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# Headache chronification: analysis of evoked potentials for stimulus

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**ABSTRACT**

**Objective.** To identify the markers of migraine chronification using automatic analysis of evoked potentials.

**Material and methods.** The study involved 24 persons with migraine without aura. Special EEG monitoring was made in all patients to identify and analyze the stimulated evoked potentials.

**Results.** Spatial distribution of the quality of evoked potentials turns out to be more as an individual characteristic of each patient. However, comparison of scalp zones of low and high quality evoked potentials revealed significant differences between patients with rare episodic and frequent migraine attacks. Perhaps, migraine chronification in this case leads to neurophysiological cerebral changes. At the same time, no difference between patients with chronic and frequent migraine causes some concerns regarding potential transformation of frequent migraines to chronic pain in certain patients. This may be due to some neurophysiological mechanism of chronification process.

**Conclusion.** The presented method in further development can reveal a tendency towards pain chronification and contribute to early therapeutic prevention of chronic migraine.

***Keywords:*** *migraine, headache, evoked potentials, diagnosis, headache chronification.*

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## Introduction

Evoked potentials in patients with migraine have been actively studied for more than 20 years. A. Raggi and R. Ferri described the differences in cognitive evoked potentials between patients with migraine and healthy people [1]. For example, there is certain decrease in cognitive functions correlating with changes in P300 component latency. M. Titlic et al. [2] reported direct association between changes in cognitive evoked potentials and cognitive dysfunction following migraine-related functional disorders. However, these changes were very heterogeneous. In addition, there is a common question on control groups for such studies due to widespread comorbidities in patients with migraine, as well as acute and chronic pain syndromes in population. This situation may be responsible for inconsistent results of such studies. In particular, some authors indicated higher P300 latency in sensorimotor cortex [3], while others indicate no significant changes of this component in patients with migraine [4].

In particular, application of evoked potentials may be aimed at integrating clinical characteristics and neurophysiological biomarkers. For example, M. Lisicki et al. [5] showed significant differences of structural characteristics of visual evoked potentials in patients with stress trigger of migraine. B. Zhu et al. [6] demonstrated the role of machine learning for clinical diagnosis of migraine and analysis of clinical status in these patients. Another important objective is analysis of neurophysiological features following migraine with aura [7, 8]. Analysis of somatosensory evoked potentials is currently used in most studies devoted to migraine. At the same time, there is a stable correlation between long-term chronic migraine and cognitive impairment [9]. We present the results of objective detection of electrophysiological characteristics in context of changes in cognitive evoked potentials in patients with different types of migraine.

Objective detection of migraine in this study was based on analysis of special characteristics for each component of evoked potentials including relative amplitude, latency and value of the component. Objective differences of electrophysiological characteristics in patients with different statuses may be useful in personalized treatment of migraine and monitoring of this process. Treatment strategy for chronic headache is based on adjuvant painkillers only for headache syndromes with high degree of chronicity exceeding 14 attacks per month. The strategy for specialized care can only rely on subjective sensations identified during patient interviews. No clear prognostic markers of treatment effectiveness and objective predictors of prefer-

