

## The Brain Topology of Fast Ripples, and their Correlation with Epilepsy

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### Abstract

High frequency oscillations (ripples 80-250 Hz and fast ripples 250-600 Hz) have been widely studied in the last decade for their potential role as a more precise biomarker of the seizure onset zone, in particular fast ripples. The hippocampus is the best described brain topology as well as its association with this activity. However, in recent years; several groups have analyzed the association of high frequency activity with extra-temporal epilepsies, which could eventually influence the decision making process in the pre-surgical evaluation ensuring a better outcome in patients suffering from different forms of intractable epilepsy. In this review, the brain topology of fast ripples and several human pre-surgical studies were analyzed using fast ripple activity as an epileptogenic biomarker, also it was reviewed the preferred methods of recording for detecting high frequency oscillations in every case.

**Keywords:** Fast ripples; High frequency oscillations; Hippocampus; Neocortex; Ripples; Seizure onset zone; Temporal lobe epilepsy

### Abbreviations:

AEDs: Antiepileptic Drug; EPSP: Excitatory Postsynaptic Potentials; Glu: Glutamate; HFO: High Frequency Oscillations; FR: Fast Ripples; HS: Hippocampal Sclerosis; IPSP: Inhibitory Postsynaptic Potentials; MRI: Magnetic Resonance Imaging; SOZ: Seizure Onset Zone; SWS: Slow-Wave Sleep; TLE: Temporal Lobe Epilepsy

### Introduction

Epilepsy is a worldwide health problem. According to the World Health Organization, 50 million people were estimated to suffer from this disease in 2012, and nearly 80% of this population is concentrated in developing countries. Given a proper treatment, epilepsy responds in 70% of the cases. However, due to the health conditions in developing countries, this percentage drops drastically.

The epileptic seizures have a broad spectrum of clinical symptoms that depending on the type of epilepsy and their cause they are associated with different degrees of cognitive impairment and response to treatment. At cellular level, seizures are caused by the continuous and hyper-synchronized firing of a group of brain neurons [1,2] which generates specific patterns in the EEG. Likewise, this hypersynchronized firing is the result of the unbalance between excitatory and inhibitory activity, caused by the increased effect of the neurotransmitter Glutamate (Glu) as well as the decrease of the GABA neurotransmitter [2-4].

One of the challenge that remain for both the clinical medicine and experimental studies is the accurate localization of the epileptogenic zone, in order to predict, diagnose and treat this disease more efficiently. This problem has led to the search of a precise biomarker for epilepsy, especially the kind that responds poorly to antiepileptic drugs (AEDs) and is associated with bad prognosis (since it can even

culminate on sudden unexpected death in epilepsy or SUDEP) and refractory seizures. This entity is also known as pharmaco-resistant epilepsy [5].

There are some predictors of pharmaco-resistance, such as the cause of the epilepsy (symptomatic epilepsy, for instance is more likely to respond less to AEDs, than idiopathic) [6], the age of onset, being more dangerous those that present at the neonatal stage and after 12 years-old [7], the presence of physical abnormalities and mental disabilities among other signs [8].

One of the most pharmaco-resistant epilepsies is temporal lobe epilepsy (TLE), which is associated with magnetic resonance imaging (MRI) abnormalities (hippocampal sclerosis) and poor response to AEDs. This sort of epilepsy often leads to surgery, and even after surgery one third of the patients will continue having seizures [9].

The analysis of the pathological networks formed in TLE notices high synchrony as one important element in the ictal event [10,11]. However, interictal activity, such as spikes, holds relevance, as they can participate in the development of comorbidities, mostly causing impairment in cognitive processes [12].

In this context, the need of a precise biomarker arose. Several study groups have presented evidence of high frequency oscillations (HFO); in particular fast ripples (FR, 250-600 Hz) as a possible response to this need [1,13].

### High Frequency oscillations related to epilepsy

This phenomenon is described as an oscillatory field potential that reflects short term synchronization of neuronal electrical activity, ranging from 80 to 600 Hz [14]. Gamma activity (30-80 Hz) will not be considered in this review, since is related to physiological activity [15], and whereas ripples (80-250 Hz) and particularly fast ripples (250-600 Hz) are often correlated with epileptogenic phenomena [14].

## Ripples

Ripples are oscillations ranging from 80 to 250 Hz, which are found in the normal rat and human hippocampus and entorhinal cortex, except in the dentate gyrus [16], where they are associated to epileptic processes. This activity has been associated in the process of long term potentiation through the communication of the hippocampus with extra hippocampal structures; there is evidence that this event occurs particularly in the Slow-Wave Sleep (SWS) [17].

