined by the output or localizing properties of a particular modality, which is related to the epileptogenic zone with varying degrees of precision. The "irritative" zone is defined as the region of cortex that generates interictal epileptiform discharges (ie, interictal spikes or sharp waves best defined by scalp EEG recording). The "pacemaker" zone is defined as the set of cortical neurons from which the habitual seizures originate and is essentially always a subset of the neurons within the epileptogenic zone. The "ictal symptomatic" zone is determined by clinical observation and is defined as the region of the brain which, when activated, elicits the aura. An "epileptogenic lesion" is defined with MR imaging, computed tomography (CT), or pathologic study and is a structural lesion that produces the seizure disorder. The "functional deficit" zone is the area of the brain that functions abnormally in the interictal period. This can be identified by means of neuropsychologic, speech, language, or amobarbital testing, or physiologic neuroimaging studies (interictal positron emission tomography [PET] or single photon emission CT [SPECT]). The degree to which these "zones" overlap varies among patients. There may be complete overlap—for example, in a patient with a small benign tumor in the precentral gyrus with simple partial motor seizures—or very little overlap. The latter types of cases present the greater challenge in localizing the epileptogenic zone.

Satisfactory postsurgical seizure control is dependent on preoperative identification and resection of the epileptogenic zone. Unfortunately, no single technique precisely defines the epileptogenic zone, yet this is the desired surgical target. In practice, the surgical target is defined by identifying zones of the brain that are related to the epileptogenic zone. Techniques for EEG recording, brain imaging, and evaluation of the brain physiologically have proliferated in recent years, and the "standard" preoperative evaluation of a patient being considered for epilepsy surgery has mushroomed to include all of these—EEG; MR imaging; SPECT; PET; neuropsychologic, psychiatric, speech, and language evaluation; sodium amobarbital testing; and at some centers MR spectroscopy or magnetoencephalography (MEG). The driving logic is that each of these tests has independent value in terms of localizing the epileptogenic zone. Each of these studies is evaluated independently, and concordant localization between the different tests provides confident localization of the epileptogenic zone.

All patients undergo interictal EEG scalp recording studies. While interictal epileptiform discharge can provide important localizing information when present, this is often too imprecise or even misleading in localizing the epileptogenic zone. Therefore, the cornerstone of the presurgical evaluation is long-term video EEG monitoring. Video EEG coupling allows precise correlation between clinical and electrographic findings during ictus. These studies are performed on inpatients or semiambulatory patients in whom seizure medication is withdrawn and ictal events are recorded. The EEG recording medium may be noninvasive (scalp electrodes), semiinvasive (eg, sphenoidal or foramen ovale electrodes), or invasive. Invasive electrodes are of two types: (*a*) Subdural strips or grids consist of stainless steel or platinum disks embedded in sheets or strips of polyurethane; (*b*) depth electrodes are multiple contact needles that are inserted into the brain through a burr hole(s) usually under stereotaxic guidance. The advantages and disadvantages of noninvasive versus invasive recording methods center on issues of sensitivity and anatomic coverage. Scalp electrodes allow one

to survey the entire cranial vault simultaneously, whereas the invasive recording techniques sample only a limited area of cortex. In addition, scalp recording is not associated with the surgical risk or surgical expense of invasive techniques. The primary disadvantage of scalp recording is lack of sensitivity to cortical generators, particularly those deep to the lateral cortical surface. The definition of appropriate clinical indications for noninvasive versus invasive EEG recording has generated considerable controversy. Until very recently at some centers, virtually all epilepsy surgeries were preceded by invasive EEG recording, while at others most surgeries were preceded only by scalp recordings.

Aside from localization of the epileptogenic zone, a second important function of electrographic techniques is localization of functionally eloquent cortex in relation to a surgical target. This is most important when considering resections near sensorimotor, visual, or speech and language areas. Functional mapping may be performed intraoperatively or extraoperatively. Extraoperative functional mapping is preceded by insertion of subdural grids or strips, which are used to record sensory-evoked potentials or to perform cortical stimulation studies. Intraoperative functional mapping may be performed either with the patient awake or under general anesthesia.

Neuroimaging studies are perhaps the next most important test(s) in the preoperative evaluation of potential surgical candidates and will be covered in detail subsequently.

Neuropsychologic testing, as well as speech and language testing, is performed pre- and postoperatively to identify deficits that might result (or have resulted) from surgery. By identifying the functional deficit zone, these tests may also help localize the epileptogenic zone.

Intracarotid amobarbital testing is performed in virtually all patients undergoing a temporal lobectomy. The carotid amobarbital test was introduced by Wada (27) in 1949 to localize the speech-dominant hemisphere. The test was later expanded by Milner et al (28) to predict material-specific postoperative memory deficits. However, the ability of the carotid amobarbital test to predict postoperative neuropsychologic deficits—specifically the verbal learning and memory deficit that may accompany a dominant temporal lobectomy—has been controversial. At most epilepsy centers, few otherwise qualified surgical candidates are denied a temporal lobectomy because they have "failed" the carotid amobarbital test (29,30). Accordingly, other forms of testing have been investigated that employ more selective irrigation of the medial temporal lobe structures with amobarbital either via the anterior choroidal artery (31) or the posterior cerebral artery (32,33). The objective of these alternative amobarbital procedures has been to deliver the amobarbital more precisely to the target tissue (in this case, the medial temporal lobe that has been identified as crucial in acquisition of declarative memory) while not perfusing the remainder of the hemisphere.