***Table 1.*** **Data on subjects scheduled for survey**

| No. | Sex | Age | BMI | Migraine type | Number of attacks in the last month |
|---|---|---|---|---|---|
| 1 | F | 38 | 18,71 | XM | 15—17 |
| 2 | F | 44 | 23,42 | ЭМ | 0—1 |
| 3 | F | 60 | 25,10 | ЭМ | 0—1 |
| 4 | F | 41 | 22,76 | ЭМ | 6—8 |
| 5 | F | 45 | 24,80 | ЭМ | 6—8 |
| 6 | F | 65 | 25,65 | ЭМ | 6—8 |
| 7 | M | 27 | 24,48 | ЭМ | 4—6 |
| 8 | F | 66 | 24,21 | ЭМ | 0—1 |
| 9 | F | 32 | 20,86 | ЭМ | 10—12 |
| 10 | F | 60 | 24,80 | ЭМ | 6—8 |
| 11 | F | 62 | 31,24 | ЭМ | 4—7 |
| 12 | M | 39 | 24,75 | ЭМ | 6—8 |
| 13 | F | 58 | 23,12 | ЭМ | 0—1 |
| 14 | M | 60 | 24,67 | ЭМ | 0—1 |
| 15 | F | 59 | 32,39 | ЭМ | 4—6 |
| 16 | F | 48 | 20,57 | ЭМ | 4—6 |
| 17 | F | 37 | 30,07 | ЭМ | 4—6 |
| 18 | M | 64 | 29,98 | ЭМ | 0—1 |
| 19 | M | 57 | 30,47 | ЭМ | 0—1 |
| 20 | F | 52 | 22,09 | ЭМ | 0—1 |
| 21 | F | 47 | 19,13 | ЭМ | 4—6 |
| 22 | F | 43 | 20,04 | XM | Daily |
| 23 | M | 62 | 24,93 | XM | Daily |
| 24 | F | 50 | 22,58 | XM | 20—25 |

*Note.* BMI—body mass index; EM — episodic migraine without aura; CM — chronic migraine without aura.

able therapy indirectly contributes to poor patient adherence to long-term therapy and dissatisfaction with the process and results of treatment.

The purpose of the study was to identify the markers of migraine chronification using automatic analysis of evoked potentials. We hypothesize that patients with migraine can be objectively classified depending on neurocognitive testing and severity of pain syndrome. One can adjust and control therapy using this classification.

## Material and methods

The study involved 24 people (6 men and 18 women) aged 27-66 years (mean 44.8 years) with migraine and no aura (20 patients with episodic migraine and 4 patients with chronic migraine). The study was conducted at the Pain Treatment Clinic (Saratov, Russia, https://bolit-golova.rf). The diagnosis of migraine was established according to the International Classification of Headache Disorders (ICHD-3, 2018) [10] and the Russian clinical guidelines «Migraine» (2021) [11]. All patients underwent clinical and neurological examination to exclude secondary nature of headache. We examined patients during headache-free period or mild pain syndrome to minimize the influence of pain on neuropsychological testing (VAS score 0-3).

Exclusion criteria: BDI score >13, HADS score >7, AHI score >5 or periodic limb movement index during overnight polysomnography >5; intake of psychotropic drugs during the last month; any disease preventing completion of all experimental work (blindness, deafness, severe language difficulties); medical or neurological condition affecting cognitive abilities (dementia, Huntington's disease, Parkinson's disease, Lyme disease, schizophrenia, bipolar disorder, major depressive disorder, previous multiple traumatic brain injuries, current alcohol/drug dependence or within the last 3 years); progressive or unstable severe illness affecting safety, tolerability and evaluation of the study or placing the participant at high risk (active hepatitis, HIV infection, severe renal failure, severe liver failure, uncontrolled or major cardiac disease including recent (within 6 months) myocardial infarction, congestive heart failure (class 3—4) or unstable angina).

All participants signed an informed consent to participate in experimental work and received all explanations regarding scientific process. All participants also gave their consent for further publication of results. Experimental data were processed in compliance with confidentiality and anonymity of respondents. The study was carried out in accordance with the principles of the Declaration of Helsinki. Local ethics committee approved the study.

Patient data are presented in **table 1**. All subjects were divided into three subgroups depending on frequency of migraine attacks per a month: rare episodic migraine without aura (up to 1 attack per month; section 2.1 of ICHD-3) — 8 patients; frequent episodic migraine without aura (2—14 attacks per a month; section 2.2 of ICHD-3) — 12 patients; chronic migraine without aura (⩾15 attacks per a month; section 1.3 of ICHD-3) — 4 patients. We assessed age differences using analysis of variance **(table 2)**. There were no obvious between-group differences in age ($p$-value >0.005).

