Role of Neuroimaging in the Management of Seizure Disorders

ELSON L. SO, MD

Neuroimaging is one of the most important advances made in the past decade in the management of seizure disorders. Magnetic resonance imaging (MRI) has increased substantially the ability to detect causes of seizure disorders, to plan medical or surgical therapy, and to prognosticate the outcome of disorders and therapy. However, MRI must be performed with techniques that will maximize the detection of potentially epileptogenic lesions, especially in candidates for epilepsy surgery. Functional imaging has an established role in evaluating patients for epilepsy surgery. It is relied on when results from standard diagnostic methods, such as clinical information, electroencephalography, and MRI, are insufficient to localize the seizure focus. Also, functional imaging is a reportedly reliable alternative to invasive methods for identifying language, memory, and sensorimotor areas of the cerebral cortex. Despite the availability of multimodality imaging, the epileptogenic zone is not determined solely by a single imaging modality. Evidence and experience have shown that concordance of results from clinical, electrophysiologic, and neuroimaging studies is needed to identify the epileptogenic zone accurately. With modern techniques in image processing, multimodality imaging can integrate the location of abnormal electroencephalographic, structural, and functional imaging foci on a "map" of the patient's brain. Computer image–guided surgery allows surgically exact implantation of intracranial electrodes and resection of abnormal structural or functional imaging foci. These techniques decrease the risk of morbidity associated with epilepsy surgery and enhance the probability of postsurgical seizure control.

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CT = computed tomography; EEG = electroencephalography; [^{18}F]FDG = 2-[^{18}F]fluoro-2-deoxy-D-glucose; fMRI = functional magnetic resonance imaging; ^{1}H MRS = magnetic resonance spectroscopy involving hydrogen nucleus; $H_2{}^{15}O$ PET = ^{15}O-labeled water positron emission tomography; MCD = malformation of cortical development; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; MTS = mesial temporal sclerosis; NAA = *N*-acetylaspartate; PET = positron emission tomography; SISCOM = subtraction ictal SPECT (single-photon emission computed tomography) coregistered to MRI; SPECT = single-photon emission computed tomography

An association between structural abnormalities of the brain and epileptic seizures has long been suspected. A causal relationship between brain lesions and seizures was first observed in the late 19th century, when surgical resection of a brain tumor[1] and post-traumatic cicatrix[2] resulted in seizure control. This article discusses the clinical application of modern imaging studies to the diagnosis and treatment of seizure disorders. The discussion emphasizes the roles and limitations of modern imaging techniques in managing seizure disorders. Readers are referred to the article by Jack[3] for a description of the radiographic appearance of each type of magnetic resonance imaging (MRI)–detected lesion (MRI lesion) associated with seizure disorders.

In many patients with epilepsy, structural imaging with computed tomography (CT) or MRI shows no abnormality. In the past 2 decades, important advances have been made in imaging the abnormal cerebral physiology associated with epileptic seizures. These diagnostic tests are referred to as *functional imaging*.[4] The 3 major functional imaging modalities discussed are positron emission tomography (PET), subtraction ictal SPECT (single-photon emission computed tomography) coregistered to MRI (SISCOM), and magnetic resonance spectroscopy (MRS).

IMPORTANCE OF IMAGING IN MANAGEMENT OF SEIZURE DISORDERS

Assessing brain structure or function with imaging studies is essential in the diagnosis and management of epileptic seizure disorders. When patients initially present with new-onset seizures, neuroimaging helps determine whether seizures were acutely provoked or unprovoked. Focal lesions associated with acutely provoked seizures often require immediate treatment, such as surgical decompression of a hematoma. Compared with patients whose seizures were provoked by an acute brain disturbance, patients with seizures due to chronic cerebral lesions (eg, a brain tumor or encephalomalacia) have a less favorable prognosis for seizure cessation and eventual remission of epilepsy.[5,6]

Detecting a potentially epileptogenic lesion affirms the clinical impression of focal seizure disorder.[7] In contrast, the basis for primary generalized seizure disorders is either genetic or idiopathic rather than a focal epileptogenic le-

From the Department of Neurology, Mayo Clinic, Rochester, Minn.

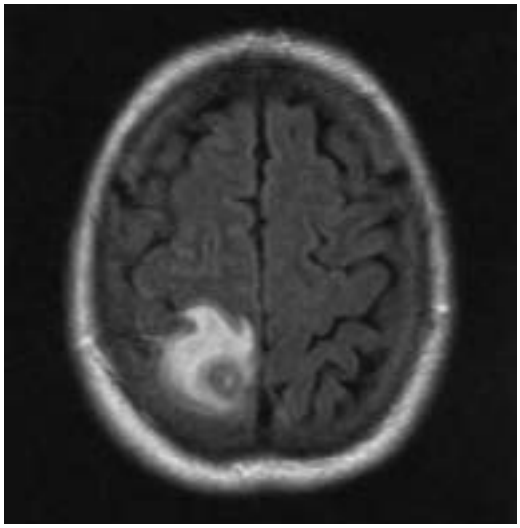

Figure 1. Fluid-attenuated inversion recovery image of a 22-year-old man who presented with a focal seizure with secondary generalization. Axial view shows a single round lesion with a small rim and a larger surrounding area of increased signal intensity. Histological examination of the lesion showed cysticercosis granuloma.

sion. The distinction between these 2 types of epilepsy is a major determinant in selecting the antiepileptic medication to treat the disorder. Most major antiepileptic drugs are effective for treating focal seizures, but only a few drugs, such as valproate sodium or valproic acid, lamotrigine, and topiramate, are effective for treating both focal seizures and primary generalized seizures.[8] Determining whether a focal lesion is the cause of a seizure also helps in diagnosing epilepsy syndromes, especially the benign or malignant epilepsy syndromes of childhood.[9,10] Brain imaging techniques help identify the seizure focus and the cortical areas that serve critical brain functions such as language or motor skills and are therefore essential for selecting candidates for epilepsy surgery.

STRUCTURAL IMAGING

New-Onset Seizure Disorder

One of the primary steps in evaluating new-onset seizure disorders is to determine whether there is an underlying brain lesion. Common causes of acute seizures are stroke, head trauma, and brain tumor.[11] In young children, perinatal hypoxic or hypoxemic events and malformations of cortical development (MCDs) are major causes of new-onset seizures. Head trauma is a predominant cause of seizure disorders in young adults, and stroke is a major cause in the elderly population. Cysticercosis granuloma is an important pathological substrate of seizures in some parts of the world and is increasingly important in some communities in the United States[12] (Figure 1).

The sensitivity of MRI in detecting structural lesions in the brain is unparalleled. In addition to its ability to detect with high sensitivity nearly all types of lesions in patients with epilepsy, it correctly distinguishes between tumors and vascular malformations in 95% of patients.[13] The superiority of MRI to CT was recognized soon after MRI was developed. Studies with early-generation MRI machines showed clinically relevant lesions in nearly 10% of adults who had new-onset epilepsy and in 5% to 20% of patients with chronic focal epilepsy and normal CT scans.[14] The yield should be even higher with current-generation MRI machines. Moreover, MRI accurately locates the brain lesion and surrounding structures. It can clearly identify structures known to serve critical brain functions such as motor performance and language. Unlike standard CT, MRI displays normal and pathological structures in 3 dimensions, thus allowing the construction of 3-dimensional images.

