# The value of high frequency oscillations (HFOs) in pre-surgical assessment of epilepsy
# La valeur des oscillations à haute fréquence (HFO) dans l'évaluation pré-chirurgicale de l'épilepsie

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**Abstract**

**Introduction** : Localisation of the epileptogenic zone is key to successful resective surgery for epilepsy. Invasive electrophysiological recording at high sampling rates to detect high frequency oscillations may provide important information to achieve this goal.

**Participants and methods :**The published literature regarding the use of high frequency oscillations in epilepsy surgery was assessed to determine the value of this technique in the investigation of candidates for epilepsy surgery.

**Results :** A number of case reports support the use of monitoring high frequency oscillations in order to optimise seizure freedom following resection. The technique has only been applied to patients undergoing invasive telemetry.

**Conclusions :** At present the technique remains a promising research tool and further studies are required before it can be considered as routine in the investigation of patients with intractable epilepsy.

**Keywords:** Epilepsy surgery- Invasive telemetry- High frequency oscillations- Fast ripples.

**Résumé**

**Introduction:** La localisation de la zone épileptogène est la clé du succès de la chirurgie de l'épilepsie. L'enregistrement électrophysiologique invasif à des taux d'échantillonnage élevé pour détecter les oscillations à haute fréquence peut fournir des informations importantes pour atteindre cet objectif.

**Matériel et méthodes:** La littérature concernant l'utilisation des oscillations à haute fréquence dans la chirurgie de l'épilepsie ont été évalués pour déterminer la valeur de cette technique dans l'enquête concernant les patients candidats à la chirurgie de l'épilepsie.

**Résultats:** Un nombre de patients a permis l'utilisation et la surveillance des oscillations à haute fréquence afin d'optimiser la saisie de la résection suivante. La technique n'a été appliquée à des patients subissant la télémétrie invasive.

**Conclusions:** À l'heure actuelle la technique reste un outil de recherche prometteur et de nouvelles études sont nécessaires avant de pouvoir être considéré comme examen de routine dans l'enquête sur les patients atteints d'épilepsie réfractaire.

**Mots-clés:** Chirurgie de l'épilepsie- télémétrie envahissantes- oscillations à haute fréquence- ondulationsrapides.

## Introduction

Resection of the epileptogenic focus has been the gold standard of epilepsy surgery ever since Hughlings Jackson first proposed cortical irritation as the cause of focal epilepsy [1] in the 1870s. The earliest reported surgical series by Victor Horsley depended on localisation of the epileptogenic focus by external stigmata (the scars of a head injury) and by comparison with known semiology from primate models [2], leading to remarkably successful outcomes. Contemporary pre-surgical assessment depends on congruence of information from multiple investigation modalities, including but not restricted to analysis of seizure semiology, MRI, EEG, video telemetry, fMRI, PET, ictal SPECT, neuro-psychological assessment, Wada test, MEG and invasive recordings. Cases may be broadly divided into those patients with lesions visible on MR, and those that are MR negative. This latter group presents the greatest challenge and assessment of suitability for surgery requires the formation of a hypothesis of the site of the epileptogenic focus based on non-invasive investigations. This hypothesis may then be tested with invasive recording, which is more accurate in localising the origin of a seizure when compared to scalp EEG. Only if this last test confirms the hypothesis can treatment progress to surgical resection [3]. Patients with normal imaging are less likely to proceed from invasive telemetry to definitive surgery (54% vs 91%) and in extratemporal epilepsy are less likely to progress to good seizure control (33%) [4].

Further information on the likely source of the epilepsy is therefore valuable in improving outcomes in MR negative epilepsy. Conventional EEG recordings operate in the frequency range up to 100Hz, with a sampling rate around 200Hz [5], but there is much interest in investigating cerebral electrical activity outside of these values.

