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Changes in EEG measurements in intractable epilepsy patients with neurofeedback training

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Abstract

To assess the effects of neurofeedback on brain electrophysiology and to determine how biofeedback works, power spectral density (PSD) and approximate entropy (ApEn) analyses are applied to the EEGs of six patients with intractable epilepsy who received neurofeedback training. After sessions of treatment, the EEG sensorimotor rhythm to theta PSD ratio calculated from the C4 electrode site becomes larger than that before the treatment, which is consistent with the biofeedback protocol. The ApEn over 16-channel EEG recordings all increase to different degrees. Larger increases occur in channels located near the training position (C4). All these results suggest that these EEG measurements are new criteria that can be used to evaluate the effect of neurofeedback.
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Keywords: Biofeedback; Electroencephalogram; Epilepsy; Power spectral density; Approximate entropy

1. Introduction

Epilepsy is a common serious neurological disorder that is characterized by recurrent seizures [1]. Approximately 1% of the world's population suffers from this chronic disease. For many epilepsy patients, seizures cannot be controlled sufficiently by antiepileptic pharmacologic therapy, and surgical treatment may be possible in only a small number of cases. About 20–30% of patients continue to have seizures that are drug-resistant and intractable to current medical and/or surgical therapies [2]. For such patients, a behavioral treatment – neurofeedback (also called EEG biofeedback) is a good choice, based on an operant conditioned reflex. Many studies have shown that neurobiofeedback is an effective therapy or adjuvant therapy and can help not only in seizure control, but also has the exciting potential of having a positive impact on both health and quality of life of epilepsy patients. For epilepsy patients, neurofeedback is usually accomplished by training the brain to de-emphasize EEG rhythms which lead to generation and propagation of seizures and to emphasize EEG rhythms which make seizures less likely to occur [3]. Various techniques of EEG biofeedback have been used in epileptic patients, including slow cortical potentials (SCPs) and sensorimotor rhythm (SMR) training [4]. Feedback of SCP, developed by Birbaumer et al. [5] and Rockstroh et al. [6], is a relatively new method and has proved effective in reducing seizure frequency [7], but not all patients are capable of regulating their SCPs. There are more studies assessing SMR self-regulation than self-regulation of SCPs [4].

The SMR (12–15 Hz) over the sensorimotor cortex, initially described in cats, is neurophysiologically associated with alert and motionless processes [4]. One change in the EEG of epilepsy patients is that SMR production is decreased while theta (4–9 Hz) production is increased compared with normal subjects. Therefore, SMR neuro-

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feedback training is always done by enhancing the production of 12–15 Hz wave activity and inhibiting the production of 4–9 Hz wave activity. Sterman and Friar first applied SMR training to patients with epilepsy, in the early 1970s [8]. They produced numerous original reports on the effects of neurofeedback training. After this pioneering research, further work was carried out by Sterman, McDonald and Finley [9–11]. In 1978, Kuhlman confirmed that reduction in seizure frequency was due to biofeedback, and not to other possibilities such as placebo [12]. In 1981, Lubar et al. reported the first double-blind ABA (A = suppress 3–8 Hz slow EEG activity, B = enhance 3–8 Hz slow EEG activity) crossover study on eight epilepsy patients [13]. Thus, over the course of many years of study, the effectiveness of the SMR technique has been justified by physiological data and supported by successful clinical trials [4].

Although a large number of neurofeedback studies have been published, there are very few systematic investigations exploring the variations in different EEG measurements during biofeedback in epileptic patients, including linear measurement and nonlinear measurement. However, such information is important to assess the overall effects of biofeedback training [14]. In this study, patients with intractable epilepsy participated in sessions of neurofeedback training, and then the variations in different EEG measures were calculated. Consequently, with the changes in these electrophysiological measurements, we could evaluate the efficacy of neurofeedback from a new perspective other than the reduction of seizure frequency, which also could provide convincing support for the therapeutic outcome. Second, from the changes of these measures before and after biofeedback training, we could determine how biofeedback works.

2. Materials and methods

2.1. Subjects

Six patients with intractable epilepsy participated in this study, three males and three females, ranging in age from 14 to 60 years. The six patients were suffering from a wide range of disorders, including grand mal epilepsy, minor epilepsy, myoclonic epilepsy and psychomotor epilepsy. Table 1 presents a description of the subjects.

