УДК 616.895.8–07–08–02:616.89–008.45/.48
https://doi.org/10.20538/1682-0363-2024-4-15-21

Features of structural and functional changes of the brain in patients with schizophrenia

Galkin S.A.[1], Kornetova E.G.[1], Kornetov A.N.[2], Petkun D.A.[1], Bokhan N.A.[1, 2]

[1] *Mental Health Research Institute, Tomsk National Research Medical Center (NRMC), the Russian Academy of Sciences*
4, Aleutskaya Str., Tomsk, 634014, Russian Federation

[2] *Siberian State Medical University*
2, Moscow Trakt, Tomsk, 634050, Russian Federation

ABSTRACT

Aim. To establish the features of structural and functional changes in the brain in patients with schizophrenia.

Materials and methods. A morphometric analysis of the brain using MRI scans was performed, along with a clinical assessment of the electroencephalogram (EEG) of 35 patients with schizophrenia (20 men and 15 women). The control group included 18 healthy sex- and age-matched individuals (10 men and 8 women). Statistical processing was carried out using the $\chi 2$ test, the Fisher's exact test, and the Spearman's rank correlation coefficient.

Results. Compared to the control group, patients with schizophrenia were significantly more likely to show signs of ventricular dilation ($p = 0.039$), asymmetry of the lateral ventricles ($p = 0.041$), periventricular edema ($p < 0.001$), and enlargement of the subarachnoid space of the cerebellum ($p = 0.004$). Changes (class >1A) in the functional activity of the brain in the group of patients with schizophrenia were detected in 65.7% of the cases. In more than half of the cases, patients with schizophrenia showed decreased bioelectric activity of the brain (class 2 in 48.6% and class 3 in 11.4%); at the same time, EEG signs of paroxysmal activity were detected in a few patients (class B in 11.4% and class C in 5.7%) ($p < 0.001$). A statistically significant direct correlation was found between the enlargement of the subarachnoid space of the cerebellum and paroxysmal EEG activity in patients with schizophrenia ($r = 0.377$; $p = 0.044$).

Conclusion. The findings of our study highlight that the combined use of MRI and EEG can provide important information about brain pathology in schizophrenia. The data obtained are also important for testing the hypothesis on the association between vascular and functional disorders of the brain in patients with schizophrenia.

Keywords: schizophrenia, brain pathology, magnetic resonance imaging, electroencephalography, paroxysmal activity

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The study was conducted as part of the state assignment No. 075-01392-23-00 "Personalized diagnosis and therapy of patients with polymorbid disorders of the schizophrenic and affective spectrum", registration number 123041900006-4.

Conformity with the principles of ethics. All study participants signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at the Mental Health Research Institute of Tomsk NRMC (Protocol No. 157 of 18.11.2022).

For citation: Galkin S.A., Kornetova E.G., Kornetov A.N., Petkun D.A., Bokhan N.A. Features of structural and functional changes of the brain in patients with schizophrenia. *Bulletin of Siberian Medicine.* 2024;23(4):15–21. https://doi.org/10.20538/1682-0363-2024-4-15-21.

✉ *Galkin Stanislav A.,* s01091994@yandex.ru

Особенности структурных и функциональных изменений головного мозга у больных шизофренией

Галкин С.А.[1], Корнетова Е.Г.[1], Корнетов А.Н.[2], Петкун Д.А.[1], Бохан Н.А.[1, 2]

[1] *Научно-исследовательский институт (НИИ) психического здоровья, Томский национальный исследовательский медицинский центр (НИМЦ)*
Россия, 634014, г. Томск, ул. Алеутская, 4

[2] *Сибирский государственный медицинский университет (СибГМУ)*
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

Цель. Установить особенности структурных и функциональных изменений головного мозга у больных шизофренией.

