Research article

Abnormal P50 sensory gating in schizophrenia: A permutation fuzzy entropy analysis

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Abstract

A permutation fuzzy entropy algorithm is proposed that uses sorting and symbolic methods to improve anti-noise performance of electroencephalogram signals known to be highly sensitive to noise disturbances during collection. It was employed to analyse abnormal event-related potentials of schizophrenics focused on P50 potentials of sensory gating, which is the most common paradigm currently used for analysing schizophrenia. The approach for analysing P50 sensory gating in schizophrenics is presented from twenty-seven schizophrenia patients and twenty healthy controls. The values calculated for the patients under the conditioning and testing stimuli were used to calculate the entropy complexity. Results demonstrate that the approach can be effectively used to analyse sensory gating deficits in patients with schizophrenia and that the algorithm can be satisfactorily be used for analysing electroencephalogram signals.

Keywords

Permutation fuzzy entropy; P50 sensory gating; electroencephalogography; schizophrenia; event related potential

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1. Introduction

Electroencephalogography (EEG) signals are unstable and nonlinear [1]. Linear methods cannot effectively detect the complex and dynamic changes of EEG time series [2]. However, nonlinear parameters such as the Hurst index [3], Lempel-Ziv complexity (LZC) [4, 5], Lyapunov exponents [5], and entropy [5–7] provide good quantification of the complexity of time series, and these methods can contribute to a deeper understanding of the dynamic changes of EEG and underlying chaotic states of the brain [8].

Among them, entropy portrays the disorder and degree of chaos of a system state as an important and characteristic value of nonlinear dynamics. Additionally, compared with other nonlinear methods, entropy has the advantage of being less dependent on data length [9]. Therefore, entropy has been widely used for the quantitative analysis of the EEG signals of different states, including disease, cognitive tasks, and sleep.

In 1991, Pincus [10] proposed an approximate entropy (ApEn) algorithm that measures from a statistical point of view the production rate and the complexity of new information in a time series. The larger the ApEn is, the more complex the time series. When ApEn counts matching values, it includes a comparison with its own data. However, the comparison has no value because entropy is used to measure the production rate of new information in the time series. Moreover, ApEn depends heavily on the length of the time series. In an effort solve this problem, Richman & Moorman [11] put forward an improved ApEn algorithm that not only eliminates the vector self-matching of ApEn, but also greatly reduces the dependence on data length. However, when ApEn and sample entropy are adopted for measuring similarity, the Heaviside binary function is always used. Therefore, the entropy value has a deficient continuity when ApEn and sample entropy are used for measurement.

Chen and colleagues [12] proposed the fuzzy entropy (fuzzyEn) algorithm, which employs a fuzzy membership function, instead of a binary function of the sample entropy, to measure the similarity and smooth the entropy changes. Although fuzzyEn improves upon ApEn and sample entropy, there are multiple problems. The sensitivity of fuzzyEn to noise depends substantially on its parameter values. However, the major features of the EEG signals include both a low signal-to-noise ratio and strong noise. Because of these problems, the paper improved fuzzyEn and increased its anti-noise stability by introducing permutation fuzzy entropy (PFEN).

The PFEN algorithm is based on the concept of symbolization of a time series, which originated from permutation entropy (PE) as an analytical method for sorting time series complexity [13]. It is based on the contrast between adjacent data and has good robustness and is strongly impervious to noise. In this study, PFEN is used to analyse the event-related potential (ERP), whose signal-noise rate is low, in schizophrenic patients in response to conditioning and testing stimuli and to evaluate PFEN.

2. Permutation Fuzzy Entropy (PFEN) Algorithm

A permutation fuzzy entropy algorithm is proposed that uses sorting and symbolic methods to improve the anti-noise performance of EEG signals during their collection.

PFEN sorts and symbolizes the original time series. It computes the fuzzyEn [12] of the symbolic series, namely, the permutation fuzzy entropy. The algorithm of PFEN was presented as follows:

Step 1. Given a time series $\{X(i) : 1 \le i \le l\}$, where l is the length of series X. For example, l = 5, $X(1)$ = 1, $X(2)$ = 1, $X(3)$ = 1, $X(4)$ = 2, $X(5)$ = 2, $X(i)$ = 1, 1, 1, 2, 2.

