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Dynamic characteristics of absence EEG recordings with multiscale permutation entropy analysis

Gaoxiang Ouyang[a], **Jing Li**[b,d], **Xianzeng Liu**[c,*], **Xiaoli Li**[a,e,**]

[a] *Institute of Electrical Engineering, Yanshan University, Qinhuangdao 066004, China*
[b] *Natural Langauge Processing Research Group, Department of Computer Science, University of Sheffield, Regent Court, 211 Portobello, Sheffield, S1 4DP, UK*
[c] *The Comprehensive Epilepsy Center, Departments of Neurology and Neurosurgery, Peking University People's Hospital, Beijing 100044, China*
[d] *Department of Electrical and Automatic Engineering, School of Information Engineering, Nanchang University, Nanchang 330031, China*
[e] *National Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China*

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Summary Understanding the transition of brain activities towards an absence seizure, called pre-epileptic seizure, is a challenge. In this study, multiscale permutation entropy (MPE) is proposed to describe dynamical characteristics of electroencephalograph (EEG) recordings on different absence seizure states. The classification ability of the MPE measures using linear discriminant analysis is evaluated by a series of experiments. Compared to a traditional multiscale entropy method with 86.1% as its classification accuracy, the classification rate of MPE is 90.6%. Experimental results demonstrate there is a reduction of permutation entropy of EEG from the seizure-free state to the seizure state. Moreover, it is indicated that the dynamical characteristics of EEG data with MPE can identify the differences among seizure-free, pre-seizure and seizure states. This also supports the view that EEG has a detectable change prior to an absence seizure.

Introduction

Absence seizures are a form of generalized seizure accompanied with spike-and-wave discharges (SWD) in the electroencephalogram (EEG) (Meeren et al., 2002; Gorji et al., 2011). These sudden and abrupt seizures are transient signs and/or symptoms of abnormal, excessive, or synchronous neural activities in the brain (Polack et al., 2007; Amor et al., 2009; Bai et al., 2010), and may have significant impact on the educational development of sufferers (Killory

* Corresponding author.
** Corresponding author. Fax: +86 335 8072979.
E-mail addresses: gx.ouyang@gmail.com (G. Ouyang), jing.li.2003@gmail.com (J. Li), liuxianzeng2004@sina.com (X. Liu), xlli@ysu.edu.cn (X. Li).

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et al., 2011). Over the past decade, seizure dynamics, from seizure-free to seizure onset and to seizure ending, have been investigated using different mathematical methods, both linear and non-linear (Kramer et al., 2010; Neymotin et al., 2010; Schindler et al., 2007). To some extent, these results indicated that the characteristic of EEG changes during pre-seizure phases may be detectable in focal epilepsy a few minutes before the actual seizure onset (Mormann et al., 2006, 2007; Stacey et al., 2011). However, the prediction of sudden and abrupt seizures by detectable dynamic changes in the EEG is still debated in absence patients (Li et al., 2007; Stacey and Litt, 2008). It is challenging to understand the transition of brain activities towards an absence seizure and look for some precursor activities (Crunelli et al., 2011; Rosso et al., 2009a, 2009b; Gupta et al., 2011). Our previous analysis of dynamic changes in the EEG (in Genetic Absence Epilepsy Rats from Strasbourg) has demonstrated that EEG epochs prior to seizures exhibit a higher degree of regularity/predictability than seizure-free EEG epochs, but they present a lower degree than that in seizure EEG epochs (Li et al., 2007; Ouyang et al., 2008). Sitnikova and Luijtelaar showed that the SWD activity (in Wistar Albino Glaxo/Rijswijk rats) is preceded by short lasting delta and theta precursor activities in cortex and thalamus, but the combination rarely occurs during control periods (Sitnikova and van Luijtelaar, 2009; Sitnikova, 2010; van Luijtelaar et al., 2011). These EEG precursors in rat models give us a clue in predicting human absence epilepsy. To investigate possible changes in the EEG activities before the onset of seizures, it is necessary to conduct further analysis in absence patients.