Computed tomography is valuable for the early detection of blood densities, as in subarachnoid hemorrhage or hemorrhagic stroke lesions. Therefore, it is generally the initial brain-imaging procedure performed in neurologic emergencies, especially when artifacts (eg, catheters or ventilation devices) associated with critically ill patients produce less interference than with MRI.[15] Also, CT is sensitive in detecting calcified lesions, which appear as signal void on MRI. Although overall CT is inferior to MRI in detecting structural lesions, it is an alternative to MRI for patients who cannot undergo MRI because of cardiac pacemakers, large body size, severe claustrophobia, or ferromagnetic objects in the head or neck (eg, aneurysm clips).

Patients who present with first-time seizures should have emergent neuroimaging if (1) a serious structural lesion is suspected, (2) the patient presents with focal seizures, or (3) the patient is older than 40 years.[16] For other situations, neuroimaging may still be needed urgently if the patient cannot be monitored appropriately after seizure occurrence and imaging is essential for planning care. In all such situations, the clinical history and neurologic examination are essential for assessing the probability of an intracranial lesion that requires emergent attention.

For children who have had a first nonfebrile seizure, emergent neuroimaging should be performed if the postictal focal deficit does not resolve promptly or if mental status does not return to baseline several hours after the seizure.[17] In a nonurgent setting, MRI should be considered if the child (1) has marked cognitive or motor impairment of unknown cause, (2) has neurologic examination findings that show unexplained abnormalities, (3) has a seizure of focal onset, (4) has electroencephalographic (EEG) findings incompatible with benign focal epilepsy of childhood or primary generalized epilepsy, or (5) is younger than 1 year.

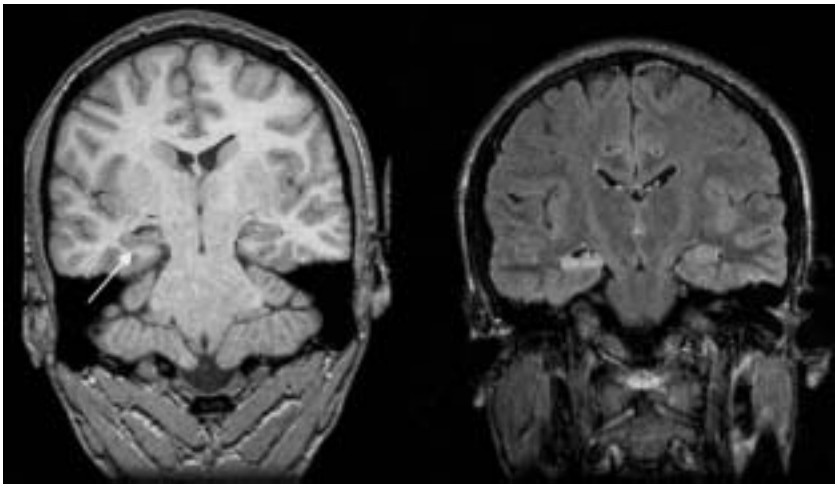

Figure 2. Magnetic resonance images of a 16-year-old patient who developed complex partial seizures at age 6 years. Left, T1-weighted coronal image showing atrophic right hippocampus (arrow). Right, Fluid-attenuated inversion recovery image showing increased signal in the right hippocampus compared with the left. With the loss of hippocampal volume, the ventricular space is more prominent immediately above the hippocampus.

The International League Against Epilepsy recommends that MRI be performed in nonemergent situations on all epilepsy patients except for those with idiopathic epilepsy.[15] The League further recommends that MRI be performed if the patient has (1) historical or EEG evidence of a focal onset of seizures at any age, (2) onset of unclassified or apparently generalized seizures in the early years of life or adulthood, (3) evidence of a focal fixed deficit on neurologic or neuropsychological examination, (4) difficulty controlling seizures with first-line antiepileptic drugs, or (5) loss of control of seizures with antiepileptic drugs or a change in pattern of seizures, which may imply a progressive underlying lesion.

Medically Intractable Epilepsy

Medically intractable epilepsy is defined as unsatisfactory seizure control despite optimized sequential use of 2 or more appropriate antiepileptic drugs. Epilepsy surgery is performed in patients with medically intractable epilepsy to improve seizure control and quality of life. Computed tomography had been used to detect structural lesions in patients with poorly controlled chronic epilepsy, but its sensitivity in detecting focal abnormalities is only half that of MRI.[18,19] Early-generation CT scanners detected lesions suitable for epilepsy surgery in only 3% of patients.[20] In contrast, MRI has been extremely valuable for evaluating patients for epilepsy surgery. Magnetic resonance imaging detects surgically relevant lesions in up to 80% of patients who undergo temporal lobectomy[21] and in about 60% of those who undergo frontal lobe surgery.[22]

The most common surgical lesion in patients who have temporal lobe epilepsy surgery is mesial temporal sclerosis (MTS), which is characterized by cell loss and astroglial proliferation in the hippocampus and neighboring structures. In approximately 70% of patients who have had temporal lobectomies, MTS is the surgical lesion,[23,24] and another 15% to 20% have a low-grade tumor, vascular malformation, or MCD. In children, the proportion of those with MTS is slightly lower (50%) and the proportion with MCD is higher (25%).[9] Thus, regardless of age, MTS is the predominant lesion in patients who have epilepsy surgery.

Magnetic resonance imaging is the most important diagnostic test for detecting MTS. The MRI features of MTS are hippocampal atrophy, increased T2 signal abnormality, and the loss of normal hippocampal architecture (Figure 2). Hippocampal atrophy and an increased T2 signal can be visualized with high accuracy by knowledgeable and experienced clinicians.[25] When these abnormalities are not apparent, hippocampal volumes and T2 relaxation times can be measured.[26,27] The degree of the decrease in hippocampal volume is correlated with the degree of cell loss and astrogliosis.[28] Moreover, the side on which MRI detects MTS (in the form of hippocampal atrophy) is correlated with the side of EEG abnormality in about 90% of patients.[29,30] The probability that seizure control will be excellent after surgical resection of the atrophic hippocampus is approximately 80%. Before the advent of MRI, MTS could not be imaged directly, and many candidates for epilepsy surgery had to undergo intracranial electrode implantation to confirm the location of seizure onset.

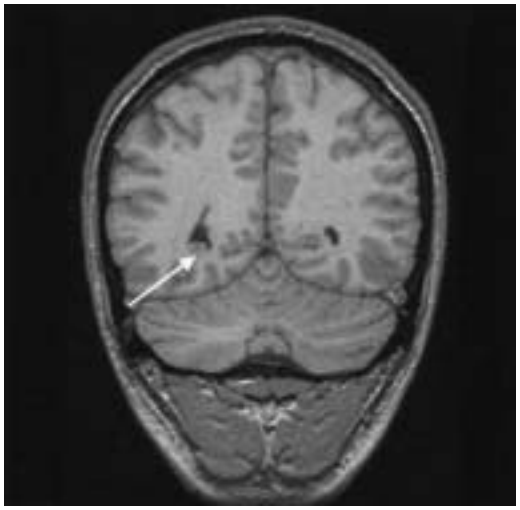

Figure 3. A T1-weighted coronal magnetic resonance image shows a nodule of heterotopic gray matter in the floor of the occipital horn of the lateral ventricle (arrow). This lesion was not detected in an earlier computed tomographic scan.

