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Conundrums of high-frequency oscillations (80-800 Hz) in the epileptic brain

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Abstract

Pathological HFOs (80-800 Hz) are considered biomarkers of epileptogenic tissue, but the underlying complex neuronal events are not well understood. Here, we identify and discuss several outstanding issues or conundrums in regards to the recording, analysis and interpretation of HFOs in the epileptic brain to critically highlight what is known and what is not about these enigmatic events. HFOs reflect a range of neuronal processes contributing to overlapping frequencies from the lower 80 Hz to the very fast spectral frequency bands. Given their complex neuronal nature, HFOs are extremely sensitive to recording conditions and analytical approaches. We provide a list of recommendations that could help obtain comparable HFO signals in clinical and basic epilepsy research. Adopting basic standards will facilitate data sharing and interpretation that collectively will aid in understanding the role of HFOs in health and disease for translational purpose.

1. Introduction

Clinical interest in the study of high-frequency oscillations (HFOs) started with observations in patients with temporal lobe epilepsy (TLE) and animal models of acquired epilepsy that found some focal seizures begin with HFOs and interictal HFOs localize to the brain area where spontaneous seizures initiate, i.e. the seizure onset zone. However, as new evidence and concepts evolved to advance the field, so did the questions on how to better understand the nature of these signals. HFOs can be recorded at the microscopic (single-cells), mesoscopic (microcircuits) and macroscopic (EEG) scales, with micro- and macro-electrodes both at the surface and in deep structures of the epileptic and normal brain, using different montages and filter settings. Do all of these types of HFOs reflect same or similar underlying neuronal processes, or are there physiological and pathological forms of HFOs? Are HFOs recorded in humans with different electrodes at different spatial scales and brain regions similar to HFOs recorded in animals? How does differential recording affect HFO waveform? Are there suitable methodological approaches to analyze and interpret HFOs?

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In this review we discuss some of the unresolved questions about HFOs to clarify what is known and what is not. Although we agree that the study of HFOs has been fruitful in epilepsy research, we believe there is value in critically discussing and highlighting the state-of-the-art from the perspective of HFO conundrums. We conclude with a list of recommendations suggested as the minimum requirement to obtain reliable and comparable HFOs from different clinical and basic research centers.

2. Physiological and pathological HFOs: is there any difference?

Pathological HFOs are historically linked to “fast ripples”, which are electrophysiological events first described with microelectrodes in the local field potential (LFP) of the hippocampus of patients with TLE and rat models of this condition (Bragin et al. 1999). In healthy non-primates and non-human primates, “ripples” (100-200 Hz; <100 msec) are typically recorded in association with sharp-waves in the cell lamina of the hippocampus and entorhinal cortex (Buzsaki et al., 1992; Skaggs et al., 2007). The term “fast ripples” was thus coined based on their ripple-like appearance and greater power at much higher spectral frequencies (>200-250 Hz) recorded in the dentate gyrus of epileptic rats (Bragin et al., 1999), a hippocampal region where ripples are not normally observed. Hippocampal ripples in healthy rats correspond to intermittent periods of increased pyramidal cell firing that is tightly regulated by interneuron-mediated perisomatic inhibition (Buzsaki et al., 1992; Ylinen et al., 1995).

Their maximal amplitude can be recorded nearby the pyramidal cell layer and all along the CA1 to subiculum in rats (Chrobak and Buzsaki, 1996). Evidence from microelectrode and intracellular recordings of ripples are consistent with the hypothesis that they reflect short sequences of phase-locked neuronal action potentials together with postsynaptic excitatory potentials (EPSPs, at the ripple trough) and inhibitory postsynaptic potentials (IPSPs, at the ripple peak) (Csicsvari et al., 1999; Ylinen et al., 1995; Maier et al., 2010) (Fig.1A).

By contrast, pathological fast ripples generally contain power from 250 up to 800 Hz although their spectral peak does not necessarily differentiate them from ripples in many circumstances (Engel et al., 2009). Neuronal firing associated with fast ripples appear to mostly reflect spontaneous bursts of spikes of many principal cells at variable degree of synchronization (Ibarz et al., 2010; Bragin et al., 2011). Because synchronous action potentials from different pools of neurons occur during fast ripples, each fast ripple cycle mostly reflects a field potential population spike (Dzhala and Staley, 2004; Foffani et al., 2007; Ibarz et al., 2010; Bragin et al., 2011). Note that the spiky nature of individual cycles of fast ripples reflect millisecond synchronization of action potential firing as first described in the early 1960s by Andersen and colleagues (Andersen et al., 1971), and are not related to the clinical EEG spike which refer to a broader event that results from filtered paroxysmal discharges. In those experiments by Andersen et al. 1971, spike synchronization was elicited by strong electrical stimulation, but spontaneous large amplitude population spikes are not observed in the normal healthy brain.

During physiological ripples, neuronal firing preferentially occurred around the ripple trough as recorded at the cell body layer and a small spiky component could be visible with

microelectrodes (glass pipettes, 13 μm tetrodes or 15 μm thick silicon probes). These events were initially termed mini-population spikes (Suzuki and Smith, 1988; Buzsaki ,1986) (Fig. 1A), and reflect synchronous firing of no more than 20% of pyramidal cells as estimated by Csicsvari (Csicsvari et al., 2000). Instead, a requirement for millisecond precision synchronization of larger pool of interconnected neurons (i.e. microcircuits) underlying spontaneous population spikes is easily met in pathological conditions such as epilepsy and therefore during fast ripples the spiky component often dominates (Bragin et al., 2002; Ibarz et al., 2002; but see Schomburg et al., 2012). Hence these transient pathological HFOs lasting less than 100 ms reflect brief synchronization of discharging cells. In some circumstances, particularly those preceding ictal events, HFOs occur as relatively continuous runs of activity (Zijlmans et al. 2011; Weiss et al. 2013; Worrell et al. 2003). In these cases, LFP recordings could reflect a global increase of neuronal activity with evolving level of synchronization of neuronal firing and excitatory and inhibitory synaptic components (Bikson et al. 2003; Jiruska et al. 2010; Gnatkovsky et al. 2008; Zhang et al. 2012). Therefore, spontaneous population spikes contributing to the high-frequency bands are probably the most distinctive hallmark of pathological HFOs, either if they are detected transiently or over relatively more continuous periods.

However, distinguishing normal and pathological HFOs is not so straightforward. Some pathological HFOs could contain significant spectral power in a band normally associated with physiological ripples (100-200 Hz). In other words, fast ripples (>250 Hz) are pathological by definition but not all pathological HFOs are fast ripples. What other cellular processes could distinctly contribute to pathological HFOs to make them recognizable? In epileptogenic tissue, abnormal excitability could reflect alterations in intrinsic membrane properties and synaptic circuitry across a wide range of brain regions that have the propensity to generate epileptic seizures. Several changes occur in these territories that potentially affect the expression of physiological HFOs, including loss of some specific interneuronal types (Esclapez and Houser, 1999), differential imbalance between dendritic and somatic inhibitory potentials (Cossart et al., 2001), defects in GABA release (Hirsch et al., 1999), and perturbation of chloride homeostasis in a population of pyramidal cells with low levels of KCC2 and increased NKCC1 expression (Cohen et al. 2002; Huberfeld et al. 2007). These changes, together with acquired or genetic channelopathies, can increase excitability of pyramidal cells (Bernard et al. 2004; Chen et al., 2011; Higgs and Spain, 2011; Simeone et al., 2013). Therefore, the question of whether a particular HFO event is physiological or pathological could be better addressed at the micro- and mesoscopic levels. From a clinical perspective, since the LPF signature of the ripple band can be ambiguous, microelectrodes targeting the microscale circuit, defined as pools of neurons which generate HFOs, may help to better understand their nature.

