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Seizure Localization Using Broadband EEG: Comparison of Conventional Frequency Activity, High Frequency Oscillations and Infralow Activity

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Abstract

In neocortical epilepsy, we showed that the seizure onset defined by ictal high frequency oscillations (HFO: 70 Hz) with subsequent evolution into slower frequency activity (i.e., HFOs+) was smaller in spatial distribution than that defined by conventional frequency activity (CFA: 1–70 Hz), and that resection of HFO+ areas resulted in favorable seizure outcome (Modur et al., *Epilepsia* 2011; 52:1792–1801). This study further investigates ictal broadband EEG in the same cohort of patients by examining the infralow activity (ISA) including ictal baseline (“DC”) shifts (IBS) and peri-ictal infralow activity (PISA: 0.02–0.2 Hz). The seizure onset zone (SOZ) had been defined and resected based on HFO+ by a prospectively-defined protocol. We reviewed 11 representative seizures from 6 patients by visual and spectral analyses using appropriate filters and time scales. The HFO seizure onset, in the high gamma or ripple frequency, preceded or followed the IBS closely (<300-ms). The IBS were negative or positive, ~1 mV in amplitude and 2–3 s long. While the HFO+ were always ipsilateral to the surgical hemisphere, the IBS could be ipsilateral or contralateral. Compared to CFA, the HFO+ and IBS were significantly smaller in spatial distribution and likely to be concordant. The PISA consisted of distinct periodic or rhythmic (0.12–0.16 Hz) patterns, poorly concordant with IBS or HFO+. Although not statistically significant, better seizure outcome tended to correlate with smaller SOZs and more complete resection of the HFO+ and IBS contacts. We conclude that IBS, like HFO+, define a smaller SOZ and probably a more accurate epileptogenic zone in neocortical epilepsy.

Keywords

Seizure; Epilepsy; Surgery; Intracranial; High frequency oscillations; HFO; Infralow; DC shift; Broadband; EEG

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None of the authors has any conflicts of interest to disclose.

INTRODUCTION

There has been considerable interest in the analysis of intracranial EEG activity outside the conventional frequency bands, particularly with respect to determination of seizure onset (Rodin et al., 2009). Many studies have investigated the value of high frequency oscillations (HFO) as a new measure for localizing seizure onset and determining epileptogenicity. Although many of these studies have focused on interictal HFO, a few studies have addressed the utility of *ictal*/HFO in seizure onset localization (Worrell et al., 2004; Ochi et al., 2007; Modur and Scherg, 2009). More recently, in a series of six patients with neocortical epilepsy, we demonstrated that the ictal HFO localized the seizure onset zone (SOZ) to a significantly smaller area compared to the conventional frequency activity (CFA), and that surgical resection based on such a prospectively-defined localization could result in favorable seizure outcome (Modur et al., 2011). In contrast to the HFO, the infraslow activity (ISA) and ictal baseline shifts (IBS), also referred to as DC shifts, have not received much attention in clinical practice. Some of this could be attributed to the widely-held misconception that dedicated DC amplifiers are needed to assess ISA (Rodin et al., 2009). Over the last couple of decades, several groups of investigators have demonstrated the occurrence of ISA and DC shifts at seizure onset in human intracranial recordings using both AC and DC amplifiers (Ikeda et al., 1996; Ikeda et al., 1999; Mader et al., 2005; Rodin and Modur, 2008; Kim et al., 2009; Modur and Scherg, 2009; Imamura et al., 2011). These studies have shown some correlation between ISA with CFA in a series of patients (Kim et al., 2009) as well as between ISA and HFO in a couple of isolated cases (Modur and Scherg, 2009; Imamura et al., 2011). In nonlesional frontal lobe epilepsy, we demonstrated the utility of intracranial broadband EEG analysis in determining the SOZ in a patient who subsequently underwent multiple subpial transections without cortical resection (Modur and Scherg, 2009). In this patient who enjoyed a class II outcome over a period of 3.5 years, we found that both ictal HFO and IBS defined a significantly smaller SOZ compared to the CFA, the IBS could occur in the same or neighboring electrodes as the HFO, and the transected gyri contained all of the HFO and most of the IBS contacts (Modur and Scherg, 2009). These encouraging results prompted us to undertake the current study in which we aimed to extend our previous observations in a larger group of patients. Our objectives were to evaluate the morphological characteristics of ictal broadband EEG activity, to compare the spatial distributions of the different types of activity, and to investigate the association between resection of different types of activity and postoperative seizure outcome.

