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A semi-automated method for rapid detection of ripple events on interictal voltage discharges in the scalp electroencephalogram

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HIGHLIGHTS

- Spike-ripple events, in which fast oscillations co-occur with voltage discharges, can be detected automatically in the scalp EEG.
- A combination of multiple quantitative features makes detection of spike-ripple events accurate.
- Rapid, quantitative identification of spike-ripple activity supports clinical application in epilepsy.

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ABSTRACT

Background: High frequency oscillations are emerging as a clinically important indicator of epileptic networks. However, manual detection of these high frequency oscillations is difficult, time consuming, and subjective, especially in the scalp EEG, thus hindering further clinical exploration and application. Semi-automated detection methods augment manual detection by reducing inspection to a subset of time intervals. We propose a new method to detect high frequency oscillations that co-occur with interictal epileptiform discharges.
New method: The new method proceeds in two steps. The first step identifies candidate time intervals during which high frequency activity is increased. The second step computes a set of seven features for each candidate interval. These features require that the candidate event contain a high frequency oscillation approximately sinusoidal in shape, with at least three cycles, that co-occurs with a large amplitude discharge. Candidate events that satisfy these features are stored for validation through visual analysis.
Results: We evaluate the detector performance in simulation and on ten examples of scalp EEG data, and show that the proposed method successfully detects spike-ripple events, with high positive predictive value, low false positive rate, and high intra-rater reliability.
Comparison with existing method: The proposed method is less sensitive than the existing method of visual inspection, but much faster and much more reliable.
Conclusions: Accurate and rapid detection of high frequency activity increases the clinical viability of this rhythmic biomarker of epilepsy. The proposed spike-ripple detector rapidly identifies candidate spike-ripple events, thus making clinical analysis of prolonged, multielectrode scalp EEG recordings tractable.

1. Introduction

Brief bursts of high frequency oscillations (80–600 Hz) have been implicated as promising biomarkers for epileptic networks (Traub and Jefferys, 1994; Traub et al., 1996; Traub et al., 2001; Bragin et al., 1999; Worrell and Gotman, 2011). Many groups have reported ripple (80–200 Hz) and fast ripple (>200 Hz) activity in

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human intracranial electrode recordings and have shown that both of these high frequency oscillations localize to the seizure onset zone (Bragin et al., 1999; Worrell et al., 2008; Worrell et al., 2004; Jirsch et al., 2006; Jacobs et al., 2009; Wu et al., 2010), correlate with seizure occurrence (Zijlmans et al., 2009), and with a lower threshold for after-discharges after electrical stimulation (Jacobs et al., 2010). Although activity in the fast ripple frequency band is generated by cortical regions that are too small to generate useful scalp EEG signals (Tao et al., 2007; Andrade-Valenca et al., 2011), ripples have been successfully detected in non-invasive scalp electroencephalogram (EEG) recordings, dramatically increasing the clinical relevance and potential of these biomarkers to include non-surgical patient populations. Ripples have been identified in the scalp EEG from children with electrical status epilepticus of sleep (Kobayashi et al., 2010); epileptic spasms (Kobayashi et al., 2004; Inoue et al., 2008) and focal epilepsy (Andrade-Valenca et al., 2011; Kobayashi et al., 2010; Andrade-Valença et al., 2012; van Klink et al., 2016). Similar to reports from invasive recordings, ripple activity in non-invasive EEG colocalizes with the seizure onset zone (Andrade-Valenca et al., 2011; Andrade-Valença et al., 2012) and correlates with severity of disease (van Klink et al., 2016).

Despite the promise that ripples hold for improved identification, localization, and tracking of the disease course in epilepsy, several challenges have impeded more aggressive application of these biomarkers in clinical epilepsy. First, it is difficult to separate pathologic from non-pathologic high frequency oscillations. Prior studies evaluating high frequency oscillations in scalp EEG have predominantly reported events in the ripple frequency range (Kobayashi et al., 2010; Kobayashi et al., 2004; Inoue et al., 2008; Andrade-Valenca et al., 2011). However, ripples have been observed in both epileptic and non-epileptic cortex (Bragin et al., 1999; Axmacher et al., 2008; Engel et al., 2009; Buzsaki and Lopes da Silva, 2012) and invasive recordings have shown that oscillations in the ripple band may not be as specific for epileptic cortex as fast ripples (>250 Hz; Bragin et al., 1999; Staba et al., 2004; Staba et al., 2007).