3. HFOs: an oscillatory event or a broad frequency band?

Another issue in the field is whether an event can be called an HFO if it is not an oscillation *sensu stricto*. In many cases, both physiological and pathological HFO runs can be regarded as reflecting different consecutive components and not necessarily appear as a continuous oscillatory sequence (or cycles). Hence, pathological HFOs could appear as single or multiple, regular or irregular sequence of population spikes depending how firing

coordination is achieved by different pools of neurons (Ibarz et al., 2010; Bragin et al., 2011).

From a spectral perspective, an appropriate definition could include the presence of a "power bump", i.e. an increase in power within a particular frequency band such as 100 to 200 Hz. For physiological ripples this definition applies well because ripple waveforms close to – but not in - the cell body layer are dominated by the positive cycling of rhythmic IPSPs (Ylinen et al., 1995). However, for fast ripples where each cycle consists of an individual population spike, the waveform does not necessarily appear to be a continuous oscillation even though it corresponds to relatively narrow peaks in the spectrogram (Bragin et al., 2011). In other cases, when abnormal population bursts occur in groups of cells, rhythmic population spikes contribute to fast ripple cycles reflecting in-phase and out-of-phase burst firing that further complicates the spectral features (Dzhala and Staley, 2004; Foffani et al., 2007; Ibarz et al., 2010).

Neuronal firing contributing to HFOs (Fig.1A) has also strong impact on the spectral properties of these events (Schomburg et al., 2012). Accordingly, multiunit activity is reflected as spectral contamination in the high-frequency band >300 Hz (Staba et al., 2002; Scheffer-Teixeira et al., 2013), but also at lower frequencies, i.e. 80-150 Hz (Ray et al., 2011; see section 11). In epileptic conditions, ectopic action potentials originating from non-somatic compartments (Stasheff et al., 1993), electric coupling (Roopun et al., 2010; Taylor and Dudek 1982; Jefferys 1995) or fast dendritic spikes (Kandel and Spencer, 1961; Traub et al., 1993) could further contribute to the spectral complexity of pathological HFOs, but these potential mechanisms are still under scientific debate. However, as previously discussed, HFOs also involve synaptic activity at a wide spectral band from 80 Hz to up to 150 Hz (Sullivan et al., 2011; Stacey et al. 2009; see Jefferys et al., 2012 for review), which complicate their spectral classification.

When one considers the number and complexity of mechanisms generating HFOs it is difficult to disentangle the relative contributions of action potentials and synaptic events to field potentials recorded at the mesoscopic and macroscopic levels. Importantly, the spectral features of HFO signals strongly depend on the position of the recording electrode (in the different cellular layers, within or adjacent to epileptogenic tissue) and on their size (e.g. bigger electrodes tend to damage neurons and therefore the spiky component would be less dominant; see section 8). Thus "high-frequency" is a relative term as HFOs encompass a range of cellular and synaptic processes contributing to a wide frequency band from 80 to 800 Hz.

4. In vivo versus in vitro models of transient HFOs

When the hippocampus is isolated in slices, disconnected from important afferent influences and not exposed to the effect of neuromodulators (i.e. cholinergic, adrenergic, etc...), spontaneous sharp-wave ripples emerge at regular intervals of 10-30 events per minute (Maier et al., 2003; Kubota et al., 2003). It seems that the strong inhibitory control of the intact brain is easily disrupted by the slicing procedure and other factors affecting the storage conditions (Tanaka et al. 2008; Maier et al., 2009, Kubota et al., 2003), so that when

hippocampal slices of normal animals are submitted to slight increases of excitability synchronous bursts of action potentials and abnormal HFOs are produced (Dzhala and Staley, 2004; Foffani et al., 2007; Karlocai et al., 2014). Other manipulations, including repetitive high-frequency stimulation (Behrens et al., 2005), cholinergic and adrenergic modulation (Liotta et al., 2011; Ul Haq et al., 2011) and fast GABAergic disinhibition (Miles and Wong 1987) have been shown to affect the degree of firing synchronization and HFO expression. Therefore, physiological HFOs (ripples) appear fragile and dependent on a balanced level of inhibition and excitation, a breakdown of which can easily transform them into abnormal forms of HFOs (Aivar et al., 2014; Karlocai et al., 2014). Slices prepared from human brain resections support the finding that HFOs can be recorded in epileptogenic territories (Köhling et al., 1998; Roopun et al., 2010), but there is controversy regarding the underlying mechanisms and the current generators. The bottom line of these experiments is that in vitro data needs to be contrasted with in vivo data because the excitability level strongly determines the expression on different forms of HFOs (Aivar et al., 2014; Karlocai et al., 2014). Therefore several mechanisms underlie in vitro HFOs that may or may not contribute to the generation of HFOs in the intact brain.

In vitro models are necessary because they tell us about the different mechanisms leading to the generation of HFOs both in the physiological and pathological context. From this perspective, HFOs could be regarded as a circuit phenotype, as several pathways can lead to overlapping yet different expression. Work from independent laboratories over the years has shown us that HFO expression is critically dependent on the level of excitability in the slice. Possibly, a framework to better understand these processes is to interpret experiments parametrically. A key variable is the excitatory/inhibitory (E/I) ratio because this directly impacts the local field potential signatures in a predictable way (Aivar et al. 2014). Independent of the manipulation (changes in connectivity, disinhibition, synaptic facilitation, extracellular ion composition, etc...), changes in the balance of excitation and inhibition determine the nature of firing recruitment and HFO expression. Channelopathies and other changes affecting intrinsic excitability are factors that directly account for the distortion of local field potential HFOs. These two axes (i.e. excitability and E/I balance) define a parameter regime for HFO expression. Understanding this landscape would help us to fill the gap in the diversity of HFO mechanism and identify the potential boundary that separates physiological and pathological HFOs.

5. Human HFOs versus animal HFOs: are they similar?

Another conundrum is whether there are common mechanisms and processes underlying HFOs in epileptic humans and animals so that we can make inferences from one species to another. Brain oscillations from slow (0.1 Hz) to fast rhythms (200 Hz) are preserved phylogenetically (Buzsaki et al., 2014) and experimental perturbation in animals suggest that a range of resulting rhythmopathies could be further exploited as disease-specific biomarkers. Fast ripples are an outstanding example.

Are HFOs in human and rodents similar? Transient pathological HFOs, i.e. fast ripples recorded with microelectrodes in the hippocampal and entorhinal cortex of people suffering from TLE (Bragin et al., 1999; Staba et al., 2002) are analogous to HFOs recorded in vivo

from equivalent regions in rodent models of epilepsy (Bragin et al., 1999). As commented before, they mostly reflect neuronal activity at millisecond scale emerging from bursts of cellular firing (Ibarz et al., 2010; Bragin et al., 2011). They might also reflect synaptic activities and spike afterpotentials that mix together (Menendez de la Prida and Trevelyan, 2011; Buzsaki et al., 2012; Schomburg et al., 2012; Reimann et al., 2013). These signals from humans and rodents are directly comparable because they are acquired with similar types of electrodes, reference montage and acquisition and filter settings. They probably represent the most straightforward evidence of analogous transient HFOs in the epileptic hippocampus of humans and animals.