Surgical Methods

Epilepsy surgeries can be divided into two broad categories: (*a*) focal cortical resection (including temporal and frontal lobectomy) and (*b*) hemispherectomy and corpus callosum resection.

Focal Cortical Resection

Depending on the institution, 90%–99% of all epilepsy surgeries will consist of focal cortical resection.

Temporal lobectomy.—Temporal lobectomy is the most effective, the most common (accounting for 75%–90% of all cortical resections at most centers), and the safest surgical procedure for epilepsy. Different types of temporal lobectomy have been described in the literature and remain in use today; however, three broad approaches can be described (34). (*a*) Temporal lobectomy based on intraoperative electrocorticography (ie, direct EEG recording from the cortex during surgery) is driven by the premise that interictal epileptic discharges recorded during surgery are the primary tool by which the degree of cortical resection is determined (17,35). (*b*) In en bloc anterior lobectomy, the lateral neocortex and mesial temporal structures are removed en bloc a standard distance posterior to the temporal pole (greater on the nondominant than the dominant side) with the patient under general anesthesia (16). (*c*) Anterior medial temporal lobectomy (36) and selective amygdalohippocampectomy (37) were devised with the goal of extensively removing the medial temporal structures including the amygdala, uncus, hippocampus, and adjacent parahippocampal tissue, while sparing all or most of the lateral neocortex. Controversy exists as to which procedure is indicated and under what circumstances.

Extratemporal resections.—Because much of the anterior portion of the frontal lobe is "functionally silent," a true frontal lobectomy can be performed. The posterior margin of the resection is determined by means of the presence or absence of a lesion defined at MR imaging (the resection must include the lesion), EEG recording, and functional mapping of the sensorimotor cortex, which must be spared. Nearly all nonfrontal extratemporal cortical resections are guided by invasive EEG recording to determine as precisely as possible the extent of the epileptogenic zone, as well as functional mapping of eloquent cortex. The presence or absence of an MR-defined lesion greatly influences the surgical approach taken.

Hemispherectomy and Corpus Callosum Resection

Even at the major epilepsy centers these surgeries are rare. A hemispherectomy or partial hemispherectomy is usually considered in patients with severe, disabling seizure disorders in whom widespread hemispheric anatomic abnormalities are present, such as Sturge-Weber syndrome, chronic encephalitis (Rasmussen syndrome), damage from infection or infarction in early life, hemimegalocephaly, or other widespread unilateral disorders of neuronal migration. The surgery is usually performed only in infants in order to allow for functional reorganization. A second radical surgical procedure is that of corpus callosum resection. This is a palliative, not curative, procedure. The aim is to disrupt the spread of seizures from one hemisphere to the other by interrupting the major interhemispheric fiber tracks. This type of surgery is usually reserved for the treatment of disabling intractable convulsive seizures in young children. A distinction is made between callosum resection in which the corpus callosum is partially or completely sectioned and a commissurotomy in which the corpus callosum and one or more of the commissures and fornix are sectioned.

Surgical Outcome

The ultimate goal of epilepsy surgery is to improve the overall well-being of the patient with medically intractable epilepsy (26,38). In the past, the goal of seizure surgery and evaluation of its outcome have been narrowly limited to an assessment of seizure control. More recently, how-

ever, it has been recognized that elimination of or dramatic reduction in the frequency of seizures is but one element to be considered. Others are cognitive, behavioral, and psychiatric dysfunction; interpersonal relationships; ability to drive; dependency; and employment. Elimination of seizures following surgery does not guarantee improvement in quality of life. In fact, these factors often remain unchanged and may worsen postoperatively even if excellent seizure control is achieved.

The most widely used classification scheme that addresses seizure control alone was proposed by Engel (38). This is a four-tiered scheme in which class I is defined as seizure free; class II, rare seizures; class III, worthwhile improvement; and class IV, no worthwhile improvement. The best surgical results are obtained with temporal lobectomies, while less satisfactory results are reported with extratemporal resections. Anywhere from 70% to 90% of patients may expect a seizure-free outcome following temporal lobectomy. Extratemporal resections result in a seizure-free outcome in less than 50% of patients. The presence of a focal resectable abnormality at MR imaging (structural lesion or mesial temporal sclerosis [MTS]) confers a markedly more favorable prognosis than a negative MR study (39–43).

ROLE OF IMAGING IN EPILEPSY SURGERY

The role of imaging in epilepsy surgery can be divided into two broad categories: (*a*) identification of focal imaging abnormalities that help localize the epileptogenic zone and (*b*) identification of the anatomic relationship between the surgical target and functionally eloquent cortex.

Localizing the Epileptogenic Zone

Imaging modalities that help localize the epileptogenic zone can in turn be divided into three broad categories: anatomic imaging modalities: MR and CT; physiologic imaging modalities: PET, SPECT, and xenon CT; and a metabolic or biochemical modality: MR spectroscopy.

Anatomic Imaging: MR Imaging

Epileptogenic lesions are identified with the structural or anatomic cross-sectional imaging modalities: CT or MR imaging. While CT will demonstrate many epileptogenic lesions, the overall sensitivity of MR imaging in the detection of structural epileptogenic abnormalities is higher (44–48). This is particularly true for lesions in the temporal lobe, where beam-hardening artifacts limit the utility of CT. The advantage for MR imaging is markedly more pronounced for certain pathologic conditions such as small neuronal migration anomalies and MTS. For practical purposes, MR imaging has replaced CT as the anatomic imaging modality in epilepsy.

