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REVIEW

Electrophysiological Biomarkers of Epilepsy

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Abstract In patients being evaluated for epilepsy and in animal models of epilepsy, electrophysiological recordings are carried to capture seizures to determine the existence of epilepsy. Electroencephalography recordings from the scalp, or sometimes directly from the brain, are also used to locate brain areas where seizure begins, and in surgical treatment help plan the area for resection. As seizures are unpredictable and can occur infrequently, ictal recordings are not ideal in terms of time, cost, or risk when, for example, determining the efficacy of existing or new anti-seizure drugs, evaluating potential anti-epileptogenic interventions, or for prolonged intracerebral electrode studies. Thus, there is a need to identify and validate other electrophysiological biomarkers of epilepsy that could be used to diagnose, treat, cure, and prevent epilepsy. Electroencephalography recordings in the epileptic brain contain other interictal electrophysiological disturbances that can occur more frequently than seizures, such as interictal spikes (IIS) and sharp waves, and from invasive studies using wide bandwidth recording and small diameter electrodes, the discovery of pathological high-frequency oscillations (HFOs) and microseizures. Of IIS, HFOs, and microseizures, a significant amount of recent research has focused on HFOs in the pathophysiology of epilepsy. Results from studies in animals with epilepsy and presurgical patients have consistently found a strong association between HFOs and epileptogenic brain tissue that suggest HFOs could be a potential biomarker of epileptogenicity and epileptogenesis. Here, we discuss several aspects of HFOs, as well as IIS and microseizures, and the evidence that supports their role as biomarkers of epilepsy.

Keywords High frequency oscillation · Interictal spike · Microseizure · Epileptogenicity · Epileptogenesis · Ictogenesis

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Introduction

The spontaneous occurrence of an epileptic seizure is the defining feature of the epileptic brain. In patients being evaluated for epilepsy and animal models of epilepsy, electrophysiological recordings are regularly carried out to capture seizures to identify the existence of epilepsy, identify a specific type of epileptic seizure, or epilepsy syndrome. In most cases, recordings are made from the scalp, but can also be obtained directly from brain parenchyma as in some presurgical diagnostic studies when subdural or depth electrode recordings are needed to localize the brain area responsible for generating spontaneous seizures. Electrophysiological recordings like these are also being used to identify biomarkers of epilepsy that are needed to prevent the development of epilepsy ("epileptogenesis"), and reverse the progression and ultimately cure epilepsy after it is established [1, 2].

Epileptic seizures themselves are a specific biomarker of epileptogenesis and epileptogenicity (the presence and severity of an epileptic condition), although owing to their unpredictable nature and irregular rate of occurrence, ictal electroencephalography (EEG) recordings are not ideal in terms of

time, cost, or risk for evaluating, for example, the efficacy of existing or new anti-seizure drugs, potential anti-epileptogenic interventions, or presurgical evaluation. However, EEG recordings in individuals with epilepsy contain other transient electrophysiological disturbances that occur between ictal episodes that can occur more frequently than seizures, such as interictal EEG spikes and sharp waves (IIS), pathological high-frequency oscillations (HFOs) between 80 and 600 Hz [3, 4], and, more recently, electrographic seizure-like events and focal periodic epileptiform discharges occurring on sub-millimeter spatial scales termed "microseizures" and "micro-periodic epileptiform discharges" respectively [5, 6]. HFOs and microseizures were discovered using wide bandwidth recordings from small diameter electrodes or microelectrodes. Intracerebral recording such as these have helped accelerate technical improvements in clinical systems—electrodes, amplifiers, data digitization—that are now being incorporated more routinely into diagnostic presurgical evaluation, and that have expanded the spatial and temporal scales for studying abnormal brain electrical activity [7, 8].

Interictal EEG spikes occur in the epileptic brain and can be useful diagnostically [9], although IIS can be detected in the EEG of a small percentage of healthy volunteers and relatively larger percentage of patients without a history of seizures [10]. In addition, patient studies found that IIS do not consistently correspond with disease activity (e.g., occurrence in relation to seizures or changes in anti-seizure medication levels) [11–15] . However, recent work in animals has identified unique aspects of IIS that correspond with experimental epileptogenesis [16–18]. Similarly detailed studies like these on the mechanisms of IIS are needed that might distinguish different types of IIS involved with ictogenesis and epileptogenesis [19–21].

For over a decade basic research of HFOs in animal models of epilepsy and presurgical patients has consistently found a strong association between pathological HFOs and epileptogenic brain tissue. Based on evidence from retrospective studies, pathological HFOs could be a biomarker of epileptogenicity that would not only assist in localization of epileptogenic tissue for resective surgery [22], but help distinguish between epileptic and non-epileptic seizures, and reduce the cost and time of clinical trials of anti-seizure drugs and therapeutic devices [23]. As a biomarker of epileptogenesis, pathological HFOs could help identify individuals at risk for developing epilepsy after an epileptogenic insult and could be useful in the design of animal screening models for discovery of new anti-seizure and anti-epileptogenic drugs [23]. However, significant work remains to be done in order for HFOs (and similarly for IIS and microseizures) to fulfill their potential as biomarkers, including identifying strategies to reliably distinguish pathological from normal HFOs in the human epileptic brain [23–25]; developing non-invasive methods to record HFOs, which are now best detected using intracerebral EEG recording; efficient and accurate detection methods and automated tools for unbiased quantification of HFOs in wide bandwidth recordings across patients [8]; and, ultimately, prospective studies that can incorporate individual patient HFO data in planning the area for resection and follow patients to determine postsurgical seizure freedom [26]. Here we discuss HFOs, microseizures, and IIS, although a significant portion of this review focuses on HFOs based on the recent number of studies supporting their potential role as an electrophysiological biomarker of epilepsy.

