CRITICAL REVIEW AND INVITED COMMENTARY

High-frequency oscillations: What is normal and what is not?

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SUMMARY

High-frequency oscillations (HFOs) in the 80–200 Hz range can be recorded from normal hippocampus and parahippocampal structures of humans and animals. They are believed to reflect inhibitory field potentials, which facilitate information transfer by synchronizing neuronal activity over long distances. HFOs in the range of 250–600 Hz (fast ripples, FRs) are pathologic and are readily recorded from hippocampus and parahippocampal structures of patients with mesial temporal lobe epilepsy, as well as rodent models of this disorder. These oscillations, and similar HFOs recorded from neocortex of patients, appear to identify brain tissue capable of spontaneous ictogenesis and are believed to reflect the neuronal substrates of epileptogenesis and epileptogenicity. The distinction between normal and pathologic HFOs (pHFOs), however, cannot be made on the basis of frequency alone, as oscillations in the FR frequency range can be recorded from some areas of normal neocortex, whereas oscillations in the ripple frequency range are present in epileptic dentate gyrus where normal ripples never occur and, therefore, appear to be pathologic. The suggestion that FRs may be harmonics of normal ripples is unlikely, because of their spatially distinct generators, and evidence that FRs reflect synchronized firing of abnormally bursting neurons rather than inhibitory field potentials. These synchronous population spikes, however, can fire at ripple frequencies, and their harmonics appear to give rise to FRs. Investigations into the fundamental neuronal processes responsible for pHFOs could provide insights into basic mechanisms of epilepsy. The potential for pHFOs to act as biomarkers for epileptogenesis and epileptogenicity is also discussed.
KEY WORDS: Epilepsy, High-frequency oscillations, Fast ripples, Epileptogenesis, Epileptogenicity.

Transient high-frequency oscillations (HFOs) are field potentials that reflect short-term synchronization of neuronal activity. They are believed to play important roles in both normal and pathologic brain function. HFOs in the range of 80–200 Hz, termed "ripples," have been well described in hippocampus and parahippocampal structures of normal animals and humans (Suzuki & Smith, 1987; Buzsaki et al., 1992; Ylinen et al., 1995; Chrobak & Buzsaki, 1996; Bragin et al., 2000b; Staba et al., 2002a). There has been increasing recent interest in pathologic high-frequency oscillations (pHFOs), which appear to reflect abnormal epileptogenic mechanisms in animals and humans (Bragin et al., 1999a, 1999b; Dzhala & Staley, 2004; Jirsch et al., 2006; Urrestarazu et al., 2006; Foffani et al., 2007; Ochi et al., 2007; Spampanato & Mody, 2007). pHFOs were originally described in the frequency range of 200–600 Hz, and termed fast ripples (FRs) (Bragin et al., 1999a, 1999b). This has led to a misconception that oscillation frequency alone distinguishes normal HFOs from pHFOs. In fact, there appears to be considerable overlap in spectral frequency between normal and epileptogenic oscillatory transients, so if pathogenicity is not about frequency, what defines it?

Normal HFOs

Ripples have been recorded from hippocampus and parahippocampal structures of rodents (Buzsaki et al., 1992; Ylinen et al., 1995; Chrobak & Buzsaki, 1996; Ponomarenko et al., 2003), nonhuman primates (Skaggs et al., 2007) and humans (Bragin et al., 1999a, 2002b; Staba et al., 2002a, 2004). These oscillations can synchronize neuronal activity over long distances, function to consolidate synaptic plasticity, and they are particularly important for episodic memory (Buzsaki, 2006). Normal ripples appear to reflect summated synchronous inhibitory postsynaptic potentials (IPSPs) generated by subsets of interneurons that regulate the discharges of principal cells (Buzsaki et al., 1992; Ylinen et al., 1995). The degree of synchronization of principal cell postsynaptic potentials during ripple oscillations never reaches a level where discharging neurons lose their identity and form population spikes [the local field potentials that occur as a result of spatially summated action potentials (Lomo, 1971)]. In vivo single-unit recordings from rodents during ripple oscillations have elucidated cell-specific firing patterns, and phase-locking on a millisecond time scale (Csicsvari et al., 1999; Klausberger et al., 2003, 2004). Similar findings were observed in humans (Le Van Quyen et al., 2008).

