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Resting state functional magnetic resonance imaging in patients with multiple sclerosis before and after high-dose immunosuppressive therapy and autologous hemopoietic stem cell transplantation

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ABSTRACT

BACKGROUND: Multiple sclerosis is a chronic autoimmune disease characterized by multifocal foci of demyelination in the central nervous system, usually affecting people of working age. The disease causes damage to the blood-brain barrier, the development of multifocal inflammation, destruction of the myelin sheath of axons and various degrees of damage. It is clinically manifested by restriction of motor activity, visual acuity, as well as other symptoms leading to loss of performance and disability of the patient.

AIM: determination of changes in the functional connectivity of brain neural networks in patients with multiple sclerosis before and after high-dose immunosuppressive therapy and autologous
hematopoietic stem cell transplantation by performing functional magnetic resonance imaging at rest.

MATERIALS AND METHODS: The data of functional magnetic resonance imaging of patients with multiple sclerosis were analyzed in dynamics before and after the use of high-dose immunosuppressive therapy followed by autologous hematopoietic stem cell transplantation. The study involved 25 patients with a verified diagnosis of multiple sclerosis. Each underwent complex magnetic resonance imaging at two time points (before and after high-dose immunosuppressive therapy followed by autologous hematopoietic stem cell transplantation) with a difference of 12 months, which included structural magnetic resonance imaging - in order to exclude the presence of pathological foci in the brain (in addition to foci of multiple sclerosis) and functional magnetic resonance imaging.-resonance imaging at rest — to assess functional connectivity. Also, according to the method generally accepted in classical neurology, a clinical neurological examination was performed.

RESULTS: At the stage of comparing data on the two groups obtained using functional magnetic resonance imaging at rest, changes in functional activity were detected in various parts of the brain, presumably responsible for clinical differences in the studied groups.

CONCLUSION: Currently, the links between brain structures and morphological changes that cause cognitive impairment in multiple sclerosis are being studied. To predict the progression of the disease, the development of biomarkers, including those based on functional magnetic resonance imaging, is required. Evaluating changes in the functional connectivity of brain neural networks can help personalize therapeutic and rehabilitation approaches.

Keywords: brain neural networks; default mode network; functional MRI; resting-state functional MRI; magnetic resonance imaging; multiple sclerosis; stem cell transplantation.

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Функциональная магнитно-резонансная томография покоя у пациентов с рассеянным склерозом до и после проведения высокодозной иммуносупрессивной терапии и аутологичной трансплантации гемопоэтических стволовых клеток

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АННОТАЦИЯ

Актуальность. Рассеянный склероз — хроническое аутоиммунное заболевание, характеризующееся мультифокальными очагами демиелинизации в центральной нервной системе, обычно поражающее людей трудоспособного возраста. Болезнь вызывает повреждение гематоэнцефалического барьера, развитие мультифокального воспаления, разрушение миелиновой оболочки аксонов и различные степени повреждения. Клинически проявляется ограничением двигательной активности, остроты зрения, а также другими симптомами, приводящими к утрате работоспособности и инвалидизации пациента.

Цель исследования: определение изменений функциональной коннективности нейросетей головного мозга у пациентов с рассеянным склерозом до и после проведения высокодозной иммуносупрессивной терапии и аутологичной трансплантации гемопоэтических стволовых клеток путем проведения функциональной магнитно-резонансной томографии покоя.

Материалы и методы. Был проведен анализ данных функциональной магнитно-резонансной томографии покоя пациентов с рассеянным склерозом в динамике до и после применения высокодозной иммуносупрессивной терапии с последующей аутологичной трансплантацией гемопоэтических стволовых клеток. В исследовании участвовало 25 пациентов с верифицированным диагнозом «рассеянный склероз». Каждому была выполнена комплексная магнитно-резонансная томография в двух временных точках (до и после высокодозной иммуносупрессивной терапии с последующей аутологичной трансплантацией гемопоэтических стволовых клеток) с разницей 12 мес, которая включала в себя структурную магнитно-резонансную томографию — с целью исключения наличия патологических очагов в головном мозге (помимо очагов рассеянного склероза) и функциональную магнитно-резонансную томографию покоя — для оценки функциональной коннективности. Также по общепринятой в классической неврологии методике выполнялось клинико-неврологическое обследование.

Результаты. На этапе сравнения данных о двух группах, полученных с помощью функциональной магнитно-резонансной томографии покоя, были обнаружены изменения функциональной активности в различных участках головного мозга, предположительно ответственных за клинические различия в исследуемых группах.