All participants underwent electroencephalographic (EEG) monitoring, and we distinguished and analyzed the evoked potentials. Monitoring took place in the first half of the day in a room with dim lighting (soft warm light) and low level of extraneous noise. None subject experienced sleep deprivation in previous days. Each participant maintained a normal

***Table 2.*** **Variance analysis of age in groups with chronic and episodic migraine**

| Analysis of variance, univariate test | Sum of squares | Degrees of freedom | Mean square | F | *p*-value |
|---|---|---|---|---|---|
| Effect | 28,03 | 1 | 28,03 | 0,2116 | 0,650068 |
| Bias | 2915,30 | 22 | 132,51 | | |

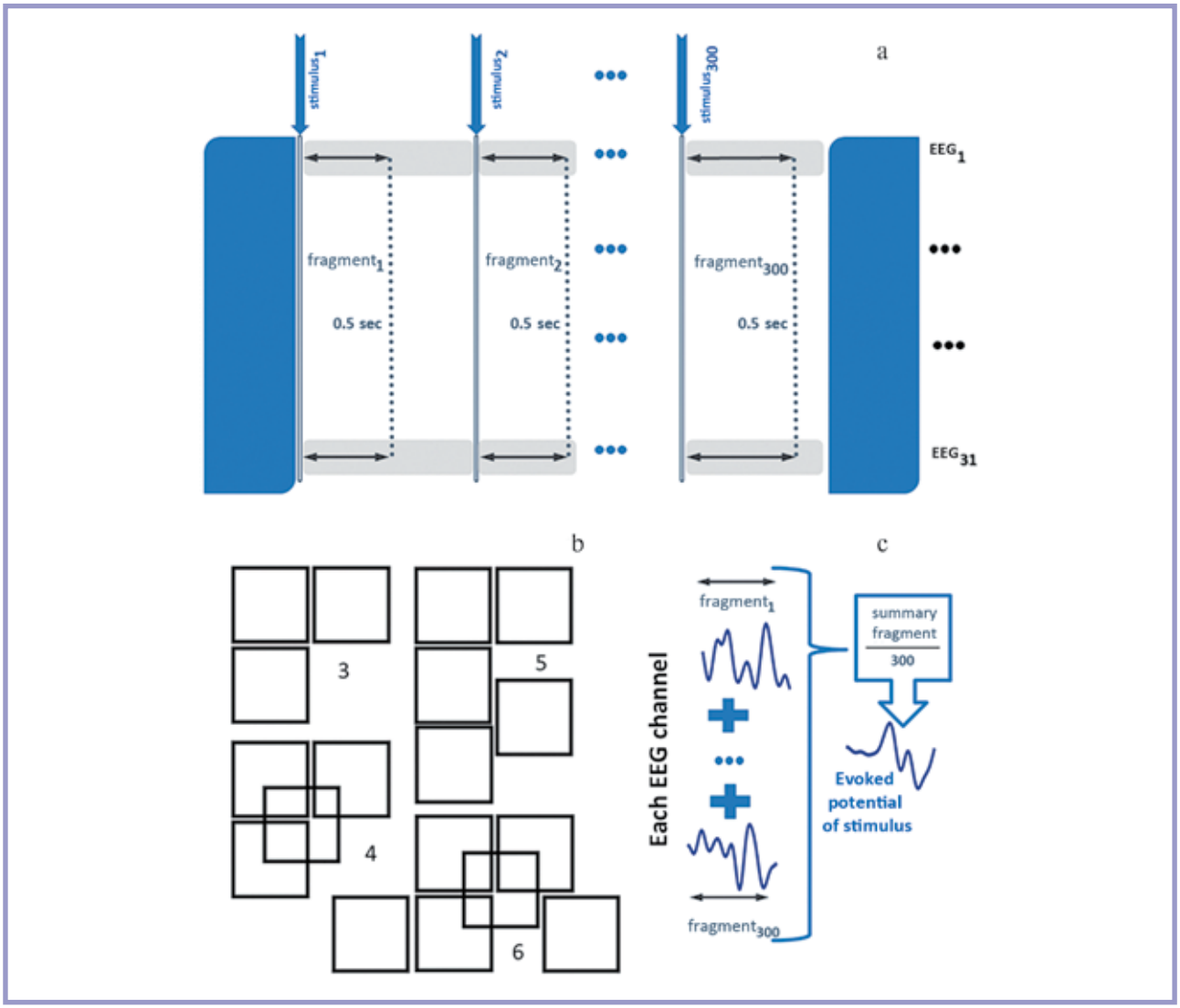


***Fig. 1.*** **Scheme of experiment.**
a — scheme of the experiment. Pauses after presentation of visual stimuli — gray; EEG fragments for further construction of evoked potentials to stimulus — black arrows; numbers 1—31 near the EEG in the subscript — EEG recording channels; b — examples of visual stimuli; c — evoked potentials to stimulus for one EEG channel.

work-rest cycle with adequate sleep (approximately 7—8 hours of sleep each night) for a week before experiment. In addition, participants did not consume alcohol or caffeinated drinks and did not perform any physical exercise the day before the experiment.

We recorded EEG signals using monopolar method and extended 10-10 electrode placement system. Electrical activity was recorded by 31 electrodes. Two reference electrodes were attached to the earlobes. The ground electrode was attached above the forehead. We used Ag/AgCl cup adhesive electrodes and Tien-20 paste (Weaver and Company, Colorado, USA). Subelectrode impedance did not exceed 20 kOhm. Immediately before the experiment, we carried out all necessary procedures to increase skin conductivity using NuPrep abrasive gel (Weaver and Company, Colorado, USA). A serial certified multichannel biopotential recorder «Encephalan-EEGR-19/26» (OOO NPKF «Medicom MTD», Russia) was used to amplify EEG signals and for subsequent analog-to-digital conversion (sampling frequency 250 Hz, quantization bit depth 16 bits per a channel). EEG signals were filtered through a band-pass filter with cut-off points of 0.016 and 70 Hz and a notch filter (50 Hz) using built-in hardware and software. Feedback with a subject was provided by wireless event marker (remote control) synchronized with the Encephalan-EEGR-19/26 scanner. Filtering of oculomo-