HFOs

Terminology

A formal definition of HFOs and electromagnetic oscillations described in terms of a central spectral frequency that can extend from <1 Hz to over 1000 Hz does not exist. EEG nomenclature and frequency band limits are often subject to individual interpretation, but EEG oscillations are generally labeled as slow (< 1 Hz), delta (1–4 Hz), theta (> 4–8 Hz), alpha and mu (> 8–13 Hz), beta (> 13–30 Hz), gamma (> 30–80 Hz), ripple (> 80–200 Hz), fast ripple (> 200–600), and sigma (≥ 600 Hz). Consistent with recommendations to standardize the description of HFOs [27], much HFO research in the epileptic brain has focused on transient, sinusoid-like events that contain spectral power between 80 and 600 Hz (Fig. 1), and occur spontaneously in the hippocampal formation and neocortex during the onset of some seizures, but most frequently during interictal episodes, primarily during slow wave sleep or waking quiescence when rates of HFOs are highest [28–30]. Discussion of the studies that follow include descriptive details to continue the effort to distinguish the likely different types of HFOs, as well as their mechanisms and function, in the normal and epileptic mammalian brain [23].

Neuronal Mechanisms of HFOs

Several reviews detail the experimental evidence for the single neuron and network basis generating HFOs [27, 31–33], and there could be important differences in the involvement of inhibitory processes between normal and pathological HFOs. In the normal mammalian brain, local inhibitory cells appear to play a prominent role in physiological HFOs. During CA1 hippocampal sharp wave-associated ripples [34], as well as neocortical ripple-frequency HFOs [28] and sensory-evoked fast ripple-frequency HFOs [35], spike firing from various types of interneurons (e.g., hippocampal basket cells and neocortical fast spiking cells) regularly occurs during the trough of the extracellularly-recorded HFO [28, 36–39]. It is believed that synchronous gamma-aminobutyric acid (GABA)-A receptor-mediated inhibitory postsynaptic potentials (IPSPs) imposed upon principal cells (i.e., in hippocampus, pyramidal

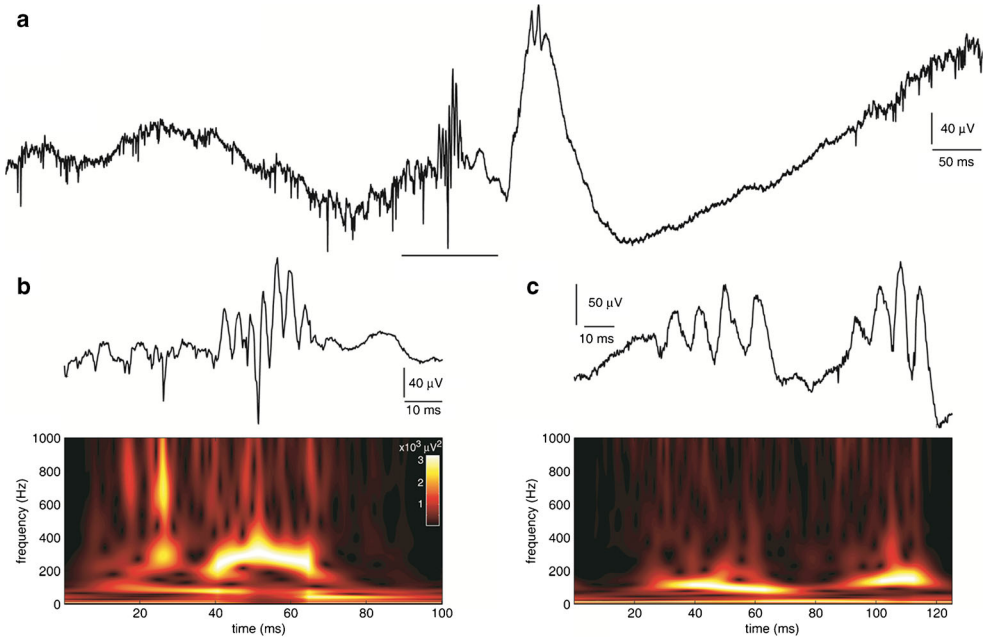

Fig. 1 (A) Interictal wide bandwidth (1 Hz–3 kHz) depth electroencephalography (EEG) recorded from a microelectrode positioned in entorhinal cortex of a presurgical patient with suspected temporal lobe epilepsy. Neuronal spike firing and higher amplitude fast ripple-frequency high-frequency oscillation [HFO; underlined segment, shown in (B)] precedes interictal EEG spike that also contains HFO activity. (B) Example of fast ripple-frequency HFO (top) and corresponding time-frequency spectrogram (bottom). Note predominant spectral power between 200 and 400 Hz (color-coded white) during HFO and vertical streaks (yellow and red) extending towards higher frequencies that likely reflect power associated with neuronal spike firing. (C) Examples of ripple-frequency HFO (top trace) recorded from microelectrode positioned in anterior hippocampus of another patient. Spectral power largely between 80 and 200 Hz during HFOs (bottom spectrogram)

cells; in neocortex, regular spiking, intrinsically bursting, and fast rhythmic bursting cells) provides precise temporal windows that regulate their firing and coordinate excitatory synaptic transmission onto postsynaptic targets. The tightly-orchestrated pattern of firing between interneurons and principal cells during normal HFOs has been implicated with encoding information [40], sensorimotor integration [41], and memory consolidation [42].

