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Interictal high-frequency oscillations in focal human epilepsy

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Abstract

Purpose of review—Localization of focal epileptic brain is critical for successful epilepsy surgery and focal brain stimulation. Despite significant progress, roughly half of all patients undergoing focal surgical resection, and most patients receiving focal electrical stimulation, are not seizure free. There is intense interest in high-frequency oscillations (HFOs) recorded with intracranial electroencephalography as potential biomarkers to improve epileptogenic brain localization, resective surgery, and focal electrical stimulation. The present review examines the evidence that HFOs are clinically useful biomarkers.

Recent findings—Performing the PubMed search 'High-Frequency Oscillations and Epilepsy' for 2013–2015 identifies 308 articles exploring HFO characteristics, physiological significance, and potential clinical applications.

Summary—There is strong evidence that HFOs are spatially associated with epileptic brain. There remain, however, significant challenges for clinical translation of HFOs as epileptogenic brain biomarkers: Differentiating true HFO from the high-frequency power changes associated with increased neuronal firing and bandpass filtering sharp transients. Distinguishing pathological HFO from normal physiological HFO. Classifying tissue under individual electrodes as normal or pathological. Sharing data and algorithms so research results can be reproduced across laboratories. Multicenter prospective trials to provide definitive evidence of clinical utility.

Keywords

biomarker; electroencephalography; epilepsy; high-frequency oscillations

INTRODUCTION

High-frequency oscillations (HFOs: 65–600 Hz) are local field potentials recorded with intracranial electroencephalography (iEEG), and have received intense interest as potential electrophysiological biomarkers to improve focal epileptic brain mapping, see reviews

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Conflicts of interest

There are no conflicts of interest.

[1,2,3▪]. For patients with drug-resistant focal epilepsy (DRE) resective surgery provides the best chance for seizure freedom. But despite recording seizures with intracranial EEG (iEEG), considered the 'gold standard' for localizing focal epileptogenic brain and the seizure onset zone (SOZ), epilepsy surgery is often unsuccessful [4,5]. In addition, despite rapid progress and class-I evidence for efficacy, focal brain stimulation as currently implemented rarely yields seizure freedom for patients [6▪▪].

Ictal HFOs spanning high-gamma (65–100 Hz), ripple (100–250 Hz), and fast ripple (250–600 Hz) frequency bands have been implicated in seizure generation in human focal epilepsy [7–12]. Research from multiple groups also report increased rates of interictal HFOs in the SOZ, including fast ripples [13–16], ripple [4,17–20], and high-gamma HFO [11]. In addition, increased HFOs are reported to correlate with disease severity, seizure frequency [19,21], and resection of their generators with seizure-free outcome [20,22,23▪]. In addition, recent studies have demonstrated the feasibility of seizure forecasting [24,25], and HFO show promise as a biomarker of the preictal state [26,27].

KEY POINTS

- Human brain generates a wide dynamic range of local field potential oscillations that include high-frequency oscillations (HFO: 65–600 Hz).
- Pathological HFO (pHFO) can be distinguished and separated from normal, physiological HFO (nHFO).
- pHFOs are electrophysiological biomarkers of epileptogenic brain.
- There is a critical need for data and computer code sharing to create reproducible research and advance the use of HFO biomarkers in brain mapping.
- Classification of tissue under each electrode as pathological or normal is required for clinical translation and requires additional research.

Thus, HFOs have emerged as promising electrophysiological biomarkers of epileptogenic tissue (see reviews [1,2,28,29]), and HFO-guided brain mapping would appear poised to translate into clinical practice. There remain, however, significant barriers to clinical translation including: distinguishing true HFO from high frequency power associated with increased neuronal firing [30–32] and bandpass filtering of interictal epileptiform sharp waves and nonspecific transients [29,33]; Distinguishing pathological HFO (pHFO) [34–36] from normal HFO (nHFO) associated with physiological functions [37–42]; Classification of tissue under individual electrodes as pathological or normal - To date, most investigations simply report increased HFO when summed across all SOZ electrodes compared to all non-SOZ electrodes, which is not sufficient for guiding epilepsy surgery [1]; Generating reproducible results - To date it has not been possible to compare results from different laboratories. Most studies analyze iEEG data that are not available and rely on expert visual review, or proprietary detectors, to detect HFO. Finally, most studies have analyzed variably selected, relatively short (~10–30 min) datasets, from relatively small numbers of patients,