Microelectrode recordings in humans show similar spectral complexity as described for animal studies (Staba et al., 2002; Ibarz et al., 2010). The power spectrum of human HFOs are contaminated by spiking activity that broadly leaks into the higher (>300 Hz) and the slower frequency bands (Staba et al., 2002). Importantly, ripple-like and transient high-gamma oscillations are observed at the LFP from epileptogenic areas and appear to be intermixed with pathological fast ripples (Bragin et al., 1999; Le Van Quyen et al., 2010). Neuronal processes at the high-gamma, ripple and fast ripple bands might naturally interact (Tort et al., 2010, Sullivan et al., 2011; Menendez de la Prida and Trevelyan, 2011), which further complicates separation of physiological and pathological HFOs. In human recordings, we still do not know whether physiological ripples just coexist with pathological HFOs in epileptic territories or if distorted cellular processes that generate spontaneous seizures can only support pathological HFOs (Engel et al. 2009; Aivar et al., 2014). Importantly, HFOs recorded by clinical macroelectrodes especially using subdural electrodes could reflect volume conducted potentials that arise from cellular generators well below the surface electrode. Therefore it is still crucial to validate genuine hallmarks of pathological HFOs when assessing their role in clinical epilepsy. While much work remains to better understand this issue one recommendation is to focus on faster frequencies (>250 Hz) using wide-band and high-temporal resolution microelectrode recordings in clinical settings, and to look at the statistical behavior of individual HFOs (e.g. power bumps discussed in section 3) to infer their pathological nature. From a clinical research perspective, this recommendation is probably better suited for depth microelectrodes than for neocortical/subdural recordings, where HFO frequencies are typically below 250 Hz. Discussion of these issues and how they might affect recording and interpretation of HFOs is continued in Sections 6 and 8.

6. Neocortical versus hippocampal HFOs

Transient HFOs also occur in neocortex of people affected by both temporal and extratemporal epilepsies. Are these HFOs related to normal activity or do they rather mark epileptogenic regions? Several studies in presurgical patients provide evidence that interictal and ictal HFOs are strongly associated with the seizure onset zone in neocortical epilepsy (Worrell et al. 2004; Ochi et al. 2007; Jacobs et al. 2009). In healthy rodents, spontaneous HFOs (100-200 Hz) at the parahippocampal and entorhinal cortical regions are typically linked to the hippocampal ripple generator and propagate accordingly (Chrobak and Buzsaki, 1994). During sleep, cortical HFOs (200-800Hz) recorded with microelectrodes are associated with high-voltage spindles generated by the thalamocortical circuit (Kandel and

Buzsaki, 1997). Fast cortical oscillations (200-500 Hz) are evoked in the somatosensory and the parietotemporal multisensory cortices by sensory stimulation (tactile, acoustic) in awake normal rats (Barth et al., 1993) and they reflect millisecond synchronization of high-frequency neuronal firing (Jones et al., 2000; Barth, 2003), similar to fast ripples. Neocortical fast oscillations can also be generated in the absence of thalamocortical inputs in the intact rat (Staba et al., 2003).Therefore, it seems that some neocortical territories contain circuits that support the generation of transient HFOs >200 Hz in response to both external (i.e. peripheral stimulation) and internal (i.e. state-dependent) activation even under normal conditions. Some reports of HFOs and microseizures in non-epileptic neocortical tissue may suggest that these fast ripples are not necessarily pathological since they are not related to epileptogenic regions but occur in relatively healthy microcircuits (Stead et al. 2010). However, it does not contradict with the idea that they are reflecting abnormal levels of synchronization (Aivar et al. 2014).

In the intact brain, propagation of HFO-associated excitatory bouts of activity through the parahippocampal synaptic pathway is typically constrained by region-specific recruitment of fast inhibitory circuits (Menendez de la Prida and Pozo, 2002; Menendez de la Prida and Gal, 2004). Thalamic activation of neocortical territories is temporally controlled by feedforward and feedback local inhibition (Swadlow et al. 2005). Data suggest that this GABAergic control might be impaired in the epileptic brain (D'Antuono et al., 2002; Menendez de la Prida et al., 2002; Gorter et al., 2001; Drexel et al., 2013; Knopp et al., 2008; Huberfeld et al., 2007; 2011). Similar processes occur in neocortical areas associated to cortical dysplasia or heterotopias (Roper et al., 1999; Sarkisian et al., 2001; Calcagnotto et al., 2005; Alonso-Nanclares et al., 2005; Poluch et al., 2008; Cid et al., 2014). Thus, GABAergic loss-of-function by any of several mechanisms promotes abnormal neuronal firing synchronization and unbalanced synaptic activity. In neocortical foci from cats and monkeys, abnormal bursting of single-cells is intermixed with more normal-like firing patterns probably reflecting such an inhibitory impairment (Calvin et al., 1968; Prince and Futamachi, 1970; Wyler et al., 1975), similar to TLE patients (Colder et al., 1996). These data advocate synchronous neuronal bursting phase-locked with fast cortical local field potentials and exacerbated synaptic activity as common mechanisms of neocortical and hippocampal epileptic HFOs (Connors 1984; Grenier et al., 2001; Axmacher et al., 2008; Schevon et al., 2008; see Jefferys et al., 2012 for review). Therefore, as for hippocampal HFOs, a combination of neuronal recordings at single-cell and field potential resolutions would be more helpful in disambiguating the abnormal character of neocortical HFOs than LFP and EEG recordings alone.

7. Potential role of HFOs in the transition to seizure

Understanding the mechanisms of transition to seizures is an active area of investigation. One key challenge is objective identification of the system state using recorded data. HFOs, here defined as oscillatory activity in the 80-500 Hz band, have emerged as a potential biomarker. Most of what is reported during seizure transition describes HFO runs lasting several hundreds of millliseconds, as compared with transient short-lived fast ripples (<100 ms duration). When one reads the literature on this matter it clearly supports the impression

that HFOs during transition periods encompasses several cellular and synaptic processes (Khosravani et al., 2005; Gnatkovsky et al. 2008; Jiruska et al., 2010; Zhang et al. 2012).

The utility of HFOs as biomarkers of ictogenesis has predominantly focused on the spatial rather than the temporal distribution of the HFO events (Schevon et al; 2009). Techniques to identify specific electrodes with HFO activity have been used extensively to guide resections; however, the changes that occur within these HFO containing electrodes as seizures begin and end have not been well characterized or exploited. The presence of HFOs and their relative rate of occurrence are proposed to better localize the seizure onset zone (SOZ) as compared to interictal spikes and other features of low frequency activity (Andrade-Valenca et al., 2011; Wang et al., 2012). The use of HFOs to identify the epileptogenic region and guide surgical resection is correlated with good outcomes (seizure-free or significant reduction in seizures) in TLE patients in some studies (Haegelen et al., 2013; Akiyama et al., 2011; Jacobs et al., 2010). Other metrics such as resection volume show no correlation with seizure-free outcome and further suggest that HFOs might uniquely identify critical regions that require resection (Haegelen et al., 2013).

What is the evidence supporting a role of HFOs in ictogenesis and how compelling is it? Evidence from the in vitro low Mg^{2+}/high K^{+} seizure model shows that HFOs in the ripple and fast ripple bands increase in power in the preictal region faster and more selectively than low frequency activity (Khosravani et al., 2005). Similarly, in the in-vitro high K^{+} seizure model, increasing HFO runs mark the transition between successive ictal events (Jiruska et al., 2010). The temporal correlation between HFO activity and seizures was corroborated in vivo using the kainic acid rat model of TLE in which the duration and power of HFOs riding atop interictal spikes increased in the final seconds of the preictal period before seizure onset (Bragin et al., 2005). During epileptogenesis, the length of time recorded before HFO emergence in the latent phase was correlated with latency to spontaneous seizures and inversely correlated with the rate of seizures during the spontaneous seizure phase (Bragin et al., 2004). Interestingly, in experimental models of TLE reducing the inhibitory tone or modifying excitability and the E/I balance causes the size of HFO generating areas to increase, coalesce, and synchronize until a critical mass ignites propagation, suggesting a mechanism of ictogenesis (Bragin et al. 2002; Jiruska et al. 2010; Karlocai et al. 2014). Combined, given their relationship with enhanced neuronal excitability these microelectrode data suggest that HFOs may provide both a long timescale measure of ictogenesis and a short timescale indicator for the transition to seizure.

