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Influence of paroxysmal activity on background synchronization in epileptic recordings

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HIGHLIGHTS

- Synchronization analysis is commonly used to assess whether interaction exists between neurophysiological recordings.
- Simultaneous presence of interictal epileptiform discharges can affect the results of synchronization measurements.
- We quantify how IED synchronization contaminates background synchronization in typical neurophysiological techniques.

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ABSTRACT

Background: The presence of spikes and sharp waves in recordings of epileptic patients contaminates background signal synchronization. When estimating functional connectivity between extended cortical areas, the influence of epileptic spikes in specific areas should be considered; however, this step is sometimes overlooked. We present a simple method for quantifying the influence of epileptic activity on background signal synchronization.
Method: Standard synchronization measures were calculated for both pure correlated Gaussian signals and correlated Gaussian signals with different levels of epileptic spikes in order to determine the influence of epileptic activity on synchronization estimates.
Results: Synchronization from invasive epileptic recordings (e.g., depth electrodes) displays a much higher bias due to epileptic activity than superficial electrodes. Moreover, statistical methods such as mutual information are more affected by spike presence than phase synchronization methods. The influence of spikes is far greater at low values of background synchronization.
Conclusions: The information provided by this procedure makes it possible to differentiate true background synchronization from spike synchronization. Thus, our procedure serves as a guide for analyzing synchronization and functional connectivity calculations in epileptic recordings.

1. Introduction

The presence of interictal epileptiform discharges (IED) in neurophysiological recordings makes it possible to discriminate between epileptic and nonepileptic patients (Noachtar and Rémi, 2009). Accurate identification of IED requires the simultaneous occurrence of discharges in at least two neighboring contacts caused by the physiological field of the generator. However, co-occurrence of IED at distant electrodes in epileptic patients is typically classed as true synchronized activity between the pathophysiological structures involved, whether during the interictal period (Bourien et al., 2005) or preictal period (Spencer and Spencer, 1994).

These findings contrast with a more recent approach, which uses the full interictal background signal to assess synchronization (Mormann et al., 2000). Thus, the relationship between the interictal background signal and the IED content of the signal is a key issue that was first addressed in Bettus et al. (2008) and further explored in Ortega et al. (2010).

We discuss how and to what extent the presence of IED influences signal synchronization in typical neurophysiological recordings of epileptic patients.

Abbreviations: IED, interictal epileptiform discharges; EEG, electroencephalogram; ECoG, electrocorticography; FOE, foramen ovale electrodes; DE, depth electrodes; TLE, temporal lobe epilepsy; PS, phase synchronization; MI, mutual information; MoS, measure of synchronization; IoB, influence of IED over background activity.

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2. Methodology

Several neurophysiological techniques, including electroencephalography (EEG), foramen ovale electrodes (FOE), electrocorticography (ECoG), and depth electrodes (DE), are routinely used to lateralize/localize epileptogenic areas in patients with drug-resistant temporal lobe epilepsy (TLE). The identification of the epileptogenic zone is the major goal of the neurophysiologist. However, it is essential to associate this zone with other important areas, such as the ictal onset zone and the irritative zone, where IED actually occur. The duration of an IED (Walczak et al., 2008) on an EEG is <200 ms. Sharp waves have a duration of 70–200 ms, whereas the duration of spikes is <70 ms. Similar durations have been recorded using different techniques, although the number of IEDs varies largely from one technique to another. A typical scalp EEG has an average spike frequency of 1 spike/min (60 spikes/h), which can increase to 4 spikes/min or more (Janszky et al., 2003). In an ECoG recording, frequencies should be multiplied by 10 (Tao et al., 2005). Given that a typical spike lasts 70 ms at most, and a sharp wave 200 ms, we can estimate the "IED content" (i.e., the percentage of time that IED occupy in the background signal) by adopting a conservative approach in which we set the duration of IED at 200 ms or 0.2 s. In the case of EEG, a spike frequency of 4 spikes/min is equivalent to (0.2 s × 4 spikes)/60 s = 0.013 of "spike content" in the recording, i.e., an IED content of 1.3%. Using this same rationale for other neurophysiological methods, the maximum IED content in the background signal would be as follows:

- EEG: A maximum spike frequency (Janszky et al., 2003; Clemens et al., 2003) of 4 spikes/min yields an IED content of 1.3%, as described above.
- FOE: A maximum spike frequency (Clemens et al., 2003; Ortega et al., 2010) of 30 spikes/min yields an IED content of 10%.
- ECoG: A maximum spike frequency (Tao et al., 2005) of 40 spikes/min yields an IED content of 13.3%.
- DE: A maximum spike frequency (Bourien et al., 2005) of 100 spikes/min yields an IED content of 33%.