(e.g., N=9 [13], N=19 [15], N=23 [11], N=6 [4], N=7 [17], N=10 [18], N=5 [43], N=9 [44], N=20 [20], N=30 [45], N=35 [36]). Whether these positive results can be achieved in wider practice is unclear. Multicenter prospective trials will be required to demonstrate the clinical utility of HFO bio-markers. In this article, we review research efforts into the gaps identified above and suggest potential avenues for translation of HFO electrophysiological biomarkers to clinical practice.

High-frequency oscillations, high-frequency power, and high-frequency activity

There are a range of important technical issues when recording and analyzing wide bandwidth electrophysiology that have been reviewed elsewhere, for example, appropriate data sampling frequency and distinguishing between increased high-frequency power (HFP), HFO and artifacts [29,33]. The distinction between HFO and HFP has been extensively reviewed, but the terms are often conflated or their distinction ignored in the literature. The term high-frequency activity (HFA) was recently suggested to encompass both HFO and HFP [46▪▪]. These terms (HFO, HFP, HFA) and others (e.g., fast and very fast activity or oscillations) are variably used in the literature to describe different frequency ranges and types of high-frequency cerebral electrical activity [38]. Therefore, defining the frequency range of interest, for example (~65–500 Hz), and what type of high-frequency activity is being analyzed is critical when reporting results. Fourier spectral decomposition of a rapidly changing iEEG signal, for example a sharp data transient, epileptiform spikes and sharp waves, all produce an increase in HFP [29,33]. Furthermore, recent studies show that filtered extracellular action potentials ‘contaminate’ high-frequency activity [30–32]. The HFP from these sources is due to the high-frequency Fourier components required to represent the raw data, and should not be confused with actual data oscillations or true HFO. In the extreme case of a data discontinuity (e.g., a square wave signal), the Fourier component sums at the discontinuity do not die out as higher frequency terms are added, a phenomenon referred to as ‘Gibbs’ artifact’ [47].

Gibbs’ phenomenon and how to distinguish HFO from HFP in iEEG has been extensively discussed [29,33]. Electrophysiological data are often filtered in particular frequency bands for analysis, and care should be taken to distinguish between HFP and HFO (Fig. 1, unpublished data). When investigating electrophysiological brain recordings the term HFO should be used to describe true high-frequency local field potential oscillations in the iEEG, that is oscillations visible in the raw recording and not the high-frequency Fourier components from a bandpass filter. In the analysis of focal epilepsy ignoring the distinction between HFO and HFP may distort results [49▪], because in focal epilepsy the HFP associated with epileptiform sharp waves (rapidly changing voltage transient [50]) are more widely distributed than HFO. In the future, research may benefit from defining specific HFO and HFP electrophysiological events in order to avoid heterogeneous signals that could degrade the performance of electrophysiological biomarkers.

Physiological and pathological high-frequency oscillations

Distinguishing normal physiological HFO (nHFO) [37–41,48▪▪] from pathological, epileptiform HFO (pHFO) [34,35,36,51] remains a fundamental challenge in clinical epileptology [52▪▪,53,54▪▪,55▪]. Classic examples of physiological and pathological HFOs

are ripple frequency oscillations [37,38]. The sharp–wave–ripple complex is a physiological HFO that results from phasic inhibitory input on the soma of pyramidal cells [56]; whereas the ripple and fast ripple oscillations superimposed on interictal epileptiform sharp waves are largely generated by synchronized pyramidal cell burst firing [54▪▪,55▪]. Although currently it is unclear how to definitively differentiate pHFO from nHFO in clinical iEEG recordings, one approach is to simply classify HFO associated with epileptiform sharp waves as pHFO and event-related HFO associated with physiological tasks as nHFO [35,40]. Using this approach, the characteristics (e.g., spectral properties, amplitude, duration, and so on) of HFO associated with physiological motor and memory tasks, that is nHFO, can be directly compared to pHFO associated with epileptiform sharp waves [35]. Using this approach, a study of event-related evoked nHFO in human motor cortex had lower amplitudes than pHFO associated with epileptiform sharp waves [35]. The amplitude of LFP, however, is highly variable and sensitively depends on the distance between recording electrodes and the local HFO generators. Of course, HFO frequency would be a more attractive measure as it would not be expected to depend on the distance to the generator [57], but multiple studies in humans report a wide range of overlapping pHFO and nHFO frequencies [11,17,44,52▪▪,58].

