Application of approximate entropy on dynamic characteristics of epileptic absence seizure

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Abstract
Electroencephalogram signals are time-varying complex electrophysiological signals. Existing studies show that approximate entropy, which is a nonlinear dynamics index, is not an ideal method for electroencephalogram analysis. Clinical electroencephalogram measurements usually contain electrical interference signals, creating additional challenges in terms of maintaining robustness of the analytic methods. There is an urgent need for a novel method of nonlinear dynamical analysis of the electroencephalogram that can characterize seizure-related changes in cerebral dynamics. The aim of this paper was to study the fluctuations of approximate entropy in preictal, ictal, and postictal electroencephalogram signals from a patient with absence seizures, and to improve the algorithm used to calculate the approximate entropy. The approximate entropy algorithm, especially our modified version, could accurately describe the dynamical changes of the brain during absence seizures. We could also demonstrate that the complexity of the brain was greater in the normal state than in the ictal state. The fluctuations of the approximate entropy before epileptic seizures observed in this study can form a good basis for further study on the prediction of seizures with nonlinear dynamics.

Key Words: epilepsy; electroencephalogram; approximate entropy; nonlinear dynamics

INTRODUCTION
Epilepsy is one of the most common serious neurological disorders1-3. Epileptic seizures are defined as transient signs or symptoms of abnormal, excessive, or synchronous neuronal activity in the brain4. Epilepsy is usually controlled, but not cured with medication, and surgery may be considered in difficult cases. The available medications are not effective in all patients, with 30% of epileptic people suffering from uncontrolled seizures4. Thus, there is a strong need for new curative treatments.

Neuronal networks manifest the property of multistable dynamics. It can be assumed that there are two possible states of the epileptic brain: the interictal state, characterized by normal, apparently random, steady-state activity, and the ictal state (seizure), characterized by the sudden onset of synchronous oscillations5. The transition between these two states can occur either as a continuous sequence of phases, or as a sudden change5. Seizures with the former type of ictal transition may be anticipated in their early, preclinical phases. In the latter case, where a sharp critical transition takes place, the seizures may be unpredictable. Electroencephalogram (EEG) signals reflect the electrical activity of the brain. At the onset of an ictal event, the EEG signal displays a complicated dynamic transition. Analysis of EEG changes in epileptic patients plays an important role in assessing the effects of treatment. Thus, new and more effective methods of EEG data analysis are urgently needed.

Using techniques developed for the analysis of complex nonlinear systems, specific spatiotemporal dynamical EEG changes that begin several seconds before, and end several seconds after, a seizure can be identified6-7. The cerebral activity during an epileptic seizure is significantly different from the normal state. It is low-dimensional during the seizure, and high-dimensional during the interval state8. Its dynamic characteristics, including chaotic fractal dimension, complexity, Lyapunov index, correlation dimension, and other indices, change significantly. A number of studies have investigated the EEG using one or several dynamic indices, sometimes including wavelet transformation9. During seizures, the EEG tends to become synchronized and cyclical10-12, and the

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correlation dimension and complexity of the EEG are reduced\(^{[13]}\). It has been demonstrated that nonlinear dynamics methods are more sensitive in detecting seizures than traditional linear methods\(^{[14-16]}\). Complexity is an important characteristic of nonlinear dynamic systems. Approximate entropy (ApEn) is a nonlinear dynamic parameter that describes the complexity of a time series\(^{[17]}\). The ApEn is greater when the time series is more complex\(^{[18-20]}\). ApEn has the following advantages over other parameters: (1) it requires fewer data points (~100 – 5 000), (2) it is robust against noise and wild data points, and (3) it is appropriate for both deterministic chaotic and stochastic processes. Given \(N\) points and the similarity criterion \(r\), ApEn \((m, r, N)\) is approximately equal to the negative average natural logarithm of the conditional probability that vectors similar for \(m\) points remain similar at the next point, where the similarity of two vectors is judged in terms of their absolute coordinates\(^{[21]}\). ApEn and improved versions of this method have been used to analyze EEG signals of healthy individuals under different physiological and cognitive states\(^{[18-22]}\).

In this paper, we used ApEn and an improved ApEn algorithm to characterize the dynamical properties of the ictal transition in subjects with absence epilepsy. We studied scalp EEG data recorded by video-EEG. Based on the observed variations in the ApEn during preictal, interictal and postictal states, we discuss the dynamic mechanisms of epileptic absence seizure.

