High frequency oscillations and infraslow activity in epilepsy

Pradeep N. Modur

Department of Neurology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Abstract

In pre-surgical evaluation of epilepsy, there has been an increased interest in the study of electroencephalogram (EEG) activity outside the 1-70 Hz band of conventional frequency activity (CFA). Research over the last couple of decades has shown that EEG activity in the 70-600 Hz range, termed high frequency oscillations (HFOs), can be recorded intracranially from all brain regions both interictally and at seizure onset. In patients with epilepsy, HFOs are now considered as pathologic regardless of their frequency band although it may be difficult to distinguish them from the physiologic HFOs, which occur in a similar frequency range. Interictal HFOs are likely to be confined mostly to the seizure onset zone, thus providing a new measure for localizing it. More importantly, several studies have linked HFOs to underlying epileptogenicity, suggesting that HFOs can serve as potential biomarkers for the illness. Along with HFOs, analysis of ictal baseline shifts (IBS; or direct current shifts) and infraslow activity (ISA) (ISA: <0.1 Hz) has also attracted attention. Studies have shown that: IBSs can be recorded using the routine AC amplifiers with long time constants; IBSs occur at the time of conventional EEG onset, but in a restricted spatial distribution compared with conventional frequencies; and inclusion of IBS contacts in the resection can be associated with favorable seizure outcome. Only a handful of studies have evaluated all the EEG frequencies together in the same patient group. The latter studies suggest that the seizure onset is best localized by the ictal HFOs, the IBSs tend to provide a broader localization and the conventional frequencies could be non-localizing. However, small number of patients included in these studies precludes definitive conclusions regarding post-operative seizure outcome based on selective or combined resection of HFO, IBS and CFA contacts. Large, preferably prospective, studies are needed to further evaluate the implications of different EEG frequencies in epilepsy.

Key Words

Epilepsy, high frequency oscillations, infraslow activity, intracranial electroencephalogram, seizure

For correspondence:

Dr. Pradeep N. Modur, Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8508, USA.

E-mail: modurp@yahoo.com

Ann Indian Acad Neurol 2014:17 (Supplement 1):S99-106

Introduction

Electroencephalogram (EEG) activity outside the 1-70 Hz band of conventional frequency activity (CFA) has attracted considerable interest in the literature recently.[1] This mainly stems from technological advances that have allowed us to record, store and analyze large amounts of human EEG data with relative ease using sophisticated hardware and commercially available software packages. The progress in data acquisition and analysis has occurred in conjunction with several groundbreaking studies demonstrating the clinical utility of EEG activity >70 Hz, termed high frequency oscillations (HFOs). HFOs are considered as a new measure for localizing the seizure onset zone (SOZ) and in determining epileptogenicity.[2] Similarly, analysis of ictal baseline shifts (IBSs, also known as direct current [DC] shifts) and EEG activity <0.1 Hz, termed infraslow activity (ISA), has gained traction in the literature after the realization that such activity can be assessed using the standard AC amplifiers without the need for dedicated DC amplifiers.[3] This article provides an overview of intracranially-recorded HFOs, IBSs and ISA, their relationship to CFA and their clinical implications in epilepsy. Intracranial EEG data from a patient with temporal lobe epilepsy (TLE) are used to illustrate the feasibility of recording such EEG waveforms in practice.

Access this article online

Quick Response Code:

Website: www.annalsofian.org

DOI: 10.4103/0972-2327.128674

HFOs

In general, the term HFOs refers to EEG activity >70 Hz, whereas activity in the 30-70 Hz band is considered as gamma.[4] Our ability to record and analyze high frequency activity can be influenced by various factors. A thorough knowledge of such factors is important to navigate and interpret the expanding literature on HFOs, particularly since different groups of investigators use different methods to report their findings. A few basic guidelines helpful in

understanding the literature pertaining to HFOs are outlined in Table 1.

Although HFOs can be recorded from scalp, it is easier to record such low-amplitude, high-frequency waveforms in a relatively artifact-free manner intracranially because of proximity to the generators of those waveforms, which tend to be smaller and located within the brain or on the brain surface. The sampling rate is an important factor determining the recording of high frequencies. Theoretically, the maximum frequency (Nyquist frequency) of the oscillations that can be evaluated corresponds to one-half of the sampling rate, i.e., a sampling rate of 1000 Hz would allow activities up to 500 Hz to be assessed. However, due to the limitations of the amplifiers used in the EEG systems, the maximum frequency that can be clearly evaluated tends to be roughly one-third of the sampling rate such that a sampling rate of 1000 Hz allows evaluation of activity up to 333 Hz.

The size of the recording electrode can greatly influence the frequencies encountered, with larger electrodes less likely to record higher frequencies [Table 1]. Studies using microelectrodes have demonstrated that physiological HFOs, particularly in the gamma band (sometimes up to 80 Hz), are associated with somatosensory, cognitive and perceptual tasks.[4] One such example is the ripple oscillations (~200 Hz activity) described by Buzsáki *et al*. in the microelectrode recordings from the CA1 pyramidal layer of the rat hippocampus, occurring in conjunction with sharp waves during states of immobility, consummatory behavior and slow wave sleep.[5] Interestingly, Bragin *et al*. subsequently noted similar ripple oscillations in the microelectrode recordings from mesial temporal structures in patients undergoing pre-surgical evaluation.[6,7] These studies reported by the University of California-Los Angeles group focused on interictal HFOs in rodents and humans recorded by depth microelectrodes (40-60 μm diameter, 0.001 mm^2 surface area) implanted chronically in the mesial temporal structures (hippocampus and entorhinal cortex).[6,7] Using 2000 Hz sampling rate, these investigators described HFOs up to 600 Hz and classified them into two frequency bands: Ripples (100-200 Hz); and fast ripples (FRs: 250-500 Hz). The ripples were considered as physiological (the equivalent of rat ripples), whereas the FRs were felt to be clearly pathological, being associated with epileptogenicity.[8] Subsequently, using slightly larger, proprietary clinical macroelectrodes (0.8 mm^2, ~800× larger than microelectrodes), the studies from the Montreal Neurological Institute reported similar, predominantly interictal HFOs in the 80-500 Hz range in patients undergoing pre-surgical evaluation with chronically implanted depth and subdural electrodes in both mesial temporal and neocortical structures.[9,10] Around the same time, using much larger, commercially-available clinical electrodes (4 mm^2, ~4000 - 9400× larger than microelectrodes), other investigators described HFOs in human depth and subdural recordings obtained from both mesial temporal and neocortical structures.[11-16] These investigators described both ictal and interictal HFOs in the 70-500 Hz range in chronic extraoperative intracranial recordings as well as intraoperative electrocorticography (ECoG). The effect of electrode size on the recorded frequency band was further explored by Worrell *et al*. in recordings using simultaneous depth microelectrodes (40 μm, 0.001 mm^2) and macroelectrodes (9.4 mm^2, ~9400× larger than microelectrodes) implanted in the mesial temporal structures.[12] They showed that FRs were most likely to be recorded by single microelectrodes, but only rarely recorded by the adjacent macroelectrodes and attributed their finding to the spatial averaging of local field potentials by the relatively large surface area of the macroelectrodes leading to spatial undersampling of the focal HFOs.[12]

