THE ISSUE OF PRESERVING INTERICTAL ACTIVITYIN LONG-TERM EEG STUDIES OF EPILEPSY

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Modern application of mathematical methods for analyzing EEG recordings is limited due to the phenomenon of information averaging. In these conditions, it is important to find the most likely method for improving the quality of diagnosis of paroxysmal pathological patterns that have a short "life", such as outbreaks and subclinical paroxysms. The purpose of the study was to evaluate the possibility of excluding interictal activity from a long-term EEG study in order to achieve its information "enrichment" by forming conditional sequences of pathological changes representing its main clinical task. Forty people of different ages and both sexes were examined. The control group included 20 patients aged 12–67 years with direct detection of spike-wave activity on the EEG. The comparison group consisted of 20 patients aged 10–66 years with no spike-wave activity in the recording. It has been shown that interictal data obtained in patients with epileptiform phenomena are not of significant interest for the main group of clinical studies. The exclusion of these data leads to the "enrichment" of information due to the sequential placement of paroxysmal patterns and makes it possible to obtain not only more compact results of examinations of the pathological component, but also to form a basis for developments using technologies for their subsequent mathematical analysis.

Keywords: electroencephalography, continued EEG studies, analysis of results, workload on the doctor

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ВОПРОС СОХРАНЕНИЯ ИНТЕРИКТАЛЬНОЙ АКТИВНОСТИ В ДЛИТЕЛЬНЫХ ЭЭГ-ИССЛЕДОВАНИЯХ ЭПИЛЕПСИИ

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Современное применение математических методов анализа ЭЭГ-записей ограничено из-за феномена усреднения информации. В этих условиях актуально найти наиболее вероятный метод повышения качества диагностики пароксизмальных патологических паттернов, имеющих малую продолжительность «жизни», таких как вспышки и субклинические пароксизмы. Целью исследования было оценить возможность исключения межприступной интериктальной активности из длительного ЭЭГ-исследования для достижения его информационного «обогащения» путем формирования условной последовательностей патологических изменений, представляющих его главную клиническую задачу. Было обследовано 40 человек разного возраста, обоих полов. В контрольную группу вошли 20 пациентов 12–67 лет с непосредственным выявлением спайк-волновой активности на ЭЭГ. Группу сравнения составили 20 пациентов 10–66 лет с отсутствием спайк-волновой активности в записи. Показано, что интериктальные данные, полученные у пациентов с наличием эпилептиформных феноменов, не представляют значимого интереса для основной группы клинических исследований. Исключение этих данных приводит к «обогащению» информации и за счет последовательного размещения пароксизмальных паттернов позволяет получать не только более компактные результаты обследований патологической составляющей, но и сформировать базу для разработок с использованием технологий их последующего математического анализа.

Ключевые слова: электроэнцефалография, продолженные ЭЭГ-исследования, анализ результатов, нагрузка на врача

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By the beginning of the current century, video-EEG monitoring had become firmly established in the provision of medical care to patients with epilepsy [1] as the basis for its differential diagnosis and a method that allows prescribing adequate treatment even in the case of drug-resistant forms of the disease [2]. This technology began to develop especially rapidly against the backdrop of the development of electronic systems for storing large amounts of information (big data), which showed its advantage for the differential diagnosis of epileptic seizures over classical routine EEG studies [3–5].

At the same time, the main technology for deciphering EEG recordings is still based on visual phenomenological analysis [6] with the identification of certain types of pathological graph elements, which, in conditions of continued recordings,

significantly increases the visual load on the specialist and can lead to both diagnostic errors and for worker fatigue and the development of occupational vision damage.

According to a survey conducted in Germany at 16 German epilepsy centers between December 2020 and January 2021 [7], EEG performance problems compromised diagnosis in approximately one in 10 patients. Therefore, today one of the most pressing issues in organizing a continued EEG study is the creation of the most comfortable environment for the doctor and, above all, a convenient presentation of the result, the issue of determining the epileptiform graph element can be violated due to visual fatigue, insufficient qualifications or the controversial clinical significance of the phenomenon, or its similarity to a recording artifact [8–10].