Universally accepted criteria that define when an MR imaging study is indicated in a patient with seizures have not been identified, to my knowledge. One approach is to study all patients with partial-onset seizures with use of MR early in their clinical course. The rationale for performing MR imaging in patients with medically refractory partial-onset seizures who are being considered for surgery is self-evident. However, MR imaging is also performed early in partial-onset patients whose conditions are well controlled medically, because identification of a lesion may alter the choice of medication (parenthetically, patients with lesions are usually not well controlled medically). Most patients with generalized-onset seizures are well controlled medically, and these patients are not imaged. Patients classified as having generalized-onset epilepsy and who are poorly controlled are imaged; classification by means of clinical and interictal scalp EEG criteria is not infallible, and identification of a lesion on MR images of these patients may prompt a reevaluation of the EEG and may sometimes change the classification from generalized to partial onset. A more aggressive approach is to image all patients at the time of the first seizure except those with obvious acute provoked seizures (eg, childhood febrile convulsions). The MR findings are used to gauge prognosis and influence the decision about whether to treat medically. The rationale for this more aggressive approach is that patients with an MR-defined lesion are more likely than those without to experience further seizures. The impetus to treat a single seizure medically in the former group is therefore stronger.

Patients with epilepsy who are referred for MR imaging at my institution undergo a specific imaging protocol that is tailored to the evaluation of the pathologic conditions commonly seen in these patients. Because most patients with partial seizures have a temporal lobe onset, the protocol is weighted toward optimal visualization of temporal lobe structures. The temporal lobe gyri are oriented longitudinally; therefore, coronal images optimally display the normal anatomy. While "standard" axial T2-weighted imaging with 5-mm-thick sections and a 2.5-mm gap will probably identify most space-occupying lesions (eg, tumor), coronal images are necessary for precise anatomic localization within the temporal lobe. I am not aware of any studies that formally compare the accuracy of "standard" axial versus thin-section coronal images in the diagnosis of MTS. It is my opinion, however, that the latter are essential to evaluate MTS adequately, due to the small diameter and longitudinal orientation of the hippocampal formation. Patients with seizures due to an established abnormality such as a prior hemispheric infarction or a progressive glioma who are referred for MR imaging do not undergo the epilepsy imaging protocol at my institution. In such cases, a specialized protocol focused on imaging of the temporal lobe anatomy is unnecessary. The epilepsy protocol at my institution consists first of sagittal T1-weighted imaging with minimum echo time (TE) and the minimum repetition time (TR) required for whole-head coverage with 5-mm contiguous sections. Second, a whole-head coronal three-dimensional volumetric spoiled gradient-echo (SPGR) acquisition is performed with minimum TE and TR, 192 views, one repetition, 1.5-mm section thickness with 124 partitions, 22-cm field of view, and 45° flip angle. Third, coronal spin-echo (SE) imaging is performed with TE of 30 and 80 msec, TR greater than 2,000 msec, 20-cm field of view, 4-mm section thickness with 2-mm intersection gap, and 192 views with one repetition. Contrast material is not routinely administered as part of our epilepsy protocol, as it does not provide increased sensitivity in the detection of epileptogenic lesions over that of an unenhanced MR study (49,50). All studies are monitored by a neuroradiologist. If a space-occupying lesion is identified on the unenhanced study, then contrast material is administered.

It is appropriate to fold a description of the pathologic substrates of epilepsy into the discussion of MR imaging for two reasons: (*a*) the goal of MR imaging is to identify in vivo the pathologic substrate (ie, the epileptogenic lesion) and (*b*) modern MR imaging will identify virtually all the established pathologic substrates of epilepsy. To illustrate this point, the Table lists the histologic substrates of

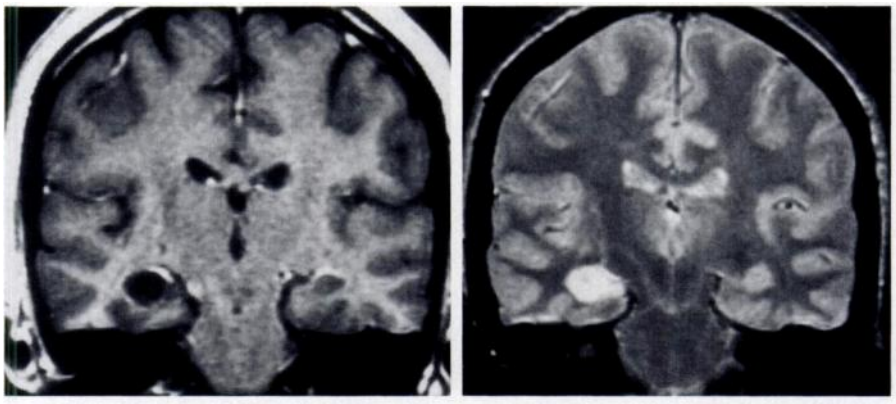
epilepsy and the sensitivity of MR imaging in their detection (51,52). The values in the Table are biased in favor of MR because patients with positive MR studies are more likely to undergo surgery than those with negative studies (the same holds true for any seizure-localizing test in which the epileptologist and neurosurgeon have confidence). However, patients with clear-cut electroclinical localization and negative MR studies are routinely operated on at my institution, and, with the exception of an occasion case with mild MTS, false-negative MR studies (with respect to pathologic findings) are not encountered.

