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High-frequency – activity in experimental and clinical epileptic foci

Premysl Jiruska¹ and Anatol Bragin²

¹Neuronal Networks Group, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham B15 2TT, United Kingdom

²Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, USA

Abstract

Pathological high-frequency electrographic activity (pHFA, >80 Hz) represents one of the major discoveries in epilepsy research over the past few decades. In this review we focus on the high-frequency activity recorded *in vivo* in chronic models of epilepsy. The presence of HFA particularly of fast ripples (250–600 Hz) reflects epileptogenic reorganization of brain tissue, endogenous epileptogenicity and ability to generate spontaneous seizures. The spatial distribution of epileptic HFA can be used to localize epileptic foci. In some regions of brain the localizing value of epileptic HFA is weakened by frequency overlap with physiological HFA. In this situation, only detailed knowledge of the regional physiological activity may provide relevant information which frequencies provide localizing information. In the epileptic hippocampus, the activity from 250 Hz to 600 Hz frequency band (fast ripples) is always epileptic and can be used as reliable marker of epileptic tissue in all hippocampal subregions. The localizing value of HFA in the identification of the epileptic focus is discussed from an experimental and clinical perspective; as the information provided by HFA can improve presurgical diagnosis and surgical outcome. Finally, research into HFA has contributed to improved understanding and new insights into the cellular and network organization of epileptic foci and the pathophysiology of epilepsy.

Keywords

high-frequency activity; ripples; fast ripples; epilepsy; epilepsy surgery

Introduction

Pathological high-frequency activity (pHFA) has strong links with epilepsy. During the past decade, this phenomenon has attracted a great deal of attention from experimental and clinical epileptologists. The main idea was that insights into the mechanisms of high-frequency activity may contribute to better understanding of the pathophysiology of epilepsy and lead to improved diagnosis and treatment of patients with epilepsy. Research on pHFA has expanded rapidly such that it now represents one of the main epilepsy research directions. The presence of pHFA has been described in patients with epilepsy (Staba et al.,

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Corresponding author: Premysl Jiruska MD, PhD, Neuronal Networks Group, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham B15 2TT United Kingdom, Tel: +44(0)1214147630, Fax: +44(0)1214147625, jiruskapremysl@gmail.com.

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2002), in chronic *in vivo* models (Bragin et al., 2000, 2004; Jiruska et al., 2010b), *in vitro* in brain slices (Dzhala and Staley, 2004; Jiruska et al., 2010a) and *in silico* in computational models of epileptic pHFA (Stacey et al., 2009; Ibarz et al., 2010).

High-frequency activity wide spectrum of activities

At present, epileptiform high-frequency activity comprises a group of disparate activities with frequency >80 Hz (Figure 1). *In vitro*, epileptic high frequency activity is observed in the low-calcium, high-potassium, low-magnesium and picrotoxin models of epilepsy (Dzhala and Staley, 2004; D'Antuono et al., 2005; Khosravani et al., 2005; Jiruska et al., 2010a). Its presence has been demonstrated in each of the major hippocampal subregions (CA3, CA1 and dentate gyrus). However, the main properties (mean frequency, shape, amplitude, spatial distribution and cellular mechanisms) may differ between types of activity, as can the relationship of pHFA to interictal activity or to seizures. Certain types of pHFA are associated only with interictal discharges (Dzhala and Staley, 2004), some were observed at the onset or during seizures (Bikson et al., 2003), or progressively strengthened preceding the seizure (Khosravani et al., 2005; Jiruska et al., 2010a). The majority of *in vitro* studies on pHFA have been undertaken in slices from normal animals. While these studies do provide information on mechanisms of generating pHFA, they model pHFA which occurs in acute or symptomatic seizures. It is probably more relevant for work on the pathophysiology of epilepsy to use *in vitro* brain slices prepared from chronically epileptic tissue (Foffani et al., 2007; Jefferys 1989) as this is likely to yield more realistic information on the mechanisms of pHFA and its role in epilepsy. *In vivo* high-frequency activity was described in unilateral kainic acid model and tetanus toxin model of epilepsy (Bragin et al., 2000; Bragin et al., 2004; Jiruska et al., 2010b). These studies also demonstrated the presence of different types of epileptic pHFA but also that there was a frequency overlap with physiological HFA. From a clinical perspective, different types of epileptic pHFA may provide different information, but the overlap with physiological HFA may complicate use of pHFA as a diagnostic tool. Fast ripple activity is subtype of epileptic pHFA within the 250–600 Hz frequency band; it has unique features and shows strong association with epilepsy and epileptic foci (Bragin et al., 2000; Jiruska et al., 2010b). In this article we will focus primarily on fast ripples, their putative cellular and network mechanisms, which may help to build an understanding of the modern concept of the epileptic focus and of why fast ripples are particularly relevant to identification of the epileptogenic zone.

