

Advanced Neuroimaging for Modern Epilepsy Surgery

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Abstract

Localizing the onset of seizures to guide epilepsy surgery can be notoriously difficult. Modern neuroimaging has revolutionized the field by improving the diagnosis and treatment of epilepsy. In order to ameliorate seizures without causing new neurologic morbidity, many imaging tools have been developed to guide safe and effective resective surgery. In this article, we discuss recent advances in structural imaging using ultrahigh-field magnetic resonance imaging, metabolic functional imaging techniques of positron emission tomography and single positron emission computed tomography, and electrophysiologic imaging using magnetoencephalography. Our goal is to provide an overview of these state-of-the-art imaging modalities, their role in guiding surgery, and how they are incorporated into the pre-surgical evaluation of epilepsy.

Keywords

Epilepsy, imaging, neuroimaging, magnetic resonance imaging, single photon emission computed tomography, positron emission tomography, magnetoencephalography, magnetic source imaging, electroencephalography, epilepsy surgery, temporal lobe epilepsy, malformation of cortical development, outcome

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When neurosurgeons first attempted to treat epilepsy by means of surgery in the late 1800s, they were operating on ‘invisible’ lesions. Without any imaging or electrophysiological technology, MacEwen and Horsley operated under the principles of functional cerebral localization developed largely by John Hughlings Jackson.¹ Epilepsy surgery has come a long way, as now epileptologists and neurosurgeons are armed with a battery of tools for diagnosis and treatment of epilepsy. These tools have fundamentally changed the way we study and treat this enigmatic disease.

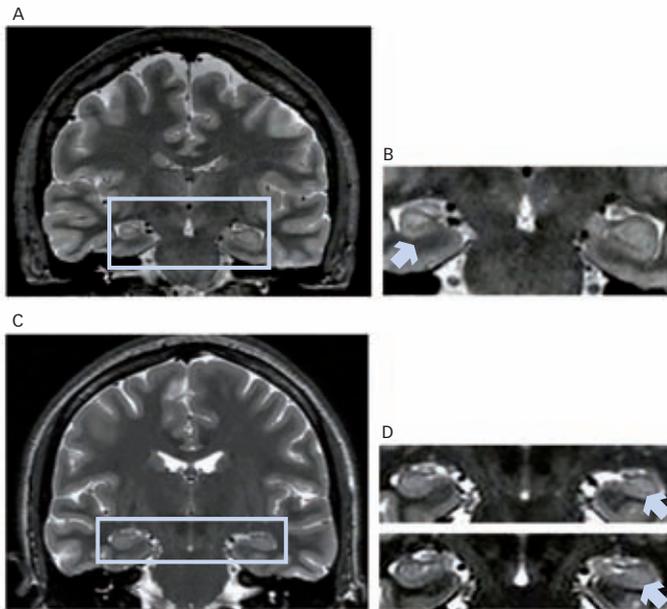
Epilepsy is one of the most common diseases affecting the central nervous system, with a prevalence of 0.5 % and a lifetime cumulative incidence of about 3 %.² Of those with epilepsy, about 40–50 % become medically refractory, causing significant impairment to quality of life and increased morbidity, mortality, and healthcare costs. Among these medically refractory cases of epilepsy, many patients are candidates for surgical intervention, which can achieve freedom from seizures in up to 70–80 % of patients.^{3,4} The goal of epilepsy surgery is to resect the epileptogenic foci in order to stop or reduce seizure burden without causing significant motor, speech, or cognitive impairments in the patient and, therefore, to improve the patient’s quality of life.

In this article, we discuss advances in imaging techniques used in epilepsy surgery. These techniques include structural imaging techniques with magnetic resonance imaging (MRI), volumetric-based analysis, and high-resolution MRI to assess lesional causes of epilepsy. We also discuss functional imaging modalities that detect changes in brain metabolism during the ictal and interictal period, such as positron emission tomography (PET) and single positron emission computed tomography (SPECT). Finally, we discuss the electrophysiological imaging technique magnetoencephalography (MEG) and its role in the identification of epileptogenic regions in the brain. Imaging is no longer limited to a mere static representation of the brain to acquire structural abnormalities. These new imaging modalities have been developed to capture dynamic brain functions and to yield crucial information about abnormal and normal brain activity. Together, these imaging techniques and future developments will continue to improve our understanding and treatment of epilepsy.