This situation has led to the search for ways to reduce the amount of visual information presented to the doctor. It is based on the development of technologies for automatically identifying short-term changes in the spectral density of a signal with their subsequent interpolation onto the conditional surface of the head in a flat or three-dimensional representation [11–16]. However, by the beginning of the 2000s it became clear that this technology is more successful in studying intracranial structural changes that produce unique pathological rhythmic activity [17–19].

At the same time, its use in epilepsy has shown mixed results [20, 21]. According to them, the best results can be achieved in the case of the production of rhythmic epileptiform activity from a focus [22] or when assessing the relationship between different foci of epileptic activity [23], which led to the preservation of routine visualization-phenomenological analysis as the main method for diagnosing epileptic activity.

The next solution was to develop systems for identifying individual epileptic phenomena in recordings [24, 25]. However, this technology required the introduction of pattern recognition systems, since the recorded epileptic phenomenon has a complex shape and it is not always possible to evaluate it using elementary procedures for assessing amplitude and frequency [26–28]. Currently, the analysis of epileptic activity in the context of a continued EEG study requires solving the following issues: 1) identifying pathological paroxysmal activity and excluding artifacts similar to it; 2) its quantitative analysis per unit of time; 3) optimization of the presentation of the result, understandable for both physiologists and clinicians.

Detection of pathological activity can currently be considered both from the position of manual signal extraction from the primary EEG recording, and from the position of complete automation of the process using artificial intelligence (AI) technologies with the development of deep learning systems [29, 30].

Considering the above, the optimal option for presenting continued studies could be the result of automated mathematical post-processing, representing, on the one hand, the selection of all pathological elements [31] when removing interictal activity from the recording. This combination will make it possible to use the entire spectrum of EEG signal processing based on rhythmic activity analysis technology, and not only combine them with two or three-dimensional images obtained during an MRI study in the form of three-dimensional spatial maps, but by solving the inverse EEG problem [32, 33] to determine with great accuracy pathological areas of the cortex that are sources of paroxysmal bioelectrical activity.

To implement this technology, it is necessary to establish how much the information from an EEG study during the interictal period differs from the background (Resting State) EEG activity of people who do not suffer from diseases with increased activity of neural structures, manifested by the appearance of pathological paroxysmal activity during an EEG study, and also how much excluding interictal activity may affect the accuracy of the final result.

Accurate comparative analysis of EEG recordings is usually difficult due to the lack of a single starting point of the event, which leads to a phase shift of the EEG signal and the impossibility of their comparative analysis. This bias does not allow the use of previously widely presented methods of signal correlation and coherence, since the signals studied in different people are absolutely unrelated to each other, and any decision indicating the presence of such a connection will be deliberately false.

However, the answer to this question is provided by the theory of EEG microstates, proposed in the 1990s by D. Lehmann et al. This approach allows one to separate a continuous stream of EEG data through a clustering procedure into individual components. An array is created from individual recording sections that have similar electrophysiological characteristics (microstates) during which the main indicators of the general scalp potential remain relatively stable. Currently, cluster analysis technologies make it possible to identify up to 39 individual EEG microstates. However, maximum representativeness can be achieved only in the first 2–8 classes, which is likely due to the activity of large neural networks responsible for the implementation of basic and most stable brain functions, the violation of which manifests itself in the form of severe changes in the mental sphere [34–36].

Thus, by considering sequences of EEG microstates, the researcher has the opportunity not only to judge the characteristics of the work of large brain networks, but also to compare them with each other.

However, changes in their characteristics are largely associated with structural and anatomical changes in the neural formations that form them, therefore, an isolated analysis of the frequency of representation or lifetime of each of the identified EEG microstates in the absence of an organic substrate that damages interneuron connections may not differ from conventionally normal values. In the structure of neurological diseases caused by increased excitability of neurons in the cerebral cortex, this is observed in patients with genetic forms of epilepsy, when the researcher does not detect organic changes using neuroimaging technologies.

