Localization in Epilepsy

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Pharmacologic therapy represents the first line of treatment of epilepsy and is effective in most patients. However, about 20% to 30% of cases develop intractable seizures that cannot be controlled by medication alone. In such cases, surgical intervention, including resection of epileptogenic brain tissue, is considered for therapeutic, often curative, purposes. The concept of surgical management of epilepsy relies on the premise of precise localization of the epileptogenic focus, which gives rise to the seizures, and multiple techniques exist to identify epileptogenic tissue. However, to appreciate the value of each of these techniques, one must first gain an understanding of the organization of the epileptic focus, and a few terms must be defined.

**ICTAL VERSUS INTERICTAL EVENTS**

Seizures, or ictal events, consist of the paroxysmal, synchronous, rhythmic firing of a population of pathologically interconnected neurons capable of demonstrating high-frequency oscillatory activity called “fast ripples” (250–500 Hz).1–3 These events are caused by an imbalance in excitatory and inhibitory mechanisms leading to hypersynchrony and hyperexcitability.4 When seizures are not occurring, electroencephalographic (EEG) recordings from patients with chronic epilepsy show abnormal paroxysmal events in a large population of neurons called interictal spikes. These spikes generally consist of a high amplitude surface negativity (1–5 mV) lasting 50 to 200 ms followed by a slow wave, with no behavioral correlate.5

Ictal events can be understood in terms of 3 separate mechanisms: initiation, propagation, and termination.6 A typical seizure event often develops from a “tonic” stage, characterized by recruitment of adjacent neurons in the face of disinhibition, to a “clonic” stage again characterized by periodic spike-and-wave events that may represent, in one theory, a return of inhibitory function that eventually terminates the ictal discharge.7,8 Interictal and ictal events are not static phenomena, and their dynamic spatiotemporal evolution can make localization challenging.

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THE EPILEPTIC FOCUS

Engel\textsuperscript{7,8} organized focal epilepsy into 3 distinct anatomico-functional regions: the epileptic focus, the epileptogenic lesion, and the epileptogenic region. The epileptic focus is the area of maximal electrophysiological interictal activity. This region is a dynamic spatiotemporal zone because interictal activity often shifts from one location to another. The epileptogenic lesion is the anatomic pathology thought to be responsible for the epileptic state. This structural lesion is generally adjacent to the epileptic focus but can also be distant.\textsuperscript{9} The epileptogenic region is a theoretical concept defined as the area of brain that is necessary and sufficient for producing recurrent ictal events, or seizures. This concept is important for epilepsy surgeons because removal of this region should lead to cessation of seizures. In addition, several other important terms are discussed. The ictal onset zone (IOZ), defined electrographically as the area of brain from which a particular seizure arises, may also shift from seizure to seizure, and is usually smaller than the epileptic focus and contained within the epileptogenic region.\textsuperscript{10} The IOZ is important in defining the epileptogenic region because it is usually the most critical target in successful surgical resections. However, removal of only the IOZ is often insufficient to completely eliminate seizures, and some percentage of surrounding epileptic focus must also be removed.\textsuperscript{11,12}

IMPLICATIONS OF SPATIOTEMPORAL DYNAMICS AND VARIABILITY

Single-unit recordings from animals with experimental epilepsy indicate that the population of neurons participating in each epileptiform event fluctuates over time\textsuperscript{13,14} and, in humans, the location of interictal spikes often has no relationship to the IOZ.\textsuperscript{15} Hence, the size and boundaries between the IOZ and the epileptogenic focus, and their relationship with the epileptogenic lesion, are in a dynamic state of flux reflecting an underlying modulation of neuronal excitability, synchronization, and inhibition that is poorly understood.\textsuperscript{15} Among clinicians there is intense disagreement as to what amount of electrographically abnormal tissue is critical for epileptogenesis and, subsequently, which areas need to be removed to obtain a surgical cure.\textsuperscript{12,16–20} Although some investigators contend that removal of the anatomic lesion is sufficient,\textsuperscript{19,21–25} others emphasize the importance of the IOZ\textsuperscript{26} or the area with frequent interictal spikes\textsuperscript{11,12,27–29} This controversy highlights a lack of clear understanding of the location of the epileptogenic region as it relates to the causative structural abnormality and the electrographic markers of epileptogenicity. For this reason, there are multiple methods for localizing the epileptic focus, the epileptogenic lesion, and the epileptogenic region. To help facilitate the presentation of these modalities, the authors divide the diagnostic modalities into 2 categories: anatomic (structural and chemical) and functional.