Cellular and network mechanisms of fast ripples

Analysis of voltage-depth profiles of fast ripples oscillations showed that the maximal amplitude is located within pyramidal and granular layers (Bragin et al., 2007a; Bragin et al., 2007b). The shape of these oscillations in the CA1 and dentate gyrus (DG) areas and their voltage depth profiles were similar to the population spikes evoked in response to electrical stimulation of either the Schaffer collaterals (for CA1) or perforant path (for DG). It is known that population spikes within the hippocampus reflect hypersynchronous action potential firing of principal cells (Lomo, 1971), leading to the conclusion that fast ripple oscillations reflect bursts of population spikes due to synchronous firing of principal cells (Bragin et al., 2007a; Bragin et al., 2007b).

Both *in vivo* and *in vitro* experiments have demonstrated that the areas generating pHFA are relatively small (about 1mm³), and that within a given brain area there are several neuronal clusters that generate pHFA (Bragin et al., 2002) and which have high density of connections between principal cells (Bragin et al., 2000; Bragin et al., 2002). Several structural, molecular and functional changes have been found within epileptic neuronal networks; these changes have the potential to increase neuronal and tissue excitability and

generate spontaneous population spikes by the pathologically interconnected neuronal clusters (PIN-cluster). Examples of these changes include: sprouting of axon collaterals and formation of autapses, local alteration of inhibition, increased density of NMDA or/and AMPA receptors and changes in intrinsic neuronal properties due to various acquired channelopathies (I_h , I_A , I_{NaP} , I_{CaL}) (Dudek & Sutula, 2007, Yaari & Beck, 2002). In normal brain the occurrence of a single action potential in one neuron does not lead to significant changes in the field electrical activity, but the situation within a PIN-cluster is different. The generation of an action potential by an individual neuron causes a chain reaction via divergent excitatory connections which forces surrounding neurons to also generate action potentials within a short (2–5ms) time window (Traub and Wong, 1982). The spatial and temporal summation of these action potentials is reflected in the occurrence of bursts of populations spikes (Ibarz et al., 2010).

Fast ripples as an out-of-phase phenomenon

The question remains, however, as to what determines the frequency of fast ripples which can be in excess of 250 Hz. The structural and functional changes described above may contribute to higher excitability but also, paradoxically, also to altered network synchronization. Foffani et al. (2007) showed that in vitro brain slices from pilocarpine epileptic animals were able to generate fast ripples while control slices generated population spikes at slower frequencies <300 Hz. This lead to the suggestion that multiple populations of neurons in epileptic focus possess decreased spike timing reliability which results in out-of-phase firing. The consequence is that initially the large neuronal population generating high-frequency activity from ripple band (<250 Hz) separates into two, each firing still at the same frequency <250 Hz. If activity of these now semi-independent populations is recorded extracellularly, it will manifest as high frequency activity with double the frequency shifting the predominant frequency into the fast ripples band (>250 Hz). It was suggested that decreased spike timing reliability could be consequence of increased synaptic noise due to axonal sprouting (Foffani et al., 2007). Another candidate mechanism for out-of-phase firing is cell loss (Foffani et al., 2007). It was demonstrated that size of hippocampal volume negatively correlated with incidence of fast ripple and that the cell loss will decrease synchronizing effect of ephaptic interactions. A recent study, however, has showed that cell loss is not prerequisite for fast ripples but it may further contribute to them. The tetanus toxin model of epilepsy is characterized by minimal cell loss (Jefferys et al., 1992), therefore the presence of fast ripples suggests that cell loss does not represent major necessary factor in pathophysiology of fast ripples, but may contribute to their genesis (Jiruska et al., 2010b). The presence of sprouting, functional changes in intrinsic neuronal properties and altered inhibition would further support that reorganization in the epileptic focus may contribute to out-of-phase firing. Therefore, it can be concluded that fast ripples probably identify epileptogenic tissue with morphological, molecular and functional changes which results in the ability to generate seizures.