Oscillations have been recorded at much higher frequencies (200–600 Hz) in normal neocortex, but not in normal hippocampus and parahippocampal structures. In rodents, these higher frequency HFOs are commonly encountered in barrel cortex during vibrissae or thalamic stimulation (Kandel & Buzsaki, 1997; Jones & Barth, 1999; Jones et al., 2000), and may reflect rapid temporal integration of tactile sensory information (Barth, 2003). Cortical oscillations are also present in neocortex of cats at slightly lower frequencies during natural states of vigilance and anesthesia (Grenier et al., 2001), and can be recorded in somatosensory cortex of humans during sensory peripheral nerve stimulation using electro- and magnetoencephalography (Cracco & Cracco, 1976; Eisen et al., 1984; Curio et al., 1994; Nakano & Hashimoto, 1999). Although the neuronal generators are unclear, evidence from animal studies indicate that these cortical oscillations involve synchronous discharges from interneurons and pyramidal cells that fire at preferred latencies corresponding to individual cycles of the field oscillation, and there are no reports that they occur spontaneously (Jones et al., 2000; Grenier et al., 2001).

Pathologic HFOs

The first pHFOs, reported almost a decade ago in patients with mesial temporal lobe epilepsy and rat models of this disorder (Bragin et al., 1999a, 1999b), were FRs in the frequency range of 250–600 Hz. An important distinction between these pHFOs and normal ripples is that the former are readily recorded from dentate gyrus, where the latter never occur under normal conditions. FRs typically occur on interictal electroencephalography (EEG) spikes and are of particular interest because they appear to be uniquely associated with regions capable of generating spontaneous seizures (Bragin et al., 1999c; Staba et al., 2002a; Jacobs et al., 2008), and could reflect the basic neuronal events underlying epileptogenicity (Bragin et al., 2000a; Engel et al., 2003). The fact that FRs occur not only interictally, but at the onset of ictal events in rodents, strongly suggests that FRs are associated with mechanisms of seizure generation and are not merely a consequence of injury (Bragin et al., 1999c, 2005). In rodents, FR-generating neurons are not homogeneously distributed throughout the epileptogenic tissue, but occur in small discrete clusters that are spatially stable over long periods of time (Bragin et al., 2002a, 2003). In patients with mesial temporal lobe epilepsy (MTLE), there is a strong association between the occurrence of FRs and hippocampal atrophy on magnetic resonance imaging (MRI) (Staba et al., 2007; Ogren JA, Wilson CL, Bragin A, Lin JJ, Salamon N, Dutton RA, Luders E, Fields TA, Toga AW, Thompson PM, Engel J Jr, Staba RJ, unpublished manuscript). Patient studies also have revealed pHFOs in neocortex that bear the same relationship to areas of ictal onset as mesial temporal pHFOs (Worrell et al., 2004; Urrestarazu et al., 2007).