An exception is found in the Kainic rodent epilepsy model in which fast ripple HFOs are distinctly pathological oscillations [14,59]. Whether HFOs in the fast ripple frequency range (>250–600 Hz) are uniquely pathological oscillations in humans remains an open question, but increased rates of high-gamma [11], ripple [17], and fast ripple HFO have consistently been described in human epileptogenic tissue. In addition, ripple frequency HFOs are recorded in dentate gyrus of epileptic rats, but not in control rodents. Thus, the anatomic location may identify what is pathological [34].

Classification of seizure onset zone and epileptogenic tissue

Although there is strong evidence that HFOs are biomarkers of epileptogenic brain, whether the signal is adequate for individualized patient care remains unclear. In order to guide surgical resection, biomarkers must be able to classify tissue under each individual electrode as pathological or normal. In addition to identifying the tissue generating seizures currently, the optimal biomarker would identify tissue at risk for generating seizures in the future, that is tissue undergoing epileptogenesis. Late seizure recurrence after a year or more of post-surgical resection seizure freedom supports the hypothesis that previously quiescent tissue undergoes epileptogenesis in some patients [5]. Interestingly, patients with seizure recurrence are often rendered seizure free after repeated operations that extend the prior resections [60], suggesting that the surgical margins of the initial resection should have been extended. Ultimately, the clinical goal is to identify electrophysiological biomarkers that not only improve SOZ localization, but can also predict the tissue and networks at risk for epileptogenesis (hypothesized to be the cause of late epilepsy recurrence in Fig. 2 [61–63]). There is evidence in rodent epilepsy models that pHFOs (200–600 Hz) are a biomarker of epileptogenesis [59,64▪▪]. This is a critically important topic for epilepsy surgery, given that many patients that are initially seizure free suffer late recurrence of their seizures.

Despite the clear need for classifying tissue under individual electrodes, most investigations to date only report group results showing that HFOs are increased when summed across all SOZ compared with non-SOZ electrodes (e.g., reviews [1,2,65]). This type of group analysis supports that HFOs are interictal biomarkers of SOZ, and even that resection of electrodes with increased HFO in aggregate is associated with seizure freedom [20], but falls far short of clinical utility. When considering individual patients the rates of HFOs are often highly variable and less specific for epileptic brain localization [44]. For example, we analyzed HFO rates in 91 patients with focal epilepsy and 12 control patients without epilepsy undergoing motor cortex stimulation for intractable facial pain (Fig. 3, unpublished data). There is strong evidence from the group analysis that increased rates of HFO are associated with SOZ, but when considering individual patients HFOs were increased in the SOZ of only 56% (51/91, $P<0.01$) patients overall. These results, like many in the literature, are confounded by nHFO, and false detections, but have the advantage of reproducibility, given they are generated by automated detectors on data that are freely available (http://msel.mayo.edu/data.html). A significant remaining challenge is to extend localization analysis to a-priori classification of individual electrodes [66▪]. Although the vast majority of research has focused on group analysis (all electrodes in SOZ versus all electrodes in non-SOZ), there are a few exceptions that report seizure-free outcomes after resection of single electrodes generating fast ripple HFO in short intra operative recordings [22,23▪].