Table 1
Summary of the patients.

Patient No.	Gender	Age	Duration of training (months)	Number of EEG records
1	Male	43	4	6
2	Female	23	18	8
3	Male	28	4	5
4	Female	60	3	3
5	Female	14	3	3
6	Male	23	8	4

2.2. Experimental design and EEG data acquisition

The apparatus used in the biofeedback training was ProComp Infiniti produced by Thought Technology Ltd. It comprised an 8-channel encoder with 14-bit resolution, which could record a variety of bio-potential signals. In our study, we applied 1-channel EEG to biofeedback training.

The patient was comfortably seated with head and arms at rest. Electroencephalic activity was recorded with one scalp electrode placed on the position C4 (International 10–20 system) against a reference electrode linked to ear lobe A2. The patient was trained to increase the production of SMR (12–15 Hz) activity and decrease the production of theta (4–9 Hz) wave activity. Biofeedback training consisted of a visual game on the computer screen and audio at the same time. The EEG signal controlled the status of the game and the audio in real-time. The game and/or the audio were active only when the SMR activity was higher than the preset threshold and the theta activity was lower than another preset threshold, which constituted the reward procedure. The patient was told to be simply relaxed and keep the game and the audio active.

All patients took part in 2–3 training sessions per week. Each training session consisted of the following sequence: about 3–5 min of baseline recording without feedback, in order to establish the thresholds; then there was about 30–45 min of feedback training including different games at different difficulty levels. The training time could be adjusted according to the status of the patient. The total training durations of the patients (in months) are shown in Table 1.

To compare the effects of the treatment using EEG analysis, EEG recordings for evaluation of training effects were acquired on another 16-channel Video-EEG system (WeiSi Medical Apparatus Co., Ltd), with a sampling frequency at 128 Hz. The 16 scalp locations were Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5 and T6 [15]. The number of EEG recordings for each patient is also listed in Table 1. The 16-channel EEG signals were usually recorded before a subject received biofeedback training and after about 10 training sessions; others were acquired at different times according to the length of treatment.

2.3. EEG measurements

In this study, the EEG linear measurement (PSD) and nonlinear measurement (approximate entropy (ApEn)) were used to evaluate the differences in EEG signals before and after treatment.

2.3.1. EEG PSD

The EEG power spectrum can be estimated by the model-based method, which consists of two steps. First, the parameters of the model are estimated from a given data sequence. Then, the PSD is estimated from these computed parameters. Because the estimation of auto regres-

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sive (AR) parameters can be done easily by solving linear equations, the AR method is the most frequently used parametric method [16]. In this study, PSD was calculated using the AR model by Burg's method. This method fits an AR model to the input data by minimizing (least squares) the forward and backward predictive errors, while constraining the AR parameters to satisfy the Levinson–Durbin recursion. A brief description of this method is given by Proakis and Manalakis [17].

2.3.2. Approximate entropy

Nonlinear dynamic approaches to studying the biopotential signals have recently come to the fore. ApEn [18], as a nonlinear measurement, can be used as a criterion of the complexity of a signal. The more regular the signal, the smaller its ApEn. Let the original EEG data be

$$\langle x(n)\rangle = x(1), x(2), \ldots, x(N)$$

where N is the total number of data points. Two parameters must be specified before ApEn can be computed: m, the embedding dimension of the vector to be formed, and r, a threshold that is, in effect, a noise filter.

(1) Form m-vectors $X(i)$ defined by:

$$X(i) = [x(i), x(i+1), \ldots, x(i+m-1)],$$
$$i = 1, \ldots, N-m+1$$

(2) Define the distance between $X(i)$ and $X(j)$, $d[X(i), X(j)]$, as the maximum absolute difference between their corresponding scalar elements, i.e.,

$$d[X(i), X(j)] = \max_{k=0,m-1} [|x(i+k) - x(j+k)|]$$

(3) For a given $X(i)$, find the number of $d[X(i), X(j)]$ ($j = 1, \ldots, N-m+1$) that is $\leqslant r$ and the ratio of this number to the total number of m-vectors $(N-m+1)$,

Let $N^m(i)$ = number of $d[X(i), X(j)] \leqslant r$, then

$$C_r^m(i) = N^m(i)/(N-m+1), \quad i = 1, \ldots, N-m+1$$

(4) Take the natural logarithm of each $C_r^m(i)$ and average it over i:

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

(5) Increase the dimension to $m+1$. Repeat steps (1)–(4) and find $C_r^{m+1}(i), \phi^{m+1}(r)$.