It is important to note that about 1 in 7 patients with MTS also has another potentially epileptogenic lesion (dual pathology), usually MCD, vascular malformation, or low-grade tumor.[31] In patients with dual pathology, surgical resection of the extrahippocampal lesion alone seldom produces satisfactory control of seizures.[32] Thus, MRI must be performed with sequences optimized for detecting various types of potentially epileptogenic lesions.[33]

Tumors detected with MRI in patients with intractable epilepsy are usually low-grade gliomas or hamartomatous lesions that have remained the same size for many years. These tumors typically have well-delineated borders and a homogeneous appearance, and they usually do not enhance when contrast agents are administered. Also, no edema is found around the lesion. Two other types of tumors characteristically associated with chronic epilepsy are gangliogliomas and dysembryoplastic neuroepithelial tumors. They are located most often in the temporal lobe. Surgical resection of these tumors controls seizures in 90% or more of patients with medically refractory epilepsy.[34]

Increasingly, MCDs are recognized as a frequent cause of epilepsy, especially medically refractory epilepsy. Before the MRI era, CT detected MCD in only a third of patients[35] (Figure 3). In contrast, MRI delineates the spectrum of developmental abnormalities to the extent that malformations can be classified presurgically (Figure 4). New epilepsy syndromes with characteristic clinical, radiological, and prognostic features have been identified as a result of MRI studies.[36] The detection of MCD as part of an epilepsy syndrome should prompt genetic evaluation and counseling of the patient's family.

Requisites for High-Resolution MRI in Seizure Disorders

The optimal application of MRI for evaluating seizure disorders requires specific imaging techniques and sequences, especially in evaluating patients for epilepsy surgery.[33,37] High-resolution MRI with use of techniques optimized to detect epileptogenic lesions is referred to at Mayo Clinic as *seizure-protocol MRI* or *epilepsy-protocol MRI*. A standard MRI study often is insufficient for detecting the pathological substrate of a seizure disorder. An MRI machine with a minimum 1.5-T magnet is necessary to provide the required field strength for good image resolution. Brain images should be displayed in coronal, axial, and sagittal views. Both T1-weighted and T2-weighted images should be obtained. Fluid-attenuated inversion recovery sequences minimize signals due to cerebrospinal fluid and increase the sensitivity for detecting lesions such as MTS or small tumors and vascular malformations.[38] To further optimize the visualization of temporal lobe abnormalities, images should be obtained in oblique coronal planes that are perpendicular to the long axis of the hippocampal formation. The thickness of the image slice should be 1.5 mm or less. It is essential that the imaging technique used allows accurate quantification of hippocampal volumes and abnormal signal intensities and construction of 3-dimensional brain images. Magnetic resonance imaging studies performed with such techniques should be reviewed and interpreted by physicians who are knowledgeable and experienced in identifying abnormalities associated with seizure disorders, especially abnormalities associated with intractable epilepsy.

The administration of contrast agent is unnecessary if a properly conducted unenhanced MRI study shows no lesions. Enhancement with a contrast agent does not increase the yield.[39,40] If a lesion is identified on a noncontrast study, contrast enhancement can help determine the type of lesion (eg, arteriovenous malformations enhance with contrast agents but many low-grade gliomas do not).

Indications for Repeated MRI Studies

Whether an MRI study needs to be repeated depends on the clinical condition of the patient. If seizures are not controlled satisfactorily and previous findings on standard MRI were unremarkable, the MRI should be repeated with techniques such as those described earlier to optimize the detection of epileptogenic lesions. This is necessary for patients who are being evaluated for epilepsy surgery. In infants, gray and white matter may not be delineated clearly in MRI because of incomplete myelination.[41] Consequently, if a child's seizures remain poorly controlled, MRI should be repeated at a later age. Other instances in which MRI may need to be repeated are (1) worsening of seizure control or unexpected breakthrough seizures after a

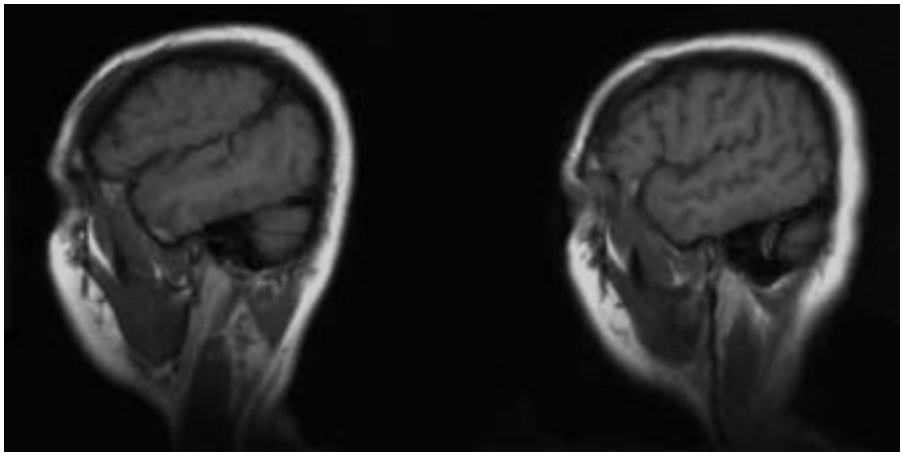

Figure 4. T1-weighted sagittal magnetic resonance images of a 29-year-old woman who had congenital right spastic hemiparesis and frequent generalized tonic-clonic seizures since age 6 years. Left, Left hemisphere shows schizencephaly, with a cleft resulting from abnormal posterior extension of the sylvian fissure. Note also abnormal gyration that appears as polymicrogyria and is especially prominent in the temporal lobe and along the inferior border of the cleft. Right, Right hemisphere with normal sylvian fissure and gyri.

period of remission, (2) unexplained change in seizure characteristics, or (3) development of abnormal neurologic signs or symptoms. Repeated MRI studies can detect progressive structural abnormalities underlying intractable seizures and neuropsychological deterioration, such as progressive atrophy of hippocampal structures.[42] Also, regardless of the degree of seizure control, serial MRI studies may be indicated if the epileptogenic lesion has the potential for enlargement or for hemorrhagic complications.

FUNCTIONAL IMAGING

Positron Emission Tomography

Positron emission tomography images regional or focal cerebral activity according to the degree of uptake of radioactive agents. One advantage of PET is the availability of a wide variety of radioactive ligands for investigating pathophysiological mechanisms underlying the epileptic process. The rate of glucose uptake can be estimated with 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), and blood flow can be determined with ^{15}O-labeled water ($H_2{}^{15}O$). Several other agents are available for assessing cellular receptors of compounds such as benzodiazepine, dopamine, and opiates. The degree of alteration in the physiological processes studied with PET can be measured quantitatively. However, the short half-life of [^{18}F]FDG, which is the agent used most frequently, and its relatively long period of cerebral uptake limit the use of PET to the period between seizures (interictal period). Consequently, most PET studies of epilepsy are conducted to detect interictal *hypo*metabolic regions that correspond to decreased [^{18}F]FDG uptake in potentially epileptogenic regions (Figure 5). In contrast, when [^{18}F]FDG is injected fortuitously during a focal seizure, PET images may show *hyper*metabolic activity that corresponds to increased [^{18}F]FDG uptake in the region of electrical seizure activity[43] (Figure 6).