Заключение. В настоящее время изучаются связи между структурами головного мозга и морфологическими изменениями, вызывающими когнитивные нарушения при рассеянном склерозе. Для прогнозирования прогрессирования заболевания требуется разработка биомаркеров, в том числе на основе функциональной магнитно-резонансной томографии. Оценка изменений функциональной коннективности нейросетей головного мозга может помочь персонализировать лечебные и реабилитационные подходы.

Ключевые слова: магнитно-резонансная томография; нейронные сети головного мозга; рассеянный склероз; сеть пассивного режима; трансплантация стволовых клеток; функциональная МРТ; функциональная МРТ покоя.

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多发性硬化症患者在接受大剂量免疫抑制治疗和自体造血干细胞移植前后的静息态功能性核磁共振成像研究

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摘要

现实意义。多发性硬化症是一种慢性自身免疫性疾病，以中枢神经系统多灶性脱髓鞘性为特点，通常影响工作年龄的人群。该疾病会导致血脑屏障受损、多灶性炎症、轴突髓鞘破坏和不同程度的损害。临床表现为运动活动受限、视力减退，以及导致患者表现丧失和残疾的其他症状。

研究目的。使用静息态功能性核磁共振成像测定多发性硬化症患者在接受大剂量免疫抑制治疗和自体造血干细胞移植前后大脑神经网络功能连接的变化。

材料和方法。对多发性硬化症患者在接受大剂量免疫抑制治疗和自体造血干细胞移植前后的静息态功能性核磁共振成像数据进行了动态分析。25名经验证诊断为多发性硬化症的患者参与了研究。每名患者在两个时间点（大剂量免疫抑制治疗和自体造血干细胞移植前后）接受了综合性的核磁共振成像检查，间隔时间为12个月。检查包括用来排除大脑中是否存在病灶（除了多发性硬化症病变）的结构核磁共振成像磁和，用来评估功能连接性的静息态功能性核磁共振成像。同时根据经典神经病学中普遍接受的方法进行临床神经学检查。

结果。在通过静息态功能磁共振成像获得的两组数据的对比阶段，在不同的脑区检测到了功能活动的变化，这可能是造成研究组临床差异的原因。

结论。目前正在研究导致多发性硬化症认知障碍的大脑结构和形态变化之间的关系。为了预测疾病进展，需要开发生物标志物，包括基于功能性磁共振成像的生物标志物。许多研究人员认为，根据功能性磁共振成像测量大脑神经网络功能连接性的变化，可以反映疾病的进程、治疗效果和神经康复情况。对这些变化的评估可能有助于制定个性化的治疗和康复的方法。

关键词：核磁共振成像；大脑神经网络；多发性硬化症；默认模式网络；干细胞移植；功能性核磁共振成像；静息态功能性核磁共振成像。

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BACKGROUND

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by spatially and temporally distributed multifocal inflammatory demyelinating lesions in the central nervous system (CNS) and usually affects people of working age [1].

In MS, the blood–brain barrier is damaged, multifocal inflammation and reactive gliosis develop, and the myelin sheath of axons undergoes degrees of destruction [1].

Clinically, MS is manifested by reduced motor activity (e.g., unsteady gait, dysmetria, and intention tremor), reduced visual acuity to complete blindness, ophthalmoplegia, nystagmus, hearing loss, monoparesis and hemiparesis, sensory disturbances, and cognitive dysfunction (e. g., reduced memory and attention and chronic fatigue and tiredness), leading to persistent loss of work capacity and disability of the patient [2].

Patients gradually lose their ability to work, function, and care for themselves as MS progresses. The Expanded Disability Status Scale (EDSS) is used to evaluate the patient's condition. Additionally, it can be employed in classifying the disability level of patients from 0 (no disability) to 10 (MS as the cause of death) [3].

Currently, the 2021 McDonald criteria are used to diagnose MS [2, 3]. They are based on two characteristics: spatial distribution (presence of two or more clinical lesions and distribution of lesions in two or more CNS regions according to magnetic resonance imaging (MRI)) and temporal distribution (clinical exacerbations involving a new CNS region and new MS lesions according to MRI) [2]. Moreover, MS diagnosis includes cerebrospinal fluid evaluation and oligoclonal immunoglobulin G (IgG) testing. The diagnosis is confirmed by MRI.