The conclusion from unit and field potential recordings in rodents and humans is that FRs represent field potentials of population spikes from clusters of abnormal synchronously bursting neurons, in contrast to ripples, which represent field potentials of summated IPSPs (Bragin et al., 2002a, 2007). Whereas synchronously bursting neurons have long been considered the hallmark of epileptogenic tissue (Schwartzkroin, 1983), and can be easily identified in acute animal models, such as the neocortical penicillin focus where up to 90% of principal neurons participate in interictal EEG events (Matsumoto & Ajmone Marsan, 1964), less than 10% do so in chronic experimental cortical foci (Ishijama, 1972; Wyler et al., 1975), and fewer than 5% in hippocampus of patients with MTLE (Babb et al., 1981, 1987). Consequently, although it can be difficult to identify, and study, chronically epileptogenic tissue using microelectrode identification of bursting units (Colder et al., 1996a, 1996b); (however, see Staba et al., 2002b), FR field potentials, even though generated by widely spaced small clusters of neurons, can be recorded much more easily and serve as a much more robust marker of epileptogenicity (Engel et al., 2003).
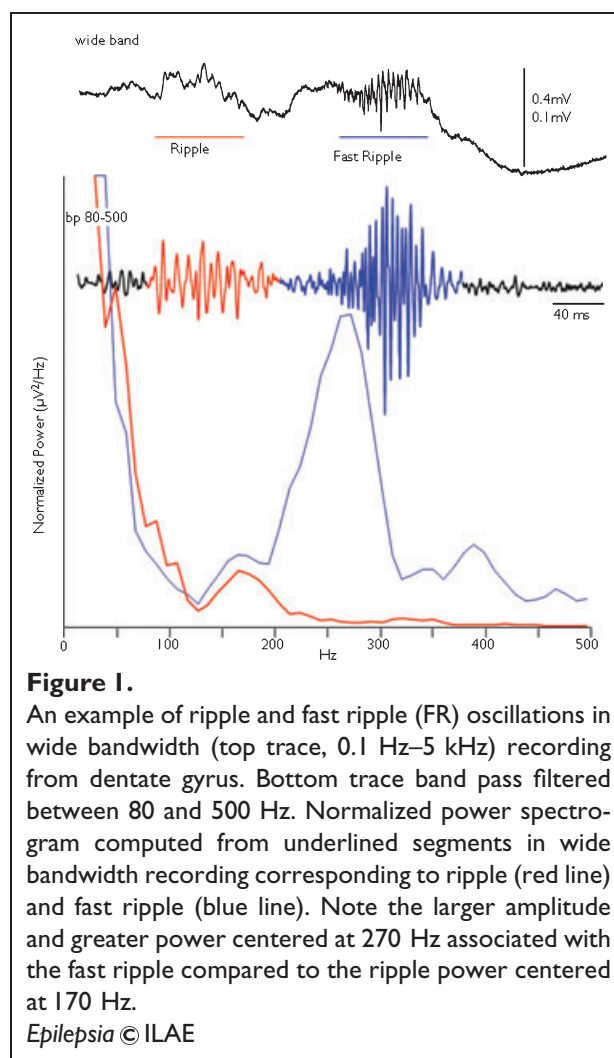
Are fast ripples a variant of normal ripples?

Recent research has been directed at understanding whether FRs represent a variation of normal HFOs, or reflect entirely different pathologic neuronal interactions. In addressing this question, investigators (including ourselves) have tended to focus only on the frequency differ-

ence between ripples and FRs when, in fact, we now know that frequency is not a reliable differential feature. For instance, Foffani et al. (2007) compared in vitro slice recordings from area CA3 of hippocampus from normal and epileptic rats. HFOs were initiated by lowering calcium and raising potassium concentrations in the medium. They elegantly demonstrated that in epileptic rats, synchronicity was actually reduced during HFOs in the FR frequency range compared to synchronicity during HFOs in the ripple frequency range, and suggested that pathologic FRs are a harmonic of normal ripples. There are numerous reasons, however, that this is not likely to be the case.

Spectral frequency alone is not sufficient for separating normal from pathologic oscillations (Bragin et al., 2007). Within days after intrahippocampal kainic acid (KA)–induced status epilepticus, HFOs in both the ripple and FR frequency range can be recorded in the dentate gyrus of rats that later develop recurrent spontaneous seizures, but not in similarly treated rats that do not develop spontaneous seizures (Bragin et al., 2004). In this case, the ripple frequency HFOs are pathologic because ripple oscillations never occur in dentate gyrus under normal conditions, although some granule cells can discharge at ripple frequency rates during sharp waves (Penttonen et al., 1997). Furthermore, whereas Foffani et al. (2007) based their conclusions, in part, on the fact that the amplitude of FR frequency oscillations was decreased compared to that of ripple oscillations, in chronic in vivo recordings, the amplitude of oscillations in the FR frequency band in dentate can be much higher than the amplitude of oscillations in the ripple frequency band recorded from the same microelectrode (Fig. 1). This suggests, at least for pHFOs, that FRs are not necessarily harmonics of ripple frequency oscillations. Note, however, that both ripple and FR frequency pHFOs are also seen in electrodes 2 and 3 in Fig. 2, where the former could be a harmonic of the latter. The weakness of power analysis for separation of pathologic and normal HFOs is also illustrated in the power histograms presented in Figs. 2 and 3, where bursts of population spikes occur with frequency peaks at 180 Hz, 250 Hz, and 350 Hz.