METHODS

Patient population

Since we recently reported our findings related to ictal HFO and CFA in a well-characterized group of patients with neocortical epilepsy (Modur et al., 2011), we selected the same cohort of patients for the purposes of the current study to extend our investigation of the ISA. Thus, our patient population consisted of 6 patients with neocortical epilepsy who had undergone intracranial monitoring followed by resective surgery at the University of Louisville Comprehensive Epilepsy Center. Informed consent was obtained from all the patients. The patients were personally followed by the authors, the EEGs were interpreted by the same epileptologist (PNM) and the resections were performed by the same surgeon (TWV). The patients had been included in the original study based on well-defined, unifocal intracranial seizure onsets characterized by discrete HFO (> 70 Hz activity). None of the patients had multifocal or bilateral independent seizure onsets. There were 3 females and 3 males, aged 19–32 years (Table 1). Two patients had heterotopia while the other 4 were nonlesional. Seizure onsets were lobar (frontal or temporal) or multilobar (parieto-occipital, parieto-temporal or temporo-occipital). Surgical resections were performed per protocol (see

below) with the following exceptions: 1) in patients A and D, the SOZ could not be completely resected due to overlap with speech area; 2) in patient B, additional resection of the medial temporal structures was performed although the seizure originated in the temporal neocortex; 3) small areas of heterotopia in patients C and E, in the occipital and anterior temporal regions respectively, were not resected. Histology was abnormal in all patients. The postoperative seizure outcome was Engel class I or II in 5/6 patients, and class III in the other over a mean follow-up period of 27 months (range 20–38 months).

Intracranial recordings

The EEGs were acquired on a 128-channel NK 1100 system (Nihon-Kohden America, Foothill Ranch, CA, USA), with 1,000 Hz sampling rate, 2 or 8 second time constant and 200 M Ω input impedance. All patients had implantation of subdural grids and strips (contact diameter 2.3 mm, inter-contact distance 10 mm); in some patients, additional intracerebral depth electrodes (4–8 contacts per electrode, contact diameter 1.1 mm, inter-contact distance 10 mm) were implanted as well. The electrodes were made of platinum, had the same characteristics across all patients, and obtained from the same manufacturer (Ad-Tech Medical, Racine, WI, USA). We performed extensive implantation ipsilateral to the suspected seizure onset hemisphere, as determined from the non-invasive studies. When lateralization was doubtful, we implanted limited additional subdural strips over the contralateral hemisphere to rule out seizure onset from that side.

Presurgical determination of seizure onset and resection boundary

As described elsewhere (Modur et al., 2011), we determined the seizure onset based on both CFA and HFO but performed the surgical resection based on the SOZ defined by HFO using a prospectively-defined protocol. Briefly, the CFA seizure onset was defined by the channels showing the earliest occurrence of discrete <70 Hz rhythmic activity using a bipolar montage, 1.6–70 Hz bandpass filter and 10-second/page time scale. The HFO seizure onset was tentatively defined by the earliest occurrence of distinct fast rhythmic discrete oscillations around the time of occurrence of conventional seizure onset using a bipolar montage, 53–300 Hz bandpass filter and 2-second/page time scale. We then localized the definitive SOZ to those channels with HFO that showed subsequent evolution (HFO+) as opposed to those that did not (HFO–). In essence, the SOZ comprised of the HFO+ channels satisfying the following criteria: 1) presence of >70 Hz activity at seizure onset followed by sustained evolution into slower frequency activity in the same channels with seizure progression; and 2) continued presence of either HFO or slower frequencies at the time of occurrence of the first behavioral change in the channels that showed the initial HFO. The time of HFO occurrence defined the temporal seizure onset while the HFO+ channels themselves defined the spatial extent of the SOZ; the HFO– channels were *not* considered part of the SOZ. If a given channel was designated as HFOs+ in one seizure and HFOs– in another seizure in the same patient, then that channel's final designation was HFOs+. The final SOZ for each patient was defined by the combination of the HFOs+ channels from all the seizures. Based on our protocol, our goal was to resect the contiguous region consisting of the SOZ, 1 cm of the cortex surrounding the SOZ and the immediate spread area (defined by the channels involved during the first 2 seconds after onset). The resection boundaries were modified, if necessary, by the presence of eloquent cortex in the vicinity as determined by functional stimulation. We evaluated the interictal data, and marked the contacts with interictal HFO but did not resect them unless they overlapped with the previously defined surgical boundary. The resection margins were confirmed before and after surgery, and any modifications to the planned resection were noted.

Post-hoc EEG analysis

For the current study, we sought to analyze and quantify the EEG activity objectively as follows. We reviewed the EEG recordings with the BESA software version 5.3 (MEGIS Software GmbH, Graefelfing, Germany). Our post-hoc analysis was essentially similar to our presurgical protocol of determining the seizure onset except for a few variations as noted below. We reviewed all the recordings in a referential montage using an average reference which excluded the contacts with persistent artifacts. In our experience, an average reference is less susceptible to the effects of a single bad contact and tends to be particularly useful for evaluating long periods of the EEG. Furthermore, it is simpler to use an average montage as opposed to a bipolar montage to evaluate the onset and polarity of IBS.