The method of analyzing HFOs could potentially lead to some inevitable discrepancies in the reported findings. Visual analysis of HFOs [Figure 1] consists of inspecting EEG traces with appropriate filter and time scale settings. Commonly, one uses a low frequency filter >50 Hz and a high frequency filter at 300 Hz or 600 Hz depending upon the sampling rate. A time scale of 1-2 s per page is required to adequately visualize the HFOs, being determined by the maximum horizontal resolution of the modern computer monitors. Despite following these recommendations, visual analysis can be subjective due to lack of an accepted definition of HFO, in turn leading to inter-observer variability. Visual analysis is also time-consuming (for e.g., it could take 10 h to analyze 10 min data containing 10 channels[17]), limiting the overall analysis to only small samples. Fatigue from prolonged visual analysis can also lead to intra-observer variability. On the contrary, automated analysis of HFOs is more promising because it tends to be more consistent and objective and allows processing of large samples. However, multiple algorithms, implemented on various platforms, to accomplish automation can also lead to significant differences in the reported findings.

The exact mechanism of generation of HFOs is unclear, but several theories have been postulated, as reviewed by

Table 1: Overview of studies on high frequency oscillations using different types of electrode

Parameter	Microelectrode studies	Macroelectrode studies	Commercial electrode studies
Size	40-60 μm, 0.001 mm^2	0.8 mm^2, ~800×*	4 mm^2, ~4000×*
State	Interictal	Mainly interictal (some ictal and pre-ictal)	Interictal, pre-ictal and ictal
Species	Rodents and humans	Mainly humans	Humans
Brain region	Mesial temporal	Mesial temporal (some neocortical)	Mesial temporal and neocortical
Duration	Chronic	Chronic	Chronic and intraoperative
Sampling rate	2000 Hz	2000 Hz	>1000 Hz
Frequency band	80-600 Hz	80-500 Hz	>70 Hz
Analysis method	Visual and automated	Visual	Visual and automated

*Approximate size compared to a microelectrode

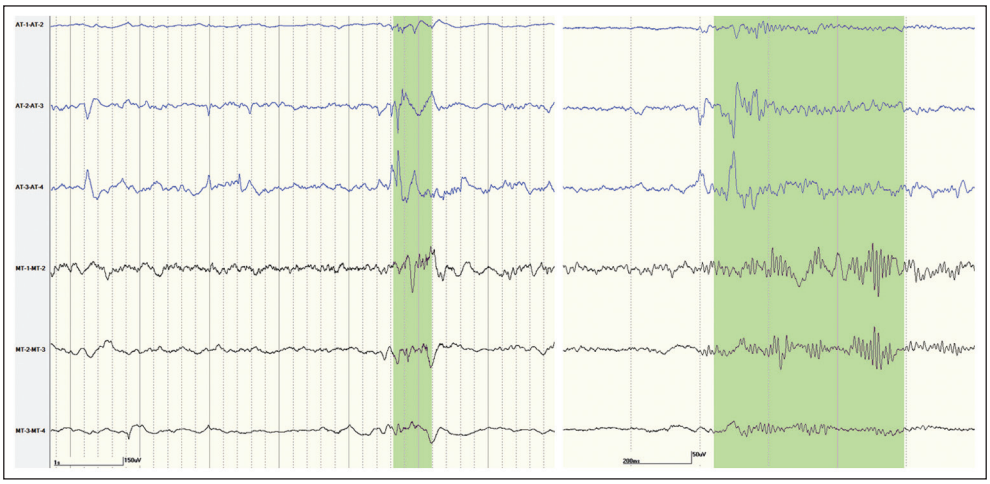

Figure 1: Interictal high frequency oscillations (HFOs). Left panel: at conventional setting of 1.6-70 Hz and 10 s per page window, the highlighted segment shows spikes in the inferomesial temporal region, occurring independently at AT3 and MT2 in a patient with temporal lobe epilepsy. Right panel: at high frequency setting of 53-600 Hz and 1 s per page window, prominent HFOs are seen in the highlighted segment occurring together with and independently of the spike at MT2; no HFOs are seen in association with the spike at AT3. Note that the highlighted segments in the two panels correspond to each other in time

Jiruska *et al*.[18] It is believed that ripples result from the summation of inhibitory postsynaptic potentials generated by the interneurons on the pyramidal cells. Another theory postulates that HFOs are generated by synchronous firing of a group of principal neurons (pyramidal cells or granule cells), with each individual high frequency cycle representing a population spike probably generated by a small group of principal neurons. Three mechanisms have been proposed to underlie such fast synchronous firing of pyramidal cells: Excitatory coupling between pyramidal cells, facilitated by axonal sprouting, resulting in the formation of clusters of pathologically interconnected neurons; electrotonic coupling through gap junctions at the axonal level; and ephaptic transmission between adjacent neurons.

HFOs: Clinical Implications

Despite the uncertainty regarding the mechanisms involved in the generation of HFOs, there is convincing evidence to suggest that they are easily recordable as long as appropriate methods are used. Reports of clinical implications of HFOs continue to appear in the literature on a regular basis and can be classified into the following 6 categories.

