Interpretation of the Intracranial Stereoelectroencephalography Signal

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- Epilepsy • Epilepsy surgery • Intracranial EEG

KEY POINTS
- Understanding and recognizing the physiologic intracranial electroencephalogram (iEEG) is important for discriminating channels with normal activity from those with epileptic activity.
- The neurophysiologic changes the brain undergoes as a result of sleep are reflected in the iEEG.
- The interpretation of the ictal iEEG is tightly linked with the interpretation of the interictal background and its epileptic iEEG discharges.
- The correlation of spatial ictal iEEG spread to clinical semiology is the cornerstone of epileptic seizure comprehension.
- Unfortunately, criteria for the interpretation of iEEG have not yet been established and constitute work in progress.

INTRODUCTION

Stereoelectroencephalography (sEEG) was developed as a minimally invasive surgical investigative process that allows 3-dimensional, bilateral, and deep access to the brain for the purpose of testing a hypothesis regarding the location and extent of the epileptogenic zone.1,2 First introduced by Talairach and Bancaud in the 1960s,3–5 sEEG has successfully survived the test of time and has become an established approach for surgical investigations in epilepsy.6,7 Its minimally invasive nature that avoids craniotomies and the complication risks that accompany them has rendered sEEG an attractive technique, particularly favorable in the treatment of pediatric populations.7–10 Developed in the pre–magnetic resonance imaging (MRI) era, the sEEG implantation strategy grew as a concept independent from the presence of brain lesions, currently rendering sEEG particularly attractive in the investigation of nonlesional focal epilepsy cases.11–14 More importantly, sEEG has revealed the dynamic character of focal epileptic syndromes,13 thereby tremendously advancing understanding of this devastating episodic brain disorder.14,15 Both the surgical and epileptologic advantages accompanying sEEG have contributed to its establishment as one of the dominant investigative approaches in epilepsy.16

As such, decision making in sEEG-guided epilepsy surgery heavily relies on the interpretation of the intracranial electroencephalogram (iEEG).17–20 Despite the long history of intracranial recordings in epilepsy surgery, however, the interpretation of iEEG is still limited by 3 major barriers. The first is that, in contrast to the extracranial electroencephalogram (EEG), knowledge of what is normal brain activity in the intracranial realm under the various levels of human vigilance is limited.21,22 The second is that the validity of interictal discharges as markers of epileptogenic localization remains questionable, given that their nature as...
either reactive or paroxysmal elements is still debated, and they have been shown to spread fast through cortico-cortical connections.\cite{23,24} The third is the lack of differentiation between a primary ictal onset pattern on iEEG that signifies successful localization of the epileptogenic zone and a secondary ictal onset pattern that represents secondary ictal recruitment of regions neighboring the epileptogenic zone.\cite{25,26} This article discusses the current status of these barriers in iEEG interpretation, outlines what is understood so far, and suggests future steps.

**PRINCIPLES**

**Surgical Planning**

Surgical planning for sEEG is based on the development of a hypothesis regarding the location and extent of the epileptogenic zone and is established through the process of anatomo-electro-clinical correlation.\cite{5,27,28} For that process, extracranial EEG, structural and functional imaging, clinical history, and ictal semiology data are evaluated. Data convergence is the main conceptual method used for the development of a primary hypothesis that delineates the areas of maximum probability of epileptogenicity and propagation of epileptic activity. Alternative hypotheses also can be developed during that process, especially in the presence of data discordant to the primary hypothesis. All hypotheses should take under consideration the limitations imposed by the surgical approach as well as the anatomic and functional boundaries of cortical resection that preserve eloquent cortex.

**Electrode Implantation**

Following the formulation of the surgical hypotheses, sEEG is a less invasive intracranial investigative process that can be used to either confirm or reject them.\cite{1,2} The number of electrodes used to achieve adequate coverage depends on the total suspected cerebral volume, which is defined by the surgical hypotheses. Although sEEG introduces a low risk of surgical complications, there is no consensus on the maximum number of sEEG electrodes implanted and the benefit-risk ratio always should be assessed.\cite{29} The target and entry point of each electrode must be justified by hard data (clinical, neurophysiologic, and imaging) used in the hypothesis formulation process.\cite{1,5,26,27} Depending on training and experience, electrode trajectories can be orthogonal,\cite{30,31} oblique, or a combination of both.\cite{32} Trajectories are influenced further by the local vasculature at the entry and target points,\cite{33} where compromises regarding the ideal target have to be made for patient safety purposes.\cite{34} Although there are no standard implantation templates corresponding to the various focal epilepsy syndromes, multicenter empirical implantation strategies have been proposed.\cite{2}

