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Identification of seizure onset zone and preictal state based on characteristics of high frequency oscillations

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HIGHLIGHTS

- High frequency oscillations (80–200 Hz) (HFO) may occur in all channels of intracranial recordings.
- Average HFO rate is higher within seizure onset zone and increase during the transition from interictal to preictal and to ictal period.
- Characteristics of HFO events within the seizure onset zone differ from those outside the seizure onset zone, and change during the interictal to ictal transition.

ABSTRACT

Objective: We investigate the relevance of high frequency oscillations (HFO) for biomarkers of epileptogenic tissue and indicators of preictal state before complex partial seizures in humans.
Methods: We introduce a novel automated HFO detection method based on the amplitude and features of the HFO events. We examined intracranial recordings from 33 patients and compared HFO rates and characteristics between channels within and outside the seizure onset zone (SOZ). We analyzed changes of HFO activity from interictal to preictal and to ictal periods.
Results: The average HFO rate is higher for SOZ channels compared to non-SOZ channels during all periods. Amplitudes and durations of HFO are higher for events within the SOZ in all periods compared to non-SOZ events, while their frequency is lower. All analyzed HFO features increase for the ictal period.
Conclusions: HFO may occur in all channels but their rate is significantly higher within SOZ and HFO characteristics differ from HFO outside the SOZ, but the effect size of difference is small.
Significance: The present results show that based on accumulated dataset it is possible to distinguish HFO features different for SOZ and non-SOZ channels, and to show changes in HFO characteristics during the transition from interictal to preictal and to ictal periods.

1. Introduction

High frequency oscillations (HFO) are events observed in EEG recordings whose descriptions and mechanisms are still under investigations. Commonly used definitions span a wide range of frequency, amplitude, and duration. Their occurrence often correlates with epileptogenicity, although it remains unclear if HFO reflect pathophysiology or are epiphenomena. However, HFO are also observed in primary visual and motor cortex and are considered physiological, spontaneous or task-induced activity (Nagasawa et al., 2012; Matsumoto et al., 2013; Wang et al., 2013).

High-frequency oscillations have been recorded during interictal (Staba et al., 2002; Urrestarazu et al., 2007), preictal (Jacobs et al., 2009) and ictal (Jirsch et al., 2006) periods. Bragin et al. (1999a,b), and Urrestarazu et al. (2007) reported higher rates of HFO in the seizure onset zone (SOZ) than in other areas during interictal periods and more frequently during slow wave sleep than during wakefulness (Staba et al., 2004; Bagshaw et al., 2009). HFO occur very frequently associated with EEG spikes, but have also been detected independently (Jacobs et al., 2008). Interictal and ictal HFO occur in similar regions (Zelmann et al., 2009), while spikes are more widely distributed, involving a wider area ictally than interictally (Zijlmans et al., 2011). Postsurgical studies

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show a correlation between the removal of tissue under channels with high HFO rates and favorable surgical outcome (Jacobs et al., 2010). Therefore the systematic study of HFO has taken on a greater importance in clinical applications. Previous studies based mainly on visual marking of HFO have proven to be challenging and highly time consuming. HFO are not clinical events and require different approaches than usual EEG event detection which for the most part are correlated with clinical events and associated EEG features. Because of lack of a formal definition, detection of HFO remains subjective and the comparison of studies that use heterogeneous definitions is difficult. Automatic HFO detectors are a crucial step to get a more complete overview of the HFO characteristics and to further investigate their relationship with epilepsy, especially with the assessment of the seizure onset zone in the context of continuous monitoring in epilepsy monitoring units.

A HFO pattern is usually defined as a finite EEG oscillation in the range of 80–500 Hz. This EEG activity was first recorded with microelectrodes (20–40 μm in diameter) implanted in temporal regions (Bragin et al., 1999a,b), and next with clinical macroelectrodes in temporal and neocortical regions (Jirsch et al., 2006; Urrestarazu et al., 2007; Worrell et al., 2008). When recorded with macro-electrodes, HFO are characterized by a typical duration of 30–100 ms, an inter-event interval of at least 25 ms, and amplitude of 10–1000 μV. The criteria selected by different investigators for HFO identification are varied, but commonly require at least four oscillations that can be clearly distinguished from background activity, and at least 25 ms apart from each other.

Detection of such low-voltage events is technically challenging, and subject to false positives introduced by signal filtering. Therefore automated detection is usually combined with visual validation of the detected events by experts. Automatic HFO detectors are largely based on comparison of the signal energy of the EEG epoch that includes the event with a background period. A recent publication (Pail et al., 2013) compares automated detection of HFO based on line length method versus a visual assessment of SEEG traces and indicates that both contribute comparably to the identification of the SOZ in patients with focal epilepsy. Taking into account, how tedious and subjective the visual analysis can be, the use of fully automatic procedures which enables evaluation of HFO even in long duration recordings can bring objective quantification to the HFO analysis paradigm.

