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Ultra-fast oscillation detection in EEG signal from deep-brain microelectrodes

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Abstract—**For the last decades, ripples 80-200Hz (R)and fast ripples 200-500Hz (FR) were intensively studied as biomarkers of the epileptogenic zone (EZ). Recently, Very fast ripples 500-1000Hz (VFR) and ultra-fast ripples 1000-2000Hz (UFR) recorded using standard clinical macro electrodes have been shown to be more specific for EZ. High-sampled microelectrode recordings can bring new insights into this phenomenon of high frequency, multiunit activity. Unfortunately, visual detection of such events is extremely time consuming and unreliable. Here we present a detector of ultra-fast oscillations (UFO, >1kHz). In an example of two patients, we detected 951 UFOs which were more frequent in epileptic (8.6/min) vs. non-epileptic hippocampus (1.3/min). Our detection method can serve as a tool for exploring extremely high frequency events from microelectrode recordings.**

Clinical Relevance—**Ultra-fast oscillations (>1kHz) were detected in epileptic hippocampus more frequently (8.6osc/min) than in non-epileptic hippocampus (1.3osc/min).**

I. Introduction

Intracranial electroencephalogram (iEEG) can be recorded with very high sampling frequency (>20kHz), however in clinical practice only frequencies lower than 100Hz are commonly analyzed. In the last two decades, high frequency oscillations (HFO) have been intensively studied as a promising biomarker of epileptogenic tissue [1–3]. Ripples 80-200Hz (R) and fast ripples 200-500Hz (FR) have been proven to be more frequent in epileptic tissue than in healthy brain [1–3]. In [4] very fast ripples 500-1000Hz (VFR) and ultra-fast ripples 1000-2000Hz (UFR) were shown to correlate with seizure onset zone (SOZ) in epileptic hippocampi proving there is clinically relevant information in higher and so far undescribed frequency bands.

High frequency events persist very shortly compared to the length of whole recording, what makes visual review of these events inefficient. Therefore, different automatic detectors of high frequency events recorded by macroelectrodes were developed [5–7]. Intracerebral macroelectrodes are clinical standard and a major source of iEEG signal for research purposes. These electrodes have an exposed conduct surface of approximately 4mm^2. Recorded local field potentials (LFP) are composed by summarized activity of many neuronal populations and the spatial resolution is limited [8]. Electrodes with microcontacts are utilized to overcome this limitation.

Surface areas of microcontacts are around 1000μm^2. Due to their small conductive area they have different electrical characteristics and record different electrophysiological phenomena [9–12]. This leads to three important differences between macro- and microcontacts. First, LFP recorded with microcontacts are created by a smaller number of neurons and can better explain HFOs and other phenomena observed in macroelectrode recordings. Second, larger surface of macroelectrode filters out the highest frequencies, therefore interictal phenomena like microseizures and microperiodic discharges could be detected only at the level of microelectrodes [13]. Finally, due to their different electrical characteristics, detectors of high frequency events that have been utilized for macroelectrode recordings need either different settings or fail completely when processing microelectrode recordings.

Even though the number of microelectrode recordings is rising, there is currently no detector of high frequency events designated for microelectrode recordings. Here we present an automatic detector of so far undescribed ultra-fast oscillations 1-8 kHz (UFO) recorded with microelectrodes. The detector was designed and tested on pilot data of two recordings from two patients, one non-epileptic hippocampus and one epileptic hippocampus which are detected, compared and evaluated.

II. Methods

A. Patients

We analyzed two patients (F, 49, M, 27) with drug resistant focal epilepsy who underwent pre-surgical evaluation using intracranial stereo EEG recordings (stereo-electroencephalography, SEEG). Along with clinical depth electrodes, each patient had one hybrid depth electrode combining standard macro and micro contacts. Both patients had seizure onset zone identified and resected with seizure free postoperative outcome. Hybrid electrodes were inserted into the epileptic hippocampus in Patient 1 and healthy hippocampus in Patient 2. EEG data were recorded in Brno Epilepsy Center, Czech Rep., E.U.