Recently, special attention has been paid to assessing changes in functional connectivity between brain structures and morphological changes in these structures, associated with cognitive impairment, as the state of brain matter is crucial in predicting MS progression. This requires developing biomarkers based on advanced neuroimaging techniques such as functional magnetic resonance imaging (fMRI), which provides information about the state of brain matter and predict disease progression.

fMRI is a neuroimaging technique for examining changes in functional connectivity to diagnose various neurological disorders based on changes in the blood oxygenation level-dependent (BOLD) signal, which in turn is affected by changes in neuronal activity in a specific brain region [1].

There are 2 types of fMRI, resting-state fMRI and dynamic fMRI [4]. Resting-state fMRI is used to investigate functional brain connectivity, whereas dynamic fMRI measures brain activation in response to specific tasks performed by patients during the examination. The tasks are divided into several categories. The first category includes sensorial and active motor tasks, such as flexion and extension of four fingers of the dominant hand, flexion and extension of the foot, manipulation of objects used daily, and opposition of the index finger to the thumb of the dominant hand. The second category involves active cognitive tasks, such as the Paced Auditory Serial Addition Test (PASAT) and Paced Visual Serial Addition Test (PVSAT), and immediate and delayed memory tasks [5–9].

Functional brain connectivity changes visualized by resting-state fMRI can be used as biomarkers of cognitive impairment, as this criterion reflects the coherence of biological neural networks.

Networks are classified as follows: default mode network (DMN), salience detection network (SDN), and central executive network (CEN) [3, 10].

Each network has its topography and scope. The DMN, which is less active during performing complex tasks requiring increased attention, involves several anatomical regions, including the ventromedial prefrontal, dorsomedial prefrontal, lateral medial, and posterior cingulate cortices [11]. The SDN acts as a filter for the most critical stimuli and provides the ability to focus on a specific intellectual task. It is located in the anterior insula and dorsal anterior cingulate gyrus. The CEN integrates the dorsolateral prefrontal cortex with the posterior parietal cortex and processes incoming information, maintaining attention, manipulating memory, and performing tasks requiring cognitive effort.

Several studies have reported that changes in the functional connectivity of the brain's neural networks indicate disease progression, treatment efficacy, and neurorehabilitation [3, 12, 13]. In the future, assessment of functional brain connectivity may be beneficial in developing personalized treatment and rehabilitation approaches according to functional impairment severity [12].

The current approach to MS treatment includes three components: attack therapy, disease-modifying drugs (DMTs), and symptomatic therapy; however, many studies focused on finding new treatment options for MS patients [2]. High-dose immunosuppressive therapy with autologous hematopoietic cell transplantation (HDIT/AHSCT) plays a role in achieving stable long-term remissions [14, 15].

The treatment involves several steps: mobilization and collection of hematopoietic stem cells (HSCs) from the patient's bone marrow, cryopreservation and storage of the HSC graft, high-dose immunosuppression (conditioning regimen), and re-infusion of the thawed HSC graft 48 hours after the last dose of the cytostatic agent [16].

This *study* aimed to determine changes in functional connectivity of neural networks in MS patients before and after HDIT/AHSCT using resting-state fMRI findings.

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MATERIALS AND METHODS

Resting-state fMRI findings in MS patients before and after HDIT/AHSCT were evaluated. The study included 25 patients with confirmed MS diagnosis. Each patient underwent comprehensive MRI at two time points (pre- and post-HDIT/AHSCT) 12 months apart, including structural MRI to rule out abnormal brain lesions (other than MS lesions) and resting-state fMRI to assess functional brain connectivity.

A 3.0 Tesla tomograph was used for MRI. Patients were instructed to lie open-eyed (not asleep) and not to fixate their gaze during scanning. A T1-weighted gradient-echo MP-RAGE pulse sequence was utilized to align fMRI images with anatomical brain structures (Table 1).

Furthermore, a clinical neurological examination using a classic method generally accepted in neurology was performed, including an objective assessment of the neurological status and evaluation of the patient using EDSS.

The inclusion criteria for HDIT/AHSCT were as follows:

1. Age 18–65 years and confirmed MS diagnosis (EDSS1.0–6.5)
2. Confirmed MS progression despite standard therapy; EDSS worsening of ⩾1 from a baseline of <5, and EDSS worsening of ⩾0.5 from a baseline of >5
3. New (including Gd+) MS lesions according to MRI findings
4. No serious comorbidities
5. No treatment with interferons and immunosuppressants within the last 3 months.

Based on HDIT/AHSCT findings, patients were divided into two groups: Group 1 (n = 18; favorable outcome group), patients with complete remission within one year, and Group 2 (n = 7, unfavorable outcome group), patients with at least one attack within one year of treatment.