In humans, the analysis of temporal changes in HFO activity during the transition to seizure has produced mixed results. Early evidence suggested highly variable transitory changes in HFO activity in the SOZ which supported no clear trend (Jacobs et al., 2009). Subsequently, weak correlations were shown between high levels of HFOs and the transition to seizure (Zijlmans et al., 2009). In contrast, Worrell et al showed a clear increase in HFO power in the SOZ of 62% of patients up to 20 minutes before seizure onset (Worrell et al., 2004). In addition, Jirsch et al (2006) found an increase in HFO power near ictal onset compared to preictal episodes in patients with localized mesial temporal and neocortical SOZ. Subsequent recordings, using segmented high-frequency activity to show increases in the ripple and fast ripple bands during the transition from interictal to preictal and finally to the

ictal state demonstrated that the effect was present both within the SOZ and outside but was most pronounced in the SOZ (Zijlmans et al., 2011, Khosravani et al., 2009). However, the rate of epileptic spike activity showed less consistency than HFOs and appeared to initially drop at the onset of seizure and increase dramatically during the ictal phase (Zijlmans et al., 2011). This probably reflects the evolving dynamics of neuronal firing and synaptic activity (Gnatkovsky et al. 2008; Jiruska et al., 2010; Zhang et al. 2012). Phase locking of HFOs with low frequency activity demarcates ictal core regions from penumbral regions, provides a temporal marker describing the propagation of ictal activity and discriminates the preictal state (Schevon et al., 2012; Weiss et al., 2013; Alvarado-Rojas et al., 2014). Importantly, any analysis of HFOs during extended periods of time leading up to seizures must take brain-state dependent transitions into account (Quyen et al. 2010; Sedigh-Sarvestani et al. 2014)

While the above evidence suggests a potential link between HFOs and the transition to seizure, the mechanisms underpinning the generation of these oscillations and how (and if) they contribute to the preictal-ictal transition remain unresolved. A major problem with the available data on the role of HFOs in ictogenesis is that a common procedure has not yet been adopted to record and analyze this activity. As an example, conflicting results such as the studies of Zijlmans et al. (2009) and Worrell et al. (2004) may arise from differing recording settings, a major problem one has to deal with when interpreting multi-center clinical data. Whereas Zijlmans et al (and Jirsch et al. 2006) used small 0.8 mm^2 stainless steel contacts, Worrell et al used large 12.6 mm^2 platinum contacts in a bipolar montage which may result in recording from incomparable underlying processes (Zijlmans et al., 2009; Worrell et al., 2009; Stacey et al., 2013) (see next section). It is also possible that differences in the location of electrodes with respect to cellular sources of HFOs give unclear results. If we want to disentangle this HFO conundrum we necessarily have to better link the microscopic (single-cells), mesoscopic (local field potential) and macroscopic (EEG) scales of HFOs and agree on common gold-standards to record and filter activity comparably in human and animal research.

8. Effect of electrode size on HFO detection

When recorded using depth macroelectrodes of different areas and shapes, HFOs lasting tens of milliseconds can be found in the human medial temporal lobe (Worrell et al., 2008; Crepon et al., 2010, Jirsch et al., 2006, Urrestarazu et al., 2007). Due to the local nature of HFOs and the large recording surface area of macroelectrodes, it is difficult to infer how macroscopic HFO signals relate to the mesoscopic scale of local field potential HFOs. Their relationship with interictal spikes and their visibility in the raw traces would depend on the acquisition standards and the distance to the cellular sources.

Simultaneous wideband recordings at high sampling rate suggest that transient HFOs have different spectral features in micro- and macroelectrodes when used simultaneously. In clinical depth macroelectrodes, the spectral power of HFOs is mostly confined to the ripple range (Worrell et al. 2008), but can also be found in the high gamma band (80-120 Hz) when recorded in bipolar montage. Simultaneous relatively adjacent microelectrode recordings, however, show HFO activity is typically found in the higher frequency bands

(Worrell et al. 2008). Wide-band high-frequency sampled ECoG signals in humans can similarly capture high-gamma activities (60-150 Hz) using distant references on the grid (Canolty et al., 2011) and skull (Gaona et al., 2011), similar to animal settings. The question that arises is do these EEG signals reflect physiological, pathological or artefactual processes? Can these spectral features be ascribed to methodological issues (filter settings, sampling rate, reference montage), or are they inherent to macroelectrode recordings due to their low spatial resolution? If one makes a very simple test of combining microelectrode recordings of physiological ripples at different yet proximal (< 1 mm) hippocampal areas the ability to still detect clearly visible HFOs in the compound signals is not straightforward as it might depend on the resulting dominant dipole at a larger spatial scale (Fig.1Ba; green signals). While a simple arithmetic combination of local LFP signals is far from reflecting the complexities of the broader electrical field recorded with macroelectrodes (Lempka and McIntyre 2013), this simple test highlights difficulties of mechanistically interpreting these recordings. Possibly, pathological HFOs involving synchronous potentials in larger pools of neurons contribute at a larger spatial reach (Kajikawa and Schroeder 2011; Linden et al. 2011).

Is there an optimal size and placement of electrodes to record HFOs? Unfortunately, the existing body of evidence does not provide a definitive answer (Worrell et al., 2012). As indicated by the studies cited in Section 6, HFOs can be recorded from electrodes positioned in subcortical structures or placed on or just beneath pial surface of cerebral cortex. Studies of neocortical HFOs, including recent work that provides evidence for HFOs in scalp-recorded EEG (Andrade-Valenca et al., 2011; Melani et al., 2013), suggest there is greater variability in the spatial scale of these HFOs than hippocampal HFOs, but studies are needed to identify the location of cell populations and mechanisms underlying neocortical HFOs (Kandel and Buzsaki, 1997; Grenier et al., 2003).

Patient studies show HFOs can be recorded using a variety of electrodes including microelectrodes (recording contact surface area: ~0.0013 mm^2), larger diameter clinical macroelectrodes (0.5-10 mm^2), and hybrid types that combine both micro- and macro-electrodes (Bragin et al., 2002b; Staba et al., 2002; Urrestarazu et al., 2007; Worrell et al., 2008). Intracerebral recordings in patients are guided by safety and clinical need, which can limit in vivo recordings in terms of the number, size, and placement of electrodes. However, in spite of the differences in the size and placement of electrodes, a result consistently found among retrospective patient studies is the association of the SOZ with the occurrence of fast ripple-like HFOs, and in some cases of neocortical epilepsy, with ripple-like HFOs. One explanation for these data is that electrode size does not significantly affect the detection of pathological HFOs, but thus far this hypothesis has not been rigorously tested. However, as indicated in section 4, recording normal HFOs such as ripples can be quite sensitive to perturbations in excitatory and inhibitory processes that could arise from positioning large diameter electrodes versus small diameter microwires (≤ 40 μm) in the hippocampal cellular layers. Actually, clinical studies using macroelectrodes indicate HFOs in the physiological ripple band to be almost as good at identifying epileptogenic regions as fast ripples (Urrestarazu et al. 2007; Worrell et al. 2008). Possibly, detailed dipole analysis would permit normal HFOs to be filtered out in these recordings (Bragin et al. 2007).