**Recording of Stereoelectroencephalography**

The main goal of sEEG monitoring and recording is to capture at least 1 spontaneous typical seizure that reveals the spatial epileptogenic map and eventually evaluates the surgical hypothesis.\cite{17,28} Reliability of recording is of utmost importance at this stage, because the ictal sEEG is a gold standard for surgical treatment decision making. A setting of 1-kHz sampling rate (providing a reliable sEEG signal in the 0.01–300 Hz range) and a greater than or equal to 16-bit analog-to-digital conversion is required to obtain the appropriate quality intracranial sEEG signal for diagnostic purposes.\cite{1,19} High signal reliability, however, must be accompanied by respective video recording resolution that allows detection of even minute clinical manifestations and evaluation of the stereotypical character of recorded seizures.\cite{35} A combination of a high-definition video recording documenting the clinical manifestation of the seizure and a high-quality intracranial sEEG signal documenting the neurophysiologic intracranial signature of the seizure is imperative for optimal surgical decision making.

**INTERPRETATION OF INTRACRANIAL ELECTROENCEPHALOGRAM**

**Preparation for Review**

The first step in interpretation of an iEEG is setting up a review environment that allows meaningful review of the record.\cite{19,36} The main constituents of such an environment are the review montage and the electrode location map.

Creating a comfortable review montage entails 3 main tasks: (1) establishing meaningful electrode naming, (2) arranging electrodes in an anatomically meaningful order, and (3) creating electrode montages in both referential and bipolar configurations. Electrode naming in intracranial evaluations has not been broadly standardized; however, there currently are 2 main cultures that predominate: the alphabetical\cite{1,2} and the anatomic\cite{57,38} conventions. The alphabetical convention allocates letters of the alphabet to anatomic positions and uses the prime symbol to discriminate left from right hemispheric electrodes (eg, A’, may represent an electrode implanted in the left amygdala and B in the right superior temporal gyrus); the latter uses abbreviations of anatomic terms that describe either the target or the entry point (eg, LAMY may represent an electrode implanted in the left amygdala...
and RTS [or RST] may represent an electrode implanted in the right superior temporal gyrus. Epilepsy centers select their naming convention based on prior training and experience. It is important that iEEG reviewers adapt and become comfortable with both forms of electrode naming. Reliable anatomic assignment for each recording iEEG channel in either custom, however, is impossible without an electrode map.

In contrast to the scalp EEG electrode positions, the localization of sEEG electrodes is not standardized, neither regarding the cortical entry and target points nor with respect to their interelectrode distance. For that reason, a detailed electrode map is necessary for the iEEG reviewer so that interpretation is accompanied by anatomic references. Typically, this process involves the coregistration of a high-resolution preoperative MRI (T1 or fluid-attenuated inversion recovery sequence) with the postimplantation CT (Fig. 1A). This fusion has the advantage that the CT electrode artifact is bright, which renders electrode mapping comfortable, but the preoperative MRI does not reflect the exact postimplantation state of the brain parenchyma. Another option, implemented by use of magnetic resonance (MR)-compatible electrodes, is a postimplantation high-resolution T1 MRI (Fig. 1B). Although the electrode artifact appears dark on T1, this approach is more accurate in providing the actual electrode positions in the postimplanted brain and spares the patient from another CT exposure. At the end, the iEEG reviewer has to be able to navigate through the electrode map and comprehend the anatomic origin of the reviewed iEEG signals.

Normal Intracranial Electroencephalogram: Background and Distinctive Waveforms

Understanding and recognizing physiologic iEEG signals is important for discriminating channels with normal activity from those with epileptic activity. The frequency bands corresponding to normal brain activity recorded on scalp EEG also can be recorded by iEEG, provided adequate sampling rate; however, waveforms tend to appear higher in amplitude and sharper in morphology. There are 2 reasons for that: (1) the iEEG is a recording closer to the generators of the scalp EEG entities, and (2) the sEEG recording corresponds to an order of magnitude less population of neurons compared with the extracranial EEG; normal synchronization among a smaller neuronal population may resemble the morphologic features of paroxysmal synchronization of a wider neuronal population. As such, the normal iEEG may well be interpreted as epileptic if scalp EEG criteria are used. Unfortunately, criteria for the interpretation of iEEG have not yet been established and constitute work in progress. This section outlines current knowledge on normal iEEG waveforms and regional background during the awake state.