Various methods have been proposed to analyze the temporal evolution of EEG recordings (Stam, 2005; Mormann et al., 2007). In particular, a series of entropy-based approaches have been widely used since they can quantify the 'complexity' of an EEG in health and disease (Li et al., 2007; Neymotin et al., 2010; Richman and Moorman, 2000; Yuan et al., 2011). Recently, Bandt and Pompe proposed the Permutation Entropy (PE) method to measure the irregularity of non-stationary time series (Bandt and Pompe, 2002), where the basic idea is to consider order relations between the values of a time series rather than the values themselves. The Sample Entropy (SampEn) algorithm, also a universally adopted approach, relies on the idea that the counts of m-long template matching within a tolerance r will also match at the next point (Richman and Moorman, 2000). Compared with SampEn, the advantages of the PE method are its simplicity, low complexity in computation without further model assumptions, and robustness in the presence of observational and dynamical noise (Bandt and Pompe, 2002; Bandt et al., 2002; Rosso et al., 2007). These advantages facilitate the use of PE for investigating the intrinsic structures in EEG data since it could extract informative features from epilepsy EEG data (Li et al., 2007; Nicolaou and Georgiou, 2012), sleep data (Nicolaou and Georgiou, 2011) and anaesthesia EEG data (Li et al., 2008, 2010; Olofsen et al., 2008).

On the other hand, traditional entropy algorithms are single-scale based and therefore fail to account for multiple scales inherent in brain electrical activities (Costa et al., 2002, 2005). To address the problem, Costa et al. proposed the multiscale entropy (MSE) (Costa et al., 2002) to measure the complexity of a time series by considering the correlations over multiple spatio-temporal scales of a time series instead of a single scale (Catarino et al., 2011; Mizuno et al., 2010). Motivated by the merits of PE and MSE, we propose a method called multiscale permutation entropy (MPE) to explore whether PE can replace SampEn in estimating multiscale entropy of EEG recordings. Moreover, we examine whether MPE can be effectively used to represent the dynamic characteristics of absence EEG recordings during different seizure states and evaluate the effectiveness of MPE measures in classifying different seizure states by linear discriminant analysis (LDA) (Webb, 2006).

Materials and methods

EEG recordings

EEG recordings were obtained from 7 patients (4 males and 3 females) with absence epilepsy, aged from 8 to 21 years old. The study protocol had previously been approved by the ethics committee of Peking University People's Hospital and the patients had signed informed consent that their clinical data might be used and published for research purposes. The EEG data were recorded by the Neurofile NT digital video EEG system from scalp surface electrodes (International 10-20 System) with 256 Hz sampling rate using a 16-bit analogue-to-digital converter and filtered within a frequency band of 0.5—35 Hz. In this study, EEG recordings from electrode C3 were selected for further analysis.

To investigate the dynamical characteristics of EEG data during different seizure phases, the EEG signals of absence epilepsy were selected and dissected from seizure-free (dataset I), pre-seizure (dataset II) and seizure (dataset III) intervals, where 60 2 s EEG epochs from 7 patients were selected for each dataset. The timing of onset and offset in spike-wave discharges (SWDs) was identified by an epilepsy neurologist (XZL), and these SWDs were defined as large-amplitude rhythmic 3—4 Hz discharges with typical spike-wave morphology lasting >1.0 s. Short (2 s) EEG recordings were used because 1) it is clinically difficult to obtain long EEG recordings during absence seizures (Sadleir et al., 2011); and 2) the duration of the pre-seizure state is only about a few seconds as determined from the rat model (Li et al., 2007; Ouyang et al., 2008). As shown in Fig. 1, the criteria for the selection of the seizure-free, pre-seizure and seizure data are that the interval between the seizure-free data and the beginning point of seizures is greater than 15 s, the interval is between 0 and 2 s prior to seizure onset, and