HFOs are recordable from all brain regions in patients with epilepsy

As noted above, interictal HFOs have been recorded intracranially using microelectrodes, macroelectrodes and commercial electrodes.[11-16] In the microelectrode studies, the recordings were confined to mesial temporal structures; the mean frequency of ripples was 96 Hz (±14 Hz) and that of FRs was 262 Hz (±59 Hz), with FRs being significantly shorter in duration than ripples.[6,7,19] Compared with ripples, FRs were found to be generated locally, in <1 mm^3 of tissue.[20,21] Similar frequency ranges were noted in the macroelectrode studies, which also demonstrated that interictal HFOs occurred together with or independently of spikes not only in the mesial temporal structures, but also in the neocortical regions.[9,10,22] Subsequent studies using commercial electrodes further demonstrated that HFOs could be successfully recorded from all brain regions with the caveat that FRs are less likely to be seen with such large electrodes.[12,13,15]

In contrast to the interictal HFOs, the ictal HFOs had been described in the literature much earlier in patients with epilepsy undergoing subdural and depth recordings using the larger, clinical electrodes. High frequency activity in the 40-120 Hz band was noted to occur at seizure onset, but not during the interictal baseline, sometimes superimposed on the electrodecremental pattern.[23-26] These studies had significant limitations because of fewer recording electrodes or a lower sampling rate. However, subsequent studies using a large subdural grids convincingly demonstrated that the ictal HFOs occurred in a widespread manner in all brain regions.[11,14,27-29]

Frequency band of HFOs alone does not denote pathologic significance

Initially, the microelectrode studies on interictal HFOs concluded that only the FRs, but not ripples, were pathologic and epileptogenic based on several observations: Rates of FRs were higher than ripple rates regardless of state; the FR/ripple ratio was higher (i.e., increased FRs, decreased ripples) ipsilateral to the side of seizure onset (with or without hippocampal atrophy); the rate of FRs was higher in the epileptogenic areas in contrast to the non-epileptogenic areas while the ripple rate was similar; higher FR/ripple ratios were associated with smaller hippocampal volumes and neuron densities.[19,30,31] However, subsequent observations from the same group concluded that ripples in the dentate gyrus could be pathologic and epileptogenic as well, based on the appearance of HFOs in the pyramidal layer and dentate gyrus in rats after kainic acid-induced status epilepticus.[32,33] Furthermore, the macroelectrode studies supported the notion that both ripples and FRs were pathologic and epileptogenic and probably represented the same phenomenon.[22,34] Thus, it is now generally believed that interictal HFOs, regardless of

the frequency band, can be pathologic in epilepsy as long as they are distinguished from the physiologic HFOs that may occur in a similar frequency range.[35]

Studies on ictal HFOs have been done using a sampling rate of 1000-2000 Hz and large commercial electrodes (4 mm^2). Relying on time-frequency methods to carefully analyze the HFOs, some investigators have shown that the ictal HFOs with sufficiently high spectral power are usually< 300 Hz in frequency.[11,13,14,27-29] An exception to this was noted in a study done with a sampling rate of 2000 Hz using macroelectrodes (0.8 mm^2), which showed the occurrence of ictal HFOs around 300-375 Hz at seizure onset followed by slower 120-190 Hz activity as the seizure evolved.[9] Although the lower frequency range for the ictal HFOs could be attributed to the larger electrode size, the possibility that the ictal front may synchronize the HFOs at a lower frequency at seizure onset than interictally needs to be entertained and further explored.

Interictal HFOs localize the SOZ

The microelectrode studies demonstrated that the interictal HFOs were confined to the SOZ which is not surprising since the HFOs were recorded from a limited brain region (i.e., mesial temporal structures) in patients with well-defined seizure foci (i.e., within the temporal lobe).[6,7,19,20] On the other hand, the subsequent macroelectrode and commercial electrode studies which recorded HFOs from all brain regions, including mesial temporal and neocortical structures, showed that the interictal HFOs could occur in a widespread manner, extending over several centimeters.[15] Interestingly, despite such widespread presence, the rates of FRs and ripples were higher inside the conventionally-defined SOZ than outside and correlated with the SOZ better than the conventional spikes.[22,36] In addition, Jacobs *et al*. also reported that the rates of HFOs were tightly linked to the SOZ (rather than the underlying lesion).[37] Thus, there is enough evidence to suggest that the interictal HFOs reliably localize the SOZ.

Spatial and temporal characteristics of ictal HFOs differ from conventional frequencies

In children, Ochi *et al*. showed that partial seizures and epileptic spasms were associated with ictal HFOs that had an extensive spatial distribution (~120 electrodes) with frequencies spanning a wide band (~250 Hz); in contrast, secondary generalized seizures showed wide-band HFOs initially with subsequent evolution into a sustained spatially-restricted (~28 electrodes), narrow-band pattern after clinical onset.[11] Similar spatial and temporal features of ictal HFOs were also noted in adults with neocortical epilepsy.[14,27] In a prospectively-defined surgical protocol, Modur *et al*. differentiated 2 types of ictal HFOs: HFO+ that appeared at seizure onset, and persisted as HFOs or transitioned into lower frequency activity with seizure evolution until the first clinical seizure symptom appeared; and HFO– that appeared at seizure onset but did not evolve.[27] It was found that HFO+ had significantly higher peak frequency, higher peak power and smaller spatial distribution than HFO–.[27] Furthermore, comparison of ictal HFOs and CFA showed that HFO+ preceded CFA by about 0.41 s, and that the spatial extent of either HFO+ or HFO– was significantly smaller than the CFA.[27] Other investigators have also reported similar observations: Ictal HFOs were found to occur in a spatially-restricted manner in mesial TLE;[29] and ictal HFOs preceded CFA by 48-136 ms in epileptic spasms.[28] These studies highlight the spatio-temporal differences between HFO-defined and CFA-defined seizure onsets, i.e., spatial restriction and temporal antecedence of ictal HFOs compared with ictal CFA [Figure 2 shows an illustration of this].