In contrast to HFOs in the normal mammalian brain, in the epileptic hippocampal formation, fast ripple-frequency HFOs reflect brief bursts of population spikes believed to be generated from a cluster of pathologically interconnected neurons (PIN cluster) [4, 43, 44]. Other studies observed bursts of populations spikes with ripple-frequency spectral power in the epileptic dentate gyrus, an area that does not normally generate such events in the naïve rat, which led to the term "pathological" HFOs to include bursts of population spikes within ripple- and fast ripple-frequency bands in the epileptic hippocampal formation [24, 44, 45]. *In vitro* results generally agree with *in vivo* data, which found that recurrent excitatory connections among CA3 pyramidal cells can generate synchronous firing and bursts of population spikes [46]. Recordings in dentate gyrus and hippocampus revealed that pathological HFOs persist after suppression of GABA-A receptor-mediated transmission [47, 48], while another study found that significant increases in principal cell spike firing and reduced interneuron firing coincide with spontaneous population spike in dentate gyrus of pilocarpine-treated epileptic mice [49]. In addition, neuronal recordings in neocortex of cats found that the precise spike firing from fast spiking cells in relation to the extracellular HFO waveform was lost during abnormal ripple-frequency HFOs compared with normal HFOs [28, 50], yet the spike firing from these cells, as well as pyramidal cells, significantly increased during abnormal compared with normal HFOs. Results from these studies suggest a reduced role of interneuron-mediated IPSPs in coordinating neuronal spike firing during some hippocampal and neocortical pathological HFOs, although it is not clear from these data whether inhibitory postsynaptic currents (IPSCs) are a significant source of the extracellular pathological HFO field potential. Results from one study recording from neocortical slices bathed in low Mg^{2+} medium provide evidence when IPSCs could significantly contribute to the pathological HFO [51]. In this work, under conditions when pyramidal cell firing was suppressed by strong inhibitory activity, as might occur during interictal or pre-ictal episodes, synchronous IPSCs onto principal cells were strongly correlated with the local HFO field potential. However, when inhibitory restraint weakened and principal cell spike firing increased (e.g., during onset and propagation of ictal discharges) the correlation between IPSCs and HFO field potential was significantly lower, suggesting there are periods when

IPSCs could be a source of pathological HFOs compared with other times when excitatory postsynaptic currents predominate in the local HFO field potential.

Synchronous principal cell firing, and in some cases interneuron firing as noted in the preceding paragraph, could explain pathological HFOs with central frequencies up to 300 Hz [46, 48, 52], yet in patients there is little evidence that single neurons fire at frequencies greater than 300 Hz and thus it is more difficult for this neuronal mechanism to explain the occurrence of fast-ripple frequency HFOs up to 600 Hz [53–55]. Recent computational models provide evidence for the role of axonal gap junctions during fast ripple-frequency HFOs, as well as ripple-frequency and ripple-to-fast ripple transition [56]. Others have proposed that fast ripple-frequency HFOs emerge from the out-of-phase firing between small groups of neurons with individual neurons discharging at low frequencies and rarely firing during successive waves of the HFO [48, 52, 57]. Results from a recent modeling study of fast ripple-frequency HFOs in a hippocampal CA1 network are consistent with this proposal [58], which seemingly better explains the precision of spike firing, as well as the frequency spectra of pathological HFO [32, 46, 48, 52]. Interestingly, the study by Demont-Guignard et al. [58] also demonstrated that, when simulated, afferent input from CA3 onto the CA1 network became more synchronous when the number of synchronously firing CA1 pyramidal cells and interneurons increased producing a large amplitude IIS instead of fast ripple-frequency HFO. It is possible that the cellular and network parameters used to model the transition from pathological HFOs to IIS in this latter work could also explain *in vivo* recordings that contain IIS superimposed with HFOs and those without HFOs. How out-of-phase firing between groups of neurons (PIN clusters) arises is not known, but weak ephaptic field effects, neuron loss, circuit reorganization, or irregular spread of activity throughout neuronal networks could contribute to the differential spatial activation of local clusters of neurons [32, 59].

Recording, Detection, and Quantification of Spontaneous HFOs

Wider bandwidth and higher sampling rates now available on many clinical EEG recording systems have facilitated studies of HFOs. An important component in any electrophysiological recording setup is the electrode, and whether there exists an optimal electrode contact size and configuration to record HFOs is not yet known owing to variability in the amount of tissue supporting their generation. Some of the first studies of ripple- and fast ripple-frequency HFOs in the epileptic brain used small diameter microelectrodes (~40–60 μm; area, 0.0013–0.0029 mm^2) that indicated ≤1 mm^3 of tissue could generate pathological HFOs [3, 4, 60]. Interestingly, studies using simulated neuronal networks consisting of ≥1000 neurons, but also as few as 120, can generate HFOs that contain spectral frequencies, duration, and amplitude similar to HFOs recorded experimentally [52, 58]. This is considerably fewer neurons than what would be expected based on *in vivo* studies, but might reflect a theoretical minimum that could generate HFOs under ideal network parameters, connectivity, and recording conditions. Subsequent patient studies using larger diameter electrodes than microelectrodes (surface area up 7.2 mm^2) confirmed and extended the spatiotemporal properties of HFOs, including results that suggested some pathological HFO-generating networks could cover several square centimeters [61–64]. One study found a significant reduction in the number of fast ripple-frequency HFOs recorded with standard clinical electrodes (surface area 9.4 mm^2) compared with microelectrodes [65]. In contrast, other experiments compared hippocampal ripple- and fast ripple-frequency HFOs recorded with electrodes of different contact sizes in epileptic rats and found no difference in HFO duration or spectral frequency with respect to electrode diameter, although the mean amplitude of all HFOs was significantly lower compared with the amplitude of HFOs recorded with microelectrodes [4, 66]. In subsequent work involving patients from this same group, similar rates of HFOs were found among electrodes with surface areas between 0.2 and 5 mm^2 [67], suggesting that smaller contact diameter would not necessarily improve the detection of HFOs. If this conclusion is correct, then differences between the aforementioned studies could be due to the position of the electrodes in relation to location and size of tissue generating HFOs or the spatial averaging of uncorrelated HFO activity between distant PIN clusters that attenuates or cancels activity occurring at higher frequencies [58]. In addition, recent work has found that choice of electrode (e.g. high impedance microelectrode) in combination with amplifier input impedance significantly affects signal-to-noise levels that could contribute to unreliable detection of HFOs [68].