Structural Imaging Temporal Lobe Epilepsy

MRI has become standard practice for any pre-surgical evaluation for epilepsy surgery. MRI can detect relevant structural abnormalities in 85 %

Figure 1: High Resolution Magnetic Resonance Imaging Showing Mesial Temporal Sclerosis

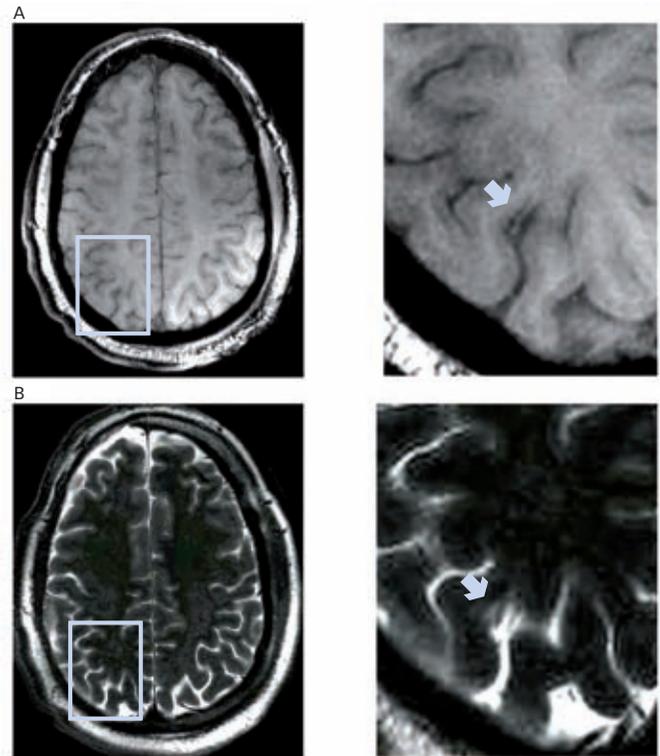


A: Coronal fast multiplanar inversion recovery (FMPIR) imaging demonstrating prominent atrophy of the right hippocampus in a 41-year-old woman with medically refractory temporal lobe epilepsy; B: Magnification of area in the left panel shows a smaller right hippocampus and subcortical signal abnormalities (arrowhead); C: Coronal FMPIR demonstrating subtle hippocampal changes in a 22-year-old woman with medically refractory epilepsy arising from the left temporal lobe; D: Two sequential slices of the hippocampus showing blurring of the CA1 region and other internal structures (arrowheads) within the left hippocampus compared with the right. Pathologic evaluation was consistent with mesial temporal sclerosis.

of patients with refractory partial seizures who are candidates for surgical treatment.⁵ The most common focal structural abnormality detected using MRI is mesial temporal sclerosis (MTS), or hippocampal sclerosis, which is commonly found in patients with temporal lobe epilepsy (TLE). Classic findings of mesial temporal sclerosis include atrophy of the hippocampus and amygdala with increased signal on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images (see *Figure 1A*).^{6,7} We now recognize that subtle cases of MTS may manifest exclusively as indistinct architectural features within the affected hippocampus rather than overt atrophy or T2 signal prolongation (see *Figure 1B*). Numerous studies have demonstrated that MTS is a positive prognostic indicator of good surgical outcome, with seizure-free rates ranging from 70 to 90 %.⁸⁻¹² By contrast, the post-operative seizure-free rate in TLE patients with unremarkable MRI is significantly lower, ranging from 50 to 60 %.¹³⁻¹⁵