Generating reproducible results

Because of a lack of shared data, algorithms, and computer code comparing research results across laboratories has been impossible. There are multiple reasons for the lack of data sharing in epilepsy electrophysiology research, including patient privacy laws. However, within IRB approved studies using appropriate data, de-identification barriers can be overcome. Recent reports about the lack of biomedical research reproducibility have highlighted the interest in data and computer code sharing [67–69]. The journal *Nature* recently published a series of articles on research reproducibility (collected at http://www.nature.com/news/reproducibility-1.17552). Reproducible research requires open source data, algorithms, and computer code [70]. The importance of data sharing has spawned EEG databases with freely available or data that can be purchased (examples include http://ieeg.org & http://msel.mayo.edu/data.html & http://epilepsy-database.eu/ & https://epilepsy.uni-freiburg.de/freiburg-seizure-prediction-project/eeg-database), which are facilitating reproducibility and algorithm development. Open access to data, methods, algorithms, and computer code will accelerate research. Recently, data sharing and crowd source analysis was used effectively to explore seizure detection and prediction [25].

Multicenter prospective trials

Most studies published to date have analyzed variably selected, relatively short (~10–30 min) datasets, from relatively small numbers of patients [1]. Although small single site feasibility trials have emerged investigating HFO [22,71], definitive demonstration will require a collaborative effort between multiple epilepsy centers [72]. These types of studies are challenging for multiple reasons, including cost, effort, patient selection, and the difficultly of multiple centers uniformly adopting a protocol. At this time, the superiority of

surgery guided by recording seizures, interictal epileptiform spikes, and HFO can be debated, but the definitive data are lacking.

CONCLUSION

There is emerging evidence that pHFO can be differentiated from physiological nHFO, and that pHFO are biomarkers of epileptogenic brain. There is a critical need to share data, algorithms, and computer code in order to realize the opportunity for rapid progress on nHFO and pHFO detection and classification. With high accuracy automated detectors and classification algorithms, the inherent variability associated with visual review can be eliminated and the feasibility of mapping normal and epileptogenic brain with HFO biomarkers can be investigated. The first step is creating a database of freely available, well annotated, wide bandwidth interictal and ictal iEEG data, and clinical metadata (electrode locations, pre and post-operative MRI, long-term seizure outcome) coupled with a commitment to share computer algorithms and code to create reproducible results.

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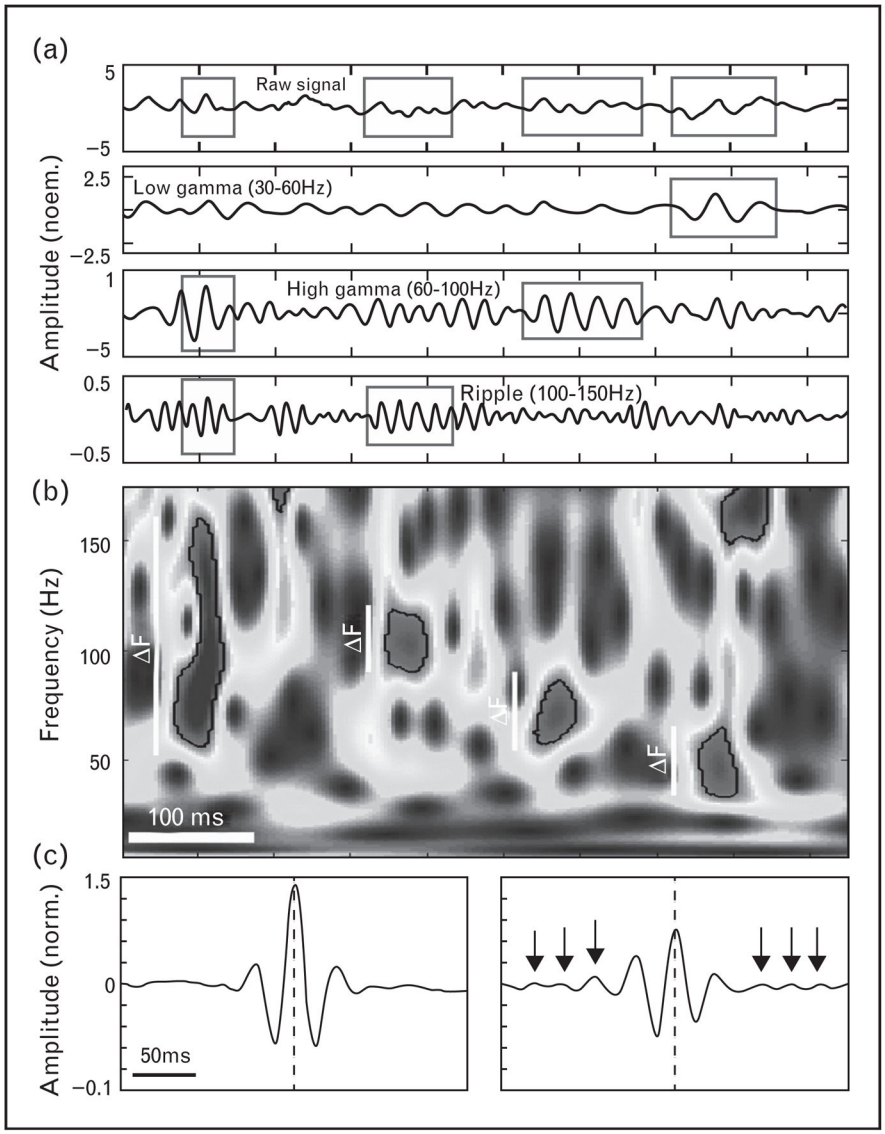

