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SHORT COMMUNICATION

Predictability analysis of absence seizures with permutation entropy

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Summary In this study, we investigate permutation entropy as a tool to predict the absence seizures of genetic absence epilepsy rats from Strasbourg (GAERS) by using EEG recordings. The results show that permutation entropy can track the dynamical changes of EEG data, so as to describe transient dynamics prior to the absence seizures. Experiments demonstrate that permutation entropy can successfully detect pre-seizure state in 169 out of 314 seizures from 28 rats and the average anticipation time of permutation entropy is around 4.9 s. These findings could shed new light on the mechanism of absence seizure. In comparison with results of sample entropy, permutation entropy is better able to predict absence seizures.

Introduction

Epilepsy affects about 50 million people worldwide; however, anti-epileptic drugs are ineffective for as many as one in three patients. Therefore, novel therapeutic approaches are urgently being sought to prevent seizure occurrence. Surgery and stimulation methods have recently gained greater prominence. Epileptic seizure prediction is a basis for these methods. Once epileptic seizures can be predicted on the basis of dynamic changes of EEG, an automated closed-loop seizure prevention system could be envisioned utilising electrical or other stimulation to reset the brain dynamic to prevent the development of the seizure (Theodore and Fisher, 2004; Morrell, 2006; Mormann et al., 2007). There is much evidence supporting the view that epileptic seizures can be predicted (Rogowski et al., 1981; Litt et al., 2001; Li et al., 2004).

Absence epilepsy is predominantly a disease of childhood. Absence seizures are short in duration, typically lasting from a few seconds up to around a minute, and may recur over 100 times a day. This may have significant impact on the educational development of sufferers. An absence seizure is a sudden and abrupt transient, but the prediction of this seizure by detectable dynamic changes in the EEG is still debated (Suffczynski et al., 2006). In this study, we investigate a new complex measure, permutation entropy (Bandt and Pompe, 2002), which is a natural measure of complexity for dynamical systems, used

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to track transient dynamics of EEG recordings. We will attempt to apply this method to analyze the predictability of absence seizures. The aim of this short paper is to confirm whether or not absence seizures have a pre-ictal state. This work is conducted on genetic absence epilepsy rats from Strasbourg (GAERS), which exhibit repeated spontaneous seizures, characterized by 5—8 Hz spike and wave discharges (SWD) on the EEG (Danober et al., 1998).

Materials and methods

Animal experiments and EEG recordings

All studies were performed on genetic absence epilepsy rats from Strasbourg of at least 13 weeks of age as, at this stage of development, all GAERS display the characteristic repeated SWD on the EEG (Danober et al., 1998). Only male GAERS were used (weight 318 ± 5 g, $n = 28$). All procedures were performed under a British Home Office project licence (UK Animals (Scientific Procedures) Act, 1986). GAERS were anaesthetised with medetomidine/ketamine (0.5 and 75 mg/kg i.p., respectively) for the duration of the surgery, with immediate post-operative reversal of the effects of medetomidine with atipamezole (1 mg/kg s.c.). In all animals, a bipolar twisted-wire EEG electrode (MS303/1; Semat Technical, St. Albans, UK) was implanted in the frontal cortex (mm, relative to bregma; AP, 2.2: L, 2.4: V, 2.6 from the dura mater). The headmounts were secured to two skull screws with dental cement (Duralay II), and the animals allowed to recover overnight with free access to water and rat diet. The following day, after connection of a cable to the EEG electrode, the animal was transferred to an EEG recording cage and left to acclimatise to this environment for at least 45 min. The signal from the EEG electrode was directly visualized on an oscilloscope and was further amplified (BioAmp ML 136), filtered, digitized (100 Hz) and stored using a PowerLab 2/20 running Chart v4.2 software (ADInstruments, Hastings, UK). Once regular SWD were being observed, 30 min of EEG was recorded from each animal. The EEG data sets were preprocessed by a 50 Hz notch filter and a high pass filter at 0.5 Hz.