This activity is generated by the “concert” of the intrinsic cellular activity and the coordination of a group of neurons. The intrinsic cellular activity is translated as inward currents of Na<sup>+</sup> and Ca<sup>2+</sup>, and outward currents of K<sup>+</sup> that cause slow after hyperpolarization [18]. The coordination of cellular groups has been hypothesized to happen in very different mechanisms: The generation of ripples is related to the presence of inhibitory postsynaptic potentials (IPSP) created by interneurons, each one of them affects the action potential generation of several neurons in the pyramidal layer of the CA1 region of the hippocampus [19,20]. However this mechanism is associated with memory formation.

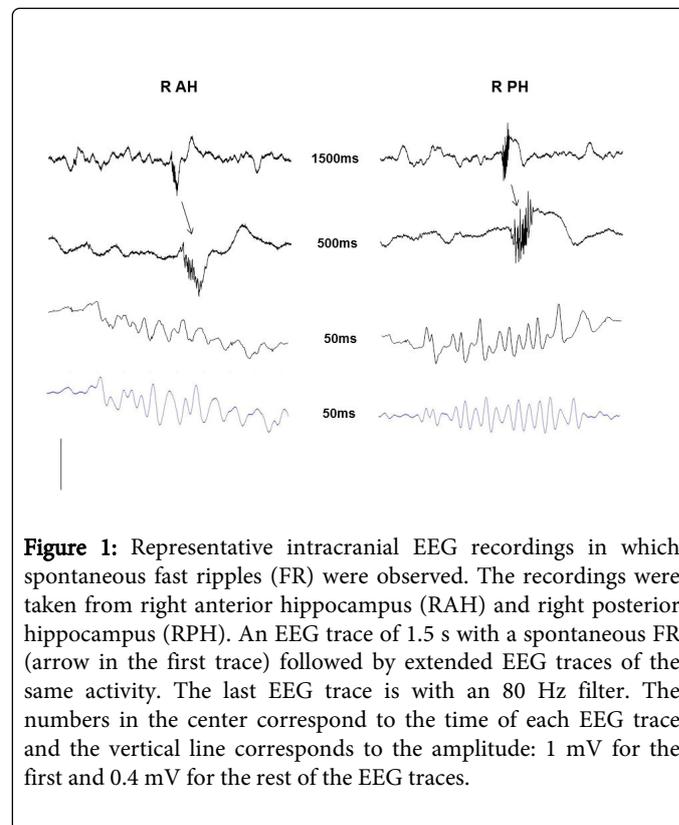
## Fast ripples

FR reflect bursts of population spikes from synchronously firing principal cells in relatively small areas (1 mm<sup>3</sup>) [21,22], these containing several pathologically interconnected neuronal clusters [1]. Their spectral range lies between 250–600 Hz, and can last from 10 to 60 ms (Figure 1). They are mostly found in dentate gyrus, CA1/CA3, subiculum and entorhinal cortex [23] and, like ripples, are elicited during SWS. FR activity occur in the same hemisphere in relation to the lesion, both in humans with TLE and rats treated with KA [14], in a total volume of brain tissue of 1 mm<sup>3</sup>, however this area can increase in the absence of inhibitory activity [21,22].

Some mechanisms related to generation of fast ripples are: The formation of aberrant synapses between pyramidal cells in the epileptic process, resulting in the generation of excitatory postsynaptic potentials (EPSP) that synchronizes hippocampal neurons [24], causing seizures. It has been also analyzed the potential role of gap junctions, where the affected neurons depolarize adjacent neurons through axonal coupling [25]. Another proposed hypothesis is the participation of ephaptic interactions, in this model; the electric field generated in the extracellular field is strong enough to depolarize adjacent neurons, thus triggering an action potential [26]. Finally, the generation of a field potential created by a group of synchronized neurons can recruit neurons nearby, increasing the field power and causing this kind of activity [26].

The fundamental difference between ripples and FR (Table 1), is the value as a biomarker that holds the later, since they can only be found in the eventually epileptic brain [14]. And it also correlates with the severity of the disease since there are more FR in the presence of more seizures [27]. In this respect, several examples of association between

the appearance of HFO in the resection zone and surgical outcome in patients have been reported. Ochi and coworkers [28] studied retrospective data of 9 children who underwent intraoperative subdural EEG, 4 of them had seizure freedom.



