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Frequency-independent characteristics of high-frequency oscillations in epileptic and non-epileptic regions

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HIGHLIGHTS

- The highest rate of fast ripples is in the seizure onset zone (SOZ).
- A worse prognosis (no seizure freedom after surgery) is associated with higher amplitudes of fast ripples outside the SOZ.
- In the SOZ, high frequency oscillations are more frequent, shorter, and have higher amplitudes.

ABSTRACT

Objective: The purpose of the presented study is to determine whether there are frequency-independent high-frequency oscillation (HFO) parameters which may differ in epileptic and non-epileptic regions.
Methods: We studied 31 consecutive patients with medically intractable focal (temporal and extratemporal) epilepsies who were examined by either intracerebral or subdural electrodes. Automated detection was used to detect HFO. The characteristics (rate, amplitude, and duration) of HFO were statistically compared within three groups: the seizure onset zone (SOZ), the irritative zone (IZ), and areas outside the IZ and SOZ (nonSOZ/nonIZ).
Results: In all patients, fast ripples (FR) and ripples (R) were significantly more frequent and shorter in the SOZ than in the nonSOZ/nonIZ region. In the group of patients with favorable surgical outcomes, the relative amplitude of FR was higher in the SOZ than in the IZ and nonIZ/nonSOZ regions; in patients with poor outcomes, the results were reversed. The relative amplitude of R was significantly higher in the SOZ, with no difference between patients with poor and favorable surgical outcomes.
Conclusions: FR are more frequent, shorter, and have higher relative amplitudes in the SOZ area than in other regions. The study suggests a worse prognosis in patients with higher amplitudes of FR outside the SOZ.
Significance: Various HFO parameters, especially of FR, differ in epileptic and non-epileptic regions. The amplitude and duration may be as important as the frequency band and rate of HFO in marking the seizure onset region or the epileptogenic area and may provide additional information on epileptogenicity.
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1. Introduction

Over the past few years, there has been growing interest in the analysis of interictal high frequency oscillations (HFO), primarily with the goal of understanding their value for identifying the epileptogenic zone and their correlation with epileptogenicity. HFO promise to be more specific than interictal spikes for epileptogenic brain tissue and even more specific than the seizure-onset area (Jacobs et al., 2008).

HFO are short-lasting field potentials, which arise as a result of the synchronization of neuronal populations. HFO have been identified and defined in terms of frequency: ripples (80–250 Hz), fast ripples (250–600 Hz) (reviewed in Bragin et al., 2010; Engel et al.,

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2009), and very high frequency oscillations (1000–2500 Hz) (Usui et al., 2015). HFO have been widely studied in animals and humans, in mesial temporal and neocortical structures, under physiological and pathological conditions, using microelectrodes or commercial macroelectrodes, and during interictal and ictal periods (Bragin et al., 1999a,b; Staba et al., 2002; Worrell et al., 2004, 2008; Urrestarazu et al., 2007; Jacobs et al., 2008, 2009; Bagshaw et al., 2009; Brázdil et al., 2010; Crépon et al., 2010). However, the reliability of HFO as a biomarker of epileptogenicity and the seizure-onset zone remains uncertain (Haegelen et al., 2013; Jobst, 2013; Wang et al., 2013).

Ripples, observed as a physiological finding in the hippocampus and parahippocampal structures, are thought to be functionally involved in memory consolidation (Buzsáki et al., 1992; Axmacher et al., 2010; Lachaux et al., 2012). The spontaneous occurrence of ripples in humans is also believed to be physiological in the primary visual cortex (Nagasawa et al., 2012; Wang et al., 2013) and in the primary motor cortex (Wang et al., 2013). The presumption of the exclusively physiological nature of ripples was, however, impugned by evidence of HFO in ripple ranges recorded in the dentate gyrus after epileptogenic insult in an animal model of kainate-induced status epilepticus (Bragin et al., 1999b, 2004).

Conversely, fast ripples were repeatedly reported as a biomarker of epileptogenesis and epileptogenicity, both in animal models and in human epilepsy (Bragin et al., 1999a,b; Staba et al., 2002). It is important that HFO in the fast ripple range (at about 600 Hz) can also be considered physiological, as they were previously evoked during stimulation of the somatosensory cortex (Curio et al., 1997). Thus the HFO frequency range, in general, is not sufficient to differentiate physiological and pathological HFO (Bragin, 2007). On the other hand, there is evidence of favorable epilepsy surgery outcome after the removal of tissue generating interictal HFO, especially fast ripples (Jacobs et al., 2010; Wu et al., 2010; Akiyama et al., 2011).