### The epileptogenic zone:

There is some controversy over the definition of the epileptogenic zone between American and French schools. Lüders defines the epileptogenic zone as 'the minimum amount of cortex that must be resected (inactivated or completely disconnected) to produce seizure freedom'

[6]. This definition is somewhat disdainfully summarised by Kahane as the 'what-to-remove area' [7], which he dismisses as a hypothetical region whose existence can only be deduced once it has been removed. Kahane advocates the Bancaud-Talairach definition based on ictal stereo EEG findings and not on interictal spikes. Regardless of definitions, the success of epilepsy surgery is defined by post-operative seizure freedom and the absence of new neurological deficits. Invasive telemetry can help achieve both these aims through defining the earliest source of epileptic activity and allowing stimulation to map functional cortex.

Invasive recording generates both inter-ictal and ictal information. Seizure recordings indicate the seizure onset zone, the earliest site of seizure activity which is generally identified as paroxysmal sustained rhythmic EEG change [8]. Ictal information about this area is complemented by inter-ictal recordings demonstrating the irritative zone, the area of cortex capable of generating inter-ictal spikes, which is usually more extensive than the epileptogenic zone [6]. The difference between these two zones is illustrated in a patient who has independent bitemporal interictal spikes but can be rendered seizure free by unilateral temporal lobe resection.

**What are high frequency oscillations?**

EEG recordings are generally sampled at 250Hz and then filtered to show electrical activity in the following ranges:

| | |
|---|---|
| Alpha: | 8-14Hz |
| Beta: | >14Hz |
| Theta: | 4-8Hz |
| Delta: | <4Hz |

It is possible to examine higher frequency activity. Gamma activity is defined at 38 to 100Hz and overlaps with high frequency oscillations (HFOs) which are defined as activity above 80Hz, with the further subdivision into ripples (80-250Hz) and fast ripples (250-600Hz) [9] (Figures 1 and 2).

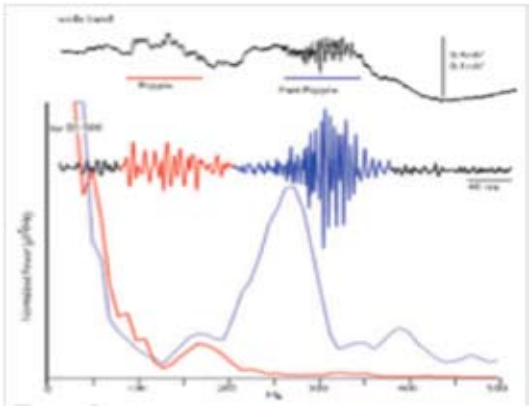


**Figure 1: An example of ripple and fast ripple (FR) oscillations in wide bandwidth (top trace, 0.1 Hz–5 kHz) recording from dentate gyrus. Bottom trace band pass filtered between 80 and 500 Hz. Normalized power spectrogram computed from underlined segments in wide bandwidth recording corresponding 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. Reproduced with permission [13].**