The functional connectivity of the neural networks was evaluated using the CONN toolbox v20a based on SPM 12. The groups were compared to identify individual areas of altered functional connectivity of resting-state neural networks.

FINDINGS

When the resting-state fMRI findings were compared between the two groups, changes in functional activity were found in several brain regions believed to be responsible for the clinical differences between the study groups.

Changes were found in the following neural networks: DMN, sensorimotor neural network, dorsal attention network, frontoparietal network, and anterior and posterior cerebellar neural networks (Table 2).

DMN Evaluation

DMN was the first resting-state neural network to be compared. This is the brain's "true" resting-state network of because it is evaluated in the absence of cognitive and motor paradigms in the patient. Several studies showed that impaired functional connectivity in this network indicate the presence of cognitive and affective disorders [7, 17]. Moreover, it was found that the process of patient disability is correlated with the disruption of the main resting neural network.

Comparison groups for changes in functional connectivity for this network showed an increase in clusters in the prefrontal region in group 1 (the successful transplant group). This shows the restoration of connections in this neural network caused by the pool of mirror/silent neurons in the prefrontal region.

Increased functional connectivity of the superior frontal gyri bilaterally (Fig. 1) and diffusely in the frontal lobes leads to changes in the clinical picture with decreased severity of affective disorders in patients and improved Symbolic Digit Modalities Test (SDMT) score.

The cluster (Fig. 2) showed increased activity in the lingual gyrus. These changes also improve the clinical

Table 1. MRI protocol

Таблица 1. Протокол МРТ-исследования

No.	MRI sequence	Scan time	Characteristics of sequences
1	t2_tse_tra_320_p2	2 min 30 sec	FOV 220 × 220 mm, slice thickness 4.0 mm, TR 6,000 ms, TE 93 ms, matrix 320 × 320, number of slices 27
2	t2_tirm_tra_dark-fluid	4 min 30 sec	FOV 199 × 220 mm, slice thickness 4.0 mm, TR 9,000 ms, TE 93 ms, matrix 256 × 232, number of slices 27
3	T 1 ВИ (MPRAGE)	9 min	FOV 240 × 256 mm, slice thickness 1.2 mm, TR 2,300 ms, TE 3 ms, matrix 256 × 240, number of slices 160
4	gre_field_mapping	1 min 30 sec	FOV 192 × 192 mm, slice thickness 1.2 mm, TR 400 ms, TE 7.4 ms, matrix 64 × 64, number of slices 36
5	ep2_120_bold_Rest	6 min	FOV 192 × 192 mm, slice thickness 4.5 mm, TR 3,000 ms, TE 30 ms, matrix 64 × 64, number of slices 36

testing results and, most importantly, the patients' quality of life. The increase in the area of the detected cluster suggests a high potential for restoring the brain's main resting-state neural network, as some of the cells in this area are associated with the medial prefrontal cortex. These changes indicate the cause of the positive change in the patients' mood, level of cognitive capabilities, and some motor functions.

As for the functional affiliation of the detected clusters, then sections 2 and 3 of the cluster (Fig. 2, 3), associated with the DMN, are located in areas close to the structures involved in the formation of this neural network, indicating the restoration of functional connectivity of the neural network itself. Based on this phenomenon, we can potentially expect to see improved memory test scores, attention, psychological components, reduced severity of motor dysfunction due to improved action planning, and increased quality of life.

Our finding of increased functional connectivity of this neural network in patients who were in remission for more than one year after therapy suggests a reparative potential, possibly based on neuroplasticity or neurogenesis.

Evaluation of the sensorimotor neural network

A sensorimotor neural network (SNN) is a resting-state neural network that is the main network when performing any motor action (Table 3).

When evaluating clusters 1 and 2 of the sensorimotor neural network, the increased functional connectivity in the frontal lobe area was noted (Fig. 4, 5).

Increased functional connectivity was found in the left temporal lobe (Fig. 6). Note that the change in functional connectivity occurs in the gray matter and the area of increased activity is quite large.

Cluster 4 (Fig. 7) showed increased functional connectivity in the angular gyrus. The angular gyrus is a brain region located primarily in the anterolateral region of the parietal lobe. Its role is associated with the transmission of visual information to Wernicke's area for the acquisition of written language.

