Circadian Dynamics of High Frequency Oscillations in Patients with Epilepsy

Jirí Balach[1], Petr Jezdik[1,2], Radek Janca[1], Roman Cmejla[1], Pavel Krsek[3], Petr Marusic[4] and Premysl Jiruska[5]

[1]*Departement of Circuit Theory, Czech Technical University in Prague, Technická 2, Prague, Czech Republic*

[2]*Department of Measurement, Czech Technical University in Prague, Technická 2, Prague, Czech Republic*

[3]*Department of Pediatric Neurology, 2nd Faculty of Medicine, Charles University in Prague, Motol University Hospital, Prague, 150 06, Czech Republic*

[4]*Department of Neurology, 2nd Faculty of Medicine, Charles University in Prague, Motol University Hospital, Prague, 150 06, Czech Republic*

[5]*Department of Developmental Epileptology, Institute of Physiology, The Czech Academy of Sciences, Prague, CZ-14220, Czech Republic*

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Abstract: High frequency oscillations (HFOs) are novel biomarker of epileptogenic tissue. HFOs are currently used to localize the seizure generating areas of the brain, delineate the resection and to monitor the disease activity. It is well established that spatiotemporal dynamics of HFOs can be modified by sleep-wake cycle. In this study we aimed to evaluate in detail circadian and ultradian changes in HFO dynamics using techniques of automatic HFO detection. For this purpose we have developed and implemented novel algorithm to automatic detection and analysis of HFOs in long-term intracranial recordings of six patients. In 5/6 patients HFO rates significantly increased during NREM sleep. The largest NREM related increase in HFO rates were observed in brain areas which spatially overlapped with seizure onset zone. Analysis of long-term recording revealed existence of ultradian changes in HFO dynamics. This study demonstrated reliability of automatic HFO detection in the analysis of long-term intracranial recordings in humans. Obtained results can foster practical implementation of automatic HFO detecting algorithms into presurgical examination, dramatically decrease human labour and increase the information yield of HFOs.

1 INTRODUCTION

High-frequency oscillations (HFOs) are sinus like oscillations significantly rising above the background in the frequency range above 80 Hz (Bragin et al., 2002; Jacobs et al., 2008; Staba et al., 2002; Urrestarazu et al., 2007). HFOs are divided into two types according to their frequency profile. Oscillations in range 80-200 Hz are classified as ripples while oscillations over 200 Hz are called fast ripples. HFOs represent a novel biomarker of epileptogenic tissue with the potential to increase the information yield of presurgical evaluations and to improve the outcomes of epilepsy surgery.

Visual analysis of HFO in intracranial recordings is a time consuming process. According to Zelmann et al., (2012) it takes 10 hours of concentrated human work to analyse 10 channel data with duration of 10 minutes. Visual review of long-term signals from a hundreds of channels is virtually impossible in a reasonable time period and it also suffers from human bias. Successful implementation of HFOs analysis into the clinical practice requires development of new techniques of automatic HFOs detection which would provide reliable information about HFO spatiotemporal dynamics. Substantial number of studies focused on the HFOs and their utilization in presurgical examination evaluated only short-term recordings. Only selected segments of invasive EEG (iEEG) usually up to 10 minutes long were evaluated in large number of HFO studies (Jacobs et al., 2010; Kerber, 2013). In these studies HFOs were labelled manually or semi-automatically using detection algorithms for preselection of candidate HFO events (Zelmann et al., 2012; Worrell, 2008; Crépon, 2010; Staba et al., 2002; Cho et al., 2014).

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Table 1: Summary of patient dataset information; *Original frequency, resampled to 512Hz.

Patient number	Age / Gender	MRI findings	Number of channels of implanted electrodes	Sampling frequency (Hz)	Record length (hours.)
1	child/M	FCD Ib	122	1000*	12
2	adult/F	Normal	128	512	24.5
3	adult/F	FCD susp.	128	512	22.5
4	child/M	FCD IIb	71	1000*	22
5	adult/F	FCD Ia	128	512	12
6	child/M	FCD IIb	109	1000*	14.5

The advantage of algorithms of automated HFO detection is their capability to analyse large amount of data in a relatively short time. Recordings are analysed with the same conditions and by the same measures and obtained results are not biased. The major downside of automated algorithms represents inconsistent number of false detections.