Regional properties of high-frequency activity and fast ripples

Morphological and functional organization of hippocampus and its subregions provide the endogenous ability to generate high-frequency activity physiological and also pathological. Only chronic epileptic hippocampus is capable to generate fast ripples. In the following paragraphs we will briefly describe properties of individual subregions to generate high-frequency activity.

High-frequency activity in CA3

The morphological and functional properties of CA3 pyramidal cells with their divergent connectivity, ability to fire burst of action potentials and presence of axonal collaterals are

ideal features which predispose this region to the generation of synchronous and oscillatory activities including high-frequency activity. Under normal conditions inhibition and excitation are well balanced within CA3 and two major network phenomena are observed in CA3 –sharp waves and gamma oscillation –both important in memory and cognition. Physiologically controlled synchronous firing of CA3 pyramidal cells is involved in the production of sharp waves which then propagate to CA1. The precise interplay between principal cells and interneurons has been demonstrated in the formation of gamma oscillations which are also involved in cognitive functions (Bartos et al., 2007). Changing the excitability in CA3 by increasing excitability of pyramidal cells with high-potassium or low-calcium ACSF results in the occurrence of bursts of high-amplitude epileptic population spikes at a frequency between 200 Hz and 300 Hz (Dzhala and Staley, 2004; Figure 1A, C). In chronic epileptic brain the CA3 is capable to generate fast ripples (Foffani et al., 2007; Jiruska et al., 2010b; Figure 1H). As physiological activity in the normal CA3 is limited to sharp wave and gamma activity, therefore any activity >100 Hz can be accepted as pathological (epileptic).

High-frequency activity in CA1

The CA1 region has also an endogenous ability to generate high-frequency activity. Synaptic inputs from CA3 and the local pyramidal-interneuron network are important in the formation of sharp-waves ripples (SWR)(Buzsaki et al., 1992; Csicsvari et al., 1999; Figure 1F). Ripple oscillations have mean frequency of ~200 Hz. SWR is a phenomenon with strong network synchrony and a crucial role of interneuron activity, which determine the oscillatory nature of ripples. It is accepted that SWR play an important role in memory formation and reactivation of previous experience (O'Neill et al., 2010). In normal brain the majority of CA1 pyramidal cells are regular firing neurons, so that ripples are an emergent phenomenon of the network. In chronic epileptic brain the CA1 region is able to generate fast ripples (Jiruska et al., 2010b). So what are the underlying mechanisms of fast ripples in CA1? Several changes in the properties of CA1 pyramidal cells and changes to the CA1 network have been described, which may contribute to ability of CA1 region generate fast ripples. In slices from chronic epileptic animals, 90% of pyramidal neurons fired a burst of action potentials in response to depolarisation to threshold depolarization and about 10% of pyramidal cells were spontaneously bursting (Sanabria et al., 2001). This is reversed situation in contrast to normal brain where majority of CA1 cells fires single action potentials. Changes in firing dynamics and conversion to bursters are consequence of an increase in persistent sodium currents and also probably due to molecular changes in calcium channels (Azouz et al., 1996; Sanabria et al., 2001). Another acquired channelopathy which occurs in chronic epilepsy and promotes burst firing is a decrease in dendritic A-type potassium channels (Bernard et al., 2004). Morphological changes like axonal sprouting were also demonstrated in CA1 (Vreugdenhil et al., 2002). In contrast to CA3, CA1 generates high-frequency activity frequency of which may overlap with frequency of pHFA from ripple frequency band. But presence of fast ripples undoubtedly marks the chronic epileptic brain.