Table 2. Clusters of the default mode network of the brain
Таблица 2. Кластеры сети пассивного режима работы мозга

Cluster No.	Position (x, y, z)	Size of Cluster	FWR	FDR	p-unc	peak p-FWE	peak p-unc	Location of cluster
1	+04, +60, +24	344	0.000000	0.000000	0.000000	0.000387	0.000000	Right frontal lobe, right superior frontal gyrus, left superior frontal gyrus, left frontal lobe, right paracingulate gyrus
2	–20, –70, +00	121	0.002707	0.002514	0.000055	0.477232	0.000003	Left lingual gyrus, left intracalcarine cortex, left occipital fusiform gyrus
3	+18, –50, –42	112	0.004425	0.002743	0.000090	0.123083	0.000001	Right cerebellar hemisphere

Note. FWR — Family-Wise Error Rate, *p*-value at the family-wise error rate; FDR — False Discovery Rate, *p*-value at the false discovery rate; p-unc — uncorrected *p*-value; peak p-FWE — peak *p*-value at the family-wise error rate; peak p-unc — peak uncorrected *p*-value

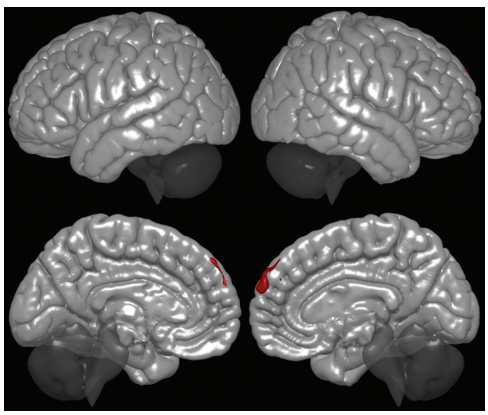

Fig. 1. Cluster N 1 of the default mode network
Рис. 1. Кластер № 1 сети пассивного режима

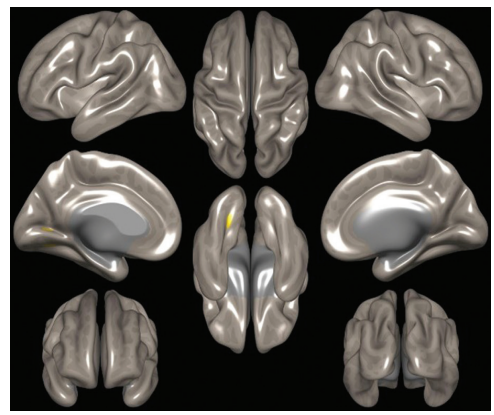

Fig. 2. Cluster N 2 of the default mode network
Рис. 2. Кластер № 2 сети пассивного режима

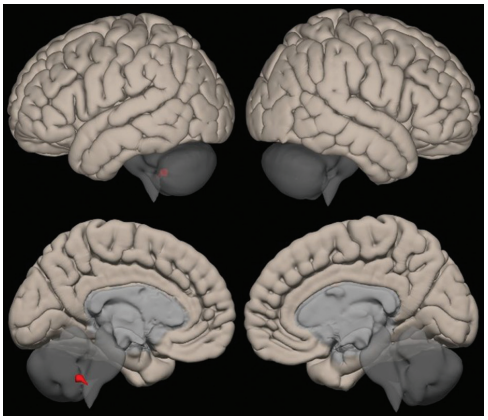

Fig. 3. Cluster N 3 of the default mode network
Рис. 3. Кластер № 3 сети пассивного режима

The SNN also showed a positive increase in functional connectivity in the areas of the SNN's structures as well as in the left frontal and temporal lobes (all patients were right-handed). This suggests that the patients have increased control over their own movements and that the areas responsible for motor skill acquisition are being restored.

DISCUSSION

MS is a chronic and potentially disabling disease that requires early diagnosis and appropriate treatment.

The current standard of care for MS patients is corticosteroids and DMTs. However, these agents do not provide a complete stable remission, so researchers are looking for new treatment methods, and HDIT/AHSCT is one of these new treatment options. The literature shows that HDIT/AHSCT reduces the annual attack rate, which is consistent with our data (more than 70% of patients achieved complete remission within 1 year).

fMRI is a potential technique for evaluating treatment and rehabilitation. In the present study, resting-state fMRI was used to assess the functional connectivity of the DMN and SNN. The neural networks described above showed the presence of clusters of increased functional connectivity in clinically significant regions of the brain in patients with a successful outcome of HDIT/AHSCT (e.g., in the frontal lobes, angular and lingual gyri). This correlated with improved SDMT scores and reduced severity of affective disorders. However, further magnetic resonance imaging with resting-state fMRI and neurological monitoring over time are warranted to compare

Table 3. Clusters of the sensorimotor neural network
Таблица 3. Кластеры сенсомоторной нейросети