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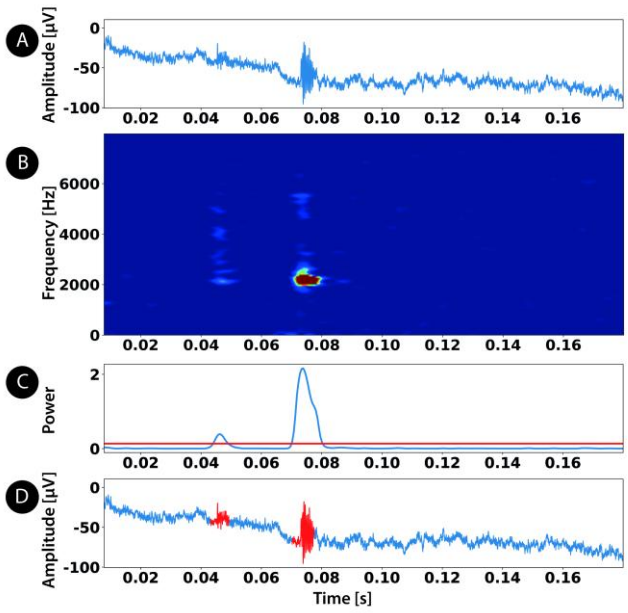

Figure 1. A) Original signal without any preprocessing. B) Spectrogram after median normalization. C) One dimensional detection signal (blue) and threshold (red) created from the 30s signal window. Y-axis has no unit because non-linear normalization was utilized in the previous step. D) Original signal with primary detections.

B. *Recordings*

The custom hybrid depth electrode (2069-ECP-8C6-35T06-2G-26, ALCIS, Besançon, France) was used in eachsubject. This electrode had eight macro contacts (each with surface area of 5.02 mm2) and six microcontacts positioned radially along the shaft (surface area of 1075 μm2) interspersed between 1., 2. and 3. macro contacts. Besides hybrid electrodes, standard intracranial depth electrodes (5, 10 and 15 contact semi-flexible multi-contact platinum electrodes (ALCIS, Besançon, France contact surface area 5.02 mm2 and inter-contact distance 1.5 mm) were used. Patient 1 was implanted with 14 macroelectrodes (142 contacts), Patient 2 with 13 macroelectrodes (140 contacts). Ground clamp served as a reference for microelectrodes, averaged signal from all macro contacts was used as a reference for macro contacts. All signals were recorded with sampling frequency of 25kHz. Recording lengths of Patient 1 and Patient 2 were 8.8 minute and 10.2 minute respectively.

C. *Detection method*

Detection was performed in a 30-sec sliding window. First, the spectrogram of the input signal was computed using fast fourier transform (FFT) with the FFT window of 0.015second with 97% overlap and detrending of the windowed signal. Resulted time-frequency (TF) map was normalized by deviding every row of the map by its median in 1-sec sliding window (Figure 1B). Rows corresponding to frequencies 1-8 kHz were used for further analysis other rows were deleted. Higher frequencies might include artefacts from the recording system and events from lower frequencies are out of the scope of this analysis. One dimensional detection signal was created by summing all rows of the filtered and frequency-bounded (1-8 kHz) spectrogram matrix (Figure 1C). 99 percentile (from 30second signal) multiplied by the factor of 5 was used as a threshold for peak detection in the one dimensional signal created from the spectrogram. UFOs manifest in detection signal as outliers and this heuristically chosen threshold proved to be suitable for their detection. Peak areas bounded by their inflex points were marked as high frequency activity (putative detection).

For every putative detection, spectral profile was created by summing all columns of detection related spectrogram. Every spectral profile was subsequently classified either as biological or noisy (Figure 2). Event was marked as biological if the ratio of maximum to mean of the spectral profile was greater than 10. Other profiles were marked as noise because there was no dominant frequency and could be considered as wide spread noise. Maximum to mean ratio served as the tuning parameter of the detector and was chosen heuristically. Lowering this number led to more detections, however their main frequency was less dominant. In some cases, the UFOs were detected simultaneously in more than three microcontacts at the same time. We declared these detections artefacts because there is a risk these oscillations are caused by electrode movement.