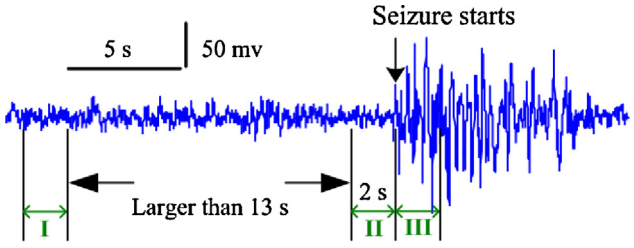

Fig. 1 The continuous EEG recordings with an absence seizure, and EEG epochs during seizure-free, preseizure and seizure intervals denoted by I, II and III, respectively.

the interval is the first 2 s of the absence seizure, respectively. In our study, intervals containing major artefacts were excluded for further analysis.

Multiscale permutation entropy

Similar to the MSE method (Costa et al., 2002), MPE incorporates two procedures. First, a ''coarse-graining'' process is applied to a time series. For a given time series $\{x_1, x_2, \cdots, x_L\}$, a consecutive coarse-grained time series is constructed by averaging a successively increasing number of data points in non-overlapping windows. Each element of a multiple coarse-grained time series $y_j^{(s)}$ is calculated according to

$$y_j^{(s)} = 1/s \sum_{i=(j-1)s+1}^{js} x_i \tag{1}$$

where s represents the scale factor and $1 \le j \le L/s$. The length of each coarse-grained time series is the integral part of L/s and the coarse-grained time series is simply the original time series when $s = 1$.

Next, PE is calculated for each coarse-grained time series and plotted as a function of the scale factor s. To compute the permutation of a coarse-grained time series y_j, $S_t = [y_t, y_{t+1}, \cdots, x_{t+m-1}]$ is generated with the embedding m and then arranged in an increasing order: $[y_{t+j_1-1} \le y_{t+j_2-1} \cdots \le y_{t+j_n-1}]$. Given m different values, there will be $m!$ possible patterns π, also known as permutations. Let $f(\pi)$ denotes its frequency in the time series, its relative frequency is $p(\pi) = f(\pi)/(L/s - m + 1)$. The permutation entropy is defined as

$$PE = -\sum_{i=1}^{m!} p(\pi_i) \ln p(\pi_i) \tag{2}$$

The corresponding normalized entropy can be defined as $PE/\log(m!)$. The largest value of PE is 1, meaning that all permutations have an equal probability; the smallest value of PE is zero, indicating that the time series is very regular. In other words, the smaller the value of PE is, the more regular the time series is.

Permutation entropy refers to the local order structure of the time series, which can give a quantitative complexity measure for a dynamical time series. Permutation entropy calculation depends only on the selection of m. When m is too small (less than 3), the scheme will not work well since there are only a few distinct states for EEG recordings. Often, for a long EEG recording, a large value of m is preferable. In this study, we calculate all EEG data with $m = 4$.

Linear discriminant analysis

Linear discriminant analysis (LDA) is adopted to evaluate the capability and effectiveness of the MPE measures in classifying different seizure states. The basic idea of LDA is to project high-dimensional data onto a low-dimensional space such that data are reshaped to maximize the class separability (Webb, 2006). Consider a classification problem with K classes ($K \ge 2$). Suppose the data contain M observations $(x_i, y_i), i = 1, 2, \cdots, M$, with $x_i \in R^p$ and $y_i \in \{1, 2, \cdots, K\}$. LDA is to find the linear combination $c'x$ which maximizes the ratio of $c'Bc/c'Wc$, where B and W denote the $p \times p$ between-class and within-class scatter matrices, respectively. The formulation is defined by:

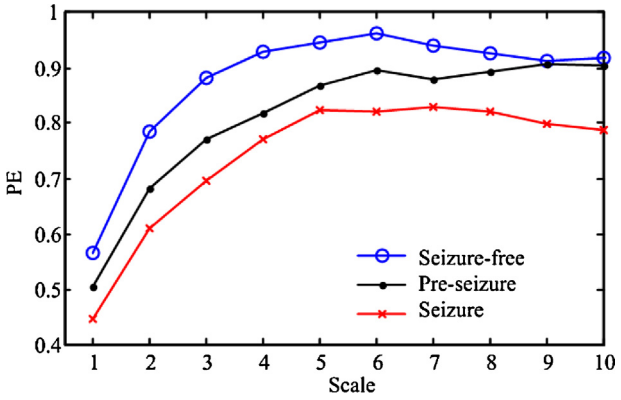

Fig. 2 Representative MPE curves derived from EEG recordings with different seizure states. PE measure is evaluated at 10 different scales.

$$B = \sum_{k=1}^{K} \frac{n_k}{N} (\mu^{(k)} - \mu)(\mu^{(k)} - \mu)^T \tag{3}$$

and

$$W = \sum_{k=1}^{K} \frac{n_k}{N} \hat{\Sigma}_k \tag{4}$$

where $\mu^{(k)}$ and $\hat{\Sigma}_k, k = 1, 2, \cdots, K$ are the sample means and covariance matrices of each class (with n_k samples) and μ is the total sample mean vector. The maximization problem in LDA is equivalent to solving the eigenproblem: $(W^{-1}B - \lambda I)c = 0$. Thus, if W is a non-singular matrix, Fisher's criterion is maximized when the projection matrix c is composed of the eigenvectors of $W^{-1}B$ corresponding to at most $K - 1$ non-zero eigenvalues (Webb, 2006).

Results

Multiscale entropy measure of EEG

The MPE method is applied to analysing the EEG recordings during different seizure states. First, the PE measure is evaluated at 10 different scales with the dimension $m = 4$. Fig. 2 shows representative MPE curves derived from EEG recordings during seizure-free, pre-seizure and seizure state, respectively. The entropy measure for EEG increases at small scales. After reaching the maximum entropy, it becomes stable when the scale factors increase. Fig. 2 also indicates that PE values are unstable at large scales, because the coarse-graining procedure reduces the sample size of templates by L/s (Park et al., 2007). The scale factor s is an important parameter in MPE. For calculating PE of each coarse-grained time series, in order to allow every possible ordinal pattern of dimension m to occur in a time series of length N, the condition $N \ge m!$ must hold and, moreover, N»$m!$ should be satisfied to avoid undersampling (Ouyang et al., 2010). For this reason, given $m = 4$, we need to choose $N \ge 4 * 4!$. To

