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High-frequency oscillations (HFOs): the state of clinical research

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Abstract

Objective: Modern EEG technology contributed to the appreciation that the EEG signal outside the classical Berger frequency band contains important information. In epilepsy, research of the last decade focused particularly on interictal high-frequency oscillations (HFOs) above 80 Hz. The first large application of HFOs was in the context of epilepsy surgery. This is now followed by other applications such as assessment of epilepsy severity or monitoring of antiepileptic therapy.

Methods: This article reviews the evidence on the clinical use of HFOs in epilepsy with an emphasis on the latest developments. It highlights the growing literature on the association between HFOs and postsurgical seizure outcome.

Results: A recent meta-analysis confirmed a higher resection ratio for HFOs in seizure-free versus non-seizure free patients. Residual HFOs in the post-operative electrocorticogram were shown to predict epilepsy surgery outcome better than pre-operative HFO rates. The review further discusses the different attempts to separate physiological from epileptic HFOs, as this might increase the specificity of HFOs. As an example, analysis of sleep microstructure demonstrated a different coupling between HFOs inside and outside the epileptogenic zone. Moreover, there is increasing evidence that HFOs are useful to measure disease activity and assess treatment response using non-invasive EEG and MEG. This approach is particularly promising in children because they show high scalp HFO rates. HFO rates in West syndrome decrease after ACTH treatment. Presence of HFOs at the time of rolandic spikes correlates with seizure frequency. The time-consuming visual assessment of HFOs, which prevented their clinical application in the past, is now overcome by validated computer-assisted algorithms.

Significance: HFO research has considerably advanced over the last decade, and use of non-invasive methods will make HFOs accessible to large numbers of patients. Prospective multicenter trials are awaited to gather information over long recording periods in large patient samples.

Keywords: scalp EEG, biomarker, surgical outcome, seizure, sleep

Key Point Box

- This article reviews the evidence on the clinical use of HFOs in epilepsy.
- The application of HFOs ranges from epilepsy surgery to the assessment of epilepsy severity and monitoring of antiepileptic therapy.
- A recent meta-analysis confirms a higher resection ratio for HFOs in seizure-free versus non-seizure free patients.
- The association with sleep features is used to separate physiological from pathological HFOs in order to increase the specificity of HFOs.
- HFOs seem to be useful to measure disease activity and assess treatment response using non-invasive EEG and MEG.

Introduction

Modern electroencephalography (EEG) technology substantially contributed to the appreciation that the EEG signal outside the classical Berger frequency band ranging from 0.3 to 70 Hz contains important information. In epilepsy, research of the last years focused particularly on interictal high-frequency oscillations (HFOs) above 80 Hz. HFOs are defined as spontaneous EEG events in the frequency range between 80 and 500 Hz, consisting of at least four oscillations that clearly stand out of the background activity.[1] HFOs are subdivided into ripples ranging from 80–250 Hz and fast ripples >250 Hz.[2] For more details on the definition of HFOs see the accompanying article in this issue by Zijlmans and colleagues on how to record HFOs. The first large application of HFOs was in the context of epilepsy surgery. This is now followed by other applications such as assessment of epilepsy severity or monitoring of antiepileptic treatment response using non-invasive methodology. This article reviews the latest

developments relevant for the clinical use of HFOs and discusses the implications of HFO assessment for clinical epilepsy care.

Milestones in human HFO research

In 1992, high-frequency (HF) activity in the EEG was first investigated at seizure onset.[3,4] Independently, in 1999, a different type of brief interictal fast oscillatory events up to 500 Hz was discovered by the group of Bragin and Engel at the University of California in Los Angeles in animals with experimental epilepsy. At the same time, they also pioneered the recording of HFO events in therapy-refractory patients with mesiotemporal lobe epilepsy.[2,5,6] In humans, Bragin and colleagues used microelectrode arrays consisting of 9-18 microwires (diameter of 40 µm) that extended beyond the tip of clinical depth electrodes and recorded from the hippocampus and entorhinal cortex. The authors found ripples (80-250 Hz) - similar to those described in experimental animals - and fast ripples (>250 Hz), which are found only in the epileptic condition.[2,5] This group further characterized microelectrode recordings of human HFOs in the entorhinal cortex[7] and during different stages of sleep.[8]

The breakthrough in clinical HFO research was made at the Montreal Neurological Institute (MNI) in 2006. The group of Gotman showed that HFOs up to 500 Hz could be recorded using macroelectrodes. In their work the authors used the MNI electrode with a surface of 1 mm^2.[9,10] The group of Otsubo in Toronto had also demonstrated activity in the 60-150 Hz range in the electrocorticogram of children at the time of spasms.[11] The detection of HFOs with macroelectrodes resulted in multiple studies by different groups around the world using commercial macroelectrodes as well as subdural electrodes with up to 7 mm^2 surface.[1] Although it was shown that the electrode contact size, within a certain range, does not influence the detectability of HFOs,[12] it is still unclear if HFOs assessed with microelectrodes represent the same phenomenon as HFOs detected with macroelectrodes. Interestingly, ripples recorded with macroelectrodes seem to be more localizing than ripples recorded with microelectrodes, and currently there is not sufficient explanation for this situation.

The next milestone was the detection of HFOs using non-invasive modalities. The pioneers in this area were the group of Kobayashi at Okayama University who

reported ripple activity in the surface EEG of children with electrical status epilepticus during slow wave sleep[13] and the group of Gotman at the MNI in the surface EEG of adults with focal epilepsy.[14] Only recently the first promising pilot studies in magnetencephalography (MEG) on the detection of HFOs were published.[15-17] These developments open a new avenue to apply HFOs for the evaluation of different questions including the assessment of disease activity to large numbers of patients.

HFOs as markers of the epileptogenic region

Interactions between HFOs & epileptic spikes

HFOs are often observed at the time of epileptic spikes. Urrestarazu and colleagues described three different patterns: (i) 64% occurred together with spikes and were visible as riding on the spike in the unfiltered signal, (ii) 17% occurred together with spikes but were invisible in the unfiltered spikes, and (iii) 19% occurred completely independently of spikes in timing and localization.[18]

Despite this frequent co-occurrence, there is now sufficient evidence that HFOs and spikes present different neurophysiological mechanisms. Rodent epilepsy models led to two main findings: (i) HFOs and spikes can occur independently of each other and show separate modulations during the period of epileptogenesis, and (ii) epileptic spikes with or without HFOs also seem to have distinct pathophysiological relevance and occur over different brain regions (see the accompanying paper of Jiruska and colleagues for more details). Furthermore, HFOs seem to increase before the occurrence of seizures,[9,19,20] while spikes are more prominent post-ictally.[21,22]

In general, HFOs were shown to be more specific for the seizure-onset zone (SOZ) than spikes.[1] Applying a threshold with 95% specificity, the highest sensitivity for identification of the SOZ was found for fast ripples (52%), followed by ripples (38%) and spikes alone (33%).[23] Interestingly, ripples co-occurring with a spike were shown to be even more closely related to the SOZ than ripples without a spike.[24]

It is probable that some HFOs result from filtering spikes,[25] but it is clear that a large proportion do not. Van Klink and colleagues found that 64% of ripples started on average 10 ms before the onset of the spike. They concluded that ripples are therefore

unlikely to result from spikes.[26] Jacobs and colleagues demonstrated that the HF power increase during spikes is less specific for the SOZ than visually identified individual HFO events.[27] It was further shown that for clinical application, it may not be necessary to separate real HFOs from "false oscillations" produced by the filter effect of sharp spikes.[28] Burnos and colleagues classified ripples based on their morphology, with types defined according to regularity in amplitude and frequency: type 1 with regular amplitude and frequency; type 2 with irregular amplitude, which could result from filtering of sharp spikes; type 3 with irregular frequency; and type 4 with irregular amplitude and frequency. The authors found that all types were significantly higher inside the SOZ than outside the SOZ.[28] While spikes and HFOs are likely to be distinct events, their common co-occurrence might therefore be used in the clinical application to identify the subset of epileptic spikes most closely related to the SOZ.

