Computational evaluation of the effectiveness of therapy method with help recurrent analysis

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Abstract. Using the method of recurrent analysis of electroencephalograms of the brain with subsequent one-way analysis of variance, the effectiveness of the therapy method used in the clinic, associated with the formation of stable functional connections of the brain in patients with disorders of the functional state of the central nervous system corresponding to the initial stage of vascular pathology, was assessed. Decrease in the percentage of recurrent points located on the diagonal lines of recurrent diagrams and the coefficient of mutual correlation between the probabilities of recurrences of the light signal and the response of the brain to the theta and beta frequencies, as well as an increase in these indicators for the alpha-range frequencies after therapeutic effects, confirm the effectiveness of the considered therapy.

1. Introduction

Among the tasks of modern medicine, it is extremely important to find effective methods of clinical therapy for disorders of the functional state of the central nervous system of a person associated with the risks of developing cognitive and emotional-personality disorders [1]. In this case, it is necessary to take into account not only the importance of using such methods, but also an assessment of their effectiveness based on the analysis of the quantitative characteristics of the bioelectric activity of the brain before and after the clinical methods used. Modern mathematics offers many methods for linear and non-linear analysis of complex non-stationary signals [2, 3]. Among them, one can single out the methods of recurrent analysis, which make it possible to assess the quantitative characteristics of electroencephalograms of the brain [4]. Earlier, we showed the possibility of applying the methods of wavelet and recurrent analysis to assess the change in the degree of neurotization in patients with neurological disorders in the form of panic attacks after therapeutic interventions aimed at the formation of functional brain connections during rhythmic photostimulation [3].

The aim of this work was to assess the effectiveness of such effects associated with the formation of stable functional connections of the brain in patients with impaired functional state of the central nervous system corresponding to the initial stage of vascular pathology. For this, after analyzing the joint recurrent diagrams of rhythmic light signals and brain responses to these signals, we used an additional, in addition to those considered earlier, indicator of these diagrams, such as the coefficient of mutual correlation between the probabilities of recurrences of the light signal and the brain's response to certain frequencies.
2. Methods

The characteristics of the electroencephalograms of the brain of 20 patients (women) were studied before and after treatment sessions conducted in the clinic of the N.P. Bekhtereva, the study was approved by the local ethics committee. According to MRI data, all tested patients showed moderate disorders of the functional state of the brain, corresponding to the initial stage of vascular pathology. The average age of the patients was 61.6 ± 5.4 years. The course of 10 treatment sessions consisted in the formation of functional connections of the brain during rhythmic photostimulation against the background of a single dose of the pharmacological drug etimizole, which in a dosage of 0.01 mg serves as a nonspecific connector that helps fix memory traces [5]. Before the start of the course and after it, the bioelectric activity of the brain was recorded using a 21-channel electroencephalograph and psychological testing was carried out to assess short-term memory (double test) [6]. Rhythmic photostimulation consisted of a sequence of eight-second series of light pulses with different frequencies with an interval of 30 seconds between series. Brain responses were recorded at the occipital loci O1, O2, where the brain’s responses to a light stimulus have the greatest amplitude. The sampling rate was 256 Hz.

The light signal was set by a sequence of \( n \) pulses following each other with a given frequency \( f_p \):

\[
p(t) = \sum_{j=0}^{n-1} 0.5 \frac{r_0}{r_0 \sqrt{\pi}} \exp\left(-\frac{(t - t_j)^2}{4r_0^2}\right),
\]

where \( r_0 = 10 \) ms – pulse width, \( t_j \) - centers of impulses in points \( t_j = t_A + j \frac{1}{f_p}, j = 0,...,n-1, t_A \) – start time of the first pulse in the sequence.

Joint recurrence with an accuracy of \( \varepsilon \)-error is defined as the return of the state \( y_j \) of the phase trajectory of the EEG signal to the state \( y_i \) and the simultaneous return of the state \( z_j \) of the phase trajectory of the light signal to the state \( z_i \) [4]. A joint recurrent diagram is a graphical representation of a matrix:

\[
R_{i,j}(\varepsilon) = \begin{cases} 
1, & y_i \approx y_j, z_i \approx z_j, \\
0, & y_i \neq y_j, z_i \neq z_j,
\end{cases}
\]

where the values 1 or 0 correspond to recurrence or no recurrence.

The phase trajectories of the states \( z(t) \) and \( y(t) \) were obtained from the initial signals in the EEG \( x(t) \) and the photostimulus \( p(t) \) by the method of time delays [7]:

\[
y(t) = (x(t), x(t + d), ..., x(t + (m - 1)d)).
\]

The optimal time delay \( d \) was found based on the search for the first minimum of the mutual information function [8]. The optimal embedding dimension \( m \) was determined by the method of finding the minimum of the nearest false neighbors [9]. Isolation of the signal in a narrow frequency band near the frequency of photostimulation made it possible to find the value \( m = 3 \) as the optimal dimension of embedding. The value of \( \varepsilon \)-error was chosen equal to 1% of the standard deviation of the analyzed signal.