**RESULTS**

**ApEn algorithm and parameters**

We first studied the impact of different values of the parameters \(r\) and \(N\) on ApEn. The number of data points used to calculate ApEn in a time series can vary from hundreds to thousands. Due to the instability of EEG signals, we choose the first 70 seconds (14 000 points) of continuous EEG data. The amplitude of the EEG signal from T5 increased dramatically during the ictal period compared with the preictal period (Figure 1).

First, we studied the effect of different values of \(r\). Usually, the threshold \(r\) has been between 0.1 and 0.2 SD (SD is the standard deviation of the original data), so we calculated ApEn for \(r = 0.1\) SD and \(r = 0.2\) SD. The ApEn algorithm showed that the value of \(r\) affected the number of \(d[x(i), x(j)] \leq r\), and that the number of \(d[x(i), x(j)] \leq r\) for \(m\) must be greater than the number of \(d[x(i), x(j)] \leq r\) for \(m + 1\). Generally, the value of ApEn is nonnegative. This result indicates that ApEn cannot embody the complexity of epileptic seizures. Pincus\(^{[19]}\) found that when ApEn \((m = 2, r_1)\) (A) \(\leq\) ApEn \((m = 2, r_2)\) (B), then ApEn \((m = 2, r_2)\) (A) \(<\) ApEn \((m = 2, r_2)\) (B) (for \(r\) larger than most of the noise). Therefore, we think that this \(r\) is too small to achieve fault tolerance, and that the interference of excessive noise is too great.

Second, we analyzed the effect of the value of \(N\) (number of data points) on ApEn. As shown in Figure 2, we can see that the value of \(N\) did not have a distinct effect on ApEn. However, increasing \(N\) will increase computation times.

Finally, we determined the appropriate step length for calculating ApEn\(^{[20]}\). We compared the sliding window method with the jumping window method. We chose the data obtained from electrode F4, moved 400 points forwards to calculate a new ApEn value, and compared with the result of the jumping window method. Figure 3 shows the difference between the two methods. When the jumping window was applied, the curve jumped too much. This can obscure lots of detail, and can cause the loss of important information. Therefore, we adopted the sliding window method for the rest of this study. Since small time steps will require longer computation times in MATLAB, while large steps will cause the loss of information, we chose a step of 300 to get a reasonable result.

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**Figure 1** Filtered electroencephalogram (EEG) segment from T5 electrode.

(A) Seventy-second segment of the EEG signal.

(B) Ten-second segment of the EEG signal shown in A.
Changes in complexity in the presence of an external high-frequency disturbance

Dynamical changes in the brain during absence seizures can be characterized by the ApEn index calculated from an EEG signal filtered according to common clinical standards. Sometimes, environmental factors during recording can cause interference in EEG recordings. For instance, sudden high-frequency disturbances can severely affect EEG recordings. We compared the ApEn of the original signal from electrode F4 with the filtered signal, to investigate the influence of external disturbances in the normal environment on ApEn. As shown in Figure 4, the amplitude of the ApEn of the original signal was larger than that of the filtered signal, but the overall shape was unchanged. This demonstrates that the ApEn algorithm has anti-jamming properties.

An external high-frequency disturbance could be seen at electrode T5 between 40 and 45 seconds (Figure 1B). The ApEn curves from both the filtered and unfiltered data show an abrupt wave crest at 40–45 seconds (Figure 4).

This character of the curves does not reflect the actual situation during the ictal period, and ApEn can therefore not accurately reflect the dynamical changes in the biological EEG signal. The phenomenon suggests that abrupt high-frequency disturbances have great impact on the ApEn.

Algorithm improvement

For many experiments, Pincus[19] suggested $m = 2$ as an appropriate dimension to give reasonable statistical validity of the ApEn. However, because the EEG is a multivariable, nonlinear, non-stationary time series, the dimension is much larger than 2 or 3. Combining methods of False Nearest Neighbors, mutual information and C-C, we have found that the EEG data have a higher dimension[20]. In this study, we obtained an ApEn series that contained some negative values (Figure 5B), which disagrees with the definition of ApEn. We defined the original algorithm as Algorithm 0, and calculated the values of $\phi^m(r)$ that returned a value of 0 in formula 1. When $m$ was increased to 5, ApEn became negative. To avoid the zero value in $c^m(N)$ and $C^{m+1}(r)$, we made a small modification to the algorithm. By changing formula (1) to

$$
\phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln C^{m+1}_i(r).
$$

we obtained a new algorithm (defined as Algorithm 1).