Interactions between HFOs & seizures

Tonic HF activity typically in the beta and gamma frequency range at seizure-onset has to be differentiated from ictally occurring isolated brief HFO events, which will be discussed in this review. HFOs were shown to increase only immediately prior to or at seizure onset.[9,19] When examining HFO fluctuations in the 15-, 5-, and 1-min intervals preceding seizure occurrence, no systematic change was found.[29] Experimental research in the animal model of mesio-temporal lobe epilepsy demonstrated that specific HFO patterns are associated with different seizure-onset patterns: Ripples (>80 Hz) predominate during low-voltage fast activity seizures, whereas fast ripples (>250 Hz) predominate during periodic spiking seizures (for further information see the paper of Jiruska and colleagues on the experimental insights of HFOs in this issue).

Sato and colleagues showed that there is a relative power reduction of the post-spike slow wave relative to the increase of spike-related HFOs in the SOZ immediately preceding ictal onset.[30] Particularly in the SOZ, this correlation is drastically reduced during the 3-min period preceding seizure-onset.[31] Whereas HFOs remain confined to the same possibly epileptogenic area during inter-ictal and ictal periods, spikes are more widespread during seizures than inter-ictally.[32] Akiyama and colleagues investigated the relationship between ictal HFOs and semiologic progression from

electrographic ictal onset to clinical manifestation. They found that the ictal HFO propagation corresponded to the ictal semiology in Jacksonian seizures.[11,33] Usui and colleagues investigated ictal very-fast HFOs exceeding 1000 Hz in 13 patients with intractable epilepsy who underwent epilepsy surgery. Six of the 7 patients with ictal very-HFOs had a favorable outcome, compared to one of 6 patients with an unfavorable surgical outcome.[34]

The increase in faster frequencies between 60-100 Hz at ictal onset was used to develop a method allowing statistical images of HFOs co-registered with the patient's MRI to further explore the relationships between ictal and interictal HFOs, and to compare these data with other localizing methods.[35] Currently no final conclusion can be drawn regarding the relative clinical relevance of ictal or inter-ictal HFOs for the identification of the epileptogenic zone.

Resection of areas with high HFO rates is associated with a good postsurgical seizure outcome

Retrospective studies using depth electrodes, grids, or intraoperative corticography showed that resection of areas with presurgical high HFO rates is associated with a better postsurgical seizure outcome than resection of areas with presurgical low HFO rates.[1,36-43] Noteworthy, it was recently shown by the group of Zijlmans using intraoperative electrocorticography that the rate of presurgically measured HFOs did not predict seizure outcome,[44] but that the rate measured after resection did.[45] This suggests that it is critical to disconnect networks generating HFOs rather than remove all areas that generate HFOs prior to surgery.[45] It might also explain the negative association with postoperative seizure outcome in some patients, in whom HFO rates were assessed in presurgical chronic intracranial EEG recordings. An example of a patient who had residual fast ripples in the postsurgical electrocorticogram and who was not seizure-free after surgery is given in Figure 1.

A meta-analysis from 2015 investigated the existing evidence for the relation between resection of HFO-generating regions and outcome after epilepsy surgery.

Höller and colleagues analyzed the probability that a patient, who is seizure-free after surgical intervention, had a high HFO resection ratio.[46] The authors defined the HFO ratio as the ratio between the number of channels with HFOs that were inside the resected area to the number of channels on which HFOs were detected. Rates of both ripples and fast ripples were shown to have a significant effect: a higher resection ratio for HFOs was found in seizure-free versus non-seizure free patients. The total effect size, however, was small for both ripples and fast ripples (Figure 2). The clinically important question of whether a patient will become seizure-free if the resection ratio is high cannot be answered by the existing data.

In contrast to this growing evidence from inter-ictal HFOs, there is only sparse evidence on the association of ictal HFOs and postsurgical seizure freedom. A Cochrane review[47] assessing this question identified 2 studies with a total of 11 participants who implemented identification of ictal HFOs in their surgical decision making. The authors concluded that no reliable conclusions could be drawn regarding the efficacy of HFO recordings in epilepsy surgery decision making, due to methodological limitations and the small sample size.[47]

One has to differentiate between the SOZ and epileptogenic zone (the area of brain necessary and sufficient for spontaneous seizures to occur). Interictal markers (such as spikes or HFOs) are only partially effective at localizing the SOZ, but in fact this correspondence is of secondary importance since we want to identify the epileptogenic zone. The SOZ is not a perfect marker of the epileptogenic zone: the region where seizures actually start is not necessarily the region where seizures can start. If the SOZ was a perfect biomarker, people undergoing epilepsy surgery in whom the SOZ was removed should be seizure-free, and clinical practice shows that this is not the case. Therefore there is a need to develop biomarkers for the epileptogenic zone apart from the SOZ, and HFOs could be one such marker to improve the approximation of the epileptogenic zone with the ultimate aim to improve surgical outcome in people with epilepsy. Level one evidence on the clinical use of inter-ictal and ictal HFOs for delineation of the epileptogenic zone and outcome prognosis during epilepsy surgery will require a prospective randomized controlled trial approach (see section “Future research”). Main challenges for the feasibility of such a prospective trial to prove

superiority of HFOs over spikes and the SOZ to improve the surgical success rate are the large sample size needed, requiring international collaboration, standardization of the analysis of HFOs (see section “Visual versus automatic detection of HFOs”), and differentiation between physiological and pathological HFOs (see section “Differentiation between physiological and pathological HFOs”).