Animal and patient studies of HFOs are complicated by the fact that HFOs are typically brief in duration (10–100 ms) and lower in amplitude (10–1000 μV) than background EEG and other epileptiform phenomena [4]. Manual detection of HFOs, which is the gold standard of EEG review and the method often used in studies of HFOs, is time-intensive and subjective. A manual strategy imposes practical limitations on the amount of clinical EEG that can be reasonably reviewed. There is some evidence that accurate detection of HFOs can be achieved in short-duration EEG recordings (e.g., 5 mins during slow wave sleep) [69], although the rate of HFO occurrence can be quite variable over time, particularly during peri-ictal periods and with changes in anti-seizure medication [70, 71]. Therefore, the EEG sample for review must be selected carefully. Furthermore, scalp and intracranial EEG recordings contain physiological and epileptiform sharp transients and often artifacts (electrode noise, eye-, and muscle-related activity) that

contain high frequency power, and digital filtering of these events could be incorrectly interpreted as HFOs [72, 73]. Studies have implemented supervised and unsupervised computer-automated algorithms, some that incorporate aspects other than spectral power to improve specificity [63, 74–77] and one for specific types of HFOs [78]. While all detection strategies thus far have demonstrated strengths and weaknesses, a feasible and accurate approach will likely include a combination of computer-automated methods to process large data sets and manual inspection of a randomly selected sample of HFOs by experienced investigators.

One of the anticipated clinical uses of interictal pathological HFOs is to localize the brain area responsible for generating epileptic seizures, and is currently supported by evidence from retrospective studies described in the following sections. In these studies, the significant association between interictal fast ripple- and, in some cases, ripple-frequency HFOs and the seizure onset zone (SOZ) derive from group-averaged statistics. However, their use in presurgical evaluation will require quantification in an individual patient owing to variability in the properties of HFOs, and differences in spatial sampling and recording electrodes between patients. While this methodology still needs to be developed, it is likely that any patient-based quantitative approach will need to consider the type of HFO, and possibly anatomical location, and use a statistically-derived threshold to identify significant HFO-generating sites. One retrospective study involving surgical pediatric patients used an approach that calculated rates of ripple- and fast ripple-frequency HFOs in combination with histogram and bootstrapping analysis to define a threshold to identify high-rate HFO sites [64]. In addition to an important result that found more complete resection of high-rate fast ripple-frequency HFO sites was associated with better surgical outcome, the novel patient-oriented HFO quantification used in this study could be appropriate for prospective studies of HFOs in presurgical evaluation.

Microseizures, HFOs, and Ictogenesis

Microseizures

Microseizures are a newly described electrophysiological phenomenon in the study of epilepsy [5, 79]. They are defined as interictal seizure-like local field potential events whose spatial extent is restricted to approximately the width of a neocortical column (~500 μm) [80]. The restricted radius of these phenomena makes their detection only possible with intracranial microwire (diameter<100 μm) recordings, being inaccessible to standard intracranial macroelectrodes (typical diameter≥ 4 mm). Microseizures are interictal events by definition, a practical restriction necessitated by the fact that seizure-like discharges occurring on microwires during a seizure are an established and expected phenomenon. On rare occasions, patients may report auras in association with microseizure events, but, in general, they are purely subclinical events. Microseizures frequently evolve in frequency and occasionally in spatial extent. Their frequency content is similar to that for macroelectrode seizures recorded intracranially. A related phenomenon, microperiodic epileptiform discharges (μPEDs), have similar restrictions in spatial extent, but morphologically resemble the macroelectrode phenomenon periodic lateralized epileptiform discharges that are nonspecifically associated with neural tissue damage [81]. μPEDs tend to continue for much longer periods of time than microseizures, and tend not to evolve in frequency.

Microseizures and μPEDs both spatially localize to the SOZ, though at this time the statistics are more robust for microseizures [5]. Spatially, microseizure domains display a fractured arrangement such that their occurrence is much more frequent in the brain regions generating seizures, but they are not contiguous and are surrounded by microdomains generating only normal-appearing physiology (interictally). Microseizures or μPEDs are seen leading directly into clinical seizures as much as 20 % of the time. Whether the phenomenon is more ubiquitous and has been missed owing to relatively sparse spatial sampling is a matter of ongoing investigation. Current data do not support the utility of microseizures as a clinical marker of impending seizure (seizure predictors), as their occurrence prior to seizure, while statistically significantly, is below the level of clinical utility. It is conceivable this may change with higher spatial sampling in the future.

Microseizures have been observed in multiple species (human, rat, pig), in multiple pathologies (mesial temporal sclerosis, trauma, tumor, cortical dysplasia), and even rarely in non-epileptic human controls. One hypothesis is that microseizures represent a final common physiological pathway in ictogenesis [5]. If this is validated, the concept that clinical seizures emerge without a physiological precursor can finally be put to rest, and equating the question of the mechanism of ictogenesis to that of the mechanisms underlying microseizures. This would be a better position for the field, as tools exist to investigate this question, but the neuronal networks underlying microseizure generation are unknown. However, based on their restricted spatial extent and the fact that they are local field potentials, one hypothesis is that the microseizure network is one of intracolumnar feedback. A single cortical column is a network of 10^3–10^4 neurons that is known to support sustained independent oscillatory activity [82]. In archicortex, such as hippocampus, which lacks the columnar organization of neocortex, PIN clusters described by Bragin et al. [43], may support the same function. Epileptogenesis, the process by which normal brain regions become susceptible to generating unprovoked seizures, may have as its anatomical substrate the accumulation of PIN clusters or “sick columns” generating microseizures [5, 43].