Under these conditions, the disease has a greater impact on the functional sequences of excitation of cortical structures, described as a system of information flows in cortical structures [37, 38].

Each individual EEG microstate represents a relatively stable version of the scalp potential, or a total set of variants of postsynaptic discharges fixed in time, associated with the activity of large neural formations involved in the implementation of a common function, therefore, solving the inverse EEG problem for each individual EEG microstate will allow us to identify several successive points on cortical structures associated with the transition of activity from one neural network to another as part of the information flow model.

As a result, the researcher will be able to determine not only the structural changes in the neural network, but also find out the functional changes associated with changes in the processes of formation of higher nervous functions in the conditions of the development of the disease.

The most widely used solution to this issue was proposed by R. D. Pascual-Marqui in the form of a system for solving the inverse EEG problem based on the technology of combining dipole localization and a layer-by-layer head model, called low-resolution electromagnetic tomography (LORETA) [39]. The technology has now added quantitative neuroanatomy based on templates provided by the Brain Imaging Center of the Montreal Neurological Institute (MNI), allowing spatial localization results at a level comparable to classical functional imaging techniques such as PET and fMRI [40–50].

Thus, the above made it possible to formulate a null theory of the experiment, which consists in the fact that the presence of significant differences in the identified results of studies of interictal recordings of patients suffering from diseases with increased activity of the neural structures of the cerebral cortex and the results of studies of background (Resting State) EEG recordings of healthy people who do not have pathological paroxysmal changes will not allow interictal data to be excluded from the general study, since the information they contain is essential for the researcher and cannot be deliberately lost from the main study record.

The purpose of the study was to evaluate the possibility of excluding interictal interictal activity from a long-term EEG study in order to achieve its information "enrichment" by forming conditional sequences of pathological changes representing its main clinical task.

METHODS

Study Groups

The study involved 40 people of different ages, both sexes, who underwent an EEG examination. The general scenario of the EEG study was carried out according to previously published recommendations [51–53]. The control group included 20 patients aged 12–67 years (average age: 25 years). Criteria for inclusion in the control group: presence of an established diagnosis of epilepsy; direct detection of spike-wave activity on the EEG.

The comparison group consisted of 20 patients aged 10–66 years (average age: 28 years). Criteria for inclusion in the comparison group: absence of an established diagnosis of epilepsy; absence of spike-wave activity in the recording.

For the study, a sample of epochs (on average at least 10 minutes) of the patient's stay in a state of passive, relaxed wakefulness with eyes closed was taken from the general recording. In patients with registration of paroxysmal epileptiform activity, a sample of data was recorded in a state of passive relaxed wakefulness with eyes closed between ictal episodes.

Exclusion criteria: presence of an established diagnosis of epilepsy in the anamnesis; absence of a characteristic ictal pattern in the recording; the presence of specific changes in the EEG recording without a previously established diagnosis of epilepsy; the presence of established epileptic dementia with the development of pronounced cognitive dysfunctions and gross structural changes in the brain substance determined using neuroimaging methods; taking pharmacologically active substances; smoking; drinking strong alcohol less than a week before the study; regular alcohol consumption; pregnancy.

Experimental design

The results were compared in a state of passive relaxed wakefulness with eyes closed in real time using the cluster analysis method (K-means), which makes it possible to calculate individual stable EEG microstates in the frequency range 2–20 Hz. To identify cognitive sequences, a model of eight EEG microstates was used, reflecting the formation of the general scalp potential as a result of the total activity of eight conditional neural networks. The use of this model made it possible to more rationally use the available computing power.

According to the proposed model, for each individual EEG microstate, an inverse EEG problem was solved with the establishment of its connection with individual cortical structures within the Brodmann field system (according to the recommendations of the Montreal Neurosurgical Institute (MNI), Canada).