ANATOMIC LOCALIZATION

\textit{Magnetic Resonance Imaging}

Magnetic resonance imaging (MRI) remains the imaging modality of choice when structural or anatomic abnormalities are suspected (Fig. 1A, B).\textsuperscript{30,31} Sequences of particular importance included T2-weighted and fluid attenuated inversion recovery (FLAIR) images, and gadolinium-enhanced T1-weighted images in lesional cases, such as tumors, vascular abnormalities, infectious or inflammatory nidi, and cortical dysplasias.\textsuperscript{30–33} Although 1.5 T MRI is widely available, higher-field magnets, such as 3.0 T, are becoming increasingly used in the context of epilepsy. The use of 3.0 T MRI produces images with improved signal-to-noise ratios,\textsuperscript{34} which can help localize
structural abnormalities that may underlie epileptogenesis. High-field MRI may be of particular importance in cases of cryptogenic epilepsy, in which subtle structural changes may be missed by conventional 1.5 T imaging. Although 3 T MRI may only identify brain abnormalities in 25% of previously normal 1.5 T scans, the addition of surface coils can increase this rate to 65%, particularly in cases of cortical dysplasia. Even with more modest numbers, the improved detection rate is critical, because detection of an imaging abnormality dramatically increases postsurgical freedom from seizures.

MRI has been shown to be particularly sensitive in identifying the structural abnormalities related to mesial temporal sclerosis (MTS). In 80% to 90% of MTS cases, MRI allows the detection of T2 and FLAIR hyperintensity in the mesial temporal structures, whereas coronal images can allow direct qualitative or volumetric comparison of the 2 hippocampi and the demonstration of unilateral hippocampal atrophy.

MR Spectroscopy

MR spectroscopy (MRS) has recently been used to help localize epileptogenic foci, particularly in the context of temporal lobe epilepsy. Abnormalities revealed by MRS include reductions in N-acetyl aspartate (NAA) levels or the NAA to choline and creatine ratios. Other findings may include an elevation in the Glx peak (Glx denotes a complex peak consisting of glutamate, glutamine and γ-aminobutyric acid [GABA]), or the Myo peak, attributed to a sugar representing an astrogial marker. MRS remains a secondary diagnostic modality in the context of epilepsy, and any findings should be corroborated by other diagnostic modalities.

FUNCTIONAL LOCALIZATION

Although anatomic diagnostic modalities remain important in the workup of seizure disorders, and MRI is now almost always included in the diagnostic algorithm, the identification of epileptogenic foci relies heavily on functional studies in most cases.

Clinical Semiology

Seizure semiology can frequently provide important clues in the localization of seizure onset. Scalp electroencephalography (sEEG) is routinely combined with video
recordings of patients during ictal events to help correlate electrographic seizures with clinical manifestations.

Overall, semilogic signs can be classified into positive or negative motor signs, automatisms, autonomic manifestations, and speech signs. Although several semilogic manifestations of seizures can predict the hemispheric lateralization of seizures, they are generally not considered reliable predictors of lobar localization of foci within a hemisphere. Moreover, rapid secondary generalization of partial seizures can produce complex semiology. Finally, the interpretation of seizure semiology becomes less important in cases of multifocal seizures. Therefore, clinical semiology alone is not used for the localization of epileptogenic foci. It is most commonly coupled with sEEG in the form of video-EEG (vEEG) in an attempt to correlate the semiology to electrical discharges. As additional, more sophisticated, functional localization studies are introduced into clinical practice, the “art” of seizure semiology interpretation may become less important. Alternatively, patients’ reports of aura symptoms and initial behavioral phenomena at seizure onset may provide clues to the localization of the onset zone that may be beyond the spatiotemporal resolution and spatial sampling abilities of many of the other modalities described in this article.

sEEG

sEEG remains the most commonly used, and the easiest to perform, functional study in epileptic patients (Fig. 2). sEEG can identify ictal and interictal events, and, combined with vEEG, the electrographic events can be correlated with the clinical semiology. Although sEEG remains a powerful diagnostic tool, it has several limitations. First, muscle and eye movement artifacts may mask the neurophysiologic recordings and thus prevent the identification of epileptogenic foci. Second, electrical signals become attenuated due to limited conductivity through the cerebrospinal fluid (CSF), skull, and skin, thus affecting the quality of the recordings. Third, sEEG relies on a finite number of surface electrodes, which may limit the spatial resolution of the recordings. Fourth, volume conduction may impair spatial specificity. The use of current source density and dipole modeling are only 2 examples of techniques used to overcome these limitations.

