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ORIGINAL ARTICLE

The Objective Assessment of Event-Related Potentials: An Influence of Chronic Pain on ERP Parameters

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Abstract The article presents an original method for the automatic assessment of the quality of event-related potentials (ERPs), based on the calculation of the coefficient ε, which describes the compliance of recorded ERPs with some statistically significant parameters. This method was used to analyze the neuropsychological EEG monitoring of patients suffering from migraines. The frequency of migraine attacks was correlated with the spatial distribution of the coefficients ε, calculated for EEG channels. More than 15 migraine attacks per month was accompanied by an increase in calculated values in the occipital region. Patients with infrequent migraines exhibited maximum quality in the frontal areas. The automatic analysis of spatial maps of the coefficient ε demonstrated a statistically significant difference between the two analyzed groups with different means of migraine attack numbers per month.

Keywords Event-related potential · Chronic migraine · ERP quality · Automatic evaluation

Introduction

Currently, one of the conventionally accepted and neurologically verified methods of analyzing electroencephalographic (EEG) records of the human brain is the measurement of event-related potentials (ERPs) [1–4]. This technique is applied to detect the stable characteristics of brain activities occurring in the course of responses to repetitive stimuli. In clinical practice, ERP examination makes it possible to accurately diagnose severe neurological disorders *via* objectively assessing the state of sensory functions in various neurological diseases, such as acute disorders of cerebral circulation, sequelae of traumatic brain injury, and some types of brain tumors [1], along with psychiatric disorders [5–8]. In addition, the spatial and temporal analysis of the cognitive evoked potential (EP) (P300) allows an objective assessment of the state of a patient's cognitive functions, thereby establishing a basis for the neurologist when developing experimental paradigms and methods of mathematical processing of EEG in the context of fundamental research into cognitive mechanisms in the human brain [9–11].

The current success of using EPs is largely associated with the high quality of the EEG recording equipment and the complete standardization of recordings. Standardization of EEG recordings includes strict compliance with the standard 10–20 arrangement of EEG electrodes [12] and strict observance of the technical requirements for the recording procedures: use of special fixing helmets, reduction of skin resistance, use of appropriate electrode pastes, bringing electrode resistance and EEG signal recording power to the values defined by the measuring equipment.

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From the standpoint of neuropsychology and neurology, within the framework of EP technology, we can generally distinguish two large areas of research. The first is devoted to searching for individual ERP characteristics [13]; while within the framework of the second area, on the contrary, approaches are developed to identify ERP parameters that allow identification of the characteristic features of certain clinical conditions [14, 15]. Now, it is already possible to demonstrate good ERP stability in patients in relation to the temporal and spatial frames of their records. Recently, it has been shown that ERP estimates in weeks [16, 17] are retained for up to several years [18, 19].

Building ERPs can be performed in several ways. Assessments of sensory potentials provide insights into underlying perceptual disturbances: e.g., using conventional visual evoked potentials [20], auditory evoked potentials [21], along with more exotic olfactory potentials [22]. The study of cognitive functions requires more sophisticated technology for recording EPs. We should, first of all, mention the oddball technique, in which the subject is instructed to highlight a significant stimulus among multiple stimuli [23]. The method of conditionally "correct" and "erroneous" responses to a certain stimulus (or a group of stimuli) is also used, when the researcher can evaluate not only the ERPs, but also error-related negativity (ERN) [24].

Besides, EPs constitute a powerful tool in brain-computer interface (BCI) development. EP-based systems are among the most effective and feasible BCI prototypes: their practical use in the rehabilitation and empowerment of patients with various neurological diseases is promising [25–27]. At present, in the course of developing various BCI devices, a number of successful procedures for automatic ERP detection during various events have been proposed [28–30], while methods for the objective assessment of qualitative and quantitative ERP parameters have been much less developed. Automatic examination of ERPs, as a rule, is reduced to the analysis of their individual components (extremums): for example, within the framework of cognitive ERPs, researchers can only evaluate the P300 component [31–34]. At the same time, it is possible to single out the characteristic latency and amplitude of each ERP component. There are studies reflecting the results of searching and analyzing average parameters of ERP components for large groups of subjects: for example, the latency of P300 is 300–350 ms [35–37]. Manual calculation of the quality and magnitude of many ERP components is very time consuming. Also, it is characterized by a certain subjectivity and arbitrariness. Contemporary approaches to clinical research require that the number of participants reaches hundreds and thousands. In such a case, labeling and estimating ERPs in as many as 32+ EEG channels is a daunting task. To resolve this issue, we propose in this article an automatic method for calculating the universal characteristic of conditional ERP quality, which would determine the compliance of ERP components with the specified parameters. The presented method would allow determining how close the latencies and amplitudes of various ERP components are to the presumed norm. The method could be easily adapted to the specific goals of performing a neuropsychological experiment. Moreover, the calculated ERP quality estimates allow further automatic analysis of the spatial distributions of various ERP components and the identification of zones of their maximum and minimum quality values. It is also possible to use this method to assess the relative quality of the potential, both in the mathematical processing of ERPs and/or ERNs in response to various cognitive stimuli, or else in the study of olfactory EPs, as in [22], and for the objective neurological analysis of EPs in response to visual stimuli.

The proposed method was applied to the assessment of ERPs recorded in groups of patients suffering from migraine. Chronic pain, in particular the headache, is common in current clinical medicine, and is becoming a challenge for neuroscience [38–40]. Its use made it possible to comprehensively evaluate the latency and amplitude of the ERP components for each subject and to carry out a statistical analysis of objective ERP characteristics in patient groups.

