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REVIEW

Advances of Intracranial Electroencephalography in Localizing the Epileptogenic Zone

Bo Jin[1] · Norman K. So[2] · Shuang Wang[1]

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Abstract Intracranial electroencephalography (iEEG) provides the best precision in estimating the location and boundary of an epileptogenic zone. Analysis of iEEG in the routine EEG frequency range (0.5–70 Hz) remains the basis in clinical practice. Low-voltage fast activity is the most commonly reported ictal onset pattern in neocortical epilepsy, and low-frequency high-amplitude repetitive spiking is the most commonly reported ictal onset pattern in mesial temporal lobe epilepsy. Recent studies using wideband EEG recording have demonstrated that examining higher (80–1000 Hz) and lower (0.016–0.5 Hz) EEG frequencies can provide additional diagnostic information and help to improve the surgical outcome. In addition, novel computational techniques of iEEG signal analysis have provided new insights into the epileptic network. Here, we review some of these recent advances. Although these sophisticated and advanced techniques of iEEG analysis show promise in localizing the epileptogenic zone, their utility needs to be further validated in larger studies.

Keywords Epilepsy · Intracranial electroencephalography · Epileptogenic zone

✉ Shuang Wang
Shuangwang1977@gmail.com

[1] Department of Neurology, Epilepsy Center, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310009, China

[2] Regional Epilepsy Center at Harborview, University of Washington, Seattle, WA, USA

Introduction

The epileptogenic zone (EZ), defined as the "minimal amount of cortex that must be resected to produce seizure freedom" [1], is a theoretical concept which cannot be known before surgery. The EZ is evaluated by the information collected from the patient history, video-electroencephalography (EEG) monitoring, high-resolution magnetic resonance imaging (MRI), and functional imaging. Intracranial EEG (iEEG) has historically provided the greatest precision in estimating the location and boundary of the EZ. As iEEG evaluation is invasive, it is only used when non-invasive evaluation cannot offer localization information adequate to perform a cortical resection. The most common indications are when the MRI findings are negative, the EZ cannot be resolved to a single region, or the postulated EZ is adjacent to eloquent cortex. In the last 15 years, many studies using wideband EEG recording have demonstrated that examining higher (80–1000 Hz) and lower (0.016–0.5 Hz) EEG frequencies can provide additional diagnostic information which may help to improve the surgical outcome. In addition, novel computational techniques of iEEG signal analysis have provided new insights into the epileptic network. Here, we review some of these recent advances.

Conventional Analysis of iEEG

Analysis of iEEG in the routine EEG frequency range (0.5–70 Hz) remains the cornerstone in clinical practice. However, it is a process that contains major subjective components based on the experience and school of training of the neurophysiologist. The primary emphasis is on the location and morphology of the ictal onset pattern (IOP),

which can be varied and for which there is no uniform terminology. But these features are commonly used to identify the seizure onset zone (SOZ), so long as the changes are relatively focal in one or a small number of electrodes and are recorded before the first clinical sign. Low-voltage fast activity [2–5] is the most commonly reported IOP in neocortical epilepsy, and low-frequency high-amplitude repetitive spiking is the most commonly reported IOP in mesial temporal lobe epilepsy (mTLE). Delta activity is usually held to be a spread pattern rather than a true IOP from the SOZ. The status of theta frequency is imprecise, given different weights depending on degree of sharpness, amplitude augmentation, rhythmicity, and spatial recruitment [2, 6]. Perucca [4] reported correlations of certain IOPs with the underlying pathology: for example, low-frequency periodic spikes in mTLE and delta brush in cortical dysplasia. Fast activity as an IOP is associated with a better surgical outcome [5, 7]. In a cohort of patients with non-lesional extratemporal lobe epilepsy, focal fast activity (>20 Hz) at seizure onset on the iEEG was correlated with an Engel Class I outcome after epilepsy surgery [7].

