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The identification of distinct high-frequency oscillations during spikes delineates the seizure onset zone better than high-frequency spectral power changes

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HIGHLIGHTS

- High frequency power increases and decreases during spikes do not occur in the same brain regions as high frequency oscillations (HFO).
- HFO indicate regions of seizure onset better than high frequency power changes during spikes.
- Significant HF decreases are most prominent over regions of seizure onset.

ABSTRACT

Objective: Interictal high-frequency oscillations (HFOs, 80–500 Hz) can predict the seizure onset zone (SOZ), but visual detection of HFOs is time consuming. Time–frequency analysis can reveal large high-frequency (HF) power changes (80–500 Hz) associated with inter-ictal spikes. The present study determines how well the rate of HFOs and spike-related HF power changes were co-localized with SOZ.
Methods: We analyzed 583 channels (68 in the SOZ) sampled from 14 patients who underwent intracranial EEG recording. We determined if the rate of visually-marked HFOs and spike-related HF power changes differed between SOZ and non-SOZ.
Results: Significantly higher rates of HFOs were found in SOZ. The degree of spike-related HF power augmentation failed to differ between SOZ and non-SOZ, whereas that of post-spike HF power attenuation was significantly more severe in SOZ compared to in non-SOZ. Regions showing HFOs and large spike-related HF-changes showed a partial overlap in distribution in 7/14 patients.
Conclusions: Strong HF augmentation during spikes and high HFO rates occurred over different brain locations. The rate of HFOs showed the best performance in identifying SOZ. Post-spike HF power attenuation may represent increased inhibition in these channels and should be investigated further.
Significance: Strong HF power changes during spikes and HFOs per se seem to reflect distinct phenomena.

1. Introduction

High frequency oscillations (HFO) have become widely recognized in recent years as EEG markers for epileptic tissues (for review see Jacobs et al. (2012)). Most commonly they are divided into ripples between 80 and 250 Hz and fast ripples between 250 and 500 Hz (Engel et al., 2009). While HFOs were first identified with intracranial microwires (Bragin et al., 1999, 2002; Staba et al., 2002), several studies have shown that they can be recorded with depth and subdural electrodes (Jacobs et al., 2008; Ochi et al., 2007) as well as less frequently on scalp EEG (Andrade-Valenca et al., 2011; Zelmann et al., 2014). Independent of the type of epilepsy and its localization, HFOs were successful in identifying regions of seizure onset (SOZ) (Jacobs et al., 2009; Worrell et al., 2004; Crepon et al., 2010). Moreover the removal of HFO generating tissue correlated with the postsurgical seizure outcome (Akiyama et al., 2011; Jacobs et al., 2010).

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In the clinical context, the application of HFOs as EEG markers is complicated by several factors including the presence of physiological oscillations in the same frequency band which might interfere with the analysis as well as the time consuming process of identification of HFOs. One study suggests that an analysis limited to HFOs occurring at the same time as epileptic spikes could be used to exclude physiological HFOs (Wang et al., 2013). Previous studies had suggested that HFOs can either occur independently of spikes or as distinct oscillations "riding" on the epileptic spikes (Urrestarazu et al., 2007). Moreover it has been shown that spikes with HFOs are more closely related to the SOZ than spikes in general (Jacobs et al., 2008). Thus an analysis limited to HFOs at the time of spikes is promising to reduce false detections of physiological HFOs and additionally might provide an opportunity to reduce the amount of time needed to identify HFOs in EEG recordings.

Kobayashi and coworkers proposed a method which allows quantifying the amount of high frequency (HF) changes during the spike as well as directly after the spike (Kobayashi et al., 2009). This method is based on a statistical analysis of time–frequency power spectra using a Gabor transformation. Significant HF increases during spikes and decreases after spikes are calculated in comparison to baseline activity. A preliminary study on selected channels suggests that HF power increases above 250 Hz are more often occurring in spikes within than outside the SOZ (Jacobs et al., 2011). It also revealed strong differences between mesio-temporal and neocortical regions with the latter having less prominent HF changes during the spikes. These studies suggest that HF changes could reliably reflect HFO occurrence as the latter are also more frequent in the mesial temporal structures and the SOZ. However, spectral changes may not necessarily correspond to changes in oscillatory activity and a pure increase of high-frequency EEG power should therefore not be equalized with an increased occurrence of HFOs. Nevertheless, demonstrating a good correlation between HF increases and higher HFO rates would facilitate the analysis of HFOs, largely increasing the possibilities for clinical application.