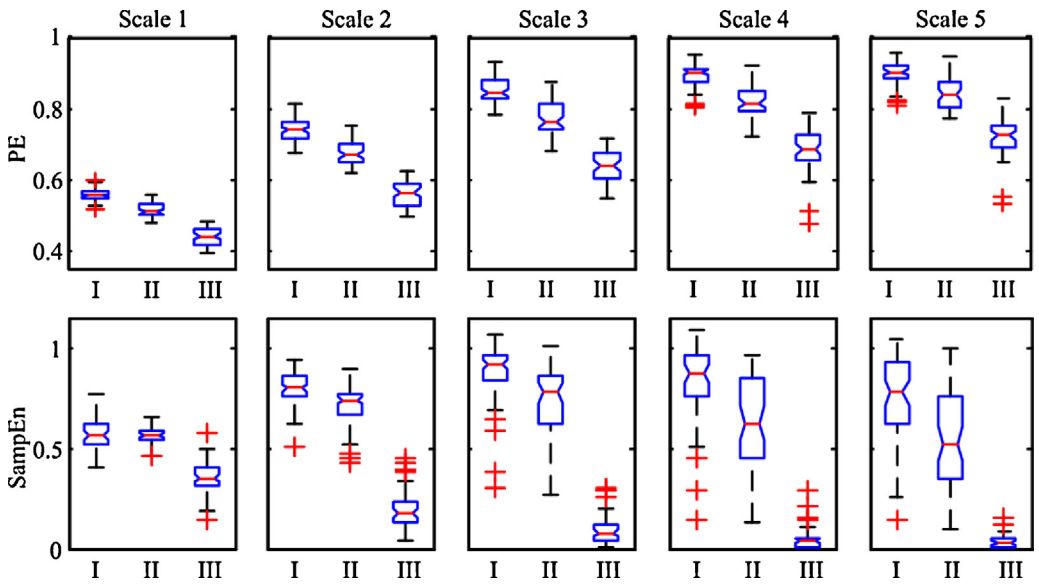

Fig. 3 *Boxplots* for the entropy PE (top) and SampEn (bottom) on scale 1—5 of the all EEG recordings, grouped by seizure-free (I), pre-seizure (II) and seizure (III) state.

obtain a more accurate and reliable evaluation of MPE, scale factors only with $s \leq 5$ are considered in this study.

Then, the MPE measure is applied to analysing all 180 2-s EEG epochs in this study (120 from each dataset I, II and III). For scale 1, which is the only scale considered by the traditional single-scale based method, the PE values for EEG epochs are averaged at 0.558 ± 0.018, 0.515 ± 0.022 and 0.435 ± 0.024 (mean $\pm$ SD) in dataset I, II and III, respectively, where the entropy values in seizure-free and pre-seizure states are much larger than those in seizure state. Similar results of PE measures can be obtained from the other four scales. To compare the extracted entropy information of EEG between MPE and MSE methods, we also apply the MSE method to analyze the EEG data. The details of MSE can be found in (Costa et al., 2002; Ouyang et al., 2009); the SampEn values for the EEG epochs on scale 1 averaged 0.578 ± 0.080 in seizure-free state, 0.563 ± 0.045 in pre-seizure state and 0.357 ± 0.078 in seizure state, respectively.

Next, in order to investigate whether their distributions over the three states are significantly different, the one-way ANOVA test (Hogg and Ledolter, 1987) is used for calculating entropy values on each scale, respectively. The population distribution of the PE and SampEn of each scale is shown in Fig. 3 as *boxplot*. The lower and upper lines of the ''box'' are the 25th and 75th percentiles of the sample, the distance between the top and bottom of the box is the interquartile range and the line in the middle of the box is the sample median. Outliers (plus sign) are cases with values that are more than 1.5 times the interquartile range. The notches in the boxes are a graphic confidence interval (95%) about the median of a sample. As seen in Fig. 3, at all scales, the entropy values of PE and SampEn in the seizure-free and pre-seizure state are higher than those in the seizure state.

To statistically test these observed mean differences, the one-way ANOVA with Scheffe's post hoc test (Hogg and Ledolter, 1987) is performed for computing entropy values of three different sets. The results of PE at scale 1, i.e. the traditional permutation entropy measure, are shown in Table 1. It can be seen that the F-test ($F = 462.0$) is significant at the probability level of $P < 0.05$, which suggests the null hypothesis, i.e., no differences among these three different groups, should be rejected. Thus, the application of Scheffe's test to all pairwise comparisons between the means of PE suggests that the average PE values in the pre-seizure state has significantly lower values than those in the seizure-free state, but they are significantly higher than those in the seizure state. Similarly, the results of SampEn on scale 1, i.e. the traditional sample entropy measure, are given in Table 2. As we can see, the differences of SampEn values cannot be distinguished well between the seizure-free and pre-seizure states. Similar statistical results can also be obtained from the scales 2—5, at which the entropy values in the seizure-free and

Table 1 One-way ANOVA with Scheffe's test for PE at scale 1.