Additional analysis of the ictal discharge pertains to its propagation and connectivity to neighboring structures. This is the notion of the early or rapid propagation area which may be a marker of associated epileptogenicity [8], but it has not been accepted by all workers. Authors from the French school emphasize the importance of the spatio-temporal dynamics of seizure discharges, and not just their starting point. Their definition of the EZ is different from the North American concept of "minimal-cortex-to-remove area" [9]. Bartolomei *et al*. from the Marseilles group coined the term "epileptogenicity index" to quantify the degree of epileptogenicity in each brain region [10]. This measurement is based on both the spectral (appearance of fast oscillations in the beta and gamma bands) and temporal (delay of appearance with respect to seizure onset) properties of ictal iEEG signals. The epileptogenicity index provides an insight into understanding the epileptogenic network [11].

Ictal recordings can be influenced by a number of technical factors, namely the type of electrode (size of contacts, depth *versus* subdural electrodes), and their numbers and location. If the SOZ is not directly sampled, the presumed IOP may actually be recorded from electrodes in the pathway of seizure spread. Sometimes this is "close enough" to the true SOZ, such as when subdural contacts point to a basal mesial temporal onset but the seizure starts from the amygdala, a closed nuclear structure. In the situation of an SOZ at the bottom of a sulcus, subdural electrodes at the convexity may at best localize to the same lobe, but can also give a very misleading picture with a distant projected IOP. Such differences in electrode type and implantation schema across different epilepsy centers may lead to rather different appreciation of iEEG patterns.

High-Frequency Oscillations

High-frequency oscillations (HFOs, 80–500 Hz) are promising epileptic markers as accrued in a substantial body of literature in the last 15 years. Recording HFOs requires an EEG sampling rate >1000 Hz. Spontaneous interictal HFOs were first recorded at the University of California, Los Angeles, using microelectrodes in patients with mTLE [12–14]. Ripples (80–200 Hz) were recorded maximally in the bilateral hippocampus and entorhinal cortex in these patients during non-rapid eye movement (NREM) sleep. Fast ripples (200–500 Hz) were only recorded on the side of the epileptic hippocampus and entorhinal cortex and closely co-localized with the SOZ [14–16]. Subsequent studies have demonstrated that HFOs can be reliably recorded using commercially-available macroelectrodes, both subdural and depth electrodes, with the highest rates during slow-wave NREM sleep. They were found to be an independent epilepsy marker both in neocortical epilepsy and mTLE [17–22]. The regions showing high rates of interictal or ictal HFOs spatially co-localize with the SOZ or EZ, and resection of areas with higher interictal or ictal HFO rates have been significantly associated with a better surgical outcome (Table 1). Fast ripples are usually more restricted in location, found in fewer electrode contacts, and show better specificity in localization of the SOZ as compared to ripples. Both ripples and fast ripples appear to localize the SOZ better than interictal spikes. Even faster HFOs with a frequency >500 Hz have been identified in epileptic cortex [23] by recording with macroelectrodes at a sampling rate of 10 kHz. Interictal and ictal very-high-frequency oscillations (>1000 Hz) have been recorded from a limited number of electrodes in a small cohort [24, 25] and their presence might be predictive of a favorable outcome.

The rate of interictal HFOs is usually considered to be the most important parameter [26]. The rates of HFOs vary across different studies. For example, in Staba's study, ripples or fast ripples in the epileptic hippocampus and entorhinal cortex had a mean rate of ~0.3/min [15]. In Urrestarazu's study based on seven patients with mTLE or neocortical epilepsy, the median rate of ripples and fast ripples was 14/min (range, 0.4–41) and 5/min (range, 0.3–33) respectively in each type of patient [17]. Cho *et al*. [27]. reported much lower mean rates of ripples (~1.1/min) and fast ripples (~0.25/min) in the SOZs in patients with neocortical epilepsy. The recorded HFO rates are influenced by the pathological types of epileptogenic