Sample entropy and permutation entropy

Considering the chaotic and non-stationary nature of EEG data, an approximate entropy (ApEn) (e.g. Pincus et al., 1991) has been applied, instead of spectral entropy (Inouye et al., 1991), to measure the complexity of EEG series. The more regular the EEG is, the smaller the ApEn will be. The exact value of the ApEn(m,r,N) will depend on three parameters: N (number of samples), m (embedding dimension) and r (noise threshold). The ApEn specifies a noise threshold, and so may be better than spectral entropy in the quantification of complexity of EEG recording (Bruhn et al., 2000, 2001). The disadvantage of ApEn is that it is heavily dependent on the record length, and is often lower than expected for short records. Another disadvantage is that ApEn lacks relative consistency (Richman and Moorman, 2000). To overcome the disadvantages of ApEn, a sample entropy (SampEn) was proposed to replace ApEn by excluding self-matches (Richman and Moorman, 2000), so reducing the computing time by one-half in comparison with ApEn. Another advantage of SampEn is that it is largely independent of record length and displays relative consistency. Further details of SampEn are described elsewhere (Richman and Moorman, 2000; Lake et al., 2002).

The complexity of an EEG series can also be quantified by using symbolic dynamic. A new permutation method was proposed by (Bandt and Pompe, 2002) to map a continuous time series onto a symbolic sequence; the statistics of the symbolic sequences was called permutation entropy. Given a scalar time series (x_t, $t = 1, 2, \ldots, T$), an embedding procedure forms a vector: $X_t = [x_t, x_{t+l}, \ldots, x_{t+(n-1)l}]$ with the embedding dimension, n, and the lag, l (here $l = 1$). Then, X_t is arranged in an increasing order: $[x_{t+(j_1-1)l} \leq x_{t+(j_2-1)l} \leq \cdots \leq x_{t+(j_n-1)l}]$. For n different numbers, there will be $n!$ possible order patterns π, which are also called permutations. Let $f(\pi)$ denote its frequency in the time series, its relative frequency is $p(\pi) = f(\pi)/(T-(n-1)l)$. The permutation entropy is defined as

$$H_p(n) = -\sum_{n=1}^{n!} p(\pi) \ln p(\pi). \quad (1)$$

The corresponding normalized permutation entropy is

$$H_p = \frac{H_p(n)}{\ln(n!)}. \quad (2)$$

The largest value of H_p is one, which means the time series is complete random; the smallest value of H_p is zero, which means the time series is very regular. In short, the permutation entropy refers to the local order structure of the time series. More details can be found in Bandt and Pompe (2002) and Bandt (2005). Permutation entropy depends on the selection of n. When n is too small (less than 3), the scheme will not work, since there are only very few distinct states for EEG recordings. Often, for a long EEG recording a large n is better, however, very large n (greater than 10), the number $n!$ of permutations which can appear in the time series causes memory restrictions. In this study, to concentrate on the detection of dynamical change of EEG recording, a short epoch of EEG data is selected, i.e. 120 samples (1 s). To satisfy the condition of $n! < 120$, thus we chose only low order $n = 4$ during the calculation of permutation entropy.

Determination of onset and selection of EEG data

In this study, seizure onset was manually determined by an experienced experimental scientist by observation of abrupt increases in EEG amplitude coupled with simultaneous behavioural immobility, twitching of the vibrissae and facial muscles, and diminished muscle tone in the neck (Danober et al., 1998). In order to predict absence seizures, the interval between onset and the previous seizure is greater than 20 s. Using this criteria, 314 seizures were selected from the 28 GAERS for further predictability analysis. To calculate the specificity of prediction method, 71 interictal EEG data were selected from the 28 GAERS as well. The criteria of selection are that the interval between the interictal data and the end and beginning point of seizures is 10 s and the length of each data is greater than 40 s.

Prediction of absence seizures

In this study, the EEG signals were divided into 1.2 s epochs (120 samples per epoch) with an overlap of 1.1 s. The timestamp for each epoch was fixed at the end of the epoch. The threshold for detecting pre-ictal state was determined by calculating the mean value μ and standard deviation σ of the permutation entropy or sample entropy variations during the first 10 s from the respective rat; it is $T = \mu - k\sigma$, where k is the constant associated with the confidence coefficient in statistics. In this study, $k = 4$ was selected (the p-value: 0.0625, which is given by the Chebyshev's inequality: $P(|\Sigma| \geq k) \leq 1/k^2$). The details of detection method can be found in (Le Van Quyen et al., 2001; Li and Ouyang, 2006). The cross-point between the entropy and the threshold is called the seizure precursor; the interval between the precursor and the onset is defined as the anticipation time in this study.

