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Automatic detection of high frequency oscillations during epilepsy surgery predicts seizure outcome

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HIGHLIGHTS

- We developed a fully automatic detector for intra-operative high frequency oscillations.
- The detector's parameters were validated on a large set of intraoperative electrocorticograms.
- The detector provides a standardized definition of clinically relevant HFO.

ABSTRACT

Objective: High frequency oscillations (HFOs) and in particular fast ripples (FRs) in the post-resection electrocorticogram (ECoG) have recently been shown to be highly specific predictors of outcome of epilepsy surgery. FR visual marking is time consuming and prone to observer bias. We validate here a fully automatic HFO detector against seizure outcome.
Methods: Pre-resection ECoG dataset ($N = 14$ patients) with visually marked HFOs were used to optimize the detector's parameters in the time–frequency domain. The optimized detector was then applied on a larger post-resection ECoG dataset ($N = 54$) and the output was compared with visual markings and seizure outcome. The analysis was conducted separately for ripples (80–250 Hz) and FRs (250–500 Hz).
Results: Channel-wise comparison showed a high association between automatic detection and visual marking ($p < 0.001$ for both FRs and ripples). Automatically detected FRs were predictive of clinical outcome with positive predictive value PPV = 100% and negative predictive value NPV = 62%, while for ripples PPV = 43% and NPV = 100%.
Conclusions: Our automatic and fully unsupervised detection of HFO events matched the expert observer's performance in both event selection and outcome prediction.
Significance: The detector provides a standardized definition of clinically relevant HFOs, which may spread its use in clinical application.

1. Introduction

In recent years, interictal high frequency oscillations (HFOs, >80 Hz) recorded in epileptic brains have been shown to be a reliable biomarker for the identification of the epileptogenic zone (Jacobs et al., 2012; Zijlmans et al., 2012b; Fernandez and Loddenkemper, 2013). HFOs are classified according to their spectral range in ripples (80–250 Hz) and fast ripples (FR, 250–500 Hz) (Bragin et al., 2010). FR in the intraoperative electrocorticography (ECoG) have been proposed as a predictor of clinical outcome (Wu et al., 2010; van 't Klooster et al., 2015b). Both studies provide examples of surgical cases where incomplete resection of electrode locations with HFOs resulted in recurrent seizures. Wu et al. (2010) recorded intraoperatively before resection while van 't Klooster et al. (2015b) recorded intraoperatively after resection.

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To date, the identification of HFOs is mainly performed by visual marking or semi-supervised detection (Urrestarazu et al., 2007; Zijlmans et al., 2009; Jacobs et al., 2010; Zelmann et al., 2010). Automatic detection of HFOs in general, and FRs in particular, suffers from an ensemble of detectability issues, such as the low signal-to-noise ratio and the noisy intraoperative environment. In order to implement the clinical use of HFOs, their value has yet to be confirmed in prospective fashion. The first small clinical trial ($N = 78$), testing non-inferiority of HFOs compared to interictal spikes during surgery, is currently being run (van 't Klooster et al., 2015a). Evidence for superiority of HFOs over spikes requires an international clinical trial with large numbers of patients, which will need fast, unsupervised and reliable automatic detection of HFOs. Besides reducing the observers' workload, automatic detection would provide a standardized procedure and definition of clinically relevant HFOs.

Several automatic HFO detectors have been developed by different research groups (Staba et al., 2002; Gardner et al., 2007; Worrell et al., 2008; Blanco et al., 2010; Zelmann et al., 2010; Dümpelmann et al., 2012; Birot et al., 2013; López-Cuevas et al., 2013; Burnos et al., 2014, 2016). The general implementation follows a two-stage procedure: a first step aims to identify a reliable threshold that is used to isolate events of interest (EoI), and a second step recognizing HFOs from spurious EoI, e.g. spikes or artifacts, on the basis of a mathematical definition of HFO. The time–frequency representation appears to be a promising approach to distinguish valid HFOs among EoI, both to detect visually marked events (wavelet transform, (Birot et al., 2013)) and to predict clinical outcome (Stockwell transform (Burnos et al., 2014)).

We improved on a previously described detector (Burnos et al., 2014) and added a third stage rejecting artifacts occurring synchronously in several channels. The detector, targeting HFOs in intraoperative ECoG recordings, was calibrated on a first dataset of pre-resection recordings with visually marked HFOs (dataset 1, (Zweiphenning et al., 2016)). After calibration, the detector was applied on a second dataset of post-resection recordings and its output was compared with visual HFO markings and patient's clinical outcome (dataset 2, van 't Klooster et al. (2015b)). We here evaluate the performance of this completely automatized tool for intraoperative HFO detection, and describe the predictive power of automatically detected post-resection ripples and FRs with respect to seizure outcome.