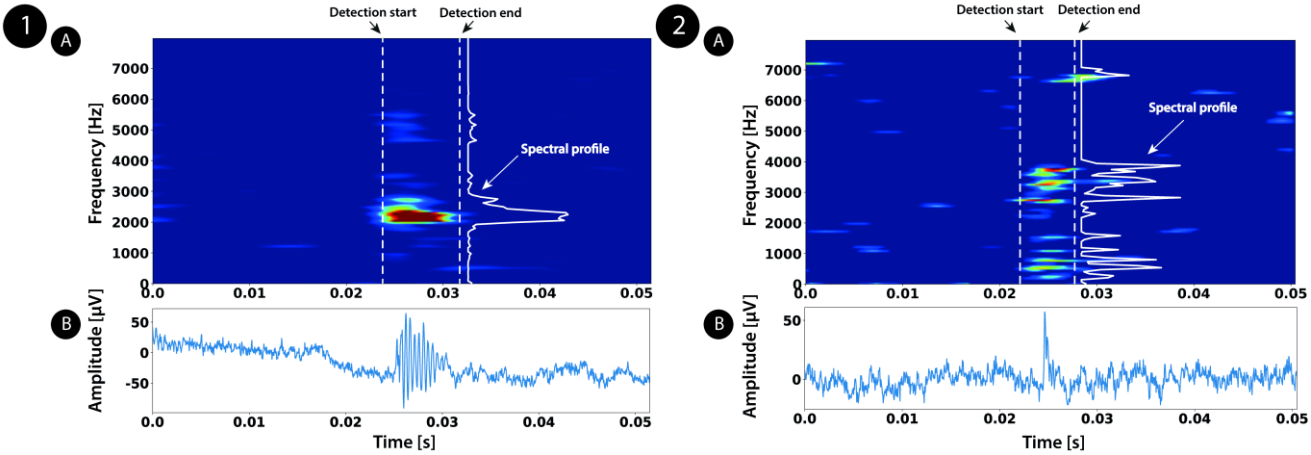

Figure 2. Panel 1 shows oscillation which contains dominant frequency, panel 2 shows oscillation without dominant frequency which is removed by the detector. A) The time-frequency map and the spectral profile. B) Corresponding raw signal

III. Results

Using the described method we detected 817 oscillations in Patient 1 and 134 oscillations in Patient 2. There was no UFO detected in any of the macroelectrodes. 51 putative detections occurred in macroelectrodes in Patient 2, however they were subsequently discarded for the lack of dominant frequency. There was no putative detection on any macroelectrode in Patient 1. Complete spatial and frequency distribution is presented in Table 1. Even though we focused on frequencies up to 8 kHz, we detected no oscillation with dominant frequency >6 kHz.

There are two consecutive steps that prevent claiming artefact for oscillation. The first, deleting oscillations which have no dominant frequency, removed 31.7% and 46.8% of putative detections in Patient 1 and Patient 2 respectively. Remaining oscillations were passed to the second step of removing simultaneous detections in more than half of contacts on the electrode. This way was removed 13.7% of oscillations in Patient 1 and no oscillation in Patient 2

While UFOs in epileptic hippocampus occurred up to 4 kHz with rate greater than 7 oscillations per minute, no rate greater than 1.6 oscillations per minute was detected in non-epileptic hippocampus.Exact rates in every frequency band are in Table 1. Spatial distribution of UFO detections differs between epileptic and non-epileptic hippocampus as well. Figure 3 shows dense UFO distribution in one contact spanning across all frequency bands in epileptic hippocampus but sparse, randomly distributed detections which do not persist in higher frequencies in non-epileptic hippocampus.

IV. Discussion

A. Physiology vs. artefacts

In [12] the authors showed that patient movement can produce signal oscillations which can be misinterpreted as HFO. Considering the parameters of their research, we claim that electrode movement generates parasitic oscillations in all contacts simultaneously. Our method includes step of removing simultaneous detections on more than half of the electrode contacts. This way we consider this phenomena compensated.