Ictal HFOs

Studies of ictal HFOs can also address basic mechanisms of ictogenesis and have important clinical implications, particularly if the presence of HFOs at ictal onset reflects the proximity of electrode to tissue responsible for generating the seizure and, therefore, more accurate localization of the epileptogenic zone (see the section "HFOs and Surgical Outcome"). Results from animal studies suggest that different neuronal mechanisms are associated with HFOs that precede or occur during ictal onset. For example, depth electrodes positioned in the dentate gyrus of epileptic rats found during the ictal onset consisting of rhythmic, large amplitude EEG spikes, often referred to as a *hypersynchronous* ictal EEG onset pattern, there was an increase in ripple- and fast ripple-frequency HFO power and duration that presumably reflects the expansion of individual PIN clusters (i.e., predominately principal cell spike firing; see the section "Neuronal Mechanisms of HFOs") and their progressive coalescence [83]. A subsequent study by another group using pilocarpine-treated epileptic rats observed, during hypersynchronous ictal onsets, significantly higher rates of fast ripple- than ripple frequency-HFO predominately in the CA3 SOZ, as well as adjacent areas of seizure spread [84]. By contrast, another type of ictal EEG onset pattern termed *low voltage fast* was associated with a significant increase in HFOs between beta- and ripple-frequencies, but not fast ripple-frequency HFO [83, 84]. Interestingly, recordings in an isolated whole brain preparation found that the beta-frequency HFO during seizure onset in entorhinal cortex was associated largely with interneuron spike firing, but IPSPs progressively declined, and principal cell spike firing increased during the evolution of the seizure [85]. In neocortex of normal cats during ketamine-induced neocortical *polyspike and wave* seizures, larger ictal ripple-frequency HFO amplitude correlated with neuron depolarization and increased spike firing [50]. Pyramidal cell-like firing was time-locked with the ictal ripple-frequency HFO, but not fast spiking cells (presumably local GABAergic interneurons), which are typically temporally coupled with the trough of normal ripple-frequency HFOs during slow wave sleep.

A number of patient studies have detected HFOs or found an increase in HFO power, generally between beta- and fast ripple-frequencies, during or preceding ictal onset by several minutes to seconds (Fig. 2) [62, 86–89]. Changes in HFO power were chiefly detected in the primary SOZ and rarely in sites of secondarily generalization of patients with focal epilepsy [90]. Similar changes in HFOs have been observed during epileptic spasms that, in some cases, occurred before the clinical onset, and were observed spreading across cortex and encompassing large cortical territories [91–95]. None of the aforementioned patient studies examined different types of HFO in relation to ictal EEG onset pattern, which is an area of research that could yield electrophysiological biomarkers [2]. Furthermore, one study did not find a consistent change (i.e., increase) in HFO power or rates during the transition to ictus [96], although total rates of ripple- and fast ripple-frequency pre-ictal HFOs (≤ 15 mins to ictal onset) were highest inside compared with outside the SOZ, similar to the results of interictal HFOs in relation to the SOZ discussed in the next section. This latter study raises uncertainty on the reliability of HFOs in predicting seizures, while overall results from animal

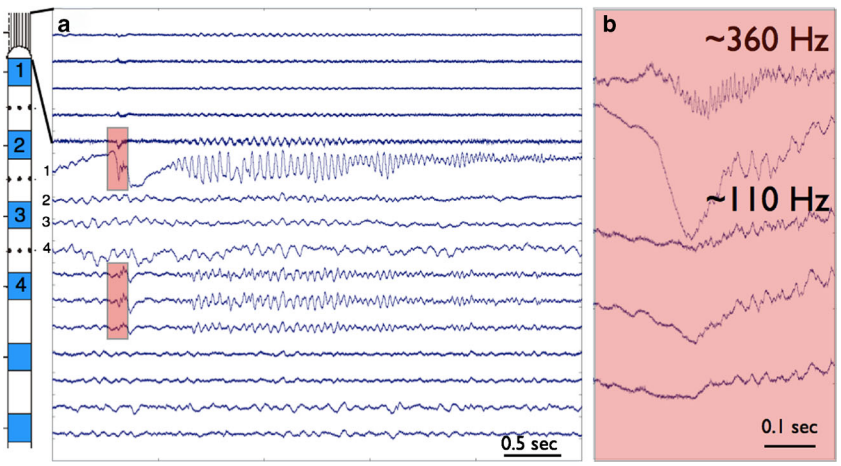

Fig. 2 Wide bandwidth recording from hybrid depth implanted in human hippocampus. (A) The upper 5 tracings are from microwires protruding from the tip of the clinical depth electrode. The middle 4 tracings are from the numbered clinical macroelectrodes, and the 7 bottom tracings from microwires embedded in the shaft of the clinical depth between the clinical macroelectrodes. The seizure onset is associated with a paroxysmal sharp wave and associated ripple frequency (~110 Hz) discharge on the clinical macroelectrode and a fast ripple frequency (~360 Hz) discharge on the tip microwire (highlighted in red). (B) Expanded scale showing the highlighted channels in (A). The top trace is a microwire extending from the tip of the clinical depth, and at seizure onset shows a fast ripple HFO (~360 Hz) coinciding with the sharp wave seen on the clinical macroelectrode contact-1 in the second trace. Note the microwires are referenced to a local microwire and only show an attenuated version of the paroyxsmal slow wave seen at onset on the clinical macroelectrode that has a distant reference. The lower 3 traces are from the shaft microwires embedded between macroelectrodes 1 and 2 (shown as black dots on the schematic)

and patients studies suggest that pre-ictal HFOs could reflect only one of the many different mechanisms of ictogenesis.