We marked the CFA seizure onset using 1–70 Hz bandpass filter and 10-second/page time scale and defined the extent of the SOZ by all the contacts involved within 2 seconds of seizure onset. Fig. 1 shows an example of CFA seizure onset defined in terms of beta activity.

We searched for the ictal HFO visually using 50–333 Hz bandpass filter and 2-second/page time scale (2,000 samples). Once found, we marked a 2-second window at the onset of the earliest HFO. Within this 2-second window, we placed a single 852-ms epoch such that it contained most of the contacts exhibiting HFO. We calculated the fast Fourier transform (FFT)-derived power spectra over this epoch for the 50–333 Hz range at 0.98 Hz resolution. Based on the power spectra, we classified a given contact definitively as an HFO contact if its peak frequency was ≥ 70 Hz or its total power in the 50–333 Hz band was greater than the median power of all the contacts in that band. The process of defining the HFO seizure onset is illustrated in Fig. 2 with the selected epoch for FFT on the left and the corresponding power spectra on the right. Among the definitive HFO contacts, we identified the HFO+ and HFO– contacts based on the presence or lack of evolution of EEG activity respectively as described above. This is illustrated in Fig. 3 which shows all the HFO contacts with the HFO+ contacts highlighted.

For evaluating the ISA, we downsampled the original EEG data at 60 Hz in order to display the EEG recordings at 20-minute/page time scale as constrained by the software. Based on our experience and that of others (Kim et al., 2009; Modur and Scherg, 2009), we defined IBS as baseline deflections of ≥ 0.5 mV peak-to-peak amplitude and ≥ 0.5 -second duration occurring in close temporal relation to the HFO seizure onset. We defined peri-ictal ISA (PISA) as any kind of ISA, distinct from the baseline, occurring in the preictal (10 minutes prior to seizure onset) or postictal (10 minutes after seizure end) periods. Using 0.02–20 Hz bandpass filter and 30-s/page time scale, we defined the IBS seizure onset visually by identifying the IBS contacts satisfying the above criteria (Fig. 4). Using slightly different settings of 0.02–0.2 Hz bandpass filter and 10-minute/page time scale, we defined the PISA by visual inspection in both the preictal (Fig. 5) and postictal (Fig. 6) periods.

Statistical analysis

We performed analysis for the whole group and for each individual patient. After logarithmic transformation of the measurements to adjust for the skewness in the data, we used a linear mixed model with random effects and the type of HFO as an indicator effect to assess the frequency and power differences between the HFO+ and HFO– contacts. We compared the amplitude and duration of the IBS with respect to its polarity using a linear mixed model that included random effects with a nested structure to account for the correlation among the multiple contacts during multiple seizures from the same patient. We compared the spatial distribution of HFO+ versus HFO– channels using chi-square or Fisher's exact test. We used McNemar's test to compare the spatial distribution of the SOZs

defined by the HFO, IBS and CFA. We evaluated the concordance (i.e., agreement) between the SOZs defined by the different types of activity using Cohen's kappa scores. In general, when two types of activity occurred in the same contact, they were considered to be concordant. However, when comparing HFO+ and IBS, the two were also considered concordant if the IBS occurred in the same or neighboring contact as the HFO based on prior observations (Mader et al., 2005; Kim et al., 2009; Modur and Scherg, 2009). We calculated the Spearman's rank correlation coefficient to evaluate the association between surgical outcome and the extent of resection of contacts with different types of activity. Statistical significance was declared for a p-value <0.05. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC) and GraphPad Prism 5 (GraphPad Software, La Jolla, CA).

RESULTS

Among the 6 patients, we analyzed 2 representative seizures from each except patient B who had only one seizure despite prolonged monitoring (Table 2). Thus, there were 11 seizures (4 complex partial and 7 secondary generalized tonic-clonic seizures). The number of implanted contacts per patient ranged from 88 to 126. Four patients had a limited number of subdural strips implanted contralateral to the suspected seizure onset side. In addition to the subdural electrodes, intracerebral depth electrodes were implanted in 3 patients.

Morphological characteristics

The CFA seizure onset was <40 Hz, in the beta or low gamma range. The HFO were seen in all the seizures. While HFO+ always occurred ipsilateral to the surgical hemisphere, HFO- occurred contralaterally in 2 patients, A and E (Table 2). The peak frequencies of ictal HFO were in the range of high gamma or ripple oscillations. Compared to the peak frequency of HFO- [mean 71.3 Hz, 95% confidence interval (CI) 61–81 Hz], the peak frequency of HFO+ (mean 60.1 Hz, 95% CI 50–70 Hz) was lower ($p < 0.0001$). In contrast, the peak power of HFO+ was about 2-fold higher than that of HFO- ($p < 0.0001$).