HFOs mirror disease activity

The first evidence that HFOs mirror disease activity comes from experimental work. Bragin and colleagues found in the kainic acid model of temporal lobe epilepsy a significant inverse relation between the time of the first HFO detection and the subsequent rate of spontaneous seizures.[48] Later, a study in human intracranial EEG showed that HFOs, in contrast to spikes, do not increase after seizures but increase after medication reduction, similarly to seizures.[49] This implies that spikes and HFOs have different pathophysiologic mechanisms and that HFOs are more tightly linked to seizures than spikes. HFOs therefore can be a useful clinical marker for disease activity. The hypothesis that the more HFOs are generated by the tissue, the higher the seizure frequency was not confirmed, although there might be a correlation for high fast ripple rates. Propofol, known for its antiepileptic effects, was shown to reduce the number of epileptic HFOs,[50] whereas etomidate, a short-acting anesthetic, activates epileptic HFOs. Importantly, the spatial distribution of these activated HFOs did not extend beyond electrodes showing HFOs without etomidate.[51] The hypothesis that in epilepsy HFOs mirror the disease activity was confirmed in patients with focal cortical dysplasia: HFO rates were higher in patients with focal cortical dysplasia type II lesions compared to type I lesions; usually type II lesions are more epileptogenic with an earlier onset of seizures as well as a higher seizure frequency.[52]

Following this concept, HFOs might be also useful for monitoring antiepileptic drug treatment.[53] Moreover, studies have shown that HFO rate correlates with disease severity, HFO rate decreases during immune-modulatory therapy, and HFO rate is able

to predict the course of disease (see section “Important Aspects of HFOs in children”).[54,55]

Contribution of non-invasive methods for measuring epileptogenicity

Scalp EEG

HF activity has been first reported at the onset of epileptic spasms on scalp recordings in children,[56,57] as well as at the onset of tonic seizures in Lennox–Gastaut Syndrome.[58] More importantly, the first studies on scalp inter-ictal HFO events (70-200 Hz) were published in children with electrical status epilepticus during slow wave sleep,[13] as well as in idiopathic partial epilepsies of childhood.[59] The first study on inter-ictal HFOs in adults with focal epilepsy was published in 2011.[14] An example of scalp HFOs as seen in the unfiltered EEG, the filtered EEG above 80 Hz and the time frequency plot is given in Figure 3.

Detection of HFOs in the scalp EEG was at first glance surprising, given the small HFO generator size of 100 to 200 µm and the postulated necessary cortical activation area of 10 cm^2 for generating a signal visible on the scalp. A recent simulation study, however, challenged this notion and showed that fast oscillations can be detected within the low noise level of the ripple band (80-200 Hz) even though their median amplitude on scalp EEG recordings is more than 10 times smaller than that of IEDs and consistent with cortical generators of approximately 1 cm^2.[60] A study using data from simultaneous scalp EEG and intracranial recording confirmed the findings of the latter stimulation study and demonstrated that scalp HFOs indeed derive from cortical HFOs.[61] In this context it is important to highlight that the skull does not filter high frequencies, it only makes their recording less likely due to the distance and the skull’s resistivity that attenuates an already small activity. For more information see the article of Zijlmans and colleagues on how to record HFOs in this issue.

HFO assessment in scalp EEG is a very relevant development, from which large number of patients could benefit. Applications could not only include gaining additional information on the localization of the epileptic generator, but could also be to assess disease activity and treatment response, as well as to differentiate distinct disease

entities. As HFO analysis in scalp EEG is still a relatively young field in HFO research, data on the localizing value of HFOs in scalp EEG is scarce at the moment. Nevertheless, all publications seem to show that HFOs localize to the affected hemisphere or lobe.[14,26,62-64]

The fact that HFOs are able to mirror disease activity has been shown by various authors (see also section “HFOs mirror disease activity” and “Important aspects of HFOs in children”). Pizzo and colleagues attempted to apply HFO assessment for the differentiation between secondary bilateral synchrony in focal epilepsy and primary bilateral synchrony in idiopathic generalized epilepsy. They found that ripples in secondary bilateral synchrony help to lateralize the epileptic focus. They did not, however, help to differentiate between focal and generalized epilepsy.[63] Interestingly, the work of Melani and colleagues showed that rates of HFOs in the scalp EEG depended clearly on the rates of epileptic spikes.[64] Furthermore, scalp inter-ictal epileptiform discharges, when frequently accompanied by HFOs were shown to be associated with larger cortical metabolic responses and with thalamic involvement lateralized to the side of cortical ripples. It was proposed that a high rate of epileptic ripples is associated with a more active pathologic cortical-thalamocortical network.[65]

Only very recently the detection of HFOs > 250 Hz was attempted in a pilot study.[66] In this proof-of-principle study it was shown that it might be feasible to record even frequencies above 250 Hz with scalp EEG; the rate of fast ripples was considerably lower than that of ripples. Table 1 provides an overview on the literature on HFO assessment in scalp EEG.

MEG

Earlier work investigated the high frequency content at the time of MEG spikes and at the time of intracranial HFOs in focal epilepsy.[67,68] Xiang and colleagues were the first to investigate and source-localize the HF content independent of spikes in children with focal epilepsy. The authors found HF components between 100-1000 Hz in 86% of the patients. The loci of this HF activity were concordant with the lesions as identified by MRI in 70% of subjects, and the SOZ as identified by intracranial EEG in 82% of

subjects.[15] The first study to assess discrete HFO events above 80 Hz according to HFO definition is from van Klink and colleagues.[16] The authors found ripples in three out of 12 patients, and showed an increase of sensitivity to fast oscillations by using virtual channels constructed using beamforming techniques based on information obtained from spikes, thus searching only the brain region generating spikes. Von Ellenrieder and colleagues showed that fast oscillation events (40-160 Hz) can be identified correctly independently from information obtained from spikes in MEG. The authors have further demonstrated that it is possible to localize the source of these oscillatory events with high spatial resolution.[17]

Apart from the investigation of interictal HFOs in MEG, two groups focused on the assessment of the ictal HF power in childhood absence epilepsy.[69,70] Co-occurring frontal and parietal corticothalamic networks were suggested to interact to produce a pathological state that contributes to the generation of spike and wave discharges.[71] Interestingly, Tang and colleagues demonstrated a correlation between the source strength of ictal HF activity in 200-1000 Hz and the number of daily seizures in childhood absence epilepsy.[72] These technical developments open now interesting potential applications for the non-invasive study of fast oscillations with MEG in epilepsy patients.

Important aspects of HFOs in children

In line with the studies in adults, several retrospective studies using intracranial EEG supported the notion that resection of areas with presurgical high HFO rates is associated with a better postsurgical seizure outcome in children compared to resection of areas with presurgical low HFO rates.[1,38,42] Whereas no difference was found between intracranial rates of HFOs in adults and children,[52] the rates of scalp HFOs were reported to be up to 100-fold higher in children compared to adults with epilepsy.[53] Higher HFO rates in the scalp EEG of young children are most likely due to a higher skull conductivity compared to adults. It is therefore not surprising that the number of HFO scalp EEG studies is considerably higher in children compared to adults. Epilepsy syndromes during childhood investigated so far are West syndrome, childhood absence

epilepsy, Lennox-Gastaut syndrome, idiopathic location-related epilepsies such as rolandic epilepsy or Panayiotopoulos syndrome, electrical status epilepticus during slow wave sleep, and early infantile epileptic encephalopathy.[53-59,73,74]

A surface EEG study in children with rolandic spikes showed that absence of ripples superimposed on rolandic spikes predicts a benign clinical course, while in presence of several ripples, the child is likely to have more seizures than classical rolandic epilepsy, and pharmacological treatment might be needed.[54] A scalp HFO study in childhood absence epilepsy also confirmed higher HFO rates during ictal generalized spike-wave discharges compared to interictal generalized spike-wave discharges or sporadic spike wave discharges.[73] One study in West syndrome revealed that the rate of HFOs significantly decreased during the course of ACTH treatment.[53] Whether a treatment response with scalp HFOs can also be observed with other antiepileptic treatments awaits future confirmation.