When analyzing the brain responses to a rhythmic photostimulus, we calculated such characteristics of joint recurrent diagrams [4] for electroencephalograms \( x(t) \) and photostimulus \( p(t) \), as the total number of recurrent points \( RR \) in the recurrence diagram:

\[
RR = \frac{1}{N^2} \sum_{i,j}^N R_{i,j}(\varepsilon),
\]

the ratio of the number of recurrent points making up the diagonal structures to the total number of recurrent points:

\[
DET = \sum_{i=t_{min}}^{N} IP(\varepsilon, I) \left( \sum_{i,j}^N R_{i,j}(\varepsilon) \right)^{-1}
\]

\[
IP(\varepsilon, I) = \sum_{i,j}^N R_{i,j}(\varepsilon)
\]

where \( t_{min} \) is the time delay obtained from the first minimum of the mutual information function.
where \( P(\epsilon, l) \) is the frequency distribution of diagonal lines of length \( l \) in the recurrent diagram, the coefficient of cross-correlation between the probabilities of recurrences of the light signal and the response of the brain \( P_1(m, \epsilon, \tau) \) and \( P_2(m, \epsilon, \tau) \) \[10\]:

\[
CPR = \frac{1}{\sigma_1 \sigma_2} \sum_{\tau=\tau_e}^{N/2} \left( P_1(m, \epsilon, \tau) - \bar{P}_1(m, \epsilon, \tau) \right) \left( P_2(m, \epsilon, \tau) - \bar{P}_2(m, \epsilon, \tau) \right),
\]

where

\[
P_1(m, \epsilon, \tau) = \frac{1}{N-\tau} \sum_{i=1}^{N-\tau} R_{i,j+d}(m, \epsilon)
\]

determines the probability of recurrence of the phase trajectory \( y(t) \) in the vicinity of the state \( y_j \) after time \( \tau \), \( \bar{P}_1(m, \epsilon, \tau) \) and \( \bar{P}_2(m, \epsilon, \tau) \) - mean probabilities, \( \sigma_1 \) and \( \sigma_2 \) - standard deviations \( P_1(m, \epsilon, \tau) \) and \( P_2(m, \epsilon, \tau) \).

Coincidence of the maxima of the recurrence probabilities \( P_1(m, \epsilon, \tau) \) and \( P_2(m, \epsilon, \tau) \) for two phase trajectories \( x(t) \) and \( y(t) \) at the same times \( k \tau \), where \( k \) – integer, means the presence of phase synchronization of two signals \[10\]. In this case, the value of the cross-correlation coefficient CPR is close to 1. If the signals are not synchronized, the maxima of the recurrence probabilities do not appear simultaneously, and the CPR value is close to 0.

The differences between the mean values of the indicators of the recurrence diagrams before and after the course of treatment sessions were assessed on the basis of one-way ANOVA. If the statistics obtained by the Fisher's F-test exceeded the critical value, then the null hypothesis about the equality of the means of the two groups was rejected.

3. Results

The dynamics of changes in the reaction of the brain to the photostimulus after a course of treatment sessions is confirmed by the change in simultaneous recurrences in the joint recurrent diagrams of electroencephalograms and light signals of certain frequencies.

Examples of such diagrams before and after the course are shown in figure 1c, d, respectively. These diagrams were constructed for a fragment of an electroencephalogram with a duration of 3 s during photostimulation with a frequency of 10 Hz with a time delay \( d = 3 \) and an attachment dimension \( m = 3 \). The corresponding fragments of an electroencephalogram during photostimulation with this frequency are shown in figure 1a, b with a bold blue line, and the photostimulus with a thin dash-dotted red line. The left recurrence diagram (figure 1c) contains very short diagonal lines localized in the vicinity of the always existing line passing at an angle of 45°. This indicates a weak joint recurrence in this photostimulus and the analyzed response. In contrast to this, the right diagram (figure 1d) has recurrent structures containing long diagonal lines, which indicates the occurrence of simultaneous recurrences in the photostimulus and response.

The lack of coincidence of the maxima of the recurrence probabilities for the phase trajectories of the photostimulus and the brain response indicates the absence of phase synchronization in the studied fragment of the electroencephalogram and the light stimulus before the treatment session (figure 1e). The occurrence of such a coincidence after this session (figure 1f) indicates the occurrence of synchronization (figure 1f). The value of the cross-correlation coefficient CPR = 0.01 before treatment, and after it, CPR = 0.61.
Figure 1. Fragments of an electroencephalogram with a duration of 3 s during photostimulation (blue line) and a light stimulus with a frequency of 10 Hz (red line) before and after a treatment session (a, b). Joint recurrent diagrams of these signals (c, d). Probabilities $P_1(m, \varepsilon, \tau)$ and $P_2(m, \varepsilon, \tau)$ recurrences for electroencephalogram (blue curve) and light signal (red curve) (e, f).

The average values of indicators of joint recurrent diagrams of electroencephalograms and photostimulus before and after treatment sessions are shown in Table 1. Averaging was carried out according to the values obtained for electroencephalograms of 17 tested patients, i.e. 85% of the total number of subjects who showed the presence of changes in the electroencephalograms.