Sensitivity of MR Imaging to Various Histologic Substrates of Epilepsy

Pathologic Substrates of Epilepsy in Surgical Series*	Prevalence (%)	Approximate Sensitivity of MR† (%)
Tumor	15	100
Arteriovenous malformation	2	100
Major migration anomaly/heterotopia/hamartoma	5	100
Encephalomalacia/gliosis	3	100
MTS	60	85–95
Nonspecific cortical gliosis or negative histologic type	15	0

* Mean prevalence over several years in patients operated on at the Mayo Clinic for seizures of temporal lobe onset. The same histologic types are present in extratemporal cases—with the obvious exception of MTS.

† Approximations based on recent reports in the literature and the personal experience of the author.



a. **b.**

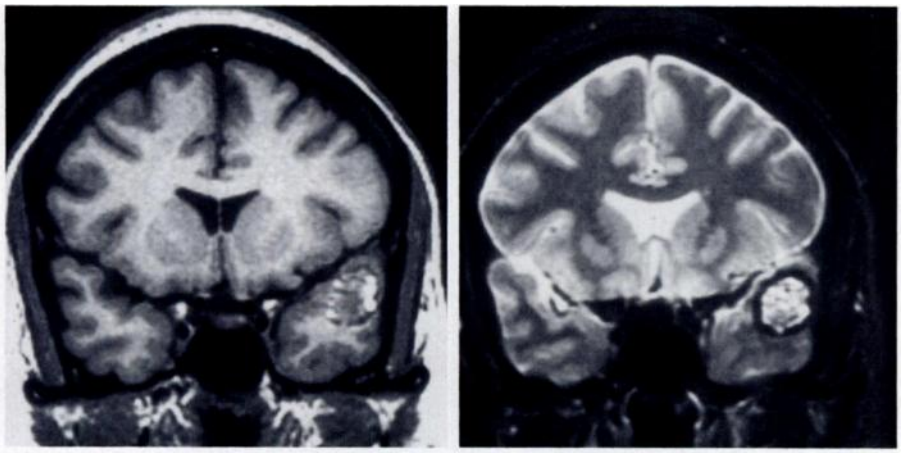
Figure 2. Tumor in a 37-year-old man with poorly controlled complex partial seizures of the right temporal lobe since age 18 years. This lesion was removed and revealed to be a grade 1–2 mixed oligodendroglioma-astrocytoma. The patient has been seizure-free since surgical removal. **(a)** T1-weighted coronal MR image with contrast material enhancement. **(b)** First-echo image of a double echo of a long TR sequence. The tumor does not enhance; it is well marginated and confined to the hippocampal formation. The imaging characteristics mirror the indolent biologic behavior of the lesion (cf Fig 5a). Tumors enlarge the hippocampus and increase T2 signal intensity. With MTS, however, the hippocampus is atrophic with increased T2 signal intensity.

Tumor.—By definition, patients with medically intractable epilepsy who are being considered for surgical intervention have a chronic disease. The types of structural lesions seen in this clinical setting are those whose primary effect is epileptogenesis. Tumors for which epilepsy surgery is performed are usually benign or low grade, and patients with these tumors tend to have a nonprogressive clinical course and no fixed neurologic deficit. Tumor types that would be considered rare in oncologic surgical series are the norm in epilepsy surgical series. These include low-grade oligodendroglioma, fibrillary astrocytoma, and mixed tumors; pilocytic astrocytoma; ganglioglioma; and dysembroblastic neuroepithelial tumors (Fig 2). The precise mechanism by which a tumor produces recurrent unprovoked seizures is unclear. It is hypothesized that seizures originate from "disturbed" but otherwise normal neurons adjacent to the tumor. Imaging features common to all these tumors mirror the biologic behavior and include typically small size, location at or near a cortical surface, sharply defined borders, little or no surrounding edema, and, with the exception of pilocytic astrocytomas, little or no contrast enhancement.

Vascular formation.—In a manner similar to tumors, vascular malformations that are found in surgical epilepsy series are small, indolent lesions. These typically are the cryptic malformations, that is, capillary angiomas or cavernous angiomas (Fig 3).