To increase the sensitivity and specificity for detecting subtle MTS in patients with TLE, several automated analysis methods have been employed with some degree of success. The technique of voxel-based morphometry (VBM) was developed to detect subtle regional changes in tissue volume or density throughout the whole brain.¹⁶ Interesting comparisons between patients with TLE and normal subjects using VBM revealed a widespread network of changes, including a reduction in grey matter volume in the cingulate, thalamus, and frontal lobes.¹⁷⁻¹⁹ A meta-analysis of VBM studies in TLE noted consistent findings of volume loss in the ipsilateral hippocampus (82 % of all studies), parahippocampal gyrus (47 %), entorhinal cortex (23 %), contralateral hippocampus (17 %), thalamus (ipsilateral 61 %, contralateral 50 %), and parietal lobes (ipsilateral

Figure 2: Ultrahigh-field-strength Magnetic Resonance Imaging in Evaluation of Cryptogenic Epilepsy

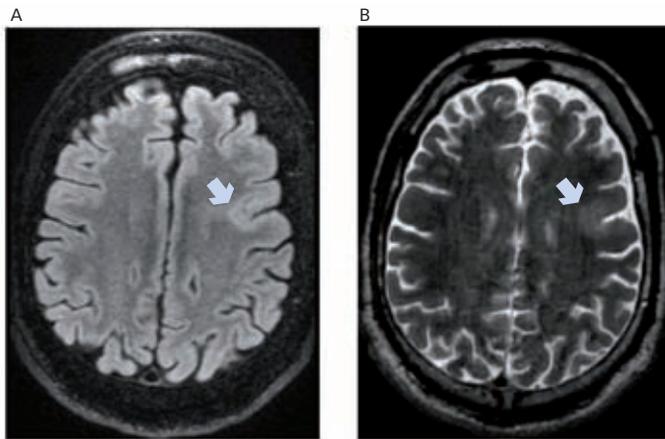


A: A 30-year-old male with complex partial seizures arising from the right supplemental motor cortex and superior parietal region with 7T axial spoiled gradient echo study showing a small focal area of cortical thinning in the right parietal lobe. The magnified view of the lesion in the right panel shows cortical dysplasia (arrowheads); B: 7T fast spin echo showing increased signal in the area of thinned cortex.

47 %, contralateral 52 %).²⁰ VBM studies are prone to low specificity given the nature of the analysis; by warping the subjects' MRI to a standardized space before comparing them, the differences may be an artifact from the warping process itself. Despite these limitations, using large control populations and other voxel-based analysis with different imaging sequences may reduce the false-positives and yield clinically relevant information regarding MTS.²¹

Recently, 3T and 7T MRI machines have been developed to provide even higher-resolution images. A study comparing 3T and 1.5T imaging in patients with MTS showed no substantial difference in surgical outcome between the two groups. However, the 3D short T1 inversion recovery (STIR) sequence using 3T is useful for evaluating the extent of hippocampal sclerosis and in identifying or clarifying uncertain findings in the 20 % of patients with previously unremarkable scans.²² Ultrahigh-field-strength (7T and higher) MR systems offer a greatly increased signal-to-noise ratio, allowing for increased spatial resolution and increased tissue contrast (see *Figure 2*).²³ In a recent prospective study performed by Henry and colleagues, 11 healthy subjects and eight patients with TLE underwent neuroimaging with 7T MRI. The authors found that ultrahigh-field-strength MRI permitted detection of selectively greater Ammon horn atrophy and paucity of digitations in the hippocampal head in patients with TLE.²⁴ As we employ more 7T MRIs in the future, these high-resolution images will undoubtedly provide more information regarding the subtle anatomic abnormalities seen in TLE and other subtle epileptogenic lesions.

Figure 3: Magnetic Resonance Imaging Demonstrates Subtle Signs of Cortical Dysplasia



Axial fluid-attenuated inversion recovery sequence (A) and fast spin echo (B) showing focal cortical thickening and increased subcortical signal intensity (arrows) in the left frontal lobe of a 33-year-old male with medically refractory epilepsy. Pathology revealed type IIB focal cortical dysplasia.