The intracranial electroencephalogram correlate of the posterior dominant rhythm

The posterior dominant rhythm (PDR), or alpha rhythm, carries the historical weight of being the first recorded scalp EEG entity, by Berger. The iEEG rhythm corresponding to PDR appears diffusely in the occipital lobe, both its lateral and mesial aspects, and extends both toward the parietal lobe and the temporal lobe in the lateral posterior regions of each (Fig. 2A). The occipital iEEG correlate of the PDR exhibits the expected reactivity to eye closure and eye opening.

The intracranial electroencephalogram correlate of the mu rhythm

The mu rhythm has a known central distribution on scalp EEG and typical reactivity to contralateral motor activity. sEEG recordings have described an iEEG entity carrying the same electrographic features across both the precentral and post-central gyri, extending anteriorly toward the supplementary motor area and the premotor lateral region (Fig. 2C). The central iEEG correlate of the mu rhythm also is reactive to contralateral voluntary or passive movement.

The intracranial electroencephalogram correlate of lambda waves

Lambda waves are sharp occipital transients seen on extracranial EEG when a patient is engaged in activities that include visual exploration. iEEG correlates of lambda waves have been recorded in the calcareous fissure, the pericalcarine mesial occipital areas, and the lateral occipital lobe (Fig. 2B). These intracranial entities share the same electrographic features with scalp lambdas and also are linked to visual scanning.

The hippocampal spindle

The hippocampus generates spindles that are morphologically similar to the scalp sleep spindles, following a waxing-waning oscillation profile (Fig. 3A), but the 2 entities are not temporally coincident. Spindles have been recorded, however, in normal human hippocampal tissue, and their frequency of occurrence was found inversely proportional to the amount of interictal activity in the epileptic hippocampus. These are the main arguments favoring the idea that the hippocampal spindle constitutes a normal iEEG graphoelement.
The intracranial electroencephalogram correlate of the 14 and 6 per second positive spikes variant

The 14 and 6/s positive spikes variant is a normal element of the scalp EEG, despite its spiky appearance that renders it epileptiform, with a posterior parietal-occipital distribution.61,67,68 The iEEG correlate of this variant recently was identified in the hippocampus and consists of a waveform with sequential high-amplitude spikes of negative polarity, after a ramping up—often ramping down—profile.69 This iEEG entity was named hippocampal barque70 and, like the scalp 14 and 6/s positive variant, is considered normal, given their tight time-locked relationship (Fig. 3B).

Intracranial electroencephalogram beta rhythms

Beta-range oscillations normally are encountered on scalp EEG in the anterior frontal and central areas during the awake state.71 iEEG rhythms in the beta range have been repeatedly recorded in the respective areas. In the precentral/postcentral complex,49 iEEG beta oscillations are prominent, often interrupted by iEEG correlates of mu rhythm (see Fig. 2C). In the anterior frontal lobe,72 beta often has a lateral distribution (Fig. 3D). Beta activity recently has been identified in regions whose activity typically is not represented on scalp EEG, such as the anterior insula and the middle cingulate.21

Intracranial electroencephalogram gamma activity

Gamma activity is difficult to identify by visual inspection of the scalp EEG but can be distinguished easily in iEEG recordings.73 It makes regular spontaneous appearances in the frontal lobe, often coinciding with beta oscillations,45,51,74 and becomes prominent in the postcentral gyrus.
during contralateral voluntary motor activity49 (Fig. 3E).

**Intracranial electroencephalogram delta waves**
Although the presence of delta waves on scalp EEG outside the realm of non–rapid eye movement (NREM) sleep is a marker of brain pathology,75–77 their presence in iEEG does not necessarily denote an underlying lesion.21 A typical example of that is the normal human hippocampus, which exhibits frequent spontaneous sequences of delta waves, even during wakefulness (Fig. 3C). The entorhinal cortex also generates delta activity, which is out of phase with respect to that originating from the hippocampus.78 Less frequent delta waves have been shown to appear in the middle temporal gyrus, the angular gyrus, the inferior occipital gyrus, the occipital pole, the mesial frontal, and the orbital areas.

The background of the temporal lobe is characterized in general by high theta and alpha frequencies, and the lateral neocortex often presents with additional delta activity.21 The occipital lobe background is rich in alpha activity. The parietal lobe iEEG background consists of a combination of alpha and beta activity. On the other hand, the frontal lobe is rich in beta and gamma background activity.

**Normal Intracranial Electroencephalogram: The Effect of Sleep**
An average of 35% of every iEEG recording represents the state of sleep. As in scalp EEG, the neurophysiologic changes the brain undergoes as a result of sleep are reflected in the iEEG.22 This section outlines current knowledge on normal iEEG waveforms and regional background during the sleep state and its separate stages.