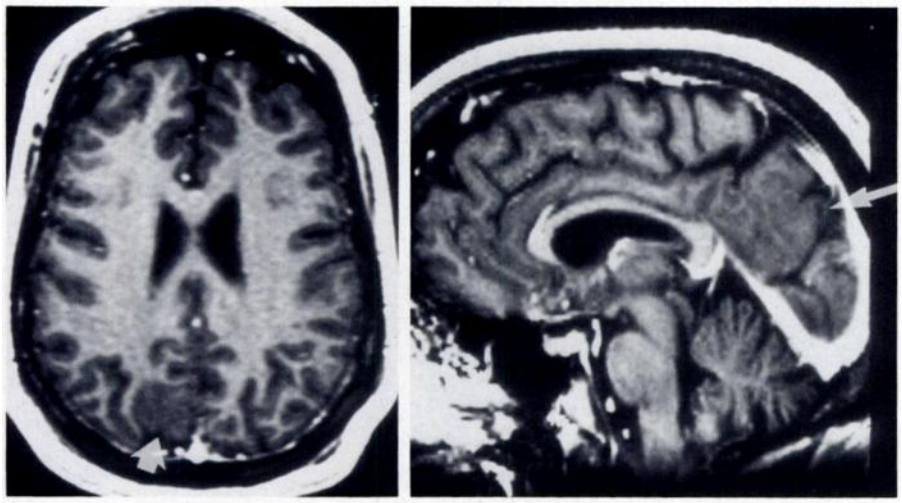
Neuronal migration abnormality.—Developmental brain anomalies commonly manifest with seizures as a prominent clinical feature. The spectrum of gray matter developmental abnormalities ranges from widespread gross deformities such as lissencephaly to small focal nodular gray matter heterotopias, and all are due to defects in neuronal migration and organization that occur in utero. These include gray matter migration abnormalities of the cortical mantle or cortical dysplasias (agyria, pachygyria, polymicrogyria), abnormal location of gray matter or heterotopia (band, laminar, or nodular heterotopias), schizencephaly, and hemimegalencephaly (53–62). It is the focal cortical dysplasias that are most often considered for surgical resection. Traditional classification of cortical dysplasias into polymicrogyri or pachygyri has to some extent broken down, as histologic examination will often reveal multiple features in the same area. The cerebral cortex is normally 4 mm thick, and cortical dysplasias appear as areas of thickened cortex, regardless of the histologic description (ie, pachygyria or polymicrogyria). Thin-section three-dimensional volumetric MR imaging is extremely useful in evaluating these anomalies. It may be difficult to resolve volume-averaged normal cortical infolding from true areas of migration anomaly if the spatial resolution of the images is coarser than 1.5 mm. In addition, multiplanar reformatting of 1.5-mm three-dimensional SPGR MR sequences is helpful both in distinguishing volume averaging from true areas of cortical thickening and for identifying the relationship between naturally occurring cortical boundaries and the imaging-defined abnormality (Fig 4).

Encephalomalacia or gliosis.—Cortical gliosis or scar can occur following any brain insult—trauma, infarction, or infection (Fig 5). The relation between head trauma and epilepsy has been appreciated for thousands of years, and in fact the first 40 years of epilepsy surgery was devoted in large part to the excision of posttraumatic



a. b.

Figure 3. Capillary hemangioma in a 47-year-old woman with partial complex seizures of the left temporal origin since age 43 years. The patient has been seizure-free for 3 years following surgery. **(a)** T1-weighted and **(b)** T2-weighted MR images demonstrate typical features of a capillary or cavernous angioma. These are an outer rim of hemosiderin or ferritin deposition, which displays decreased signal intensity on T1-weighted images and to a much greater extent on T2-weighted images. A nonhomogeneous central portion is hyper- to isointense on T1-weighted images and hyper- to hypointense on T2-weighted images.



a. b.

Figure 4. Cortical dysplasia in a 44-year-old woman with poorly controlled seizures since early childhood. MR images demonstrate an area of cortical dysplasia (arrow) in the medial right parietal lobe, which was resected stereotaxically. **(a)** Axial three-dimensional SPGR image. **(b)** Reformatted off-axis sagittal image from the same three-dimensional sequence. These images demonstrate an area of cortical thickening in the right precuneus, which is clearly demarcated by the parieto-occipital sulcus posteriorly.

cortical scars (6–8). Epilepsy following head trauma is more frequent with missile injuries, which penetrate the skull, than with closed head injuries. Among penetrating injuries, those that involve penetration of the dura are more often associated with posttraumatic epilepsy than those that do not.

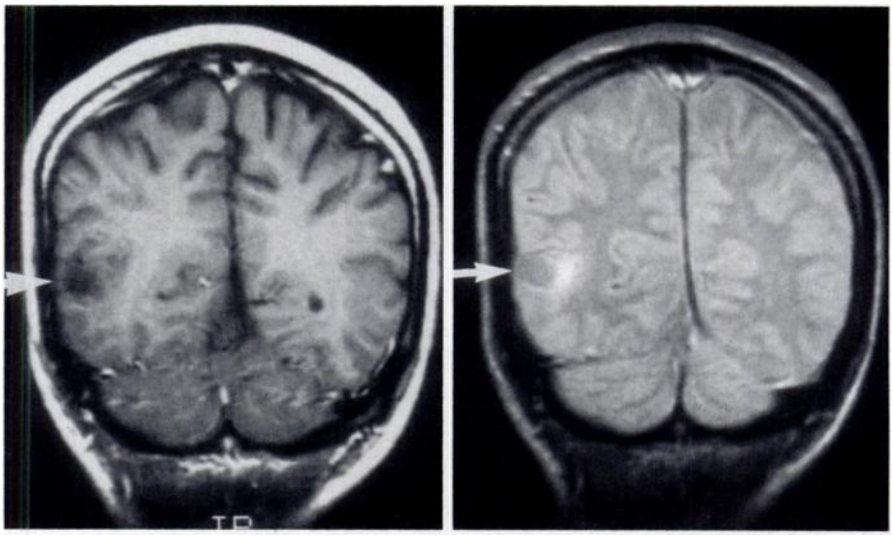
MTS.—MTS has been known by a variety of names including hippocampal sclerosis and Ammon horn sclerosis, but the preferred terminology (MTS) was coined by Falconer et al (63) to indicate the fact that the pathologic changes extend beyond the hippocampus proper to involve the amygdala and sometimes the adjacent parahippocampal gyrus. The first gross pathologic description of MTS was given by Bouchet and Cazauvieilh in 1825 (64), and the first microscopic description was given by Sommer in 1880 (65). Much of the early literature on MTS is published in German, reflecting the activity of German pathologists in this area in the 1800s and early 1900s (65–68). Histologically, MTS consists of neuron loss and gliosis. The classic Ammon horn sclerosis pattern of MTS, which is most specific for epilepsy, consists of cell loss primarily involving the pyramidal cell layer of the hippocampus in the CA1 sector, with lesser involvement in the CA3 and CA4 sectors and dentate gyrus (69,70). Cell loss alone, however, will not produce spontaneous recurrent seizures. Recent studies have indicated that cell loss is accompanied by synaptic reorganization within the hippocampus, which creates abnormal intrinsic synchronous excitatory circuitry (71). Changes of MTS often are present bilaterally but have a marked unilateral prominence in patients with habitual seizures emanating from one temporal lobe.