As mentioned earlier, continuous sEEG or vEEG can identify interictal epileptiform discharges, which are generally not seen in patients without seizures. Interictal spikes include periodic lateralized epileptiform discharges (PLEDs), which are strongly associated with clinical seizures. Other interictal events that represent slow neuronal population oscillations rather than paroxysmal spikes include temporal intermittent rhythmic δ activity, which represents a reliable predictor of epileptic seizures, and focal polymorphic δ activity, which, on the contrary, is not generally linked to epilepsy. Interictal discharges, although sometimes concordant with the localization of ictal events, may also be grossly discordant, as described in the earlier section.

The most important data obtained with sEEG pertains to the localization of ictal foci. Ictal events can begin in several ways, of which the most common are periodic spiking, low voltage fast activity, or an electrodecremental response. However, rapid seizure generalization or ictal origin in brain areas not adequately covered by scalp electrodes, such as the inferior aspect of the frontal lobes, may preclude localization. High-density arrays and complex methods for signal analysis, such as independent component analysis and phase congruency, may increase the sensitivity of sEEG. Nevertheless, the spatial resolution of sEEG at determining the IOZ is limited to an area of several centimeters, which is hardly adequate for surgical planning.
Magnetoencephalography

Magnetoencephalography (MEG) is a novel technique used for localization of ictal foci. Its premise lies in the detection of magnetic fields generated by current flow occurring during synchronized neuronal discharges. Such current flow must be parallel to the surface of the brain and skull to produce magnetic fields in a perpendicular orientation that can then be detected extracranially. The technique is applicable not only to the identification and localization of epileptogenic foci (Fig. 3A, B) but also to the functional mapping of adjacent brain, which is essential for planning safe surgical resections of seizure foci.49,50

Compared with conventional sEEG, MEG has distinct advantages and issues associated with its use.50 Advantages of MEG include a theoretically higher spatial

Fig. 2. Scalp EEG represents the most widely used functional diagnostic modality in epilepsy patients. In this example, the traces show the initiation (red line) and evolution of a clinical seizure. The inset in the upper panel shows the power spectrum of the Fourier transforms of the traces. (Adapted from Jung KY, Kang JK, Kim JH, et al. Spatiotemporospectral characteristics of scalp ictal EEG in mesial temporal lobe epilepsy with hippocampal sclerosis. Brain Res 2009;1287:206–19; with permission.)
discrimination related to lower detection thresholds; superior conductivity of magnetic fields through the CSF, skull, and skin; potentially improved signal-to-noise ratios; and the existence of algorithms for three-dimensional source modeling, which can allow for stereologic localization of ictal foci. Disadvantages associated with MEG include a much higher cost and limited availability; the need for extensive magnetic insulation to ensure an interpretable signal-to-noise ratio, limited to recording interictal rather than ictal events; and limited interpretation of data if head movement is involved during ictal events, because the MEG sensors are not fixed to the head.

Although several centers have recently implemented MEG technology in the context of localizing ictal foci, mapping eloquent brain, and planning epilepsy surgery,51,52 the high cost of acquiring and maintaining the technology is prohibitive to most institutions. Moreover, a recent systematic review of the literature failed to demonstrate a benefit of MEG in seizure-free outcomes after epilepsy surgery.53,54

**Positron Emission Tomography**

Positron emission tomography (PET) is a neuroimaging modality that involves the metabolic use of a radioactive substrate as an index of brain metabolic changes that may be coupled to seizures.30,55,56 The most commonly used tracer is $[^{18}F]$fluorodeoxyglucose (FDG). FDG is a glucose analog that is taken up by metabolically active cells. However, because it cannot be metabolized by glycolytic enzymes, it accumulates in the cytoplasm. FDG-PET has been particularly useful in cases of temporal lobe epilepsy, in which it has a sensitivity of approximately 90%.30,31,57 Typically, interictal PET identifies focal areas of hypometabolism (Fig. 4A, B); however, such hypometabolic areas are generally considered to be larger than the actual epileptogenic foci. A possible explanation for the spatial discrepancy between the interictal FDG-PET and the ictal focus may be the phenomenon of surround inhibition following seizures. FDG-PET is currently being used for surgical planning in the resection of pediatric cortical dysplasia.58