Several studies have demonstrated that spatial distribution of HFOs correlates with the localization of seizure onset zone (Bagshaw et al., 2009; Brázdil et al., 2010; Jacobs et al., 2009, 2008; Urrestarazu et al., 2007). Moreover, resection of HFO generating regions has been associated with better surgical outcomes (Akiyama et al., 2011; Cho et al., 2014; Fujiwara et al., 2012; Haegelen et al., 2013; Sakuraba et al., 2015). Long-term HFOs dynamics and spatiotemporal profile are, however, modulated by several factors like levels of inhibition, vigilance and by sleep. It has been shown that HFO rate increases during slow wave sleep (Clemens et al., 2007 , Bagshaw et al., 2009) but individual stages of NREM sleep (NREM1-NREM4) do not influence HFO rates. Ripples and the fast ripples were confined to SOZ during NREM. Another study demonstrated that good surgical outcome was achieved, if the resection involved brain tissue where ripples occurred during REM stage (Sakuraba et al., 2015).

These long-term changes in HFO properties must be taken in account in analysis of HFOs and interpretation of the results. In the current study, we aimed to examine the long-term HFO dynamics using automatic HFO detector (Balach et al., 2014).

2 DATA & METHODS

2.1 Database

We analyzed long-term recordings from three paediatric and three adult patients implanted with subdural and/or depth electrodes as a part of the presurgical examination (Table 1.). Signals were sampled at 512 Hz (adults) and 1 kHz (children). High sampling rate signals were resampled to 512 Hz. The average length of recordings was 17.9 ± 5.7 hours. Each dataset contained 114 ± 22 contacts. Electrode contacts inside the SOZ were marked by experienced neurologists. The SOZ was defined as the area of the brain with the earliest occurrence of ictal discharges (Litt et al., 2001; Marsh et al., 2010; Thornton et al., 2011). Research procedures and data collection were approved by the institutional ethical committee and patient or parent informed consent was obtained.

2.2 Methodology

HFO detector was applied to recorded data. The HFO detection algorithm is based on the dynamical thresholding of short-time energy changes, followed by calculation of the number of cycles within the detected HFO event and identification of peak frequency within HFO frequency bands (Balach et al., 2014). To obtain average HFO rate per minute we used 5-minute sliding window with 80% overlap. Due to high inter-patient variance of HFO rate, the rate was normalized by maximal rate observed in each dataset. Evaluation of circadian changes in HFO properties required identification of sleep and wakefulness. Because standard polysomnographic (PSG) signals (scalp EEG, EOG and EMG) could not be recorded during invasive monitoring, we determined the sleep and wakefulness indirectly from iEEG. First, signals with frequent interictal epileptiform discharges were removed. The discharges were detected using highly sensitive spike detector (Janca et al., 2014).Channels with interictal epileptiform discharge rate higher than the first quartile were excluded. Selected data were band-pass filtered in 2-15 Hz, segmented by 3.5 minutes window with 70 % overlap. For each data segment we calculated mean energy and signal zero crossing frequency. To minimize the energetic and spectral impact of artefacts, both parameters were normalised by their 99th percentiles and recalculated to a *PSG parameter*. This parameters represents frequency to energy ratio, eq. 1.