Материалы и методы. Проведен морфометрический анализ магнитно-резонансных изображений головного мозга, а также клиническая оценка электроэнцефалограммы (ЭЭГ) 35 больных шизофренией (20 мужчин и 15 женщин). В контрольную группу вошли 18 здоровых лиц (10 мужчин и 8 женщин), которые были подобраны по возрасту и полу основной группе пациентов. Статистическая обработка проводилась с помощью критерия χ2 и точного критерия Фишера, а также корреляционного анализа Спирмена.

Результаты. По сравнению с группой контроля у больных шизофренией статистически значимо чаще обнаруживаются признаки расширения желудочков ($p = 0{,}039$), асимметрии боковых желудочков ($p = 0{,}041$), отека перивентрикулярных зон ($p < 0{,}001$) и расширения субарахноидального пространства мозжечка ($p = 0{,}004$). Модификации (класс >1A) функциональной активности мозга в группе больных шизофренией были выявлены в 65,7% случаев. Более чем в половине случаев у больных шизофренией обнаруживалось замедление биоэлектрической активности мозга (класс 2 – 48,6% и класс 3 – 11,4%), одновременно с этим у небольшой части пациентов выявлялись ЭЭГ-признаки пароксизмальной активности (класс B – 11,4% и класс C – 5,7%) ($p < 0{,}001$). Выявлена статистически значимая прямая корреляция между расширением субарахноидального пространства мозжечка и пароксизмальной активностью у больных шизофренией ($r_s = 0{,}377$; $p = 0{,}044$).

Заключение. Полученные данные в нашем исследовании подчеркивают, что совместное использование магнитно-резонансной томографии и ЭЭГ может предоставить важную информацию о мозговой патологии при шизофрении. Полученные нами результаты имеют значение для проверки гипотезы о связи дисциркуляторных и функциональных нарушений головного мозга у больных шизофренией.

Ключевые слова: шизофрения, мозговая патология, магнитно-резонансная томография, электроэнцефалография, пароксизмальная активность

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование проведено в рамках выполнения госзадания № 075-01392-23-00 «Персонализированная диагностика и терапия больных полиморбидными расстройствами шизофренического и аффективного спектра», регистрационный номер 123041900006-4.

Соответствие принципам этики. Все участники исследования подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом НИИ психического здоровья Томского НИМЦ (протокол № 157 от 18.11.2022).

Для цитирования: Галкин С.А., Корнетова Е.Г., Корнетов А.Н., Петкун Д.А., Бохан Н.А. Особенности структурных и функциональных изменений головного мозга у больных шизофренией. *Бюллетень сибирской медицины.* 2024;23(4):15–21. https://doi.org/10.20538/1682-0363-2024-4-15-21.

INTRODUCTION

The study of the structural and functional features of the brain in patients with schizophrenia remains one of the most actively developed areas in psychiatry [1, 2]. Many previous studies have clearly shown that in schizophrenia, gray matter atrophy is observed in various parts of the brain [1–4]. Even at early stages of the disease, patients with the first episode of schizophrenia have a decrease in gray matter content in regions, such as the temporal gyrus, dorsolateral prefrontal cortex, inferior frontal gyrus, thalamus, hippocampus, amygdala, etc. [4, 5]. In addition, the presence of dyscirculatory foci and multiple cysts, as well as dilation and asymmetry of the lateral ventricles were found [6, 7].

The literature devoted to neurophysiological (electroencephalographic) testing has extensively described flattening of the amplitude of the negative wave – N100 auditory evoked potentials (EP) in schizophrenia, although there is contrary information [10] indicating that the amplitude of N100 does not change significantly in patients with schizophrenia compared to the control group. On the other hand, a relatively high percentage of individuals with this disorder show changes in the EEG in the form of generalized slow wave activity (delta and theta waves), asymmetry, the presence of sharp waves and/or spike–and–wave complexes (paroxysmal patterns) [11–13].

Summarizing the above data, we can say that, despite the large number of original research conducted earlier, the results of studying structural and functional changes in the brain in patients with schizophrenia are quite debatable, which causes a lot of discussion regarding the variety of mechanisms (pathogenesis) of the disease and its diagnostic instability.