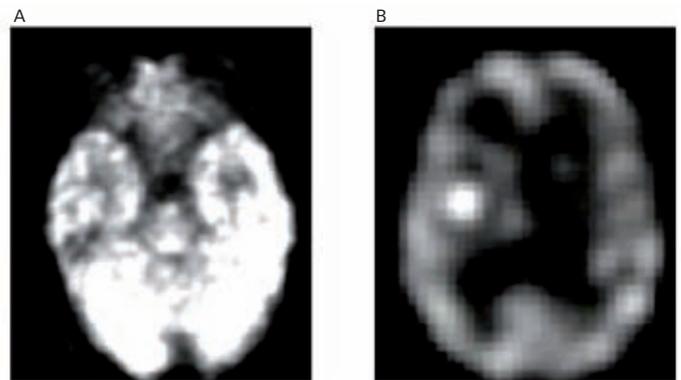
Malformation of Cortical Development

Besides having an important role in identifying MTS, conventional MRI is crucial in identifying neocortical lesions in malformation of cortical development (MCD). MCD encompasses a spectrum of developmental disorders that are thought to result from abnormal neuronal proliferation and/or migration during cortical development. These disorders include mild MCD, focal cortical dysplasia, polymicrogyria, hemimegalencephaly, schizencephaly, and lissencephaly. MCD is one of the most common causes of medically refractory epilepsy in children and young adults. Some of the characteristic findings on imaging include abnormal gyration, thickened cortex, loss of gray–white junction, heterotopia, and signal changes on T2 (see *Figure 3*).^{25–27} In a recent retrospective study of 143 patients with MCD, complete resection of structural lesions on MRI and/or electrocorticographic abnormality was strongly associated with freedom from seizures (72 % at two years).²⁸ In addition, gray–white blurring on MRI and smaller lesions are favorable prognostic factors for post-operative outcome.

In another study, the authors found that patients with focal cortical dysplasia have a strong tendency to have identifiable MRI abnormalities and better surgical outcome compared with those with MCD.²⁹ Because detection of epileptogenic focal cortical malformation is the most reliable predictor of freedom from seizures, sensitive and specific pre-surgical detection of these abnormalities is critical for improving surgical outcome.

Automated MRI imaging analysis such as VBM or surface-based morphometry (SBM) can be employed to identify subtle anatomic anomalies. One study showed that SBM was able to identify 92 % of cortical lesions with 96 % specificity, successfully discriminating patients from controls 94 % of the time.³⁰ However, this method failed to adequately describe the extent of the lesion in most of the cases. Future efforts can aim at improving these imaging analysis methods for detection of MCD lesions.

Figure 4: Positron Emission Tomography and Single Photon Emission Computed Tomography



A: 18-fluorodeoxyglucose-positron emission tomography (¹⁸F-DG-PET). This axial slice through the temporal lobes demonstrates moderate hypometabolism involving the right medial, anterior, and lateral temporal cortex in a 32-year-old woman with temporal lobe epilepsy without magnetic resonance imaging (MRI) evidence of mesial temporal sclerosis. Pathologic evaluation was consistent with mesial temporal sclerosis, with neuron loss especially prominent in the dentate gyrus; B: Ictal ethyl cysteinyl diethylester single photon emission tomography overlying axial MRI. This axial slice shows focal hyperperfusion of the right insular cortex in a 43-year-old man with frequent nocturnal focal seizures.