Materials and Methods

Data Analysis Methodology

Here, we consider the case when all the stimuli delivered to the subject are targeted, and we analyze the ERPs *per se* rather than their differences. The general technique for ERP detection is well known [1, 41–46]. The subject is presented with a series of stimuli, each of which is followed by a response of the brain in the EEG channel. Due to the considerable variability of brain biopotentials, the ERP assessment *via* a single stimulus provides little information on the stable response to this particular stimulus; therefore, averaging is applied over the EEG recorded during the repetition of stimuli. To do so, it is important to know the moment of stimulus presentation, otherwise averaging could give a shifted characteristic or, figuratively speaking, a "fuzzy image". If ERP calculation is performed correctly, then after the presentation of the stimulus, a series of extrema (maxima and minima) are recorded, traditionally referred to as ERP components, while random components of the EEG signal that are not related to the response to this stimulus are close to zero after averaging. Overall, ERPs for different stimuli have different shapes.

Figure 1 shows the general scheme for calculating EPs in response to the visual stimuli used in our experimental paradigm. In the course of the experiment, during EEG

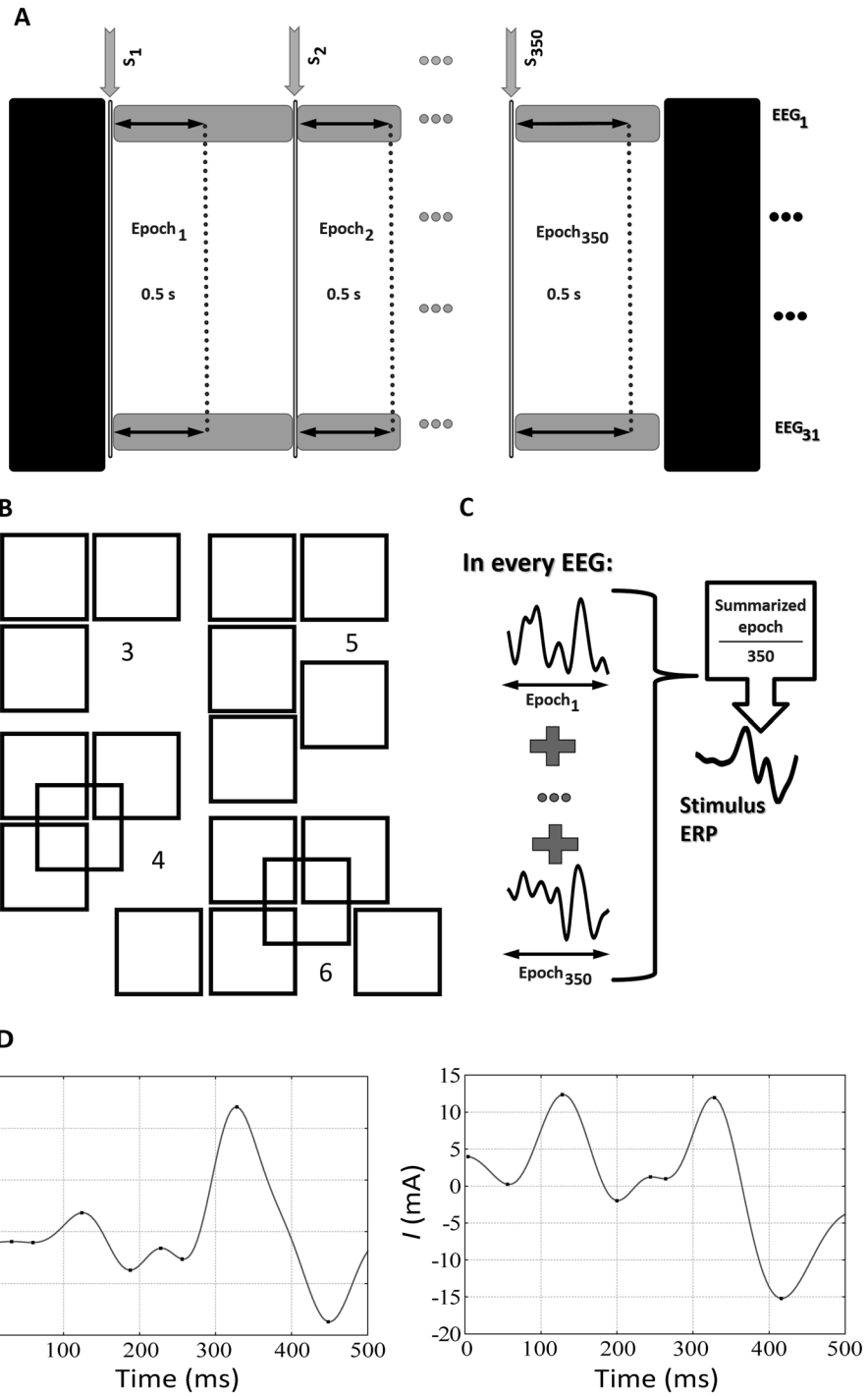

Fig. 1 **A** Scheme of epoch selection after presenting visual stimuli. Gray indicates pauses after the presentation of visual stimuli. Black arrows indicate time fragments of EEG recordings used to further build EPs in response to the stimulus. Gray arrows indicate time moments of stimulus presentation. **B** Examples of visual stimuli. **C** Illustration of EP construction of the response to a stimulus from the EEG signal of one of the monitoring channels. **D** Examples of several EPs with plotted extrema. The examples represent two subjects and one of the central channels (FCz).

monitoring, a subject observed 350 stimuli, S_i (Fig. 1A). With each presentation of a stimulus, we allocated an epoch lasting 0.5 s for each EEG channel. During the experiment, the subject observed various types of stimulus (Fig. 1B) presented to all subjects in the same order as described in the supplementary material. Next, in each EEG channel, the ERP was calculated by averaging over presentations of all visual stimuli (Fig. 1C). Figure 1D shows several cognitive ERPs calculated as described above. Here, the moment of stimulus presentation is considered the zero time point. A pronounced maximum was observed at time $t > 300$ ms, while the next minimum occurred after time $t = 400$ ms.