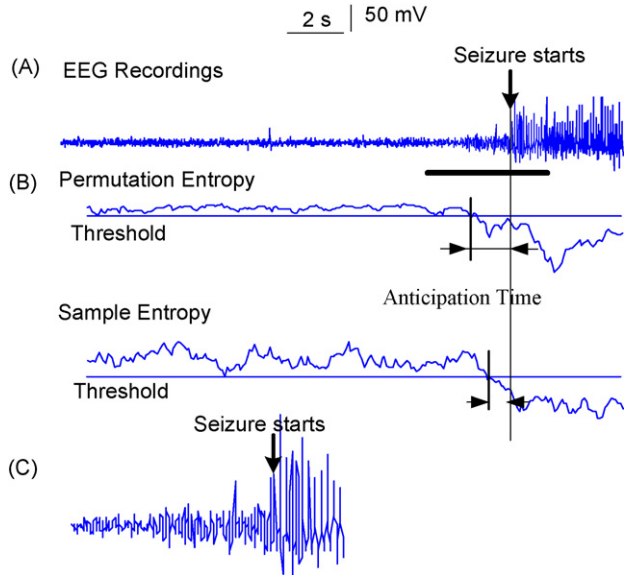

Figure 1 The prediction analysis of absence seizure by using EEG recordings. (A) Original EEG recordings with a seizure. (B) The permutation entropy and sample entropy profiles. The threshold value ($\mu - k\sigma$) $k = 4$, of permutation entropy and sample entropy is 0.9225 and 2.1134, respectively. The anticipation time of the permutation entropy is 1.4 s for permutation entropy. (C) The zoomed seizure onset.

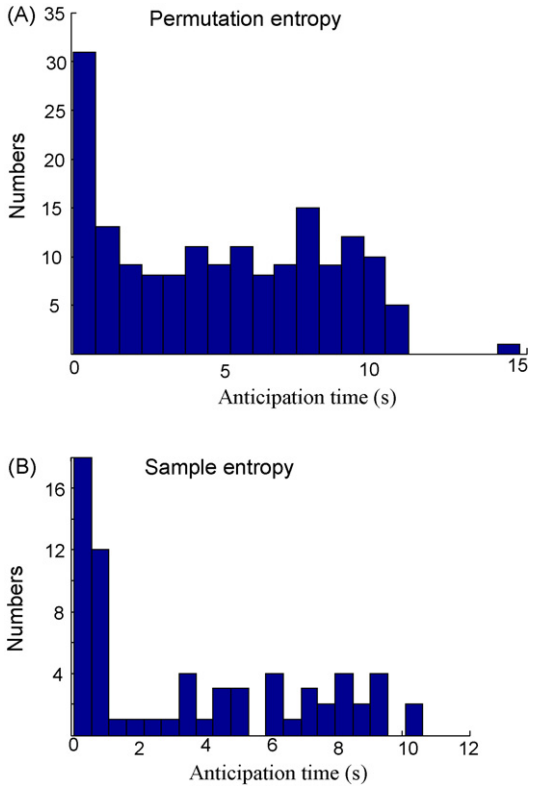

Figure 2 The histogram of anticipation time for permutation entropy and sample entropy. (A) Permutation entropy; (B) sample entropy. The maximum and minimum anticipation time is 14.8 and 0.1 s for permutation entropy, 10.6 and 0.1 s for sample entropy, respectively.

Results

Fig. 1 shows the predictability analysis of an absence seizure by using permutation entropy and sample entropy. The EEG recording of 25 s was firstly divided into epochs of 1.2 s with an overlap of 1.1 s; the original EEG recording is shown in Fig. 1(A). At the end of the EEG recording, an absence seizure occurs, the details of seizure onset is zoomed in Fig. 1(C). The permutation entropy ($n = 4$ and $l = 1$) and sample entropy ($m = 2$ and $r = 0.2$) of each EEG epoch were calculated, as shown in Fig. 1(B), a threshold and anticipation time were plotted as well.

This test shows that: (1) the values of permutation entropy and sample entropy are at a higher level during the normal state in comparison with the seizure state; (2) permutation entropy and sample entropy begin to gradually decrease prior to the seizure, which may indicate the dynamical complexity of neural activity of the network changing from complex to simple (synchronization) prior to the experience of the epileptic seizure; (3) the permutation entropy is essentially flat during the normal state, but the sample entropy is very unstable. Also, the anticipation time of permutation entropy was longer than that of the sample entropy. In brief, permutation entropy and sample entropy can successfully track the dynamical changes, from normal to absence seizure. Often the permutation entropy of EEG recordings was more robust.