Table 1 Characteristics of included studies

First author	Institute	Number of patients	Population	Epilepsy type	Electrode type	Favorable surgical outcome and HFOs
Ramachandrannair *et al.* [90]	Hospital for Sick Children, Toronto, Canada	5	Children	Temporal and extemporal	Subdural and depth electrodes	Ictal ripple and fast ripple
Wu *et al.* [21]	Mattel Children's Hospital, Los Angeles,USA	24	Children	Temporal and extemporal	ECoG	Interictal fast ripple
Jacobs *et al.* [20]	Montreal Neurological Institute and Hospital, Canada	20	Adults	Temporal and extemporal	Subdural and depth electrodes	Interictal ripple and fast ripple
Modur *et al.* [71]	University of Texas Southwestern Medical Center, Dallas, USA	6	Adults	Temporal and extemporal	Subdural and depth electrodes	Ictal ripple and fast ripple
Akiyama *et al.* [22]	Hospital for Sick Children, Toronto, Canada	28	Children	Temporal and extemporal	Subdural and depth electrodes	Interictal fast ripple
Fujiwara *et al.* [39]	Cincinnati Children's Hospital Medical Center, USA	44	Children	Temporal and extemporal	Subdural and depth electrodes	Ictal ripple and fast ripple
Haegelen *et al.* [91]	Montreal Neurological Institute and Hospital, Canada	30	Children and adults	Temporal and extemporal	Subdural and depth electrodes	Interictal ripple
Okanishi *et al.* [92]	Hospital for Sick Children, Toronto, Canada	10	Children	Neocortexl	Subdural and depth electrodes	Interictal ripple and fast ripple
Cho *et al.* [27]	Samsung Medical Center, Seoul, Korea	15	Children and adults	Neocortex	Subdural and depth electrodes	Interictal high rate ripple and fast ripple
van Klink *et al.* [59]	University Medical Center Utrecht, Netherlands	14	Children and adults	Temporal and extemporal	ECoG	Interictal fast ripple
Usui *et al.* [24]	Shizuoka Institute of Epilepsy and Neurological Disorders, Japan	13	Children and adults	Neocortex	Subdural electrodes	Interictal VHFO
van 't Klooster *et al.* [93]	University Medical Center Utrecht, Netherlands	54	Children and adults	Temporal and extemporal	ECoG	Interictal fast ripple

HFOs High-frequency oscillations, *ECoG* electrocorticogram

lesions [28]. HFO rates are higher in mesial temporal sclerosis and focal cortical dysplasia than in other lesion types. According to our own observations, the mesial temporal structures seem most prone to generate pathological HFOs even if they are not the primary epileptogenic area. It is impossible to use absolute HFO rates to determine if the tissue is epileptogenic, as occurrence rates are very variable, even for epilepsy caused by the same lesion. A recent study identified high-rate HFOs in neocortical epilepsy using an individualized threshold, and found that they help to mark the EZ better than spikes or the SOZ [27].

A significant proportion of ripples and fast ripples co-occur with spikes, but many spikes also occur independently [19, 29, 30]. In addition, fast oscillations in the gamma and low ripple range (30–100 Hz) have been found to precede interictal epileptiform spike discharges (IEDs), and these so called gamma-IEDs are strongly associated with the SOZ in TLE [31]. Although HFOs and spikes are closely related, their dynamics differ. Zijlmans [32] reported that HFOs increase after medication is reduced and remain the same after seizures, whereas spike rates increase after seizures. The rate of HFOs may reflect the epileptogenicity of tissue better than spikes.

The cellular mechanism underlying HFO generation is not clear. Data suggest that a reduction of summated synchronous inhibitory postsynaptic potentials (IPSPs) mediated by inhibitory interneurons plays a role in the

generation of pathological HFOs [33]. Some studies suggest that principal cell firing or inhibitory postsynaptic currents contribute to their generation. There is little evidence that single neurons can fire at frequencies >300 Hz. Fast ripples have also been proposed to emerge from out-of-phase firing within small groups of neurons, perhaps through coupling *via* axonal gap junctions [34].