Step 2. Reconstruct this series, and obtain the following matrix:

$$\begin{bmatrix} x(1) & x(1+\tau) & \dots & x(1+(pm-1)\tau) \\ x(2) & x(2+\tau) & \dots & x(2+(pm-1)\tau) \\ \dots & \dots & \dots & \dots \\ x(j) & x(j+\tau) & \dots & x(j+(pm-1)\tau) \\ \dots & \dots & \dots & \dots \\ x(K) & x(K+\tau) & \dots & x(K+(pm-1)\tau) \end{bmatrix} j = 1,2,\dots,K \quad (1)$$

where τ and pm are the delay time and permutation dimension, respectively, and $K = l-(pm-1)\tau$. Each line of the matrix can be considered a reconstructed component; that is, the above matrix includes a total of K reconstructed components. For example, pm = 3, τ = 1, l = 5, $K = l-(pm-1)\tau$ = 5 - 2 = 3.

$$\begin{bmatrix} x(1) & x(2) & x(3) \\ x(2) & x(3) & x(4) \\ x(3) & x(4) & x(5) \end{bmatrix} = \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & 2 \\ 1 & 2 & 2 \end{bmatrix}$$

Step 3. Re-sort all the elements of every reconstructed component into an ascending numerical order. If two elements are equal when sorting the data, the respective subsequent element of the reconstructed components can serve as the current compared result for sorting, thereby reflecting the immediate trend of the time series. If respective subsequent element pairs are equal again, the elements are sorted according to their index in ascending order. Next, extract the index of every element for the original reconstructed components, and obtain a different symbolic series. Respectively make each of the pm! kind of symbolic series corresponding to a value between 1 and pm!. Thus, transform $\{X(i) : 1 \le i \le l\}$ into a new series in which each element has a value between 1 and pm!:

$$\{U(i) : 1 \le i \le l-(pm-1)\tau\} \quad (2)$$

For the above example, the first reconstructed component is {1, 1, 1}, the second reconstructed component is {1, 1, 2}, the third reconstructed component is {1, 2, 2}. Extract the index of every element for the first reconstructed component and get {1, 2, 3}. In a similar way, the indexes of the second reconstructed component and the third reconstructed component are {1, 2, 3} and {1, 2, 3} respectively. Here pm = 3, so $pm!$ = 6.

The permutation of the index is {1, 2, 3}, {1, 3, 2}, {2, 1, 3}, {2, 3, 1}, {3, 1, 2}, {3, 2, 1}. The number of the permutation is $pm!$ = 6. {1, 2, 3} corresponds to 1 and 1 is a digit symbol, {1, 3, 2} corresponds to 2, {2, 1, 3} corresponds to 3, {2, 3, 1} corresponds to 4, {3, 1, 2} corresponds to 5, {3, 2, 1} corresponds to 6. The above 2, 3, 4, 5, 6 is a digit symbol respectively. Thus, transform $\{X(i) : 1 \le i \le l\}$ into a new series in which each element has a value between 1 and pm!. In our example, $\{U(i) : 1 \le i \le l-(pm-1)\tau\}$ = U(1), U(2), U(3) = {1, 1, 1}.

Step 4. Reconstruct U in order, and let the length of symbolic series U be N. Then, generate a group of vectors with m dimensions:

$$Y_i^m = \{u(i), u(i+1), \dots, u(i+m-1)\} - u_0(i) \quad (3)$$

where $i = 1,2,\dots,N-m+1$, $m \le N-2$, $u_0(i)$ is its average and $u_0(i)$ is defined as:

$$u_0(i) = \frac{1}{m}\sum_{j=0}^{m-1} u(i+j) \quad (4)$$

Step 5. Define the distance d_{ij}^m between vectors Y_i^m and Y_j^m as the maximum difference between their corresponding elements:

$$\begin{aligned} d_{ij}^m &= d\left[Y_i^m, Y_j^m\right] \\ &= \max_{k\in(0,m-1)} \{|u(i+k)-u_0(i)-(u(j+k)-u_0(j))|\} \quad (5) \\ &(i,j = 1 \sim N-m, j \ne i) \end{aligned}$$

Step 6. Define the distance D_{ij}^m between vectors Y_i^m and Y_j^m through the fuzzy membership function $\mu(d_{ij}^m, n, r)$:

$$D_{ij}^m = \mu\left(d_{ij}^m, n, r\right) = \exp\left(\frac{-\left(d_{ij}^m\right)^n}{r}\right) \quad (6)$$

where the fuzzy function $\mu(d_{ij}^m, n, r)$ refers to the exponential function and n and r are the width and gradient of the exponential function, respectively.