Functional Imaging

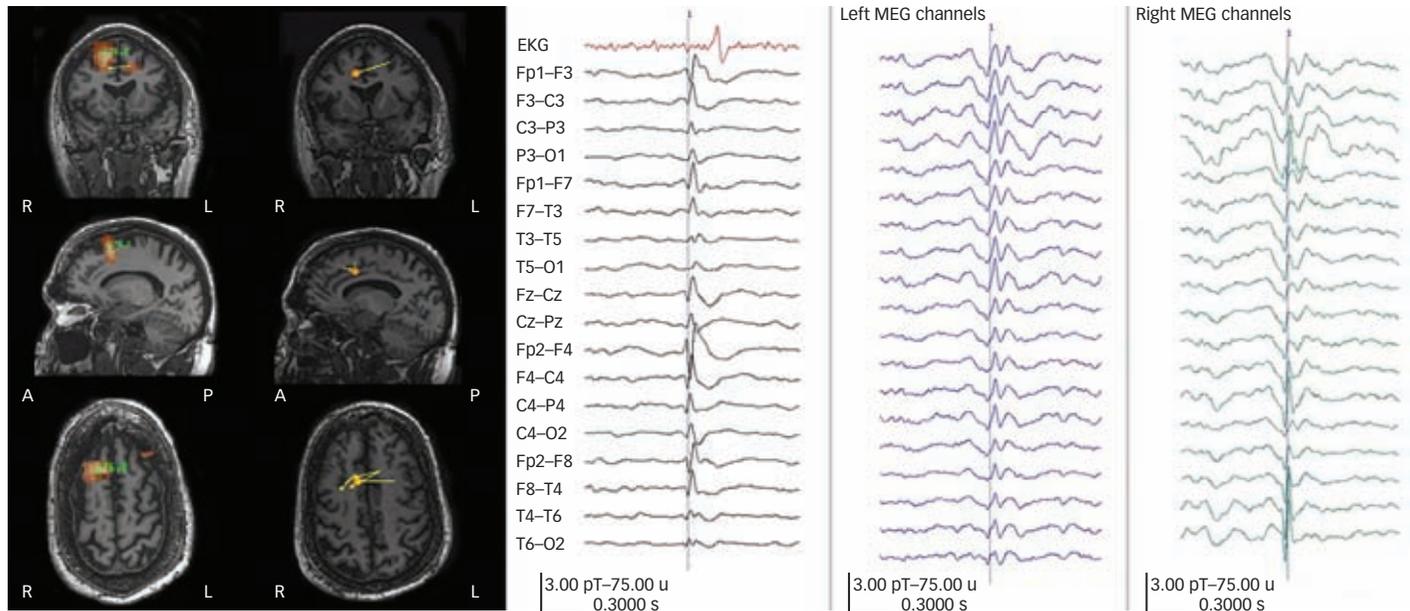
While MRI is an essential work-up for epilepsy, it does not capture the dynamic physiologic processes that occur in the brain during ictal and interictal periods. Furthermore, what can be done when the MRI is normal? In this next section, we discuss the utility of functional imaging in detecting epileptogenic foci.

Positron Emission Tomography

PET detects pairs of photons emitted indirectly by a positron that collides with an electron in the surrounding environment. The majority of PET uses 18-fluorodeoxyglucose (¹⁸FDG), which is taken up by the neurons and reflects the local cerebral metabolic rate of glucose. ¹⁸FDG-PET is used primarily to reflect dynamic seizure-related changes in cerebral cellular functions during interictal states.³¹ Numerous studies have reported the utility of PET in patients with TLE, with a sensitivity of 70–85 %.^{32,33} Interestingly, PET studies in patients with TLE demonstrated hypometabolic regions ipsilateral to seizure onset beyond the region of MRI abnormalities, which included lateral temporal (78 %), mesial temporal (70 %), thalamic (63 %), basal ganglia (41 %), frontal (30 %), parietal (26 %), and occipital (4 %) regions.³⁴ This widespread hypometabolism may reflect subtle network dysfunctions that are not seen by static structural imaging.

In patients with good MRI and electroencephalography (EEG) concordance, PET may be largely redundant. However, in the 20–25 % of patients with refractory focal epilepsy who have normal MRI scans, focal PET hypometabolism can provide useful data towards the decision to carry out invasive intracranial EEG recording (see *Figure 4A*). In a prospective study of patients with non-localizing EEG and MRI findings, sensitivity for PET imaging to detect lesions as revealed by the gold standard of intracranial EEG was reported to be 58–64 % with a specificity of 53–63 %.^{35,36} In the same study cohort, the adjusted odds ratio for concordant, localized PET as a predictor of seizure-free outcome was 7.1, although the negative predictive value was low.^{35,36} This is consistent with the results of a meta-analysis showing that in TLE, ipsilateral focal hypometabolism was a predictor of good surgical outcome.³⁷ One