On the other hand, despite the widespread use of new high-tech methods (positron emission tomography, single-photon emission computed tomography, magnetoencephalography, functional magnetic resonance imaging (MRI), etc.), studies of structural and functional features in the research of brain diseases, electroencephalography (EEG) and magnetic resonance imaging (MRI) methods remain the most adequate in displaying pathological processes in the brain. Electroencephalography has almost a hundred-year history and is one of the first physiological methods used to study the functional activity of the brain in patients with schizophrenia. Today it remains a fairly popular way to examine the brain. In general, bioelectric signals arise as a result of the combined dendritic inhibitory and excitatory postsynaptic activity of billions of neurons, primarily pyramidal cells in the neocortex of the brain [14]. One of the main limitations of the method is the difficulty in determining the source of recorded activity, since pulse activity generators in different parts of the brain can reproduce the same EEG pattern recorded distally on the scalp [15]. EEG has high temporal and low spatial resolution, which is compensated by structural MRI, which, instead, is characterized by high spatial and low temporal resolution [16]. Structural MRI provides detailed information about the regions of the brain that have pathological changes in many diseases, including schizophrenia [17].

The aim of the study was to establish the features of structural and functional changes in the brain in patients with schizophrenia.

MATERIALS AND METHODS

The study was approved by the local Ethics Committee at the Mental Health Research Institute of Tomsk NRMC (Protocol No. 157 of 18.11.2022). All study participants signed an informed consent to participate in the study.

In total, 35 patients with schizophrenia (20 men and 15 women) who underwent treatment in the Endogenous Disorders Department of the Mental Health Research Institute Clinic of Tomsk NRMC were selected for this study. Inclusion criteria were as follows: patients aged 18–55 years old; they were diagnosed with schizophrenia according to the criteria of ICD–10 (F20); the duration of the disease is at least 1 year; and patients signed a written consent to participate in the study. Exclusion criteria were the following: psychoactive substance dependence (except tobacco), dementia, no significant neurological history (brain injury, stroke), refusal to participate in the study.

The age of the patients included in the study was 37 [32; 44] years. The duration of the disease was 15 [11; 21] years. At the time of inclusion in the study, patients received basic therapy with second-generation atypical antipsychotic medications (CPZeq – 400 [200; 600] mg / day), the duration of basic therapy was 4 [3; 8] years. The severity of psychopathological symptoms was assessed using the PANSS (Positive and Negative Syndrome Scale) [18] in the adapted Russian version – SCI–PANSS [19]. The overall PANSS score of the patients was 81 [68; 101]. The severity of positive symptoms was 12 [9; 27] points versus 23 [20; 26] points for negative ones, while the severity of general psychopathological symptoms was 44 [39; 53] points.

The control group included 18 healthy individuals (10 men and 8 women) who matched the main group of patients in terms of age and gender ($p > 0.05$) with similar exclusion criteria.

The methodology of the clinical examination (MRI and EEG) is presented in detail in our previous articles [6, 11].

The statistical analysis was carried out using the R 4.2.2 software. Compliance with the law of normal distribution was checked using the Shapiro – Wilk test. The data did not follow the normal distribution. Quantitative data were presented as the median and the interquartile range Me [Q_1; Q_3]. Qualitative data were presented by frequency parameters in absolute and relative units – *n* (%). The chi-squared test and the Fisher's exact test were used to compare frequencies (in the case of frequencies less than 5). The Spearman's rank correlation coefficient (r_s) was used to identify the relationships between the studied parameters. The threshold level of statistical significance of *p* was assumed to be 0.05.

RESULTS

According to the analysis of brain morphometry using MRI, the following pathological changes were found in the studied groups of patients and controls: dilation and / or asymmetry of the lateral ventricles, periventricular edema, enlargement of the subarachnoid space of the large hemispheres and / or cerebellum, the presence of cysts in the brain (Table 1).

