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Bilateral preictal signature of phase-amplitude coupling in canine epilepsy

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ABSTRACT

Seizure forecasting would improve the quality of life of patients with refractory epilepsy. Although early findings were optimistic, no single feature has been found capable of individually characterizing brain dynamics during transition to seizure. Cross-frequency phase amplitude coupling has been recently proposed as a precursor of seizure activity. This work evaluates the existence of a statistically significant difference in mean phase amplitude coupling distribution between the preictal and interictal states of seizures in dogs with bilaterally implanted intracranial electrodes. Results show a statistically significant change ($p < 0.05$) of phase amplitude coupling during the preictal phase. This change is correlated with the position of implanted electrodes and is more significant within high-gamma frequency bands. These findings highlight the potential benefit of bilateral iEEG analysis and the feasibility of seizure forecasting based on slow modulation of high frequency amplitude.

1. Introduction

Epilepsy is one of the most common neurological disorders affecting people of all ages. According to the World Health Organization (WHO), around 50 million people in the world are diagnosed with epilepsy. In about 60% of the cases, seizures are controlled by medical therapy. Up to 5% of epileptic patients are candidates for brain surgery with a success rate of only 60%. The remaining 35% suffer from uncontrolled epilepsy and have seizures on an unpredictable basis. Closed-loop intervention systems based on seizure forecasting and detection have been proposed as an attempt to control seizures in patients with refractory epilepsy (Mormann et al., 2007).

Although more favorable performances are reported with seizure detection in comparison to seizure prediction, the latter ensures more time for intervention in chronic implantable devices. Seizure detection aims to raise alarms or trigger interventions after the seizure has started. However, an already spreading seizure is difficult to abort, and will generally evolve into a clinically significant seizure. Although much effort has been put towards identifying a unique precursor of seizure activity, no single feature has been found capable of individually characterizing brain dynamics during transition to the ictal state (Bou Assi et al., 2017; Mormann et al., 2007). Spectral band power is the most commonly used feature in seizure prediction and aims to display amplitude modulations within defined frequency bands over time. While this feature can quantify phase changes, it fails in identifying interactions between different frequencies. Cross-Frequency Coupling (CFC) among different frequency bands has been proposed to be the carrier mechanism for relationships of local and global neuronal processes (Jirsa and Muller, 2013). Recent intracranial electroencephalography (iEEG) based investigations found a modulation of cortical high-frequency oscillations in the gamma band (40–120 Hz) by slow cortical potentials. As emphasized in Alvarado-Rojas et al. (2014), low-frequency oscillations seem to trigger high-frequency oscillations. Edakawa et al. (2016) showed a significant increase in Phase-Amplitude Coupling (PAC) during the ictal state. Several studies have demonstrated that PAC between high-frequency amplitude and slow wave's phases is a gradual phenomenon that can start hours prior to a seizure (Alvarado-Rojas et al., 2014; Jiruska et al., 2010; Khosravani et al., 2009). Alvarado-Rojas et al. (2014) explored the coupling between the phase of slow oscillations (slow wave and theta) and amplitude of different sub-bands of gamma rhythm as a precursor of seizure activity. Interestingly, promising seizure forecasting capabilities were reported overcoming traditional band power features in a quasi-prospective setting. However, signals were acquired using electrodes implanted in focal areas as guided by a prior non-invasive presurgical evaluation. Recently, iEEG recordings were acquired from dogs with naturally occurring epilepsy using the NeuroVista ambulatory monitoring device (Davis et al., 2011). Although dogs were diagnosed with focal epilepsy,

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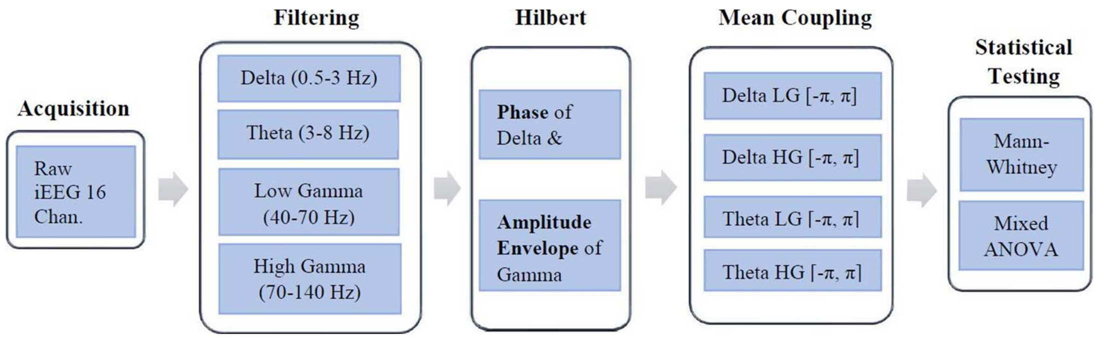

Fig. 1. Block diagram of PAC extraction algorithm. Acquisition, filtering, Hilbert Transform and mean coupling phase were executed sequentially for each channel with 5-s windows and execution for 16 channels was parallelized on a 16-core computer.