Blanco et al. (2010) analyzed a large number of HFO (N = 290,273) detected by automatic analysis. After detection based on the energy threshold designed by Staba et al. (2002), the authors developed an algorithm for automated classification of HFO. Using an unsupervised clustering approach that did not specify the number of clusters, three distinct classes of transient oscillations within the 100–500 Hz frequency range were identified. Two of the classes were consistent with ripple and fast ripple oscillations, and a third consisted of mixed-frequency events. Blanco et al. (2011) present an analysis of these classified groups of events with respect to seizure onset zone channels and other regions. The same dataset and methodology was used (Pearce et al., 2013) to investigate temporal changes of different types of HFO, their rate and proportions during interictal, preictal, ictal and postictal periods. Using data from 5 patients (2 mesial; 3 neocortical), the authors did not show clear systematic trends in HFO behavior across patients but patient-specific changes in HFO morphology linked to fluctuation in the relative rate of ripples, fast ripples, and mixed frequency events were observed.

Although many groups investigate HFO rate and their changes in time and relationship with spikes and seizure onset zone, so far only a few studies have tried to analyze features of HFO to find difference between pathological and physiological activity (Matsumoto et al., 2013; Nagasawa et al., 2012; Wang et al., 2013). One other recent work (Kerber et al., 2014) shows that specific ripple patterns, ripples occurring during flat background activity, better help identify epileptogenic areas for surgical procedures.

To investigate HFO as biomarkers of epileptogenic tissue we are proposing a novel automated HFO detection method based not on local energy but on the amplitude and shape of the HFO event. We examine changes of HFO activity before and during complex partial seizures in humans. We also assess the potential use HFO as a marker for preictal state testing if there are significant changes in the characteristics of HFO in the period leading to the seizure onset and if based on HFO rate and characteristic it is possible to identify the SOZ.

2. Methods

2.1. Data

Forty-five consecutive patients with intractable partial epilepsy undergoing presurgical evaluations at the Johns Hopkins Epilepsy Center recorded between 2004 and 2006 were screened for this study. We selected records from patients diagnosed either with mesial temporal (N = 13) or neocortical (N = 20) onset seizures and with at least 2 h of interictal activity before the seizure during clinical monitoring. Our final pool of patients contains 33 patients (14 males, 19 females) age 27.4 ± 13.5 years.

Intracranial recordings included combinations of subdural multicontact grids and strips placed over the area of interest and targeted multi-contact depth electrode arrays. Typical implantation includes 64–128 electrodes in 4 or 8 contact strips and grid arrays with 16–64 contacts. Seizures were recorded using a Stellate™ system with Schwarzer amplifiers. A 300 Hz low-pass, Butterworth anti-aliasing filter (order = 5; 20 dB/oct) was applied prior to 16-bit digitization over a ± 3196 μV range. Analyses were carried out using bipolar montages using neighboring electrodes for improved localization of ictal onset activity. For each patient between 20 and 102 channels were analyzed.

Seizure events included complex partial seizures with or without secondary generalization. All seizures were spontaneous events occurring over the course of the evaluation (5–7 days), and then marked based on visual analysis of recorded EEG by an experienced neurologist. Only the first seizure for each patient was taken into consideration for this analysis. Seizure onset is defined as the onset of epileptiform activity leading to the ictal event without return to baseline in between seizures. The channel with the first changes of epileptiform activity and surroundings electrodes (up to 8 for grid only, 2 for strips only, and more if combinations of electrodes were localized around focus channel) were considered here as seizure onset zone channels (SOZ).

The seizure onset patterns consisted of sustained low voltage fast activity (21 patients), sustained rhythmic spikes discharges (8 patients), or sustained rhythmic slow wave discharges (4 patients). The onsets with low voltage fast activity very often evolved into rhythmic spikes discharges.

The research protocol was reviewed by the IRB and data were stored in compliance with HIPAA regulations.

2.2. HFO detection method

Periods of 2 h before and up to 2 min after the seizure onset of each marked seizure (a total of 122 min) were divided into 2 min segments and filtered at 80–200 Hz (band-pass filter using two-way least-squares FIR filtering, EEGLab, Matlab™). For HFO detection we applied an automated method, which implements identification of HFO based on the following criteria. To be marked as an HFO, the event must consists of at least 4 consecutive oscillations on filtered EEG with amplitudes above 10 μV and be