Although the definition of $\phi^m(r)$ is different, ApEn($\phi^m(r)$) tends towards the same results as the original definition as $N$ approaches infinity. However, when both $c^m_i$ and $C^{m+1}_i$ are extremely small ($\phi^m(r) \approx 0$), ApEn can have a zero value. To avoid a non-reasonable zero value of ApEn, we modified formula (1) to

$$
\phi^m(r) = \frac{1}{N-m+1} \ln \sum_{i=1}^{N-m+1} C^{m+1}_i(r).
$$

to obtain another new algorithm (defined as Algorithm 2).

In experiments using increasing values of $m$, Algorithm 2 performed better than Algorithms 0 and 1. Figure 5A shows the different ApEn results obtained by the different algorithms when $m = 2$, at electrode F4. We found that the ApEn calculated by all the algorithms could reflect the dynamical changes in the EEG signal over time. There was a larger difference between the preictal and ictal periods in the ApEn curves obtained using Algorithms 1 and 2, compared to Algorithm 0. Figure 5B shows the difference between the algorithms when $m = 5$. Part of the curve calculated by Algorithm 0 dropped below zero, which does not agree with the definition of ApEn. In addition, there was little difference between the preictal and ictal periods in the curve calculated by Algorithm 1. The curve of Algorithm 2 was
the best curve for distinguishing between the preictal and ictal periods. By comparison, we found that Algorithm 2 was suitable for ApEn calculation of multi-dimensional data.

Figure 6 shows the ApEn curves for different values of \( m \) calculated by Algorithm 2. The difference between the ictal and preictal periods was greater at larger values of \( m \). Thus, when \( m \) increased, ApEn described more clearly the dynamical change of the brain. In addition, the curve between 38 and 45 s was smoother at larger values of \( m \). This shows that the ApEn algorithm performed better under conditions of interference by a sudden high-frequency disturbance when \( m = 7 \) in this experiment. In this figure, the ApEn tended to decrease progressively during the preictal period. However, the ApEn value increased before this decline. In the ictal period, the ApEn maintained a lower value, and after the seizure, the ApEn increased again and sometimes even exceeded the preictal values. In the ApEn curves, there was a trough between 20 and 30 seconds and that was co-incident with eye blink artifacts detected in the video.

Figure 5 shows that electrodes T3 and C3 are not suitable for using ApEn to distinguish between ictal and preictal periods in the EEG\(^{[24]}\).

DISCUSSION

In this study, we report that the ApEn of an EEG signal during the ictal period is smaller than during the preictal period. This finding supports some hypotheses proposed in previous studies\(^{[5, 25]}\). The methods used to analyze biomedical signals have received increasing attention in recent years. Some scholars have improved the algorithms to increase computation speed, and other studies have tried to use ApEn to quantify changes in brain function\(^{[17, 18, 21, 26]}\). In our study, we described the fluctuations of ApEn in preictal, ictal, and postictal EEG signals from a patient with absence seizures. The increasing value of ApEn in the preictal state indicated that the complexity of the brain changed before epileptic seizures. This implies that the increase in ApEn could be used to predict the onset of the epileptic seizure, when the parameters \( m, r, \) and \( N \) are chosen appropriately.

In this study, we have found that the EEG signal at certain electrode positions can be used to describe the dynamical changes during absence seizures. Detailed evaluation of the best choice of electrodes will require another study. We also found that ApEn sensitively reflects the biological signal. Common interference signals can have positive influences during computation and analysis. Since the sensitivity of the preictal and ictal periods to interference varies, the interference signals make the value of ApEn partially larger (Figure 4A). Consequently, the difference in ApEn between the interval and ictal periods is increased, making it easier to identify the change. The ApEn values for the filtered EEG signal decrease in total, with greater reductions for the interictal EEG and smaller reductions during the ictal phase. However, interference signals have little influence on the shape of the ApEn curve. Therefore, this ApEn algorithm is able to resist certain types of noise, because the chosen value of \( r \) is larger than most of the noise. However, irregular, sudden interference signals and myoelectricity during EEG monitoring, especially signals with frequency components within the recorded range, can have marked influences on the ApEn.