FIGURE 1.

Distinguishing of HFO and HFP activity based on their spectral properties. (a) Discrete bursts of power increases can be detected using a sensitive spectral analysis method [48▪▪] and grouped according to their frequency span (Δ*F*) into broad and narrow band detections (boxed data segments). Top panels show the original signal together with its three bandpass filtered traces below; the bottom spectrogram visualizes four detections of increased power delineated by the black outline. (b) Average raw signal waveforms of the two event types detected at 45 Hz aligned to the peak of the filtered oscillation (center dashed line). Note consistent oscillations around peak amplitude of the narrowband events (right panel: arrows point to peaks of each cycle) in contrast to the broadband power increases (left panel).

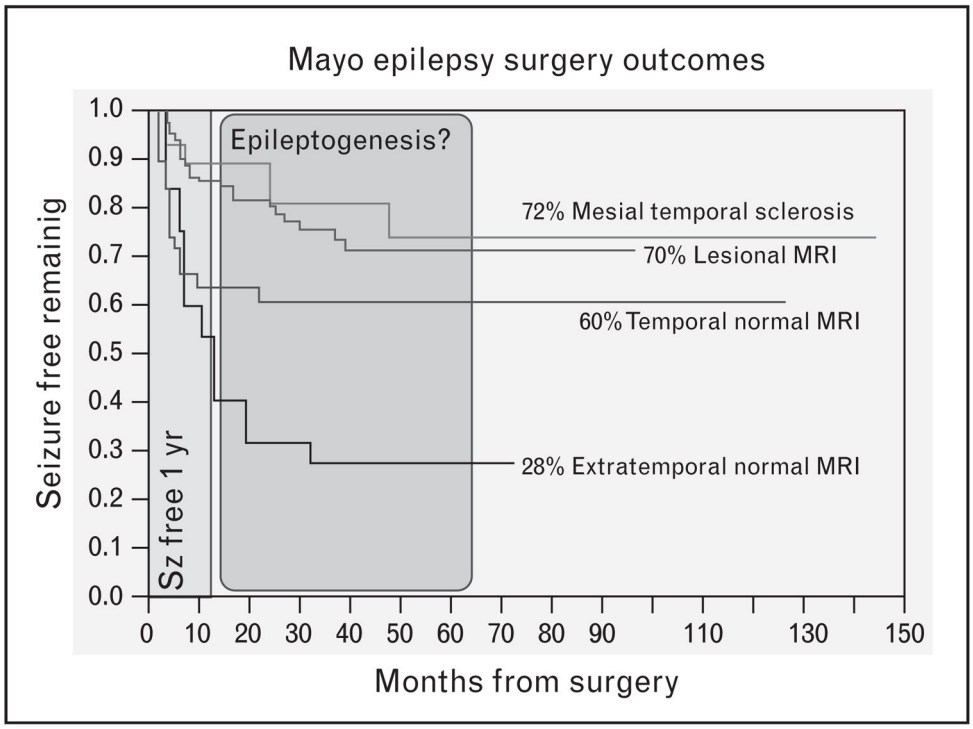

FIGURE 2.