An argument for the hypothesis that pHFOs in the dentate gyrus reflect synchronous bursts of population spikes is that the maximum amplitude is within the granule cell layer and the shape has similar voltage depth profiles as potentials evoked by perforant-path stimulation (Fig. 2). In contrast, ripple oscillations are more prominent in the hilus–CA3 area (Fig. 2). Analysis of these oscillations without knowledge of the exact location of recording sites could also lead to misinterpretation of the results, as illustrated by the bipolar recording at the bottom of Fig. 2 (Bipolar 2–6). Here ripple oscillations appear to precede FR oscillations in the same area, when the monopolar recordings show that they actually are generated by differ-

Figure 1.
An example of ripple and fast ripple (FR) oscillations in wide bandwidth (top trace, 0.1 Hz–5 kHz) recording from dentate gyrus. Bottom trace band pass filtered between 80 and 500 Hz. Normalized power spectrogram computed from underlined segments in wide bandwidth recording corresponding to ripple (red line) and fast ripple (blue line). Note the larger amplitude and greater power centered at 270 Hz associated with the fast ripple compared to the ripple power centered at 170 Hz.
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ent neuronal populations. Evidence that pHFOs reflect bursts of population spikes also derives in part from multiunit recordings demonstrating that neurons increase their discharge frequency before pHFOs appear. At the onset of pHFOs it is impossible to separate unit activity because all neuronal events collapse into the field population spike (Fig. 3). When the recording microelectrode is in the granule cell layer, however, brief "mini spikes" are visible on the descending part of the population spikes, supporting the idea that the field oscillation is the result of spatial summation of action potentials