The IBS occurred in all the seizures. They were seen contralateral to the surgical hemisphere in 2 patients, A and D, involving up to 11 contralateral contacts in patient A (Table 2). They were negative or positive in polarity in 7 ± 1 and 9 ± 1 contacts respectively ($p = 0.23$). The amplitudes of the baseline shifts were variable above the 0.5 mV cutoff, reaching a maximum of 3.34 mV. However, there was no difference in the amplitudes between negative and positive IBS (0.98 ± 0.11 mV vs. 1.03 ± 0.10 mV, $p = 0.52$). The duration of the baseline shifts were also variable above the 0.5-s cutoff, reaching a maximum duration of 15.8-s. The negative IBS were longer than positive shifts (2.9 ± 0.4 s vs. 1.9 ± 0.4 s, $p = 0.002$). Distinct PISA patterns were seen both preictally and postictally. They consisted of either periodic transients or rhythmic, usually 0.12–0.16 Hz, oscillations.

Temporal relationship and spatial distribution

The CFA seizure onset was generally delayed by <1-s compared to HFO or IBS seizure onsets (Table 2). The HFO seizure onset preceded or followed the IBS seizure onset by <300-ms except in one seizure (patient B) where the HFO onset preceded the IBS onset by 2.5-s. Large baseline shifts were often seen in the middle of ongoing seizures (several seconds after the HFO seizure onset) and at the termination of the seizures; however, such shifts were not considered IBS for the purposes of this study. The PISA patterns occurred intermittently or continuously, and lasted up to 10 minutes preictally or postictally. Presence of such activity beyond 10 minutes could not be assessed due to lack of archived data.

Group level analysis showed that both CFA and HFO occurred in a widespread manner at seizure onset, involving an average of 45 ± 6 and 53 ± 4 contacts respectively. In contrast, the spatial distribution of IBS was much smaller, involving only 15 ± 2 contacts. Although the distribution of HFO as a whole was widespread, HFO+ occurred in a much smaller distribution than HFO- [18 ± 2 vs. 35 ± 4 contacts, odds ratio (OR) 0.41, 95% CI 0.34–0.50, $p < 0.0001$]. Of note, the spatial extents of HFO+ and IBS were similar not only at the group level ($p = 0.09$) but also for each patient. Furthermore, HFO+ and IBS were most concordant in distribution ($\kappa = 0.50$). The concordance between HFO+ and CFA was somewhat less ($\kappa = 0.36$) whereas IBS and CFA were poorly concordant ($\kappa = 0.16$). The concordance between IBS and preictal or postictal ISA was generally poor as well.

Association between seizure outcome and surgical resection

As reported before (Modur et al., 2011), the HFO+ contacts were nearly 10-fold more likely to have been resected than the HFO- contacts in these patients, consistent with our presurgical protocol of restricting the surgical resections mainly to the HFO+ contacts. However, there were two exceptions: patients A and D underwent only partial resection of the HFO+ contacts in the left frontal lobe because of overlap with the Broca's area. Overall, seizure outcome was class I or II in 5 patients (83%), and class III in one (patient A). To extend our prior observations, we investigated the association between postoperative seizure outcome and the amount of resected tissue containing the different types of activity (Table 3). We found that better seizure outcome tended to correlate with smaller spatial extents of the SOZs defined by the HFO+ and IBS contacts individually or concordantly (Spearman's $\rho = 0.31$, $p = 0.56$). Furthermore, better seizure outcome also tended to correlate with more complete resection of the SOZs defined by HFO+ ($\rho = -0.31$, $p = 0.56$) and IBS contacts ($\rho = -0.47$, $p = 0.36$) individually or concordantly ($\rho = -0.31$, $p = 0.56$). We were unable to assess the association between outcome and removal of both HFO+ and IBS contacts since our presurgical protocol did not specify inclusion of the latter as part of the resection. While better seizure outcome tended to correlate with a smaller spatial extent of the SOZ defined by CFA ($\rho = 0.46$, $p = 0.36$), it did not correlate with a more complete resection of the CFA contacts ($\rho = 0.28$, $p = 0.56$). We caution that the above findings related to outcome and resection should not be considered definitive because of the small number of patients and lack of statistical significance.

