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Differentiation of specific ripple patterns helps to identify epileptogenic areas for surgical procedures

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HIGHLIGHTS

- Removal of areas generating fast ripples and areas of seizure onset correlate with a seizure-free post-surgical outcome.
- Ripple oscillations can either occur from a flat or oscillatory background activity.
- Only removal of areas with ripples occurring in flat background activity is correlated with a seizure free outcome.

ABSTRACT

Objective: High frequency oscillations (HFOs) at 80–500 Hz are promising markers of epileptic areas. Several retrospective studies reported that surgical removal of areas generating HFOs was associated with a good seizure outcome. Recent reports suggested that ripple (80–200 Hz) HFO patterns co-existed with different background EEG activities. We hypothesized that the coexisting background EEG pattern may distinguish physiological from epileptic ripples.
Methods: Rates of HFOs were analyzed in intracranial EEG recordings of 22 patients. Additionally, ripple patterns were classified for each channel depending either as coexisting with a flat or oscillatory background activity. A multi-variate analysis was performed to determine whether removal of areas showing the above EEG markers correlated with seizure outcome.
Results: Removal of areas generating high rates of 'fast ripples (>200 Hz)' and 'ripples on a flat background activity' showed a significant correlation with a seizure-free outcome. In contrast, removal of high rates of 'ripples' or 'ripple patterns in a continuously oscillating background' was not significantly associated with seizure outcome.
Conclusion: Ripples occurring in an oscillatory background activity may be suggestive of physiological activity, while those on a flat background reflect epileptic activity.
Significance: Consideration of coexisting background patterns may improve the delineation of the epileptogenic areas using ripple oscillations.

1. Introduction

In many patients with pharmacorefractory epilepsy, epilepsy surgery represents an important treatment option. When noninvasive methods fail to localize an epileptogenic focus, intracranial electroencephalographic (iEEG) investigations are used to identify the epileptogenic zone (Diehl and Luders, 2000). Currently the identification of the seizure onset zone and interictal spikes are used to delineate epileptic tissue but still 30–40% of patients

Abbreviations: HFO, high frequency oscillation; SOZ, seizure onset zone.

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remain to have seizures after surgical resection (Spencer and Huh, 2008) .

High-frequency oscillations (HFOs), ripples (80–200 Hz) and fast ripples (200–500 Hz), recently emerged as new markers for epileptic areas. They can be recorded with macro-electrodes during clinical iEEG investigation. Inter-ictal HFOs proved to be more specific in indicating the SOZ than spikes (Jacobs et al., 2008). Additionally, they were linked to the SOZ independently of the underlying lesion (Jacobs et al., 2009) and removal of HFO-generating brain tissue correlated with a good postsurgical outcome (Wu et al., 2010; Akiyama et al., 2011).

The exact definition of HFOs as well as their analysis is however variable. While some groups use automatic detection others use visual EEG review to identify events (Crepon et al., 2010; Gardner et al., 2007; Staba et al., 2002). Both methods rely on the identification of distinct oscillatory activity which has higher energy and amplitude than the baseline activity of the respective channel. During the visual analysis it is striking that baseline oscillatory activity varies largely between channels. Therefore, Melani and coworkers for the first time tried to differentiate between interictal HFO patterns depending on the background activity observed at the time of HFO occurrence using intracranial depth electrodes. Consequently three types of HFO patterns were described in the ripple range (80–200 Hz) (Melani et al., 2013): Pattern 1 was defined as channels with a background almost completely occupied by a continuous/semicontinous HFO activity lasting >500 ms; Pattern 2 consisted in channels with sporadic HFO activity out of a flat baseline.; Pattern 3 was defined as irregular pattern with HFO lasting >200 ms and <500 ms.

At the same time, our group analyzed ripple rates in patients implanted with neocortical grid electrodes. In our data ripple occurrence seemed less localized than described in depth electrodes; again different HFO patterns in regard to baseline activity were found. This study investigates whether distinct inter-ictal HFO patterns have different relevance for the identification of epileptic tissue. For this purpose, we analyze the occurrence of HFO patterns in the SOZ as well as the correlation between the surgical removal of HFO generating tissue and the postsurgical outcome. We hypothesize that channels with sporadic HFOs within a flat baseline activity (pattern 2) reflect epileptic activity to a far greater extent than a continuously/semicontinuously oscillating HFO activity (pattern 1).