HFOs are probably related to seizure genesis

Clearly, the occurrence of ictal HFOs at seizure onset suggests that they may be involved in seizure genesis although the exact mechanism by which HFOs initiate a seizure remains unknown. Interestingly, analysis of the pre-ictal period has shown that HFOs increase significantly up to 20 min prior to seizure onset,[26] and the power of ripples and FRs increase significantly in the immediate

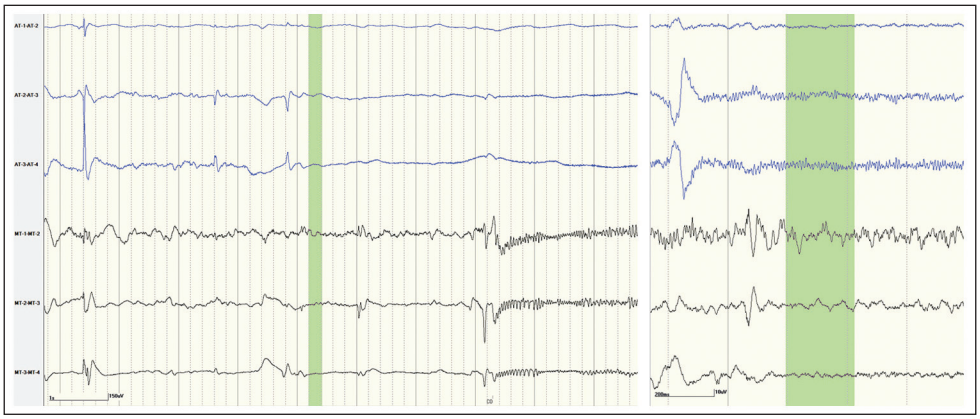

Figure 2: Ictal high frequency oscillations (HFOs). Left panel: at conventional setting of 1.6-70 Hz and 10 s per page window, conventional seizure onset (marker CO) consisting of rhythmic beta activity is seen in the MT channels located in the inferomesial temporal region of the same patient as in Figure 1. At the time of and preceding the conventional seizure onset, the adjacent AT channels show attenuation (highlighted segment). Right panel: at high frequency setting of 53-600 Hz and 1 s per page window, prominent rhythmic ictal HFOs are seen in AT2-3 and AT3-4 channels but not in the adjacent MT channels, demonstrating temporal and spatial differences between seizure onsets defined by conventional frequency activity and HFOs. Note that the highlighted segments in the two panels correspond to each other in time

pre-ictal period of 8 s.[13] These observations further support the idea that HFOs may be involved in seizure genesis. In addition, indirect evidence for the relationship between HFOs and seizure genesis comes from the observation that interictal ripples and FRs increased after antiepileptic drug withdrawal while the conventional spikes increased after seizures; in other words, the HFOs behaved more like seizures.[38] However, this study was limited to 12 patients, and was based on visual analysis of only 1 min of presumed non-REM sleep data per patient.

HFOs are linked to epileptogenicity

There are several studies linking interictal and ictal HFOs to underlying epileptogenicity in all age groups, suggesting that HFOs may serve as biomarkers for the illness. The evidence for interictal HFOs mainly comes from retrospective analyses of surgical case series demonstrating that resection of brain tissue containing HFOs was likely to be associated with good post-operative seizure outcome. Specifically, good seizure outcome was associated with resection of contacts with higher rates of HFOs in contrast to spikes[39] and resection of contacts with higher rates of ripples ($P = 0.018$) and FRs ($P = 0.049$) in TLE (but not in extratemporal epilepsy).[40] Similarly, more complete resection of contacts with ripples (odds ratio [OR] 1.04, $P = 0.091$) and FRs (OR 1.1, $P = 0.046$)[41] was associated with good outcome. In addition to these studies which evaluated chronic extraoperative monitoring data, an intraoperative ECoG study by Wu *et al*. in children also showed that complete resection of FR-containing cortex was associated with good outcome.[16] On the contrary, post-operative seizure outcome was not found to be associated with resection of contacts inside the SOZ,[39,41] or the resected tissue's size or volume.[40,41] In interpreting these results it is important to keep in mind that the SOZ was defined based on conventional frequencies, not ictal HFOs (see below), and that the odds ratios of achieving better outcome were rather small.

Similar to interictal HFOs, there is clear evidence linking ictal HFOs to underlying epileptogenicity. Such evidence again comes from analyses of surgical case series demonstrating that resection of brain tissue containing ictal HFOs was likely to be associated with good post-operative seizure outcome. In adults with neocortical epilepsy, resection of contacts containing HFOs was found to be associated with favorable seizure outcome.[25,26,42] As an extension of these findings, a more limited resection confined mainly to ictal HFOs with sustained evolution (HFO+) as opposed to those without evolution (HFO−) based on a prospectively-defined protocol was shown to be associated with good outcome in 5/6 (83%) patients.[27] Favorable outcome was also seen in a case of frontal lobe epilepsy after multiple subpial transections of the gyri containing HFOs.[14] Encouraging results have also been demonstrated in the pediatric population. In one study, more HFOs were found inside the resection area than outside in the seizure-free group and vice versa in the residual-seizure group.[11] In another study, Fujiwara *et al*. showed that complete resection of HFOs led to seizure freedom in 82% of children whereas incomplete resection led to seizure freedom in only 21%.[43] Favorable outcome was also seen after complete resection of sites showing early augmentation of ictal HFOs in children with epileptic spams.[44]

IBSs and ISA

The term DC EEG has been widely used in the literature to imply a frequency response of the EEG with a minimum at 0 Hz, which is typically recorded using special DC-coupled amplifiers that preserve the slow baseline fluctuations from significant distortion by the built-in high-pass filters.[45] During pentylenetetrazole-induced tonic-clonic seizures recorded with conventional and DC amplifiers, the depolarization of pyramidal neurons has been shown to cause a negative DC shift which gradually recedes and changes into a positive shift in the postictal period.[46] In cats with penicillin-induced seizure foci, similar DC shifts were noted to be characterized by a horizontal dipole, having maximum amplitude at the focus with the field extending to about 10 mm.[47] In the early studies, DC shifts were not seen on conventional EEG recordings obtained from the AC amplifiers, possibly because of the short time constant of 0.3 s (~0.53 Hz low frequency filter) used during that time,[1] giving rise to the notion that dedicated DC amplifiers were needed to record such activity. However, Ikeda *et al*. refuted this by demonstrating that ictal DC shifts could be recorded in human scalp and intracranial recordings using conventional AC amplifiers with a 10 s (~0.016 Hz low frequency filter) time constant.[48,49] More recent studies by other investigators further confirmed that DC shifts were indeed recordable using AC amplifiers if long time constants were used during acquisition, and appropriate filters and time scales were used for display.[14,50-55] In line with these observations, more recent studies using dedicated DC-coupled amplifiers have also shown the occurrence of ictal DC shifts in both scalp and intracranial recordings in humans.[56-58] To avoid confusion with the terminology when AC recordings are analyzed, the term IBSs was used to refer to the DC shifts.[14]