This explanation is similar to the conclusion from a study in epileptic rats that evaluated rate of occurrence, mean spectral frequency, amplitude, and duration of hippocampal ripple- and fast ripple-like HFOs in relation to contact surface area (Chatillon et al., 2011). Analysis found no difference in rates of occurrence or other aspects of HFOs with respect to electrode contact surface area (0.018, 0.051, and 0.85 mm^2), although HFO rates were higher and mean amplitude was lower in this study compared to those reported in a different study using smaller electrodes (0.0028 mm^2; Bragin et al., 1999b). These latter differences could be attributed to the HFO detection methods used in each study, but the higher rates on larger electrodes might reflect sampling from a larger volume of tissue that could potentially contain multiple HFO-generating sites, while lower mean amplitude could indicate a longer distance between recording site and HFO-related current sources. If this is correct, it is not clear why the former study did not find differences in HFO rates and amplitude between the largest and smallest contact evaluated (~47x larger surface area).

In other work by Chatillon and colleagues, this study involving patients that was designed similarly to their animal study (Chatillon et al., 2013), results showed no difference in HFO rates of occurrence or other features with respect to clinically relevant contact size (0.2, 0.3, 0.8, and 5.0 mm^2). However, higher rates of ripple-like HFOs and seemingly much greater variability in rates of fast ripple-like HFOs were found in this study compared to another patient study recording with smaller microelectrodes (0.0013 mm^2; Bragin et al., 1999a). In addition, a separate patient study using hybrid depth electrodes detected a larger proportion of HFOs, particularly fast ripple-like HFOs, on microelectrodes (0.0013 mm^2) compared to macroelectrodes (9.4 mm^2; Worrell et al., 2008). Most (83%) of the microelectrode-recorded HFOs were detected on a single microelectrode, while the remainder of HFOs appeared on two microelectrodes (1 mm separation) or single macroelectrode. It should be considered that large diameter electrodes (1.0-1.5 vs. 0.04 mm^2) could produce greater tissue disturbances that make it more difficult to record fast ripple-like HFOs in close proximity to the electrode. This possibility, however, appears less likely since there was no difference in HFOs recorded from microelectrodes that extended several millimeters beyond the distal tip of each clinical electrode versus those that were fixed and even with the surface of the clinical electrode (Worrell et al., 2008). Volume conducted signals could also complicate interpretation of macroelectrode recordings. Evidence from a computational study suggests that compared to microelectrodes, macroelectrodes were more likely to record temporally uncorrelated fast ripple-like activity from spatially distant cell populations that could significantly attenuate the amplitude and power associated with the fast ripple-frequency HFO signal (Demont-Guignard et al., 2012).

It is difficult to reconcile the differences among these studies without information on the position of the electrodes with respect to the cellular layers, but collectively results suggest that detection of ripple- and fast ripple-like HFOs could be affected when there are very large differences in contact surface area (e.g., 150-7200x), while the detection of HFOs will be more consistent between contacts of comparable size (<50x). It appears an advantage of macroelectrodes is the capability to sample a large volume of tissue and potentially record multiple HFO sites. However, longer distances between recording electrode and HFO-generating sites could lead to greater spatial averaging of uncorrelated HFO activity and inclusion of interfering signals such that the measured HFO field potential does not

accurately reflect local HFO activity. On the other hand, microelectrodes can be positioned more closely to cell lamina and provide better spatial resolution to record local current sources, but if pathological HFO-generating sites are widely scattered and supported by a small volume of tissue, then this would require precise placement of the microelectrodes to avoid missing the active cell populations. Positioning microelectrodes and localization is more reliable in animals than patients, as is the use of high-count, high-density microelectrode arrays to increase the likelihood of detecting HFOs. High-density microelectrode array recording in the human epileptic brain seems necessary to better understand mechanisms generating normal and pathological HFOs and to inform studies of HFOs in clinical epilepsy.

9. Differential recording and bipolar montage: A critical problem for interpretation of HFOs

Differential amplifiers measure the voltage difference between two electrodes (e.g., A and B) and are commonly used in basic research and clinical electrophysiological setups. Ideally, the common mode voltage present at each of the electrodes, which often consists of ambient noise, is nulled while the desired voltage signal (i.e., HFO) recorded at one of the two electrodes is passed as output such that: output = $V_A - V_B$ = (noise + $signal_A$) – (noise) = $signal_A$. However, in this configuration, the location of electrodes in relation to one another and in relation to the location and size of HFO source(s) could make it challenging to accurately isolate/interpret the signal of interest. For example, if two electrodes record in the vicinity of a given HFO generator, then depending on the signal polarity at each electrode the recorded HFO could appear spuriously larger or smaller than the actual HFO. Alternatively, if two electrodes are recording different HFOs that are temporally displaced at one site versus the other, then it is likely the HFO at the output will not resemble the HFOs at either electrode site (see Engel et al. 2009). Thus, it can be very difficult to interpret and study the underlying neuronal mechanisms using locally differential recordings with two electrodes positioned in HFO generating sites.

Clinical scalp and depth EEG is regularly recorded using a distant common reference electrode and then reviewed and analyzed as referentially-recorded signals, but often reformatted in a bipolar montage. Similar to the example above, if HFOs occur synchronously on two separate recording sites, then the mathematical subtraction of one electrode from the other will cancel the HFO in the bipolar montage. The effects of bipolar reformatting can be illustrated by a simple experiment in Fig. 1Bb (blue trace) where ripples were recorded from two separate electrodes in relation to distant reference electrode. Subtracting the ripple on microelectrode 2 from the ripple on microelectrode 1 produces a signal that clearly does not resemble the ripples on either microelectrode or the spectral frequency profile of the ripples. Thus, similar to differential recordings, analysis of HFOs using reformatted bipolar montage must carefully consider the possibly of spurious HFOs that can produce artifactual events.

In many cases, one electrode is positioned in cellular layers to record HFO and the other electrode is positioned distantly, e.g. at the mastoid or on the skull, where there is a lower probability of recording the desired signal. Conceptually, this configuration consists of an

"active" electrode and "non-active" reference respectively, but in practice both electrodes are active with the reference susceptible to volume conducted effects and state-dependent changes in levels of neuronal synchronization that can produce measurable voltages by the skull reference. Thus, using common references possess additional problems that should be further contrasted and discussed (Guevara et al. 2005). In addition, the recent discovery of HFOs recorded in scalp EEG further complicates the issue of whether there is an ideal configuration to record HFOs. However, most studies use multiple spaced electrodes that are recorded in relation to a common reference and based on results that suggest the volume of tissue generating HFOs could be as small as 1 mm^3, the occurrence of HFO on all electrodes could indicate the reference electrode is contaminated with HFO. By contrast, the occurrence of HFO on some but not all electrodes, combined with spatiotemporal analysis of HFOs, could provide convincing evidence that the HFOs are generated by independent local sources and not a function of the reference location.

10. Is automatic detection of HFOs possible?

The problem of HFO identification in both human and rodent intracranial recordings remains unresolved and is complicated for several reasons. Firstly, the target signals, HFOs, are by nature small amplitude (on the order of hundreds of microvolts) and frequently nested within other large amplitude activity which can make their identification both visually and algorithmically difficult (Bragin et al., 1999a; Bragin et al., 1999b; Belluscio et al., 2012). Secondly, varying definitions of HFO activity, which generally suggest a wide frequency range of 80-500Hz (see section 3), and a duration that requires at least 4-6 cycles have a led to a broad definition that encompasses single or consecutive population spikes (Staba et al., 2002; Bragin et al., 2010; see section 2). Using arbitrary thresholds to track for these features of HFOs fundamentally biases the types of events to be selected for analysis. Thirdly, HFO activity is spatially localized to small volumes of tissue and its morphology is location specific in laminar structures (Bragin et al., 2002, Scheffer-Texeira et al., 2012). Fourthly, multiunit activity and sharp edges in recorded signals act as contaminants and may spuriously appear like HFO activity (Scheffer-Texeira et al., 2013; Kramer et al., 2008; see next section). Finally, high density and sample rate recordings produce large data sets which preclude manual inspection and require automated methods to identify events of interest for further analysis or for statistical purposes.