Several different MR imaging findings have been described as characteristic of MTS: hippocampal atrophy; signal changes consistent with increased tissue free water, most typically increased signal intensity on T2-weighted images; loss of normal internal hippocampal architecture; and thinning of the collateral white matter in the adjacent parahippocampal gyrus (72–78) (Fig 6). Of these, the most widely recognized are hippocampal atrophy and an increased T2 signal. The former is a reflection of neuron loss that characterizes MTS, and the latter, presumably a reflection of gliosis. The reported sensitivity of MR imaging in detection of MTS has varied considerably, ranging from 0% to 93% (72–80). To some extent the wide range in reported sensitivity reflects the fact that the different case series were published during a time of technical maturation of MR imaging. It is now recognized, however, that simple visual inspection of MR images for increased hippocampal signal intensity and unilateral hippocampal atrophy will allow detection of perhaps 80%–90% of cases of MTS, provided the MR images are acquired and interpreted correctly (73–78). Sensitivity and specificity of the MR diagnosis are difficult to identify precisely, because the pathologic criteria used to define MTS vary somewhat across different institutions. Both T1- and T2-weighted images should be acquired in the coronal plane. We find that the former optimally display hippocampal atrophy, and the latter display signal intensity change. As the cross-sectional area of the hippocampus changes along its anteroposterior axis, visual estimation of relative unilateral hippocampal atrophy is sensitive to rotation of the patient's head in the coronal plane. Three-dimensional SPGR images are helpful in this

regard, as they may be reformatted into a true anatomic coronal plane.

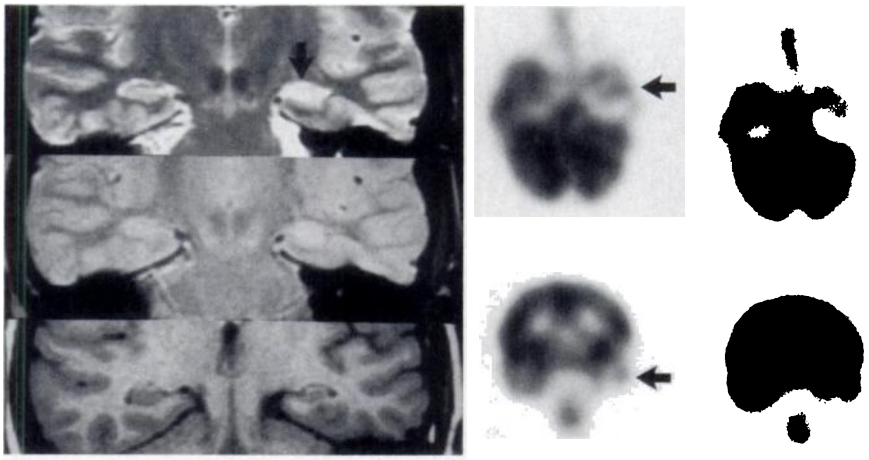
The MR changes of MTS may be quantified as well as identified visually. Jackson et al have described T2 relaxometry in MTS (81). Hippocampal atrophy may be quantified by performing volumetric measurements of the hippocampus on thin contiguous T1-weighted coronal MR images (75,82–86). With regard to the clinically important determination of the presence or absence of MTS, this can usually be determined simply by means of visual inspection of MR images alone. Quantitation, either with T2 relaxometry or hippocampal volume measurement, improves the sensitivity in detection of MTS by a small incremental amount, but it is not necessary for day-to-day clinical work. In a recent study at my institution (C.J.R., unpublished data), the sensitivity of hippocampal volume measurements in identifying histologically proved MTS was 91.3%, while the sensitivity of visual inspection of both T1- and T2-weighted images was 83.3%. On the other hand, quantitative techniques are essential for research applications involving hypothesis testing in which pathologic conditions of the hippocampus in vivo are correlated with other biologic variables. Measurement of hippocampal volume, the more widely applied of the two quantitative techniques, has been shown to be accurate, reproducible, and highly correlated with the degree of cell loss found in surgical pathology specimens (83,87). The ability to quantitate hippocampal atrophy for purposes of hypothesis testing has demonstrated significant relations between hippocampal atrophy and postoperative seizure control (41), verbal memory performance (83,88), the age of onset of seizure disorder (89), and epileptiform EEG abnormalities (75,82–86).