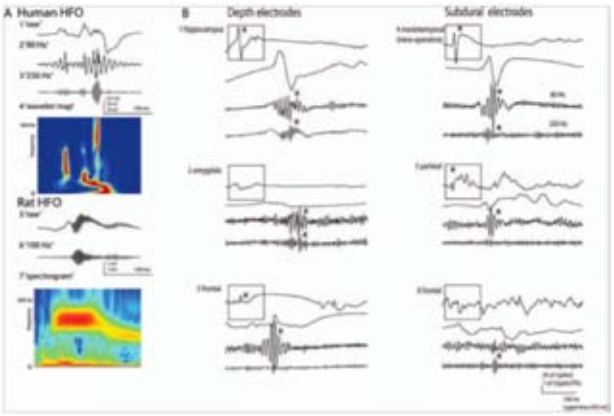


**Figure 2: Examples of HFOs. (A) HFOs recorded with depth macroelectrode in human (1–4) and rat (5–7) hippocampal area. (1) Raw intracranial EEG with sharp wave from human hippocampal area (macroelectrode). (2 and 3) Filtered with high-pass filter of 80Hz and 250Hz. Note the differences in amplitude scales. Such an event would not stand out in normal EEG. (4) Wavelet transform of frequencies up to 500Hz. (5) Raw intracranial EEG data from rat with right intrahippocampal injection of tetanus toxin (microelectrode). A fast ripple with peak frequency 359Hz followed by activity at 240Hz is visible in the raw data. (6) Filtered with high-pass filter of 100Hz. (7) Spectrogram up to 500Hz after Fourier transformation. (B) HFOs recorded with depth and subdural macroelectrodes, in mesiotemporal areas and neocortical areas in patients with epilepsy. For each event the display shows the standard EEG signal, the same signal with extended time scale and this signal after 80Hz and 250Hz high-pass filtering. Different examples are shown from different sites. This illustrates that all combinations are possible: spike with ripple and fast ripple (114), ripple and fast ripple without spike (2), spike with ripple without fast ripple (315) and fast ripple without ripple or spike (6). An asterisk (*) means that the event was marked at this frequency. EEG 5 electroencephalogram; FRs 5 fast ripples; HFO 5 high-frequency oscillation [9].**

They are best recorded at sampling rates up to 2000Hz. Early work identified HFOs in rat models and postulated that they might lend more accuracy to the detection of epileptiform spikes by improving the signal to noise ratio [10]. HFOs were subsequently identified in interictal recordings of mesial temporal structures of patients with epilepsy [11] and further work suggested that HFOs were located within or near to epileptogenic regions [9]. HFOs can be physiological as well as pathological. Ripple frequency oscillations have been recorded in normal primary motor cortex and hippocampus, where they are thought to correspond with consolidation of memory [12]. HFOs in the fast ripple range are believed by some to be always pathological but have been recorded in normal neocortex although not in normal hippocampal structures [13,14].

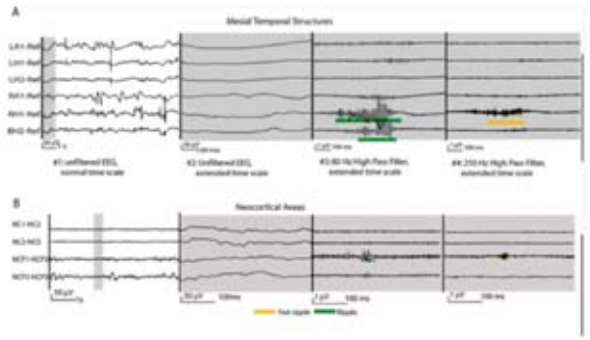
Normal ripples within the hippocampus arise from relatively large areas of parenchyma, whereas pathological HFOs are localised to small neuronal clusters. Fast ripples in the hippocampus have been recorded at the onset of seizures as well as inter-ictally, suggesting that they are associated with mechanisms of seizure generation. Hippocampal HFOs in the ripple range may also be pathological and have been recorded from the dentate gyrus in rats that developed recurrent spontaneous seizures following intrahippocampal kainic acid [13].

Although the mechanisms underlying HFOs are not fully understood, they are thought to represent localised networks of mutually activating neuronal ensembles. In a physiological context this is postulated to allow integration of post-synaptic potentials and thus increase the functional impact of a group of cells, for example while laying down memory or integrating various features in a visual scene. During epileptic activity, however, these synchronous events may be due to pathological interconnection of groups of neurons and may provide a biomarker of epileptogenicity [5]. This abnormal connectivity results in fast recruitment of cells from firing of a single or small group of neurons, resulting in synchronous action potential firing and manifesting as HFOs [9]. It is also hypothesised that pathological HFOs might result from the synchronous discharge of principal cells, each of which fires at a lower frequency than the ensemble [14].

Furthermore, it has been demonstrated that HFOs are specific to epileptogenic tissue rather than merely indicating the presence of a lesion [15].