During the ApEn computation, we found that the
SUBJECTS AND METHODS

Design
A study of the nonlinear dynamics of neuroelectrophysiological data from human subjects.

Time and setting
This study was performed at the Department of Neurology, the First Affiliated Hospital of Sun Yat-sen University, China, from May 2004 to August 2005.

Subjects
Four patients (3 males, 1 female) with childhood absence epilepsy were recruited from the Department of Neurology, the First Affiliated Hospital of Sun Yat-sen University, China. These patients had an average age of 11.1 ± 3.7 years, and were enrolled with informed consent.

Inclusion criteria
(1) 4–18 years old.
(2) Seizures characterized by sudden transient confusion without convulsions.
(3) Typical 3 Hz spike-wave complex in EEG.
(4) No family history of epilepsy.
(5) Normal motor and cognitive development.
(6) No anti-epileptic drug or sedative before and during the examinations.

Exclusion criteria
(1) Progressive central nervous system diseases.
(2) Acute infection during the examinations.
(3) History of partial seizures.

Methods
The patients underwent a 24-hour video-EEG examination. Experimental scalp EEG data were obtained by a video electroencephalograph (Stellate Inc, Montréal, Canada) with 16 electrodes. Continuous EEG signals were typically analyzed for 70 seconds, and included one seizure episode (36 seconds preictally, 22 seconds ictally and 12 seconds postictally; Figure 1). The signal was sampled at a frequency of 200 Hz and the number of data points was 14,000 points per electrode.

The scalp EEG data contained some interference signals or electrical noise. Before analyzing EEG signals, we filtered them according to standard clinical procedures. The signal was high-pass filtered to remove frequencies below 0.30 Hz, low-pass filtered at 35 Hz, and notch filtered at 50 Hz.

Complexity is a general concept with various definitions, which can be employed from different angles to evaluate biological signals. Pincus suggested the concept of ApEn as an index of complexity, and used it to quantify the randomness of complex systems. More irregular time series data correspond to greater values of ApEn. The algorithm is computed as follows:

First step: Given a time series of data \( u(1), u(2), \ldots, u(N) \), from measurements equally spaced in time, form a sequence of vectors \( x(1), x(2), \ldots, x(N - m + 1) \) in \( R^m \), defined by \( x(i) = [u(i), u(i + 1), \ldots, u(i + m - 1)] \) and \( x(j) = [u(j), u(j + 1), \ldots, u(j + m - 1)] \) (define for each \( i, 1 \leq i \leq N - m + 1 \) and \( j, 1 \leq j \leq N - m + 1 \)).

Second step: Calculate the distance between \( x(i) \) and \( x(j) \).

\[
d[i(i), x(j)] = \max_{k=1,2,\ldots,m} |u(i + k - 1) - u(j + k - 1)|. \quad (4)
\]

Third step: Define \( r \) and for each \( i \leq N - m + 1 \), calculate the number of \( d(x(i), x(j)) \leq r \) and divide by \( N - m + 1 \).

\[
d[i(i), x(j)] = \max_{k=1,2,\ldots,m} |u(i + k - 1) - u(j + k - 1)|. \quad (5)
\]

Fourth step: Define \( \phi^m(r) \) as the average value of \( \ln C^m(r) \).

Fifth step: for \( m + 1 \), repeat steps 1–4, and note down \( \phi^{m+1}(r) \).

Sixth step: Calculate ApEn.

\[
ApEn(m, r, N) = \phi^m(r) - \phi^{m+1}(r). \quad (6)
\]

In accordance with the definition and the algorithm of ApEn, we should establish an \( m \)-dimensional vector before analyzing time series. Usually, \( m = 1 \) or \( m = 2 \) have been used in previous studies. Due to the complicated nature of biological signals, \( m = 2 \) has often been chosen for myoelectricity and EEG signals, when \( N \) was about 800. Generally, we adopt \( m = 2 \) and \( r = 0.1 \pm 0.2 \) SD [SD is the standard deviation of the original data \( u(i) \)].

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Ethical approval: The project received full ethical approval from Zhongshan School of Medicine, Sun Yat-sen University in China.

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