Approximately 70% of patients with temporal lobe epilepsy have a visible temporal lobe hypometabolic abnormality on interictal PET studies.[44] The sensitivity is improved by quantitative measurement of [^{18}F]FDG uptake.[45] The location of the PET abnormality corresponds to the EEG-detected seizure focus (EEG seizure focus) in 90% of patients. Moreover, hypometabolism in the lateral temporal cortex independently predicts a seizure-free outcome after temporal lobectomy in a group of patients with mostly nonlesional epilepsy. Asymmetry of [^{18}F]FDG uptake of more than 15% between the left and right lateral temporal lobes strongly suggests that the seizure focus is located in the lobe with less uptake.[46]

Earlier studies of extratemporal epilepsy showed that the sensitivity of interictal PET studies ranged from 33%[47] to about 65%.[48] When present, the hypometabolic abnormality has a high concordance with the EEG seizure focus. Results are less impressive if a structural lesion is not seen with MRI; only 56% of patients with temporal lobe epilepsy and 9% of patients with extratemporal epilepsy had a localized abnormality on PET.[44] Newer generations of PET machines may have improved the yield. More recently, [^{18}F]FDG PET has shown a unilateral frontal hypometabolic region in 85% of patients with frontal lobe epilepsy and normal MRI findings.[49]

Positron emission tomography is used particularly to identify a focal abnormality for surgical resection in pa-

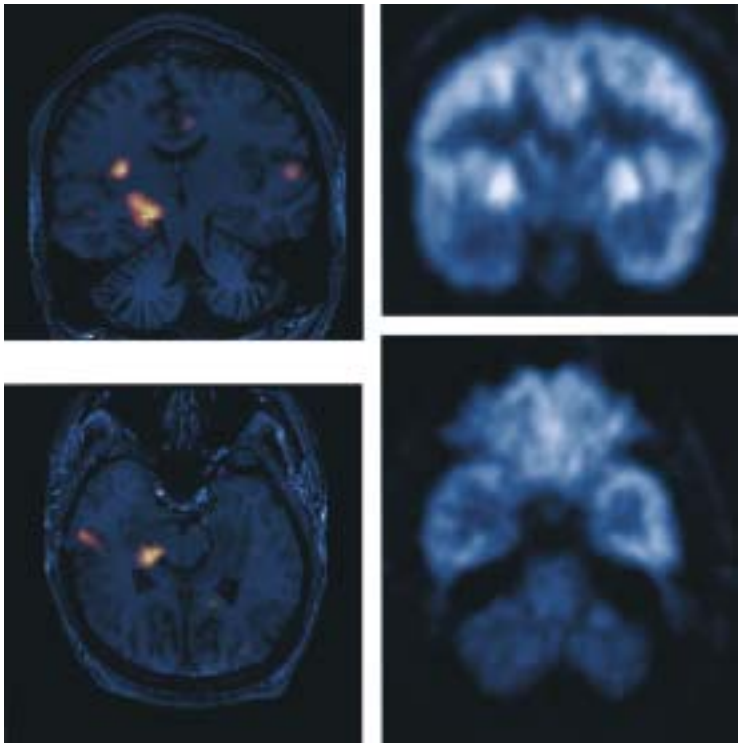

Figure 5. Subtraction ictal SPECT (single-photon emission computed tomography) coregistered to MRI (magnetic resonance imaging) (SISCOM) and 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) positron emission tomographic (PET) images of a 27-year-old man who had experienced febrile seizures at age 1 year and since childhood has had medically refractory complex partial seizures with secondary generalization. Upper left and lower left, Ictal SPECT with SISCOM technique shows a dominant focus of hyperperfusion in the right mesial temporal region. Upper right and lower right, An interictal PET study shows a concordant hypometabolic focus of [^{18}F]FDG uptake that is less intense than in the left temporal lobe.

tients with infantile spasm, an epileptic disorder otherwise characterized by generalized and nonfocal clinical and EEG abnormalities. Although earlier MRI studies showed no obvious structural abnormalities in many infants with infantile spasm, resection of the hypometabolic region resulted in cessation of the spasms in nearly 80% of the infants.[50] With PET, efficacious surgical treatment is possible for patients without an obvious localized abnormality seen on MRI. Recent PET studies measured serotonin synthesis in patients with tuberous sclerosis and distinguished epileptogenic tubers with increased uptake of α-[^{11}C]methyl-L-tryptophan from nonepileptogenic tubers with decreased uptake of the radiotracer.[51]

Subtraction Ictal SPECT Coregistered to MRI (SISCOM)

Single-photon emission computed tomography (SPECT) has several advantages over PET. The SPECT equipment and facilities are less expensive, and no cyclotron is needed to generate the radiotracer used in SPECT. The half-life of radiotracers used in SPECT is longer than that of radiotracers used in PET. Consequently, for a SPECT study, it is feasible to anticipate the occurrence of a seizure and inject the radiotracer during the seizure (ictal SPECT study). The principle of ictal SPECT in localizing seizure onset is based on the phenomenon of increased cerebral blood flow in regions affected by seizure activity.[52,53] When the radiotracer is injected soon after seizure onset, it is distributed and bound by cerebral tissues in proportion to the amount of local cerebral perfusion. Because the distribution and uptake of SPECT radiotracers usually are completed within 1 minute, the procedure can provide a "snapshot" of brain perfusion as altered by seizure activity. In contrast, PET studies, with rare exception, are interictal studies.

The sensitivity of interictal SPECT studies in identifying the focus of seizure onset is lower than that of ictal

SPECT studies.[54,55] Furthermore, in 10% of patients with intractable temporal lobe epilepsy and 26% of those with frontal lobe epilepsy, the focus identified by using interictal SPECT may be discordant with the focus identified by using EEG.[44] Therefore, ictal SPECT studies are preferred to interictal SPECT studies. However, interictal studies should be performed for comparison with ictal studies so that alterations in blood flow caused by seizure activity can be appreciated visually. This conventional method of visually comparing the ictal and interictal images is the basis of most reported ictal SPECT studies. The SISCOM technique, a more recently developed tool for analyzing SPECT images,[56] was developed to overcome several drawbacks of conventional SPECT studies.[57] The interpretation of conventional SPECT studies relies on a subjective visual appreciation of any differences in intensity between the ictal and interictal scans. However, the overall intensity of the 2 scans may vary because of technical factors such as the amount of radiotracer injected and the time between the injection and image acquisition. Ictal and interictal SPECT images frequently vary in the level of image slices, which is influenced by differences in head position during scanning. Also, conventional SPECT images lack the anatomical detail that MRI offers. With SISCOM, the ictal image is subtracted digitally from the interictal image to produce a "difference" image. Before subtraction, the mean cerebral pixel intensities of the ictal and interictal scans are normalized to a mean intensity of 100, and the 2 scans are coregistered in space to each other by either surface point or voxel-to-voxel matching. The threshold of the difference image is set to display only pixels with intensities greater than 2 standard deviations. The resultant peak intensity image is then coregistered onto the magnetic resonance image (Figure 7).

