Functional MRI-guided Repetitive Transcranial Magnetic Stimulation in Cognitive Impairment in Cerebral Small Vessel Disease

Dmitry Yu. Lagoda, Ilya S. Bakulin, Alexandra G. Poydasheva, Dmitry O. Sinitsyn, Alfiia H. Zabirova, Zukhra Sh. Gadzhieva, Maryam R. Zabitova, Kamila V. Shamtieva, Larisa A. Dobrynina, Natalia A. Suponeva, Michael A. Piradov

Research Center of Neurology, Moscow, Russia;

Abstract

Introduction. *Cerebral small vessel disease (CSVD) is one of the leading causes of vascular and mixed cognitive impairment (CI). Treatment options for CSVD-associated CI are limited. Repetitive transcranial magnetic stimulation (rTMS) is a promising non-drug treatment option.*
The aim of the study was to evaluate the effects of 10 rTMS sessions of the left dorsolateral prefrontal cortex (DLPFC) on cognitive functions in CSVD patients.
Materials and methods. *The study included 30 patients with CSVD and moderate CI randomized to the active (DLPFC stimulation; n = 20) and control (vertex stimulation; n = 10) groups. Both groups received 10 sessions of high-frequency rTMS. The DLPFC target was selected based on the individual paradigm fMRI data with a focus on executive functions. Cognitive function was assessed using the Montreal Cognitive Assessment Scale (MoCA), the Trail Making Test (TMT), the Tower of London Test, and the Rey–Osterritz Complex Figure Test before, immediately after, and 3 months after the stimulation. Adverse events were assessed using standardized questionnaires.*
Results. *The active group showed a significantly better effect compared to the control group according to MoCA, TMT A and B, The Tower of London Test, delayed recall on the Rey–Osterrieth Complex Figure Test immediately after the stimulation and MoCA, TMT A and B and The Tower of London 3 months after the stimulation. Adverse events in the study were mild and did not affect treatment adherence.*
Conclusion. *rTMS is a promising, safe, and well-tolerated treatment option for mild cognitive impairment in CSVD. However, additional research is needed to make recommendations for its clinical use.*

Keywords: *repetitive transcranial magnetic stimulation; non-invasive brain stimulation; mild cognitive impairment; vascular cognitive impairment; cerebral small vessel disease*

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the Research Center of Neurology (protocol No. 12-4/16, December 14, 2016).

Source of funding. This study was not supported by any external sources of funding.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For correspondence: 80 Volokolamskoye Shosse, Moscow, 125367, Russia. Research Center of Neurology.
E-mail: lagoda.d@neurology.ru. Lagoda D.Yu.

For citation: Lagoda D.Yu., Bakulin I.S., Poydasheva A.G., Sinitsyn D.O., Zabirova A.H., Gadzhieva Z.Sh., Zabitova M.R., Shamtieva K.V., Dobrynina L.A., Suponeva N.A., Piradov M.A. Functional MRI-guided repetitive transcranial magnetic stimulation in cognitive impairment in cerebral small vessel disease. *Annals of Clinical and Experimental Neurology*. 2024;18(2):24–33. (In Russ.)

DOI: https://doi.org/10.17816/ACEN.1087

Received 02.02.2023 / Accepted 08.04.2023/ Published 25.06.2024

фМРТ-направленная ритмическая транскраниальная магнитная стимуляция в терапии когнитивных расстройств при церебральной микроангиопатии

Д.Ю. Лагода, И.С. Бакулин, А.Г. Пойдашева, Д.О. Синицын, А.Х. Забирова, З.Ш. Гаджиева, М.Р. Забитова, К.В. Шамтиева, Л.А. Добрынина, Н.А. Супонева, М.А. Пирадов

Научный центр неврологии, Москва, Россия;

Аннотация

Введение. *Церебральная микроангиопатия (ЦМА)/болезнь мелких сосудов – основная причина сосудистых и смешанных с дегенерацией когнитивных расстройств (КР). Возможности терапии КР при ЦМА ограничены. Ритмическая транскраниальная магнитная стимуляция (рТМС) является перспективным методом их немедикаментозной терапии.*

Цель исследования *– оценить эффект 10 сессий рТМС левой дорсолатеральной префронтальной коры (ДЛПФК) на когнитивные функции у пациентов с ЦМА.*

Материал и методы. *В исследовании участвовали 30 пациентов с ЦМА и умеренными КР. Они были рандомизированы в активную (стимуляция ДЛПФК; n = 20) и контрольную (стимуляция вертекса; n = 10) группы. В обеих группах проведено 10 сессий высокочастотной рТМС. Мишень в пределах ДЛПФК выбиралась по индивидуальным данным фМРТ с парадигмой на управляющие функции мозга. Когнитивные функции оценивали по Монреальской шкале оценки когнитивного статуса (МоСА), тесту построения пути (ТМТ), «башне Лондона» и комплексной фигуре Рея–Остеррица до, сразу после и через 3 мес после стимуляции. Нежелательные явления оценивали по стандартизированным опросникам.*

Результаты. *Сравнение эффектов между группами показало статистически значимо лучший эффект в активной группе, чем в контрольной, по результатам шкалы МоСА, тестов построения пути А, В, «башня Лондона», отсроченному воспроизведению комплексной фигуры Рея–Остеррица сразу после стимуляции и шкалы МоСА, тестов ТМТ А, В и «башня Лондона» через 3 мес после стимуляции. Наблюдаемые в исследовании нежелательные явления были лёгкими по выраженности и не влияли на приверженность пациентов лечению.*

Заключение. *рТМС является многообещающим, безопасным и хорошо переносимым методом терапии умеренных КР при ЦМА, однако для формирования рекомендаций по применению в клинической практике необходимы дополнительные исследования.*

Ключевые слова*: ритмическая транскраниальная магнитная стимуляция; неинвазивная стимуляция головного мозга; умеренные когнитивные расстройства; сосудистые когнитивные расстройства; болезнь мелких сосудов; церебральная микроангиопатия.*

Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен Этическим комитетом ФГБНУ «Научный центр неврологии» (протокол № 12-4/16 от 14.12.2016).