ANOVA source of variation	Sums of squares (SS)	Degrees of freedom (DF)	Mean square (MS)	F-test
Between Samples	0.462	2	0.2310	462.0 $P < 0.05$
Within samples	0.081	177	0.0005	
Total	0.543	179		

Scheffe's test: the seizure-free vs. the pre-seizure state $S = 55.89$ ($P < 0.05$); the seizure-free vs. the seizure state $S = 461.18$ ($P < 0.05$); the pre-seizure vs. the seizure state $S = 195.98$ ($P < 0.05$).

Table 2 One-way ANOVA with Scheffe's test for SampEn at scale 1.

ANOVA source of variation	Sums of squares (SS)	Degrees of freedom (DF)	Mean square (MS)	*F*-test
Between Samples	0.180	2	0.0900	180.0 $P < 0.05$
Within samples	0.085	177	0.0005	
Total	0.265	179		

Scheffe's test: the seizure-free vs. the pre-seizure state $S = 0.70$ ($P > 0.05$); the seizure-free vs. the seizure state $S = 147.62$ ($P < 0.05$); the pre-seizure vs. the seizure state $S = 128.05$ ($P < 0.05$).

Table 3 Classification results of the MPE measure.

Desired result	Output result		
	Group I	Group II	Group III
Group I	59	1	0
Group II	16	44	0
Group III	0	0	60

Table 4 Classification results of the MSE measure.

Desired result	Output result		
	Group I	Group II	Group III
Group I	54	6	0
Group II	18	41	1
Group III	0	0	60

pre-seizure state are significantly higher than those in the seizure state; and the entropy values in the seizure-free are significantly higher than those in the pre-seizure state.

Classification

As shown above, there is significant difference among PE values of the seizure-free, pre-seizure and seizure states. However, a considerable overlap occurs between the PE values in the seizure-free and pre-seizure states, which prevents the traditional single-scale entropy measure from clearly distinguishing between the seizure-free and pre-seizure states. The performance of the above measures for classifying different seizure states is evaluated by linear discriminant analysis (LDA). The calculated MPE measures are used as input data with 5 features (dimension of the extracted feature vectors — PE values on scale 1—5) in LDA. As shown in Fig. 4 A, these features are projected onto a two-dimensional space and the data are separated into well-defined clusters. In more detail, LDA correctly classifies 163 out of 180 subjects (as illustrated in Table 3), giving approximately 90.6% accuracy. The calculated MSE measures are also used as input data with 5 features (dimension of the extracted feature vectors — SampEn values on scale 1—5) in LDA. In the same way, these features are projected onto a two-dimensional space, which is shown in Fig. 4B. The classification results are illustrated in Table 4 — among 180 EEG recordings in three groups, 155 are correctly classified. The average classification accuracy is 86.1%. In order to compare the performance of multiscale entropy method with that of the traditional single-scale entropy method, the classification accuracy based only on scale 1 is calculated. Of 180 EEG recordings in three groups, 152 and 123 are classified correctly from PE and SampEn, respectively. The average classification accuracy is 84.4% and 68.3%, respectively.

Discussion

The EEG signal is a measure of the summed activities of approximately 1—100 million neurons lying in the vicinity of the recording electrode. Since it may provide insight into the functional structure and dynamics of the brain (Buzsaki, 2006), exploration of hidden dynamical structures within EEG signals is of both basic and clinical interest and has attracted more and more attention (Stacey and Litt, 2008). Nowadays, EEG has become one of most useful