**Sleep spindles**
The sleep spindle is one of the hallmarks of NREM II that manifests on scalp EEG in 2 types: the fast type (14–17 Hz), with a central-parietal distribution, and the low type (11–13 Hz), with anterior frontal distribution.61,70 Sleep spindles in the iEEG manifest the same frequency categorization (Fig. 4A, B) but their spatial distribution and temporal behavior are markedly distinct because they appear widespread in various cortical areas79—although higher in the centro-parietal regions and lower in the frontal lobes80—and exhibit a low level of synchrony both between intracranial areas and with respect to their extracranial counterpart.84 The rate of spindle occurrence is lower in the mesial occipital regions.22

**Non–rapid eye movement delta waves**
Although delta waves predominate diffusely during the deepest stage of NREM sleep, their rate of appearance varies across the brain22 (Fig. 4C). The mesial part of the precentral gyrus and the parietal operculum exhibit the highest rate of delta
waves during NREM III. On the other hand, areas, such as the lateral part of the precentral gyrus, the transverse temporal gyrus, the cuneus, and the calcarine fissure, manifest the lowest rates of NREM III delta activity. And, although the baseline background of the hippocampus during the awake state is already rich in delta activity, this activity increases even further during NREM II and NREM III stages. In addition, hippocampus-generated and amygdala-generated delta activity persists during rapid eye movement (REM) sleep.

The intracranial electroencephalogram background features during sleep
The iEEG activity becomes diffusely homogeneous during NREM III. Slow wave activity is characterized by a semirhythmic alternation between activated and deactivated states that aggregates high-frequency physiologic rhythms (beta and gamma) to the slow wave activated state. During REM sleep, the iEEG background amplitude assumes a level similar to that of wakefulness.

Epileptic Intracranial Electroencephalogram: Interictal Activity
Interictal epileptic iEEG discharges associated with epileptogenic cortex are important to identify, because it has been well established that their inclusion in surgical resection maximizes chances of postoperative improved seizure control. Discriminating interictal iEEG activity generated in epileptogenic tissue from activity in nonepileptogenic tissue, however, is a challenging task. Moreover, the importance of addressing interictal activity has gained more attention in the context of breakthrough seizures after years of postoperative seizure freedom. The hypothesis that this recurrence is the result of latent or dormant epileptogenic tissue that was not clinically and electrographically relevant to the epileptogenic zone at the time of intracranial evaluation renders the interpretation of interictal iEEG patterns a core task. This section discusses the features of iEEG interictal activity and their relationship with underlying epileptogenic pathologies.

The main morphology of interictal iEEG activity resembles that of the extracranial EEG and is composed of a high-amplitude spike often immediately followed by a slow wave (Fig. 5A). The specificity of the spike-wave iEEG interictal discharges to epileptogenicity has been linked through 4 main features: (1) frequency of occurrence: continuous or frequent or semicontinuous interictal activity appearing consistent in terms of morphology and localization is more specific to epileptogenic tissue than isolated, infrequent, rare discharges; (2) spatiotemporal relation: leading spikes, that is, discharges that consistently precede iEEG interictal spikes in other locations, have higher specificity to epileptogenic tissue than the spikes that follow; (3) iEEG background: interictal discharges appearing over an abnormal iEEG background, such as one with continuous slow wave activity or diffuse attenuation, more likely are markers of epileptogenic tissue than discharges appearing over a normal iEEG background; and (4) persistence throughout the invasive recording: spikes attenuating in frequency and/or amplitude after the first or second day of recording, potentially disappearing entirely afterward, are more specific to neural tissue irritated by the implantation process than...
epileptogenicity. Other features of the interictal iEEG spike pattern, whose importance and relevance are still under investigation, are morphology and rhythmicity.

A less often met but equally robust form of interictal iEEG activity is intermittent paroxysmal fast activity (Fig. 5B). This type of iEEG interictal activity can appear independent over the iEEG background or can coincide with spike-wave discharges, and its presence has been reliably shown to be specific for epileptogenic tissue. In particular, fast ripples are considered reliable markers of epileptogenicity and their morphology has been suggested to provide prognostic information.

