Advanced Neuroimaging for Modern Epilepsy Surgery

Doris D Wang,1 Carlos Santos-Sanchez,2 Paul A Garcia3 and Edward F Chang4

1. Resident, Department of Neurological Surgery and Comprehensive Epilepsy Center; 2. Junior Specialist, Comprehensive Epilepsy Center and Department of Neurology; 3. Professor of Clinical Neurology, Comprehensive Epilepsy Center and Department of Neurology; 4. Assistant Professor of Neurological Surgery and Physiology, Department of Neurological Surgery and Comprehensive Epilepsy Center, University of California, San Francisco

Abstract

Localising the onset of seizures to guide epilepsy surgery can be notoriously difficult. Modern neuroimaging has revolutionised the field by improving the diagnosis and treatment of epilepsy. In order to ameliorate seizures without causing new neurological 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 photon emission computed tomography and electrophysiological 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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Correspondence: Edward F Chang, Department of Neurological Surgery, University of California, San Francisco, 505 Parnassus Avenue, Box 0112, San Francisco, CA 94143-0112, US. E: changed@neurosurg.ucsf.edu

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 localisation 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 photon 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 many imaging modalities, their role in guiding surgery, and how they are incorporated into the pre-surgical evaluation of epilepsy.
false-positives and yield clinically relevant information regarding MTS.21 Voxel-based analysis with different imaging sequences may reduce the differences may be an artifact from the warping process itself. Despite these limitations, using large control populations and other 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 gray 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 47 %, contralateral 52 %).20 VBM studies are prone to low specificity given the nature of the analysis; by warping the subjects’ MRI to a standardised space before comparing them, the sensitivity and specificity for detecting subtle MTS in patients with TLE, several automated analysis methods 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.21 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).22 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.22 As we employ more 7T MRIs in the future, these high-resolution images will undoubtedly provide more information regarding the subtle anatomical abnormalities seen in TLE and other subtle epileptogenic lesions.

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, hemimegencephaly, 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).24–27 In a recent retrospective study of 143 patients with MCD, complete...
Numerous studies have reported the utility of PET in patients with TLE, with a sensitivity of 70–85%. 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. 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-localising 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%. In the same study cohort, the adjusted odds ratio for concordant, localised PET as a predictor of seizure-free outcome was 7.1, although the negative predictive value was low. This is consistent with the results of a meta-analysis showing that in TLE, ipsilateral focal hypometabolism was a predictor of good surgical outcome. One 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. 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 localising.

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-MPPP) (serotoninergic tracers), 18F-fallypride (dopaminergic tracer), and 11C-flumazenil (GABAergic tracer). For instance, Chugani and colleagues reported that in paediatric 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. 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.
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### Epilepsy

#### Single Photon Emission Computed Tomography (SPECT)

SPECT uses photon-emitting radiotracers 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 (99mTc-HMPAO) or technetium-99m ethyl cysteinate diethylster (99mTc-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 that get irreversibly trapped in the epileptogenic hyperemic region at the time of the seizure, SPECT should be used for partial seizure evaluation but may not be useful for generalised seizures.

Many studies have assessed the sensitivity and specificity of SPECT imaging in revealing epilepsy and have reported favourable results. A meta-analysis showed that the highest sensitivity reported in ictal SPECT is 97–100 %, post-ictal 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 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 localised supplementary motor area seizures to the bilateral cingulate.45 This result has been confirmed in a large cohort of patients with non-localising 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 ictal processes 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.46 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.47,48 This result has been confirmed in a large cohort of patients with non-localising MRI and EEGs, where the presence of focal SPECT hypermetabolism has the highest odds ratio prediction of seizure-free outcome.49 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)

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 method for measuring the magnetic fields generated by neuronal activity, which can be used to infer the location and timing of neuronal activity. MEG has been found to be particularly useful in the evaluation of focal temporal lobe epilepsy, as it can reveal the ictal and interictal activity associated with seizures. MEG recordings have been shown to be useful in localising seizure foci in patients with refractory epilepsy, and in differentiating between ictal and interictal activity.

In another study, patients with mesial TLE were found to have localised 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.50 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 lobs.51 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.52 Future controlled studies with improved temporal resolution with SPECT injection and scanning are needed to elucidate the dynamics of the seizure network.

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#### Figure 5: Magnetoencephalography

A 35-year-old man presented with long-standing generalised 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 panel), 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-teslas; s = seconds; u = units. Adapted from Chang et al., 2009,56 with permission.
neuroimaging method that can be combined with MRI to generate magnetic source imaging (MSI) to localise 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 localisation. 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 seizure foci remains uncertain. In the largest series, consisting of 455 patients with non-localising lesions has shown general agreement with invasive EEG recording, with a sensitivity of 58–64% and specificity of 79–88%. In a prospective blind study, Sutherland 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. Chang and colleagues demonstrated that the improved spatial resolution of MEG could localise the epileptogenic source in patients with EEG-confirmed secondary bilateral synchrony that otherwise appeared as generalised. 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 localising evidence is lacking or discordant.

Conclusion

With the aid of these neuroimaging tools, epilepsy surgeons are no longer operating on "invisible" lesions. Ultra-high-resolution MRI will be able to provide greater anatomical 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 the epileptogenic zone but also provide a greater prognostic value in predicting seizure outcome. In the future, MEG may become a routine part of pre-surgical evaluation for epileptogenic focus localisation 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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