(6) Theoretically, the approximate entropy is defined as

$$\mathrm{ApEn}(m, r) = \lim_{N\to\infty} [\phi^m(r) - \phi^{m+1}(r)]$$

In practice, the number of data points N is finite, and the result obtained through the preceding steps is an estimate of ApEn, which is denoted by

$$\mathrm{ApEn}(m, r, N) = \phi^m(r) - \phi^{m+1}$$

Goldberger showed [19] that values of r from 0.1 to 0.25 times the SDx, where SDx is the standard deviation of the original data $\langle x(n)\rangle$, together with a value of m equal to 2, produced a good statistical validity of ApEn(m, r, N).

3. Results

After a number of biofeedback training sessions, all six patients exhibited a reduction in seizure frequency, and the seizure symptoms were all significantly relieved. The PSD and ApEn analyses that were used to evaluate the changes in EEG signals before and after treatment are detailed below.

3.1. Changes in PSD after biofeedback training

3.1.1. The order of the AR method

One of the most important aspects of the AR method is the selection of the order p. Much work has been done by various researchers on this problem. In this work, the order of the AR method was estimated under the evaluation methods of the Akaike Information Criterion (AIC), and the Bayesian Information Criterion (BIC) [20]. One EEG record was randomly selected to calculate the AIC and BIC with p. When the AIC and BIC values all reached a minimum and changed very little, the optimal value of p was chosen, and it was 13.

3.1.2. Changes in PSD after biofeedback training

For all six patients, 16-channel EEG signals were recorded before and after different sessions of neurofeedback training as described in Section 2.2. To study the changes in PSD before and after treatment, the PSDs were calculated for each of the signals using Burg's method (AR

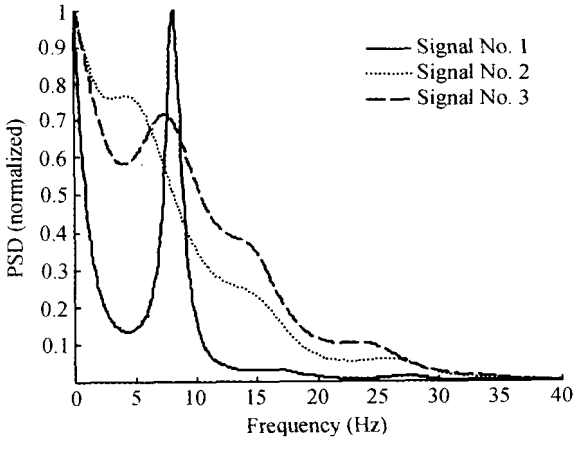

Fig. 1. PSD changes of patient No. 4 before and after biofeedback.

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model). Fig. 1 shows the PSDs of patient No. 4 calculated from electrode C4, which is identical to the biofeedback training site. In Fig. 1, EEG signal No. 1 was recorded before this patient received neurofeedback treatment, and signals No. 2 and No. 3 were recorded at different times in the therapeutic period.

It can be observed from Fig. 1 that, as expected, the relative intensity of theta activity (4–9 Hz) after training (signal No. 2–No. 3) became weaker than that before training (signal No. 1), while the SMR activity (12–15 Hz) was the opposite. The PSD ratio of SMR to theta changed from 5.5% to 23.9% and to 35.1%. This result can be supported by the therapeutic protocol: increasing the SMR activity and decreasing the theta activity. Other patients showed similar results.

3.2. Changes in ApEn after biofeedback

3.2.1. The effect of data length on ApEn

Usually, long data sequences are needed to accurately estimate nonlinear parameters. How long should the data be so that robust estimates can be obtained for this EEG measurement? Three records of stationary EEG signals were randomly chosen to resolve this question. Each record was divided into segments with different lengths: ranging from 256 points to 6400 points by 256-point steps, with the sampling time of each segment varying from 2 to 50 s. The ApEn of each segment was calculated and the results are shown in Fig. 2.