Several studies have examined the pre-ictal and ictal changes of HFOs [4, 35, 36]. The rate of HFOs has been found to increase a few seconds before seizure onset [35] and its distribution remains largely confined to the same epileptogenic area during both the interictal and ictal periods, whereas spikes are more widespread during seizures than in the interictal period [35]. An increase in HFO rate or power has been found in many other studies [4, 37, 38]. Fujiwara [39] showed that resection of the area with ictal high-frequency oscillations may lead to a favorable surgical outcome in pediatric epilepsy.

Both clinical and experimental studies have shown that physiological HFOs can be recorded in the neocortex as well as in mesial temporal structures [40, 41]. Physiological ripples can be recorded in the non-epileptic hippocampus and parahippocampal structures in normal rats [42, 43] and may reflect IPSPs generated by subsets of interneurons that regulate the discharges of principal cells [41]. The function of these physiological ripples is to consolidate synaptic plasticity and they are important for episodic memory [44] and memory consolidation [45]. In the neocortex, fast oscillations are induced in specific areas by sensory stimulation or during language and motor tasks in humans. EEG oscillations in the high gamma or low ripple frequency range, so called "high gamma oscillation", are evoked in humans by sensory stimulation, a motor task, or a language task in the corresponding cortical areas: visual cortex [46], auditory cortex [47], motor cortex [48], and language cortex [49]. Sensory-evoked fast ripples with a frequency up to 600 Hz can be recorded in the rat neocortex [50]. There is increasing evidence for spontaneous physiological ripple activity in the neocortex. Spontaneous ripples have been reported in the sensory and association cortices of the cat, more often during slow-wave sleep [51]. In humans, spontaneous physiological ripples have been identified in the visual cortex [30, 52] and the motor cortex [30, 53]. These findings are in line with a recent report that ripples in non-epileptic regions are consistently located in the occipital lobes and peri-rolandic regions [54].

It is difficult to differentiate physiological ripples from pathological ripples by rate, duration, and amplitude because they overlap greatly in each parameter [30, 40, 41, 54, 55]. The morphology of HFOs does not improve delineation of the EZ either [56]. Analyzing the EEG characteristics associated with ripples may be useful for identifying pathological ripples. Interictal ripples occurring in an oscillatory background activity may be suggestive of physiological activity, while ripples on a flat background probably reflect epileptic activity [57]. Alternatively, neocortical ripples nested in an interictal epileptiform discharge, so-called 'Type I ripples', have been found to be specifically distributed in the SOZ or primary propagation areas [30].

There are intriguing reports identifying HFOs from scalp and other non-invasive recordings. Interictal scalp gamma or ripple oscillations have been reported in patients with focal epilepsy and correlated with the location of the SOZ [58, 59]. Interictal HFOs have also been found in generalized epilepsy. Fast oscillations have been recorded in childhood absence seizures using magnetoencephalography [60], and in West syndrome using scalp EEG recording [61]. However, technical challenges remain a barrier to the routine recording of HFOs from the scalp.