2. Methods

2.1. Datasets and set-up

We used two datasets of patients with refractory epilepsy who underwent surgery with intraoperative ECoG (sampling rate 2048 Hz) at the University Medical Center Utrecht (UMCU) between 2008 and 2012. These datasets were collected conform the guidelines of the institutional ethical committee of the UMCU.

Dataset 1 consisted of 28 intraoperative pre-resection one minute recordings from 14 patients, two recordings from each patient (Zweiphenning et al., 2016). The first minute will be called training set and the second minute test set. Dataset 2 consisted of one minute of intraoperative post-resection recordings from 54 patients in which resection sites and clinical outcome had been carefully documented (van 't Klooster et al., 2015b). The post-resection recordings of the 14 patients with pre-resection recordings in dataset 1 were included in dataset 2.

ECoG was collected using 4×5 or 4×8 electrode grids and 1×6 or 1×8 electrode strips (Ad-Tech, Racine, WI) placed directly on the cortex. Platinum electrodes with 4.2 mm^2 contact surface, embedded in silicone, and 1 cm inter-electrode distances were used. Recordings were made with a 64-channel EEG system (MicroMed, Veneto, Italy) at 2048 Hz sampling rate with an anti-aliasing filter at 538 Hz. Data were analyzed in a bipolar montage along the length of the grid. General anesthesia was induced and maintained using a propofol infusion pump. Propofol was tapered during ECoG registration until a continuous ECoG background pattern was achieved.

The patients were interviewed in the clinic (UMCU or elsewhere) at the regular follow-up intervals. Postsurgical seizure outcome was classified according to Engel's score, dichotomized into good (Engel 1) and poor (Engel $\geqslant 2$) outcome. Follow-up was >1 year.

2.2. Visual analysis

As stated in the previous publication (van 't Klooster et al., 2015a,b), visual marking of HFO was performed semi-automatically by validating the HFOs identified by the Montreal Neurological Institute detector (MNI detector, Zelmann et al., 2010) adapted for intraoperative ECoG (van Klink et al., 2014). HFOs were detected if the energy of the signal was larger than baseline during a certain period with a minimum of 4 oscillations. The MNI detector has a high false positive rate, which requires visual validation.

Data were visually inspected in Stellate Harmonie Reviewer (v7.0, Montreal, QC, Canada). ECoG was high-pass filtered using a finite impulse response (FIR) filter >80 Hz for ripples and >250 Hz for FRs. Split screen allowed to simultaneously visualize ripples (gain 5 μV/mm) and FRs (gain 1 μV/mm) with time interval of 0.4 s/page (Jacobs et al., 2010). Events were visually discarded if it did not fit with the requirements of having at least four oscillations and clearly standing out from the baseline or if it was an artefact.

In dataset 1 (pre-resection recordings, $N = 14$ patients) the visual marking was performed in consensus by two reviewers. For dataset 2 (post-resection recordings, $N = 54$ patients), the procedure has been described in detail in (van 't Klooster et al., 2015a, b). The two expert observers were not independent in their visual marking but reached consensus for each event already during the marking process with a 100% agreement.

2.3. Automatic detection

The automatic detector consists of three stages, which are described in detail below. The analysis was conducted separately for ripples (80–250 Hz) and FRs (250–500 Hz). The signal was filtered for the ripple and FR frequency bands by a FIR equiripple filter. For the ripple range filter parameters were set to band-pass 80–240 Hz, with a stopband of 70 Hz and 250 Hz. For the FR range the band-pass filter was set at 250–490 Hz, with a stopband of 240 Hz and 500 Hz. In both cases the stopband attenuation was set to 60 dB.

2.3.1. Stage I: baseline detection

We defined as baseline those segments of artifact-free ECoG without oscillations. The baseline was identified by time–frequency resolved entropy in the frequency band of interest, similarly to what was previously reported for wavelet entropy (Rosso et al., 2001; Zelmann et al., 2010). As entropy kernel, we introduced the Stockwell-transform (Stockwell et al., 1996). The maximum theoretical Stockwell entropy (SE_{max}) is obtained for white noise. Intervals with sufficiently high Stockwell entropy band, were considered good candidates for the baseline (i.e. no oscillation present). We defined the threshold for baseline entropy $BL_{thr} \times SE_{max}$, with BL_{thr} being the parameter setting the entropy threshold. The high entropy samples (entropy > $BL_{thr} \times SE_{max}$)