DISCUSSION

In this study, we compared the characteristics of ictal CFA, HFO and IBS, and investigated the association between their resection and seizure outcome in a well-characterized, previously-reported group of 6 patients with neocortical epilepsy. All the patients had extensive (often bilateral) subdural and intracerebral depth electrode implantations, and underwent resection after their SOZs were localized based on HFO with evolution (i.e., HFO+) by a prospectively-defined presurgical protocol as described in detail elsewhere (Modur et al., 2011). Our main findings were: 1) the HFO seizure onset preceded or followed the IBS but the two occurred in close temporal relation to each other (usually < 300 -ms); 2) the ictal HFO occurred consistently in the frequency range of high gamma or ripple oscillations, with the HFO+ being always ipsilateral to the surgical hemisphere and more robust than the HFO-; 3) the IBS occurred consistently either ipsilateral or contralateral to the surgical hemisphere, manifesting as large-amplitude (~ 1 mV), long-duration (2–3 s), negative or positive baseline deflections at seizure onset; 4) the ictal HFO+ and IBS had significantly smaller spatial extents than CFA and were more likely to occur in the same or neighboring contacts; and 5) despite the lack of statistical significance, better seizure outcome tended to correlate with smaller spatial extents of the SOZ regardless of the type of electrical activity as well as a more complete resection of the individual or

concordant HFO+ and IBS contacts. The clinical implications of these findings are discussed below.

Identification of ictal broadband EEG activity

Besides the expected presence of CFA and ictal HFO, our study demonstrates the presence of IBS at the onset of neocortical seizures in intracranial recordings obtained from commercially-available AC amplifiers and platinum intracranial electrodes. This is in line with previous observations made by us (Rodin and Modur, 2008; Modur and Scherg, 2009) and others (Ikeda et al., 1996; Ikeda et al., 1999; Mader et al., 2005; Imamura et al., 2011). We re-demonstrate that the IBS, which are the equivalent of true DC shifts, can be recorded using AC amplifiers without the need for dedicated DC-coupled amplifiers as reported by other investigators (Kim et al., 2009).

We found the ictal HFO to be in the high gamma or ripple frequency range, with the HFO+ being ipsilateral to the surgical hemisphere, more robust, and of lower mean frequency than HFO-. The latter finding could be attributed to methodological differences (particularly, the longer FFT epochs and inclusion of contacts with higher power in the HFO band) in the of post-hoc definition of HFO in this study compared to the previous study (Modur et al., 2011).

The IBS could be negative or positive in polarity, with mean amplitude around 1 mV (maximum >3 mV), and the mean duration around 2–3 s (maximum 16-s, slightly longer for negative shifts). The above findings are generally consistent with our observations and that of others indicating that IBS precede, coincide with or follow ictal HFO (Ikeda et al., 1996; Ikeda et al., 1999; Modur and Scherg, 2009; Imamura et al., 2011). One notable exception was that the amplitudes of IBS observed in our study were significantly smaller than those recorded from DC-coupled amplifiers (Kim et al., 2009), suggesting that dedicated amplifiers may be superior in that regard.

Seizure localization based on broadband EEG activity

Temporally, the CFA seizure onsets were found to be delayed by <1-s compared to the HFO or IBS seizure onsets. Although we specified the close temporal proximity of IBS to HFO as a criterion for its definition, the easily discernible IBS were actually noted to precede or follow the HFO by <300-ms interval in most seizures except in one patient where the IBS occurred about 2.5-s after the HFO onset. While the findings in our study regarding the temporal relationship between CFA and HFO on one hand and the IBS on the other are mostly consistent with earlier studies (Ikeda et al., 1999; Modur and Scherg, 2009; Imamura et al., 2011), they differ from one study which reported that the DC shifts could occur up to 493-s (i.e., >8 minutes) after seizure onset (Kim et al., 2009). We found evidence similar to the latter in many seizures in our study where large baseline shifts occurred several seconds after clinical seizure onset and particularly towards the end of clinical seizures. We did not label such baseline shifts occurring remote from the time of seizure onset as IBS for the purposes of this study. Of note, none of the seizures we analyzed lasted longer than 3 minutes. Besides the IBS, we also found distinct PISA patterns that lasted up to 10 minutes before seizure onset and 10 minutes after seizure end. These patterns consisted of periodic transients or rhythmic oscillations, usually around 0.12–0.16 Hz. The observed peri-ictal rhythmic infraslow oscillations resemble those described by us (Rodin and Modur, 2008) and others (Ren et al., 2011), and most likely represent ongoing fluctuations in the background ISA which may undergo sudden changes at seizure onset and seizure end to cause large baseline deflections characteristic of IBS (or DC shifts). In conjunction with the published studies, our observations raise important questions as to what constitutes IBS and how they should be defined. Widely accepted definitions of IBS and ISA should serve to

streamline further research into our understanding of their mechanism of generation and role in seizure onset.