HFOs in different types of lesions

There are three studies which aimed at investigating this question. Jacobs et al. selected 12 patients with three types of lesional focal epilepsy (five with unilateral mesial temporal atrophy, four with focal cortical dysplasia, and three with nodular heterotopia). No specific HFO pattern could be identified for the different lesion types.[75] A recent study in a larger sample of 37 patients (13 focal cortical dysplasia, 12 mesial temporal sclerosis, five cortical atrophy, three polymicrogyria, three nodular heterotopia, and one tuberous sclerosis) showed that in patients with intractable epilepsy, the HFO rates vary considerably with different pathologies, and might hence reflect different types of neuronal derangements. Specifically, mesiotemporal lobe sclerosis, focal cortical dysplasia and nodular heterotopia displayed higher HFO rates compared to polymicrogyria, tuberous sclerosis complex or atrophy. The authors emphasized the potential usefulness of HFOs as an additional method to better define the extent of the epileptogenic dysplastic tissue in focal cortical dysplasia.[76] Kerber et al. compared HFO rates in patients with focal cortical dysplasia type I versus type II. As known from the literature, patients with focal cortical dysplasia type 2 had significantly more seizures

than those with type 1. Interestingly, rates of HFOs were significantly higher in patients with focal cortical dysplasia type 2 versus type 1, suggesting that the activity of HFOs mirrors disease activity.[52]

Impact of sleep on HFOs

High frequency oscillations (HFOs) are influenced by sleep. Following the distribution of epileptic spikes, HFO rates are highest during NREM sleep and lowest during REM sleep and wakefulness; these results are independent of the types of electrodes used. Importantly, rates of HFOs were - independently of the sleep stage - higher inside than outside the SOZ.[8,77-80]

Staba and colleagues highlighted that ripples decline more drastically compared to fast ripples during REM sleep – a state of maximal desynchronization. This behavior points to fast ripples as the product of pathological neuronal hypersynchronization.[8] Bagshaw and colleagues showed that HFOs have their maximal rate in the same sleep stages as the spikes. They also showed that the duration of HFOs is relatively stable across the sleep wake cycle.[78] Dümpelmann and colleagues were interested to examine regional state-specific changes, as most of the previously published evidence is derived from patients with temporal lobe epilepsy. The authors found that HFOs in all brain regions (temporal lobe, rolandic area, parietal lobe, occipital lobe) except the frontal lobe were modulated by sleep.[79] Clemens and colleagues showed that ripple activity increases before spindle peaks and distinctly decreases after the peak.[77]

Recent research focused on the influence of the microstructure of sleep on HFOs. Frauscher and colleagues investigated if the sleep-related activation of HFOs is uniformly distributed across NREM sleep or if it is in fact facilitated by sleep slow oscillations <1Hz.[81] These slow oscillations are characterized by a rhythmic alternation between activated (“up”, when pyramidal cortical neurons are depolarized) and deactivated (“down”, when pyramidal cortical neurons are hyperpolarized) states, and are shown to influence physiological brain rhythms. Frauscher and colleagues found that 65% of ripples occurred during high amplitude widespread slow waves <1 Hz compared to 35% occurring during control segments of an equal duration. Interestingly, ripples occurred at the transition from the “up” to the “down” state which might underline

the role of synchronization, as opposed to hyperexcitability, in the facilitation of HFOs during sleep. Furthermore, HFOs in channels exhibiting epileptic activity or being part of the SOZ occur during the transition from the “up” to the following “down” state, whereas HFOs occurring in channels showing physiological activity occur at the beginning of the next “up” state. A typical example of this difference in coupling is provided in Figure 4.[81] In line with this finding, the same group demonstrated that HFOs, known to be suppressed by REM sleep, are even more suppressed during phasic compared to tonic REM sleep; desynchronization is even more increased during phasic compared to tonic REM sleep.[82] Sakuraba and colleagues showed that the suppression of HFOs during REM sleep was less evident inside compared to outside of the epileptogenic zone.[80] The less suppressive effect of REM sleep inside the SOZ may provide a specific marker of epileptogenicity. All studies investigating HFOs across the sleep-wake cycle support the notion that HFO rates are in general higher inside the SOZ compared to outside the SOZ across the different states of vigilance. Assessing HFOs during sleep is advisable, as artifacts are lowest then. Further sleep specific characteristics such as coupling to slow waves, and the suppressive effect of REM sleep particularly during phasic REM sleep might add to better delineate the epileptogenic zone and should be further investigated in large multicenter trials.

Differentiation between physiological and pathological ripples

One question, which has been only recently systematically investigated, is how to differentiate physiological ripples, which are thought to reflect summated excitatory postsynaptic potentials, from pathological ripples, which are believed to be slower fast ripples reflecting summated action potentials of synchronously bursting neurons (for more details see the accompanying review of Jiruska and colleagues). This issue is important, but not easy to address, as rates of ripples vary substantially across different brain areas, as shown by von Ellenrieder and colleagues in an investigation of 45 subjects.[83] In humans, physiological HFOs are reported most frequently in the paracentral areas, the hippocampus and the occipital cortex.[84-86] Investigators attempted to separate physiological from pathological HFOs by considering the coupling

with epileptic spikes,[24] the background EEG activity,[41,85] task-induced HFOs,[86,87] the anatomical location of implanted electrodes,[24,85,88] the classic features including amplitude, duration, spectral frequency and rate,[88,89] and the manner of interaction with the accompanying slow wave.[81,83,90~~82,84,91~~] An overview of the different methods is given in Table 2.

Wang and colleagues showed that neocortical fast ripples and ripples with spikes are specific markers of the SOZ, whereas ripples not going along with spikes are not. The authors concluded that ripples without spikes outside the SOZ may represent spontaneous physiologic ripples in the human neocortex.[24] Melani and colleagues described a continuous high frequency activity, independent of epileptogenicity, which was present almost exclusively in the hippocampus and occipital cortex. They speculated that this continuous activity may be an intrinsic characteristic of specific brain regions, reflecting a particular type of physiological neuronal activity.[85] In line with this finding, Kerber and colleagues suggested that ripples intermixed with an oscillatory background activity may be suggestive of physiological activity, while those on a flat background reflect epileptic activity.[41]

Other groups assessed task-induced presumably physiological HFOs using visual tasks, visual motor tasks, and visual memory tasks,[86,87] or investigated the morphological characteristics of HFOs in epileptic and non-epileptic regions.[88,89] Despite the different approaches, a clear differentiation of presumably physiological HFOs and pathological epileptic HFOs was not possible, as both types largely overlap with respect to spectral frequency, duration, and amplitude.[86-89] A similar conclusion was also reached by a recent experimental work in the human epileptic subiculum. Alvarado-Rojas et al. demonstrated that different ripple types have a considerable overlap in spectral frequency despite distinct dynamic changes in inhibition and excitation during interictal and pre-ictal states[91] (see also the review article on fundamental mechanisms of HFOs of Jiruska et al. in this issue).