***Table 3.*** **Mean latency and standard deviation for various evoked potential components [21—25]**

| Component | Mean latency (L),ms | Standard deviation (ΔL), ms |
|---|---|---|
| P1 | 58 | 6 |
| N1 | 100 | 9 |
| P2 | 179 | 26 |
| N2 | 258 | 36 |
| P3 | 336 | 73 |
| N3 | 405 | 87 |

tor artifacts was based on a previously described method of oculography [12].

We presented stimuli on a 24-inch LCD monitor with spatial resolution of 1920×1080 pixels and refresh rate of 60 Hz. The monitor brightness was 185 cd/m$^2$ (for white) and 0.2 cd/m$^2$ (for black), static contrast — 919:1. Participants were at a distance of 125—135 cm from the monitor, and viewing angle was approximately 0.25 rad. Stimulus size on the monitor was 14.2 cm, angular stimulus size — approximately 0.1 rad. Subjects were advised to be relaxed and avoid any muscle activity.

At the beginning and end of monitoring (10 min each), we recorded passive wakefulness when the patient was resting with eyes closed (white in **fig. 1, a**). Active part included presentation of 350 visual stimuli, i.e images **(fig. 1, b)**. Total duration of neuropsychological monitoring was approximately 1 hour 20 min.

Stimuli were presented using a special computer program [13]. This program automatically records testing protocol synchronously with EEG monitoring. Visual stimuli were images with different numbers (2—6) of squares **(fig. 1, b)**. Duration of stimulus presentation was 0.12 s, subsequent pause — 2.5—3.5 s (gray background on the monitor). The order of stimulus presentation and duration of pauses were generated in advance in pseudorandom fashion. Thus, experimental protocol was identical for all subjects. Subjects were instructed to judge whether they observed even or odd number of squares for each visual presentation. Participants were asked to press the left or right control key by appropriate hands if they saw even or odd number of objects, respectively. In this experimental neuropsychological testing, we assessed the evoked potentials in a somewhat unusual paradigm for assessing cognitive functions, when each presented stimulus was significant for the subject. In this case, presentation of each stimulus was conditionally unexpected and no habituation occurred.