To address these issues, a number of techniques have been used beginning with manual HFO identification. However, visual detection of HFOs is limited by investigator experience and possibly bias, low inter-rater reliability and problems with reproducibility which are similar to the issues encountered in interictal spike and seizure identification (Gardner et al., 2007; Deacon et al., 2003). Automated techniques for HFO detection began with Staba et al., 2002 who employed a FIR bandpass filter to isolate the 80-500 Hz frequency range. HFOs were subsequently marked using an RMS power metric where events were defined to be regions in which the power exceeded mean + 5·SD of the entire signal (Staba et al., 2002). This identification system was followed by manual review to remove artifactual events and further automated filtering to combine adjacent events and eliminate events less than 6 cycles in duration (Staba et al., 2002). Gardner and colleagues prewhitened the spectrum of the signal before detection to address 1/f roll-off inherent in

electrophysiological recordings, used line-length as a detection metric in order to deemphasize outliers and used a non-parametric threshold as the collected data was not Gaussian (Gardner et al., 2007).

An alternate approach integrates automated detection and human reviewers where the automated detection system is hypersensitive by design and artifactual and otherwise misclassified events are manually removed by an expert reviewer (Worrell et al., 2009, Crepon et al., 2010). All of these techniques require selection of a baseline region for comparison which can be difficult to identify within active recordings. To address the difficulty in identifying appropriate baseline regions for comparison, two methods have been proposed. Wavelet entropy measures to define non-rhythmic regions and normalization of the raw local field potential both provide improved definitions of baseline that can be used as comparisons for HFO identification (Zelman et al., 2010; Salami et al., 2012).

To further decrease human intervention, identification systems employing machine learning techniques were first applied by Dumpelmann et al 2012 who used features identified from bandpass filtered versions of the recorded signal which represented both HFOs and the surrounding baseline. Using a visually identified training set, a radial basis function classifier was designed to identify HFOs (Dumpelmann et al., 2012).

In summary, there are three potential complications related with automatic spectral characterization of HFOs: a) the filter settings, either during acquisition or for offline analysis, may fundamentally affect proper identification of real HFO events; b) high-amplitude sharp peaks which are characteristics of pathological HFOs may produce spectral leakage and result in spurious fast spectral components, and c) multi-unit activity contamination of genuine LFP oscillations. Unfortunately, the problem is far from being solved. A valid recommendation is to thoroughly address all potential methodological concerns with a given dataset and to provide enough details so that different methods and results could be contrasted.

11. The filtering/edge/harmonics conundrums of HFOs

Possibly, the most clear example on how filters affect recording of a particular oscillation are HFOs themselves. Traditional acquisition standards in clinical neurophysiology employ narrow-band filters from 1 to 70 Hz, which significantly attenuate high-frequency components (Fig.1B; red trace). Fast ripples were discovered by Bragin et al. because they used basic research standards to acquire signals in a broad band from 0.1 Hz to at least 3 kHz (Bragin et al., 1999). Because of the diversity of cellular processes underlying HFOs, from high-gamma (>80 Hz) to very fast frequency components (600-800 Hz), acquisition parameters including filter settings and the sample rate fundamentally affect recorded signal waveforms. Choosing the sampling frequency as $fs > 2F_{upp}$, where F_{upp} is the filter upper cutoff frequency, follows the Nyquist-Shannon theorem and guarantees reconstructability for signals of infinite duration; however, this guideline provides little help when dealing with transient events in short recordings. The situation is further complicated by non-sinusoidal physiological activity which contains frequency components far in excess of the fundamental and requires significant oversampling to faithfully represent the complex

waveforms present in HFO activity. Choices of F_{upp} close to the HFO frequency range, such as 300 Hz, will yield distorted representations of components close to F_{upp} and will prevent accurate interpretation of HFOs regardless of the montage chosen or analysis techniques applied. It is also important to check for ringing effects of filters near the bandpass.

Once acquired, evaluating HFOs is time-consuming. Automated detection techniques reduce the workload of identifying HFOs and address consistency issues inherent to human raters; however, they are susceptible to detection of spurious HFOs that can arise from a variety of sources. All of the techniques reviewed rely on offline filtering and/or time-frequency analysis using either Fourier or Wavelet methods, which are susceptible to the detection of false HFOs because rapid transitions in the signal manifest as oscillatory behavior in high pass filtered version of the signal (Kramer et al., 2008; Benar et al., 2010). These rapid transitions can arise due to the sharp and asymmetric waveform of HFO. This effect is reviewed by Benar et al 2010 who demonstrate spurious HFOs arising from high pass filtering of artificially created sharp peaks inserted into pseudo local field potential data (Benar et al., 2010). Filtering of sharp artefacts leads to signals that closely resemble the ripples induced by short duration HFOs. The slew rate, or rate of change of the signal, is the key determinant of edge bleed with higher slew rates inducing ripples in progressively higher regions of the HFO frequency spectrum.

In addition to these effects, multiunit activity present in recordings complicates HFO spectral identification in that it bleeds across frequency bands and upon filtering produces spectral components in high frequency bands which can be mistaken for HFOs (Scheffer-Texeira et al., 2013; Ray et al. 2011). It is important to note that a genuine brain oscillation refers to cycles of LFP (or EEG) waves occurring at a regular frequency which are characterized by a power spectrum with a peak at that frequency. Multi-unit activity contributes to genuine HFOs if phase-locked (Foffani et al. 2007; Ibarz et al. 2010; Schomburg et al. 2012). It would be impossible to distinguish multi-unit activity and LFP cycles if neuronal firing is coherent and occur in phase, because action potential from individual cells sum together to generate a population spike. In some circumstances however, especially for microelectrodes inserted close to cell lamina where action potentials are more easily recorded, non-correlated firing can be distinguished from genuine LFP cycles and this contaminates the spectrum. Since firing coordination fluctuates event to event, multiunit contamination strongly varies. If electrodes are inserted relatively distant from cell bodies, then multiunit contamination will be poor. Figure 2A shows an example of ripples recorded simultaneously with two microelectrodes at different distance to the CA1 cell body layer and the corresponding time-frequency spectrum in the 100-400 Hz band. Upper channel is relatively poorly contaminated by multi-unit activity, though it may be visible in some events. A lower channel shows strong multi-unit contamination. In Fig.2B one of these events is enlarged. Genuine LFP cycles and multi-unit firing can be clearly dissociated in the lower, but not in the upper channel where LFP cycles dominate the spectrum. As this example illustrate, since multiunit activity is most prominent near dense cell bodies recording activity in the vicinity but not directly in cell layers may help in separating false and genuine HFOs (Scheffer-Texeira et al., 2013).

12. Alternative methodological approaches to analyze HFOs

Are there new analytical approaches to better unravel the complex spectral nature of HFOs? Approaches combining automated detection systems, alternative frequency decompositions and machine learning techniques address many of the difficulties in reliably identifying HFOs in a variety of datasets. Time-frequency analysis using Fourier or wavelet transforms allows manual exclusion of regions in which activity broadly bleeds across frequencies; however, bleeding frequencies resulting from multiunit activity or sharp edges may obscure underlying activity and produce false negative classification results (Benar et al., 2010).