Cluster No.	Position (x, y, z)	Size of Cluster	FWR	FDR	p-unc	peak p-FWE	peak p-unc	Location of cluster
1	+06, +58, +22	371	0.000000	0.000000	0.000000	0.006336	0.000000	Right frontal lobe, left frontal lobe, left superior frontal gyrus, right superior frontal gyrus, left paracingulate gyrus, right paracingulate gyrus
2	+36, +46, +14	190	0.000100	0.000069	0.000002	0.974484	0.000027	Right frontal lobe, right middle frontal gyrus
3	–50, +08, –42	141	0.001061	0.000382	0.000022	0.840376	0.000011	Left temporal lobe
4	+48, –46, +12	140	0.001117	0.000382	0.000023	0.776472	0.000008	Right angular gyrus, right middle temporal gyrus, right temporo-occipital region, right posterior part of supramarginal gyrus

Note. FWR — Family-Wise Error Rate, *p*-value at the family-wise error rate; FDR — False Discovery Rate, *p*-value at the false discovery rate; p-unc — uncorrected *p*-value; peak p-FWE — peak *p*-value at the family-wise error rate; peak p-unc — peak uncorrected *p*-value

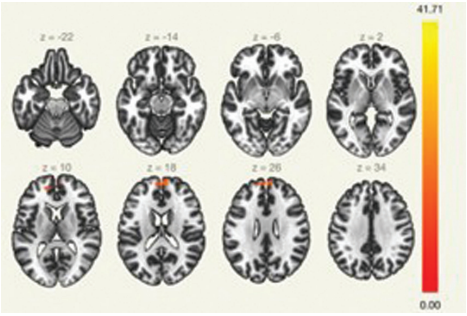

Fig. 4. Cluster N 1 of the sensorimotor neural network
Рис. 4. Кластер № 1 сенсомоторной нейросети

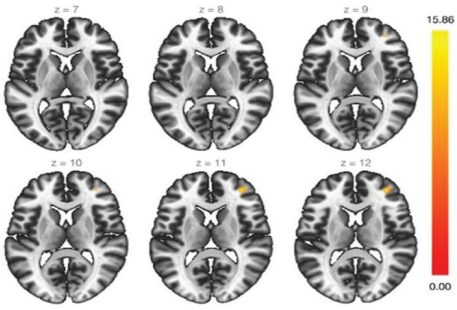

Fig. 5. Cluster N 2 of the sensorimotor neural network
Рис. 5. Кластер № 2 сенсомоторной нейросети

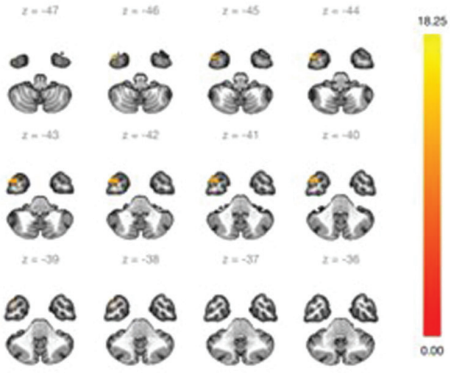

Fig. 6. Cluster N 3 of the sensorimotor neural network
Рис. 6. Кластер № 3 сенсомоторной нейросети

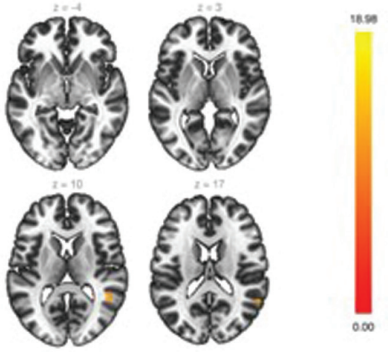

Fig. 7. Cluster N 4 of the sensorimotor neural network
Рис. 7. Кластер № 4 сенсомоторной нейросети

MRI with clinical and neurological findings, and a larger patient population should be evaluated.

CONCLUSION

Resting-state fMRI allows quantitative and objective detection of changes in the functional connectivity of neural networks in patients with successful outcome of high-dose immunosuppressive therapy with autologous HSC transplantation.

Further evaluation of the functional connectivity of neural networks in this patient population may enable identifying functional markers that could predict the HDIT/AHSCT outcome. This requires targeted exploration of the brain's neural networks using resting-state fMRI and dynamic MRI.