Recording of evoked potentials is well described in the literature [14—20]. We used a standard technique. For each presentation of a visual stimulus, we used a fragment lasting 0.5 s from each EEG channel throughout the entire duration of EEG monitoring **(fig. 1, a)**. The next stage was smoothing over all 300 fragments of each EEG channel **(fig. 1, c)**. Thus, we assessed biopotentials in response to repeated stimuli. After each stimulus presentation, we used the first 0.5 s of recording in each EEG channel to construct evoked potentials. Next, extrema (maximum and minimum) were automatically detected at each evoked potential. Then, we assessed whether all maxima and minima fell within usual latency intervals for each component of standard evoked potential. Mean latencies and standard deviations for a large number of components of evoked potentials were taken from large samples [21—25]. Appropriate values are presented in **table 3**.

Next, we assessed the quality of each evoked potential using the following method [26]:

$$\varepsilon=\sum_{i=1}^{N} Mg_i\Delta L_i/(50\cdot|L_i-\bar{L}_i|), \quad (1)$$

where N — number of components in evoked potential; $M_i=|A_i-A_{i-1}|+|A_i-A_{i+1}|$ — relative amplitude of the i$^{th}$ component depending on appropriate value of this and neighboring extrema (if neighboring extrema are not defined, their amplitude

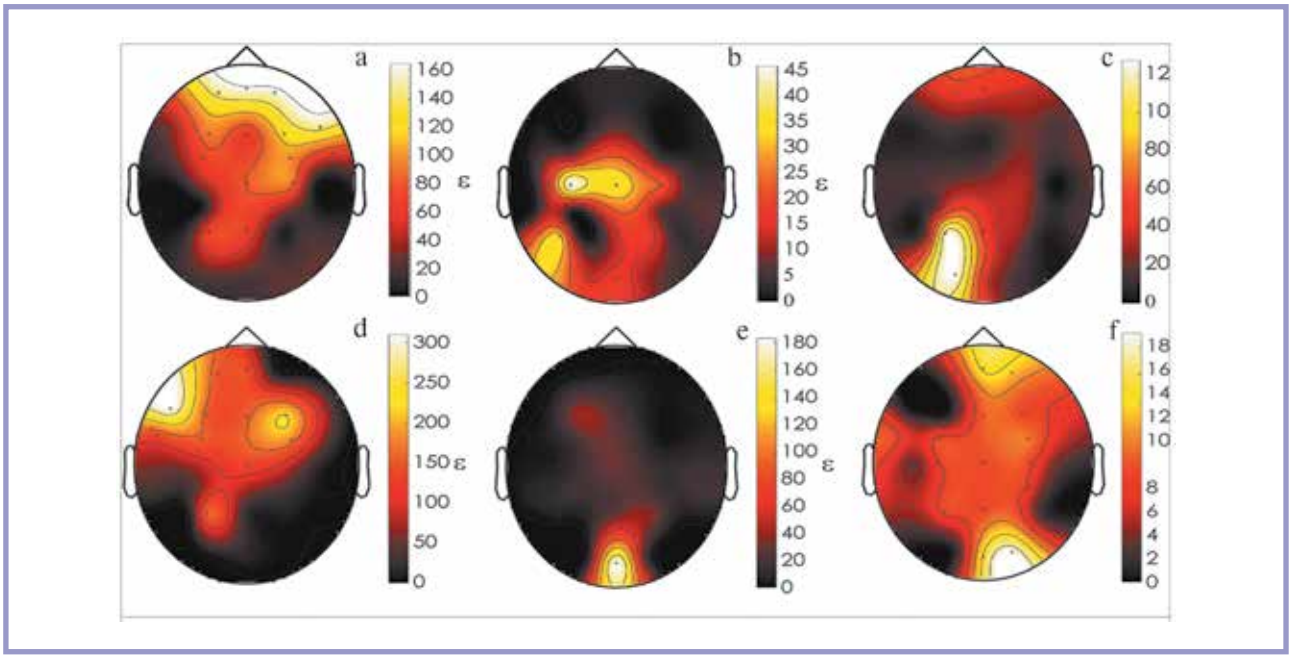


***Fig. 2.*** **Spatial maps of coefficient ε.**
Color scale of appropriate values is to the right of each spatial map. a—f—spatial maps of coefficient ε for 6 participants (No. 2, 10, 3, 5, 17, 6). Calculations were made using free FieldTrip module (MatLab, http://www.fieldtriptoolbox.org).

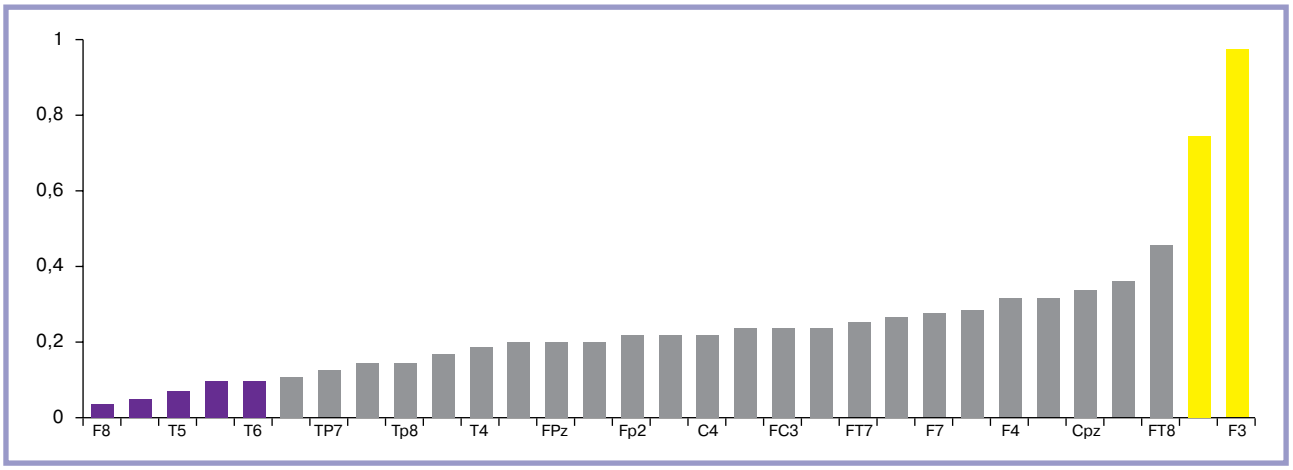


***Fig. 3.*** **Ranking of EEG channels according to coefficient ε of evoked potential quality for the participant No. 1.**