**Figure 1:** Representative intracranial EEG recordings in which spontaneous fast ripples (FR) were observed. The recordings were taken from right anterior hippocampus (RAH) and right posterior hippocampus (RPH). An EEG trace of 1.5 s with a spontaneous FR (arrow in the first trace) followed by extended EEG traces of the same activity. The last EEG trace is with an 80 Hz filter. The numbers in the center correspond to the time of each EEG trace and the vertical line corresponds to the amplitude: 1 mV for the first and 0.4 mV for the rest of the EEG traces.

In comparison to the residual seizure group, the seizure free group showed more frequency of HFO within the resection zone ( $p < 0.001$ ) after the clinical onset of the seizures. In the same way, the group of Akiyama [29] studied 28 pediatric patients with history of intractable epilepsy. They found through the intracranial video EEG (VEEG) of patients a significant relation between the FR resection ratio ( $p = 0.046$ ) and seizure outcome within a 2 years post-surgical period. They also found that the 18 patients scheduled for multiple lobe resections had a larger FR size than those with single lobe involvement. Regarding ripples, they only found improvement of seizures when resected the region in which they were contained but not seizure freedom. In other study [30] were analyzed retrospectively the intracranial EEG recordings performed in 44 pediatric patients with intractable epilepsy in both temporal and extra-temporal regions. It was found 41 patients with HFO (ripples and FR). From 22 patients with the HFO region resected, 18 had a seizure free outcome, whereas only 21% of patients achieved seizure freedom with incomplete HFO region resection.

HFO	Ripples	Fast Ripples
<b>Spectral frequency</b>	80-250 Hz	250-600 Hz
<b>Location</b>	Hippocampal formation (mostly in CA1 and entorhinal cortex), physiological ripples can be found in neocortex as well.	Hippocampus, entorhinal cortex, neocortex.

<b>Duration</b>	30-160 ms	10-65 ms
<b>Rate per minute</b>	0.1-60/min	0.5-6/min
<b>Physiological activity</b>	Memory formation	Evoked somatosensorial response

**Table 1:** Comparison of high frequency oscillations (HFO) associated to epileptogenesis.

The presence of ripple or FR activity in the dentate gyrus can be linked to early appearance of spontaneous seizures [31]. Recent studies have proven that is important not only to distinguish the width band of the activity, but its pattern, since FR occurring in a discontinuous manner tend to be more closely related to the seizure onset zone (SOZ), than continuous FR with high frequency activity in the background [32].

## Brain Topology of Fast Ripples

### Temporal lobe epilepsy

It has been well described the characteristics of FR in TLE, both in animals (particularly in rats) and humans. In animal models of TLE, FR are observed in dentate gyrus, in CA1/CA3, subiculum and entorhinal cortex [23]. Two important elements in the interpretation of high frequency activity are the time of onset of HFO, which correlates strongly with the time of onset of spontaneous seizures and topology, even within the hippocampal formation, ripple frequency detected in dentate gyrus strongly correlates with an ongoing pathological process as well as FR. Animals with HFO detected earlier in dentate gyrus, presented spontaneous seizures before other animals [31].

The most frequent morphological alteration in TLE is hippocampal sclerosis (HS), this lesion is characterized by extensive neuron loss and formation of pathological networks [33]. The presence of HS with a significant decrease of hippocampal volume correlates with higher rates of FR and lower rates of ripples, which supports the theory that ripples require the integrity of bigger network, whereas FR can generate in very small clusters of pathologically interconnected principal cells [1].

### Extra-temporal epilepsies

Neocortical epilepsies also manifest HFO, and have very different forms of presentation and severity. A study made in patients with intractable partial epilepsy showed FR only in focalized seizures [34]. It has also been found, that regardless of the site of lesion, pediatric patients with symptomatic forms of neocortical epilepsies presented a better outcome when the area of FR was resected, in relation with visible lesions on MRI [35] (Table 2). An interesting proposal for a noninvasive approach in children with absence seizure was the utilization of magneto encephalography, where the activity in the ripple and FR band was localized, primarily in the medial prefrontal cortex [36].