Consistent with our prior study (Modur et al., 2011), both CFA and HFO were noted to occur in a widespread manner at seizure onset. In contrast, the HFO+ and IBS had significantly smaller spatial extents than CFA. Furthermore, HFO+ and IBS were highly likely to be concordant with each other, i.e., they tended to occur in the same or neighboring contacts. Such higher degree of concordance, not seen between HFO+ and CFA or between IBS and CFA, is not surprising given the large spatial extent of CFA. However, the poor concordance between IBS and PISA was rather unexpected and needs further investigation. To our knowledge, the above findings supporting an intricate spatial relationship between HFO+ and IBS have not been described before. Consistent with our prior observation that HFO+ localize the seizure onset to a smaller restricted area compared to the CFA (Modur et al., 2011), it is evident that IBS can provide a similar restricted seizure localization as well. Our results are also in agreement with prior studies suggesting a smaller SOZ defined by the IBS or DC shifts (Ikeda et al., 1999; Kim et al., 2009; Modur and Scherg, 2009; Imamura et al., 2011).

Surgical resection based on broadband EEG activity

Based on our prospectively-defined protocol of restricting the resection to HFO+ contacts, the overall seizure outcome was favorable (class I or II) in 5 patients (83%), and poor (class III) in one (Modur et al., 2011). Further analysis revealed that better seizure outcome tended to correlate with smaller spatial extents and more complete resection of the SOZs defined by the HFO+ and IBS contacts individually or concordantly. Interestingly, in patient B the spatial extents of the SOZ defined by HFO+ and IBS were extremely small (2–3%), and all of the SOZ (100%) was resected. Yet, there was no completely seizure free outcome as one would expect from the foregoing discussion. This is probably due to inadequate definition of the SOZ despite extensive coverage (for e.g., seizure onset in deep sulci) which may have been well compensated by a larger resection containing most of the epileptogenic zone to account for the rather favorable class II outcome. While better seizure outcome tended to correlate with a smaller spatial extent of the SOZ defined by CFA, it did not correlate with a more complete resection of the CFA contacts. This finding of poor outcome with more complete resection of CFA contacts seems paradoxical, and is probably due to the significantly larger spatial extent of CFA resulting in a greater likelihood of CFA contacts being resected in both good and poor outcome patients. Although none of these results were statistically significant, they support the notion that a composite of the SOZs defined by HFO+ and IBS provides a better approximation of the epileptogenic zone than the individual or overlapping SOZs defined by them. We were unable to directly assess the association between outcome and removal of both HFO+ and IBS contacts since our protocol did not specify inclusion of the latter as part of the resection. However, other studies have shown favorable outcome when IBS (or DC shift) contacts had been included in the resection (Ikeda et al., 1999; Kim et al., 2009). In essence, we believe that it is clinically meaningful to define the SOZs based on not only HFO+ (Modur et al., 2011) but also IBS since both seem to provide spatially restricted and reasonably concordant SOZs that would be feasible surgical targets in neocortical epilepsy. While the HFO+ and the majority of IBS were ipsilateral to the surgical hemisphere, some IBS were noted to occur contralaterally. This finding has not been described before, and it may also be clinically relevant since the one patient with class III outcome in our series had several contralateral contacts with IBS.

The exact mechanisms underlying the generation of HFO and IBS, and their relationship to seizure genesis remain unclear. Proposed mechanisms of generation of the HFO include synchronization of inhibitory postsynaptic potentials, hypersynchronous bursting of action potentials from small clusters of pathologically connected neurons, sustained inhibition of

principal neurons followed by excitation mediated by local increase in extracellular potassium and excess neuronal activity mediated by gap junctions (Ylinen et al., 1995; Bragin et al., 2000; Gnatkovsky et al., 2008; Traub et al., 2010). Similarly, the origin of DC shifts is also felt to be related to multiple mechanisms including neuronal activity, glial activity, neuron-glia interaction and blood-brain barrier alteration (Ikeda et al., 2000; Vanhatalo et al., 2003; Voipio et al., 2003). Emerging evidence suggests a prominent role for the astrocytes in epileptogenesis, complementing the long held neuron-centric view (Tian et al., 2005). Based on the complex interplay between the neurons and glia (Allen and Barres, 2009), we speculate that common, as yet poorly understood, unifying mechanisms underlie seizure genesis and propagation. Careful examination of the broadband EEG in epilepsy surgery patients is a valuable tool in improving our knowledge of such mechanisms.

Limitations of our study include the small sample size which precludes definitive conclusions regarding seizure outcome based on broadband EEG analysis. The results cannot be directly applied to seizures of mesial temporal onset since such patients were not included. We did not correlate the ictal findings with interictal data in the study although the latter were partially considered in presurgical planning. Nevertheless, our study describes a method to record, identify and analyze ictal broadband EEG activity using equipment that is readily available in most centers. Furthermore, our study demonstrates the utility of HFO+ and IBS in defining a restricted SOZ and the potential for favorable outcome by resecting that SOZ. Future studies should address the pathophysiologic basis and the inter-relationship among the different types of broadband EEG activity, and prospectively examine their value as predictors of seizure outcome in larger cohorts.