REFERENCES

1. Prosperini L, Piattella MC, Giannì C, Pantano P. Functional and Structural Brain Plasticity Enhanced by Motor and Cognitive Rehabilitation in Multiple Sclerosis. *Neural Plast.* 2015;2015:481574. doi: 10.1155/2015/481574

2. Clinical guidelines — Multiple sclerosis — 2022–2023–2024 (13.07.2022) — Approved by the Ministry of Health of the Russian Federation. As of July 13, 2022 on the website of the Ministry of Health of the Russian Federation. Available from: http://disuria.ru/_ld/12/1226_kr22G35p0MZ.pdf (In Russ.)

3. Hejazi S, Karwowski W, Farahani FV, et al. Graph-Based Analysis of Brain Connectivity in Multiple Sclerosis Using Functional MRI: A Systematic Review. *Brain Sci.* 2023;13(2):246. doi: 10.3390/brainsci13020246

4. Giorgio A, De Stefano N. Advanced Structural and Functional Brain MRI in Multiple Sclerosis. *Semin Neurol.* 2016;36(2):163–176. doi: 10.1055/s-0036-1579737

5. Rocca MA, Schoonheim MM, Valsasina P, et al. Task- and resting-state fMRI studies in multiple sclerosis: From regions to systems and time-varying analysis. Current status and future perspective. *Neuroimage Clin.* 2022;35:103076. doi: 10.1016/j.nicl.2022.103076

6. Manca R, Sharrack B, Paling D, et al. Brain connectivity and cognitive processing speed in multiple sclerosis: A systematic review. *J Neurol Sci.* 2018;388:115–127. doi: 10.1016/j.jns.2018.03.003

7. Rocca MA, De Meo E, Filippi M. Functional MRI in investigating cognitive impairment in multiple sclerosis. *Acta Neurol Scand.* 2016;134 Suppl 200:39–46. doi: 10.1111/ane.12654

8. Demir S. Multiple Sclerosis Functional Composite. *Noro Psikiyatr Ars.* 2018;55(Suppl 1):S66–S68. doi: 10.29399/npa.23349

9. Nelson F, Akhtar MA, Zúñiga E, et al. Novel fMRI working memory paradigm accurately detects cognitive impairment in multiple sclerosis. *Mult Scler.* 2017;23(6):836–847. doi: 10.1177/1352458516666186

10. Jandric D, Doshi A, Scott R, et al. A Systematic Review of Resting-State Functional MRI Connectivity Changes and Cognitive Impairment in Multiple Sclerosis. *Brain Connect*. 2022;12(2):112–133. doi: 10.1089/brain.2021.0104
11. Smallwood J, Bernhardt BC, Leech R, et al. The default mode network in cognition: a topographical perspective. *Nat Rev Neurosci.* 2021;22(8):503–513. doi: 10.1038/s41583-021-00474-4
12. Tavazzi E, Cazzoli M, Pirastru A, et al. Neuroplasticity and Motor Rehabilitation in Multiple Sclerosis: A Systematic Review on MRI Markers of Functional and Structural Changes. *Front Neurosci.* 2021;15:707675. doi: 10.3389/fnins.2021.707675
13. Tavazzi E, Bergsland N, Cattaneo D, et al. Effects of motor rehabilitation on mobility and brain plasticity in multiple sclerosis: a structural and functional MRI study. *J Neurol*. 2018;265(6):1393–1401. doi: 10.1007/s00415-018-8859-y
14. Tolf A, Fagius J, Carlson K, et al. Sustained remission in multiple sclerosis after hematopoietic stem cell transplantation. Acta Neurol Scand. 2019;140(5):320–327. doi: 10.1111/ane.13147
15. Msheik A, Assi F, Hamed F, et al. Stem Cell Transplantation for Multiple Sclerosis: A 2023 Review of Published Studies. *Cureus.* 2023;15(10):e47972. doi: 10.7759/cureus.47972
16. Nicholas RS, Rhone EE, Mariottini A, et al. Autologous Hematopoietic Stem Cell Transplantation in Active Multiple Sclerosis: A Real-world Case Series. *Neurology.* 2021;97(9):e890–e901. doi: 10.1212/WNL.0000000000012449
17. Bonavita S, Sacco R, Esposito S, et al. Default mode network changes in multiple sclerosis: a link between depression and cognitive impairment? *Eur J Neurol.* 2016;24(1):27–36. doi:10.1111/ene.13112