Ref. Number	Patients	Type of epilepsy	HFO	Recording Technique	Electrode Number/position	Associated Technique	Surgical outcome
[1]	9	TLE	R, FR	Depth microelectrode EEG	14 (A, H, EC, PS,PH)	MRI	NE
[28]	9	Symptomatic Neocortical	R	Subdural EEG with macroelectrodes SR 1000 Hz	25-120, variable position	MRI, Scalp video EEG, MEG	4 seizure free 60% HFO in RA 5 cases 36% HFO in RA, residual pathology
[38]	10	TLE, Neocortical	R, FR	Cortical and depth electrodes SR 2000	4-9 (A,H,PH)	EMG, EOG	NE
[39]	4	TLE, Neocortical	R, FR	MEA, subdural and depth microelectrodes SR 30000 Hz	96+ temporal and frontal lobes	ECOG	NE
[40]	4	Epilepsy secondary to cortical dysplasia	R, FR	Stereo EEG, depth multicontact macroelectrodes SR 1024 Hz	Operculum, prefrontal cortex, precentral sulcus, orbitofrontal cortex	MRI	4 cases seizure free, 2 cases significantly reduced
[29]	13	Temporal and extra-temporal	R, FR	Subdural and depth electrodes SR 1000 Hz	2-16	MRI, MEG, sensory evoked potentials	Resection of FR correlated with better

							surgical outcome.
[37]	45	BCECTS, PS	R	Scalp sleep EEG SR 500 Hz	10-20 system	None	Non Surgical
[30]	44	Lesional and nonlesional	R, FR	Subdura SR 2000 Hz	variable	MRI, CT	Resection of HFO correlated with better surgical outcome.
[41]	32	Frontal, parietal, central, temporal, occipital	R	Scalp EEG SR 1000 Hz	10-20 system+6	MRI	NE
[32]	22	FCD, HS, frontal, nonlesional	R, FR	Neocortical grid electrodes SR 1024 Hz	variable	MRI	Resection of FR areas showed more affinity with seizure freedom
[42]	35	Neocortical	R, FR	Subdural, depth electrodes and stereo EEG SR 2000 Hz	variable	MRI	FR only in SOZ, surgical outcome NE
[43]	12	TLE, Multifocal	R, FR	Depth microelectrodes SR 2000 Hz	6-10	MRI	Highly variable
[44]	14	TLE, frontal	R, FR	ECoG SR 2048 Hz	128 channels	MRI	9 with FR, 5 good outcome

**Table 2:** Representative studies of the brain topologies where high frequency oscillations can be found and technical specifications of recording.

**Abbreviations:** A: Amygdala; H: Hippocampus; EC: Entorhinal cortex; PS: Presubiculum, PH: Parahippocampal gyrus, TLE: Temporal Lobe Epilepsy; MRI: Magnetic Resonance Imaging; EEG: Electroencephalography; MEG: Magnetoencephalography; RA: Resection Area; BCECTS: Benign Childhood Epilepsy with Centro-Temporal Spikes; PS: Panayiotopoulos Syndrome; ECoG: Electrocorticogram; EOG: Electroculogram; EMG: Electromyography; MEA: Microelectrode Array; FCD: Focal Cortical Dysplasia; HS: Hippocampal sclerosis; CT: Computed tomography; R: Ripples; FR: Fast Ripples; HS: Hippocampal Sclerosis

## Conclusion

In order to associate a high frequency activity to an epileptogenic process, there must be an extensive search of the discrete topology of this activity. In this context temporal structures have been more studied, and as several groups support the identification of ripples within dentate gyrus and FR in any localization, highly correlate with the SOZ and good surgical outcome when these clusters are removed.

FR in neocortical epilepsies have also proven their value as a biomarker, the preferred technique to obtain the EEG is with a combination of depth and subdural electrodes, and a high sampling rate at 1000 Hz or above. The recordings have shown that FR highly correlates with SOZ. Even if surgical outcome is mostly positive when FR is resected, the possibility of multifocal epilepsies hinders these percentages when compared with the surgical outcome observed in TLE surgeries from previous works.

FR are increasingly gaining attention due to their potential role as a biomarker; however there are many challenges that must be overcome before its use could become habitual in the clinical practice.

These challenges are, mostly, the difficulty of recording FR non-invasively, as noted before; ripples frequencies are elicited by larger amounts of tissue, and therefore easier to record in scalp EEG [37]. In this study the ripple activity was detected in neocortex. The proposed noninvasive recordings must be compared with the traditional approach in order to accurately determine its specificity and sensibility.

This situation must be considered, particularly in non-surgical types of epilepsy in order to analyze the role of FR as a key in the decision making process regarding the pharmacotherapy of newly diagnosed patients, as well as those considered in remission.

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