The usefulness of SISCOM has been compared with that of conventional SPECT in the study of epilepsy.[56] We found that the sensitivity of SISCOM for detecting a focus of hyperperfusion is twice that of conventional SPECT (88% vs 39%). Moreover, SISCOM provides valuable information that is independently prognostic of epilepsy surgery outcome; conventional SPECT does not provide this information. For patients with a seizure focus that could not be localized by standard tests such as EEG and MRI, the probability of excellent postsurgical seizure control is considerably higher when surgical resection includes the SISCOM abnormality than when it does not (60% vs 20%).

Occasionally, the SPECT radiotracer cannot be injected promptly when the seizure is ongoing, and injection is instead postictal.[58] The phenomenon of postictal *hypo*perfusion in the region of seizure activity can also be imaged with SISCOM (Figure 8). The postictal hypoperfusion focus generally has a wider distribution than the ictal hyperperfusion focus.[59]

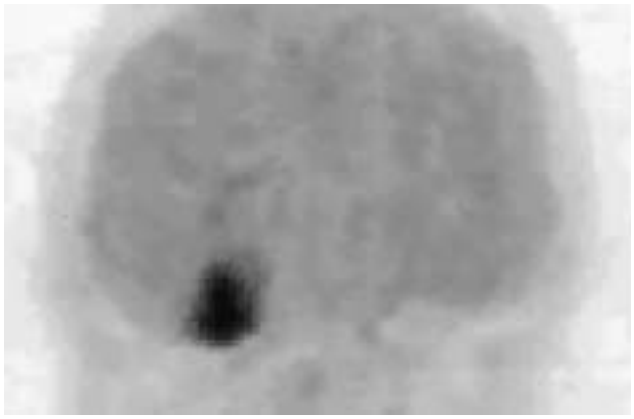

Figure 6. Ictal 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) positron emission tomographic image of a 9-year-old girl showing a hypermetabolic focus of markedly intense [^{18}F]FDG uptake in the right mesial temporal lobe. The [^{18}F]FDG agent was injected when the girl was experiencing a typical seizure with confusion, behavioral arrest, and automatisms.

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopic imaging is based on the principle that when a magnetic field is applied to a chemical compound, the natural frequency at which the nuclei resonate is shifted to a frequency unique to the compound. This allows noninvasive measurement of certain chemical compounds in the living brain. An advantage of MRS is that it uses the same MRI machine used for high-resolution imaging of structural lesions of the brain.

Magnetic resonance spectroscopic studies in epilepsy usually involve the hydrogen nucleus (^{1}H) because it is sensitive to applied magnetic fields and is abundant in cerebral metabolites such as *N*-acetylaspartate (NAA), creatine, and choline. *N*-acetylaspartate occurs in neurons but not in mature glial cells. Thus, it is considered a marker of neuronal abundance or function. In comparison, creatine activity and choline activity are associated more with glial cells than with neurons. *N*-acetylaspartate and creatine signals can be measured with ^{1}H MRS to assess 2 major pathological features of MTS: decreased NAA for neuronal loss and slightly increased or unchanged creatine for astroglial proliferation. The ratio between NAA and creatine signals is frequently used to detect temporal lobe abnormalities in candidates for epilepsy surgery (Figure 9). The correspondence between the decreased NAA:creatine ratio and the side of MTS or EEG-detected seizure onset (EEG seizure onset) is as high as 90% in temporal lobe epilepsy.[60] Also, ^{1}H MRS is especially helpful in patients who do not have hippocampal atrophy.[61] In such patients,

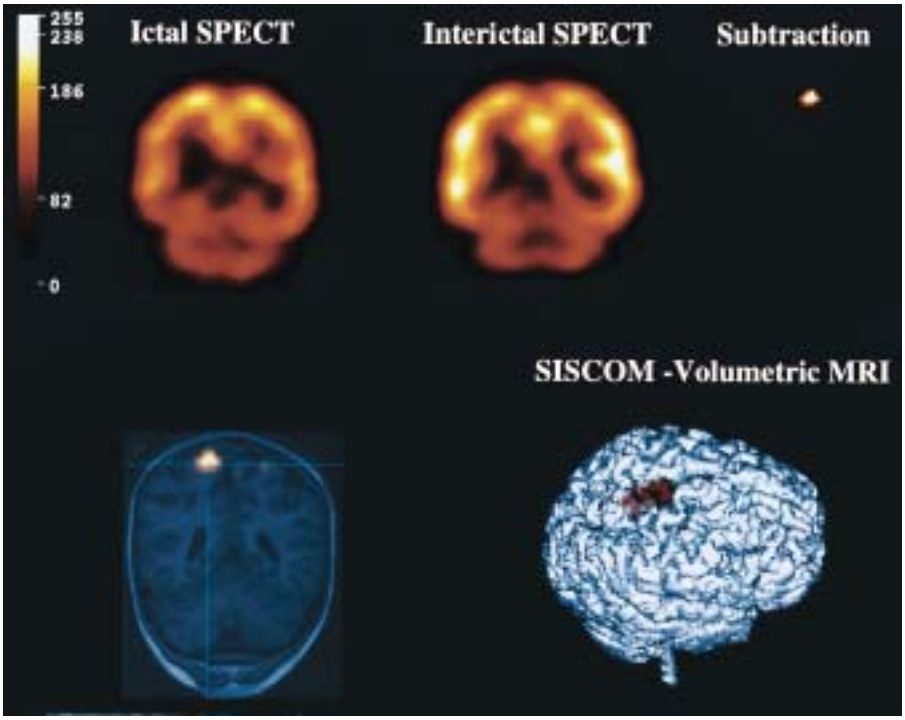

Figure 7. Steps to obtaining subtraction ictal SPECT (single-photon emission computed tomography) coregistered to MRI (magnetic resonance imaging) (SISCOM) image. Ictal (upper left) and interictal (upper middle) SPECT images are obtained. After normalization of their mean intensities and coregistration with each other, subtraction is performed to obtain a "difference" image (upper right). The difference image is then coregistered with magnetic resonance images at specific planes (lower left) or on the surface of a 3-dimensional magnetic resonance image (lower right).

correct lateralization of the surgical focus with MRS depends on accurately detecting the asymmetry in NAA signals between the left and right temporal lobes. Up to 90% of patients with epilepsy have asymmetric NAA signals, with EEG-detected seizures usually arising from the side with the lower NAA signal. Pathological examination of nonatrophic temporal lobes with abnormal MRS findings has shown mild MTS. Thus, ^{1}H MRS is sensitive enough to detect mild cases of MTS, ie, MTS not severe enough to be identified as hippocampal atrophy on MRI. Frequently, MRS detects bilateral abnormalities when MRI shows only unilateral atrophy. Compared with a unilateral MRS abnormality, bilateral MRS abnormalities are associated with less favorable seizure control after temporal lobectomy.[62] If ^{1}H MRS shows an abnormality in the temporal lobe of the language-dominant hemisphere, resection of the opposite temporal lobe can impair verbal memory function. Such patients have lower postoperative verbal memory function than patients who have had temporal lobectomies and whose dominant temporal lobe is normal on ^{1}H MRS studies.[63]