The number of extrema in the averaged EEG of different patients may not match the standard number of cognitive ERP components. In the course of further analysis, it is important to consider the amplitude of existing extrema and

their falling into the region of normal latency for the right component. Normal in this case is the latency falling into the interval $[\overline{L} - \Delta L; \overline{L} + \Delta L]$, where $\overline{L}$ is the average latency of this component, and ΔL is the SD of its latency. These parameters have been estimated for large samples, for example, in [1, 32–37, 41–43]. Table 1 lists the mean values of the latency and SDs from the mean of these survey studies.

Based on the given tabular average latencies, we applied an automatic and comprehensive assessment of the ERP quality in a patient. We then labeled all extrema present in the ERPs, as indicated by the dots in Fig. 1. Further, of all extrema, we selected those that corresponded to various ERP components with the latencies shown in Table 1.

All maxima or minima falling within a certain interval $[\overline{L} - \Delta L; \overline{L} + \Delta L]$ were assessed by amplitude. If several extrema of a relevant type fell into the latency interval for a certain component, i.e., maxima for P-components and minima for N-components, then the extremum with the largest absolute value was selected as the component. If no single extremum of the corresponding type fell into the interval of a certain latency, we then concluded that this component did not appear in that ERP. Hence, we compared the obtained ERP with "ideal" cognitive ERPs, the components of which are presented in Table 1.

Figure 2 presents examples of distinguishing the main EP components. At that stage of data processing, we obtained information about the latency and amplitudes of the ERP components. It is evident that processing such information for a large number of subjects presents considerable difficulties, even taking into account 1–2 channels of EEG recording. In the case of examining the complex effect of a certain disorder on the ERP components, taking into account spatial locations of the multichannel EEG, the issue becomes virtually unresolvable. Besides, in the studies, especially significant components are typically distinguished for each type of ERP, and therefore it is necessary to consider the difference in the ranks of various ERP components (in terms of their importance). For example, for cognitive ERPs, the P300 component is most often highlighted [35–37].

It is imperative to point out that when analyzing ERPs, it is not the absolute amplitudes of the higher-ranking components, but rather their relative amplitudes, compared to neighboring extrema. For this reason, in the further ERP analysis, the relative (as compared to neighboring extrema), rather than absolute, amplitude of the EP components was evaluated, and

Table 1 Average latency and standard deviations for some ERP components, according to data from published sources [1, 32–37, 41–43].

Components	$\overline{L}$, mean latency (ms)	ΔL, standard deviation (ms)
P1	58	6
N1	100	9
P2	179	26
N2	258	36
P3	336	73
N3	405	87

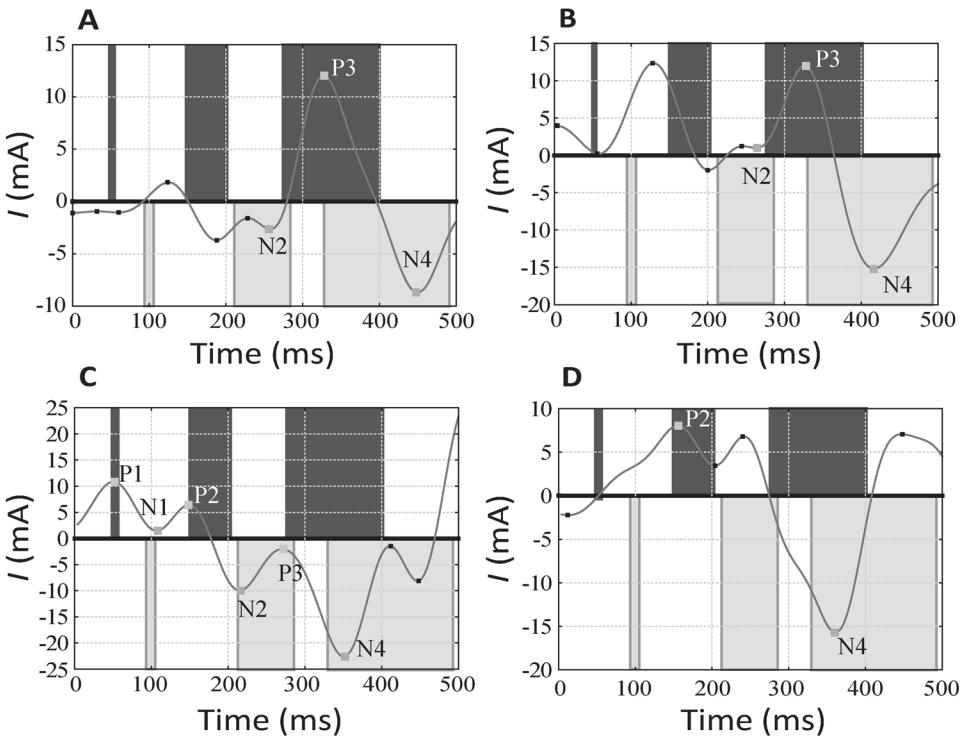

Fig. 2 The scheme of examination and the results of detecting ERP components. The examples are related to four subjects (**A**–**D**) and one of the central channels (Cz). N-components correspond to ERP minima and are marked with gray rectangles. P-components corresponding to ERP maxima are shown in black rectangles.

it will be henceforth denoted by the term magnitude. The formula for the relative magnitude is as follows:

$$M_i = |A_i - A_{i-1}| + |A_i - A_{i+1}|, \quad (1)$$

where A_i is the amplitude of the estimated component, A_{i-1} and A_{i+1} are the amplitudes of neighboring components. We especially emphasize that the assessment did not take into account the amplitudes of neighboring extrema, but rather of neighboring components, and if the component was not identified, then its amplitude was assumed to equal zero. According to such assessment, the P3 component (corresponding to P300) in Fig. 2A had a larger magnitude than in Fig. 2C.