Step 7. Define a function as follows:

$$\phi(n,r) = \frac{1}{N-m}\sum_{i=1}^{N-m}\left[\frac{1}{N-m-1}\sum_{j=1,j\ne i}^{N-m} D_{ij}^m\right] \quad (7)$$

Step 8. Change the reconstructed dimension from m to $m+1$, and repeat steps 4 to 7 to generate a group of vectors with $m+1$ dimensions. Subsequently, define a function as follows:

$$\phi^{+1}(n,r) = \frac{1}{N-m}\sum_{i=1}^{N-m}\left[\frac{1}{N-m-1}\sum_{j=1,j\ne i}^{N-m} D_{ij}^{m+1}\right] \quad (8)$$

Step 9. Define the fuzzyEn of the given U series as equation (9).

$$FuzzyEn(m,n,r) = \lim_{N\to\infty}\left[\ln\phi^m(n,r) - \ln\phi^{m+1}(n,r)\right] \quad (9)$$

Step 10. When the length N of series U is a fixed value, the estimated value of the corresponding fuzzyEn is expressed as

$$FuzzyEn(m,n,r,N) = \ln\phi^m(n,r) - \ln\phi^{m+1}(n,r) \quad (10)$$

where m and r are the dimension of the phase space and the similarity tolerance, respectively.

Step 1–3 above are performed to symbolize the original time series $X(i)$ as $U(i)$, and step 4–10 are performed to compute the fuzzyEn of $U(i)$ and thereby to obtain the PFEN of the original time series $X(i)$.

In the process of sorting and symbolization, when the length of time series $N < 200$, pm is set to 3; when $N > 200$, pm is set to 4. These values are based on the following factors: when $pm <$ 3, there is less permutation and combination, which will make the process meaningless; however, a larger pm is not necessarily better. Although a larger pm can correspond to more permutation cases, the time complexity of the algorithm increases accordingly. Bandt and Pompe [13] suggested that pm should be between 3 and 7. Li *et al.* [14] suggested that pm should satisfy $pm! + (pm-1)\tau \ll N$ when pm is selected as the parameter; that is, under the premise that

the requirement of being sensitive to changes in systemic transient features is satisfied, *pm* should be set to a smaller value to reduce the time complexity of the algorithm. The time delay τ, which is used during sorting and symbolization, is set to 1 to allow more information to be obtained from an EEG [15–18].

Further, when computing the fuzzyEn based on the symbolic time series, the dimension m of phase space is set to 2, and the similarity tolerance is set to 0.25 times the standard deviation of the original data.

3. Methods

One of important symptom of schizophrenia is a deficit of sensory gating [19]. Sensory gating reflects the inhibitory function of the brain, and P50 sensory gating, which is a reliable electrophysiological indicator of inhibitory brain function, is a useful tool for the analysis of schizophrenia [20]. The detection modes for sensory gating include the conditioning-testing stimulus paradigm and the stimulus sequence mode; with the former more widely used. Under the conditioning-testing stimulus paradigm, subjects are stimulated by repeated pairs of short sounds with a homogeneous pure tone (usually clicks, inter-click interval 500 ms) [21].

The tests were performed according to the requirements for ERP recording proposed by Hashimoto *et al.* [22]. The auditory conditioning (S1)-test (S2) stimulation paradigm was applied to detect the P50 auditory evoked potentials of all subjects. The stimulating materials were coupled short sounds with a pure tone, generally clicks, evoked by a rectangular wave. The sound intensity was 80 dB, and the duration 50 ms. Sounds were played through headphones to the subjects. The interval between the coupled stimuli was 500 ms, and the interval between each pair of stimuli was 10 s. There were 60 sets of paired stimuli and they appeared in three blocks Each subject participated in an experiment lasting approximately 12 minutes. A brain electrical physiological recording device with 64 leads that was used to record the brains electrical signals. A Brain Amp amplifier was used, and the data sampling rate was 500 Hz.

Data were collected in a hospital in Shanxi province, where there were 80 schizophrenic patients and 312 normal subjects. To avoid the influence of age on the analysis of results, the age of subjects was limited to between 40 and 50 years old for both the schizophrenic (test) and normal (control) groups. After this filtering, there were 27 test subjects, of whom 17 were male and 10 were female. Although many subjects in the control group participated in the experiment, the majority of them did not give their age. Therefore, 20 subjects who satisfied the age requirement and whose channel information records were complete were selected, of these 8 were male and 12 were female.

4. Results

The data analysis procedure was: (i) Preprocess raw data; (ii) Compute the entropy complexity of every subject for stimuli S1 and S2, and average the entropy of every subject under every stimulus; (iii) Perform a statistical analysis of the entropy of test and control groups under S1 and S2, and examine any differences.

The work flow of ERP data preprocessing is given in Fig. 1. First, the reference electrodes were reselected, as different reference electrodes may have different impacts on ERP results. The more commonly used average reference electrodes were selected for the data pretreatment of ERP. 0.5 $\sim$ 50 Hz and 24 dB/oct were adopted for the digital filtering to constrain the signal between 0.5 Hz and 50 Hz.