B. Detector

HFO detectors are commonly based on narrow band filtration without considering underlining aperiodic background 1/f, which is a natural part of every EEG signal. Rise in narrow band power is often considered for an oscillation even though it can be caused by shift of aperiodic slope (1/f component) or broadband offset [13]. Analogically, real oscillations can be masked by dominating lower frequencies. Article [16] suggests either prewhitening data in time domain or normalizing the TF map. By using nonlinear median normalization of TF map and choosing only oscillations with one dominant peak we compensated the problem of misjudging changes in background power for an oscillatory event or loosing oscillations masked by lower frequencies.

Table 1 UFO rates [oscillations per minute] in epileptic and non-epileptic hipocampi. While in non-epileptic hippocampus, UFOs above 2kHz can be observed very sparsely, in epileptic hippocampus with frequencies 3-4kHz are present with rate >7 oscillations per minute. Rates >2 are highlighted.

		Fequency				
	Contact	1-2kHz	2-3kHz	3-4kHz	4-5kHz	5-6kHz
Patient 1 Epileptic hippocampus	1	12.9	4.2	7.2	0	0
	2	0	0	0	0	0
	3	14.7	0	0	0	0
	4	0	0	0	0	0
	5	12.4	0	0.2	0	0
	6	0	0	0	0	0
Patient 2 Non-epileptic hippocampus	1	1.2	0	0.3	0.2	0
	2	0.8	0.2	0	0	0
	3	1.1	0.4	0	0.1	0
	4	0	1.6	0	0	0
	5	0.5	0.2	0	0	0
	6	0.6	0.3	0	0	0.1

C. Microelectrodes

Even though both macroelectrodes and microelectrodes were sampled at the same sampling frequency and number of macrocontacts exceeded the number of microcontacts more than 20 times, there was no UFO detected in any macrocontact. This fact implies that microrecordings can bring a new outlook on iEEG not only due to its better spatial resolution but also because of their better sensitivity to higher frequencies.

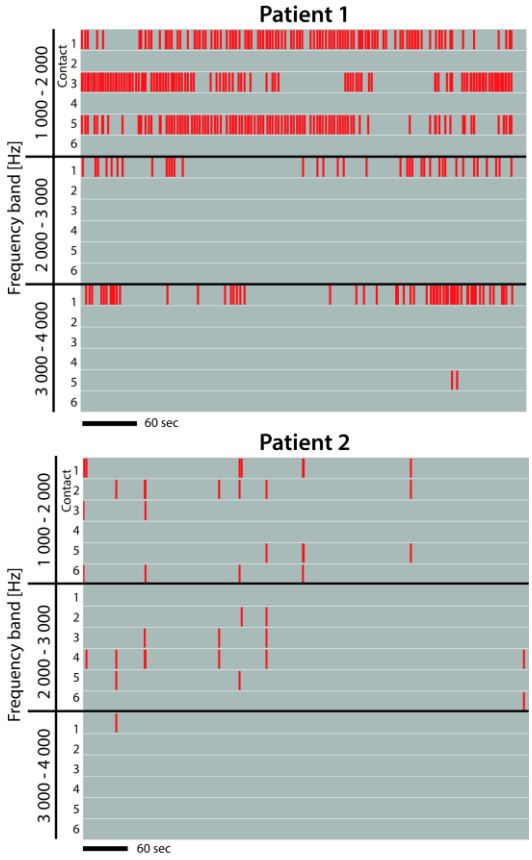

Figure 3.Distribution of individual detections in both frequency and time domains for every microcontact. While Patient 1 shows persisting detections in contact number 1 in frequencies 1-4kHz, distribution of detections in Patient 2 seems random in time and decreasing with growing frequency.

V. Conclusion

We designed a detector which is capable of detecting extremely high frequency oscillations (>1kHz) in iEEG microelectrode recordings. These oscillations have so far no clinical interpretation in neurology, however article [4] showed, that oscillations above 1kHz detect seizure generating tissue better than standard HFO.

The mean rate of UHFO detected by our algorithm was in the epileptic hippocampus one order of magnitude higher compared to the non-epileptic hippocampus. Even though this statement is concordant with results from other studies which analyzed HFO on lower frequencies, we cannot generalize this result because there are too few patients in our study.

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