Table 1

Analysis of brain morphometry using MRI in the studied groups of patients and controls, *n* (%)

MR parameter	Patients with schizophrenia, *n* = 35	Control, *n* = 18	*p*
Ventricular dilation	12 (34.3%)	1 (5.6%)	0.039*
Asymmetry of the lateral ventricles	11 (31.4%)	1 (5.6%)	0.041*
Periventricular edema	31 (88.6%)	6 (33.3%)	<0.001*
Enlargement of the subarachnoid space of the large hemispheres	13 (37.1%)	4 (22.2%)	0.358
Enlargement of the subarachnoid space of the cerebellum	30 (85.7%)	8 (44.4%)	0.004*
Cysts	8 (22.8%)	2 (11.1%)	0.463

* Statistically significant differences here and in Tables 2, 3.

Compared to the control group, patients with schizophrenia were significantly more likely to show signs of ventricular dilation ($p = 0.039$), asymmetry of the lateral ventricles ($p = 0.041$), periventricular edema ($p < 0.001$), and enlargement of the subarachnoid space of the cerebellum ($p = 0.004$).

When summarizing the obtained EEG data, changes (class > 1A) in the functional activity of the brain were detected in 65.7% of cases in the group of patients with schizophrenia (Table 2).

Table 2

EEG modifications in the studied patient and control groups, *n* (%)

EEG modifications		Patients with schizophrenia, *n* = 35	Control, *n* = 18
Slowing on EEG (class)	1	14 (40%)	18 (100%)
	2	17 (48.6%)	–
	3	4 (11.4%)	–
	4	–	–
Paroxysmal activity (class) (class)	A	29 (82.9%)	18 (100%)
	8	4 (11.4%)	–
	C	2 (5.7%)	–
	D	–	–-

* $p < 0.001$.

In more than half of the cases, patients with schizophrenia showed slowing of the bioelectric activity of the brain (class 2 in 48.6% and class 3 in 11.4% of cases). At the same time, EEG signs of paroxysmal activity were detected in a few patients (class B in 11.4% and class C in 5.7% of cases).

Table 3 shows the correlation analysis data on EEG changes depending on the detected pathological changes according to the analysis of brain morphometry using MRI in patients with schizophrenia.

Table 3

The relationship between the parameters of brain MRI and EEG in patients with schizophrenia

MR parameter	Slowing on EEG	Paroxysmal activity
Ventricular dilation	$r_s = 0.022$ $p = 0.923$	$r_s = 0.189$ $p = 0.409$
Asymmetry of the lateral ventricles	$r_s = 0.092$ $p = 0.691$	$r_s = 0.148$ $p = 0.521$
Periventricular edema	$r_s = 0.099$ $p = 0.666$	$r_s = 0.116$ $p = 0.613$
Enlargement of the subarachnoid space of the large hemispheres	$r_s = 0.144$ $p = 0.531$	$r_s = 0.152$ $p = 0.509$

End of table 3

The relationship between the parameters of brain MRI and EEG in patients with schizophrenia

MR parameter	Slowing on EEG	Paroxysmal activity
Enlargement of the subarachnoid space of the cerebellum	r_s = 0.025 p = 0.326	r_s = 0.377 p = 0.044*
Cysts	r_s = 0.111 p = 0.632	r_s = 0.146 p = 0.527

A statistically significant correlation was found between paroxysmal activity on EEG and the enlargement of the subarachnoid space of the cerebellum in patients with schizophrenia ($r_s = 0.377$; $p = 0.044$). We could not find statistically significant correlations with the clinical parameters of patients (age, duration of the disease, duration of basic therapy, severity of psychopathological symptoms according to PANSS) ($p > 0.05$ for all).

DISCUSSION

The data presented in our original study indicate the presence of extensive structural and functional changes in the brain in patients with schizophrenia. The dyscirculatory disorders detected using MRI in schizophrenia are consistent with the results of earlier studies [4, 5, 20, 21]. As is known, the detected MRI parameters are not independent diseases, but arise in response to pathological processes occurring in the brain. Nevertheless, unlike a number of previous studies [4, 5], we were unable to establish significant correlations of brain abnormalities with the clinical and dynamic features of schizophrenia, which may be due to the innate nature of pathological changes in the brain. For example, parents of newborn children often learn about the enlargement of the subarachnoid space after examination. These phenotypic features reflect disorders of embryonic morphogenesis resulting from the constellation of hereditary factors and perinatal effects, the clinical assessment of which is important for the identification of abnormalities in the development of the nervous system [22].

