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Original article

Change in brain electrical activity connectivity in migraine patients without aura

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Abstract:
Objective: In this study, we consider how the structure of the brain EEG activity changes in patients with migraine, compared with virtually healthy volunteers without complaints of acute or chronic headache.
Materials and Methods. The study of the connectivity of EEG activity was carried out on the basis of an objective assessment of pairwise synchronization between different recording channels, for which we used a method based on wavelet bicoherence.
Results. Within the framework of the performed experimental study, we demonstrated an increased reactivity in the structure of connections in brain electrical activity of the patients experiencing a weak visual impact.
Conclusion. A prospective study could determine the value of the described diagnostic procedure in support of the clinical decision on appropriate pharmacological and non-pharmacological prophylactic measures.

Keywords: EEG, connectivity, headache, migraine without aura, wavelet transform, bicoherence.

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Introduction

Currently, one of the usual and neurologically verified methods for analyzing brain activity is electroencephalography (EEG) registration and subsequent manual and/or mathematical analysis of the obtained records [1–5]. In contemporary neuroscience, EEG monitoring is frequently combined with simultaneous neuropsychological tests. Testing permits to selectively activate certain cognitive functions of a person and, presumably, the corresponding areas of the cerebral cortex. Such experimental approaches are widely used in various branches of neuroscience. In addition to the fundamental research of the cognitive mechanisms in human brain, such studies are promising in the development of brain-computer systems used to educate or rehabilitate patients with various diseases. In particular, various manifestations of pain syndromes attract much attention, since chronic pain can cause the development of neurological and psychiatric disorders [6–8]. In this paper, we will focus on migraine, the disease underlying primary headache, which currently affects up to 15% of the worldwide adult urban population under the age of 50 years old.

In this study, we consider how the structure of the brain EEG activity changes in patients with migraine, compared with virtually healthy volunteers without complaints of acute or chronic headache. In addition to being of fundamental interest, knowledge of pathophysiological mechanisms of migraine is of practical importance, since it can be integrated into a comprehensive approach to patient treatment in order to improve their quality of life.

Study Subjects and Design

All participants volunteered in our experiments on a complimentary basis. Our study subjects signed an informed medical consent to participate in the experimental work; they received all necessary explanations about the research, and agreed to the subsequent publication of the study results. Collected experimental data were processed sensu the principles of confidentiality and anonymity of research participants. The design of our experimental studies was approved by the local Ethics Committee.

The experimental study subjects were recruited among the outpatients with sleep disorders at the Pain Management Clinic (Saratov, Russian Federation).

The inclusion criteria for our study were as follows:

Male/female gender, over 40 and under 75 years of age;

Complaints for headache; primary migraine.

The exclusion criteria were as follows:

Beck Depression Inventory score (BDI) > 13 [9];

A score > 7 on the Hospital Anxiety and Depression Scale [10];

Sleep-onset insomnia (>30 min to fall asleep) and/or sleep maintenance disorder (two or more awakenings per night of >15 min long and/or wakefulness after sleep onset [WASO] time of >30 min);

A physical and/or psychiatric disorder;

Psychotropic medicine use over the last month.

All patients underwent neuropsychological status assessment by means of the Schulte Table test, Digital

Symbol Substitution Test (DSST), Hospital Anxiety and Depression Scale (HADS), somnolence and sleep quality test; as well as tests for semantic and phonemic awareness, and memory. A comparative assessment of the cognitive functions in study participants via DSST did not reveal significant differences in indicator values; all patients successfully completed the task with no more than two errors in 90 seconds, which was acceptable.

The study included two groups of subjects. The control group comprised of 25 healthy subjects (Group I, n=25; BMI: 21.8±3.2 kg/m2; BDI: 6±3; HADS: 5±2.1). The primary migraine group included 33 patients (Group II, n=33; BMI: 27±7.1 kg/m2; BDI: 7±2; HADS: 6±1.3). The ailment duration in Group II averaged 2.7 years.