Frauscher and colleagues found that HFOs in channels exhibiting interictal epileptiform activity or being part of the SOZ occur during the transition from the “up” to the following “down” state of the slow wave cycle, whereas presumably physiological HFOs (because they occur in presumably normal brain) occur at the beginning of the

next “up” state.[81] This coupling to the state of the slow wave might therefore help to disentangle physiological from pathological HFOs. This hypothesis was investigated in a larger study using automatic HFO detection by von Ellenrieder and colleagues.[83] The authors found that the association between slow waves and HFOs to be different in normal and epileptic brain regions, emphasizing the different origin of the two HFO types. They also showed that when using this interaction to automatically classify channels as recording from normal/epileptic brain regions, the performance is better than when using other HFO characteristics.[83] Nonoda and colleagues investigated the coupling of HFOs to slow waves of 0.5-1 Hz and 3-4 Hz. The authors found that physiologic ripples generated in stimulation-defined eloquent areas were frequently coupled to the 0.5–1 Hz slow waves, whereas epileptic ripples generated in the SOZ were coupled to the 3-4 Hz slow waves.[90] Furthermore, HFOs in channels with physiological activity versus HFOs in channels with epileptic activity were shown to express a different coupling to rapid eye movement during REM sleep. In contrast to ripples in the SOZ or exclusively irritative zone, physiologic ripples were more abundant during phasic REM sleep.[82] It may therefore be more important to know the EEG context of occurrence of an HFO than its morphology to determine if it is normal or pathological.

Visual versus automatic detection of HFOs

Visual analysis of HFOs is considered as the gold standard for HFO assessment. Visual analysis however goes along with serious obstacles making HFO assessment impossible for clinical routine: visual marking of HFOs is very time-consuming, requires expertise, and might be subjective if an interrater agreement is not sought. To overcome these drawbacks, various detectors were developed and validated over the last years (for more details see the accompanying paper of Zijlmans and colleagues). Automated and visual detection of HFOs yield comparable identification of the SOZ;[92] a meta-analysis showed that removal of automatically detected HFOs and visually detected HFOs in pre-surgical data yield similar results with respect to good surgical outcome.[46]

Unfortunately, it is not possible to directly compare sensitivity and specificity between the publications on automated detection of HFOs, since most algorithms

depend on many parameters that need to be tuned and on the ground truth used, which is again the subjective visual identification. Existing comparison studies which were based on the same ground truth data showed that there are differences when applying the different detectors. Nevertheless, the ranking of channels with high versus low HFO rates is comparatively consistent.[93] In addition, it seems that sensitivity of algorithms is not the most important criterion. Removal of regions with a high rate of HFO occurrence is more strongly related to good surgical outcome than removal of all HFO generating tissue.[46]

One aspect which is very important when using automatic HFO detection is artifact removal. Whereas, some detectors are semi-automatic, requiring visual validation, others have implemented fully automated post-processing steps for artifact removal, so that the detector can be used to work autonomously for large datasets as needed in clinical routine. The general validity of this approach has not been established.

Finally, in order to make the results of these technical developments useful for clinical practice they need to be implemented in software that satisfies the needs of clinical routine.

Future directions

Increasing evidence has been collected over the last decade underlining that HFOs might be a promising biomarker for the epileptogenic zone, and that removal of regions with high HFO rates is associated with a good postsurgical outcome. All existing data are derived from comparatively small retrospective studies. No study so far was adequately powered and methodologically designed to investigate the probably more important clinical question of whether a patient is more likely to become seizure-free if the HFO resection ratio is high than if HFO-generating regions are not resected. There is therefore a need for properly designed, high quality and adequately powered, randomized multicenter trials to determine if inter-ictal HFOs are true markers for the epileptogenic zone. One such trial is currently underway in the Netherlands for intraoperative electrocorticography.[94] In this trial, surgery is tailored by HFOs (arm 1) or interictal spikes (arm 2) in the intra-operative electrocorticography. The trial has a non-

inferiority design to test feasibility and at least equal performance in terms of surgical outcome. If this trial is positive, future multicenter collaborations with large sample sizes using a superiority design and objective easy HFO analysis in order to standardize HFOs assessment are warranted to demonstrate that the use of HFOs as a biomarker for tailoring will increase the success rate of epilepsy surgery while reducing resection volume potentially leading to a reduction of neurological deficits and a better quality of life.

It will be also interesting to compare HFO detection with other approaches for ictal determination of the epileptogenic zone. Indeed, recent methods were introduced to quantify the presumed degree of epileptogenicity of brain structures recorded by depth-EEG electrodes[35,95-97] for comparative study of quantitative methods. Moreover, it will be of interest to translate the knowledge gathered from experimental work indicating that different HFO seizure onset patterns are expressions of different mechanisms of epileptogenesis (see the accompanying paper of Jiruska et al. in this issue for more information). This knowledge might help to identify more efficacious antiepileptic strategies tailored directly on the underlying mechanisms.

Although there is no class 1 evidence for the use of HFOs yet, evidence is accumulating, and as in many other fields where class 1 evidence is lacking, this accumulation of concordant evidence indicates that it may be time to start implementing HFOs in clinical patient care**.** Particularly the assessment of HFOs using non-invasive methods will open a new avenue allowing not only for identification of the SOZ, but also to assess disease activity in large numbers of patients.

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Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose in relation to this manuscript.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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FIGURE LEGENDS

Figure 1. Patient with a left central lesion, with fast ripples (FRs) in post-electrocorticography (ECoG) and recurrent seizures (auras) after surgery. (A) Spike and high-frequency oscillation events in a selection of bipolar channels (indicated as 1–5 in part C). (B) Pre-resection photograph. (C) Post-ECoG. The resected area is delineated by a dotted white line. The area being near the resection (#1 cm, resection margin) is marked transparent white. Two ECoG recordings post-resection were performed. We represent the location of the bipolar channels analyzed. Note that FRs (rate: 25/min/electrode) (yellow) were present in the margin of the resected lesion (dysembryoplastic neuroepithelial tumor), in a larger region with spikes (range rate: 4–41/min/electrode) (blue). Almost all electrodes showed ripples and are therefore not

depicted. Based on the FRs present in the resection margin, a different surgical decision could have been made if FRs would not have been that close to eloquent central cortex. Source: Figure from van 't Klooster MA, van Klink NE, Leijten FS, et al. Residual fast ripples in the intraoperative corticogram predict epilepsy surgery outcome. Neurology 2015;85:120-8[45] with permission of Wolters Kluwer.

Figure 2. Meta-analysis results for ripples (A) and fast ripples (B). The resection ratio for both ripples and fast ripples is higher in seizure-free patients compared to non-seizure free patients. For each study, a graphical representation of the effect (i.e., the difference of the resection ratio between the good- and bad-outcome group) and of the confidence interval (CI) is given along with the exact values (EV) and the weights. Source: Figure from Höller Y, Kutil R, Klaffenboeck L, et al. High-frequency oscillations in epilepsy and surgical outcome. A meta-analysis. Front Hum Neurosci 2015;9:574[46] wit permission of Oxford University Press.