The data in Table 1 show that after the therapy sessions, the total number of recurrence points (RR) in joint recurrence diagrams, the percentage of recurrence points located on diagonal lines (DET), and the coefficient of mutual correlation between the probabilities of light signal and brain response (CPR) recurrences, decrease for frequencies of 4 and 6 Hz, i.e. theta range, and for a frequency of 14 Hz, i.e. beta range. At the same time, for the frequencies of the alpha range (for frequencies of 10 and 12 Hz), these indicators increase after therapeutic effects. For example, for a photostimulus with a frequency of 6 Hz, the values RR = 0.36 ± 0.04, DET = 0.91 ± 0.09, CPR = 0.51 ± 0.05 before treatment sessions, and after these values are equal, respectively, RR = 0.03 ± 0.003, DET = 0.69 ± 0.07, CPR = 0.07 ± 0.007. For a photostimulus with a frequency of 12 Hz, before treatment sessions, RR = 0.07 ± 0.008, DET = 0.65 ± 0.06, CPR = 0.07 ± 0.006, and after these values RR = 0.32 ± 0.04, DET = 0.92 ± 0.09, CPR = 0.78 ± 0.08.

Table 1. Average values of the number of recurrent points (RR) in the joint recurrent diagrams of the electroencephalogram and light signals, the percentage of recurrent points located on diagonal lines (DET) and the coefficient of mutual correlation between the probabilities of recurrences of the light signal and the brain response (CPR).

| Patients (N = 17 out of 20) | Patients (N = 17 out of 20) |
|-----------------------------|-----------------------------|
| RR                          | RR                          |
| DET                         | DET                         |
| CPR                         | CPR                         |


| Frequency (Hz) | before treatment sessions | after treatment sessions |
|--------------|---------------------------|--------------------------|
|              | number of recurrent points RR |                          |
| 4            | 0.42 ± 0.04               | 0.11 ± 0.01              |
| 6            | 0.36 ± 0.04               | 0.03 ± 0.003             |
| 10           | 0.03 ± 0.003              | 0.24 ± 0.02              |
| 12           | 0.07 ± 0.008              | 0.32 ± 0.04              |
| 14           | 0.28 ± 0.03               | 0.09 ± 0.009             |

The ratio of the number of points making up the diagonal structures to the total number recurrent points DET

| Frequency (Hz) | before treatment sessions | after treatment sessions |
|--------------|---------------------------|--------------------------|
| 4            | 0.93 ± 0.09               | 0.62 ± 0.06              |
| 6            | 0.91 ± 0.09               | 0.69 ± 0.07              |
| 10           | 0.71 ± 0.07               | 0.89 ± 0.09              |
| 12           | 0.65 ± 0.06               | 0.92 ± 0.09              |
| 14           | 0.85 ± 0.08               | 0.59 ± 0.06              |

Cross-correlation coefficient between the probabilities of light signal recurrence and brain response (CPR)

| Frequency (Hz) | before treatment sessions | after treatment sessions |
|--------------|---------------------------|--------------------------|
| 4            | 0.78 ± 0.09               | 0.12 ± 0.01              |
| 6            | 0.51 ± 0.05               | 0.07 ± 0.007             |
| 10           | 0.01 ± 0.002              | 0.67 ± 0.06              |
| 12           | 0.07 ± 0.006              | 0.78 ± 0.08              |
| 14           | 0.62 ± 0.06               | 0.09 ± 0.01              |

Pairwise comparison of the mean values of the indicators of recurrent diagrams before and after treatment sessions, performed on the basis of one-way analysis of variance ANOVA, showed that for all frequencies of the photostimulus, the values of Fisher's statistics exceed the critical values and correspond to small values of the significance level p (p <0.003) ... This indicates the presence of significant differences between the average values of RR, DET and CPR for all frequencies of the photostimulus before and after treatment sessions. Such changes in the indicators of joint recurrent diagrams of electroencephalograms and photostimuli of certain frequencies indicate that after therapeutic sessions aimed at the formation of stable functional connections of the brain in patients with disorders of the functional state of the nervous system corresponding to the initial stage of vascular pathology, a weakening of the tions of the brain to a rhythmic photostimulus in theta and beta ranges. This, in turn, indicates the normalization of the functional state of the nervous system [11] and confirms the effectiveness of the applied therapy method. Strengthening the reaction of indicators of joint recurrent diagrams of electroencephalograms and photostimuli of the alpha-band frequencies after therapeutic sessions, also confirms the improvement in the functional state of the cerebral cortex and the improvement of its regulatory mechanisms [12]. Psychological testing for assessment of short-term memory (double test) confirmed the improvement of the functional state of the nervous system of patients after the applied course of therapeutic effects, showing a threefold increase in the index of short-term memory. Thus, like our previous work, which showed the applicability of recurrent analysis to assessing changes in the degree of neurotization in patients with neurological disorders in the form of panic attacks after therapeutic interventions aimed at the formation of functional brain connections during rhythmic photostimulation [3], the results of this work confirm the effectiveness of such effects.
for patients with impaired functional state of the brain, corresponding to the initial stage of vascular pathology.

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