High-frequency activity in dentate gyrus

One of the first regions where fast ripples were described was the dentate gyrus. Normal dentate gyrus generates gamma activity the highest frequency of local field potentials does not exceed 100 Hz (Bragin et al., 1995; Towers et al., 2002; Csicsvari et al., 2003), but is predisposed to generate high-frequency activity above 100 Hz if the excitation-inhibition balance is altered. Reducing inhibition in the normal dentate gyrus by picrotoxin elicits epileptiform discharges which are associated with high-frequency activity of ~200 Hz (D'Antuono et al., 2005). In the *in vivo* kainate model, following the period of status epilepticus, population bursts in the frequency range of 100–600 Hz appeared in animals

that later became epileptic (Bragin et al., 2004). Therefore it was decided that all oscillations in the dentate gyrus that have a frequency higher than 100 Hz should be classed as pathological-epileptic. Fast ripples were described only in dentate gyrus from chronic epileptic animals associated with sprouting of mossy fibers, loss of inhibition etc. (Dudek & Sutula, 2007).

High-frequency activity in entorhinal cortex

In addition to the hippocampus, fast ripples have also been demonstrated in entorhinal cortex (Bragin et al., 1999b), which has a different anatomical organization in that it more resembles the neocortex. Whether similar mechanisms are involved in the genesis of fast ripples in entorhinal cortex is still matter of conjecture. It has been demonstrated that oscillations in the frequency range of 300–600 Hz are present in the neocortex and they reflect normal function of neocortical networks in response to a sensory stimulation (Baker et al., 2003), but the amplitude of this activity is very small (few microvolts) and probably reflects firing of single cells rather than compound activity. These oscillations highlight the fact that not all oscillations in the fast ripples frequency range are pHFA and not all pHFA are oscillations in the fast ripples frequency range. To distinguish between them it is crucial to identify properties of individual brain areas under normal and epileptic conditions (acute and chronic).

Fast ripples and epileptogenesis

We can conclude that fast ripples are markers of epileptogenic tissue and reflect changes in neural tissue in epileptic brains; but are fast ripples only an epiphenomenon or are they also involved in the pathophysiology of epilepsy? *In vivo* fast ripples have been shown to occur early during the epileptogenesis and only animals with fast ripples developed spontaneous seizures (Bragin et al., 2004). It was suggested that fast ripples could be used as biomarker of epileptogenesis (Engel, Jr. et al., 2003) and they may be directly involved in epileptogenesis. In chronic experimental epilepsy and in patients the rate of occurrence of pHFAs is low (about 2–10/min). Over a long time period, however, for example a month, they occur about 0.5 million times, which may cause a modification of synaptic transmission in the target areas and increase the chances of triggering seizures. Highly synchronous synaptic inputs will also result in stronger postsynaptic responses and higher probability of propagation of pathological epileptic activity. In the tetanus toxin model, it has been shown that this interictal activity often rapidly spreads to the contralateral hippocampus (Jiruska et al., 2010b). In theory, such repeated synaptic input may facilitate secondary epileptogenesis in the contralateral hippocampus.

HFA and epileptic focus localization – experimental evidence

Currently, the major strength of the ability to record high-frequency activity is that it may provide information about the area of predominant epileptogenicity, the seizure onset zone and probably the epileptogenic zone. The epileptogenic zone is defined as the cortical area that is necessary and sufficient for initiating seizures, and which if resected, will result in the complete disappearance of seizures (Rosenow and Luders, 2001). At present, there is no satisfactory method to identify it. Its location is indirectly defined by location of other zones: irritative zone, lesion, functional deficit zone and mainly the seizure onset zone (Staba et al., 2002). The seizure onset zone is the region where seizures originate and is very closely related to epileptogenic zone. In experimental models of temporal epilepsy elicited by focal intrahippocampal lesion (kainic acid, tetanus toxin), the majority of seizures have an origin ipsilateral to the lesion. However, identification of seizure onset zone is not always straightforward and may be particularly difficult in diffuse onsets. *In vivo*, the rapid spread of seizure activity to the contralateral hippocampus (~ 5 ms) (Finnerty and Jefferys, 2002)

may be falsely interpreted as a bilateral seizure onset, especially if the signal is recorded with insufficient time resolution. Identification of the epileptogenic zone using spatial distribution of interictal discharges (irritative zone) can also be problematic. Epileptic networks generating interictal discharges can be spatially extensive, involving both epileptogenic and normal cortex. In experimental temporal lobe epilepsy, the irritative zone can extend over both hippocampi and include other limbic structures (entorhinal cortex, amygdala). Properties of interictal discharges (incidence, amplitude) can be also misleading and they can be higher in contralateral hippocampus (Jiruska et al., 2010b). Bilateral occurrence of interictal discharges may suggest the certain level of involvement of the contralateral hippocampus in pathophysiology of temporal lobe epilepsy, but it does not provide reliable information about location of the epileptogenic zone and/or seizure onset zone. In the tetanus toxin model, the specificity of interictal discharges in lateralization of seizure onset zone was ~50% (Jiruska et al., 2010b).