In the present study, we aim to retrospectively investigate the amount and localization of distinct inter-ictal HFOs and significant HF-changes during spikes in a group of patients with strictly neocortical implantations. The correlation between both measures and the SOZ will be investigated. We hypothesize that a strong augmentation in the HF band during spikes partially reflects the occurrence of HFOs during spikes and therefore strongly co-localizes with brain regions generating high rates of HFOs.

2. Methods

2.1. Patients

Between 2004 and 2011, all patients who underwent intracranial recordings at the Montreal Neurological Institute and who fulfilled the following inclusion criteria were selected:

- At least one night and day of intracranial recording with 2000 Hz sampling rate and at least 4 h of interictal EEG uninterrupted by seizures.
- Electrode implantation involving neocortical brain regions
- Neocortical seizure onset

The last two inclusion criteria were defined due to our preliminary study which suggested strong differences in HF occurrence between mesio-temporal and neocortical regions independent of the SOZ localization (Jacobs et al., 2011) and led to the conclusion that a uniform group of patients should be analyzed to evaluate SOZ-related HF changes.

All clinical data was drawn from the patient's inpatient and postsurgical follow-up charts. All EEG channels of each patient were included in the analysis except those with continuous artefacts. Channels were classified as SOZ or non-SOZ depending on the judgment of an independent clinical neurophysiologist. Only habitual seizures were analyzed for this classification (Kovac et al., 2014). The EEG reviewers for this study were blinded to this classification. The SOZ channels were defined as those showing the first ictal activity during the intracranial recordings. Channels were also classified as removed or not removed according to the MRI obtained in all patients who underwent surgery. Patients underwent pre-surgical MRI and stereotactic electrode implantation, followed by a CT scan to localize electrode placement after the implantation, followed by a postsurgical MRI after the respective surgery. All images were aligned to each other and information of all the images was used to determine whether an electrode contact was removed during surgery. In five out of 7 postsurgical MRIs, traces of the electrode placement additionally were still visible, which further facilitated the identification of removed channels. This study was approved by the Montreal Neurological Institute and Hospital Research Ethics Committee and all patients signed an informed consent.

2.2. EEG recordings and segment selection

Depth electrodes were implanted stereotactically using an image-guidance system (SNN Neuronavigation System, Mississauga, Ontario, Canada) (Olivier et al., 1994). All electrodes were manufactured onsite (9 contacts per electrode with a contact surface of 0.8 mm^2), as described earlier (Urrestarazu et al., 2006; Jacobs et al., 2008). SEEGs were low-pass filtered at 500 Hz, sampled at 2000 Hz and recorded using Harmonie software (Stellate, Montreal, Canada). The recordings were performed referentially with an epidural reference electrode placed in the parietal lobe of the hemisphere least likely to include the main epileptic focus. Analyses were performed on bipolar montages. EEG segments were taken from one of the first three days of the intracranial investigation to reduce influences of antiepileptic medication reduction and all EEG segments were selected so that they were separated by at least 2 h from any seizure.

For the HFO analysis, EEG segments were chosen during slow wave sleep, as this is the period of most frequent HFO occurrence (Bagshaw et al., 2009; Staba et al., 2004). Periods of slow-wave sleep were selected using EEG, EOG and EMG, as described before (Jacobs et al., 2008).

For the HF-analysis, EEG segments were chosen from daytime periods of wakefulness. Again EEG, EOG and EMG were used to assure wakefulness. This was because HF analysis requires at least 2.5 s inter-spike interval and previous studies had shown that intracranial EEG during sleep often shows too frequent spiking; wakefulness is therefore preferable. A minimum of 4 h of seizure-free awake periods were chosen for each patient and these were either selected from the day prior or after the night-time recording selected for HFO analysis.

2.3. Event identification

2.3.1. HFO

We selected 5 min of slow wave sleep in all patients and visually marked ripples, fast ripples and epileptic spikes during this period. The first minute of EEG of each patient was marked by two independent reviewers and Cohen's kappa coefficient was calculated (Landis and Koch, 1977) and used to improve marking as has been described before for each contact (Zelmann et al., 2009).

For identifying HFOs, contacts were displayed with the maximum time resolution of the computer monitor (0.6 s, 1200 samples