In a subset of signals, in which the high frequency oscillation is modulated by a low frequency rhythm during seizure transition and propagation (Schevon et al., 2012; Alvarado-Rojas et al., 2014; Ibrahim., et al 2014; Florez et al. 2013), cross frequency coupling (CFC) measures might provide a sensitive method to detect the presence of HFOs (Canolty et al., 2006; Tort et al., 2010; Belluscio et al., 2010; Scheffer-Teixeira et al., 2012; Weiss et al., 2013). Importantly, cross frequency coupling measures the correlation between the low frequency phase and the amplitude of a high frequency rhythm in a power independent fashion thus identifying HFOs in a sensitive manner (Scheffer-Teixeira et al., 2013). While cross frequency coupling can identify HFOs, the CFC measurement techniques are based upon filtering or wavelet-transforms being susceptible to detecting false HFOs (Tort et al., 2010; Dvorak and Fenton 2014). The phase relationship between multiunit activity and HFOs with the underlying modulatory rhythm (e.g. theta) can define whether the HFO is indeed a false ripple in some circumstances (Scheffer-Teixeira et al., 2013).

Multiunit activity and HFOs which could align with different phases of the low frequency rhythm phase likely indicate the presence of distinct HFO and multiunit processes while the opposite indicates either multiunit activity contamination of the HFO or phase locked activity. These effects can be further distinguished with HFO or spike triggered averages which highlight the periodicity of HFO activity on a particular phase of the underlying rhythm or generate a sharp spike (Scheffer-Teixeira et al., 2013; Dvorak and Fenton 2014).

Measuring the phase locking of high gamma using normalized amplitude, in a manner similar to phase locking value, was recently proposed by Weiss et al as a sensitive measure of seizure associated sustained HFO activity lasting more than 200 ms (Weiss et al., 2013). Bicoherence, which quantifies the relationship between two rhythms of frequency *f1*, *f2* and their sum, *f1+f2* (Kramer et al., 2008), produces a specific pattern of harmonics which is not present in the case of genuine HFOs and thus provides a measure to exclude false HFOs (Kramer et al., 2008). Matching pursuit, a frequency decomposition using a predefined library of primitives is an alternative in which the signal can be decomposed into a dictionary of frequency and time localized primitives (Benar et al., 2009; Jmail et al., 2011). Matching pursuit with a Gabor basis can effectively separate large spikes from underlying oscillations under many conditions and partially address the false ripple detection issue; however, in the case where the signal is not readily explained by a small number of atoms from the library - a similar phenomenon to spectral bleed is observed (Jmail et al., 2011).

Empirical mode decomposition (EMD) and ensemble empirical mode decomposition (EEMD) are other signal decomposition techniques which seek to decompose non-stationary signals into non-overlapping intrinsic mode functions (IMF) in an unsupervised manner (Huang et al., 1998; Wu et al., 2009). The technique repeatedly finds local extrema to create upper and lower envelopes which are used to create a mean signal which is iteratively refined until an IMF can be extracted from the original signal (Huang et al., 1998). The EMD process produces a series of IMFs of progressively decreasing average frequency which can separate low frequency and high frequency oscillations without a priori knowledge of the oscillation frequency (Colic et al., 2013). This technique is less susceptible to frequency bleed as it does not explicitly select frequency bands and can therefore effectively extract quasiperiodic and asymmetric rhythmic activity.

Unsupervised clustering of HFOs identified using a highly sensitive detection algorithm can produce distinct clusters which separate HFOs into ripples, fast ripples, mixed events and artefacts (Blanco et al., 2010). This technique allows single stage removal of all artifactual events given a priori knowledge of artefact morphology was used in selecting the features used for clustering. Matsumoto and colleagues (2013) used support vector machine learning to separate normal from pathological HFO in presurgical patients. The variety of frequency decomposition techniques, CFC measures and clustering approaches to HFO identification provides a broad array of tools that address many of the difficulties encountered when working with the HFOs. In particular, automation for large data sets, exclusion of false HFOs, and consistency.

13. Conclusions, future directions, and technical recommendations

In spite of technical issues, HFOs as a biomarker are a promising addition to the repertoire of tools available for delineation of epileptogenic zone, as well as seizure prediction and anticipation. Implantable seizure warning (Cook et al., 2013) and closed loop stimulation systems (Morrel et al., 2011) are both devices which use features computed from low frequency intracranial recording to alert patients of impending seizures or deliver timely electrical stimulation (Sun et al., 2008, Gardner et al., 2006). Trials of these systems produced promising but highly variable results indicating that the metrics used to measure state do not provide a sufficiently detailed picture to reliably detect the transition to seizure (Cook et al., 2013, Morrel et al., 2011). The addition of HFOs may be supplementary information to increase performance of prediction and anticipation algorithms.

The sections above provide evidence that support the hypothesis that pathological HFOs are dominated by the extracellular currents that underlie action potentials, as well as contributions from intense synaptic activity and afterpotentials that are likely to occur in epileptogenic tissue, and dependent on the recording conditions and the precise band under consideration. By definition, HFOs reflect overlapping frequencies from the lower 80 Hz to the very fast frequency bands. Pathological HFOs could be spectrally similar to physiological HFOs but their cellular processes are fundamentally different. HFOs are extremely sensitive to recording conditions (electrode size, filter settings, sampling rate) and offline processing methods. A consensus is urgently required to unify the many diverse practices used to record and analyze HFO data. Without such basic standards, a comparison

of data and results between groups is difficult and the synthesis of data from diverse sources is rendered impossible.

The following is a list of recommendations based on common neurophysiological principles that could help standardize the acquisition of HFO signals for joint clinical and basic research.

- Given that action potentials and coherent synaptic activity are major contributors to HFOs, minimally injuring high-density microelectrode arrays are recommended to increase the likelihood of detecting and classifying different forms of HFOs.
- Because pathological HFO-generating sites are widely scattered and supported by a small volume of tissue, microelectrodes should be positioned closely to cell lamina to provide better access to local current sources. Since in most cases HFO-generating sites are unknown a practical recommendation is using minimally damaging multi-site probes to simultaneously target different regions.
- Given the variable amplitude of HFOs (from few hundreds to thousands of microvolts), a minimum of gain of 100 with low-noise amplifiers should be considered, depending on electrode size and properties.
- Since HFOs encompass cellular processes contributing to a wide frequency range, acquisition filters should range from 0.1-1 Hz to at least 3 kHz and the sampling frequency should allow analysis throughout this band
- A common neutral and distant reference should be used for comparable clinical and animal data. Differential recordings and/or current-source density analysis are informative to potentially exclude volume conduction effects, but these should be complementary. Synchronization measurements should be carefully considered using this standard.
- Given that individual HFO events reflect involvement from variable pool of neurons a minimum of 50-100 events should be considered in statistical terms
- Offline processing and analysis should be described in detail. In particular, those potential pitfalls affecting HFO waveforms should be considered (filtering, harmonics, etc.).

Now and in foreseeable future is the ideal time to record human brain electrical activity with greater spatial and temporal resolution due to the regular use of commercial wide bandwidth EEG recording systems that support high sampling rates and channel capacity, and advances in electrode materials and designs (Stacey and Litt 2008). Adopting common recording procedures combined with infrastructure projects will facilitate sharing of wide bandwidth data and analytical techniques, and accelerate investigations on the mechanisms of HFOs and their role in human health and disease.