Methods for hippocampal volume measurements may be broken into two separate tasks—image acquisition and image processing. A technique for performing temporal lobe and hippocampal volume measurements was developed at my institution in 1987 (90), and the image acquisition technique employed thin, contiguous interleaved T1-weighted SE images, which were acquired perpendicular to the long axis of the hippocampal formation. Since that time, technical improvements in MR imaging have occurred. At this time, an optimal acquisition sequence could be either thin-section fast SE (2–3 mm) or three-dimensional SPGR images. Both of these approaches represent an improvement over the more traditional SE approach, primarily due to faster acquisition or greater spatial resolution in the section-select direction. We have performed the image-processing portion of the operation offline on a stand-alone workstation. This involves manual tracing of the inplane boundary of the hippocampus on sequential oblique coronal sections. Despite the proliferation of image segmentation techniques in the past several years, to my knowledge no fully automated technique has been developed that will allow disarticulation of the hippocampus from surrounding structures, and therefore manual tracing is still necessary.



a. b.

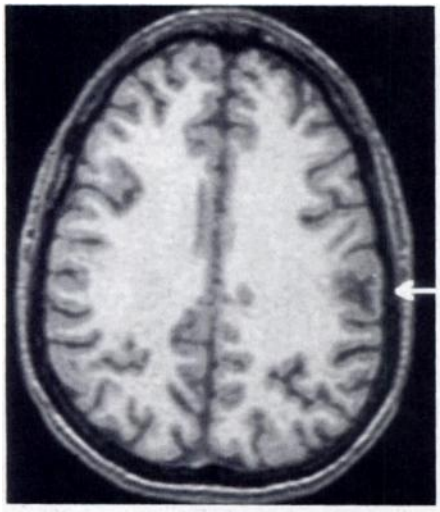
Figure 5. Cortical scar in a male patient who experienced complex partial seizures of right temporal origin due to a remote head injury. MR images demonstrate a focal cortical (arrow) abnormality, which was resected and shown to be a posttraumatic scar. **(a)** T1-weighted image and **(b)** first-echo image from a double-SE sequence demonstrate a small cystic area in the lateral right temporal neocortex with underlying signal intensity change, presumably gliosis.



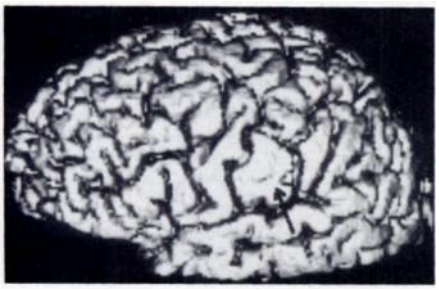
a. b.

Figure 6. MTS in a 25-year-old woman with poorly controlled partial complex seizures of left temporal origin since age 10½ years. **(a)** Collage of MR images with the second-echo image of a long TR MR sequence at the top, the first-echo image in the middle, and a T1-weighted coronal image at the bottom. This figure demonstrates the classic MR findings of MTS on the left (arrow), increased signal intensity on the long TR images, and atrophy on the T1-weighted image. **(b)** Interictal SPECT scan demonstrates decreased perfusion in the anterior and basal left temporal lobe (arrows). Axial images are in the top row, and coronal images are in the bottom row.

Neocortical gliosis or negative histologic findings.—Approximately 15% of all surgically resected tissue specimens will contain no definite epileptogenic abnormality. Not surprisingly, the ability of MR imaging to depict a localizing abnormality in such cases is nonexistent. Whether seizures originate in the temporal lobe or outside the temporal lobe, cases with negative imaging findings typically have a worse prognosis for postoperative



a.



b.

Figure 7. Surface rendering of a cortical tuber in a 27-year-old man with medically intractable simple partial sensorimotor seizures involving primarily the right hand since age 2 years. On the basis of the preoperative cross-sectional images **(a)**, it could not be determined whether the tuber (arrow) that was responsible for the patient's habitual seizures was located in the precentral or postcentral gyrus. Therefore, a volume-rendered image of the left hemisphere was obtained **(b)**. This demonstrated that the postcentral gyrus was expanded by the cortical tuber (arrow). (The patient's head faces the reader's left.) The lesion was therefore resected, and the patient has remained seizure-free for 3 years. (Part a reprinted from reference 119.)

seizure control than those with positive MR images. These cases represent the next major challenge for imaging.

Physiologic Imaging

Physiologic cross-sectional imaging modalities that have been used for localization of the epileptogenic zone (more accurately, the "functional deficit zone") are PET, SPECT, and, to a lesser extent, xenon CT. PET studies of oxygen utilization, glucose metabolism, blood flow, and receptor distribution have been performed with oxygen-15, carbon-11, and fluorodeoxyglucose (FDG) (91–97). SPECT studies have employed iodine-123 iodoamines (IMP, HIPDM) and technetium-99m hexamethyl-propyleneamine oxime (HMPAO) (98–107). Both PET and SPECT tend to demonstrate a zone of hypometabolism or hypoperfusion interictally, which is considerably larger than the epileptogenic zone. The most widely studied PET technique has been FDG imaging, which has shown a 70%–91% sensitivity in identifying the abnormal temporal lobe in patients with partial seizures. Several studies comparing MR and PET in lateralizing seizures of temporal lobe onset were performed in the 1980s (80,108–110). These studies included patients with a mixture of histologic substrates (ie, tumor, MTS). Conclusions drawn from these studies were that PET was accurate both in patients with MTS and in patients with space-occupying lesions (eg, tumors), whereas MR imaging was accurate in depicting lesions but not MTS (80,108–110). As a result, clinical practice at centers with PET availability has been predicated on the idea that both MR imaging and PET should be performed in all patients preoperatively, with MR imaging providing surgical localization of space-occupying lesions and PET lateralizing information in all cases, particularly in patients with MTS. With the recent demonstration that MR is highly accurate in identifying both space-occupying lesions and MTS (ie, the majority of patients considered for surgery) (72–78), it is now less clear that every patient should undergo both MR and a physiologic imaging study (PET or SPECT) preoperatively. The sensitivity of SPECT is roughly half that of PET in temporal lobe seizure lateralization (Fig 6) (98). The sensitivity of PET and SPECT in identifying the epileptogenic zone extra temporally is not clearly defined, but it is lower than for temporal lobe onset.