![Fig. 3. MEG helps identify epileptogenic foci in conjunction with EEG. (A) The scalp EEG demonstrated a seizure that appeared to originate from the right centroparietal area. (B) Identification of spike sources with MEG and superimposition on MRI confirmed that the spikes originated predominantly from abnormal cortex surrounding the right central sulcus. Note the right hemispheric polymicrogyria evident in the MRI image. (Adapted from Galicia E, Imai K, Mohamed IS, et al. Changing ictal-onset EEG patterns in children with cortical dysplasia. Brain Dev 2009;31:569–76, with permission.)](image-url)
Other substrates are now being developed for PET applications. Notably, \([^{11}C]\) or \([^{18}F]\) flumazenil, an antagonist at the benzodiazepine binding site of the ionotropic \(\gamma\)-aminobutyric acid A (GABA\(_A\)) receptor, has recently been used to image the relative distribution of GABA\(_A\) receptors in the brains of patients with epilepsy. Moreover, PET imaging with \([^{11}C]\) carfentanil, which selectively binds the \(\mu\)-opioid receptor, has shown increased binding near temporal lobe epileptogenic foci. Imaging with substrates that selectively bind the 5-HT\(_{1A}\) serotonin receptor, nicotinic acetylcholine receptor (nAChR) and type 1 cannabinoid receptor (CB1R) is also being pursued. PET imaging with \([^{11}C]\) methyl-L-tryptophan, a serotonin precursor, has been used to identify epileptogenic tissue in certain types of epilepsy. These novel PET imaging applications can help identify foci with aberrant inhibition and neuromodulation, which may be somewhat colocalized with epileptogenesis.

**Single Photon Emission Computed Tomography**

Single photon emission computed tomography (SPECT) represents a functional imaging modality believed to represent cerebral perfusion. The substrates that are imaged are usually \(^{99m}\)Tc-labeled molecules, such as \([^{99m}\)Tc]HMPAO or \([^{99m}\)Tc]ECD. They are rapidly taken up by brain tissue within less than 1 minute after intravenous injection, and remain trapped within brain tissue for up to 4 additional hours. Because of such kinetics, SPECT can be used to acquire an ictal profile if the substrate is injected at the time of the seizure (Fig. 5), even though the actual imaging may be obtained after the ictal event has subsided. Ictal SPECT can be compared with interictal SPECT to help identify the perfusion alterations during the ictal event. Subtraction ictal SPECT coregistered to MRI (SISCOM) refers to a combined imaging modality in which the interictal SPECT is subtracted from the ictal SPECT and the subtraction image is merged with an MRI to anatomically define the area with the
perfusion abnormality. SISCOM was shown to be superior to ictal and interictal SPECT in localizing epileptogenic foci and predicting the outcome of epilepsy surgery. In the case of temporal lobe epilepsy, SISCOM was shown to have a localization sensitivity of 97%. The subtraction of ictal and interictal profiles is highly dependent on accurate coregistration and elaborate statistical algorithms, such as statistical parametric mapping.

Fig. 5. Ictal SPECT superimposed on coronal T1-weighted MRI demonstrates hyperperfusion of the right temporal lobe, consistent with epileptogenic activity. (Adapted from McNally KA, Paige AL, Varghese G, et al. Localizing value of ictal-interictal SPECT analyzed by SPM (ISAS). Epilepsia 2005;46:1450–64; with permission.)
Much like PET, novel substrates are being developed for SPECT imaging. An example is $[^{125}I]$iomazenil, which binds the benzodiazepine site of the GABA$\text{A}$ receptor.

The major limitation in ictal SPECT imaging is the difficulty in orchestrating the injection. The tracer must be injected rapidly, and is generally only useful for a period of 4 hours. Hence, the facility must generate several vials of the tracer, most of which will be wasted waiting for a seizure to occur. A dedicated individual has to sit at the bedside waiting for a seizure to be able to inject the tracer in a timely fashion. This expense is prohibitive at most centers.

**Functional MRI**

Functional MRI (fMRI) represents another diagnostic modality based on the acquisition of cerebral blood flow and oxygenation data during ictal or interictal discharges. The premise of the technique lies in the principle of neurovascular coupling, which denotes an expected increase in cerebral blood flow in epileptogenic areas during seizures and alterations in oxygen metabolism. The fMRI data are obtained from the blood oxygenation level–dependent (BOLD) signal, which represents magnetic resonance interference brought about by a decrease in the concentration of deoxyhemoglobin (Fig. 6). It is theorized that the increased BOLD signal during seizures reflects an increase in cerebral blood volume and flow without a commensurately...
increased rate of oxygen consumption, thereby leading to decreased deoxygenated hemoglobin levels and an increase in the signal. The acquisition of fMRI is often coupled to continuous sEEG recordings in an attempt to correlate fMRI and electrographic information. Moreover, fMRI may be used for functional mapping of eloquent brain when planning epilepsy surgery. Even though fMRI is becoming more popular as a diagnostic modality in epilepsy, it is routinely used as one of many sources of information in the patient’s workup. However, there are several limitations in its use. First, ictal events are difficult to capture during imaging sessions, and movement artifacts are often prohibitive. Second, the temporal resolution is limited. Hence, ictal onset may be missed, which preferentially favors areas of early ictal