Besides using an AC amplifier with long time constant, successful recording of IBSs is facilitated by the use platinum electrodes (as opposed to gold or stainless steel), larger surface area of the electrodes (e.g., subdural as opposed to depth electrodes) and higher input impedance of the amplifier (usually >50 M Ω).[59] Figure 3 shows IBSs at the onset of a focal seizure in the inferomesial temporal subdural contacts with a low frequency filter of 0.016 Hz and a time scale of 30 s per page.

Compared with IBSs, there is much less information in the literature regarding background ISA. The same factors that determine the recording of IBSs also influence the recording of ISA. There is no accepted definition for ISA, but investigators have generally analyzed it visually using bandpass filters of 0.01-0.1 Hz or 0.02-0.2 Hz and longer time scales of 10 or 20 min per page.[51,53,55]

The origin of ictal DC shifts appears to be multifactorial. The proposed mechanisms of its generation include neuronal activity, glial activity and blood-brain barrier alteration.[60] It has been shown that sustained neuronal depolarization during a seizure causes an increase in extracellular potassium, which in turn causes glial depolarization that is conducted electrotonically within the glial network.[46] This neuron-glia interaction results in spatial buffering of potassium and manifests as a monophasic negative DC shift in the deep

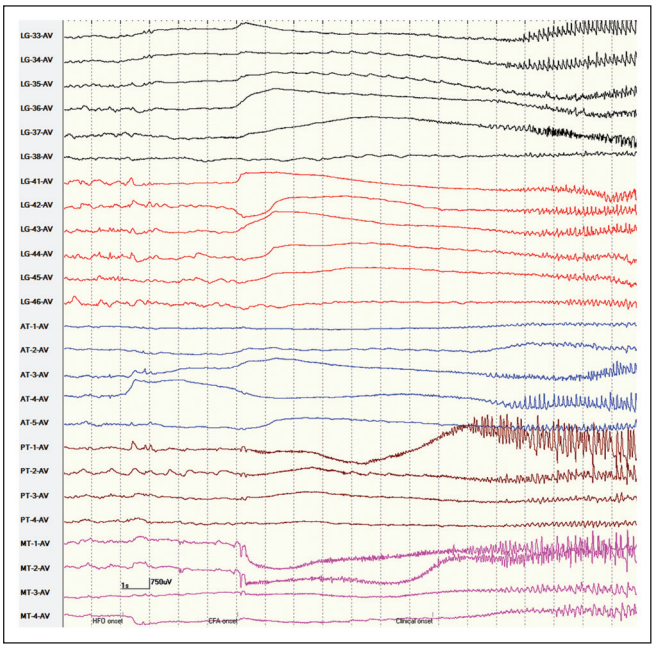

Figure 3: Ictal baseline shifts (IBSs). Selected subdural contacts over the lateral temporal (LG), anterior inferomesial temporal (AT and MT) and posterior inferomesial temporal (PT) regions in the same patient as in Figure 1 are shown. At the infraslow setting of 0.016-30 Hz and 30 s per page window, seizure onsets defined by high frequency oscillations (HFO onset) and conventional frequency activity (CFA onset) are shown along with the earliest clinical change (clinical onset). HFO onset was defined in the AT channels, whereas CFA onset was defined in the PT and MT channels. Prominent negative and positive IBSs are seen at or after the CFA seizure onset in a widespread distribution. However, careful inspection shows smaller but distinct IBSs at the time of HFO seizure onset in a restricted distribution involving only three contacts (AT3, AT4 and MT4). Note that a referential montage with an average reference is used

recordings and as a negative or positive shift in the superficial recordings during generalized tonic-clonic seizures in animal models.[46]

IBSs and ISA: Clinical Implications

Unlike HFOs, the practical utility of IBSs and ISA remains less clear. There are only a handful of reports in patients with epilepsy regarding their clinical implications, which can be summarized as follows.

IBSs are recordable from all brain regions in patients with epilepsy

Human studies have shown that IBSs with negative or positive polarity occur in the majority of intracranially-recorded seizures arising from either mesial temporal or neocortical regions.[48-51,58] Seizure onsets with an electrodecremental pattern are felt to be more likely associated with IBSs.[54,61] As expected, the amplitude of IBSs tends to be higher (800 μV-10 mV) with DC amplifiers and smaller (0.3-2.2 mV, average 1 mV, maximum 3.3 mV) with AC amplifiers.[53,54,58] Duration of IBSs is variable (1.9-2.9 s, maximum 15.8 s).[53] Spatially, the IBSs were found to be distributed in a widespread manner as demonstrated in studies with extensive intracranial implantation.[53,58] Compared to the SOZ defined by CFA, the IBSs were spatially restricted in distribution although the IBS electrodes could be found overlapping with or adjacent to the CFA electrodes.[14,48,49,51,53] Temporally, IBSs preceded, coincided with or followed the conventional EEG onset.[14,48,49,51,53]

IBSs can localize the SOZ

Several studies have shown that IBSs are useful in localizing the SOZ. The baseline shift at seizure onset is large and easily identifiable compared to conventional frequencies when hundreds of intracranial electrodes are displayed on a single screen. As discussed above, the spatial restriction of IBSs compared with ictal CFA defines a smaller SOZ that would be more feasible to resect. In keeping with these observations, retrospective studies have shown that resection of the IBS electrodes can be associated with favorable seizure outcome.[48,49] In another study, 5 of 6 patients with class I outcome were found to have the DC contacts concordant with the conventional EEG contacts that were resected.[58] Although the precise relationship between IBSs and SOZ needs further investigation, it is important to note that even with a focal lesion, the IBSs can be widespread and multi-lobar in distribution.[51] These observations suggest the possibility of widespread epileptogenicity even with a focal lesion and provide insight into the mechanisms underlying epilepsy surgery failure.