The experiments were conducted in the late afternoon hours at a specially equipped laboratory. The day before and on the day of the experiment, every test subject did not have any episodes of a daytime sleep. During the experiment, while the participants were lying comfortably in a relaxed mode, their brain activity was measured (via EEG) in passive wakefulness with periodic visual stimuli (~35 minutes). All test subjects were instructed to stay awake with eyes open. In order to estimate their state of awakening/sleep, they were instructed to press a specific button on the remote control after each short visual stimulus. Visual stimuli alternated with pauses, the duration of which was set randomly in the range of [10;22] seconds. We automatically estimated the duration of time interval T_r between the visual stimulus and the test subject response (i.e., pressing the button). Time was recorded simultaneously for all protocols and EEG data.

The multichannel surface EEG data were collected using the Encephalan-EEGR-19/26 recorder (Medicom MTD, Ltd, Russia). Data were recorded at 250 Hz sampling rate using the conventional monopolar method of registration with two referential points and N=31 electrodes. The adhesive Ag/AgCl electrodes in prewired head caps were used to obtain the EEG signals. Two reference electrodes, A1 and A2, were located on mastoids, while the ground electrode N was placed above the forehead. EEG signals were filtered by a band-pass filter with cutoff points at 0.5 Hz (HP) and 70 Hz (LP) and a 50 Hz notch filter.

Methods

The study of the connectivity of EEG activity was carried out on the basis of an objective assessment of pairwise synchronization between different recording channels. To assess the degree of synchronization between different channels of EEG data, a method based on the use of wavelet bicoherence was used [11]. At the first step, the complex coefficients, W_n (f,t) , of the continuous wavelet transform are calculated for each EEG channel, x_i (t) :

$$W_i(f,t) = \sqrt{f}\int_{t-4/f}^{t+4/f} x_i(t)\psi^*(f,t)dt, \qquad (1)$$

where i=1,...,N is the number of the considered EEG channel (and N=6 is the total number of EEG channels), * denotes complex conjugation, and ψ(f,t) is the main wavelet function. In the framework of our research, the Morlet wavelet, often employed for processing biological signals, was used as a basic function:

$$\psi(f,t) = \sqrt{f}\pi^{1/4}e^{j\omega_0 f(t-t_0)}e^{f(t-t_0)^2/2}, \qquad (2)$$

where ω_0 is a wavelet scale parameter providing optimal time-frequency resolution in these biological signals. To estimate the degree of coherence between two EEG signals, x_I (t) и x_j (t), the corresponding complex wavelet coefficients are calculated, W_i (f,t)=a_i+ib_i and W_j (f,t)=a_j+ib_j.

Wavelet bicoherence, τij (f,t), is estimated on basis of the wavelet cross-spectrum, $W_{(i,j)}$ (f,t), of signals, x_i (t) and x_j (t). In a similar way to how it was done in [11], the sets of coefficients, "Re" [τ_{ij} (f,t)] and "Im" [τ_{ij} (f,t)], are the real and imaginary parts of the wavelet cross-spectrum, and they can be calculated as:

$$\mathrm{Re}[\tau_{ij}(f,t)] = \frac{a_i(f,t)a_j(f,t) + b_i(f,t)b_j(f,t)}{\sqrt{a_i^2(f,t)+b_i^2(f,t)}\sqrt{a_j^2(f,t)+b_j^2(f,t)}} \qquad (3)$$

and

$$\mathrm{Im}[\tau_{ij}(f,t)] = \frac{b_i(f,t)a_j(f,t) - a_i(f,t)b_j(f,t)}{\sqrt{a_i^2(f,t)+b_i^2(f,t)}\sqrt{a_j^2(f,t)+b_j^2(f,t)}}. \qquad (4)$$

If the signals, x_i (t) и x_j (t), show a fully coordinated (or synchronized) dynamics, then τ_{ij} (f,t)=1, and vice versa; if the value becomes zero (τ_{ij} (f,t)=0), then these signals are completely out of sync. In all other cases, the value of τ_{ij} (f,t) can be anything between 0 and 1, which characterizes the degree of synchronization of the studied signals at a given time, and their frequency.