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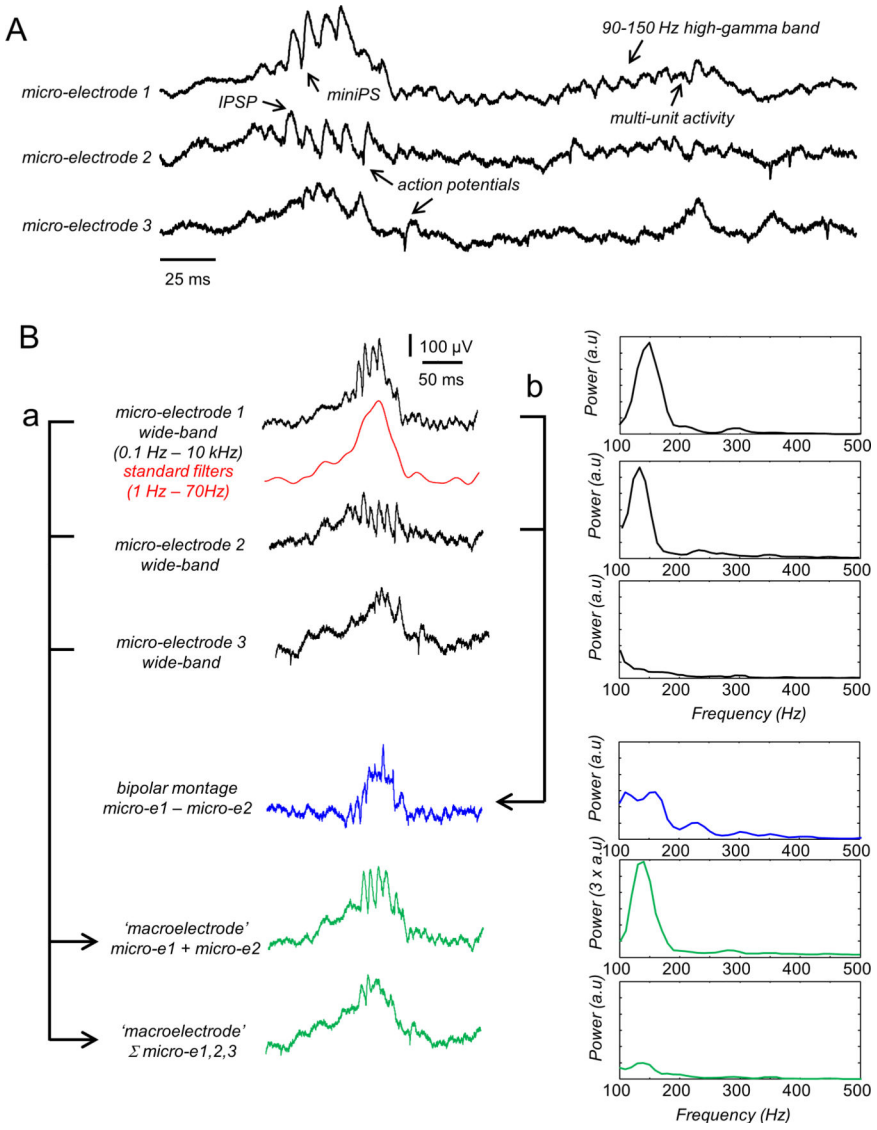

Figure 1.

A, Example of local field potential (LFP) ripples simultaneously recorded with microelectrodes in the dorsal hippocampus of a normal rat. Electrodes were situated at different levels and separated about 1 mm each. Note the complexity of cellular processes associated with ripple oscillations, including multi-unit activity, positive LFP deflections which are consistent with extracellular recordings of inhibitory postsynaptic potentials (IPSPs) and individual action potentials. On occasions, individual ripple cycles adopt a spiky appearance presumably reflecting tightly synchronization of firing from few pyramidal cells, and termed mini-population spikes (miniPS). Ripple cycles recur at 100-200 Hz but episodes of gamma activity at 90-150Hz can be also detected. **Ba**, A simple experiment considers the effect of combining together recordings from individual microelectrodes to roughly simulate macroelectrode recordings (shown in green) and the effect on the power spectrum (shown at right). The effect of standard filtering at 1-70Hz is

shown for one microelectrode in red. **Bb**, The effect of a bipolar montage is shown for microelectrode recordings 1 and 2 and the corresponding frequency spectrum (blue).

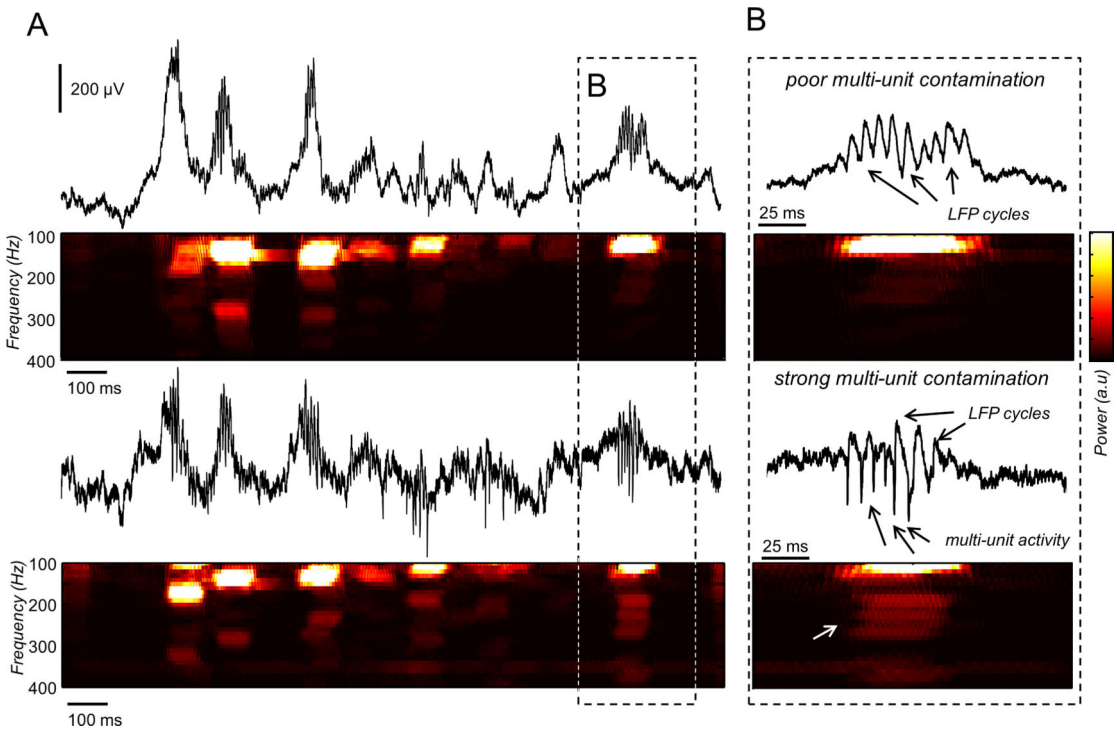

Figure 2.

A, Ripples recorded from a normal rat in vivo using two microelectrodes targeting the dorsal CA1 regions at different distance to cell body layer. Upper channel shows several consecutive ripple events and the corresponding time-frequency spectrum. Given a distant position to the stratum pyramidale, this electrode shows poor contamination by multiunit activity, though it might be appreciable in some isolated events (second and third events). A lower channel shows activity recorded simultaneously with a microelectrode within the stratum pyramidale. This recording was strongly contaminated by multi-unit firing, as evident in the time-frequency spectra. **B**, One ripple event (boxed in A) is enlarged to illustrate how individual action potentials from multiple units can be intermixed with genuine local field potential (LFP) cycles of ripples in the lower but not in the upper electrode. Spectral power is in arbitrary units but similar scale is used for both channels.