Figure 3. Ripple oscillations in the scalp EEG recorded from a child with Landau–Kleffner syndrome. Representative spikes (left and middle columns, arrowhead) are associated with ripple oscillation, which was largely invariant irrespective of low-cut frequency (LCF) of whether 60 or 120 Hz (EEG traces filtered at 0.5, 60, and 120 Hz are shown in green, blue, and red, respectively). The EEG was recorded during NREM sleep and therefore did not include muscle activity or eye movements. Identical EEG data are presented in a referential montage (top: O1 with reference to the average EEG of bilateral earlobes, indicated as O1-Aav) and a bipolar montage (bottom: P3-O1). Note that spike-related ripples with at least four consecutive oscillations are clearly observed in both montages. Each panel of time–frequency spectra shows a corresponding discrete blob (arrow) with a frequency at around 130 Hz irrespective of referential or bipolar montage. In contrast, muscle activity (right column) contaminated to scalp EEG recorded during wakefulness is dominant over the temporal region (T4, F8-T4) close to muscles and has very irregular morphology and a noisy spectral pattern with no

outstanding blobs. Source: Figure from Worrell GA, Jerbi K, Kobayashi K, et al. Recording and analysis techniques for high-frequency oscillations. Prog Neurobiol. 2012;98:265-78[98] with permission of Elsevier.

Figure 4. Representative examples for the coupling of epileptic spikes and HFOs across the slow wave cycle. Example of a slow wave and an epileptic spike (left panel), a slow wave and an HFO in a channel with epileptic activity (middle panel) and an HFO in a channel with normal EEG activity (right panel). The top row shows the slow wave in a scalp channel, the second row shows the same time period for an intracranial channel with normal EEG activity, and the third row an intracranial channel with epileptic EEG activity. The fourth row shows the ripple band signal with a different time and amplitude scale, corresponding to the shaded periods in the intracranial channels. All the channels are in the left frontal region, each example corresponds to a different patient. The scalp slow wave on the right panel is of shorter duration than the scalp slow waves on the left or middle panel. *In this example a normal sleep slow wave and no epileptic spike is seen in a channel called “Epileptic” because it has spikes at other times. Note that the spike and the HFO in the intracranial channel with epileptic activity (middle) occurs prior to the peak of the scalp negative half-wave, whereas the HFO in the channel with normal EEG activity (right) occurs after the peak of the scalp negative half-wave. Source: Figure from Frauscher B, von Ellenrieder N, Ferrari-Marinho T, et al. Facilitation of epileptic activity during sleep is mediated by high amplitude slow waves. Brain 2015; 138:1629-41[81] with permission of Oxford University Press.

Authors	Patients	Epilepsy type	N	Method	Investigated frequency band			Application
					Gamma	Ripples	FR	
Kobayashi et al., 2010[13]	Children	ESES	10	time frequency plot and visual		X		proof-of-principle study
Kobayashi et al., 2011[59]	Children	BCETS, PS	32	time frequency plot and visual		X		prognosis
Andrade-Valenca et al., 2011[14]	adults	focal epilepsy	15	visual	X	X		SOZ identification: accuracy for gamma: 70%, accuracy for ripples: 81%
Melani et al., 2013[64]	Adults	focal epilepsy	32	visual	X	X		correlation between IED and gamma and ripple rates
Fahoum et al., 2014[65]	Adults	focal epilepsy	22	visual	X	X		relationship with BOLD response
Kobayashi et al., 2015[53]	Children	West syndrome	17	time frequency plot and visual	X	X		therapy-response under ACTH treatment
Chaitanya et al., 2015[73]	Children	Absence epilepsy	9	ICA, time frequency analysis		X		identification of HFOs
Toda et al., 2015[74]	Newborns	early infantile epileptic encephalopathy	6	time frequency analysis		X		presence of HFOs during the suppression-burst EEG patterns
van Klink et al., 2016[26]	Adults	focal epilepsy	31	visual		X		relationship between ripples and IEDs
van Klink et al., 2016[54]	Children	Rolandic epilepsy	22	visual		X		prognosis, disease severity

Pizzo et al., 2016[63]	Adults	GGE and focal epilepsy	17	visual		X	differential diagnosis
Pizzo et al., 2016[65]	Adults	focal epilepsy	10	visual		X	proof-of-principle
Qian et al., 2012[86]	Children	atypical benign partial epilepsy	14	visual		X	severity, treatment response
Matsumoto et al., 2013[55]	5	Comparison of task-		Substantial overlap in all classical features between task-induced and			

Authors **N** **Method** **Main finding**

Nagasawa et 10 Coupling with delta waves Epileptic HFOs are coupled with slow waves of 3-4 Hz more tightly compared

to physiological HFOs which are coupled to slow waves of 0.5-1 Hz

TABLES

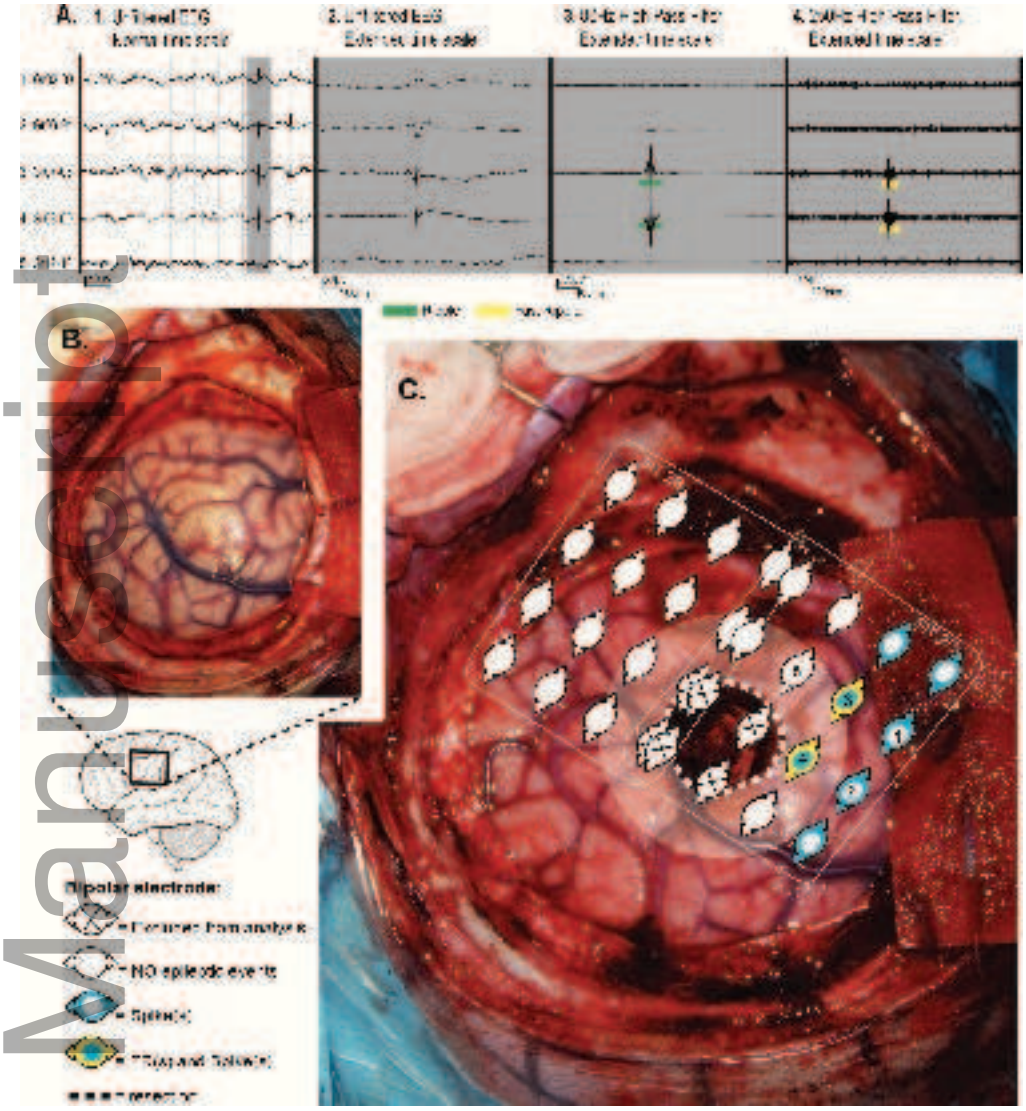
Table 1. Overview on the literature on assessment of interictal HFOs in scalp EEG