HFOs and Epileptogenicity

Interictal HFOs

A potential advantage of interictal HFOs as a biomarker of epileptogenicity for presurgical evaluation or assessing efficacy of therapeutic interventions is that such studies can be done without waiting for seizures to occur. However, to be useful as a biomarker, evidence is needed that interictal HFOs localize to epileptogenic brain tissue and their occurrence is associated with disease activity or severity of epilepsy. The initial studies of interictal HFOs in patients with mesial temporal lobe epilepsy (MTLE) found a strong association between microelectrode-recorded fast ripple-, but not ripple-, frequency HFOs and the SOZ [3, 4], results that were consistent with subsequent quantitative studies [29, 74]. *In vitro* and *in vivo* microelectrode recordings noted the limited volume of tissue (as small as 1 mm^3) capable of supporting fast ripple-frequency HFOs [60, 97]. Studies relating interictal HFOs and pathology of MTLE found higher rates of fast ripple-frequency and lower rates of ripple-frequency HFOs correlated with hippocampal atrophy and reduced neuron densities [74, 98, 99]. These data suggest that morphological alterations associated with hippocampal sclerosis in MTLE could be an anatomical substrate for hippocampal fast ripple-frequency HFOs, but it also suggests that hippocampal damage could disrupt the generation of normal ripple-frequency HFOs.

A number of noteworthy results derive from studies using larger diameter electrodes and commercial clinical electrodes. For example, ripple- and fast ripple-frequency HFOs could be recorded using clinical macroelectrode, and the volume of tissue and/or spatial distribution associated with fast-ripple frequency HFOs was larger than predicted from microelectrode recordings [65, 66, 100]. The link between the rates of fast ripple-frequency HFOs and SOZ was also confirmed [65, 101, 102], and from these studies evidence for the association of ripple-frequency HFOs and the SOZ in MTLE and neocortical epilepsies was obtained, although fast ripple-frequency HFOs appear more specific to the SOZ, particularly in MTLE [63]. In addition, HFOs were observed in epileptogenic tissue extending beyond areas of pathology in other lesional epilepsies [102], and another study found HFOs in the SOZ of magnetic resonance imaging (MRI)-negative patients [103], although histological analysis of resected tissue indicated gliosis and neuron loss in many of these patients.

Multiple studies have reported that gamma-frequency HFOs [89] and ripple-frequency HFOs [14, 65, 101] are also increased in the SOZ. Differences in the association of ripple-frequency HFOs with the SOZ between micro- and macroelectrode studies reflect an outstanding issue of reliably distinguishing normal from pathological HFOs. It is likely that some of the ripple-frequency HFOs localizing with the SOZ are similar to pathological ripple-frequency HFOs found in the epileptic dentate gyrus [45]. Some have suggested a bias of larger-diameter electrodes to sample a larger volume of tissue and capture pathological (ripple-frequency) HFOs *versus* normal HFO [23, 63, 67]. Alternatively, recent work has described prolonged (> 500 ms in duration) episodes of high-frequency activity (80–250 Hz) in mesial temporal lobe and neocortex of presurgical patients [104, 105]. Continuous episodes of interictal high-frequency activity itself does not appear specific to the SOZ, but compared with irregular or sporadic episodes was associated with higher rates of IIS and bursts of HFOs, which could, in part, explain the higher rates of ripple-frequency HFO occurrence on larger electrodes. A recent study characterized physiological HFO by measuring frequency, duration, and power of HFO induced by a visual or motor task in single trial time frequency spectra [25]. These putative physiological HFOs were compared with putative pathological HFOs primarily associated with epileptiform sharp waves. Pathological HFOs were primarily characterized by higher mean power and longer duration than physiologically-induced HFOs. In individual patients, a support vector machine analysis correctly classified pathological HFOs with high sensitivities and specificities, with the exception of one patient with infrequent high power HFO arising in epileptic motor cortex just before movement onset [25].

Several of the studies mentioned in the previous paragraph also noted a strong spatial and temporal association between HFOs and IIS [61, 101]. A large percentage of IIS occur independently of HFOs and vice versa, although some IIS do contain HFOs that are not visible in wide bandwidth recordings unless the signal is filtered or the spectral power extracted using statistical time–frequency analysis [61, 106]. While prior work had found that IIS can extend beyond the SOZ depending on state of vigilance [107–109], recent evidence indicates that IIS containing HFOs, as well as HFOs alone, particularly ripple-frequency HFOs [110], more accurately localize to the SOZ than IIS alone [101, 111]. The mechanisms that give rise to IIS containing HFOs are not known, but studies have found important differences between IIS and HFOs associated with disease activity and cortical excitability that suggest the pathophysiological mechanisms are different. One study observed that after seizures rates of IIS increased, whereas rates of HFOs, as well as IIS containing HFOs, did not change [70]. In the same study, the rate and duration of HFOs increased after a reduction in medication, although there was no statistical change in rates of IIS alone or IIS containing HFOs. Another study by the same group found that the rate of HFOs increased from interictal to pre-ictal to ictal episodes, and electrodes from which HFOs were recorded remained consistent across these episodes [112]. In contrast, IIS increased from interictal (but not pre-ictal) to ictal episodes

and were recorded on different electrodes during ictal compared to interictal episodes. Finally, high rates of HFOs correlated with lower threshold of electrical stimulation (ES)-evoked responses inside the SOZ, although in neocortex outside the SOZ high rates of fast ripple-frequency HFOs were also associated with lower thresholds of ES-evoked response [113]. The association between IIS, ES-evoked response, and SOZ was not evaluated in the latter study, but overall results suggest HFOs reflect levels of neuronal excitability inside the SOZ and possibly areas of epileptogenicity beyond where seizures begin.