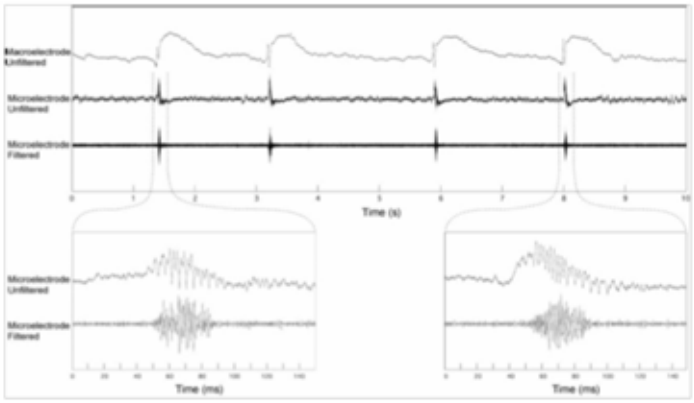
**How are high frequency oscillations recorded?**

HFOs were originally recorded with microelectrodes (diameter 40μm, surface area ≈10-3mm2) in rat models, and with this method fast ripples were shown to be associated with interictal and ictal spikes in tissue capable of generating spontaneous seizures. They were subsequently demonstrated in humans using macroelectrodes (surface area 0.80mm2) and shown to be related spatially to the clinical seizure-onset zone [5] (Figure 2). Simultaneous recording using both techniques reveals a much lower frequency of fast ripple activity with macroelectrodes, suggesting that fast ripple oscillations are localised to small regions measuring less than 1mm3 and cannot be detected with the large recording area of a macroelectrode [16] (Figure 3).



**temporal (A) and neocortical structures (B). HFOs are visualized on a different time scale and with different filter settings than the usual clinical EEG. In the two EEG segments on the left the amplitude scale is 50 times increased compared to those on the left to demonstrate the very small scale HFOs. HFOs in the mesial temporal structures are larger, of higher amplitude and more frequent than those in neocortical areas. Both EEGs derived from patients with non-lesional epilepsies. Reproduced with permission[22]**

**Figure4: (Top panel) Interictal epileptiform spike microwire**



**and adjacent clinical macroelectrodes. The after-coming slow-wave seen on the referential macroelectrode recording is not present on the microwire because of the local recording reference used for microwires. (Lower) Unfiltered and high-pass filtered (480 Hz) microwire recordings highlighting the high-frequency oscillation that is not present on adjacent macroelectrode recording. The high pass filtered microwire recording (600 ^ 6000 Hz) shows robust multi-unit activity in association with the fast-ripple oscillation [16].**

The larger surface area of macroelectrodes results in undersampling of focal HFO activity. However, the majority of HFOs recorded with macroelectrodes are abnormal.

There are technical challenges involved in identifying and analysing HFOs from an EEG recording and as yet there is no standard technique for achieving this. For example Jacobs et al. recorded EEG at a sampling rate of 2000Hz, then selected 5 minutes of slow-wave sleep. Contacts were then displayed with a time resolution of 0.6 seconds on a vertically split screen with an 80Hz high-pass filter on the left and a 250Hz low pass filter on the right. Events seen only on the left were defined as ripples and those on the right as fast ripples. At least four consecutive oscillations were considered necessary to comprise a HFO, and two events were considered distinct when separated by at least two non-HFO oscillations [17]. An alternative computerised method developed by Staba et al. involves band-passing the signal between 100 and 500Hz and calculating the root mean square amplitude of the filtered signal [18]. HFOs were identified as events where the amplitude of the root mean square deviated more than 5 standard deviations above the mean and lasted more than 6ms.

They are seen both as isolated events, and superimposed onto interictal spikes. Not every interictal discharge is associated with HFOs and it is thought that the HFO zone is smaller than the irritative zone and may be more specific to the seizure onset zone. HFOs tend to be more constant in location as compared to interictal spikes, whose origin can be labile.