When performed periictally, functional imaging studies demonstrate a local increase in cortical blood flow (102–107). Because of the spontaneous and episodic nature of seizures, as a rule ictal functional imaging can be performed only with SPECT. The distribution of Tc-99m-HMPAO in the brain is determined as a function of regional cerebral blood flow at the time of the first pass of the isotope. Dramatic shifts in regional cerebral blood flow occur during and immediately following an ictal event, and the sensitivity of the SPECT study is dependent on when the isotope is injected (105). Sensitivity in lateralizing seizure onset to one or the other temporal lobes has been estimated as follows: true ictal scans (ie, the isotope is injected during the seizure itself), 97%; periictal scans (isotope is injected 0–4 minutes after termination of ictus), 73%; interictal scans, 43% (106,107). The sensitivity of periictal SPECT for extratemporal seizure onset is not firmly established but is lower. Routine ictal SPECT scanning would logically be performed in conjunction with preoperative long-term inpatient video EEG recording studies.

Metabolic/Biochemical

Localizing metabolic abnormalities have been reported both with proton (hydrogen-1) and phosphorus (phosphorus-31) MR spectroscopy. Both volume-of-interest and MR spectroscopic imaging techniques have been used. Most clinical studies have been performed interictally in patients with temporal lobe seizures. Decreased *N*-acetyl aspartate in the epileptogenic temporal lobe appears to be a highly reliable lateralizing finding (111–115). Other findings that have been inconsistent among different interictal H-1 MR spectroscopy studies include alterations in glutamate and choline. Interictal findings in P-31 MR spectroscopy include increased pH, increased inorganic phosphate level, decreased phosphomonoester levels, and decreased phosphocreatinine–inorganic phosphate ratio (116,117). Ictally, lactate level increases (pH decreases) and phosphocreatinine level decreases in patients with status epilepticus, as well as in experimental studies. Although clinical studies of MR spectroscopy in epilepsy are in the early stages, the initial results are promising. Positive localizing MR spectroscopic findings have been reported in patients with normal MR imaging studies.

Estimation of Surgical Risk: Clinical Applications of Image Processing

The primary role of imaging in surgery for epilepsy is the identification of focal imaging abnormalities that mark the epileptogenic zone. A second role for imaging is that of estimating the risk to normal function from a proposed surgical procedure. The relation of the surgical target to functionally eloquent areas is important not only for planning the procedure but also for selecting patients for surgery. Surface renderings of the brain from three-dimensional volumetric gradient MR images can reveal precise topographic relations between epileptogenic lesions and gyral

anatomy, which cannot be appreciated on standard cross-sectional images (Fig 7) (118,119). Techniques for multimodality registration allow integrated display of information from different modalities on a high-resolution MR imaging anatomic template (120–122). Three-dimensional displays of such integrated information can demonstrate the topographic relations between physiologic information from PET, SPECT, or MEG; cortical anatomy; and lesions that have been targeted for resection.

Initial enthusiasm for MEG as a replacement for seizure localization by means of invasive EEG recording has waned. However, presurgical localization of the functional sensory cortex is a potentially valuable application of this technology (123). MEG dipole localization is integrated into an MR imaging anatomic template in both two-dimensional and three-dimensional surface displays. It remains to be seen how recent advances in functional MR imaging will impact this application of MEG (124).

Imaging in Epilepsy: The Future

MR imaging and MR-based imaging techniques such as MR spectroscopy and perhaps functional MR imaging will assume an increasingly prominent role in epilepsy surgery. Improved identification of epileptogenic lesions with MR imaging has already markedly decreased the frequency with which invasive EEG recording is performed in many centers. This has had a particularly dramatic impact in cases of temporal lobe onset seizures due to MTS, which represent the most common form of chronic epilepsy in adults.

A second trend will occur as a result of cost-containment efforts. At many centers, the prevalent method of practice for the past decade or so has been to conduct a number of preoperative tests in every patient in the search for concordance. Included in this testing battery would be multiple different imaging studies. In the future, cost-efficient and selective use of imaging tests prior to epilepsy surgery will be demanded. An example of such a paradigm might be as follows: All patients undergo MR imaging preoperatively. If results of MR imaging localization (lesion or MTS) and prolonged scalp EEG monitoring are concordant, then no further imaging would be performed. If the MR imaging study is nonlocalizing, or the MR images and EEG recording are discordant, then a second-level imaging study such as PET or ictal SPECT will be indicated. ■

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