We also identified significant changes in the functional activity of the brain in patients with schizophrenia in the form of a slowdown in biopotentials and emergence of paroxysmal activity on EEG. It is assumed that these changes are associated with inhibitory deficit of GABAergic projections of the cortex to pyramidal neurons. This can lead to uncontrolled excitation (hyperexcitation) of pyramidal neurons, which, in turn, affect their targets, causing excitotoxic changes leading to regression of neural networks due to loss of dendrites and synapses. This model is confirmed by data on soma volume deficit in the primary and secondary cortex (soma volume of pyramidal cells correlates with the degree of dendritic branching [23]. It should also be noted that impaired GABAergic-glutamatergic interaction in the pyramidal neurons of the brain is one of the main mechanisms of epileptogenesis [24].

In addition, we found a significant relationship between MRI and EEG data, namely a direct correlation between the enlargement of the subarachnoid space of the cerebellum and the presence of paroxysmal activity in patients with schizophrenia, which is consistent with clinical cases of patients with epilepsy [25, 26]. As is known, the detection of paroxysmal activity on EEG indicates a trend toward convulsive states. Paroxysmal activity reflects a change in the functioning of basic neurophysiological processes with an increase in the activity of subcortical synchronizing regulators that contribute to the occurrence of seizures. In clinical practice, information about brain structures that can cause paroxysmal activity on EEG is of great value, especially for patients with schizophrenia receiving long-term therapy with antipsychotics and, in some cases, antidepressants.

CONCLUSION

Thus, the data obtained in our study emphasize that the combined use of MRI and EEG can offer key insights into brain pathology in schizophrenia. Our findings also contribute to the search for specific structural and functional neurobiomarkers of schizophrenia.

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Authors' contribution

Galkin S.A. – neurophysiological examination of patients, analysis of data, drafting of the manuscript. Kornetova E.G. – conception and design, clinical, psychopathological, and psychometric examination of the sample, critical revision of the manuscript for important intellectual content. Kornetov A.N. – conception and design, review of publications on the topic of the manuscript, drafting and editing of the manuscript. Petkun D.A. – psychometric examination of patients. Bokhan N.A. – final approval of the manuscript for publication.

Authors' information

Galkin Stanislav A. – Cand. Sci. (Med.), Researcher, Mental Health Research Institute, Tomsk NRMC, Tomsk, s01091994@yandex.ru, http://orcid.org/0000-0002-7709-3917

Kornetova Elena G. – Dr. Sci. (Med.), Head of the Endogenous Disorders Department, Mental Health Research Institute, Tomsk NRMC, Tomsk, ekornetova@outlook.com, http://orcid.org/0000-0002-5179-9727

Kornetov Alexander N. – Dr. Sci. (Med.), Professor, Head of the Fundamental Psychology and Behavioral Medicine Division, Siberian State Medical University, Tomsk, alkornetov@gmail.com, http://orcid.org/0000-0002-2342-7504

Petkun Dmitry A. – Junior Researcher, Mental Health Research Institute, Tomsk NRMC, Tomsk, substantia_p@mail.ru, http://orcid.org/0000-0002-6587-6347

Bokhan Nikolay A. – Dr. Sci. (Med.), Professor, Distinguished Scientist of the Russian Federation, Academician of the Russian Academy of Sciences, Director of the Mental Health Research Institute, Tomsk NRMC, Head of the Psychiatry, Narcology and Psychotherapy Division, Siberian State Medical University, Tomsk, bna909@gmail.com, http://orcid.org/0000-0002-1052-855X

(✉) **Galkin Stanislav A.,** s01091994@yandex.ru

Received 02.07.2024;
approved after peer review 30.08.2024;
accepted 12.09.2024