Several authors have tried to distinguish between pathological and physiological HFO on the basis of a specific regional distribution in respective mesial temporal structures (Jiruska and Bragin, 2011); some have investigated the difference between task-induced and spontaneous HFO (Nagasawa et al., 2012; Matsumoto et al., 2013; Brázdil et al., 2015); others have studied the association of HFO with epileptiform discharges (Crépon et al., 2010; Urrestarazu et al., 2007; Wang et al., 2013). Interictal HFO (both ripples and fast ripples) rates were proven significantly higher within the seizure onset zone (SOZ) than outside it (Jacobs et al., 2009).

The purpose of the present study is to identify whether there are any other frequency-independent HFO parameters that potentially differ in areas within the SOZ, within the irritative zone (IZ), and in areas outside the IZ/SOZ.

2. Methods

2.1. Subjects

Our sample comprised 31 patients (19 females; 12 males) ranging in age from 13 to 56 years (mean age 33.4 years, SD = 10.5), all with medically intractable focal epilepsies (Table 1). All the subjects fulfilled the diagnostic criteria for either medically intractable temporal lobe epilepsy (TLE) – 22 subjects or extratemporal lobe epilepsy (ETLE) – 9 subjects. The diagnosis was made according the ILAE criteria (Commission on Classification and Terminology of ILAE, 1989). The main demographic and clinical characteristics of the included subjects are shown in Table 1.

2.1.1. Presurgical evaluation

All 31 patients underwent a comprehensive presurgical evaluation, including a detailed history and neurological examination, magnetic resonance imaging (MRI), neuropsychological testing, and scalp and invasive video-EEG monitoring (Table 1). Most of the subjects had not previously undergone intracranial surgery. One subject underwent resection of venous malformation within the left P-O region before SEEG and re-operation; in one subject a resection of the pole of the left temporal lobe had been performed, and in one subject a limited left AMTR was performed before SEEG monitoring. Prior to invasive EEG, two subjects had a vagus nerve stimulation system implanted, with unfavorable seizure frequency outcome. The duration of clinical monitoring and the location and number of implanted electrodes were determined in accordance with clinical considerations.

2.1.2. Surgery and outcome measure

Most of the patients (28) underwent surgical intervention (implantation of VNS was performed in 7 patients and brain resection in 21 patients; details are shown in Table 1). The follow-up interval after epilepsy surgery was at least 12 months. After surgical resection, 8 patients were rated as Engel IA, one patient was Engel IIA, and 11 patients were Engel III or IV; the Engel rating is unknown for one patient (due the loss to follow-up care).

This study was approved by the St. Anne's University Hospital Research Ethics Committee and the Ethics Committee of Masaryk University. All patients signed an informed consent form.

2.2. SEEG

Depth electrodes (mostly SEEG; grids and strips were used in two patients) were implanted to localize the seizure origin prior to surgical treatment. The sites of electrode placements were individualized according to seizure semiology, clinical history, noninvasive EEG investigations, and neuroimaging results. Standard intracerebral 5-, 10-, and 15-contact Micro Deep semi-flexible multicontact platinum electrodes (ALCIS) were used with a diameter of 0.8 mm, a contact length of 2 mm, an inter-contact distance of 1.5 mm, and a contact surface area of 5 mm^2. Their position within the brain was afterwards verified by MRI with electrodes in situ (see Table 1). In two patients, platinum subdural strip and grid electrodes (Radionics) were used. Thirty minutes of artifact-free continuous interictal SEEG data (recorded during wakefulness) was analyzed for each subject. This period is sufficient based on the results of previously published papers (Jacobs et al., 2008; Zelmann et al., 2009; Andrade-Valença et al., 2012). The EEGs were acquired at 25 kHz sampling frequency and subsequently low-pass filtered and downsampled to 5 kHz. High harmonics produced by the system (artificial harmonics) are accounted for during EEG acquisition. A reference average montage was used for the analysis.

2.2.1. Labeling of analyzed contacts

The contacts in each subject were divided into three groups for further HFO analysis. The distribution was done visually (by co-authors M.P. and I.D.) by a standard analysis of ictal and interictal SEEG recordings. The first group was labelled SOZ contacts: the channels that revealed the first ictal activity. The second group was labelled IZ contacts: the channels where interictal epileptiform discharges were detected, but no seizure onset was detected. The remaining non-spiking contacts were labelled nonSOZ/nonIZ. Only contacts localized in gray matter were included in the study.

2.2.2. Automated detection of HFO in resting awake SEEG

The algorithm for HFO detection is explained in more detail in the Supplementum. HFO were detected by a custom Matlab detection algorithm. The raw signal (Supplementary Fig. S1) was divided

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