Second, identification of high frequency oscillations on scalp EEG is manually laborious, limiting the size of the datasets that can be screened. Because these events are brief (50–150 ms) and have low amplitude, review of 10 min of data from a limited number of electrodes can take an expert reviewer up to 15 h (Jacobs et al., 2009). Although several automated detectors have been developed for intracranial recordings (Zelmann et al., 2012; Blanco et al., 2010; Gardner et al., 2007) non-invasive recordings introduce more artifacts, which result in significantly more false positive events (Von Ellenrieder et al., 2012), thereby limiting the practical application of this tool to smaller datasets. A more selective detector of ripple events would facilitate investigation of larger datasets, enabling a better understanding of how fast oscillations track with and contribute to disease and normal physiology.

Both intracranial and non-invasive recordings have demonstrated that the majority of ripple and fast ripple events in epileptiform cortex co-occur with interictal epileptiform discharges or "spikes" (Urrestarazu et al., 2007; Von Ellenrieder et al., 2012; Jacobs et al., 2009; van Klink et al., 2016). Population based studies have demonstrated that interictal spikes are highly specific for epilepsy, present in only 0.5–2.4% of the general population (Eeg-Olofsson et al., 1971; Bennett, 1967; Gregory et al., 1993). Here we propose to detect the co-occurrence of ripples and spikes in the scalp EEG using a semi-automated spike-ripple detector. This approach leverages the well-characterized signal features of ripples with the specificity of the interictal spike to improve the efficiency of identification and quantification of ripples in non-invasive scalp EEG recordings. We show that the spike-ripple detector performs well in simulations and human non-invasive EEG data from ten patients with benign epilepsy with centrotemporal spikes. Compared to the standard manual detection method, the proposed semi-automated procedure for spike-ripple detection has a high positive predictive value and low false positive rate.

2. Methods

2.1. Implementation of the spike-ripple detector

Implementation of the spike-ripple detector proceeds in two steps. We first provide a qualitative outline of these steps, shown schematically in Fig. 1. We then describe each step in detail. The spike-ripple detector is available for application and further development at https://github.com/Mark-Kramer/Spike-Ripple-Detector-Method. The first step is to identify candidate ripple events by bandpass filtering the data between 100 and 300 Hz (see Step 1 below), computing the amplitude envelope, and finding times where this envelope is large (*i.e.*, times where the envelope is in the top 15% of all envelope values observed in the data) and remains large for more than 20 ms. The second step is to identify candidate spike-ripple events. To do so, we compute six features for each candidate ripple event. These features capture the existing notions of a regular and persistent high frequency oscillation initiating on the ascent of an interictal spike (Zelmann et al., 2009; Zijlmans et al., 2009; Von Ellenrieder et al., 2012; van Klink et al., 2016).

Candidate spike-ripple events are subsequently validated through visual inspection. This visual inspection consists of the following display elements near the candidate spike-ripple event: (1) the unfiltered EEG data, (2) the bandpass filtered data (bandpass 100–300 Hz, see Step 1 below), and (3) the spectrogram. These visualizations are common for the manual detection or validation of ripple events (van Klink et al., 2016; Kobayashi et al., 2010; Bénar et al., 2010; Crépon et al., 2010).

Step 1: Select candidate ripple events. We first bandpass filter the data for the chosen channel. The bandpass filter is an equiripple FIR filter of order 170, with pass-band from 100 to 300 Hz (pass-band ripple 0.1 dB), a frequency of the first stop-band of 60 Hz (stop-band attenuation 80 dB), and a frequency of the second stop-band of 350 Hz (stop-band attenuation 40 dB). We choose the wide (40 Hz) frequency interval between the edges of the first stop-band and first pass-band to reduce the filter order; a lower filter order reduces the impact of artifacts created by sudden, large changes in voltage. The choice of the first stop-band is determined by the frequency of electrical noise (60 Hz). We note that the filter attenuates activity at 80 Hz by only 10 dB, so that events at this frequency pass through the filter with moderate attenuation. We also include frequencies up to 300 Hz in the pass-band; this is consistent with visual inspection of the spike-ripple events, in which the activity is only high-pass filtered (van Klink et al., 2016). We then construct the analytic signal by applying the Hilbert transform to the filtered data, and compute the amplitude envelope. We select an *envelope threshold* as the value of the amplitude envelope greater than a percentage of the amplitude envelope values computed for the entire data set. In this way, the distribution of all observed amplitude envelope values for the channel is used to define the envelope threshold. We show in Results that an envelope threshold of 85% is a reasonable choice. Next, we find all time points at which the amplitude envelope exceeds the envelope threshold; if two of these time points are separated by less than 5 ms, all values between these time points are declared above the envelope threshold. The purpose of this last operation is to increase the robustness of the detections to noisy perturbations during which the amplitude envelope briefly falls below the envelope threshold. Finally, we identify all time intervals of at least 20 ms during which the amplitude envelope exceeds the envelope threshold. These inter-