The second important factor to take into account in the analysis of ERPs was the proximity of the selected component latency to the average latency. As we observe in Fig. 2C and D, the ERP components were distinguished at the borderline values of "permissible" SDs. In that case, it was necessary to take into account the improvement in the quality of those ERPs, the component latencies of which lay not just within the range of values $[\overline{L} - \Delta L; \overline{L} + \Delta L]$, but as close as possible to the value of the average latency $\overline{L}$. Therefore, there was a need to simultaneously assess both the magnitudes of ERP components and their proximity to the average latency value within the SD.

Thus, the closer the latencies of the components were to the average, and the higher their amplitudes, the higher the quality of the considered ERPs. However, the task of assessing the quality of ERPs was not limited to these two parameters. It was noted earlier that for cognitive ERPs, the P3 component is of the greatest interest, along with (to a lesser extent) N2 and N3. Then, if in the study of cognitive ERPs, N1 and P1 components have significant magnitudes and are close to the mean latency values, but P3 and N3 components are absent, then the quality of such ERPs is low.

Based on the foregoing, we proposed to use the following formula to estimate the ERP quality coefficient ε, with simultaneous consideration of (i) the magnitude of components, (ii) the proximity of component latency to the mean latency, and (iii) the rank (importance) of the component:

$$\varepsilon = \sum_{i=1}^{N} M_i g_i \Delta L_i / \left(50 \cdot \left|L_i - \overline{L_i}\right|\right), \quad (2)$$

where N is the number of allocated components; M_i is the magnitude of the component from among N, calculated according to Eq. 1; if the neighboring components are not defined, then their amplitude is determined as $A_0 = 0$; g_i is the rank coefficient of this component, chosen for a specific task, experimental design, and stimulus type; L_i is the latency of this component from among N; $\overline{L_i}$ and ΔL_i are the mean and SD for the latency of a given component according to Table 1. Latency value, average latency, and latency SD were estimated in signal counts (e.g., in this experiment, the EEG signal rate was 500 Hz, i.e., one signal count was equal to 2 ms), and thereby the difference $\left(L_i - \overline{L_i}\right)$ was always an integer. If the latency of the selected component coincided with the average, then $\left|L_i - \overline{L_i}\right|$ was taken equal to 1, giving a limit to the maximum of the parameter ε, assuming the magnitude M_i and rank coefficient g_i of the given component.

Hence, the complex coefficient ε (Eq. 2) characterizes ERPs as a whole, based on the calculation of the relative amplitudes of the components, their location in a given latency region, and their rank (i.e., importance) for the researcher. For example, in our study, all values ε of rank coefficients of the components were chosen equal to 1, except for the P3 component, for which the coefficient was enlarged to 2. If another component played an important role, the ERP quality assessment method was easily reconfigured by changing the rank coefficients g_i. Similarly, it was easy to vary the sensitivity of the method by decreasing or increasing the areas of latency in Table 1. Even though without direct neurophysiological meaning, the coefficient ε (Eq. 2) can, however, describe ERPs overall quite well. Besides, such quantitative assessment of quality is well suited to further use in statistical data processing.

Materials and Data

Test subjects volunteered to participate in the experiment. The reward for participating in this study included discounted doctor's appointments and procedures at the Pain Management Clinic (Saratov, Russia, https://xn----8sbbfe2audweb7b.xn--p1ai/). The biomedical data were processed honoring the confidentiality and anonymity of the study respondents. All procedures in studies involving human participants were conducted in accordance with the principles of the Declaration of Helsinki and approved by the Research Ethics Committee at Saratov State Medical University. Written informed consent was given by all participants.

A total of 44 patients with migraine responded to a study announcement at the Pain Management Clinic. The participants were diagnosed in compliance with the diagnostic criteria of the International Classification of Headache Disorders (ICHD-3, beta version). We used the migraine questionnaire to evaluate the data on migraine attacks and disease courses. The exclusion criteria were acute headache, other neurological disorders, and intake of medicines targeting the central nervous system (including medications for migraine prophylaxis) within the preceding 24 h, as well as a Beck Depression Inventory (BDI) score >12 points. In accordance with these criteria, we excluded 20 patients from the pool

of study participants: 3 with BDI score >12 points, 2 with migraine attacks within 24 h preceding data sampling, 10 with sleep problems, and 5 with uncontrolled hypertension associated with coronary artery disease. Consequently, the final sample comprised 24 subjects.

Standard visual evoked potentials were recorded from all patients using the checkerboard pattern. The study was conducted on the Neuro-MEP-4 multimodality EP system (Neurosoft LLC, Ivanovo, Russian Federation). Stimulation of visual response was monocular full-field, based on 1-Hz pattern reversal of checkerboard stimuli. Recording was performed at O1 and O2 of the standard 10–20 system (Fig. 3A) with a reference electrode located at Fz. The main response components (N75-P100-N145-P200) were recorded, and the configuration of visual EPs, latency (ms), P100 wave amplitude (mV), and interhemispheric asymmetry were assessed.

The study group included patients with chronic and recurrent migraine. The subjects had no other serious health problems, or drug or alcohol addictions. Patients were 27–66 years of age. Data on gender and age obtained from questionnaires filled out before the experiment, and the type of migraine determined by the clinician are presented in Table 2. All participants had a secondary education, and some had higher education, which reduced the variability in their cognitive status [30]. The Montreal Cognitive Assessment was included as a screening test of general cognitive abilities, and the resulting score in the volunteer group was 25.514 ± 4.179.