From Fig. 2, we can see that the ApEn varied very little when the data sample time reached 30 s. The standard deviations of three EEG records were 0.0024, 0.0045 and 0.0034 (from bottom to top) when the data length N varied from 3840 (30 s) points to 6400 (50 s) points. So we selected 30 s EEG data as our computational length, which contained 3840 points. Other parameters used for the ApEn calculation were as follows: m taken as 2 and r as 0.2 SDx.

3.2.2. Changes in ApEn after biofeedback

During the course of biofeedback treatment, each patient had a different number of EEG records. Each record had 16-channel signals, and each channel acquired about 5 min of data. For ApEn computation, the EEG data of each channel were divided into consecutive 30 s segments with an overlap of 10 s. ApEn analysis was applied to all segments. Then we averaged the calculated ApEn over all segments for each record of each channel. The results calculated from electrode C4 are shown in Table 2.

In Table 2, the first EEG records of all patients were acquired before the subjects received biofeedback training, and the second records were made after about 10 training sessions when the training duration was about one month. Others were acquired at different times over the treatment duration. From Table 2, we can see that the nonlinear measurements, ApEn, of the six patients were all increased compared with the first record (before training) at about 10 sessions from the beginning of the treatment. For example, in case 2, the ApEn increased from 0.746 to 1.092 after about 10 sessions, while in case 6, the ApEn increased from 1.079 to 1.699. With treatment continuing, all ApEn values increased from those before treatment to some extent, although with some fluctuation.

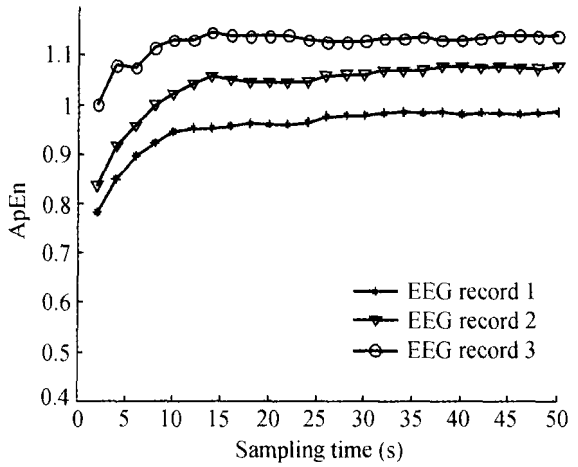

Fig. 2. Values of ApEn changed with different data length.

Table 2
ApEn calculated from the C4 site for each record of each patient.

Record No.	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
1	1.058	0.746	1.190	1.060	0.948	1.079
2	1.157	1.092	1.880	1.736	1.328	1.699
3	1.128	0.880	1.436	1.189	1.425	1.167
4	1.735	0.942	1.759	–	–	1.180
5	1.194	1.064	1.774	–	–	–
6	1.102	0.770	–	–	–	–
7	–	1.142	–	–	–	–
8	–	0.995	–	–	–	–

The cortex is more active and more chaotic under normal physiological conditions, while in pathological conditions, the cortex becomes inactive and EEG becomes less random. The above result reveals that biofeedback training can increase the degree of random electrical activity of the cortical neuron population under pathological conditions, so that the symptoms of epilepsy are improved and seizures alleviated. Thus, the ApEn criterion can be used to evaluate the effect of EEG biofeedback. It may give an indication of the electrophysiologic basis of EEG biofeedback.

3.2.3. Changes in ApEn at 16 scalp locations

To investigate the trend of ApEn at the 16 scalp locations after treatment, the growth rates of ApEn over 16 electrode sites after biofeedback training compared with the ApEn before treatment were calculated. The average growth rate of the six patients overall is shown in Table 3 with the growth rates arranged in descending order.

From Table 3, we can see that the channels with a growth rate of ApEn greater than 20% were C4, P4, O2, F4, F8, FP1 and FP2. In order to observe the change in

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Table 3
Average growth rates of ApEn calculated from the 16-channel EEG of six patients.