Peri-ictal and interictal increase in background ISA can occur

An increase in ISA prior to seizure onset was noted in a recent study by Rodin and Modur, suggesting that IBSs could be part of this widespread increase in ISA.[51] Subsequent studies by the same investigators demonstrated the presence of long periods of ISA not only during the pre-ictal and postictal periods, but also during the interictal state.[53,55] When recordings were analyzed using 0.02-0.2 Hz bandpass filter and 10 min per page window, peri-ictal ISA appeared as periodic transients or 0.12-0.16 Hz rhythmic oscillations that were poorly concordant spatially with IBSs.[53] Analysis of continuous interictal data using an open low frequency filter and 0.1 Hz high frequency filter with a 20 min per page window showed that the increase in background ISA could last for long periods (several minutes to 2.5 h) in multiple channels, unrelated in timing to clinical or subclinical seizures.[55] Such interictal ISA was found to occur within and remote from the conventional SOZ, again suggesting the presence of a wider epileptic network.[55]

Broadband EEG Analysis of High, Infraslow and Conventional Frequencies

Despite numerous studies investigating the various EEG frequency bands individually, the literature pertaining to the relationship between high, infraslow and conventional frequencies is scant. In a patient with non-lesional left frontal lobe epilepsy analyzed with 0.016-300 Hz bandwidth EEG, it was noted that there was temporal co-occurrence and partial spatial overlap of ictal HFOs and IBSs at seizure onset.[14] While the seizure onset was found to be best localized by the ictal HFOs, the IBSs seemed to provide a broader localization and the conventional frequencies were non-localizing.[14] This patient achieved a class II outcome over 3 years after multiple subpial transections that involved the broadband

EEG contacts.[14] Similarly, in a patient with right TLE analyzed with 0.016-600 Hz bandwidth EEG, the IBSs were found to precede the HFOs by 1.6 s and conventional EEG by 20.4 s, and the patient achieved seizure freedom after resection of the broadband EEG contacts.[52] In addition to these 2 case reports, in a series of 6 patients with neocortical epilepsy analyzed with 0.016-300 Hz bandwidth EEG, Modur *et al*., found that the seizure onset defined by CFA was delayed by <1 s compared to HFO+ (ictal HFOs with evolution, see above) or IBSs. Temporally, the HFO+ preceded or followed the IBSs by ~300-ms; spatially, the HFO+ and IBSs had similar distribution (18 vs. 15 contacts, $P = 0.09$) and concordance (Cohen k = 0.50).[53] Better seizure outcome tended to correlate with smaller spatial extent of HFO+, IBSs or CFA contacts and more complete resection of HFO+ or IBS contacts but the results were not statistically significant; interestingly, in one patient with class III outcome, prominent contralateral IBSs were seen.[53] In essence, these studies point to the utility of ictal HFOs and IBSs in defining a smaller SOZ and the potential for favorable seizure outcome after resecting that SOZ.

Conclusions

Recent research in patients undergoing pre-surgical evaluation has not only improved our understanding of the EEG activity outside the conventional frequency band but also raised important questions regarding the pathophysiology of seizure genesis and epileptogenicity. On the "high" end of the spectrum, interictal and ictal HFOs have been successfully recorded intracranially from all brain regions. Pathologic HFOs are considered to: Localize the SOZ; correlate with underlying epileptogenicity; play a potential role in seizure genesis; and serve as one of the biomarkers of epilepsy. On the "low" end of the spectrum, studies have sufficiently demonstrated the ability of routine AC amplifiers to record IBSs, which seem to have clinical utility in localizing the SOZ. Limited available evidence regarding analysis of ictal broadband EEG including HFOs, IBSs and CFA suggests that the seizure onset is best localized by the ictal HFOs while the IBSs tend to provide a broader localization and the conventional frequencies may be non-localizing. However, the important question of whether such an analysis impacts post-operative seizure outcome remains open and larger studies are needed to provide an answer. Interestingly, the coexistence of HFOs and IBS at seizure onset suggests both neuronal and glial contributions to seizure onset. In addition to the established neuron-centric view, this supports a prominent role for the astrocytes in epileptogenesis.[62] Assuming a complex interaction between the neurons and glia,[63] it is possible that there are as yet poorly understood mechanisms that give rise to the broadband EEG activity at seizure onset. In this context, it is important to evaluate all the EEG frequencies to improve our knowledge of such mechanisms underlying seizure genesis and epileptogenicity.