of many synchronously discharging neurons (Fig. 3, dashed box). In fact, the shape of pHFO oscillations varies significantly from one recording site to another. Within the granule cell layer, pHFO activity can have a shape resembling discrete population spikes but takes on the appearance of oscillations at more remote recording sites (Fig. 2). The identification of pathologic oscillations in other brain areas where ripple oscillations occur under normal conditions is more problematic. In these areas, oscillations in the FR frequency band (250–600 Hz) should be considered as
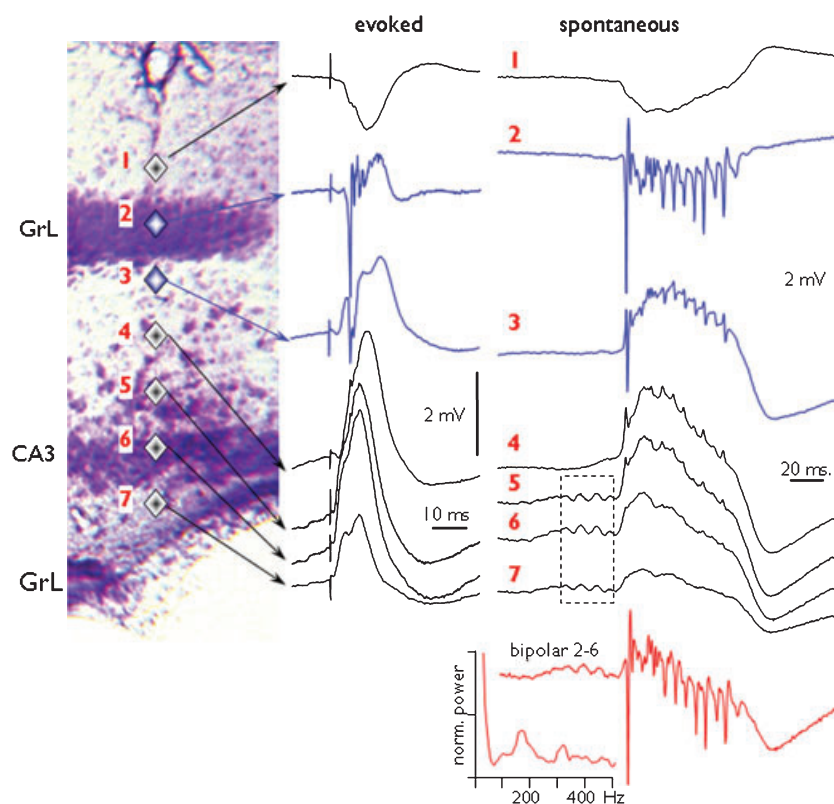
Figure 2.
Voltage-depth profiles of dentate gyrus potentials evoked by perforant-path stimulation (EP), and spontaneous pathologic high-frequency oscillations (pHFOs) recorded at the same position of the array of recording microelectrodes separated by 200 μm. pHFOs with both fast ripple (FR) and ripple frequencies are recorded by the microelectrodes located within the granular cell layer. Here the FR frequency oscillations could be harmonics of the ripple frequency oscillations, which have the shape of population spikes, whereas in the neighboring microelectrodes the shape of the electrical signal changes and appears more as oscillations than as population spikes. Ripple frequency oscillations occur in the CA3 area (dashed box) before FRs in the dentate gyrus granular layer. The bottom (red) line represents electrical activity recorded in a bipolar montage between recording sites 2 and 6 (between dentate gyrus and CA3 area), with power histogram on the left. GrL and CA3 indicate correspondingly the dentate gyrus granular layer and CA3c areas of hippocampus. Diamonds indicate the location of recording sites reconstructed based on analysis of histologic sections and the shape of evoked potentials.
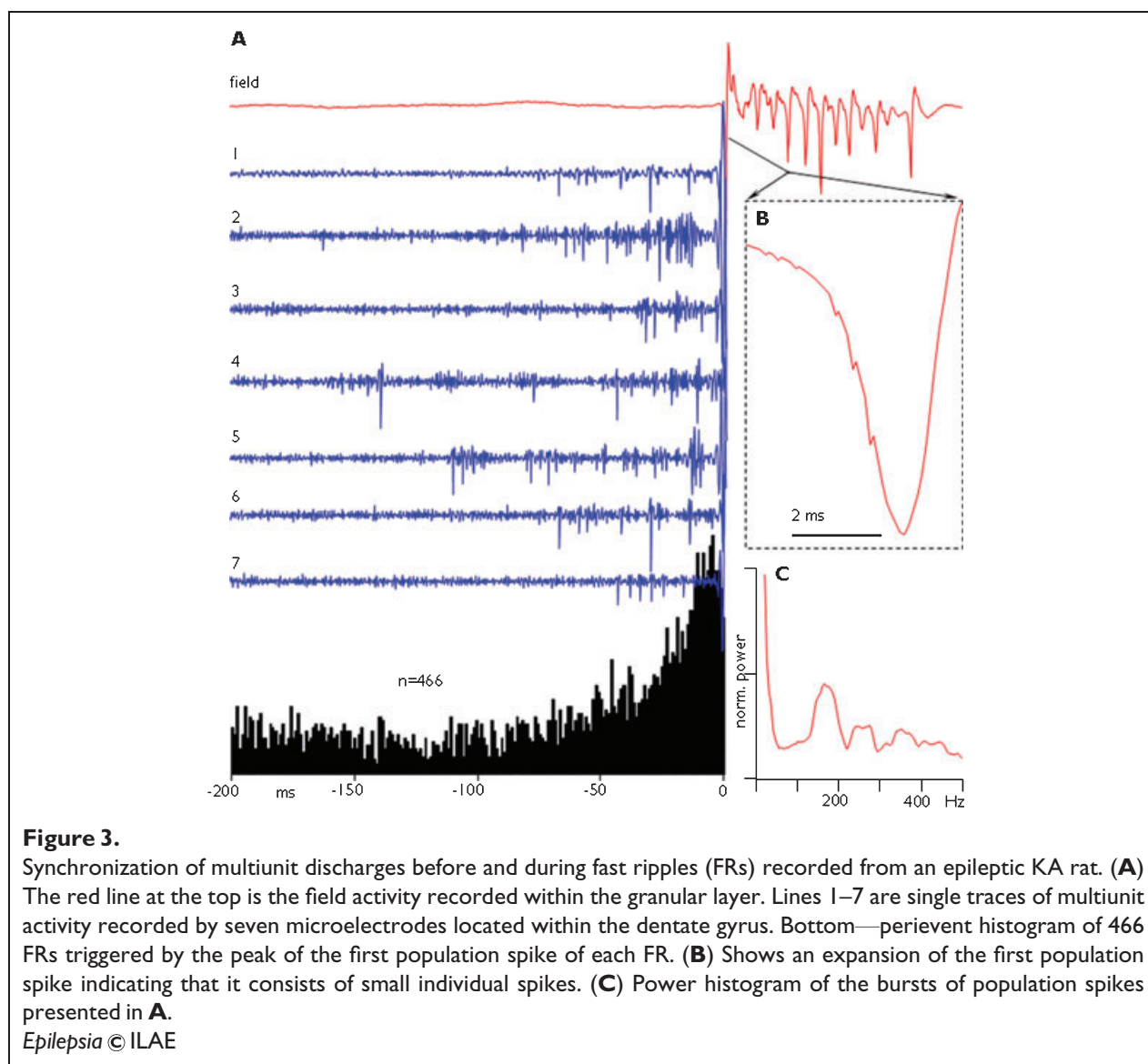*Epilepsia* © ILAE