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Fig. 1.

Localization of seizure onset based on conventional frequency activity (CFA). Subdural contacts involved in a secondary generalized tonic-clonic seizure (seizure F2) are displayed at 1–70 Hz filter and 10-s/page time scale. The occurrence of readily identifiable rhythmic activity indicating seizure spread is shown (RSSA). Reviewing backwards from this point reveals the CFA seizure onset occurring a few seconds earlier, consisting of beta activity in the top contacts and a sharp transient followed by low gamma activity in the bottom contacts (corresponding to the solid gray line). Onset of high frequency oscillations preceding the CFA is shown (H). Earliest clinical change occurred much later (not shown). Interval between dotted vertical lines is 1-s.

Fig. 2. Identification of high frequency oscillations (HFO). Selected subdural contacts of seizure F2 (same as Fig. 1), are displayed at 50–300 Hz filter. Onset of HFO (H) and ictal baseline shifts (S) are marked. An 852-ms epoch is placed at HFO onset (corresponds to the solid gray line). The fast Fourier transform-derived power spectra over this epoch (>70 Hz in gray, <70 Hz in black), the peak frequencies (Hz) and peak power (μV^2) are shown at the right side of the figure. All the depicted contacts are ictal HFO contacts because either the peak frequency was >70 Hz or the total power in the 50–300 Hz band power was $>$ median power. The block E1 enclosed by the square brackets is 200-ms long.

Fig. 3.

Seizure localization based on high frequency oscillations (HFO). Selected subdural contacts of seizure F2 (same as Fig. 1), are displayed at 50–300 Hz filter. Onset of HFO (H) and ictal baseline shifts (S) are marked. All the depicted contacts are ictal HFO contacts. The highlighted contacts evolve into slower frequency activity subsequently (HFO+) but the others do not (HFO–). The definitive HFO seizure onset is defined by the HFO+ contacts. The block E1 enclosed by the square brackets is 200-ms long.

Fig. 4. Seizure localization based on ictal baseline shifts (IBS). Subdural contacts involved in a secondary generalized tonic-clonic seizure (seizure F1) are displayed. At conventional low frequency filter of 1 Hz (panel A), no IBS are seen. After opening the low frequency filter to 0.02 Hz (panel B), IBS are clearly seen in the top five contacts. High frequency oscillations (H) precede the IBS by about 285-ms at seizure onset. Onset of earliest clinical change consisting of repetitive eye blinks is shown (cc). Interval between dotted vertical lines is 1-s.

Fig. 5. Preictal infraslow activity. Subdural contacts involved in a secondary generalized tonic-clonic seizure (seizure E2) are displayed: In panel A, the rhythmic and periodic preictal ISA are clearly seen (highlighted) at 0.02–0.2 Hz filter and 10-min/page time scale settings, preceding the seizure onset defined by high frequency oscillations (H) by several minutes. In panel B, a 10-s epoch of panel A (corresponding to the short horizontal line below the 'Marker' in panel A) is shown at conventional 1–70 Hz filter and 10-s/page time scale. Note that at conventional settings, the ISA appears as indistinct irregular slow activity. Interval between vertical lines is 10-s (panel A) and 1-s (panel B).

Fig. 6. Postictal infraslow activity. Subdural contacts involved in a secondary generalized tonic-clonic seizure (seizure E2, same as Fig. 5) are displayed: In panel A, the rhythmic postictal ISA are clearly seen (highlighted) at 0.02–0.2 Hz filter and 10-min/page time scale settings, appearing a few minutes after the seizure ends (e) and continuing for several minutes thereafter until the file ends. In panel B, a 10-s epoch of panel A (corresponding to the short horizontal line below the 'Marker' in panel A) is shown at conventional 1–70 Hz filter and 10-s/page time scale. Note that at conventional settings, the ISA appears as bursts of irregular slow activity. Interval between vertical lines is 10-s (panel A) and 1-s (panel B).

Table 1

Patient characteristics *

Patient	Age/Sex	MRI	Seizure onset	Pathology	Follow-up (months)	Engel outcome class
A	32/M	Normal	Left frontal	Gliosis, heterotopic neurons	38	III
B	26/F	Normal	Right inferior and lateral temporal	Focal dysgenesis	30	II
C	19/F	Right parietal focal cortical dysplasia and nodular heterotopia	Right parieto-occipital	Gliosis, focal dysgenesis, subcortical heterotopia	25	I
D	20/M	Normal	Left frontal	Gliosis, heterotopic neurons	24	II
E	24/F	Right parieto-temporal nodular heterotopia	Right parieto-temporal	Gliosis, subcortical heterotopia	22	I
F	19/M	Normal	Right posterior temporal-occipital	Gliosis, heterotopic neurons	20	I