Technique

The EEG study was carried out on a 52-channel bioamplifier of domestic production (Zelenograd) with a base frequency of the analog-to-digital converter of 500 Hz, which made it possible to confidently obtain data in the range from 1 to 250 Hz without loss of information content. The obtained information was processed on a PC in the software package sLORETA v20210701 Switzerland v20210701 (University of Zurich; Switzerland), as well as by implementing technological prototypes using interpreted software packages EEGLAB and BRAINSTORM, implemented under the control of the MATLAB system (Mathworks ver. 98 (2020); USA).

Statistical analysis

Statistical data processing was carried out using the SPSS Statistics ver.23.0 software package (IBM; USA). The normality of the distribution was checked using the Kolmogorov–Smirnov test, and the statistical significance of the differences was established using the Chi-Square test.

 Table 1. Frequency of registration of individual EEG microstates in the control observation group

	I	II	III	IV	V	VI	VII	VIII
Mean	2.28	2.25	2.32	2.2	2.3	2.29	2.31	2.48
Deviation	0.55	0.45	0.46	0.66	0.35	0.54	0.49	0.3
Min	0.414	0.88	1.3	0.3	1.6	0.04	0.38	2.01
Max	3.04	3.03	3.49	2.91	2.95	2.93	3.15	3.16

Table 2. Frequency of registration of individual EEG microstates in the comparative observation group

	I	11		IV	V	VI	VII	VIII
Mean	2.28	2.27	2.31	2.38	2.43	2.29	2.48	2.39
Deviation	0.43	0.3	0.36	0.37	0.36	0.31	0.35	0.24
Min	1.55	1.55	1.7	1.87	2	1.64	1.97	1.85
Max	2.78	2.869	2.89	3.2	3.33	2.91	3.07	2.714

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	I	Ш	Ш	IV	V	VI	VII	VIII
Mean	0.05	0.05	0.05	0.05	0.05	0.06	0.05	0.06
Deviation	0	0	0.01	0.01	0	0.02	0.01	0
Min	0.05	0.04	0.04	0.04	0.05	0.05	0.05	0.05
Max	0.06	0.06	0.06	0.06	0.06	0.14	0.07	0.06

Table 3. Lifetime of individual EEG microstates in the control observation group

Table 4. Lifetime of individual EEG microstates in the comparison group

	I	II	III	IV	V	VI	VII	VIII
Mean	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Deviation	0	0	0	0	0	0	0	0
Min	0.04	0.04	0.05	0.05	0.05	0.05	0.05	0.05
Max	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.07

RESULTS

Study of time-frequency characteristics of EEG microstates

The frequency and time characteristics of individual EEG microstates show the preservation of the structural connections of the neural network involved in the implementation of bioelectrical activity, forming a separate EEG microstate.

Therefore, analysis of the frequency of registration of each individual EEG microstate and the time of its existence (life) was necessary to identify a possible violation of the integrity of the structure of brain neural networks in people suffering from epilepsy. If this pathology were detected, the question of excluding information about interictal activity in the recording would not make sense due to the inadequacy of the material being studied. However, the data obtained (Tables 1–4) showed that the time-frequency characteristics of individual EEG microstates did not have statistically significant changes between the study groups (Chi-square test; p > 0.5). These observations allow us to reject the null hypothesis of the experiment and justify the possibility of excluding interictal recording from a long-term EEG study for people with epilepsy

since its characteristics are quite comparable to the brain activity of a healthy person.

Solution of the inverse EEG problem for the activity of individual EEG microstates

Solving the inverse EEG problem for a selected set of EEG microstates (Fig. 1–3) made it possible to identify the sequence of transition of bioelectrical activity according to the topography of individual fields of K. Brodmann. These data reflected the current activity present in the subjects in a state of passive, relaxed wakefulness with their eyes closed, both in the control group and in the comparison group.