Location	C4	P4	O2	F4	F8	FP1	FP2	F3
Average growth rate (%)	33.02[a]	30.10[a]	25.73[a]	25.09[a]	23.04[a]	22.69[a]	19.65[b]	18.40[b]
	P3	T4	C3	F7	O1	T6	T3	T5
Average growth rate (%)	15.60	15.18	12.11[b]	8.00	4.73	4.66	1.22	0.85

[a] $p \leqslant 0.01$.
[b] $p \leqslant 0.05$.

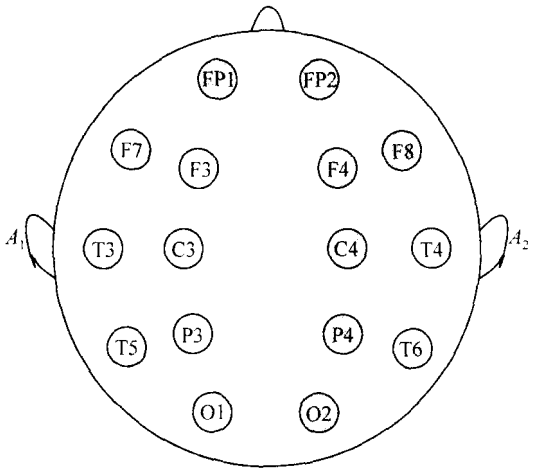

Fig. 3. Changes in ApEn over 16 electrode sites (blackened are locations with growth rates higher than 20%).

ApEn over the 16 electrode sites, all these locations are blackened on the Head Model map in Fig. 3.

Paired t-tests were conducted in order to validate whether there was a significant difference between the paired values before and after treatment over the 16 electrode sites. The statistical results showed that there was a highly significant difference ($p < 0.01$) at sites C4, P4, O2, F4, F8 and FP1, and a significant difference ($p < 0.05$) at sites FP2, F3 and C3, while others showed no difference.

After a number of training sessions, the seizure symptoms of patients were all relieved significantly. From Fig. 3 and the t-test results, we can presume that the ApEn calculated from the EEG recordings all increased synchronously by different degrees: a larger increase occurred mainly in channels located near the training position (C4) and in the same hemisphere as C4. This result indicates that biofeedback training can work effectively, mainly surrounding the training position. This may help in making the choice of training position in patients with different foci.

4. Discussion

Neurofeedback as a behavioral therapy approach, based on self-modulation of the EEG, has proved effective in the treatment of epilepsy. The goal of this study was to explore the variations of different EEG measurements, including a linear measurement and nonlinear measurement before and after biofeedback training, which are important to assess the effects of neurofeedback and to determine the mechanism of biofeedback.

In this study, six patients with drug-resistant epilepsy were trained to increase 12–15 Hz EEG activity and to decrease 4–9 Hz activity. After a number of sessions of treatment, the seizure symptoms of all the patients were improved, and, at the same time, the EEG PSD of theta calculated from the C4 electrode site became weaker, while the SMR was the opposite, which is consistent with the biofeedback protocol. The change in the nonlinear measurement, ApEn, was also explored. The results demonstrated that all ApEn increased at about 10 sessions after the beginning of treatment compared with those of the EEG recordings before training. The ApEn over the 16-channel EEG recordings all increased, but by different degrees. Greater increases occurred in channels located near the training position (C4) and in the same hemisphere as C4. All these results suggest that EEG biofeedback training helps the electrophysiological activity of the cortical neuron population to become more chaotic and, thus, alleviate the symptoms of epilepsy. ApEn is a criterion that can be used to evaluate the effect of EEG biofeedback.

Further work can be done as follows:

(1) In our study, a relatively small number of patients were studied, and no control was involved. A larger patient pool should be investigated in future studies, and a control group should be included.
(2) In the future, the nonlinear measurements, such as ApEn discussed above and fractal dimensions could be incorporated into the biofeedback setting, which mainly consists of frequency parameters at present. Further work should be done to incorporate the above-mentioned nonlinear measurements into online apparatus: how to accelerate the computation speed and how to select the appropriate parameters should first be studied carefully.

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