* Modified from Modur et al., *Epilepsia* 2011; 52:1792–1801

Table 2

Intracranial seizure data

Patient/ Seizure	Seizure type	No. of contacts monitored	No. of HFO+ contacts		No. of HFO- contacts		No. of IBS contacts		No. of CFA contacts		Time difference between seizure onsets* (s)	
			Ipsi / Contra	Ipsi / Contra	Ipsi / Contra	Ipsi / Contra	Ipsi / Contra	Ipsi / Contra	Ipsi / Contra	Ipsi / Contra		
A/1	CPS	72 / 26	24 / 0	24 / 8	21 / 10	41 / 0	0	<-1				
A/2	CPS	72 / 26	29 / 0	39 / 17	25 / 11	56 / 3	0	<-1				
B/1	GTCS	110 / 14	4 / 0	20 / 0	3 / 0	12 / 0	-2.5	0				
C/1	CPS	96 / 0	19 / 0	36 / 0	20 / 0	37 / 0	+0.10	0				
C/2	GTCS	96 / 0	18 / 0	28 / 0	16 / 0	58 / 0	+0.25	0				
D/1	GTCS	110 / 15	23 / 0	26 / 0	18 / 1	69 / 0	0	<-1				
D/2	GTCS	110 / 15	16 / 0	32 / 0	20 / 1	70 / 1	0	<-1				
E/1	CPS	100 / 16	16 / 0	45 / 4	9 / 0	44 / 0	0	0				
E/2	GTCS	100 / 16	18 / 0	41 / 2	14 / 0	40 / 0	0	<-1				
F/1	GTCS	126 / 0	13 / 0	63 / 0	11 / 0	20 / 0	-0.29	<-1				
F/2	GTCS	126 / 0	12 / 0	31 / 0	8 / 0	42 / 0	-0.28	<-1				

The contacts are ipsilateral (Ipsi) or contralateral (Contra) to the surgical hemisphere.

* HFO seizure onset occurs before (-) or after (+) the other activity.

HFO, high frequency oscillations; HFO+, high frequency oscillations with evolution; HFO-, high frequency oscillations without evolution; IBS, ictal baseline shifts; CFA, conventional frequency activity; CPS, complex partial seizure; GTCS, secondary generalized tonic-clonic seizure.

Table 3

Intracranial coverage and resection of contacts containing broadband EEG activity

Patient	Intracranial recording sites and no. of contacts on each side		Total no. of contacts, N	HFO+ contacts, %		IBS contacts, %		Concordant HFO+ and IBS contacts, %		CFA contacts, %	
	Left hemisphere (N)	Right hemisphere (N)		Implanted / Resected [§]	Extent / Resected [§]	Implanted / Resected [§]	Extent / Resected [§]	Implanted / Resected [§]	Extent / Resected [§]	Implanted / Resected [§]	Extent / Resected [§]
A	F-P convexity, PF, MF, LT (72)	MF*, LF* (26)	88 / 17		42 / 38		35 / 16		28 / 44		68 / 28
B	MF*, LF* (14)	F-P convexity, OF, MF, LT, MT, ST, insula (110)	124 / 15		3 / 100		2 / 100		3 / 100		10 / 83
C	None (0)	P-O convexity, LT, ST, MO (96)	96 / 30		28 / 41		28 / 59		19 / 50		66 / 25
D	F-P convexity, PF, MF, LT (110)	MF*, LF* (15)	125 / 25		22 / 50		20 / 44		15 / 68		66 / 25
E	LF* (16)	F-P convexity, PF, LT, ST, MT (100)	116 / 31		21 / 71		16 / 67		10 / 92		43 / 52
F	None (0)	F-P convexity, LT, ST, LP, LO, MO (126)	126 / 29		14 / 78		12 / 67		13 / 81		40 / 24
					r = 0.31 / -0.31		r = 0.31 / -0.47		r = 0.31 / -0.31		r = 0.46 / 0.28
					p = 0.56 / 0.56		p = 0.56 / 0.36		p = 0.56 / 0.56		p = 0.36 / 0.56

* Limited coverage to rule out seizure onset from those areas.

[§] Extent refers to the % of contacts defining the seizure onset zone compared to the total number of implanted contacts; Resected refers to the % of contacts removed compared to the seizure onset zone.

r, Spearman's rank correlation coefficient

HFO+, high frequency oscillations with evolution; HFO-, high frequency oscillations without evolution; IBS, ictal baseline shifts; CFA, conventional frequency activity; F-P, fronto-parietal; P-O, parieto-occipital; P-T, parieto-temporal; PF, prefrontal; MF, medial frontal; LF, lateral frontal; OF, orbitofrontal; LP, lateral parietal; LT, lateral temporal; MT, mesial temporal; ST, subtemporal; LO, lateral occipital; MO, medial occipital.