Fig. 7. Optical recordings of intrinsic signals during 2 spontaneous seizures (A, B) in a patient. The top panel indicates the optical recordings, the middle panel a color-coded power spectrum of the frequency profile of the local field potentials (LFPs), and the lower panel the raw LFPs over time. Time 0 indicates the electrographic onset of seizures. (Adapted from Zhao M, Suh M, Ma H, et al. Focal increases in perfusion and decreases in hemoglobin oxygenation precede seizure onset in spontaneous human epilepsy. Epilepsia 2007;48:2059–67; with permission.)
spread. Data from optical imaging spectroscopy indicate that seizure onset is heralded by increases in oxygen metabolism that are not identified with fMRI.

**Optical Recording of Intrinsic Signals**

Optical recording of intrinsic signals (ORIS) refers to a novel technique that relies on the recordings of the optical properties of cortical tissue at multiple wavelengths. The premise of the technique lies in the variation in the optical properties of hemoglobin between its oxygenated and deoxygenated state. Such recordings can demonstrate changes in oxygen requirements and cerebral blood volume during an ictal event, in animal models,79,80 and in humans,81,82 with a much higher spatial and temporal resolution than with fMRI. It has been shown that interictal spikes and the initial moments of ictal evolution are associated with a dramatic increase in oxygen requirements that initially are not matched by comparable increases in blood flow. The technique has also been used successfully on human brain intraoperatively for the identification of functional cortex (Fig. 7).82,83 Drawbacks include a slow optical signal (hundreds of milliseconds) compared with the electrophysiological events (milliseconds), movement artifacts, difficulty imaging ictal events in the operating room, and the need for signal processing before data can be interpreted. Although optical imaging techniques hold great promise for providing high-resolution hemodynamic data associated with epilepsy, clinical usefulness has been limited to date because of technical limitations.

**Invasive EEG**

These diagnostic modalities can occasionally provide either nonlocalizing or discordant information. In such cases, invasive EEG with subdural strip and grid electrodes and intraparenchymal depth electrodes can help localize epileptogenic foci (Fig. 8). Such electrodes overcome the limitations of scalp electrodes, namely signal

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**Fig. 8.** Examples of interictal spikes (red box in A) and seizures (red arrows in B) recorded with temporal depth electrodes.
attenuation from the intervening skin, bone, CSF and dura, and muscle artifacts, thus representing the most accurate electrophysiological diagnostic technique. The superiority of intracranial electrodes over scalp EEG in localizing seizure foci has been documented in comparisons of simultaneous scalp and intracranial recordings. Invasive electrodes are currently the gold standard in localizing the epileptogenic zone and focus and the IOZ. The major limitations of intracranial electrodes are the risk of implantation (~5% morbidity) and the ability to sample only areas of cortex adjacent to each electrode. Hence, ictal onsets from uncovered regions of brain may not be identified accurately and may even provide falsely localizing information.

SUMMARY

The dynamic spatiotemporal variability in the epileptic focus renders seizure localization a challenge to the clinician. For this reason, a plethora of diagnostic modalities have been developed to identify different aspects of the epileptic focus. Although the clinical semiology and the surface EEG still remain the most widespread methods of localizing seizures, these older techniques are being increasingly supplemented by a variety of anatomic and functional imaging modalities that can help clarify discrepancies when the data are discordant. Identification of a structural lesion, aided by the development of stronger magnets and surface coils is increasing the importance of MRI scans. Novel PET ligands, which can be coregistered with stereotactic MRI scans, are also becoming clinically useful to guide neurosurgical resections. MEG may ultimately be too expensive and may not provide enough ictal data to become a standard of care. Techniques that rely on neurovascular coupling offer increased spatial and temporal resolution but, ultimately, are measuring hemodynamic surrogates of neuronal activity. Whether these will be adequate for surgical planning is still a matter of debate. Ultimately, when the data are equivocal, invasive EEG remains the gold standard for identifying epileptic foci and guiding the surgeon to successful resections. Future research will have to clarify the ideal extent of resection of the epileptogenic lesion, region, focus, and IOZ to achieve the highest rate of freedom from seizures, incorporating a variety of seizure localizing modalities.

REFERENCES