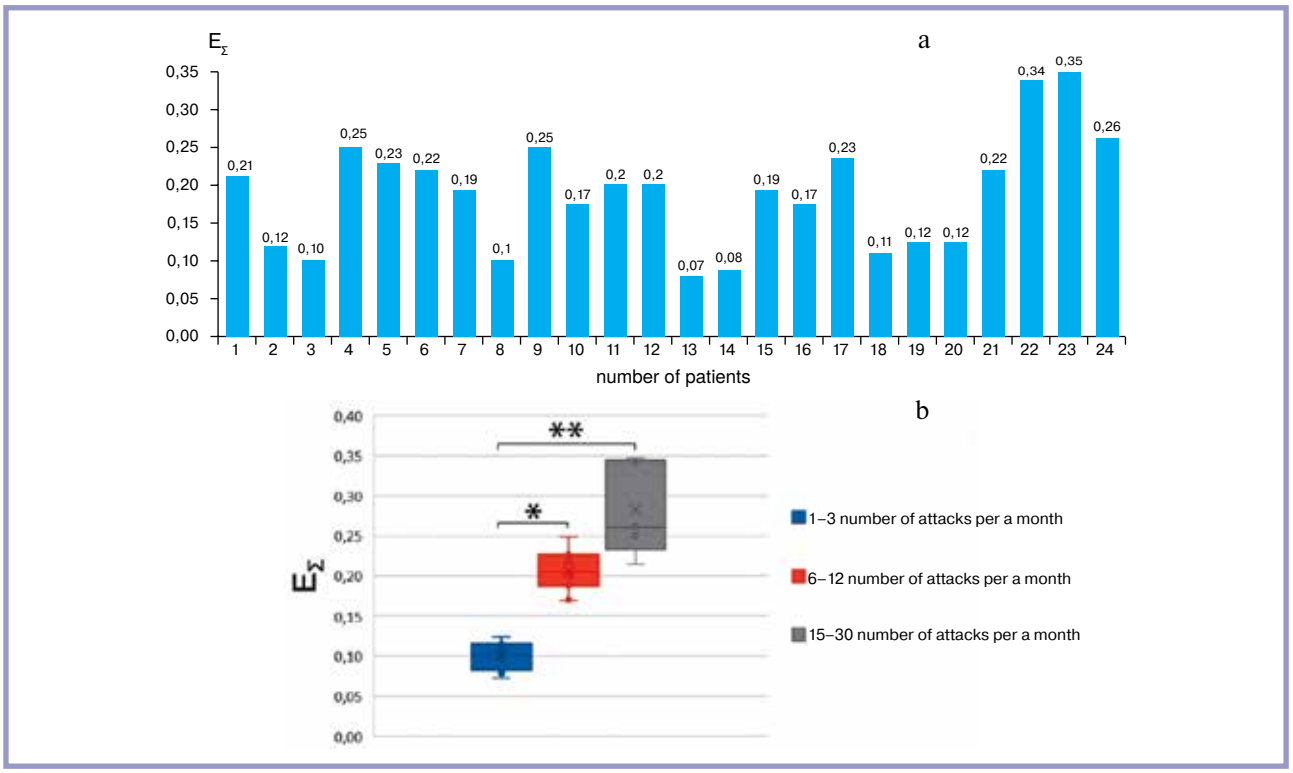


***Fig. 4.*** **Relative values EΣ.**
a — assessment of relative values EΣ for a group of patients; b — assessment of the relative values of EΣ for subgroups of patients divided by the number of migraine attacks per a month (* and ** — Wilcoxon-Mann-Whitney test $p<0.001$ and $p<0.05$, respectively).

is assumed to be zero, i.e. $A_{i-1}=A_{i+1}=0$; $g_i$ — importance coefficient for a certain component selected for a specific objective, experimental design and type of stimulus; $L_i$ — latency of a certain extremum from the number N; $L_i$, $\Delta L_i$ — mean latency and standard deviation for a certain component **(table 2)**. Latency time, mean latency and standard deviation of latency were estimated in signal samples (in this experiment, EEG sampling rate was 250 Hz, one signal sample was 4 ms). Thus, the difference $(L_i-L_i)$ is always an integer. If latency of a certain maximum coincides with mean, $|L_i-L_i|$ is taken to be equal to 1. This limits its maximum ε for a certain magnitude and importance coefficient of the component.

The coefficient ε characterizes the evoked potential as a whole. It is based on relative amplitudes of components, their location in a certain latency region and importance for the researcher. All coefficients were chosen equal to 1, except for P3 component. The last one was equal to 2. Particular attention to P3 component is due to certain evidence of changes in its latency in patients with chronic migraine and migraine with aura [1—4].

Mean, median, range deviation, quartile deviation and standard deviation were used in descriptive analysis of data. To compare quantitative data, we used the Wilcoxon—Mann—Whitney test for independent samples [27]. Differences were sig-

nificant at $p$-value <0.05. Statistical analysis was performed using Statistica version 10.0 for Windows (StatSoft Inc.).