Results

Based on the method, described above, for assessing the degree of synchronization, we analyzed multichannel EEG recordings in experimental groups. Since the experimental paradigm considered the body's response to presented visual stimuli (short dim flashes), we limited the consideration of the alpha-band oscillatory processes in the brain (Δf_α [8–12] Hz). Despite the fact that EEG activity parameters are extremely variable across the population [12, 13], it is the alpha rhythm that is a very stable trait in subjects of different ages [14–16]. It is well known that the alpha-rhythm activity in the brain increases with a decrease in the levels of sensory signals: e.g., when eyes are closed, the alpha rhythm power increases in the occipital brain cortex lobe [17, 18]. At the same time, it is known that the amplitude of the alpha rhythm changes in the course of cognitive activities, such as cognitive performance, visual attention, memory, and complex abstract tasks [17–21].

For the alpha band, the dependence of synchronization degree between different EEG channels on time was calculated for the entire data array. Further on, for each pair of channels, a probabilistic distribution of the synchronization degree was constructed for each frequency range. With visual stimulation, we conditionally divided EEG monitoring during experimental work into two phases: active and passive. In case of visual stimulation, the active phase was understood as two seconds after the stimulus was presented, and the passive phase was understood as two

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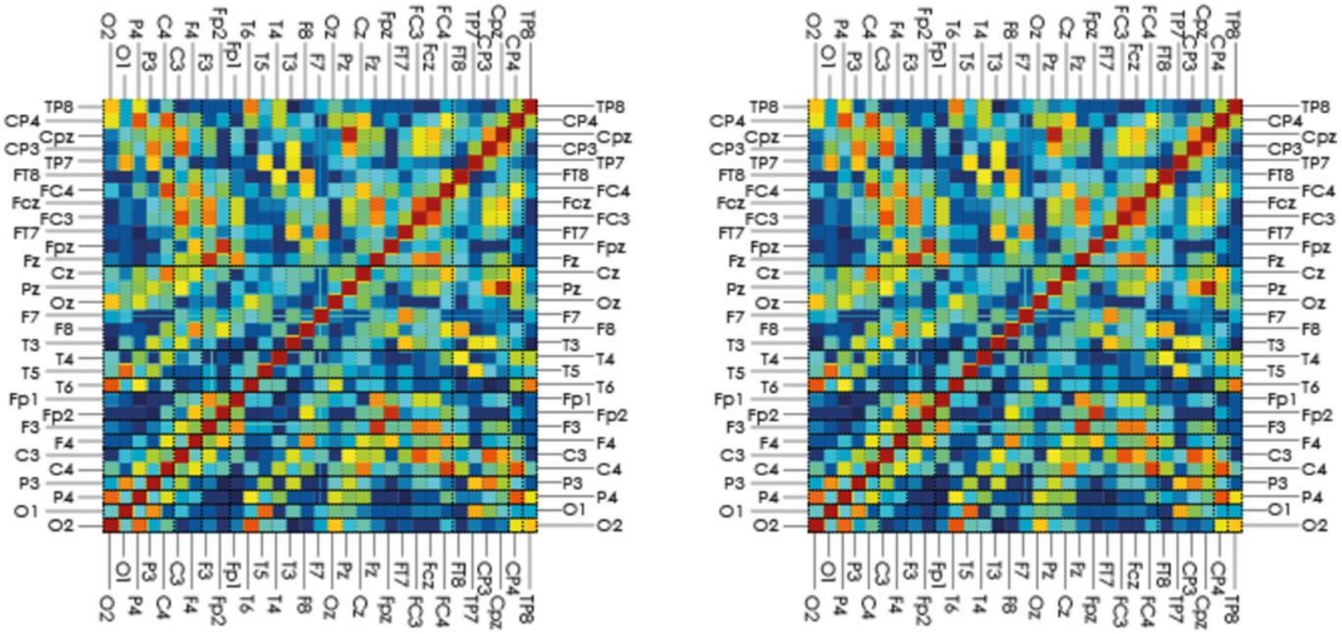
seconds before the stimulus was presented. Then, after evaluating the individual characteristics of each tested subject, the calculated characteristics within Group I and Group II were averaged.