During all experiments, the multichannel EEG data were recorded using the EEG recorder Encephalan-EEGR-19/26 (Medicom MTD, Taganrog, Russian Federation). The data were recorded at a sampling rate of 500 Hz using the conventional monopolar recording technique with two reference electrodes and multiple recording electrodes ($n = 31$), as shown in Fig. 3A. EEG signals were obtained using special headcaps with prewired Ag/AgCl adhesive electrodes. Two reference electrodes, A1 and A2, were located on the mastoid processes, and the ground electrode (N) was placed above the forehead. EEG signals were filtered using a band-pass filter with cutoff frequencies of 0.5 Hz (high pass filter) and 30 Hz (low pass filter), and a notch filter of 50 Hz.

The experiments were carried out in the early afternoon hours at a specially equipped laboratory. During monitoring, the subjects were in a comfortable reclining position in a neurophysiological chair with support for the neck and the back of the head in order to avoid the occurrence of artifacts associated with muscle tension in these areas.

The neuropsychological experiment allowed for distinguishing cognitive ERPs. At the beginning and end of the experiment, passive wakefulness was recorded for 10 min each time (black rectangles in Fig. 1A; PW1 and PW2 in the diagram of Fig. 3B). In between, the active part of the

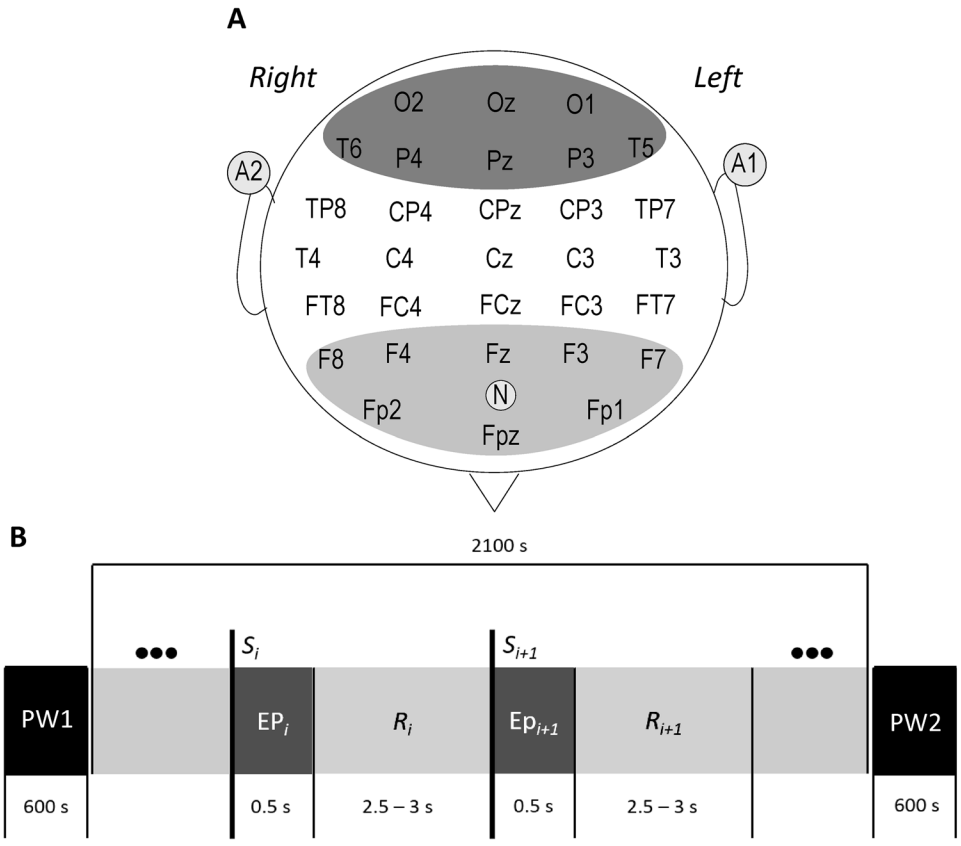

Fig. 3 **A** The scheme of the standard 10-20 arrangement of EEG electrodes. Dark and light gray correspond to the frontal and occipital scalp spatial zones, respectively. **B** Experimental protocol: dotted gray zones depict the first and last passive wakefulness stages of the experiment, PW1 and PW2; 2,100 s is the mean duration of the active stage, S_i represents time points of visual stimuli; EP_i is the duration of the subject's response to the stimulus; R_i is the duration of the period after pressing the remote control until the next presentation of the stimulus.

Table 2 Characterization of test subjects.

No.	Gender	Age (years)	Type of migraine	Number of attacks per month
1	Female	60	Frequent migraine without aura	10–11
2	Female	47	Frequent migraine without aura	9–10
3	Female	39	Frequent migraine without aura	8–9
4	Female	60	Frequent migraine without aura	10–11
5	Male	65	Frequent migraine with aura	9–10
6	Female	58	Frequent migraine without aura	10–12
7	Female	59	Frequent migraine without aura	6–7
8	Female	37	Frequent migraine without aura	7–8
9	Male	62	Frequent migraine without aura	5–7
10	Female	60	Chronic migraine without aura	16–18
11	Female	41	Chronic migraine without aura	18–19
12	Female	45	Chronic migraine without aura	15–17
13	Male	27	Chronic migraine with aura	15–16
14	Female	66	Chronic migraine without aura	15–17
15	Female	32	Chronic migraine without aura	15–16
16	Female	43	Chronic migraine without aura	16–18
17	Male	60	Chronic migraine without aura	18–19
18	Female	48	Chronic migraine without aura	16–18
19	Male	57	Chronic migraine without aura	17–19
20	Female	52	Chronic migraine without aura	15–16
21	Female	47	Chronic migraine without aura	18–19
22	Female	64	Chronic migraine without aura	15–16
23	Male	62	Chronic migraine without aura	17–18
24	Female	50	Chronic migraine without aura	15–17