A comparison of these characteristics in representatives of the control group and the comparison group (Fig. 1) showed that the results characterizing the rhythmic activity of Brodmann areas responsible for perception (18, 19) and cognitive processing of data (6, 7) have a low degree of difference (statistical significance according to the Chi-Square test was p = 0.6) (Fig. 2).

However, in the projection of fields 22, 27, 30, 31, 39 and 40 (Fig. 3), associated with the centers of sound perception and speech function, as well as the retrosplenial cerebral cortex



Fig. 1. Percentage of registration of default brain activity when solving an inverse EEG task (Chi-squared test; p = 0.04)



Fig. 2. Default activity in individual Brodmann fields that implement the processes of gnosis and information processing (Chi-squared test; p = 0.6)

(spatial orientation), significant changes in characteristics were recorded (Chi-square test; p = 0.01).

Thus, by analyzing changes in the sequences of excitation of cortical structures, it is possible to reject the null hypothesis of the experiment, especially if the researcher sets the goal as an analysis of basic cognitive functions, and not a study of their physiological characteristics in the spectrum of the conditional norm, for example, the fact of evidence of epilepsy in the subject or localization epileptic foci in the cortex to justify the possibility of subsequent surgical treatment. networks in those examined with paroxysmal changes in the electroencephalogram made it possible to reject the null hypothesis of the experiment, especially when studying diseases without organic damage being detected through neuroimaging studies, representing the cause of the disease. These observations correspond to data from previously conducted clinical examinations [43, 54], indicating that in at least 50% of clinical cases of established epilepsy in the interictal period, no significant disorders of higher nervous functions are detected, and patients with such disorders, with properly organized treatment, are quite adequate cope with educational and professional loads.

DISCUSSION

Our research showed mixed results. Thus, the lack of data confirming the presence of structural changes in neural

It is also confirmed that cognitive impairment in patients with epilepsy is either a manifestation of the seizure itself or a consequence of depressive states caused by impaired



Fig. 3. Default activity in individual Brodmann fields that implement speech function (Chi-squared test; p = 0.01)



Fig. 4. Two-dimensional EEG mapping of a long-term EEG study performed for the entire volume of data (A); for data excluding epileptiform activity (B); for epileptiform activity excluding interictal activity (C). (EEGLAB program (MATHWORKS). Artifact activity is excluded from the data using independent signal component analysis technology)

perception of the disease, which can be successfully relieved by prescribing adequate drug therapy [55].

However, a study of the functional sequences of transition of bioelectrical activity along cortical structures showed that the activity of speech centers observed in individuals with paroxysmal epileptiform changes in EEG recordings was significantly different from the activity detected in healthy people, which demonstrates the implementation of auditory-speech function in the form of a tono-musical model, typical for children aged from two to five years). These observations make it possible to explain the peculiarities of the occurrence of auditory hallucinations in patients with epilepsy and the changes in the characteristics of bioelectrical activity when listening to certain pieces of music, described previously [56, 57].

This organization of speech function rather represents a developmental option, probably associated with the influence of paroxysmal changes in the bioelectrical activity of the brain on the development and learning of such people, since the human speech function is the youngest of all cognitive functions, the formation of which is observed after birth.

CONCLUSIONS

The results obtained allow us to formulate the main decision of the study that to solve the main clinical problems of continued EEG studies, the use of interictal EEG recordings is not of significant clinical interest. Moreover, its exclusion and, as a consequence, "enrichment" of information due to the sequential placement of ictal patterns allows one to obtain more compact results of examinations of the pathological component using both the existing arsenal of tools for mathematical analysis of electroencephalograms, and new developments using machine learning and artificial intelligence technologies (Fig. 4–5). We hope that this approach will not only reduce the information presented to the specialist, but also improve his working conditions by significantly reducing the amount of visual load.



Fig. 5. Implementation of technology (technological prototype) for eliminating interictal activity during a long-term (9 h) EEG study. (BRAINSTORM program (MATHWORKS). Artifact activity is excluded from the data using independent signal component analysis technology)

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