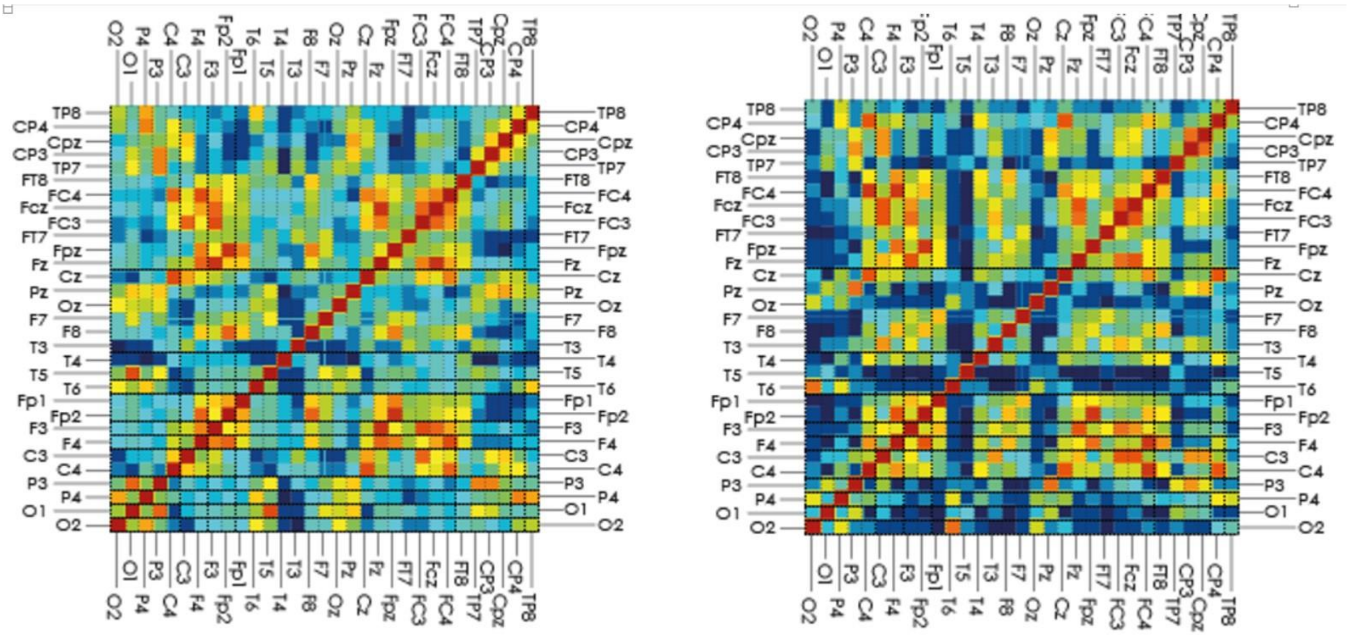
It was revealed that spatial synchronization in the control group of virtually healthy volunteers was an extremely stable characteristic, which was changing only slightly during the transition from the active phase to the passive phase of experimental work, as shown in *Figure 1*.

However, a similar analysis of the states for patients with headache demonstrated a significantly greater response of brain structures to visual stimulation. As shown in *Figure 2*, the structure of spatial synchronization in such patients was changing substantially during the transition from the active phase to the passive phase, and more so, in the frontal and temporal projection zones of the cerebral cortex.



Active phase **Passive phase**

Figure 1. Spatial maps of EEG synchronization for the alpha frequency range, averaged over registrations of volunteers in the control group



Active phase **Passive phase**

Figure 2. Spatial maps of EEG synchronization for the alpha frequency range, averaged over registrations of patients with chronic headache

Discussion

Within the framework of the performed experimental study, we demonstrated an increased reactivity in the structure of connections in brain electrical activity of the patients experiencing a weak visual impact. Although neurophysiological procedures have not yet been recognized as meaningful and effective tools for diagnosing chronic headache-related pathologies, systematic applications of objective mathematical methods were agreed upon as being useful tools for diagnosing nonacute primary headache disorders [22]. The latter source has indicated subcortical-cortical activity in migraine.

EEG-based tools are of particular value due to the fact that such results can be obtained under normal clinical conditions, and the entire procedure requires minimal cooperation on the part of the patient.

Conclusion

A prospective study could determine the value of the described diagnostic procedure in support of the clinical decision on appropriate pharmacological and non-pharmacological prophylactic measures.

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Conflict of interest: None declared.

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