Figure 5: Magnetoencephalography



This 35-year-old man presented with long-standing generalized tonic-clonic seizures with magnetic resonance imaging revealing a subtle cortical dysplasia in the right frontal lobe. Left: A magnetoencephalography (MEG) study with simultaneous electroencephalography recording demonstrated frequent high-amplitude spike and slow-wave discharges that were maximal in the right frontal region (right panels); manual single equivalent current dipole fitting was performed on these spikes (shown in orange) and dipoles (shown as yellow triangles on all MEG images) clustered in the right frontal regions. The patient underwent a lesionectomy and was seizure-free after surgery. EKG = electrocardiogram; pT = pico-testas; s = seconds; u = units. Adapted from Chang et al., 2009,³⁶ with permission.

recent study showed that in a series of patients with MRI-negative but PET-positive lesions in TLE, 71 % were Engel Class I at one year.³⁸ Given the cost-effectiveness of FDG-PET, it is a useful study to select for surgical candidates and guide decision-making when MRI and EEG are not concordant or localizing.

Much interest has been generated over the use of specific receptor ligands that confer increased uptake in seizure, such as ¹¹C-alpha-methyl-L-tryptophan (¹¹C-AMT) and ¹⁸F-fluoro-benzamidoethylpiperazine (¹⁸F-MPPF) (serotonergic tracers), ¹⁸F-fallypride (dopaminergic tracer), and ¹¹C-flumazenil (GABAergic tracer).²¹ For instance, Chugani and colleagues reported that in ³⁰ pediatric patients with MCD who received ¹¹C-AMT-PET imaging, increased AMT was found in all five patients with type IIB dysplasia and all three patients with polymicrogyria and heterotopia; all of these patients had good surgical outcome.³⁹ This may indicate that uptake of specific tracers can identify specific pathologies and have good prognostic value. PET scanning with ligand-specific tracers may prove to be a valuable tool in advancing our knowledge of the basic mechanisms of epileptic disorders.

Single Photon Emission Computed Tomography

SPECT uses photon-emitting radioisotopes attached to molecules to label brain regions of interest, mainly areas of hypermetabolic activity during ictal activity. The images are captured using relatively fast and low-resolution gamma cameras. The majority of studies in epilepsy use technetium-99m hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) or technetium-99m ethyl cysteinate diethylester (^{99m}Tc-ECD), both of which are lipophilic compounds that get irreversibly trapped in the epileptogenic hyperemic region at the time of the seizure.^{21,31} Because of the rapid initial tracer uptake and distribution, the radiotracer can be injected at the time of seizure onset. The patient can then be sedated

and transferred to SPECT scanners to acquire the brain scan. SPECT imaging has the advantage of capturing the dynamic ictal process and being less subject to movement artifacts (see Figure 4B).²¹

Many studies have assessed the sensitivity and specificity of SPECT imaging in revealing epilepsy and have reported favorable results. A meta-analysis showed that the highest sensitivity reported in ictal SPECT is 97–100 %, postictal SPECT 75–77 %, and interictal SPECT 43–44 %.^{40,41} The different radiotracers may confer different detection rates in different types of epilepsy. For instance, in TLE, HMPAO and ECD have shown similar sensitivities in detecting the epileptogenic region, but HMPAO is superior to ECD in terms of both sensitivity and degree of hyperperfusion in neocortical epilepsy.⁴² Despite the high sensitivity of ictal SPECT, several studies have questioned the specificity of SPECT imaging, especially when SPECT does not correlate with EEG data.^{43,44} In one study, SPECT erroneously localized supplementary motor area seizures to the bilateral cingulate.⁴³ SPECT should be used for partial seizure evaluation but may not be useful for generalized seizures.

In another study, patients with mesial TLE were found to have localized hyperperfusion not limited to the temporal lobe but also in the basal ganglia, which may reflect more of the ictal dystonia caused by seizure propagation rather than area of seizure onset.⁴⁵ In addition, other brain regions have been noted to show SPECT changes in TLE, including hyperperfusion in the posterior frontal lobes, parietal lobes, and cerebellum, and hypoperfusion in the bilateral frontal lobes.⁴⁶ These differences may indicate inter-subject differences in functional network connectivity or may reflect different temporal evolution of an ictal event based on when the tracer was injected. A large TLE series attempted to examine this very question of evolving dynamics of the seizure network

in 37 TLE patients with varying delays in tracer injection. The authors found significant ictal hyperperfusion in the ipsilateral temporal lobe and hypoperfusion in the ipsilateral orbitofrontal, bilateral superior frontal, contralateral cerebellar, and ipsilateral striatum regions.⁴⁷ Future controlled studies with improved temporal resolution with SPECT injection and scanning are needed to elucidate the dynamics of the seizure network.