LIMITATIONS OF NEUROIMAGING IN SEIZURE DISORDERS

Neuroimaging has several limitations in evaluating seizure disorders. In approximately 30% to 40% of epilepsy surgery patients, no potentially epileptogenic lesion is seen with MRI.[22,24] Although MRI detects MTS in 90% of patients whose intractable seizures are caused by the lesion, mild cases of MTS can escape detection with MRI.[64] Complete resection of the lesion seen on MRI and of the tissue immediately surrounding the lesion is effective in controlling seizures.[65] However, areas that underlie epileptic seizure discharges may be more extensive or may be distant from the lesion.[66] In 1 study, the MRI lesion was not the site of seizure onset in 5% of patients who had epilepsy surgery.[67] Even if MRI identifies a lesion in the temporal lobe, the rate of excellent postsurgical outcome is only 60% when interictal EEG discharges are not all concordant with ictal onset.[24]

In extratemporal epilepsy, [^{18}F]FDG PET findings are more likely to be positive if a focal EEG or MRI abnormality has been documented. The [^{18}F]FDG PET yield is lower when EEG and MRI findings are normal,[44] but it is in such

situations that PET as a functional imaging modality is expected to contribute additional information. Also, an abnormality visualized with [^{18}F]FDG PET often has a diffuse distribution, affecting both temporal and frontal lobes in either temporal or frontal lobe epilepsy.[68] The frontal hypometabolic region identified with [^{18}F]FDG PET does not correspond to the focus of EEG seizure onset in about 20% of patients.[49] Also, the region of hypometabolism is more extensive than the ictal EEG abnormality in about 40% of patients. In patients with temporal lobe epilepsy, an abnormality seen with PET often involves the lateral and the mesial temporal regions equally, regardless of whether seizures arise in the lateral or mesial temporal region.[69] False lateralization can occur but is uncommon.[70] False localization may result when an unrecognized seizure occurs during a presumed interictal PET study, and a region is mistaken to be pathologically hypometabolic when in fact the metabolism only appears reduced in relation to the unrecognized ictal *hyper*metabolic region. For this reason, the EEG and a PET study should be recorded simultaneously to detect seizure occurrence.

Information from a SPECT study is based on the particular seizure episode during which the SPECT injection was made. The value of a focal SISCOM abnormality in localizing a surgical seizure focus is greatest when the patient has a single or predominant type of seizure. Caution must be exercised when assessing the importance of an abnormal SISCOM focus if the patient has multifocal epilepsy. The clinician must rely on all clinical and laboratory evidence to ensure that other types of disabling seizures are not overlooked. False localization can occur, usually if the radioisotope is injected well after seizure onset, when seizure activity has propagated to a distant site.[71] In our laboratory, patients undergo video-EEG monitoring during radioisotope injections for ictal and interictal SPECT studies. Because frontal lobe seizures typically have a short duration, special effort should be made to inject the radioisotope promptly after seizure onset. Thus, the radiotracer and staff should be in the patient's room so that the injection can be given once the seizure has commenced. For patients with nocturnal seizures, sleep deprivation and subsequent daytime naps increase the chances of a successful ictal SPECT study.

Similar to the results found in [^{18}F]FDG PET studies, careful study of the spatial extent of MRS abnormalities has shown that an abnormal region often extends into the extratemporal region in patients with temporal lobe epilepsy[72] and, conversely, into the temporal region in those with extratemporal epilepsy. Although 94% of patients had an MRS abnormality in the ictal EEG focus, 35% also had abnormalities distant from the EEG focus. Magnetic resonance spectroscopic studies of the frontal lobe have been useful in evaluating frontal lobe epilepsy.[73] Nonetheless, the usefulness of MRS in nonlesional frontal lobe epilepsy has not been established, especially for medial frontal lobe epilepsy. This is partly due to the large area of the frontal lobes, which makes it difficult to efficiently measure with MRS. For optimal sensitivity, MRS can assess only a limited volume of tissue at a time. Also, the spatial resolution of MRS is less than that of MRI, PET, or SISCOM.

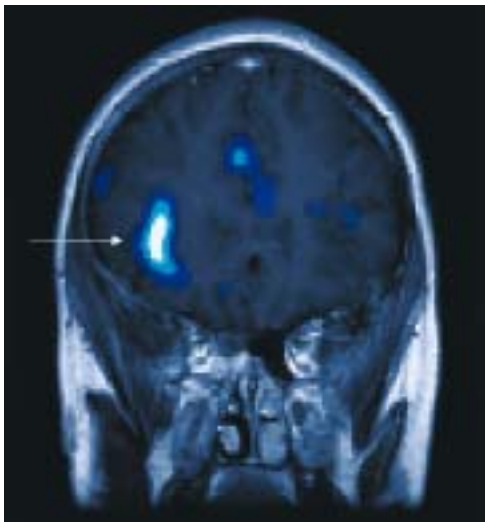

Figure 8. Postictal single-photon emission computed tomography (SPECT) image using the subtraction ictal SPECT coregistered to MRI (magnetic resonance imaging) technique to display the hypoperfusion focus (arrow) in the right insular region of a 14-year-old patient whose refractory complex partial seizures had resulted in falls. Depth electrode recording confirmed EEG seizure onset at the focus. Since resection of the focus, the patient has had only sporadic seizures without falls.

ROLE OF MODERN IMAGING IN EPILEPSY SURGERY

Identifying the Seizure Focus for Surgical Resection

High-resolution MRI is the most important procedure for identifying the epileptogenic zone in patients who are being considered for epilepsy surgery.[37] However, MRI must be performed with techniques that have been optimized for seizure disorders. The MRI lesions that are associated with highly favorable postsurgical outcome are low-grade tumors, vascular malformations, MTS, and focal cortical dysplasia. The probability of excellent seizure control after resection of these lesions has been reported to be as high as 70% to 90%.