Infra-Slow Activity

At the other end of the conventional frequency range, infra-slow activity (ISA) has been identified as related to the SOZ. In the literature, this is also called baseline shifts or direct current (DC) shifts. Ictal baseline shifts have been described in animal models of chemically-induced seizures since the 1960s [62, 63]. Using a commercial EEG system, Ikeda [64, 65] found that slow shifts can be recorded on scalp EEG and iEEG. Many studies have shown that AC amplification is able to reveal ISA when the high-pass filter is removed [65–68]. ISA has a smaller electrical field than the conventional frequencies [68–74]. Analyzing ictal ISA may assist in localize the seizure focus [75]. Ictal ISA has been reported on iEEG in most seizures and all patients with mTLE [68]. Ictal ISA was also found in all seizures in a cohort of patients with temporal and extra-temporal lobe epilepsy [74]. It is noteworthy that the ictal ISA, conventional iEEG, and HFOs are temporally related. The onset of an ictal baseline shift precedes the onset of ictal HFOs or conventional EEG onset [68, 76–78]. Interestingly, Ren [79] found in three patients that periodic slow negative baseline shifts, named "very low frequency oscillation", precede seizure onset by 8–22 min. Rodin reported on interictal ISA from intracranial and scalp EEG [67, 72], seen most prominently in the vicinity of the seizure onset area and/or frequent interictal spiking regions. However, interictal ISA has also been found in distal areas and even in the contralateral hemisphere. It is unclear whether interictal ISA in distal areas represents physiological activity, given the absence of comparative studies in healthy volunteers.

So far, very few studies have compared the resection of regions showing ISA and surgical outcome. It is unclear

whether ISA helps to localize the EZ. The generator of ISA is also unknown [80, 81], and the current hypothesis is that glia may play a role [65, 66, 72]. The activation of glia integrates neuronal firing and contributes to seizure initiation [82].

Quantitative Analysis Using Computational Models

The visual analysis of iEEG can miss important information. Analysis of iEEG using computational models provides additional useful information on the epileptogenic network in the resting state or during the propagation of ictal discharges. One study analyzed the resting-state coherence of the EEG frequency band between 5 and 50 Hz in TLE, and found that patients who had stronger and more heterogeneous connections within the temporal lobe were more prone to seizure recurrence [83]. Other studies have focused on ictal studies. Kim *et al*. used graph theoretical analysis of iEEG recordings in Lennox-Gastaut syndrome in which the conventional methods usually provide obscure localizing information. In this pilot study, they found that the "primary hubs" of the ictal network coincided well with the surgical resection areas in the four patients with good surgical outcome [84]. Wilke *et al*. aimed to identify the ictal sources based on the "directed transfer function" which is a causal measurement method. They found that the estimated sources were highly correlated with the seizure-onset zones identified by epileptologists [85]. Epstein *et al*. used Granger causality analysis of pre-ictal HFOs and found that it helped to improve surgical outcomes in two cases of ambiguous iEEG onset [86]. Another study reported regions with strong ictal HFO (80–270 Hz) coherence coincided with regions with high ictal HFO intensity in 4 out of 5 patients with extratemporal lobe epilepsy [87]. Weiss *et al*. [88]. found that phased-locked high gamma activity, defined by ictal high gamma activity (80–150 Hz) phase-locked to the low-frequency phase (1–25 Hz), may mark the "seizure core territory". Later, in a retrospective study including 45 patients, the same group reported that resection of regions showing early ictal phased-locked gamma activity, together with the SOZ, was correlated with a better surgical outcome [89], suggesting that it may better mark the EZ and potentially minimize the volume of resection in future.

Conclusions

In the future, epileptologists will probably expect a change in the pathological spectrum of epileptogenic lesions in patients undergoing iEEG. Because when advanced functional imaging and structural MRI come into use, a significant proportion of surgical candidates, such as those with pharmacoresistant epilepsy caused by subtle lesions such as focal cortical dysplasia, previously considered to be MRI-negative, can receive surgery without chronic iEEG evaluation. Accordingly, the epileptogenic network in those "complete imaging-negative" patients may be more complicated and require more spatial coverage. In addition, to analyze the iEEG activity in the routine frequency band, examining the HFOs and ISA, and applying quantitative iEEG analysis with proper computational models may help to localize the EZ. Although these techniques are promising as demonstrated in the current literature, the sample sizes were small and the follow-up time was usually short in these studies. Before these novel techniques can be used in the clinic, their value should be further confirmed in multi-center studies with long-term observations and larger sample sizes.

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