experiment was recorded for ~40 min. During the active part, short presentations of visual stimuli were delivered in a pseudorandom sequence. For all subjects, the order of stimulus presentation, duration of stimulus presentation, and duration of pauses between stimuli were identical, according to the experimental protocol presented in the supplementary material. Each subject observed 350 stimuli: S_i in the scheme is the moment of stimulus presentation (Fig. 3B). The stimulus was presented for 0.4–0.8 s. After its presentation, during a pause until the next stimulus, the subject saw solely a gray screen. After each stimulus presentation, 0.5 s of the EEG recording was used to build the EP (EP_i in Fig. 3B); then 2–10 s were given to rest after the response to the stimulus (R_i in Fig. 3B). Each visual stimulus *per se* was an image with a different number of squares (3–8), as shown in Fig. 1B. The task of the subject was to estimate an even or odd number of squares and make a choice by pressing one of two buttons on the remote control.

The ERP was calculated for each of the 31 EEG channels, followed by the calculation of the coefficient ε (Eq. 2) for each channel using the described method. Then, the 31 coefficients were summed for each subject, $\Sigma\varepsilon$.

Figure 4 shows the scalp distributions of ε coefficients for three randomly selected subjects, presented *via* the FieldTrip MatLab module [47].

Results

Visual Evoked Potentials

The mean latencies and amplitudes of the P100 potential did not differ from the norm accepted in the literature [48]. Mean P100 latencies in the right (O2) and left (O1) hemispheres were 98.62 and 99.58 ms, respectively. The P100 amplitudes in these symmetrical leads were 7.09 and 7.16 μV, respectively. Significant EP asymmetry was not found.

ERPs Per Stimulus

In the tested subjects, the maximum values (ε) of coefficient ε were found in different projection areas of the brain, prevailing mainly in the frontal or occipital areas. The maximum values (ε) of the coefficients ε (Fig. 4) were found in those channels where the magnitude of the P3 component

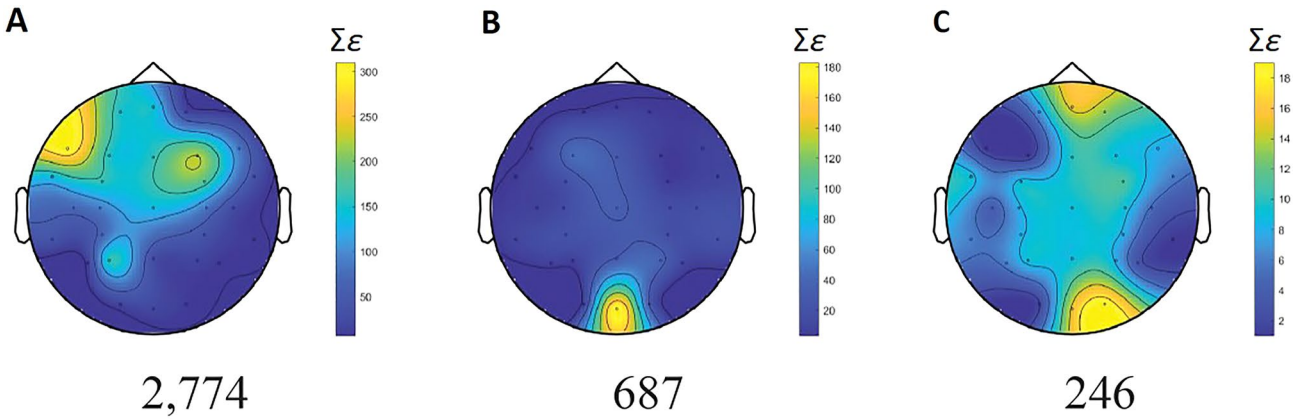

Fig. 4 **A–C** Scalp distributions of ε coefficients in three subjects. The color bar designates the amplitude of the coefficient, where the maximum amplitude corresponds to yellow, and the minimum values are dark blue. Below each image, the sum of all coefficients, taken over all channels, $\Sigma\varepsilon$, is indicated.

was substantial, and the latency was close to the arithmetic mean of a large number of stimuli. However, in this case, the contributions of other components were taken into account, albeit with smaller values of their respective coefficients. The largest values (ε) of the calculated coefficients ε corresponded to an ERP of high quality that was localized in 1–2 channels (Fig. 4B) or located in a larger area, as in Fig. 4A and C.

At the same time, the sum coefficient $\Sigma\ \varepsilon$ may have similar values in subjects demonstrating significantly different spatial maps of the distribution of the largest coefficients ε. In this case, the sum of all coefficients could take comparable values due to the ratios of different amplitudes of ε values in the channels, as shown in Fig. 5. Note that the patient in Fig. 5B has a unique situation in which the highest quality ERP occurred in the central area of the scalp. The sum coefficient did not correlate with characteristic parameters of the patient's clinical condition, apparently being a consequence of a purely individual representation.

Taking into account the identified features, we focused on an objective assessment of the ERP spatial distribution, first of all, by analyzing the ratio of their severity in the frontal and occipital lobes: specifically, we evaluated the following numerical characteristic:

$$\varepsilon_{f\backslash o} = \frac{\varepsilon_{Fp1} + \varepsilon_{Fp2} + \varepsilon_{F7} + \varepsilon_{F8} + \varepsilon_{F3} + \varepsilon_{F4} + \varepsilon_{Fz}}{\varepsilon_{o1} + \varepsilon_{o2} + \varepsilon_{T5} + \varepsilon_{T6} + \varepsilon_{P3} + \varepsilon_{P4} + \varepsilon_{Pz}} \quad (3)$$

Furthermore, high-quality ERP localization was assessed in each patient *via* taking into account the number of channels, N_m, that had ε coefficients >50% of the maximum value, max (ε), recorded in that patient. Table 3 presents the results of ERP analysis for patients, classified by the number of migraine attacks per month.