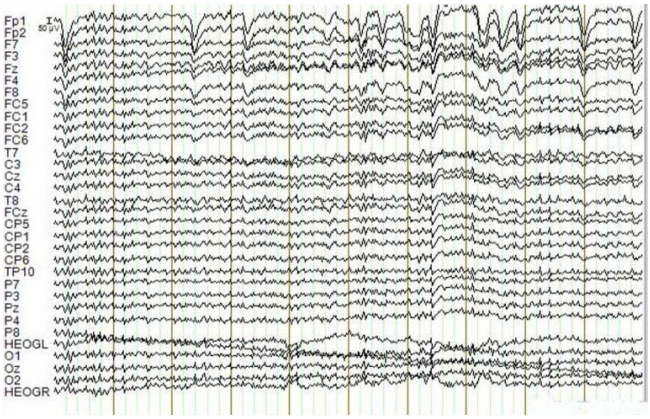

Fig. 1. Steps of preprocessing ERP data using Analyzer software. Raw data can be pretreated in the work flow.

When segmenting, the beginning and end of S1 was set to -500 ms and 900 ms, respectively, to give 60 segments. The width of the window was 400 ms for the complexity analysis and it was started from the beginning of either S1 or S2.

To study the changes in different regions of the brain, 11 channels located in different brain regions were selected; they are circled in red in Fig. 2. Following preprocessing, 11 boxes of channels, namely, F3, Fz, F4, T7, C3, Cz, C4, P3, Pz, P4 and T8, were exported and saved. PFEN was repeatedly used to compute the characteristics of entropy complexity.

(1) For every subject, the entropy complexity of the EEG was computed from 400 ms after either S1 or S2 for each stimulus pair.

(2) For all subjects, the average of the entropy obtained during S1 and S2 were computed.

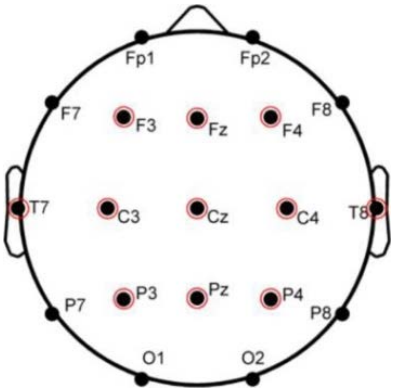

Fig. 2. Position of the 11 selected electrodes. Channels were located in different brain regions.

To determine how the conditioning stimulus affects the testing stimulus under conditioning-testing stimulation, the differences in the entropy complexity of both groups under S1 and S2 were compared. The average curves of entropy complexity for the two groups are shown in Fig. 3, where the black and grey plots give the entropy curve for S1 S2, respectively.

Wilcoxon's signed rank test was applied to test whether any significant differences existed between the entropy complexes obtained

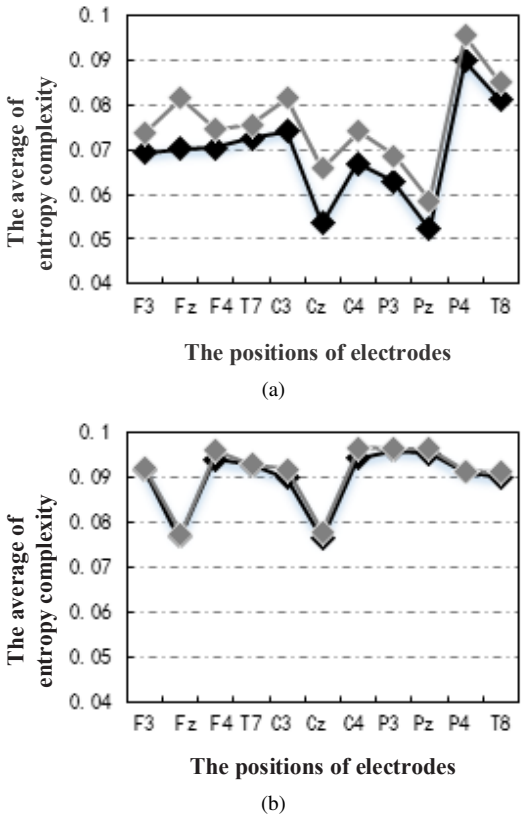

Fig. 3. (a) Mean PFEN plot for control subjects under stimuli S1 and S2. The black and grey plots give the entropy curve under S1 and S2, respectively. (b) PFEN mean plots of test subjects in response to S1 and S2 stimulation. The black and grey plots give the entropy under S1 and S2, respectively.

for the two subject groups in response to S1 and S2. A significance level of 0.01 was assumed for the analysis. Results are shown in Table 1 and Table 2.