The above method was applied to analyze all of the seizures (314). The anticipation time was used to indicate the pre-seizure state. Once a positive anticipation time could be obtained, this meant that the absence seizure could be predicted. The distribution of anticipation time is shown in Fig. 2. The mean anticipation times for permutation entropy and sample entropy were 4.9 and 3.7 s, respectively. Analysis of the entire EEG dataset found that permutation entropy successfully detected pre-ictal state prior to the seizure in 169 in 314 seizures (54%), while sample entropy only detected pre-ictal state in 67 of the 314 seizures (21%). These findings show that permutation entropy is better able to predict absence epileptic seizures than is sample entropy. On the other hand, the same prediction methods are applied to 71 interictal EEG data for specificity test. The test for permutation entropy and sample entropy has correctly identified 70 out of 71 interictal EEG data. The specificity of this test is therefore $70/71 = 98.6\%$.

The above case study showed that the permutation entropy of a single channel EEG of 1.2 s could be calculated in less than 2 ms by using MATLAB (Math Works Inc.) on a 1.6 GHz personal computer. Therefore, the permutation entropy calculation has a high computational efficacy, and could be applied to clinical real-time on-line monitoring of absence seizures.

Discussion

Absence epilepsy is currently classified as a generalized type of epilepsy, in which the seizures are associated with spike-and-wave complexes that are believed to develop within the thalamo-cortical pathways (Futatsugi and Riviello,

1998). During absence seizures, the firing pattern of the thalamo-cortical neurons shifts to an oscillatory, rhythmic, synchronized state of the EEG (Steriade et al., 1993). Recent evidence, however, has suggested a focal initiation site for absence seizures within the facial somatosensory cortex (Meeren et al., 2002, 2005; Polack et al., 2007), which can then recruit and entrain neighbouring cortical and thalamic neurons into a critical mass, i.e. an increasing synchronization of neuronal activity. Whilst the SWD in GAERS are generally considered to reflect an abrupt change from interictal state to ictal state, this study shows that almost 60% of absence seizures have a 'short' pre-ictal state that may reflect propagation of this synchronous activity from the focal initiation site.

The interactions betweens neurons play a crucial role in absence seizure generation, and the EEG signal is a reasonable measure of the summed activity of approximately 1—100 million neurons lying in the vicinity of the recording electrode (Sleigh et al., 2004). The transfer of electrical energy within the neural network is caused by the fact that neurons transfer packets of electrical charge between themselves using chemical and electrical synapses. At each instant of time, each neuron will have a certain soma potential, and probability of transfer of electrical energy to a neighbouring neuron. This basic process is very similar to a thermodynamic system: the EEG corresponds to energy; particles to neurons. Thus, the entropy concept that has been applied to describe the tendency for energy to be degraded and dispersed in thermodynamics could be valid to understand the mechanisms of absence seizure, as has been described elsewhere (van Drongelen et al., 2003). The entropy of the EEG may be acting as a reliable indicator of changes in cortical neuronal interactions, i.e. the entropy within the EEG may window a real change in cortical functional organization. The EEG is, to some degree, a window on cortical processes. The changes in entropy of the EEG may be expected to indirectly coarsely measure changes in the entropy occurring within the neural network itself. In short, the term 'entropy' may be more than merely a statistical measure of EEG pattern, but may in some way truly reflect the intracortical information flow (Sleigh et al., 2004). Therefore, the entropy measure of the electroencephalogram (EEG) has been used to quantify the transitions of neuronal synchronisation in absence epilepsy patients (Burioka et al., 2005).

Unfortunately, existing entropy measures for EEG data may be very inaccurate to reveal the 'hidden' information flow. In this study, it seems that the permutation entropy is a more appropriate complexity measure for EEG series than sample entropy. Permutation entropy is associated with the order structure of events in a phase space. However, sample entropy is based on the similarity of events in a phase space. Secondly, the effect of amplitude of EEG data on the permutation entropy is very weak, and permutation entropy is less sensitive to noise embedded in EEG recordings. Finally, the advantage of permutation entropy is that it can be applied to clinical real-time on-line monitoring of absence seizures because of its simple algorithm and fast computation. Therefore, it is an excellent candidate for designing an automated closed-loop seizure prevention system for absence epilepsy. In brief, the permutation entropy is more suitable to describe the nonlinear activity of EEG data, or better extract the pattern of EEG data for the prediction of absence seizure.

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