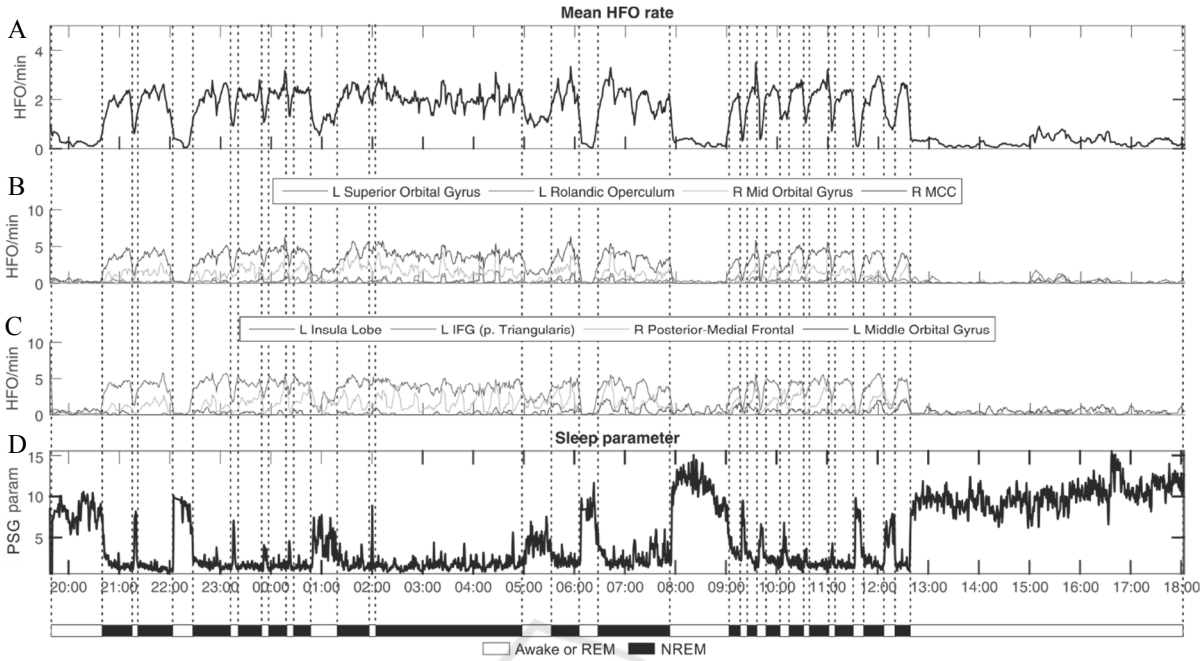

Figure 1: HFO rates in a one-day cycle in patient 3. Awake and sleeping stages were set manually according to HFO rates, daytime and PSG parameter. A) Mean HFO rate during day/night cycle. B, C) Example of HFO rates from selected brain structures. Electrode contacts were assigned to anatomical structures according to anatomical atlas (Eickhoff et al., 2005). Assignments were made manually from the CT/MRI co-registered images. D) Temporal profile of PSG parameter.

$$PSG\ parameter = \frac{norm.frequency}{norm.energy} \quad (1)$$

During the NREM sleep, the normalised frequency decreases towards the lower frequencies from delta frequency band while the normalised energy increases. PSG values drop during the NREM stage and increase during REM sleep and wakefulness.

We manually identified wakefulness, REM and NREM from the PSG parameter. Due to difficult differentiation between REM sleep and awake states we classified them as a single awake+REM state. Utilizing automatic HFO detector we aimed to address following questions:

1) Does HFO rate varies between awake+REM and NREM states?
2) Does HFO rate in SOZ and outside display different circadian dynamics?
3) Does HFO rate correlates with localization of SOZ?

3 RESULTS

In total 833,199 HFO events were detected in 107.5 hours of iEEG data from all six patients. The normalised HFOs rates were significantly higher during NREM than in awake+REM state in 5/6 patients (p<0.05, Wilcoxon's test, Figure 2).

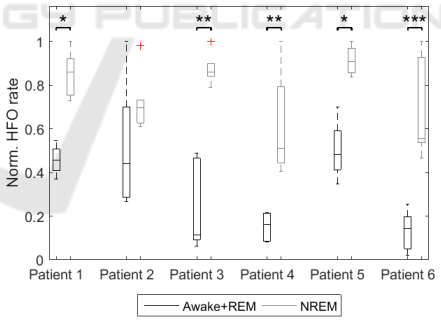

Figure 2: HFO rates in NREM and Awake+REM states in each patient (*p<0.05; **p<0.01; ***p<0.001). Patient 2 p=0.1255.

HFO rates during Awake+REM state did not differ inside and outside SOZ. However, in NREM state HFO rates in SOZ significantly increased (p<0.001, Wilcoxon's test, Figure 3).

The most HFO active regions overlapped with the SOZ. Better overlap was observed during NREM (62.8±40%) than during awake+REM state (44.8±33.7%).

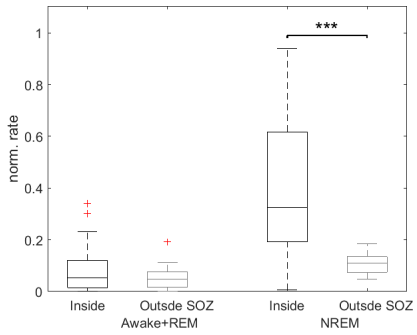

Figure 3: HFO rates significantly increased inside SOZ during NREM stages. (***p<0.001).

Table 2: Localization ability of channels with HFO maximal rates (> 75 percentile).