Overall, in patients with no more than 15 migraine attacks per month, the value of $\varepsilon_{f\backslash o}$ exceeded 1 and, therefore, we recorded conditionally high-quality ERPs near the forehead. At the same time, the number of channels, *Nm*, in which ERPs were characterized by a significant value of the

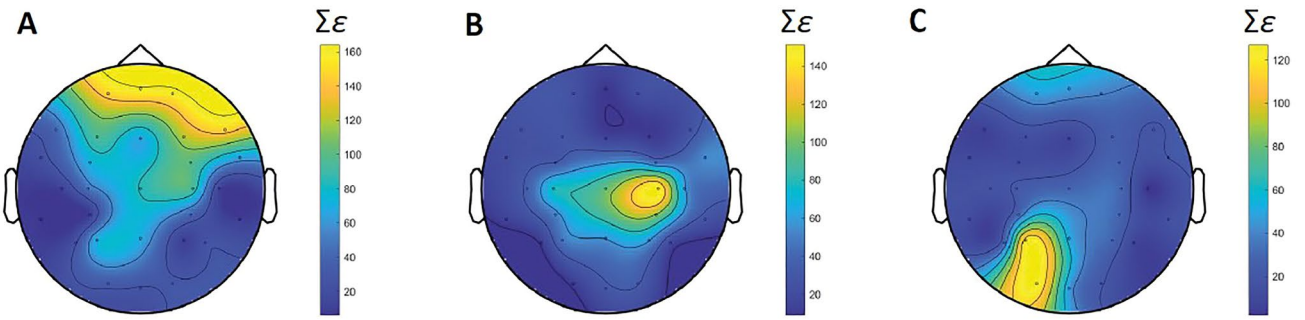

Fig. 5 **A–C** Scalp distributions of ε coefficients in three subjects with the sum of the coefficients for all channels taking values within the range [1.010; 1.015].

Table 3 Automatic estimate ratios of the spatial distribution and localization of the coefficients ε in patients with frequent and chronic migraines. Patients that do not correspond to the general patterns are highlighted in bold.

No.	Coefficient ratio, $\varepsilon_{f\backslash o}$	Channel number, N_m
(*Cases of frequent migraine, i.e., < 14 times per month*)		
1	**1.8**	**2**
2	1.58	10
3	1.33	22
4	1.38	13
5	**0.33**	**4**
6	1.6	10
7	**3.96**	**6**
8	1.55	12
9	**1.6**	**5**
(*Cases of chronic migraine, i.e., > 15 times per month*)		
10	0.65	4
11	0.52	2
12	0.8	3
13	**0.41**	**10**
14	0.38	2
15	0.74	6
16	0.19	5
17	0.42	4
18	0.41	3
19	0.43	1
20	0.93	9
21	0.87	6
22	**1.20**	**10**
23	**1.07**	**7**
24	0.18	3

coefficient ε, was quite large and exceeded 10. In patients with severe chronic pain, the reverse situation was found: the sum coefficient for the occipital half of the channels exceeded the sum coefficient for the frontal half of the channels, $\varepsilon_{f\backslash o} < 1$, and the number of channels, *Nm*, with relatively high values of coefficients ε was usually lower. In Table 3, patients not complying with such findings are highlighted in gray.

The statistical analysis is illustrated in Fig. 6 Using the Mann–Whitney *U* test demonstrated that the calculation of $\varepsilon_{f\backslash o}$ allowed the reliable separation of groups of patients with chronic and recurrent migraines, $P < 0.05$. However, the assessment of *Nm* localization of high-quality ERPs did not yield statistically significant differences. Still, it could be used as an additional estimate, because the level of significance was quite high, $P = 0.063$. For the ratio coefficient ($\varepsilon_{f\backslash o}$) and *Nm*, the statistical power of a patient

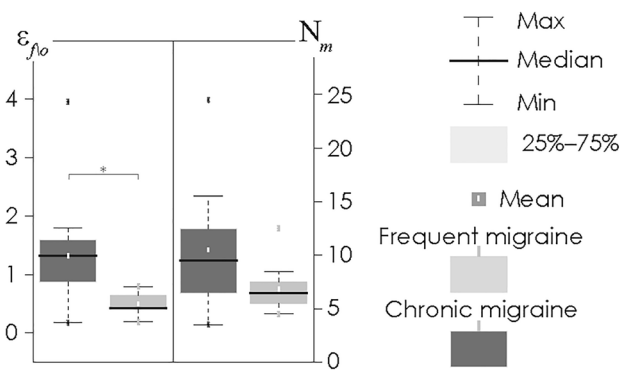

Fig. 6 Diagrams of $\varepsilon_{f\backslash o}$ (**A**) and channel number N_m (**B**) in two patient groups. The diagrams depict the following statistical characteristics of numerical indicators: the first and the third quartiles (25%–75%, inside the box); the median and the mean (transverse line and point inside the box, respectively); 1.5 interquartile range (shown by whiskers); and outliers are represented by asterisks. $^*P < 0.05$; $n = 9$ and 15 for the frequent migraine group and chronic migraine group, respectively; Mann–Whitney *U* test.

condition assessment exhibited different values. For the ratio coefficient ($\varepsilon_{f\backslash o}$), $1 - \beta$ was estimated at the level of 0.875, whereas for the number of channels (*Nm*) it was just at 0.75.