One disadvantage of SPECT is the qualitative nature of image interpretation, which is subject to interpreter bias. One way to circumvent this problem is to create automated comparison of the baseline interictal SPECT with subtraction ictal SPECT co-registered to MRI (SISCOM). Implementation of this analysis method showed high predictive value when the hyperperfused area was completely resected.^{48–52} This result has been confirmed in a large cohort of patients with non-localizing MRI and EEGs, where the presence of focal SPECT hypermetabolism has the highest odds ratio prediction of seizure-free outcome.³⁵ The clinical value and unique ability to capture dynamic network processes during ictal activity make SPECT an attractive imaging modality in the detection and study of epilepsy.

Magnetoencephalography

MEG was first introduced in 1968 and works by detecting magnetic fields generated by neuronal activity using arrays of superconducting quantum interference devices (SQUIDS). MEG is a non-invasive neuroimaging method that can be combined with MRI to generate magnetic source imaging (MSI) to localize epileptogenic zones (see *Figure 5*). MEG has the advantage over conventional EEG because magnetic signals can pass through skull and other tissues without significant distortion. In addition, MEG spikes are usually shorter in duration with a steeper ascending slope than EEG spikes, leading to a larger signal-to-noise ratio and greater source localization.^{53,54} One disadvantage of MEG, however, is that it only detects tangential components of a current source. Therefore, MEG selectively measures sulcal activity whereas EEG can detect both sulcal and cortical activity. Another major disadvantage is that MEG is mostly restricted to the detection of interictal spiking, as it is not practical or feasible to continuously monitor patients in the MEG device.

The use of MEG in the clinical setting has largely been limited to mapping of the eloquent cortex for surgery; its diagnostic yield in detecting focal seizure foci remains uncertain. In the largest series, consisting of 455 epilepsy patients, 131/455 (28.8 %) underwent surgical treatment and MEG succeeded in identifying the epileptogenic zone in 70 % of patients and lobar localization in 89 % of patients. MEG supplied additional information in 5 % of patients and crucial information for the final decision for surgery in 10 % of patients.³⁵ Interictal MEG used in the pre-surgical evaluation of patients with non-localizing lesions has shown general agreement with invasive EEG recording, with a sensitivity of 58–64 % and specificity of 79–88 %.^{35,36} In a prospective blinded study, Sutherling and colleagues found MSI to yield non-redundant information in 33 % of 69 patients with suspected neocortical epilepsy; this information consisted of additional areas to sample intracranial EEG or modifications of the surgical decision.⁵⁵ Chang and colleagues demonstrated that the improved spatial resolution of MEG could localize the epileptogenic source in patients with EEG-confirmed secondary bilateral synchrony that otherwise appeared as generalized.⁵⁶ Altogether, these studies and suggest that MEG/MSI has an important role in guiding the decision-making process for invasive monitoring and surgical resection for epilepsy surgery, especially when other localizing evidence is lacking or discordant.

Conclusion

With the aid of these neuroimaging tools, epilepsy surgeons are no longer operating on ‘invisible’ lesions. Ultrahigh-resolution MRI will be able to provide greater anatomic and structural detail that will reveal more information regarding the pathophysiology of epilepsy. The realm of functional imaging will also continue to grow as we discover more specific molecular tracers that will not only map the functional connectivity of epileptogenic networks but will also confer greater prognostic value in predicting seizure outcome. In the future, MEG may become a routine part of pre-surgical evaluation for epileptogenic foci localization and functional mapping. These techniques, among other emerging imaging methods, will undoubtedly push the field of epilepsy surgery to new frontiers. ■

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