Legend. BCECTS, benign childhood epilepsy with centrotemporal spikes; ESES, electrical status epilepticus during slow wave sleep; FR, fast ripples; GGE, genetic generalized epilepsy; ICA, independent component analysis; IED, interictal epileptiform discharges; PS, Panayiotopoulos syndrome

Table 2. Overview on the different methods applied to separate physiological from pathological HFOs

al., 2013[87]		induced HFOs vs. spontaneous HFOs	spontaneous HFOs
Melani et al., 2013[85]	22	Evaluation of background EEG	Continuous high frequency activity as a physiological pattern
Wang et al., 2013[24]	35	Ripples with accompanying epileptic spike vs. isolated ripples	Ripples associated with spikes are more specific for the SOZ compared to ripples not co-occurring with spikes
Alkawadri et al. 2014[88]	7	Differences in classical features* between epileptic and non-epileptic brain regions	Substantial overlap in all classical features between the normal and the epileptic zone
Kerber et al., 2014[41]	32	Evaluation of background EEG	HFOs on flat background are more specific for SOZ than HFOs on oscillatory background
Frauscher et al., 2015[81]	8	Coupling with slow waves	Different coupling of physiological and pathological HFOs in relation to slow waves
Malinowska et al., 2015[89]	33	Differentiation in classical features* between SOZ and non-SOZ	Significant differences in classical features, however substantial overlap
Von Ellenrieder et al., 2016[83]	45	Coupling with slow waves	Interaction with slow waves during sleep improves discrimination of physiologic and pathologic HFOs
Frauscher et al., 2016[82]	12	Coupling with rapid eye movements	Different coupling of physiological and pathological HFOs in relation to rapid eye movements during REM sleep
Nonoda et al., 2016[90]	13	Coupling with different frequencies of slow waves	Epileptic HFOs are coupled with slow waves of 3-4 Hz more tightly compared to physiological HFOs which are coupled to slow waves of 0.5-1 Hz

Legend, SOZ, seizure onset zone. *Here, the classical features of HFO morphology include: amplitude, duration, and spectral frequency



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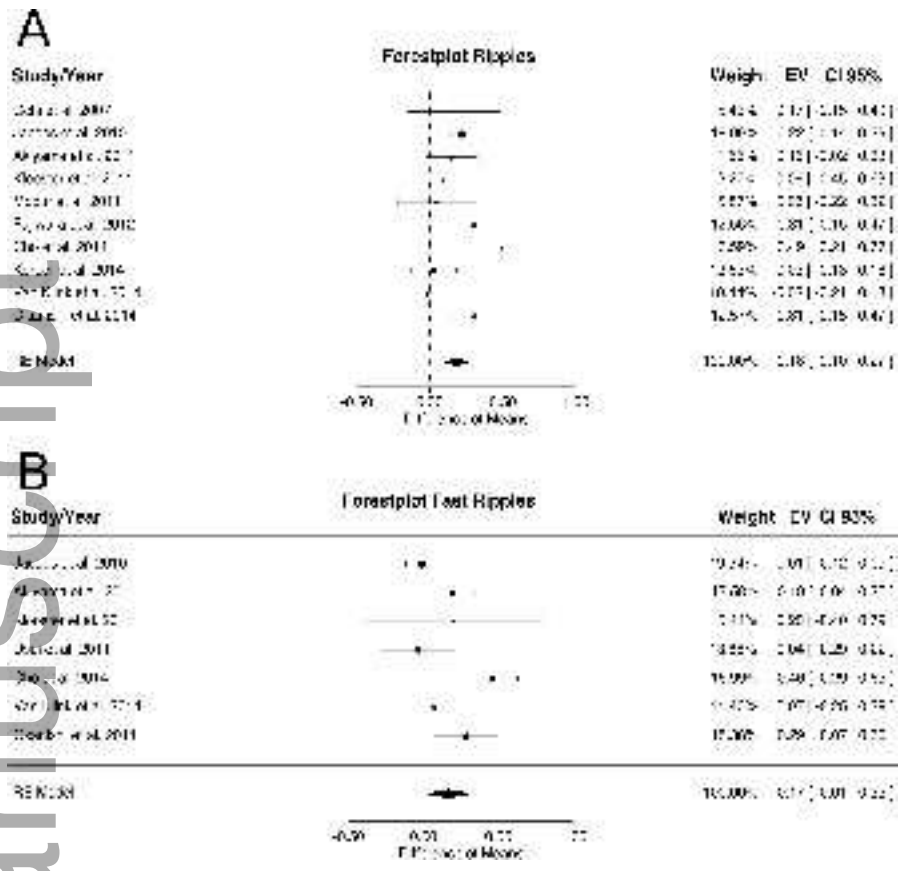