pathologic, while oscillations in the ripple frequency band (100–200 Hz) could be normal or pathologic.

When are ripple frequency oscillations abnormal?

Rather than ask whether pHFOs may be a variant of ripples, an alternative, perhaps more relevant, question is whether some ripple frequency oscillations outside the dentate gyrus could in fact be pHFOs. Whereas it is easy to identify the pathologic nature of HFOs that occur in the dentate gyrus, where ripples are normally absent, it is not yet possible to definitively conclude that all ripple frequency oscillations recorded in epileptic hippocampus and parahippocampal structures outside of the dentate gyrus are normal. Indeed, it is more reasonable to assume,

given the data that the frequency of pHFOs in epileptic dentate gyrus can range from 80–600 Hz, that not only FRs, but some oscillations in the ripple frequency range, outside of dentate gyrus, also reflect epileptogenicity. It is then possible to suggest that at least some, and perhaps all, ripple frequency HFOs recorded in slice preparations in vitro reflect pathologic rather than normal mechanisms, as a result of neuronal disconnections and artificial environmental conditions. This might then explain why some authors have concluded that ripple frequency oscillations recorded in vitro reflect a brief series of population spikes, with maximum amplitude in the cellular layer (Draguhn et al., 1998; Dzhala & Staley, 2004; D'Antuono et al., 2005). An alternative interpretation of the data presented

Figure 3.
Synchronization of multiunit discharges before and during fast ripples (FRs) recorded from an epileptic KA rat. (**A**) The red line at the top is the field activity recorded within the granular layer. Lines 1–7 are single traces of multiunit activity recorded by seven microelectrodes located within the dentate gyrus. Bottom—perievent histogram of 466 FRs triggered by the peak of the first population spike of each FR. (**B**) Shows an expansion of the first population spike indicating that it consists of small individual spikes. (**C**) Power histogram of the bursts of population spikes presented in **A**.
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by Foffani et al. (2007), therefore, would be that oscillations in all frequency ranges described in their paper reflect bursts of population spikes and are pathologic, although some of them are in the ripple and others in the FR frequency range. FRs could then occur as a result of out-of-phase firing in part of the generating neuronal network, owing to a reduction of spike-timing reliability (as might be the case for the recordings from electrodes 2 and 3 in Fig. 2). In these conditions, both frequency bands of oscillations would be pathologic.