Patient	Number of channels in 4th quartile	In/Total SOZ contacts in awake/REM	In/Total SOZ contacts in NREM
1	28	3/16 (19%)	6/16 (38%)
2	29	0/11 (0%)	0/11 (0%)
3	27	17/23 (74%)	20/23 (87%)
4	16	5/19 (26%)	10/19 (52%)
5	16	3/4 (75%)	4/4 (100%)
6	27	3/4 (75%)	4/4 (100%)

In patient 2 we analyzed 14 days of iEEG recording to evaluate reliability of automated HFO analysis over very long time period (Figure 4). Processing of the whole dataset took 130 hours and 4,393,892 HFO events were detected. According to Zelmann et al., (2012), visual review of such dataset from HFO perspective would take approximately 258048 hours (~29 years) of human work. We observed the dynamical changes of HFO occurrence from the start of the recording. The HFO rate was stable in majority of brain structures and displayed circadian fluctuations. However, in left middle temporal gyrus HFO rates were progressively increasing. After day 8, the HFO rates were stable in all studied structures, but the quality of signal deteriorated due to increased number artefacts leading to higher number of false detections.

4 DISCUSSION

In this study we have demonstrated reliability of automatic HFO detection in the analysis of long-term intracranial recordings in humans. Utilization of automatic detectors is able to reveal circadian and long-term dynamics of HFO rate. Obtained results can foster practical implementation of automatic HFO detecting algorithms into presurgical examination, dramatically decrease human labour and increase the information yield of HFOs (Zelmann et al., 2012).

This study demonstrates the importance of understanding of long-term spatiotemporal dynamics of HFO rates for appropriate interpretation of the obtained results. Dynamical changes in HFO rates during NREM sleep inside and outside can provide better localizing information about SOZ than recordings obtained during the REM sleep or wakefulness (Clemens et al., 2007; Bagshaw et al., 2009; Sakuraba et al., 2015).

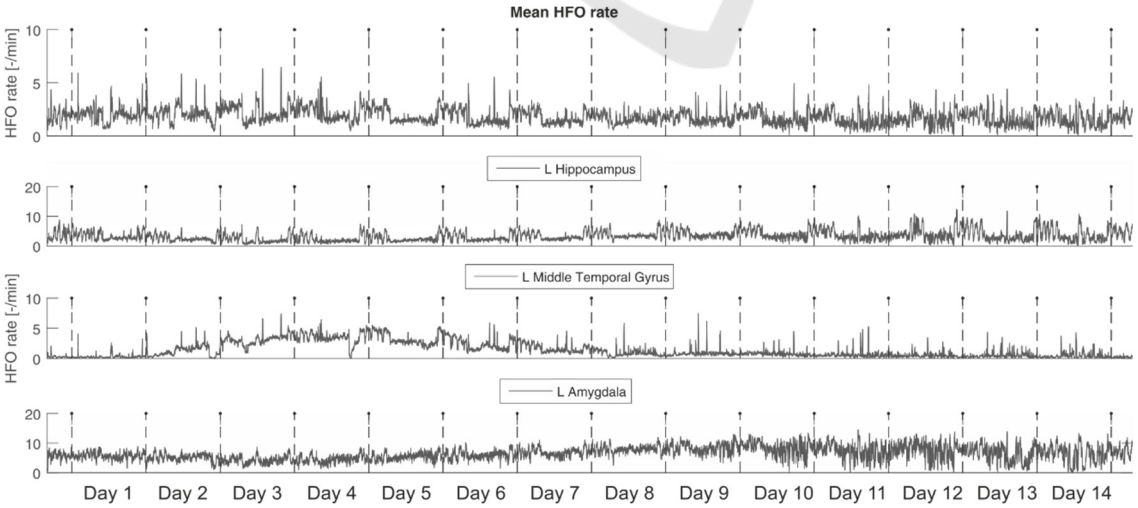

Figure 4: HFO rate analysis of continuous 14 day recordings. Mean HFO rate across all implanted electrodes and rates from electrodes which are inside three chosen anatomy structures. Dashed vertical lines are marks of midnights.

Application of the analysis to data with very long duration revealed fast dynamical changes of HFO rate in respect to circadian rhythms, but also slow ultradian changes which may reflect various phenomena like effect of anaesthesia, changes medication, changes in neurotransmitter and neuromodulator systems, propensity to generate seizures and tissue response to implanted electrodes (Haut, 2006; Zijlmans et al., 2009). Future studies focused on HFOs will be required to gain insight into the mechanisms responsible for long-term changes in HFOs dynamics.

Implemented method of sleep and wakefulness estimation from iEEG records is not optimal and must be also considered when interpreting result of the current study. Combination of EOG and EMG channels with iEEG may substantially increase the specificity of the PSG parameter to discriminate each brain states.

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