## Results

The proposed method for analysis of ε coefficient was used to assess cognitive evoked potentials in 31 EEG recording channels. This assessment allowed us to delineate the scalp regions where the components of evoked potentials most closely correspond to standard cognitive evoked potentials. Thus, we could suggest brain regions demonstrating the most obvious response to stimulus. Spatial density maps for coefficient ε in several subjects is presented in **fig. 2**.

In this paradigm, spatial changes of cortical bioelectrical activity occur individually in response to visual stimulus. However, a common property is minimum and maximum values of conditional quality of evoked potentials. For each subject, we sorted EEG recording channels depending on ε coefficient **(fig. 3)**.

We automatically identified groups of channels with minimum values for assessing the quality of evoked potentials ($\varepsilon_{min} \leqslant 0.1$, purple (dark gray) in **fig. 3**) and maximum values ($\varepsilon_{max} \geqslant 0.7$, yellow (light gray) in **fig. 3**). After that, we analyzed the ratio of total values for channels with $\varepsilon_{min}$ and $\varepsilon_{max}$ ($E\Sigma=(\Sigma\varepsilon min)/(\Sigma\ \varepsilon max)$) for each subject. In case of rare migraine, total coefficients $\Sigma\varepsilon_{min}$ and $\Sigma\varepsilon_{max}$ were [0.17; 0.50] and [1.47; 4.14], respectively. Frequent migraine was characterized by appropriate coefficients of [0.38; 1.41] and [1.75; 6.27], chronic migraine — [0.44; 1.25] and [1.70; 3.67], respectively. Relative values EΣ for all subjects are presented in **fig. 4**.

Scatterplots of ε coefficients for each subgroup are presented in Fig. 4b. Patients with rare episodic migraine without aura are significantly different from other two groups (frequent episodic migraine without aura and chronic migraine without aura). The Wilcoxon—Mann—Whitney test revealed significant differences between patients with rare episodic migraine without aura and chronic migraine without aura. At the same time, quantitative indicators of evoked potentials were similar in groups of frequent episodic and chronic migraine without aura. Therefore, EEG dynamics is very similar.

## Discussion

The authors analyze classification of brain response when comparing mean number of migraine attacks per a month. This approach expands the understanding of significant changes in cognitive functions and potentials in patients with migraine.

Changes of potentials evoked by visual stimulus relate to complex assessment combining correspondence of amplitudes and latencies of individual components to standard ones and spatial localization of evoked potentials and components that are closest to normal. Spatial distribution of quality of evoked potentials turns out to be more of individual characteristic of each subject. However, comparison of scalp zones of low and high quality of evoked potentials allows us to determine the differences between patients with rare episodic and more frequent migraines. Perhaps, chronic pain leads to neurophysiological changes in brain activity. No difference between patients with chronic and frequent migraine raises some concerns regarding potential transformation of frequent migraine to chronic pain in some patients. This may be associated with certain neurophysiological mechanism of chronic transformation. It is known that brain in migraine is characterized by continuous and repeated plastic functional changes in brainstem-thalamus-cortex axis. These structures are essential in selection, processing and assimilation of sensory information. Therefore, these functional changes may be a sign of short- and long-term synoptic mechanisms underlying chronic dysfunctions. These mechanisms physiologically underlie the phenomenon of sensitization. However, duration of interictal and ictal periods can influence these characteristics.

In our opinion, this method may be valuable to identify the tendency towards chronic pain at the early stage. This approach will contribute to early therapeutic prevention of chronic migraine.

## Conclusion

We presented objective automatic analysis of evoked potentials in patients with rare, frequent and chronic migraine without aura. An automatic method for assessing the quality of evoked potentials was described. Patients with rare migraine attacks and no aura demonstrate significant differences in certain characteristics from patients with frequent and chronic migraine without aura.

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**The authors declare no conflicts of interest.**

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