To assess the ε-sensitivity of automatic classification of patients based on the calculation of the ERP-quality in the occipital and frontal lobes (Eq. 3), we consider a different number of EEG/ERP recording channels. The sensitivity of the method is evaluated by direct numerical comparison of the results of automatic detection and classification based on the patient's clinical diagnoses. In other words, we estimate in percentage the relative number of matches for groups of patients with frequent and chronic migraine. Reducing the number of channels in Eq. (3) leads to reduced sensitivity of the method: viz., for $\varepsilon' = \varepsilon_{\mathrm{Fp1}} + \varepsilon_{\mathrm{Fp2}} / \varepsilon_{\mathrm{o1}} + \varepsilon_{\mathrm{o2}}$, $\varepsilon'' = \varepsilon_{\mathrm{Fz}} / \varepsilon_{\mathrm{Pz}}$, $\varepsilon''' = \varepsilon_{\mathrm{Fcz}} / \varepsilon_{\mathrm{Cpz}}$ the sensitivity of the method was 79.16% for ε' and ε'', and 66.67% for ε'''. Basically, the decrease in sensitivity was due to the lack of averaging with a decrease in the number of EEG sensors. Equation (3), calculated for large groups of channels, allows accounting for possible individual deviations from the optimal values. It is well known that the EEG recording procedure has the advantages of both speed and convenience of clinical and experimental use, and the disadvantages of recording interference and noise that are difficult to distinguish from the signal. The listed advantages and disadvantages are technical in nature and are caused by individual physiological/neuropsychological characteristics. We assume that the drop in quality is associated with the individual interference and noises that occur when using 31 EEG channels in the calculations.

Discussion

Our proposed methodology automatically evaluates a certain quality of ERPs. At the same time, the mathematical method adapts well to various conditions of the experimental design for neuropsychological monitoring and different approaches to ERP calculation. In particular, the ERP quality calculated on the basis of single events, such as that proposed by Huang *et al.* [49], can be assessed in a similar way. Besides, this method can be applied to BCI technologies. Here, we considered using this method for the clinical study of neurological patients. The presented method divided the groups of patients based on the frequency of migraine attacks with high accuracy. The conventional approach to assessing visually evoked potentials did not reveal significant intragroup differences and deviations from generally accepted population characteristics.

The development of methods for the objective assessment of brain biopotentials is currently attracting considerable attention from researchers, especially in connection with attempts to create systems for the objective diagnosis of various migraine types [50, 51]. Also, patients with migraine are at risk for developing cognitive dysfunctions [52, 53], and therefore, many publications focus on the search for cognitive dysfunctions when analyzing cognitive ERPs in patients of this group [54]. However, a classification of various clinical conditions within the framework of migraine diagnosis *via* ERP analysis has not been implemented to date [55].

The approach we developed for assessing the quality of ERPs made it possible to demonstrate changes in cognitive ERPs, and not so much in the amplitudes and latencies of individual components but in different spatial localization of ERPs with components closest to the conditionally normal. Substantial chronicity of pain leads to switching the severity of recorded ERPs from the frontal to the occipital area, compared with cases of frequent migraine. At the same time, in patients with chronic migraine, the situation with a significantly smaller number of EEG channels usually prevails; and in those channels, high-quality ERPs are usually recorded, compared with frequent migraine patients. The observed situation correlates with the pronounced specificities of the potentials in the occipital region, described in the study by Steppacher, Schindler, and Kissler [56]. In addition, the research by Guo *et al.* demonstrated that patients with migraine exhibit a reduced P3 amplitude and delayed N1 and N2 latencies [57]. Furthermore, these deviant cognitive ERPs correlated with the frequency and duration of migraine attacks. Hence, an objective analysis of a group of patients with migraine made it possible to clarify the relationship of already known pathological ERP changes in patients with a moderate monthly frequency of migraine attacks.

At the same time, some patients did not exhibit the identified patterns. Perhaps this was due to the fact that in our study patients were investigated outside migraine attacks, and they could have been at different points of the migraine cycle. De Tommaso *et al.* reported that changes in brain sensitivity and activity patterns are associated with different stages of the migraine cycle, as migraine patients appear to have increased response and poor adaptation, which is only normalized before the attacks [58]. Also, we should point out that it is necessary to consider the slightly older age of those patients compared with the main group. Patients 12, 22, and 23 were >62 years old, while the ages of the rest of the group did not exceed 60 years. Perhaps the neurophysiological response changes in patients and an overall decrease in the reaction rate becomes significant with age.

Thus, the constructed spatial distributions of ERPs demonstrated a statistically significant difference in the dynamics of neurophysiological activity in patients with migraine at different stages of disease persistence. We hypothesize that the identified electrophysiological features of brain activity indicate the possibility of searching for markers of the development of the pathological condition and the chronicity of migraine attacks, and could also help with early assessment of the presence of cognitive dysfunction. Further research is planned on developing the technology of objective search for early pain persistence markers, both for migraines and other headache types.

Conclusion

In conclusion, we would like to point out that the automatic labeling and evaluation of the integrated ERP quality may be somewhat inferior in accuracy to the analysis of an expert neurophysiologist. However, its use allows fast evaluation of multichannel data on groups of patients with the required sets of criteria. The proposed method is easy to implement, does not require large computing power, and is easily adaptable if the special attention of a researcher is focused on the presence of a specific EP component. For instance, depending on the known characteristics of the EP for a certain group of patients and/or the design of the experiment, we can vary the latency values in Table 1 to ensure the required sensitivity and quality in highlighting significant ERP components. Besides, the method can be successfully applied within the framework of the oddball paradigm, for which we could compare the quality of responses for each separate component for targeted and non-targeted stimuli, as well as for all components combined. The use of automatic detection of ERPs and spatial assessment of their quality demonstrated good sensitivity to the level of migraine persistence in patients.

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Conflict of interest The authors declare that they have no conflicts of interest.

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