If HFOs do prove to provide reliable localisation of the epileptogenic zone there could be reduction in the duration of telemetry required, as it might not be necessary to record multiple ictal events. The relationship between interictal HFOs recorded during slow-wave sleep with invasive macroelectrodes and the seizure onset zone has been examined [17]. A significant correlation between resection of HFO generating tissue and Engel outcome at two years was demonstrated. Of the 20 patients in the study, 12 had poor outcome (Engel 3 or 4) and among these, only three had complete resection of HFO generation areas. These patients may highlight a significant problem related to sampling error in intracranial EEG due to limited brain coverage. Seven of the eight patients with good outcome (Engel 1 or 2) had resection of all HFO generating tissue. Jacobs et al found that removal of areas that generated HFOs was more predictive of good outcome than removal of the seizure onset zone as defined by interictal spikes.

**Evidence in favour of HFOs localising to the epileptogenic zone**

A number of studies have demonstrated the value of resection of HFO generating areas of brain. Fujiwara et al retrospectively analysed 44 patients who underwent intracranial EEG and subsequent surgical resection and analysed ictal EEGs for the presence of HFOs [19]. They found that complete resection of HFO generating areas resulted in seizure freedom at two years in 18 of 22 patients (82%), while 4 of 19 patients (21%) with incomplete HFO resection achieved seizure freedom at two years.

Limitations of the study include the fact that resection was based on multiple sources of information including MRI and post resection ECOG and thus does not demonstrate that using HFOs to guide resection will result in improved outcomes. Ochi et al. have previously demonstrated better seizure control when the area resected included the predominant HFO generating regions, and postulated that unresected areas with high frequencies of HFOs have the potential to develop into epileptogenic zones following the surgery [20].

A case report demonstrates the value of using HFOs to define the epileptogenic focus in a patient with bitemporal independent spikes on noninvasive telemetry. Jiruska et al were unable to lateralise the site of seizure onset despite multiple investigations including PET and even conventional invasive recording with macroelectrodes. However examination of the invasive recordings, using a high-pass filter with a cut-off frequency of 80Hz and increased gain, revealed a 24 second period of activity between 85 and 140Hz in the left temporal pole prior to left hippocampal onset. During this period the patient experienced no symptoms. Further periods of left temporal pole HFOs were noted without spread to the hippocampus and without clinical signs or symptoms. Limited resection of the left temporal pole resulted in seizure freedom at one year [21].

**Evidence against HFOs**

The evidence in favour of using HFOs to guide resection is low-level, and many questions remain. Small case series are limited by patient selection bias, and are usually performed by single surgeons in specific centres leading to a potential inability to generalise conclusions. The mechanisms underlying epileptic HFOs remain poorly understood and the distinction between pathological and physiological HFOs is not always clear.

There is no clearly defined threshold above which the rate of HFO occurrence is pathognomonic for epileptogenesis. Most studies use relative rates, comparing the incidence of HFOs in the various areas undergoing recording and ranking them from most to least epileptogenic. These rates may vary in different stages of sleep, different levels of antiepileptic medication and between individual patients [22].

Further, the pathophysiological mechanisms by which abnormal HFOs propagate to develop into clinical seizures are not understood. As yet, long term outcome data relating HFO resection to seizure freedom is not available [23].

**Conclusions**

A growing number of case reports support the value of monitoring HFO generation in order to optimise seizure freedom following resection. These data can currently be applied only to patients undergoing invasive telemetry, and as yet the relation between HFOs recorded with micro and macroelectrodes is not certain. There has been some success in recording HFOs from scalp EEG [24] and MEG.

At present the use of HFOs in pre-surgical workup remains a research tool. Multicentre trials with larger patient numbers and using various recording techniques are needed to validate this technique further before it becomes mainstream.

It is however clear that the current clinical intracranial EEG using narrow bandwidths at low sampling rates from large widely spaced electrodes is missing potentially important electrophysiology. The 'optimal temporal and spatial resolution of human intracranial electrophysiology for diagnostic and therapeutic applications' remains in question [16]

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