Pathological HFA can provide more specific information about the location of the epileptogenic zone (Figure 2). In particular, fast ripples provide relevant information about the lateralization of seizure onset zone in experimental temporal lobe epilepsy. In animals that became epileptic after kainic acid-induced local lesions of hippocampus (Bragin et al., 1999b), fast ripples were observed only in the dentate gyrus adjacent to the lesion and in the ipsilateral entorhinal cortex. In the tetanus toxin model, fast ripples had higher incidence in injected hippocampus and in 50% of animals they were present exclusively only in injected hippocampus (Jiruska et al., 2010b). The majority of spontaneous seizures in these models of epilepsy were observed in the areas that generated fast ripples oscillations, suggesting that fast ripple oscillations are associated with the seizure onset zone. From the experimental perspective, it seems crucial to differentiate fast ripples from other pathological activities. In contrast to fast ripples, pathological high-frequency activity from lower frequency bands (ripple band 100–250 Hz) does not have localizing information and can occur in both hippocampi with a distribution similar to that of interictal discharges. In the tetanus toxin model, pathological pHFA was described in contralateral hippocampus in 50% of animals, however, the incidence of fast ripples was consistently lower in contralateral hippocampus (Jiruska et al., 2010b).

Discharges of high-frequency activity are often more complex. During an episode pHFA, the mean frequency can change (Jiruska et al., 2010b; Figure 1G). Despite this, the mean frequency is always higher in the ipsilateral hippocampus than in the contralateral hippocampus (Jiruska et al., 2010b). The presence of slower frequencies in the contralateral hippocampus may suggest that the epileptogenic structural reorganization in the contralateral hippocampus is absent or less severe and that contralateral hippocampus behaves similarly to normal hippocampus exposed to proconvulsive drugs observed *in vitro* experiments.

Overall, experimental evidence suggests that the incidence of fast ripples or the mean frequency of pathological high-frequency may provide information about the lateralization and localization of seizure onset zone and contribute to the identification of epileptogenic zone (Figure 2).

HFA and epileptic focus localization – clinical evidence

An increase of HFA at the seizure onset was described by several authors but these data were perhaps regarded as curiosities (Allen et al., 1992; Fisher et al., 1992). The first systematic investigation of interictal pHFA (Bragin et al., 1999a) did show that high-frequency activity does exist in a human epileptic brain and that particularly oscillations in the frequency range of 250–600 Hz (fast ripples) provide the localizing information. They

occur more frequently during slow wave sleep than during REM or awake states, and the ratio of fast ripple to ripple oscillations is higher in the area of seizure onset than in the contralateral homotopic area (Staba et al., 2002). Oscillations with frequencies in the ripple and fast ripple band, are present within a seizure onset zone, but also outside of it, however, the ratio of incidence of fast ripples oscillations is higher within the seizure onset zone (Staba et al., 2002).

The discovery that pHFA can be recorded by clinical electrodes allows the role of pHFA in the human epileptic brain broadly in real clinical conditions to be investigated. This has advanced our understanding of their role in the epileptic brain (Worrell et al., 2004; Jirsch et al., 2006; Jacobs et al., 2008; Worrell et al., 2008). The important finding was that these pHFA are not related to any specific type of epilepsy such as temporal lobe epilepsy, which was the focus of the initial publications. Jacobs et al (2009) showed that pHFA is present in epileptic patients with mesial temporal atrophy as well as in patients with focal cortical dysplasia and epileptic patients with nodular heterotopias.