Of particular interest are the interictal iEEG patterns associated with focal cortical dysplasia (FCD) type II. Three distinct interictal patterns have been confirmed: (1) a remarkable pattern of continuous spiking and repetitive bursting of polyspikes, with more than 75% specificity for FCD type II (Fig. 5C); (2) a combination of paroxysmal fast activity with semicontinuous spikes, which is considered a highly localizing iEEG interictal pattern for FCD (see Fig. 5B); and (3) a less impressive pattern of discontinuous, less frequent, interictal spikes over an abnormal background. These patterns appear well localized during wakefulness and very well localized during REM sleep, but less localized during NREM sleep where synchronization is increased. The exclusion of brain tissue manifesting these interictal iEEG patterns from resection has been associated with seizure recurrence and less favorable postoperative seizure control.

On the contrary, no specific interictal iEEG patterns have been associated with FCD type I. What often is described in these cases is an abundance of slow wave and spiking activity accompanied by diffuse changes in normal iEEG background in both awake and asleep states. This is not surprising given the spatially extended and often multilobar distribution of this condition that renders both electrode implantation planning and localization of the epileptogenic zone challenging.

**Epileptic Intracranial Electroencephalogram: Ictal Onset Patterns**

The interpretation of the ictal iEEG is tightly linked with the interpretation of the interictal background and its epileptic iEEG discharges. This is because the border between the 2 can be defined by the following rule of thumb: the iEEG becomes ictal the moment it stops being interictal. The reliable detection of the first electrographic change in time, where the interictal iEEG pattern disappears and a distinctive ictal pattern appears, is central in the clinical evaluation of iEEG seizures. For that reason, the iEEG reviewer has to be very familiar with the background and interictal features of each electrode separately, in both wakefulness and sleep states, before reviewing the ictal onset iEEG.

Although there is significant variety in ictal onset patterns recorded by sEEG, 2 main patterns stand out in the literature: (1) the abrupt recruitment of fast discharging spikes, that may or may not resemble the interictal ones, over a slow depolarizing shift (Fig. 6A), and (2) the appearance of low-voltage high-frequency activity, sometimes
over a slow depolarizing shift\textsuperscript{118,119}; this pattern can appear out of the interictal background but also often is observed following the first pattern (Fig. 6B). For both patterns to be considered genuine ictal onsets, they are expected to follow an evolving progression to highly synchronized paroxysmal iEEG. Reproducibility of the ictal onset and progression pattern across several seizures is desirable in order to increase the reliability of ictal iEEG interpretation\textsuperscript{19}.

The appearance of low-voltage high-frequency activity at the ictal onset is highly specific for the localization of epileptogenic tissue. The combination of the previous patterns, that is, increased paroxysmal spikes that cease abruptly on the appearance of low-voltage fast activity, is highly specific for underlying FCD\textsuperscript{114,115,120}. In addition, the epileptogenic neuronal substrate seems to have specific windows of paroxysmal oscillation: in the hippocampal 3-layered archicortex, low-voltage fast ictal onsets occur in the 15-Hz to 30-Hz range\textsuperscript{121}, whereas in the 6-layered neocortex, they occupy the gamma range (30–100 Hz and more)\textsuperscript{26}.

In addition to analyzing the ictal onset pattern, there are 3 important factors for the iEEG reviewers to consider: (1) the time interval between the first ictal change and the first clinical change on video: confidence of seizure-onset localization is high when the electrographic changes precede the clinical ones, whereas in the opposite scenario, localization confidence is low; (2) the spatial pattern of propagation to other monitored regions: a comprehensive description of the seizure-onset pattern should include areas of early epileptic activity spread as well as the level of synchrony between those regions; and (3) the temporal evolution characteristics of the ictal iEEG activity in each electrode separately: rapid synchronization into high-amplitude rhythmic spikes denotes regions primarily involved in organization and recruitment of the epileptic ictal discharge, whereas the presence of slow wave rhythmic or semirhythmic activity most likely represents a secondary reaction of nonepileptogenic tissue to the occurrence of the seizure.

Finally, the correlation of spatial ictal spread to clinical semiology is the cornerstone of epileptic seizure comprehension\textsuperscript{122,123} (the role and significance of semiology in surgical planning are described in more detail by McGonigal in this issue). As the clinical seizure manifests and evolves, subjective (aura and percepts) and objective (elementary motor and complex behavior) symptoms become the constituents of the semiological picture, reflecting the ictal recruitment of anatomically and functionally interconnected cortical and subcortical regions that form the epileptic network. The process of localization of the ictal iEEG discharge at onset and subsequent propagation and its temporal correlation with the appearance of discrete semiology features on video constitute the anatomo-electro-clinical correlation of sEEG that provides a strong link between neurophysiology and clinical phenomenology\textsuperscript{35}.

**DISCLOSURE**

The author has nothing to disclose.
REFERENCES