Table 1. Statistical Test Results of Entropy Analysis of Schizophrenia Data

Channel (electrode position)			F3	Fz	F4	T7	C3	Cz
Normal	p value	PFEN	0.0002	0.0001	0.0022	0.0051	0.0012	0.0001
		PE	0.7938	0.0072	0.2043	0.2959	0.2180	0.3507
		FuzzyEn	0.0859	0.1560	0.0304	0.0057	0.0859	0.8519
	Significance	PFEN	***	***	**	**	**	***
		PE		**				
		FuzzyEn				**		
Schizophrenia	p value	PFEN	0.1864	0.0754	0.0163	0.5322	0.0837	0.3130
		PE	0.4279	0.9234	0.7731	0.8101	0.1075	0.7007
		FuzzyEn	0.1075	0.5642	0.0186	0.8288	0.5971	0.8664
	Significance	PFEN						
		PE						
		FuzzyEn						

*** indicates that the differences have statistical meaning($p < 0.001$),
** indicates that the differences have statistical meaning($p < 0.01$).

Table 2. Statistical Test Results of Entropy Analysis for Schizophrenia Data (continued Table)

Channel (electrode position)			C4	P3	Pz	P4	T8
Normal	p value	PFEN	0.0003	0.0001	0.0001	0.0010	0.0051
		PE	0.1084	0.0333	0.0017	0.4115	0.7369
		FuzzyEn	0.0930	1.0000	0.9405	0.3135	0.4330
	Significance	PFEN	***	***	***	**	**
		PE			**		
		FuzzyEn					
Schizophrenia	p value	PFEN	0.0411	0.4279	0.4711	0.4140	0.0679
		PE	0.0306	0.5165	0.6480	0.7916	0.7548
		FuzzyEn	0.9044	0.2488	0.0643	0.1563	0.9808
	Significance	PFEN					
		PE					
		FuzzyEn					

*** indicates that the differences have statistical meaning($p < 0.001$),
** indicates that the differences have statistical meaning($p < 0.01$).

5. Discussion

According to the statistical analysis of the results given in Table 1 and Table 2 and in comparison with Fig. 3, the PFEN index displayed two main features:

(i) The entropy plot of patients with schizophrenia under S1 was not different from that under S2, and the entropy complexity that patients with schizophrenia presented under conditioning stimulus S1 was not significantly different from that under test stimulus S2.

(ii) The entropy curve of the normal control group under testing stimulus S2 is higher than that under conditioning stimulus S1, and the three types of the entropy indices indicate significant differences in every observed brain area.

According to Fig. 3, the PFEN curve for the control group under the testing stimulus S2 is higher than that under the conditioning stimulus S1. This is because the control group maintains the normal function of sensory gating and can rapidly activate inhibitory pathways in response to the conditioning stimulus S1. The inhibitory pathways initiate a smaller response to test stimulus S2 than that evoked by the conditioning stimulus S1, thereby enhancing the unordered activity of the subject's brain, thus recovering to a more normal level compared with S1. Therefore, the entropy under testing stimulus S2 is higher than that under conditioning stimulus S1. However, the two PFEN plots from the group with schizophrenia approximately overlap, and the above features are not found, This reflects the fact that the sensory gating of schizophrenic patients has flaws and cannot effectively inhibit stimulus S2. Thus, the entropy complexity under stimulus S2 is not significantly higher than that seen for stimulus S1.

According to the data listed in Table 1 and Table 2, the PFEN values in every observed brain area of the control group under conditioning stimulus S1 and testing stimulus S2 all indicate significant differences ($p < 0.001$). In other words, the PFEN index exhibits strong performance in the analysis of ERP data.

Moreover, the entropy associated with electrode position Cz shows a larger difference than the entropies obtained from the other electrode positions in the plot graphed for the control group (see, Fig. 3a). This indicates that the signals collected at position Cz more effectively detect P50 potentials. Similarly, Smith *et al.* [23] found that the P50 potentials in Cz were more marked than those at other

electrode positions. This again demonstrates that PFEN is suited to the analysis of the abnormal ERP signals of schizophrenia.

6. Conclusion

PFEN was applied to analyse the ERP signals of patients with schizophrenia. ERP signals had lower signal-to-noise ratios than EEG signals do in response to conditioning and testing stimuli. Results suggest that the performance of PFEN in the analysis of P50 sensory gating in schizophrenics is significant.

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Conflict of Interest

All authors declare no conflict of interest.

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