Jacobs and co-authors (2008) reported that pHFA is indicator of the epileptogenic zone independently of the EEG interictal spikes. In contrast, Worrell et al. (2008) showed that pHFA is tightly related to the EEG spikes recorded by depth clinical electrodes. This work also demonstrated that while recording from the same area the number of pHFA in the frequency band >200 Hz was much lower when recorded from clinical macroelectrodes than from microelectrodes. The authors suggest “it is not currently possible to rule out that the macroelectrode itself disrupts the generation of fast ripples HFA; possibly by producing an equipotential surface disrupting the generation of fast ripples oscillations. (Worrell et al., 2008). Several publications showed that the rate of pHFA was higher in the seizure onset zone of patients with mesial temporal atrophy as well as the rate of interictal discharges. The differences were not significant in patients with focal cortical dysplasia; whereas the rate of pHFA, both in ripple and fast ripple frequency range, was much higher in the seizure onset zone of patients with nodular heterotopia (Jacobs et al., 2009). Similar data were published by Worrell et al. (2008) who showed that the rate of pHFA both in ripple and fast ripple frequency range is higher in seizure onset zone in patients with temporal lobe epilepsy.

HFA and modern concept of epileptic focus

Studies on high-frequency activity have aided the understanding of the cellular mechanisms of epileptic focus. Since early work on mechanisms of focal epilepsy, the general concept about the epileptic focus was that it is characterized by presence of epileptic neurons generating paroxysmal depolarization shifts (de Curtis & Avanzini, 2001). At the network level, hypersynchronous activity of epileptic neurons manifests as an interictal discharge. Activity of epileptic neurons is controlled by surround inhibition and failure of the inhibition may result in transition to seizures. Modern technology, particularly the use of microelectrode recordings in chronic experimental models and in humans has revealed the functional organization of the epileptic focus in greater detail. It has demonstrated that epileptic focus is organized into small neuronal clusters of pathologically interconnected epileptic neurons. The activity of these small neuronal clusters manifests extracellularly as pathological high-frequency activity (see above). In humans, it has been demonstrated that pHFA is generated locally by clusters of spatially separated neurons. These clusters are diffusely distributed in the epileptic tissue. Using two-dimensional electrode arrays Schevon et al. (2009) showed that these pHFAs are generated locally and they may occur in association with EEG interictal spikes or they may occur independent of EEG spikes. In spite of local generation, these oscillations are spatially stable and occur under the same set of electrodes during the awake state or during sleep. Another electrographic phenomenon generated by small neuronal clusters are microseizures which may be observed only in one

microelectrode (Stead et al., 2010). When the synchrony of discharges between clusters reach a certain level it will manifest as macroseizures visible in several microelectrodes but also in standard macroelectrodes. Therefore, the modern concept of epileptic focus is that is characterized by small neuronal clusters which can generate local activity – pHFA and microseizures, but also some global patterns – interictal discharges and seizures. Seizure can start in any of these clusters but adjacent clusters have the propensity to be recruited to seizure activity, resulting in an augmentation of the activity and ultimately merge with other clusters to generate spatially larger clusters of synchronous activity which will manifest as macroseizure (Jiruska et al., 2010a; Stead et al., 2010).

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Figure 1.

Different types of epileptic high-frequency activity. A: Burst of high-amplitude high-frequency activity in CA3 in low-calcium model. B: Low-amplitude high-frequency activity in CA1 in low-calcium model. C: Bursts of high-frequency activity in CA3 and in CA1 (D) in high-potassium model. E: Low-amplitude pHFA in high-potassium model. F: Physiological pHFA (sharp-wave ripples) recorded in normal animal in CA1 area. G: High-frequency activity in chronic tetanus toxin model of epilepsy characterized by presence of epileptic fast ripples of different frequencies. H: Fast ripples from CA3 area. I: Epileptic ripples recorded from contralateral hippocampus.

Figure 2.

A: In models of temporal lobe epilepsy following the focal lesion several morphological and molecular changes are present in ipsilateral hippocampus. Majority of seizures have their onset in ipsilateral hippocampus. Incidence of fast ripples or mean frequency of pathological pHFA may help to localize major seizure onset zone. B: Schematic of individual zone types in cases of experimental temporal lobe epilepsy with pHFA or fast ripples occurring exclusively in ipsilateral hippocampus. C: Schematic of individual zone types in case of temporal lobe epilepsy with bilateral occurrence of pathological activity. In this case fast ripples provide localizing information of the seizure onset zone but not pHFA.