Mayo Clinic Surgery Outcomes. Kaplan-Meir curves show 5-year seizure freedom for patients with unilateral mesial temporal sclerosis (MTS) is 72%, lesional MRI excluding MTS is 70%, and normal MRI temporal lobe epilepsy and extratemporal lobe epilepsy is ~60% [62,63] and 28% [64▪▪], respectively. Normal MRI patients have worse long-term outcomes, and for all patients the risk of seizure recurrence extends well beyond 1 year. A hypothesis for the recurrence after 1 year is epileptogenesis in tissue at the margin of prior resection.

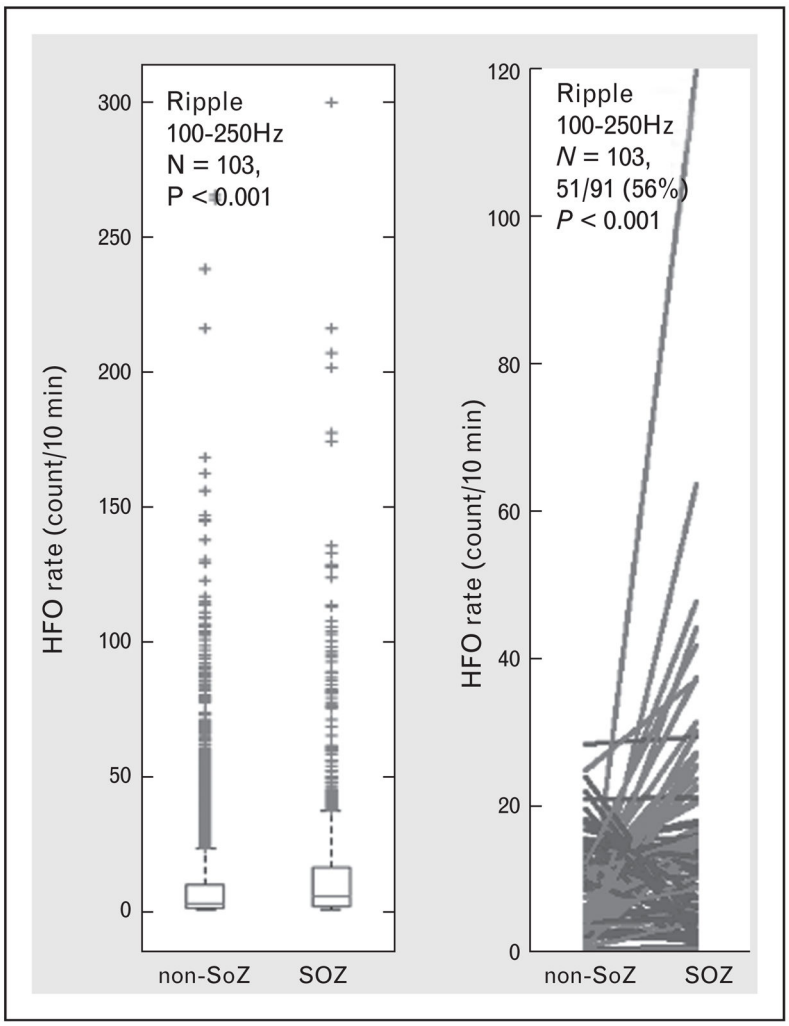

FIGURE 3.

High-frequency oscillations (HFOs) are increased in seizure onset zone (SOZ). Data from *N* =91 patients with focal epilepsy patients and 12 control patients undergoing motor cortex stimulation for drug resistant facial pain. An automated HFOs detection algorithm using a signal line-length threshold was used to detect HFOs (65–600 Hz) events in 2 h of continuous data. (a) HFO (65–600 Hz) rates (#counts/min-channel) are increased in SOZ versus non-SOZ when considering all channels in all patients (total electrodes =5862, *N* =103 patients). (b) When considering individual patients, however, only 56% (51/91, paired *t* test $P < 0.0001$) of all ($N = 91$) focal epilepsy patients showed significantly increased HFO rates in the SOZ.