Studies in epileptic rats found that a higher number of electrodes recording fast ripple-frequency HFOs correlated with seizure frequency [114], indicating that fast ripple-frequency HFOs could correspond with severity of epilepsy. One patient study did not find a correlation between seizure frequency and rates or proportion of electrodes with ripple- or fast ripple-frequency HFOs [112]. However, in the same study, higher seizure frequency correlated with a greater number of electrodes with high (> 20/min) rates of fast ripple-frequency HFOs in patients with temporal lobe epilepsy. Another study found that higher rates of fast ripple-, but not ripple-, frequency HFOs correlated with local areas of hippocampal atrophy in patients with MTLE [99], suggesting that higher rates and broader spatial distribution of fast ripple-frequency HFOs could reflect disease burden in some cases of temporal lobe epilepsy.

The preponderance of work on HFOs in epileptic animals and patients used direct brain recordings and, in spite of the advantages interictal HFO recordings might possess in terms of time, cost, and possibly accuracy for presurgical evaluation, it does not obviate the risk associated with invasive recording. Moreover, it is clear invasive recording is an obstacle for the use of HFOs as a biomarker of epileptogenesis. However, recent work has detected spontaneous ripple-frequency HFOs associated with spikes in scalp EEG from children with continuous spike and wave during slow wave sleep [115]. Two subsequent studies detected gamma- and ripple-frequency HFOs in the scalp EEG of adults with epilepsy [116, 117]. In these studies, HFOs were often associated with IIS, but some occurred independently of IIS, and rates of HFO and IIS were higher inside than outside the SOZ. Importantly, compared with IIS, the specificity and accuracy of HFO in localizing with the SOZ was higher, although sensitivity was lower. Results from these preliminary studies are exciting and raise the possibility that other non-invasive modalities, such as magnetoencephalography or functional MRI, either independently or in combination with EEG recordings, can capture HFO signals and advance studies of HFOs in patients at risk for developing epilepsy or those newly diagnosed with epilepsy.

HFOs and Surgical Outcome

Several retrospective studies that have followed up on patients after resective surgery found that removal of tissue generating interictal pathological HFOs correlated with a good outcome, that is, becoming seizure-free or having a significant reduction in disabling seizures (Table 1) [64, 111, 119–121]. One study using single pulse electrical stimulation found, in 2 patients, that complete or near complete removal of tissue that contained evoked fast ripple-frequency HFOs was associated with a seizure-free outcome, whereas in 7 patients who had removal of <50 % of sites that contained evoked fast ripple-frequency HFOs, only 2 were seizure-free, while the remaining 5 patients continued to have seizures [122]. Additionally, studies of ictal or peri-ictal HFOs found, in most cases, a larger proportion of patients who had ictal HFOs had better postsurgical outcome than patients who did not have ictal HFOs [91, 95, 123, 124], but some did not find an association between fast ripple-frequency HFOs and outcome [125]. With respect to ictal HFO studies, if the area of seizure onset was completely removed in all patients, then the surgery outcome results suggest that in those patients who continued to have seizures, recording sites without ictal HFO could be distant from where seizures actually began.

To date, there appears to be only two studies that included ictal HFO information in surgical planning (Table 1). In one study that included 5 patients with epileptic spasms, site(s) of seizure onset with ictal HFOs (80–250 Hz), as well as location of MRI lesion, magnetoencephalography spike source dipole, and eloquent cortex, was(were) used to determine cortical area for resection [94]. Of these 5 patients, 3 were seizure-free at follow up between 14 and 29 months, 1 had >90 % reduction in seizures at 12 months, and the remaining patient had a 50–75 % reduction in seizures at 18 months. In the other study involving 6 patients with drug-resistant neocortical seizures, the SOZ was determined from the combination of all channels with seizures that contain HFOs at onset (≥ 70 Hz) and resection area defined as the contiguous region consisting of the SOZ, 1 cm of surrounding cortex, and sites of early spread within 2 s of onset [126]. Of these 6 patients, 3 had Engel class I outcome between 20 and 25 months, 2 had class II outcome at 24 and 30 months, and the remaining patient had class III outcome at 38 months. Owing to small sample sizes and absence of comparison surgical groups, no conclusion can be drawn on the efficacy of incorporating HFOs in resective surgery planning. Nonetheless, results from these two studies are consistent with retrospective data reviewed in the previous paragraph and indicate the need to carry out careful, rigorous prospective studies of HFOs in epilepsy surgery.

IIS, HFOs, and Epileptogenesis

Owing, in part, to the technical challenges and time required to carry out prolonged EEG recordings and data analysis in behaving animals, there have been far fewer studies of HFOs during epileptogenesis than on HFOs and epileptogenicity.

Table 1 Association between high-frequency oscillations (HFOs) and postsurgical outcome