2. Methods

2.1. Patient selection

Between September 2004 and April 2009, a total of 58 patients underwent intracranial electrode implantation in the epilepsy unit of the University Medical Center Freiburg. The decision to use iEEG resulted exclusively from clinical reasons. The data was analyzed retrospectively. Inclusion criteria for this study were as follows: patients with focal epilepsy, neocortical grid electrodes and at least one EEG segment without artifacts recorded with a sampling rate of 1024 Hz. Patients with neocortical electrodes were selected, as different HFO patterns in our previous studies were mainly present in grid electrodes. Patients with a high seizure frequency that prevented the selection of an EEG segment with an inter-ictal interval of two hours were excluded. This study was approved by the Freiburg Ethics Committee of the Freiburg University Medical Center and all patients gave informed consent for use of collected data for scientific purposes.

2.2. Recording methods

A combination of grid and strip electrodes was implanted. All electrodes were manufactured out of stainless steel by AD-TECH Medical Instrument Corporation (Racine, WI, USA). Grid electrodes had a surface area of 2.3 mm × 2.3 mm and were located at a 1 cm distance from each other. Electrodes were implanted by open craniotomy.

iEEGs were recorded using the IT-Med EEG system (Natus Europe GmbH, Munich, Germany). The signals sampled at 1024 Hz and filtered in the recording system with a high pass filter with a time constant of 1 s and a low pass filter with a cutoff frequency of 344 Hz. EEGs were recorded using a referential montage with an epidural reference electrode placed at the frontal vertex. Analyses were performed on bipolar montages.

2.3. Channel selection and marking of interictal events

Interictal samples of 3 min of slow-wave sleep were analyzed, as HFOs and spikes occur more frequently during slow-wave sleep (Bagshaw et al., 2009; Staba et al., 2004). The EEG analysis was conducted using the Harmonie system (Stellate, Montreal, Canada). Spikes and HFOs were marked by two independent reviewers as described in Jacobs et al. (2010). In short, EEG was displayed with the maximum time resolution and the display was split vertically with an 80 Hz high-pass filter on the left side and a 200 Hz high-pass filter on the right side. An event was regarded as a ripple if it was clearly visible on the left (80 Hz) side and not on the right (200 Hz) side. A fast ripple was marked if it was visible on the right (200 Hz). HFOs consisting in at least 4 consecutive oscillations were marked and 2 events were considered distinct when separated by at least 2 non-HFO oscillations.

2.4. Identification of patterns

The contacts were visually classified into Pattern 1, 2, 3 and 0 by 2 independent reviewers taking into account the selected segment of slow wave sleep also used for HFO marking. Visual criteria included the length of oscillations, the presence of a clear separation between transient HFO elements and non-oscillatory baseline activity and the difference in amplitude between baseline activity and oscillations. If two reviewers could not agree on either pattern 1 or pattern 2, pattern 3 was attributed to the channel. All visual reviews used an amplitude scale of 2 μV/mm. A typical example for the identified patterns is shown in Fig. 1.

Pattern 1: background almost completely occupied by a continuous/semicontinuous oscillatory activity with HFO like activity lasting >500 ms.

Pattern 2: sporadic short HFO out of a flat baseline activity, HFO amplitude at least twice as high as baseline amplitude.

Pattern 3: irregular pattern with HFO lasting >200 ms and <500 ms.

Pattern 0: no HFO activity.

2.5. Statistical analysis

Rates of HFOs as well as HFO patterns in each channel were analyzed in regard to their relation to the SOZ as well as their importance for surgical removal. Rates of ripples, fast ripples and spikes as well as the co-occurrence of spikes and HFOs (defined as the intersection between a spike marking and an HFO marking) were calculated for each contact by using MATLAB (The Mathworks Inc., Natick, Massachusetts, USA).

Channels were classified as SOZ or non-SOZ channels by a clinical neurophysiologist during iEEG recording independent of the present study. The traditional display of the iEEG does not allow visualization of HFOs, and HFOs that may have been present at seizure onset were therefore not taken into account for the determination of the SOZ. If seizures were originating from more than 1