References

1. Rodin E, Constantino T, Rampp S, Modur P. Seizure onset determination. J Clin Neurophysiol 2009;26:1-12.
2. Jacobs J, Staba R, Asano E, Otsubo H, Wu JY, Zijlmans M, *et al*. High-frequency oscillations (HFOs) in clinical epilepsy. Prog Neurobiol 2012;98:302-15.
3. Rodin E, Funke M. Cerebral electromagnetic infraslow activity. J Clin Neurophysiol 2012;29:289-90.
4. Gotman J, Crone NE. High-frequency EEG activity. In: Schomer D, Lopes da Silva FH, editors. Niedermeyer's Electroencephalography: Basic Principles, Clinical Applications and Related Fields. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011. p. 749-66.
5. Buzsáki G, Horváth Z, Urioste R, Hetke J, Wise K. High-frequency network oscillation in the hippocampus. Science 1992;256:1025-7.
6. Bragin A, Engel J Jr, Wilson CL, Fried I, Buzsáki G. High-frequency oscillations in human brain. Hippocampus 1999;9:137-42.
7. Bragin A, Engel J Jr, Wilson CL, Fried I, Mathern GW. Hippocampal and entorhinal cortex high-frequency oscillations (100-500 Hz) in human epileptic brain and in kainic acid – Treated rats with chronic seizures. Epilepsia 1999;40:127-37.
8. Engel J Jr, Wilson C, Bragin A. Advances in understanding the process of epileptogenesis based on patient material: What can the patient tell us? Epilepsia 2003;44 Suppl 12:60-71.
9. Jirsch JD, Urrestarazu E, LeVan P, Olivier A, Dubeau F, Gotman J. High-frequency oscillations during human focal seizures. Brain 2006;129:1593-608.
10. Urrestarazu E, Chander R, Dubeau F, Gotman J. Interictal high-frequency oscillations (100-500 Hz) in the intracerebral EEG of epileptic patients. Brain 2007;130:2354-66.
11. Ochi A, Otsubo H, Donner EJ, Elliott I, Iwata R, Funaki T, *et al*. Dynamic changes of ictal high-frequency oscillations in neocortical epilepsy: Using multiple band frequency analysis. Epilepsia 2007;48:286-96.
12. Worrell GA, Gardner AB, Stead SM, Hu S, Goerss S, Cascino GJ, *et al*. High-frequency oscillations in human temporal lobe: Simultaneous microwire and clinical macroelectrode recordings. Brain 2008;131:928-37.
13. Khosravani H, Mehrotra N, Rigby M, Hader WJ, Pinnegar CR, Pillay N, *et al*. Spatial localization and time-dependant changes of electrographic high frequency oscillations in human temporal lobe epilepsy. Epilepsia 2009;50:605-16.
14. Modur PN, Scherg M. Intracranial broadband EEG analysis and surgical outcome: Case report. Clin Neurophysiol 2009;120:1220-4.
15. Crépon B, Navarro V, Hasboun D, Clemenceau S, Martinerie J, Baulac M, *et al*. Mapping interictal oscillations greater than 200 Hz recorded with intracranial macroelectrodes in human epilepsy. Brain 2010;133:33-45.
16. Wu JY, Sankar R, Lerner JT, Matsumoto JH, Vinters HV, Mathern GW. Removing interictal fast ripples on electrocorticography linked with seizure freedom in children. Neurology 2010;75:1686-94.
17. Zelmann R, Zijlmans M, Jacobs J, Châtillon CE, Gotman J. Improving the identification of high frequency oscillations. Clin Neurophysiol 2009;120:1457-64.
18. Jiruska P, Powell AD, Chang WC, Jefferys JG. Electrographic high-frequency activity and epilepsy. Epilepsy Res 2010;89:60-5.
19. Staba RJ, Wilson CL, Bragin A, Fried I, Engel J Jr. Quantitative analysis of high-frequency oscillations (80-500 Hz) recorded in human epileptic hippocampus and entorhinal cortex. J Neurophysiol 2002;88:1743-52.
20. Bragin A, Wilson CL, Staba RJ, Reddick M, Fried I, Engel J Jr. Interictal high-frequency oscillations (80-500 Hz) in the human epileptic brain: Entorhinal cortex. Ann Neurol 2002;52:407-15.
21. Bragin A, Mody I, Wilson CL, Engel J Jr. Local generation of fast ripples in epileptic brain. J Neurosci 2002;22:2012-21.
22. Jacobs J, LeVan P, Chander R, Hall J, Dubeau F, Gotman J. Interictal high-frequency oscillations (80-500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain. Epilepsia 2008;49:1893-907.
23. Fisher RS, Webber WR, Lesser RP, Arroyo S, Uematsu S. High-frequency EEG activity at the start of seizures. J Clin Neurophysiol 1992;9:441-8.
24. Allen PJ, Fish DR, Smith SJ. Very high-frequency rhythmic activity during SEEG suppression in frontal lobe epilepsy. Electroencephalogr Clin Neurophysiol 1992;82:155-9.