Because invasive electrode recordings are performed to delineate epileptogenic tissue, it is not possible to characterize HFO occurrence in normal human brain. The existence of neuronal clusters generating pHFOs outside of the seizure onset zone (Jirsch et al., 2006; Jacobs et al., 2008), however, is consistent with the view that epilepsy is a disorder involving diffuse neuronal networks (Spencer, 2002).

The most significant parameter that separates normal from pathologic HFOs is the evidence that the latter represent abnormal bursts of population spikes. The fact that the shape of population spikes changes dependent on the distance between the recording electrodes and the area of generation can cause pHFOs to look like normal oscillations. Therefore, there is a need for additional means to differentiate pathologic from normal oscillations.

POTENTIAL CLINICAL VALUE OF pHFOs

Interictal EEG spikes are used clinically as biomarkers for epilepsy but have been imperfect in this regard, perhaps because these events are not unitary phenomena. The general impression is that there are specific "red spikes," which are generated within epileptogenic tissue, and

nonspecific "green spikes," which are generated in more normal tissue, but so far EEGers have been unable to tell them apart (a statement attributed to Theodore Rasmussen). Investigations of pHFOs are of potential importance not only because they could reveal fundamental mechanisms responsible for epileptogenesis and epileptogenicity, but because these transients have potential clinical value as putative biomarkers in combination with other electrographic patterns. For instance, interictal spikes with pHFOs could be red spikes, whereas those without pHFOs could be green spikes. The situation is somewhat more complicated, however, because pHFOs also occur without interictal spikes (Jacobs et al., 2008), and these isolated events could have yet a different clinical significance.

Clinical research is needed to determine the relationship between pHFOs and interictal spikes, whether interictal spikes with pHFOs are more likely to indicate epileptogenesis or epileptogenicity than interictal spikes without pHFOs, and whether pHFOs unassociated with interictal spikes have the same relationship to epileptogenicity as pHFOs associated with interictal spikes. Unfortunately, however, detection of pHFOs in patients has required direct brain recordings, initially with microelectrodes, but more recently using standard depth and subdural grid electrodes (Jirsch et al., 2006; Urrestarazu et al., 2006; Ochi et al., 2007; Worrell et al., 2008). To be useful for most of the needed clinical applications of biomarkers, it will be necessary to record pHFOs noninvasively. This may be possible with magnetoencephalography (MEG), or there may be functional magnetic resonance imaging (fMRI) correlates of pHFOs.

The fact that pHFOs can be recorded shortly after intrahippocampal KA injection in rats that ultimately develop spontaneous seizures, but not in those that do not (Bragin et al., 2004), suggests that these oscillations could be biomarkers of epileptogenesis. If pHFOs could be detected noninvasively, such biomarkers could be used to predict the development of epilepsy following potentially epileptogenic cerebral insults or prolonged febrile seizures, in order to introduce preventive therapies. Biomarkers of epileptogenesis might also distinguish between static and progressive epileptogenic disturbances, which would be useful in deciding when to consider aggressive therapeutic interventions, such as surgery. If pHFOs reliably indicate the presence of an epileptic condition, noninvasive detections could be used to diagnose epilepsy after a single seizure so treatment could be initiated immediately. If pHFOs accurately determine the location and extent of epileptogenic tissue, invasive or noninvasive detections could serve to define the epileptogenic region for surgical resection without the need for expensive ictal recordings.

Studies in the KA rat suggest that ictogenesis could result from local decreases in inhibitory influences, which then cause widely spaced clusters of pHFO-generating neurons to increase in size, coalesce, and synchronize (Bra-gin et al., 2000a; Engel et al., 2003). This view is supported by the observation that spontaneous seizure frequency in KA rats correlates with the density of these neuronal clusters (Bragin et al., 2003). If some noninvasively detected aspect of pHFOs reliably indicated the likelihood of seizure occurrence, it could be used to determine the efficacy of antiepileptic drugs or other treatment interventions without the need to wait for another seizure to occur. Finally, any or all of these potential biomarker functions of pHFOs might be employed to devise animal models that could provide cost-effective rapid throughput screening for potential antiepileptogenic and antiseizure compounds and other preventive and therapeutic interventions.

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