Traditionally, EEG discharge during seizures has been considered the signature of epileptic seizure activity. Consequently, the location of the EEG seizure onset usually has been accepted as the standard against which all other diagnostic tests are compared for accuracy in localizing the seizure focus for surgical resection. However, only 25% of patients have an excellent outcome if the location and

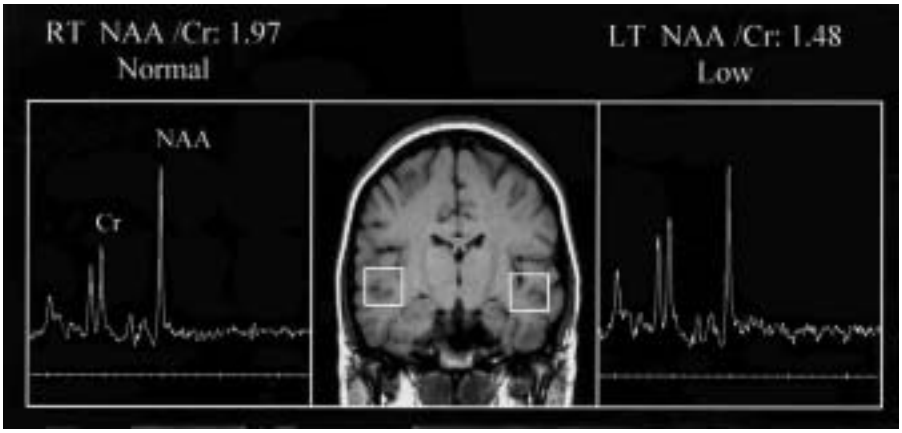

Figure 9. Magnetic resonance spectroscopy ^{1}H spectra measured in the temporal lobes (small boxes in middle panel) of an 18-year-old patient with intractable epilepsy. Graphs of the spectra show major peaks of signal intensity corresponding to *N*-acetylaspartate (NAA) and creatine (Cr). The NAA/Cr ratio in the left (LT) temporal region is considerably lower than control values, whereas the ratio is normal on the right (RT) side. Since undergoing a left temporal lobectomy, the patient has been seizure free.

extent of the surgical resection are determined primarily by EEG abnormalities and not by the structural substrate.[74] The outcome is much better when surgical excision includes the structural lesion than when it involves only the EEG focus.[75] Experience at our institution shows that postoperative seizure control in patients with low-grade gliomas depends largely on the completeness of the removal of the lesion and less on the extent of the EEG abnormality.[76] In patients with MCD, completeness of the resection of the lesion is also a major prognostic factor for postsurgical seizure control. Total excision of focal or regional abnormalities such as focal cortical dysplasias has a strong probability of conferring marked improvement in seizure control.[77] In comparison, the probability of a good outcome is lower with partial excision of large MCDs such as diffuse polymicrogyria.

The primary means of localizing the seizure focus for epilepsy surgery are the clinical history and examination, interictal EEG, epilepsy-protocol MRI, and video-EEG recordings of seizures. If the primary methods of seizure localization are all congruent in detecting the focus or region for surgery, information from other functional imaging studies is redundant and unlikely to improve surgical outcome.[78] However, if the primary methods are deficient in localizing seizures or produce conflicting results, we seek additional evidence of seizure localization by conducting functional imaging studies. This approach is relevant especially for patients whose MRI or video-EEG recordings are indeterminate or nonlocalizing for the surgical focus. In these cases, we favor the use of SISCOM studies and also PET studies in nonlesional epilepsy. An abnormal SISCOM focus is more likely to be localizing than an abnormal PET focus. The PET abnormalities are more likely to be lateralizing to 1 hemisphere than within a hemisphere, especially in extratemporal epilepsy. We perform MRS when the available evidence strongly suggests the likelihood of temporal lobe epilepsy; currently, MRS is less useful for extratemporal epilepsy.

An important role of functional imaging is to provide the target for intracranial electrode implantation. The lack of a target may necessitate extensive surgery for implanting intracranial electrodes, often with less guarantee of obtaining useful information. The risk of major complications increases by 40% for every 20 additional subdural electrodes implanted, and the risk is as high as 82% for bilateral hemisphere implantations.[79] In many instances, intracranial electrode implantation can be avoided if a functional imaging study detects an abnormality that is concordant with the scalp ictal EEG focus or with an MRI-identified epileptogenic lesion. Intracranial EEG recording provides no additional useful information in patients with temporal lobe epilepsy if the abnormality seen on PET agrees with the surface or sphenoidal EEG seizure onset.[80]

Mapping the Functioning Cortex

Positron emission tomography and MRI can be used to image physiological events that occur in cortical areas activated by specific tasks performed by the subject. The $H_2{}^{15}O$ PET accurately identifies language or sensorimotor areas by measuring focal changes in cerebral blood flow during the performance of language, sensory, or motor tasks.[81] Magnetic resonance imaging is also used to delineate functioning cortex. Functional MRI (fMRI) is based on the principle that blood flow and oxyhemoglobin increase in the task-activated cortex, resulting in a relative

decrease of deoxyhemoglobin.[82] The change in deoxyhemoglobin magnetic signals in the focus of the task-activated cortex can be detected with T2-weighted MRI. The technique is referred to as the *blood oxygen level–dependent* technique of fMRI.

The usual method for identifying language and memory capacity in candidates for epilepsy surgery has been with intracarotid injection of the sedative amobarbital to inactivate 1 hemisphere. This procedure requires cerebral angiography, and the sedating effects of amobarbital often interfere with language testing. The localization of functioning cortex with $H_2{}^{15}O$ PET or fMRI compares favorably with that of electrical stimulation of the cerebral cortex, currently the standard method for identifying areas of cortical function.[83-86] However, electrocortical stimulation is an invasive procedure that requires intracranial implantation of electrodes. Electrocortical stimulation identifies cortical function indirectly by using electrical pulses to interrupt ongoing cognitive tasks, whereas PET and fMRI directly assess physiological processes induced by the tasks. With either fMRI or $H_2{}^{15}O$ PET, the focus of activation that is detected can be coregistered on MRI, which allows for anatomical localization and surgical planning. In contrast, the intracarotid amobarbital procedure lateralizes language function to only 1 hemisphere and does not identify the anatomical structures underlying this function. Nonetheless, the use of functional PET or fMRI requires considerable expertise, which currently is available at only a few major medical centers.

Integrating Multimodality Images for Surgical Planning

Recent advances in computer-based image analysis have made it possible to display all structural and functional imaging abnormalities on the anatomical background of the brain[87] (Figure 10). This provides a map that is essential for surgical planning, especially for maximizing surgical resection of abnormal foci and minimizing complications of the resection. The display of images derived from various imaging modalities confers details of relationships between foci and also between each focus and normal brain structure. The clinician can assess the degree of concordance between the foci and determine the proximity of each focus to cortical areas that serve critical language and motor functions.

Using Computer Image–Guided Surgery

Computer image–guided surgery has important applications for lesional and nonlesional epilepsy surgeries.[71] After a lesion has been detected on MRI or a focus has been identified with SISCOM, stereotactic brain MRI is performed with registration of several external scalp markers (Figure 11, upper left[87]). The surgical target, which often is

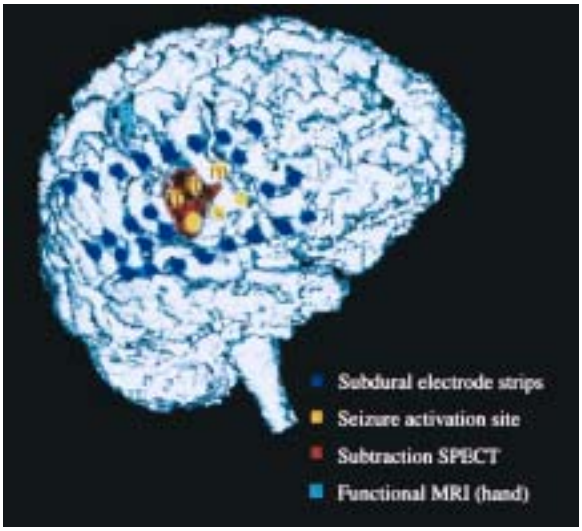

Figure 10. Three-dimensional rendition of magnetic resonance image (MRI) of brain with coregistration of sensory area of the hand identified with functional MRI (green), subtraction ictal SPECT (single-photon emission computed tomography) coregistered to MRI hyperperfusion focus (red), subdural electrodes (blue), and electrodes where EEG-detected seizures commenced (yellow). m = electrode sites where facial motor activity was elicited with electrocortical stimulation; s = electrode site where sensory function was elicited.