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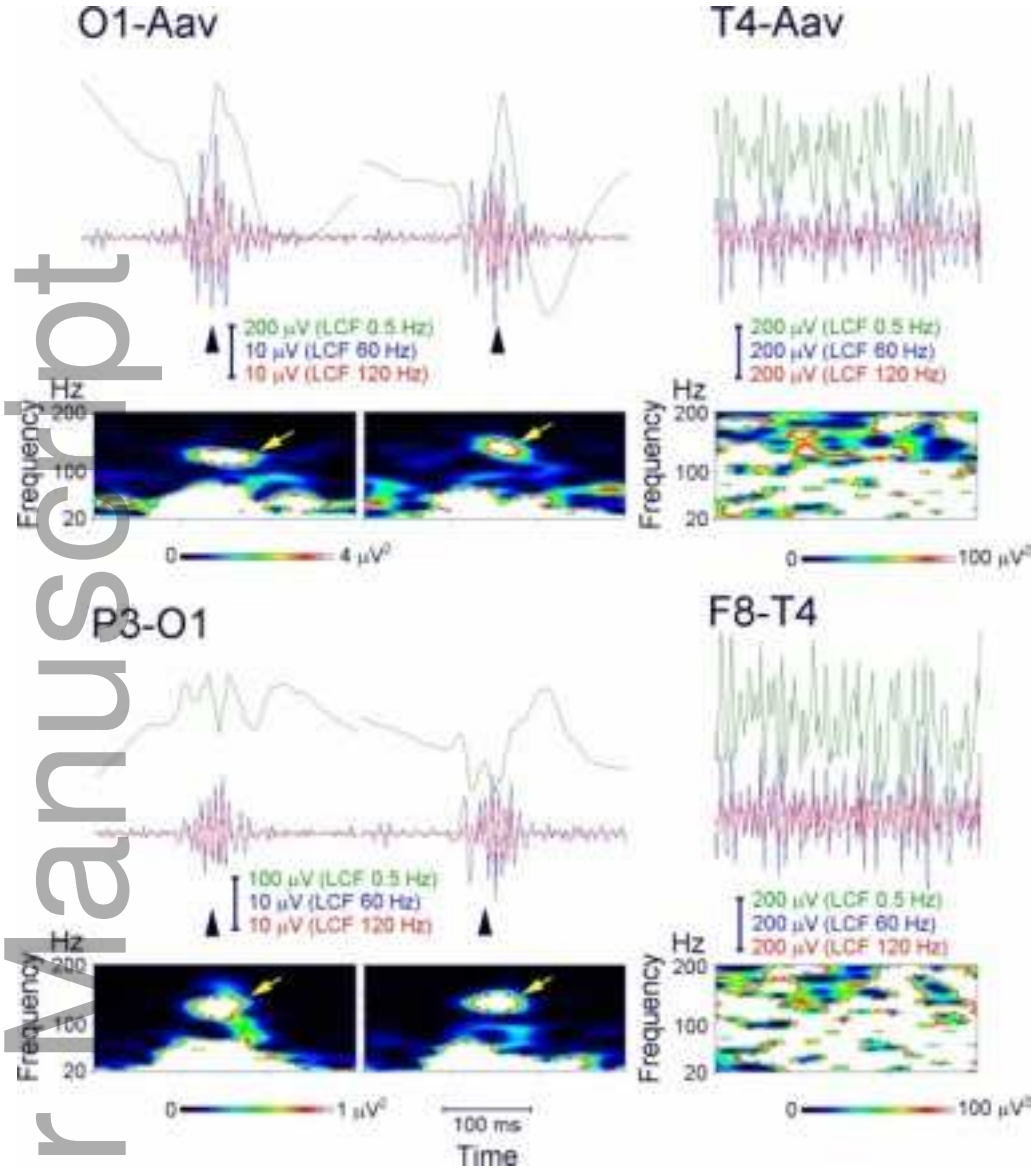

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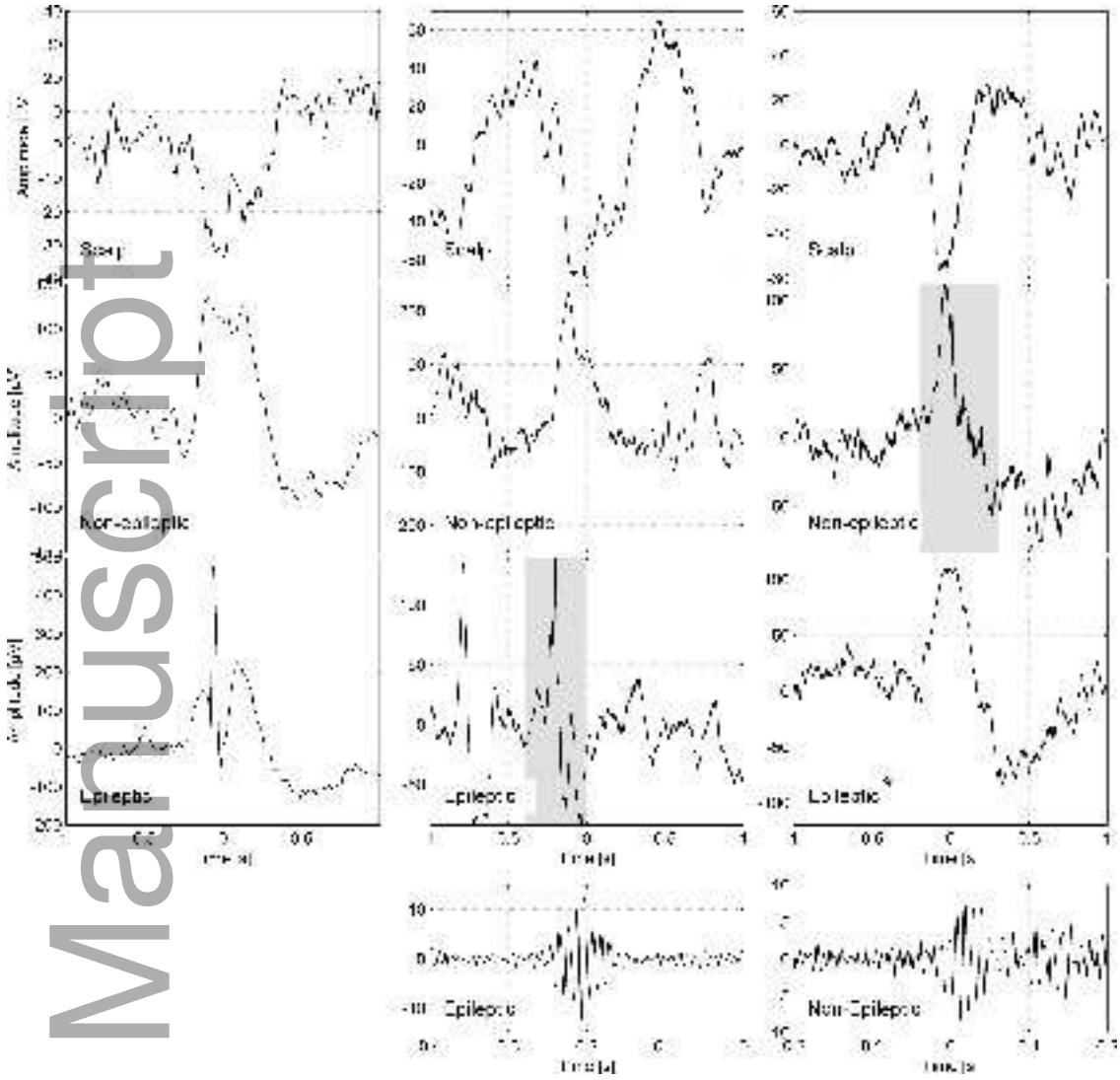

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