25. Alarcon G, Binnie CD, Elwes RD, Polkey CE. Power spectrum and intracranial EEG patterns at seizure onset in partial epilepsy. Electroencephalogr Clin Neurophysiol 1995;94:326-37.
26. Worrell GA, Parish L, Cranstoun SD, Jonas R, Baltuch G, Litt B. High-frequency oscillations and seizure generation in neocortical epilepsy. Brain 2004;127:1496-506.
27. Modur PN, Zhang S, Vitaz TW. Ictal high-frequency oscillations in neocortical epilepsy: Implications for seizure localization and surgical resection. Epilepsia 2011;52:1792-801.
28. Nariai H, Matsuzaki N, Juhász C, Nagasawa T, Sood S, Chugani HT, *et al*. Ictal high-frequency oscillations at 80-200 Hz coupled with delta phase in epileptic spasms. Epilepsia 2011;52:e130-4.
29. Usui N, Terada K, Baba K, Matsuda K, Nakamura F, Usui K, *et al*. Clinical significance of ictal high frequency oscillations in medial temporal lobe epilepsy. Clin Neurophysiol 2011;122:1693-700.
30. Staba RJ, Wilson CL, Bragin A, Jhung D, Fried I, Engel J Jr. High-frequency oscillations recorded in human medial temporal lobe during sleep. Ann Neurol 2004;56:108-15.
31. Staba RJ, Frighetto L, Behnke EJ, Mathern GW, Fields T, Bragin A, *et al*. Increased fast ripple to ripple ratios correlate with reduced hippocampal volumes and neuron loss in temporal lobe epilepsy patients. Epilepsia 2007;48:2130-8.
32. Bragin A, Wilson CL, Almajano J, Mody I, Engel J Jr. High-frequency oscillations after status epilepticus: Epileptogenesis and seizure genesis. Epilepsia 2004;45:1017-23.
33. Bragin A, Wilson CL, Engel J Jr. Voltage depth profiles of high-frequency oscillations after kainic acid-induced status epilepticus. Epilepsia 2007;48 Suppl 5:35-40.
34. Zijlmans M, Jacobs J, Kahn YU, Zelmann R, Dubeau F, Gotman J. Ictal and interictal high frequency oscillations in patients with focal epilepsy. Clin Neurophysiol 2011;122:664-71.
35. Engel J Jr, da Silva FL. High-frequency oscillations - Where we are and where we need to go. Prog Neurobiol 2012;98:316-8.
36. Andrade-Valença L, Mari F, Jacobs J, Zijlmans M, Olivier A, Gotman J, *et al*. Interictal high frequency oscillations (HFOs) in patients with focal epilepsy and normal MRI. Clin Neurophysiol 2012;123:100-5.
37. Jacobs J, Levan P, Châtillon CE, Olivier A, Dubeau F, Gotman J. High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type. Brain 2009;132:1022-37.
38. Zijlmans M, Jacobs J, Zelmann R, Dubeau F, Gotman J. High-frequency oscillations mirror disease activity in patients with epilepsy. Neurology 2009;72:979-86.
39. Jacobs J, Zijlmans M, Zelmann R, Chatillon CE, Hall J, Olivier A, *et al*. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. Ann Neurol 2010;67:209-20.
40. Haegelen C, Perucca P, Châtillon CE, Andrade-Valença L, Zelmann R, Jacobs J, *et al*. High-frequency oscillations, extent of surgical resection, and surgical outcome in drug-resistant focal epilepsy. Epilepsia 2013;54:848-57.
41. Akiyama T, McCoy B, Go CY, Ochi A, Elliott IM, Akiyama M, *et al*. Focal resection of fast ripples on extraoperative intracranial EEG improves seizure outcome in pediatric epilepsy. Epilepsia 2011;52:1802-11.
42. Park SC, Lee SK, Che H, Chung CK. Ictal high-gamma oscillation (60-99 Hz) in intracranial electroencephalography and postoperative seizure outcome in neocortical epilepsy. Clin Neurophysiol 2012;123:1100-10.
43. Fujiwara H, Greiner HM, Lee KH, Holland-Bouley KD, Seo JH, Arthur T, *et al*. Resection of ictal high-frequency oscillations leads to favorable surgical outcome in pediatric epilepsy. Epilepsia 2012;53:1607-17.
44. Nariai H, Nagasawa T, Juhász C, Sood S, Chugani HT, Asano E. Statistical mapping of ictal high-frequency oscillations in epileptic spasms. Epilepsia 2011;52:63-74.
45. Vanhatalo S, Voipio J, Kaila K. Infraslow EEG activity. In: Schomer DL, Lopes da Silva FH, editors. Niedermeyer's Electroencephalography: Basic Principles, Clinical Applications and Related Fields. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011. p. 741-8.
46. Speckmann EJ, Elger CE, Ulrich A. Neurophysiologic basis of the electroencephalogram. In: Wyllie E, editor. The Treatment of Epilepsy: Principles & Practice. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 127-39.
47. Gumnit RJ, Takahashi T. Changes in direct current activity during experimental focal seizures. Electroencephalogr Clin Neurophysiol 1965;19:63-74.
48. Ikeda A, Terada K, Mikuni N, Burgess RC, Comair Y, Taki W, *et al*. Subdural recording of ictal DC shifts in neocortical seizures in humans. Epilepsia 1996;37:662-74.
49. Ikeda A, Taki W, Kunieda T, Terada K, Mikuni N, Nagamine T, *et al*. Focal ictal direct current shifts in human epilepsy as studied by subdural and scalp recording. Brain 1999;122 :827-38.
50. Mader EC Jr, Fisch BJ, Carey ME, Villemarette-Pittman NR. Ictal onset slow potential shifts recorded with hippocampal depth electrodes. Neurol Clin Neurophysiol 2005;2005:4.
51. Rodin E, Modur P. Ictal intracranial infraslow EEG activity. Clin Neurophysiol 2008;119:2188-200.
52. Imamura H, Matsumoto R, Inouchi M, Matsuhashi M, Mikuni N, Takahashi R, *et al*. Ictal wideband ECoG: Direct comparison between ictal slow shifts and high frequency oscillations. Clin Neurophysiol 2011;122:1500-4.
53. Modur PN, Vitaz TW, Zhang S. Seizure localization using broadband EEG: Comparison of conventional frequency activity, high-frequency oscillations, and infraslow activity. J Clin Neurophysiol 2012;29:309-19.
54. Rampp S, Stefan H. Ictal onset baseline shifts and infraslow activity. J Clin Neurophysiol 2012;29:291-7.
55. Constantino T, Rodin E. Peri-ictal and interictal, intracranial infraslow activity. J Clin Neurophysiol 2012;29:298-308.
56. Vanhatalo S, Holmes MD, Tallgren P, Voipio J, Kaila K, Miller JW. Very slow EEG responses lateralize temporal lobe seizures: An evaluation of non-invasive DC-EEG. Neurology 2003;60:1098-104.
57. Miller JW, Kim W, Holmes MD, Vanhatalo S. Ictal localization by source analysis of infraslow activity in DC-coupled scalp EEG recordings. Neuroimage 2007;35:583-97.
58. Kim W, Miller JW, Ojemann JG, Miller KJ. Ictal localization by invasive recording of infraslow activity with DC-coupled amplifiers. J Clin Neurophysiol 2009;26:135-44.
59. Ikeda A, Luders HO, Shibasaki H. Neurophysiology of epileptic seizures: Ictal direct-current shifts. In: Luders HO, Noachtar S, editors. Epileptic Seizures: Pathophysiology and Clinical Semiology. Philadelphia: Churchill Livingstone; 2000. p. 53-62.
60. Vanhatalo S, Voipio J, Kaila K. Full-band EEG (FbEEG): An emerging standard in electroencephalography. Clin Neurophysiol 2005;116:1-8.
61. Bragin A, Wilson CL, Fields T, Fried I, Engel J Jr. Analysis of seizure onset on the basis of wideband EEG recordings. Epilepsia 2005;46 Suppl 5:59-63.
62. Tian GF, Azmi H, Takano T, Xu Q, Peng W, Lin J, *et al*. An astrocytic basis of epilepsy. Nat Med 2005;11:973-81.
63. Allen NJ, Barres BA. Neuroscience: Glia — more than just brain glue. Nature 2009;457:675-7.

How to cite this article: Modur PN. High frequency oscillations and infraslow activity in epilepsy. Ann Indian Acad Neurol 2014;17:99-106.
Received: 30-09-13, **Revised:** 02-10-13, **Accepted:** 02-10-13
Source of Support: Nil, **Conflict of Interest:** Nil