Study	Patients/n	Type of recording/seizures	Surgery	HFOs	Association w/ outcome	Outcomes, n (follow-up)
Ochi et al. [91]	Children/9	Subdural/epileptic spasms	Focal, multi-lobe resection	Ictal R	R with seizure-free	IA, 4 *vs* IB-IVB, 5 (17)
RamachandranNair et al. [94]*	Children/5	Subdural, depth/epileptic spasms	Focal resection	Ictal HFO (80–250 Hz)	Undetermined	I, 3 (22) III, 2 (15)
Nariai et al. [95]	Children/11	Subdural/epileptic spasms	Focal resection, lobectomy	Ictal R, FR (210–300 Hz), β, γ	R with good outcome	I-IC, 6 (22) *vs* II, 5 (14)
Modur et al. [126]*	Adults/6	Subdural, depth/focal, GTC	Focal, multi-lobe resection	Ictal HFO (70–300 Hz)	HFO with good outcome	I, 3 (22) II, 2 (27) III, 1 (38)
Fujiwara et al. [124]	Children/44	Subdural	Focal, multi-lobe resection	Ictal HFOs (80–150, 150–300, 300–500 Hz)	HFO with seizure-free outcome	Full removal: I, 18 *vs* II-IV, 4 Partial removal: I, 4 *vs* II-IV, 15
Park et al. [118]	Adults/23	Subdural, depth/focal	Focal resection	Ictal high γ (60–99 Hz)	High γ with seizure-free	IA, 6 (39) *vs* IB-IV, 9 (28)
Usui et al. [125]	Adults/19	Depth/focal	Focal resection	Ictal FR (200–300 Hz)	No correlation between FR and outcome	Sites with FR: I, 6 (31) *vs* II-IIIA, 3 (18) Sites without FR: I, 5 (37) *vs* II-IIIA, 3 (38)
Jacobs et al. [111]	Adults/20	Depth	Focal resection	Interictal R, FR	R and FR with good outcome	I-II, 8 (20) *vs* III-IV, 12 (24)
Wu et al. [119]	Children/30	ECoG intraoperative	Focal resection, hemispherectomy	Interictal FR	FR with seizure-free outcome	I, 19 *vs* II-IV, 5
Akiyama et al. [64]	Children/28	Subdural, depth/focal, GTC, epileptic spasms	Focal resection, lobectomy	Interictal R, FR	FR with seizure-free outcome	IA, 10 *vs* IB-II, 18 (> 24)
van't Klooster et al. [122]	Children, Adults/13	Subdural	Focal resection	SPES-evoked R, FR	Evoked FR with good outcome	> 94 % FR sites removed: I, 2 < 50 % FR sites removed: I, 2, and III-IV, 5
Cho et al. [120]	Adults/7	Subdural	Focal resection	Interictal R, FR	R and FR with good outcome	IA-B, 6 (7) *vs* IIIA, 1 (8)
Haegelen et al. [121]	Adults/37	Subdural, depth	Focal resection	Interictal R, FR	R and FR with good outcome (TLE)	I-II, 9 (36) *vs* III-IV,12 (17)

GTC = generalized tonic-clonic seizure; ECoG = electrocorticography; R = ripple-frequency HFO; FR = fast ripple-frequency HFO; SPES = single pulse electrical stimulation; TLE = temporal lobe epilepsy

*Study considered HFO information in the surgical resection plan. Outcomes data (based on Engel Outcome Classification; numbers denote patients in each outcome group and, in parentheses, mean follow-up in months) reflect basis for association between HFOs and postsurgical outcome

Studies of epileptogenesis are frequently performed in chronic models of epilepsy that use either chemical or electrical stimulation to induce an episode of status epilepticus, which is an epileptogenic insult in many animals. After a variable delay of days to weeks spontaneous seizures can appear that often progress in number or severity, or both [127]. In one such model using unilateral intrahippocampal kainic acid injection that reproduces many features of human temporal lobe epilepsy, depth electrode recordings during epileptogenesis found shorter latencies to the first appearance of pathological HFOs correlated with shorter latencies to first spontaneous seizure [45]. After seizures appeared, brain areas generating pathological HFOs were typically stable over time (days to months), and a greater number of electrodes recording fast ripple-frequency HFOs correlated with a higher daily rate of seizure occurrence [114].

To date, no studies have replicated these results, although one study using a systemically injected pilocarpine model found that a higher rate of IIS containing fast ripple-, but not ripple-, frequency HFOs in CA3 correlated with a higher daily rate of seizure occurrence in epileptic rats [128]. Interestingly, other animal studies of epileptogenesis have found that the appearance of IIS and subsequent changes in the pattern of occurrence and shape features of IIS, for example slow wave component, were associated with development of spontaneous seizures [16–18]. Furthermore, *in vitro* work and computation modeling indicate that a reduction in GABA-mediated dendritic inhibition could explain changes in IIS waveform morphology [18], which might also contribute to the hyperexcitability within a PIN cluster supporting pathological HFOs [60]. Collectively these data suggest that the occurrence of pathological HFOs and IIS, either alone or in combination with each other, could predict the development of seizures and possibly severity of an epileptic condition in chronic animal models. Clearly, much more experimental work in animals remains to be done, and patient studies could contribute to this body of work if preliminary work on scalp EEG-recorded HFOs and epileptogenicity are substantiated.

Conclusions and Future Perspective

The experimental animal and patient studies described here provide compelling evidence that supports HFOs as a biomarker of epileptogenic brain tissue. Recent studies identifying differences in IIS waveform morphology and an association between some IIS, with or without HFOs, and development of seizures will likely stimulate future research on IIS and epileptogenesis. While microseizures, as well as HFOs and IIS, could be useful in studies of ictogenesis. Many of the conclusions drawn from interictal and ictal studies of HFOs in relation to epileptogenicity and postsurgical outcome derive from group-averaged data between patients and electrodes. It is anticipated that improvements in electrode design and configuration, new strategies to differentiate normal from pathological HFOs and quantify the extent of HFOs on an individual patient basis will help clarify questions relating HFOs to epileptogenicity and help design prospective trials to evaluate HFO in planning resective surgery. Continued research on HFO using scalp EEG combined with intracerebral EEG, magnetoencephalography, or functional MRI should provide new information on the mechanisms and spatial distribution of networks supporting HFOs. Furthermore, non-invasive recordings would make it feasible to study HFOs in relation to disease activity and evaluate HFOs as a biomarker of epileptogenesis in patients at risk for developing epilepsy, as well as those newly diagnosed with epilepsy.

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