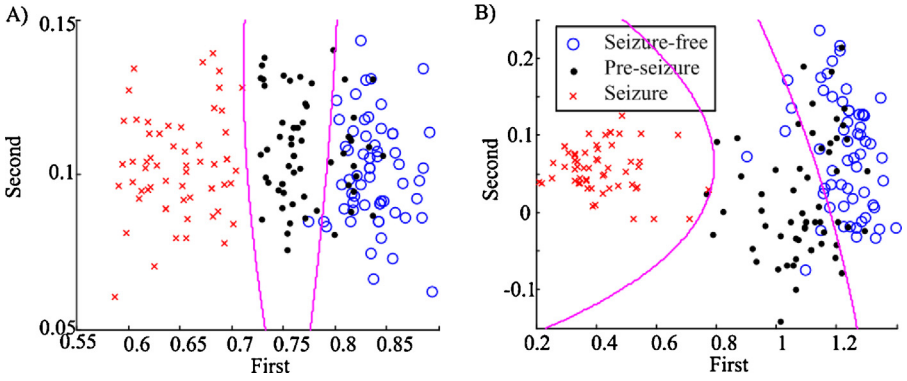

Fig. 4 LDA of three groups: the seizure-free, pre-seizure and seizure states. The high-dimensional feature vectors of MPE (A) and MSE (B) are projected ontpto a two-dimensional feature space, respectively.

tools for studying the cognitive processes and the physiology/pathology of the brain, especially the processes involved in absence seizures.

In this study, we investigat whether the period just preceding absence seizures is characterized by a significant change in EEG from absence patients and whether this can serve as a criterion to distinguish this period from seizure-free and seizure states. To this end, we propose the MPE method to analyze the dynamical characteristics of EEG data during different absence seizure states. For scale 1, it has been found that there is a significant increase of the PE values of the EEG data from seizure-free state to seizure state in absence epilepsy patients. In addition, the one-way ANOVA with Scheffe's post hoc analysis indicates that the PE and SampEn values in the seizure-free state are statistically larger than those during the seizure state. Lower entropy values during the seizure state suggest that the regularity/predictability of brain EEG signals increases during absence seizures. This is consistent with the general hypothesis that reduction in the entropy of biologic signals is associated with disease (Costa et al., 2002; Neymotin et al., 2010). Similar results have been reported based on an approximate entropy measure of EEG data from absence epilepsy patients (Burioka et al., 2005). A possible reason is that the absence seizure is initiated by abnormally discharging neurons that recruit and entrain neighbouring neurons into a critical mass. This process manifests itself during the increasing synchronization of neuronal activities (Meeren et al., 2002; Polack et al., 2007; Amor et al., 2009), which implies an increasing regularity/predictability of EEG data. Moreover, the one-way ANOVA with Scheffe's post hoc analysis indicates that the PE values in seizure-free state are statistically larger than those during the pre-seizure state. However, there is no significant difference between the seizure-free state and pre-seizure state for SampEn values. This suggests the single-scale SampEn is not effective in discriminating the seizure-free state from the pre-seizure state, and PE is a more appropriate regularity/predictability measure for EEG series. To discriminate among three epileptic seizure states, the average classification accuracy is 84.4% and 68.3% when using the traditional single-scale entropy PE and SampEn, respectively. These results are similar with the previous study that the PE measure is better for predicting absence seizures than the SampEn measure (Li et al., 2007).

On the other hand, although the single-scale PE is statistically higher in the seizure-free state than in the pre-seizure state, there is an overlap between the entropy values in the seizure-free and pre-seizure state. For larger scales, it has been found that the differences of entropy values are distinguishable among different seizure states. To discriminate among three epileptic seizure states, the LDA algorithm, which separates samples from different classes far away while keeping samples within the same class close to each other, was applied to evaluating the performance of the MPE and MSE measures. A classification accuracy of 90.6% is achieved based on the newly proposed MPE measure, while the classification accuracy is 86.1% for the MSE measure. Both the MPE and MSE methods can significantly differentiate and classify different seizure states in this dataset, but the classification accuracy of the MPE method is higher. The database analyzed in this study is not sufficiently large to draw any definite conclusions concerning the distinction among the seizure-free, pre-seizure and seizure states in absence epilepsy. Nevertheless, our results provide the evidence for supporting the existence of a pre-seizure state in absence epilepsy. The characteristics of entropy changes of EEG could be considered as a candidate precursor of the impending absence seizures. It is the intent of future studies to test the MPE method with a larger database and cross-validate its performance with multiple independent databases.

Acknowledgments

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