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Differentiating epileptic from non-epileptic high frequency intracerebral EEG signals with measures of wavelet entropy

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HIGHLIGHTS

- Background activity in the ripple band is described by measures of wavelet entropy.
- A channel is more likely to be epileptic with high standard deviation of entropy.
- A model based on entropy measures can select a subset of the epileptic channels.

ABSTRACT

Objective: To assess whether there is a difference in the background activity in the ripple band (80–200 Hz) between epileptic and non-epileptic channels, and to assess whether this difference is sufficient for their reliable separation.
Methods: We calculated mean and standard deviation of wavelet entropy in 303 non-epileptic and 334 epileptic channels from 50 patients with intracerebral depth electrodes and used these measures as predictors in a multivariable logistic regression model. We assessed sensitivity, positive predictive value (PPV) and negative predictive value (NPV) based on a probability threshold corresponding to 90% specificity.
Results: The probability of a channel being epileptic increased with higher mean ($p = 0.004$) and particularly with higher standard deviation ($p < 0.0001$). The performance of the model was however not sufficient for fully classifying the channels. With a threshold corresponding to 90% specificity, sensitivity was 37%, PPV was 80%, and NPV was 56%.
Conclusions: A channel with a high standard deviation of entropy is likely to be epileptic; with a threshold corresponding to 90% specificity our model can reliably select a subset of epileptic channels.
Significance: Most studies have concentrated on brief ripple events. We showed that background activity in the ripple band also has some ability to discriminate epileptic channels.

1. Introduction

High frequency oscillations (HFOs) above 80 Hz are considered a biomarker for epilepsy (Bragin et al., 2010; Zijlmans et al., 2012; Staba et al., 2014). They can be defined as four or more oscillations that clearly stand out from the background EEG. HFOs are divided in ripples (80–250 Hz) and fast ripples (250–500 Hz) (Zijlmans et al., 2012; Staba et al., 2014). Although several studies show that ripples are biomarker for epilepsy, physiological ripples also exist and their distinction from 'epileptic' ripples is not simple (Bragin et al., 2010; Zijlmans et al., 2012; Staba et al., 2014).

HFOs can be marked visually or detected automatically. Both methods are based on comparison of amplitude of potential HFOs with amplitude of baseline activity. Visually marking HFOs is time consuming and can be challenging. The choice of what 'clearly stands out' is subjective. Automatic HFO detectors are less

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subjective because they use a predefined minimum difference between amplitude of events and background, but such methods often suffer from over detection (Zelmann et al., 2012; Burnos et al., 2016). Both visual and automatic detection become complicated in channels with continuous oscillatory activity (Zelmann et al., 2012).

The aim of this study was to determine if activity in the ripple band could also serve as a biomarker for epilepsy if, instead of analyzing short, isolated events that stand out from the background, we considered the whole signal. This signal must be considered independently of absolute amplitude, because amplitude is highly variable and not particularly meaningful in intracerebral recordings. We developed a method based on wavelet entropy, a quantitative measure of rhythmicity independent of amplitude (Melani et al., 2013) that indicates the degree of disorder of a signal (Rosso et al., 2001; Rosso, 2007). If all frequencies in the ripple band are present in equal amounts, entropy will be high; if there is one dominant frequency, entropy will be lower. After calculating entropy over several short epochs for each channel, we can calculate mean and standard deviation of entropy. The mean entropy is an indication of the overall rhythmicity of a signal, whereas the standard deviation can be used to distinguish channels with a changeable EEG pattern from channels with a signal that is stable with respect to rhythmicity. Entropy calculations take little time, so we can describe each channel with these two measures in a fast and objective way.

We addressed the following questions. (1) Is there a difference in the combination of mean entropy and standard deviation of entropy between epileptic and non-epileptic channels? (2) If there is such a difference, can a prediction model based on these measures correctly classify individual channels as epileptic or non-epileptic?