СПИСОК ЛИТЕРАТУРЫ

1. Prosperini L., Piattella M.C., Giannì C., Pantano P. Functional and Structural Brain Plasticity Enhanced by Motor and Cognitive Rehabilitation in Multiple Sclerosis // Neural Plast. 2015. Vol. 2015. Art. 481574. doi: 10.1155/2015/481574
2. Клинические рекомендации — Рассеянный склероз — 2022–2023–2024 (13.07.2022) — Утверждены Минздравом РФ. По состоянию на 13.07.2022 на сайте МЗ РФ. Режим доступа: http://disuria.ru/_ld/12/1226_kr22G35p0MZ.pdf (дата обращения: 20.04.2024).
3. Hejazi S., Karwowski W., Farahani F.V., et al. Graph-Based Analysis of Brain Connectivity in Multiple Sclerosis Using Functional MRI: A Systematic Review // Brain Sci. 2023. Vol. 13, N 2. P. 246. doi: 10.3390/brainsci13020246
4. Giorgio A., De Stefano N. Advanced Structural and Functional Brain MRI in Multiple Sclerosis // Semin. Neurol. 2016. Vol. 36, N 2. P. 163–176. doi: 10.1055/s-0036-1579737
5. Rocca M.A., Schoonheim M.M., Valsasina P., et al. Task- and resting-state fMRI studies in multiple sclerosis: From regions to systems and time-varying analysis. Current status and future perspective // Neuroimage Clin. 2022. Vol. 35. Art. 103076. doi: 10.1016/j.nicl.2022.103076
6. Manca R., Sharrack B., Paling D., et al. Brain connectivity and cognitive processing speed in multiple sclerosis: A systematic review // J. Neurol. Sci. 2018. Vol. 388. P. 115–127. doi: 10.1016/j.jns.2018.03.003
7. Rocca M.A., De Meo E., Filippi M. Functional MRI in investigating cognitive impairment in multiple sclerosis // Acta Neurol. Scand. 2016. Vol. 134, Suppl 200. P. 39–46. doi: 10.1111/ane.12654
8. Demir S. Multiple Sclerosis Functional Composite // Noro Psikiyatr. Ars. 2018. Vol. 55, Suppl. 1, P. S66–S68. doi: 10.29399/npa.23349
9. Nelson F., Akhtar M.A., Zúñiga E., et al. Novel fMRI working memory paradigm accurately detects cognitive impairment in multiple sclerosis // Mult. Scler. 2017. Vol. 23, N 6. P. 836–847. doi: 10.1177/1352458516666186
10. Jandric D., Doshi A., Scott R., et al. A Systematic Review of Resting-State Functional MRI Connectivity Changes and Cognitive Impairment in Multiple Sclerosis // Brain Connect. 2022. Vol. 12, N 2. P. 112–133. doi: 10.1089/brain.2021.0104
11. Smallwood J., Bernhardt B.C., Leech R., et al. The default mode network in cognition: a topographical perspective // Nat. Rev. Neurosci. 2021. Vol. 22, N 8. P. 503–513. doi: 10.1038/s41583-021-00474-4
12. Tavazzi E., Cazzoli M., Pirastru A., et al. Neuroplasticity and Motor Rehabilitation in Multiple Sclerosis: A Systematic Review on MRI Markers of Functional and Structural Changes // Front. Neurosci. 2021. Vol. 15. Art. 707675. doi: 10.3389/fnins.2021.707675
13. Tavazzi E., Bergsland N., Cattaneo D., et al. Effects of motor rehabilitation on mobility and brain plasticity in multiple sclerosis: a structural and functional MRI study // J. Neurol. 2018. Vol. 265, N 6. P. 1393–1401. doi: 10.1007/s00415-018-8859-y
14. Tolf A., Fagius J., Carlson K., et al. Sustained remission in multiple sclerosis after hematopoietic stem cell transplantation // Acta Neurol. Scand. 2019. Vol. 140, N 5. P. 320–327. doi: 10.1111/ane.13147
15. Msheik A., Assi F., Hamed F., et al. Stem Cell Transplantation for Multiple Sclerosis: A 2023 Review of Published Studies // Cureus. 2023. Vol. 15, N 10. P. e47972. doi: 10.7759/cureus.47972
16. Nicholas R.S., Rhone E.E., Mariottini A., et al. Autologous Hematopoietic Stem Cell Transplantation in Active Multiple Sclerosis: A Real-world Case Series // Neurology. 2021. Vol. 97, N 9. P. e890–e901. doi: 10.1212/WNL.0000000000012449
17. Bonavita S., Sacco R., Esposito S., et al. Default mode network changes in multiple sclerosis: a link between depression and cognitive impairment? // Eur. J. Neurol. 2016. Vol. 24, N 1. P. 27–36. doi:10.1111/ene.13112

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