the SISCOM-identified focus in nonlesional epilepsy, is incorporated into the matrix of the stereotactic MRI data. A noninvasive computer-guided stereotactic system[88] is used to register the scalp markers into the computer to create a transformational matrix in which the MRI lesion or SISCOM focus is related to the physical space of the patient's head (Figure 11, upper right[71]). This allows the surgeon to relate the surgical field to the images that show the location of the MRI lesion or SISCOM focus. When the surgeon uses a wand to point to a spot in the surgical field (Figure 11, lower left[87]), the distance from the tip of the wand to the MRI lesion or SISCOM focus can be determined on the computer screen (Figure 11, lower right[71]). This technique is used to accurately implant subdural electrodes for recording EEG activity at the site of the MRI lesion or SISCOM focus and the surrounding cortex. The technique is especially important when MRI shows no structural lesions and the only surgical target is a SISCOM hyperperfusion focus that is invisible on the surgical field. Computer image–guided surgery is also used in resecting the area of a SISCOM focus, which by itself has no structural landmarks to guide the extent of the resection.

SUMMARY

Neuroimaging is an essential diagnostic tool for evaluating new-onset seizure disorders and chronic uncontrolled epi-

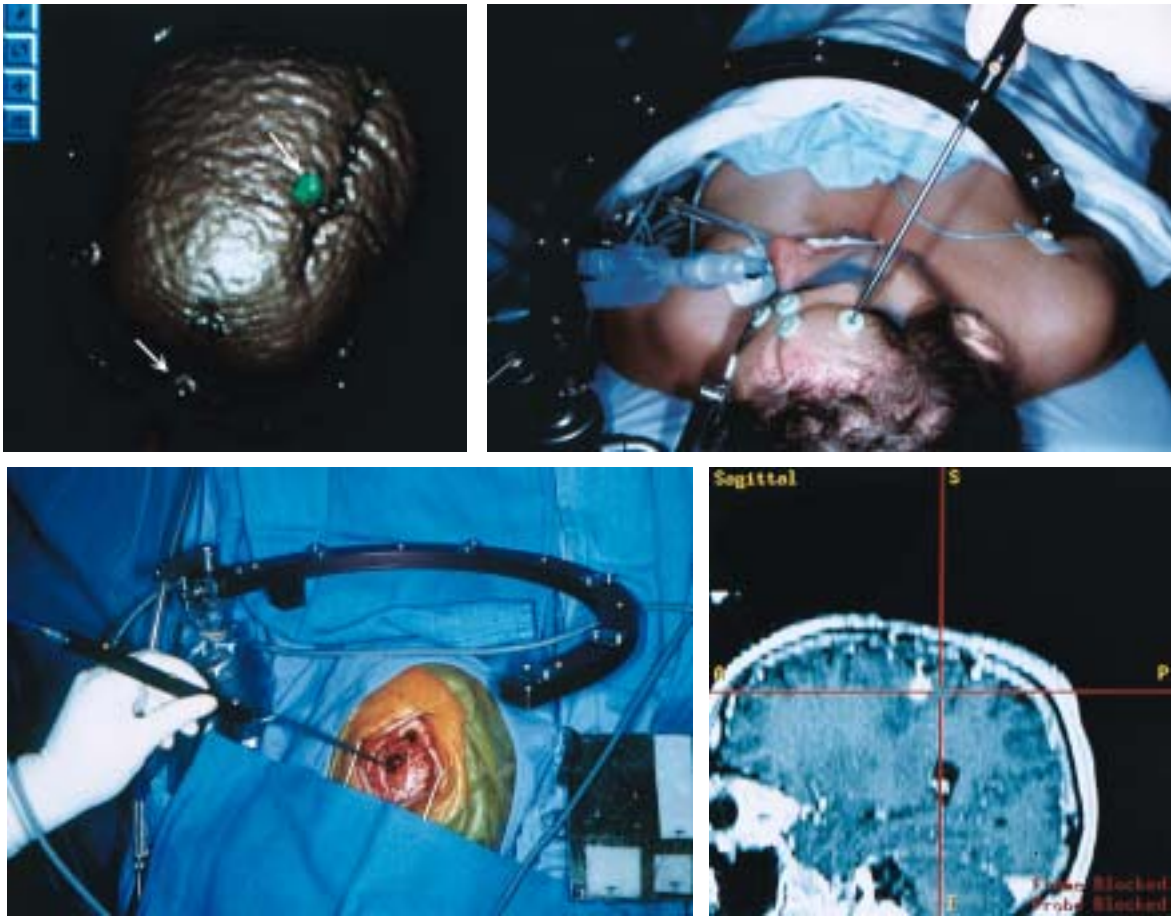

Figure 11. Upper left, Three-dimensional reconstruction of a patient's head from frameless stereotactic magnetic resonance imaging (MRI) procedure, showing scalp markers (lower arrow) and the surface-rendered subtraction ictal SPECT (single-photon emission computed tomography) coregistered to MRI (SISCOM) focus (upper arrow). Reprinted with permission from So.[87] Upper right, The scalp markers are then registered into a computer to create a transformational matrix so that the MRI space can be related to the physical space of the patient's head. Reprinted with permission from So et al.[71] Lower left, Intraoperatively, the surgeon uses a wand to point to locations in the surgical field. Reprinted with permission from So.[87] Lower right, The surgeon views the computer monitor screen where the crosshairs indicate how close the tip of the wand is to the SISCOM abnormality; this is used to guide implantation of subdural electrodes or to resect the seizure focus. A = anterior; I = inferior; P = posterior; S = superior. Reprinted with permission from So et al.[71]

lepsy. Recent advances in neuroimaging have enhanced the clinician's ability to identify the underlying causes of seizure disorders in many patients; thus, the appropriate medical or surgical therapy can be used. Modern neuroimaging has also benefited patients with medically intractable epilepsy. The identification of a structural epileptogenic lesion and its surgical resection are the major determinants of the success of epilepsy surgery in such patients.

Functional imaging helps delineate the seizure focus to be resected, especially when imaging with advanced MRI techniques is insufficient for detecting the focus. Progress in computer-aided stereotactic surgery has also made possible the accurate implantation of intracranial electrodes on a structural or functional imaging abnormality. This technique is used also for surgical planning and resection of the structural or functional abnormality so that seizure control can be achieved and operative morbidity can be minimized. An increasing number of investigative studies have shown that functional imaging techniques can identify cortical areas that serve critical functions such as speech and motor performance.

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The Symposium on Seizures will continue in the December issue.