We hypothesize that epileptic channels have high standard deviation of entropy and intermediate mean entropy. We base this hypothesis on observations, made while visually marking ripples, that epileptic channels often seem to have a more changeable EEG than non-epileptic channels. Such a changeable signal may give rise to some epochs with higher and some with lower entropy and hence high standard deviation. We further hypothesize that non-epileptic channels have low mean and low standard deviation of entropy. Melani et al. (2013) and Kerber et al. (2014) describe channels with continuous high frequency activity and they consider this a physiologic (i.e., non-epileptic) phenomenon. Oscillations of a dominant frequency result in low entropy, and continuous oscillations result in the same low entropy for every epoch. Therefore, both mean and standard deviation of entropy of such channels will be low.

2. Methods

2.1. Patients

We retrospectively studied intracerebral EEG (iEEG) data from 50 patients with drug-resistant epilepsy. Patients underwent placement of depth electrodes at the Montreal Neurological Institute and Hospital, Montreal, Canada, between January 2010 and March 2015 for localization of the seizure focus and evaluation of surgical options. All patients gave written informed consent in agreement with the Research Ethics board of the Montreal Neurological Institute and Hospital.

2.2. iEEG

Patients were implanted with depth electrodes that were manufactured on site (nine contacts of 0.5–1 mm, distance between contacts 5 mm) or with commercially available electrodes (5–18 contacts of 2 mm, distance between contacts 1.5 mm, DIXI Medical, France). The iEEG was recorded with Stellate Harmonie (Stellate, Montreal, Canada). Low pass anti-alias filter at acquisition was 300 Hz for data sampled at 1000 Hz (47 patients) and at 500 Hz for data sampled at 2000 Hz (3 patients). We analyzed the iEEG signal in a bipolar montage of neighboring contacts. The spatial filtering effect of bipolar recordings is a desirable effect since it removes widespread aspects of the EEG, prominent in referential recordings, helping in the localization of spatially restricted phenomena, the purpose of this study.

2.3. Inclusion criteria for channels

Per depth electrode, we selected all bipolar channels based on the following inclusion criteria.

First, we selected channels that were classified as epileptic, i.e., located in seizure onset zone (SOZ) or exclusive irritative zone (EIZ), or non-epileptic. The channels were classified independently by two epileptologists. In case of ambiguous findings, a consensus was reached in a common scoring session. The SOZ was defined as the area showing the first unequivocal ictal iEEG change at seizure onset. The EIZ was defined as the area with interictal epileptic spikes outside the SOZ. A non-epileptic channel was defined as located outside the SOZ and EIZ, and not in a lesion visible on MRI. A channel that was located outside the SOZ and EIZ but inside a lesion did not fulfill the inclusion criteria for epileptic or non-epileptic channels and was therefore excluded. It is important to stress that a channel cannot be epileptic or non-epileptic; we use these terms to refer to the signals recorded by channels located in epileptic (SOZ and EIZ) or non-epileptic brain areas.

Second, we selected channels that were located in neocortex, hippocampus, cingulate gyrus, or amygdala. We included neocortical channels from frontal, parietal, insular, occipital and temporal lobes. Electrode locations were determined using either post-implantation CT co-registered with a pre-implantation MRI using SPM 8 software, post implantation MRI, or the neurosurgical plan with a 3D Neuronavigation system used during implantation of electrodes.

Third, we selected only the most medial and/or the most lateral intracerebral channel per electrode, to avoid analyzing overlapping signals. When the most medial and the most lateral channel fulfilled the first two inclusion criteria, we retained both if they were located in different brain structures. For example, for an electrode inserted through the temporal lobe, we selected the most medial channel, located in the hippocampus, and the most lateral channel, located in the temporal neocortex.

These inclusion criteria resulted in the selection of one or two channels per electrode. In total, 637 channels were selected.

2.4. Data selection

Patients undergoing iEEG at the Montreal Neurological Hospital and Institute are asked to perform a routine protocol consisting of simple tasks, such as opening and closing the eyes, fist clenching, and reading. For 44 patients, the analyzed EEG was recorded at the very beginning of the investigation when patients were still on their habitual dosages and before most seizures took place. For six patients, we used a recording made at the end of the implantation period instead, for the following reasons: two had seizures during the early recording and in four the early recording had technical problems or was too short. For all patients we verified that they were not in an immediate post-ictal state.

We analyzed the recording made while patients closed their eyes for about one minute. If this period lasted longer than one minute, we analyzed the first 60 s; this was the case for 44