Fig. 1A shows a representative FOE recording from a patient with right TLE. Four recordings (two from the left side and two from the right side) show interictal activity from mesial temporal lobe structures. However, the activity from electrodes on the right contacts shows IED in at least four locations (rectangles). Calculation of synchronization between both right FOE contacts based on the Pearson correlation coefficient yields a value of 0.87. When IED activity is eliminated from recordings, the value of the correlation decreases to 0.80, thus reflecting the strong influence of high-amplitude IED on synchronization. Consequently, synchronization increases by almost 9% as a result of the presence of IED. The Pearson correlation between the left FOE contacts is 0.93.

To determine whether paroxysmal activity "contaminates" synchronization estimates, we implemented the following procedure. Two typical IED were extracted from a FOE recording and inserted into two correlated white Gaussian signals with a known correlation value to occupy a specific percentage of the recording time. Fig. 1B shows this construction. The third IED in the FOE recording of Fig. 1A was inserted three times in both simulated correlated Gaussian signals. In this particular case, the total IED activity occupied approximately 12% of the whole recording displayed, and the correlation between background Gaussian signals was 0.375. Although the IED in both channels were similar, they were not identical (some differed in amplitude, for example). However, the correlation between both IED was 0.92. When these IED were inserted into the correlated Gaussian signals, the correlation increased to 0.43, thus highlighting the contamination of IED synchronization over the background synchronization. The amplitude of the IED was approximately three times the standard deviation of the background Gaussian signals. Therefore, the presence of IED in the recordings modified signal synchronization at 0.375/0.43 = 0.83.

We explored this finding in more general terms. Specifically, we generated two stochastic signals with a bivariate normal distribution, a given mean value ($\mu = 0$ in every case), and a given covariance matrix. In the covariance matrix, we fixed the standard deviation σ of both signals at one and changed the correlation, ρ, between them so that $0 < \rho < 1$. Several programming packages (e.g., *R*) facilitate implementation of this procedure (Genz et al., 2011). Since IED must be clearly differentiated from background activity (Walczak et al., 2008), we varied the inserted IED amplitude in relation to the σ of the background signal. We refer to this ratio as A2S, that is:

$$\mathrm{A2S} = \frac{\mathrm{Amplitude(IED)}}{\sigma(\mathrm{background\ signal})} \tag{1}$$

Given that σ was set at one in each run, the relative amplitude of IED to the background signal, A2S, was always the absolute amplitude of the inserted IED.

The three values of A2S used were one, three and five. As shown in Fig. 1B, the correlation value ρ between the background signals was 0.375, and the A2S was approximately three. Because both IED have slightly different amplitudes (Fig. 1A), the IED with the lower amplitude was consistently used as the reference IED amplitude in Eq. (1).

Three frequently used methods were applied to assess synchronization (Pereda et al., 2005; Lehnertz et al., 2009; Ortega et al., 2010; Jiruska et al., 2013), namely, Pearson correlation, phase synchronization (PS), and mutual information (MI). We refer to these methods generically as measures of synchronization (MoS). In particular, PS was estimated using mean phase coherence (Mormann et al., 2000).

Finally, we generated two correlated Gaussian signals of 13,500 data points in length, with $\mu = 0$, $\sigma = 1$, and $0 < \rho < 1$. The synchronization between both signals was measured using Pearson correlation, PS, and MI. The procedure was repeated using signals containing different percentages of IED. The proportion of inserted IED increased from 0% (no IED) to 100% (300 IEDs).

3. Results

The influence of IED synchronization on background synchronization (IoB) can be quantified as follows:

$$\mathrm{IoB} = 1 - \frac{\mathrm{MoS(stoch, stoch)}}{\mathrm{MoS(stoch + IED, stoch + IED)}} \tag{2}$$

The presence of simultaneous IED in both signals increases the synchronization value, with the result that the denominator increases faster than the numerator in the second term, leaving the IoB close to one for the case of high influence of IED presence. In the example of the right contacts shown in Fig. 1A, IoB (Pearson) = 1 − (0.80/0.87) = 0.08.

Fig. 2A shows the IoB for each MoS (rows) and different values of A2S (columns). An IoB near zero (white) implies a slight influence of IED on the synchronization measured. This influence is clearly observed in the lower region of each panel, where the percentage of IED is low and, therefore, both measures are similar. In contrast, an IoB near one (red) implies that the MoS in the IED-contaminated signals are much higher than in the pure signals. In other words, regions of Fig. 2A with low IoB values (<0.5) represent "safer areas" in which to analyze synchronization between signals without contamination due to the presence of IED. The vertical dot-dashed line in Fig. 2A corresponds to a correlation value of $\rho = 0.5$ between the background signals. Horizontal solid, dotted, dot-dashed, and dashed lines correspond to EEG, FOE, ECoG, and DE maximum IED