16 electrodes were implanted bilaterally (over both hemispheres) using a standardized protocol (Davis et al., 2011). The promising results obtained when analyzing electrodes in the focal seizure onset zone lead our team to hypothesize that preictal PAC change may be significant in remote regions of the brain as well as in the seizure onset zone (SOZ). Canine epilepsy has been demonstrated to be a suitable model for human epilepsy (Potschka et al., 2013) with similar clinical representation, epidemiology (Pellegrino, 2004; Berendt et al., 1999), therapeutic response and physiology (Chandler, 2006). In this work, we investigated the localization of PAC changes in bilateral iEEG recordings and whether this promising characteristic can be used as a feature capable of identifying the preictal state in a seizure forecasting algorithm. Adequate statistical testing is performed to assess if there is a statistically significant difference of PAC between preictal and interictal periods. Furthermore, whether these changes correlate with frequency bands or with channel localization was investigated. The main aim of the study was to assess the feasibility of seizure forecasting based on cross-frequency PAC and discuss the importance of bilateral recordings in the analysis of preictal activity.

2. Materials and methods

2.1. Database

Mean coupling phases during preictal and interictal periods were extracted from continuous iEEG recordings acquired in mixed hounds with naturally occurring temporal focal epilepsy. One objective of the study was to analyze the magnitude and consistency of the preictal PAC change in both hemispheres of the brain. Therefore, a database which has a large seizure to patient ratio was favored. The recordings were obtained from the NIH-sponsored International Electrophysiology portal (https://www.ieeg.org/). Dogs were implanted with the NeuroVista ambulatory monitoring system and recordings were acquired at 400 Hz from 4-contact electrode strips implanted bilaterally on both hemispheres of the brain as described by Davis et al. (2011). Although recent studies have demonstrated a gradual transition between interictal and ictal states (defined as the preictal state), no preictal time has been defined as a gold standard for seizure prediction (Bou Assi et al., 2017). For each seizure, one hour of continuous recording, with a 5-min intervention time prior to the start of the ictal phase, was used as the preictal state. This preictal period choice was in consensus with that adopted by the American Epilepsy Society Seizure Prediction Challenge. Interictal data was randomly selected from the record to balance preictal data. Each interictal hour was selected outside a 24-h restriction before or after a seizure. The procedure for data acquisition and distribution had prior approval of the University of Minnesota Institutional Animal Care and Use Committee where the animals are maintained.

2.2. PAC extraction

Cross-frequency coupling, as described by Alvarado-Rojas et al. (2014), is a statistical measure of the interaction between different-frequency bands of a single-channel recording. More precisely, the modulation of high-frequency signals by low-frequency signals was measured by comparing the amplitude of fast wave oscillations to the phase of slow oscillations of the iEEG signals. A statistically significant increase in this interaction has been observed during the ictal period of seizures and has proven successful in seizure detection (Edakawa et al., 2016). This feature is extracted from continuous recordings which are segmented into windows. Sequential, 5-s long, non-overlapping windows were used to extract the average coupling phase in this study.

The moment of maximum high-frequency amplitude corresponds to the average coupling phase of the window. Similar to previous investigations (Alvarado-Rojas et al., 2014; Edakawa et al., 2016; Amiri et al., 2016), we have evaluated the coupling between the phase of delta (0.5–3 Hz) or theta (3–8 Hz) frequency bands and the amplitude envelope of low gamma (LG: 40–70 Hz) or high gamma (HG: 70–140 Hz) oscillations. We extracted the cross-frequency coupling using an algorithm similar to that proposed by Tort et al. (2010). This algorithm is summarized in a block-diagram scheme (Fig. 1). First, raw signals were filtered to isolate the frequency bands of interest using an 8th order band-pass Butterworth filter. A Hilbert transform was applied to the filtered signals to isolate the phase of low frequencies and the amplitude envelope of high frequencies. The range of phase signal, with values located between $-\pi$ and π, was divided into bins φ_i (40 bins). Then time indexes K_i when the phase fell in the interval $\varphi_i < \varphi_x(k_i) < \varphi_{i+1}$ were quantified. For each bin, amplitudes at time K_i of the high frequency time series were averaged. The distribution of mean amplitude as function of phases was then assessed and quantified by approximating the distribution to a Von Mises function, which is a circular Gaussian function (Alvarado-Rojas et al., 2014). Finally, preferred coupling phase was evaluated by extracting amplitude-phase distribution's mean phase. The algorithm extracted coupling phase using a non- overlapping 5 s window. Filtering and feature extraction were done on Matlab. The algorithm was first tested and validated on synthetic signals.

2.3. Validation of PAC extraction algorithm

To validate the precision of the algorithm, it was tested on a synthetic wave-based signal in which we imposed a constant coupling phase of π. The synthetic signal, shown in Fig. 2(a, b), is composed of two pure-cosine waves. The slow wave, of frequency 2.5 Hz, modulates the amplitude envelope of the fast wave, which has a frequency of 50 Hz. More precisely, the amplitude envelope of the fast oscillations reaches its maximum value when the phase angle of the slow oscillations is equal to π as depicted in Fig. 2(b). The results from running the cross-frequency coupling algorithm of the synthetic signal show a mean