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

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

Адрес для корреспонденции: 125367, Москва, Волоколамское шоссе, д. 80. Научный центр неврологии.
E-mail: lagoda.d@neurology.ru. Лагода Д.Ю.

Для цитирования: Лагода Д.Ю., Бакулин И.С., Пойдашева А.Г., Синицын Д.О., Забирова А.Х., Гаджиева З.Ш., Забитова М.Р., Шамтиева К.В., Добрынина Л.А., Супонева Н.А., Пирадов М.А. фМРТ-направленная ритмическая транскраниальная магнитная стимуляция в терапии когнитивных расстройств при церебральной микроангиопатии. *Анналы клинической и экспериментальной неврологии*. 2024;18(2):24–33.

DOI: https://doi.org/10.17816/ACEN.1087

Поступила 02.02.2024 / Принята в печать 08.04.2024 / Опубликована 25.06.2024

Introduction

Cerebrovascular disease is the second most common cause of cognitive impairment after Alzheimer's disease [1]. Cerebral small vessel disease (CSVD) is a leading cause of vascular cognitive impairment [2, 3]. Currently, treatment options for vascular cognitive impairment are limited [4].

Mild cognitive impairment (MCI) is a decline in cognitive function that exceeds that of normal aging but does not meet the clinical criteria for dementia [5]. In the population aged 65 years and older, the MCI prevalence is equal to or greater than that of dementia and may reach 42% [6]. However, MCI not only deteriorates quality of life [7], but is also an independent risk factor of dementia; 20–30% of cases of mild cognitive impairment progress to dementia within 6 years [1].

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method increasingly used to treat neurological disorders [8]. The mechanism of the therapeutic rTMS effect is usually associated with TMS-induced synaptic plasticity [9].

rTMS is best studied for treatment of Alzheimer's cognitive impairment. A meta-analysis included 12 studies (n = 231) with different rTMS protocols, including multi-target stimulation and stimulation of the dorsolateral prefrontal cortex (DLPFC). A statistically significant improvement in cognitive function was found in the active stimulation group compared to the control group. The effect was greater in milder forms of Alzheimer's disease [10]. The most compelling evidence for efficacy was obtained using a multi-target rTMS protocol combined with target-specific cognitive training, called rTMS-COG. In the international expert recommendations, this protocol was assigned a level of evidence C [8]. A randomized, placebo-controlled study showed a statistically significant effect of high-frequency rTMS of the left DLPFC on memory in elderly patients with amnestic MCI [11].

A relatively large number of studies evaluated the use of TMS in Alzheimer's disease and amnestic MCI (as a predementia stage of Alzheimer's disease). The use of TMS in vascular cognitive impairment has been less studied. Most studies evaluated the diagnostic use of TMS, while only few studies evaluated the therapeutic effect of rTMS [12–14]. Two studies investigated the effect of a single rTMS session on the left DLPFC. I. Rektorova et al. showed that executive functions (EF) measured with the Stroop test improved after 1 rTMS session [12]. S. Sedlackova et al. found no statistically significant differences between stimulation of DLPFC and M1 (control target) [13]. One of more recent studies showed the effect of supplementary motor area rTMS on cognitive functions in CSVD patients with MCI [14]. There are no studies on the efficacy of multiple sessions of the left DLPFC rTMS in CSVD patients.

It is important to explore the potential of personalized targets for rTMS due to the structural and functional heterogeneity and interindividual anatomical variability of the cerebral cortex. One way of personalization is to use structural neuroimaging to construct a 3D model of the head and then to overlay functional neuroimaging data such as resting-state fMRI and task fMRI [15]. For example, functional connectivity-based personalization is being actively studied in depression [16-19]. Task fMRI-guided navigated TMS is actively used in studies with healthy volunteers [20], but is rarely applied in clinical practice (J.P. Szaflarski et al. reported its use in patients with post-stroke aphasia [21]).

The **aim** of this study was to evaluate the immediate and delayed effects of 10 sessions of fMRI-guided high-frequency rTMS of the left DLPFC on cognitive functions in CSVD patients with MCI.

Materials and methods

This randomized, double-blind, placebo-controlled, parallel study was conducted at the Research Center of Neurology.

Inclusion criteria:
- Age of 45 to 80 years,
- CSVD diagnosed according to STRIVE guidelines (2013) [22],
- MCI diagnosed using VASCOG criteria [23],
- No changes in treatment for cognitive impairment or use of other central nervous system agents for 1 month before rTMS, during rTMS, and for 3 months after the stimulation.

Exclusion criteria:
- Contraindications to rTMS and/or MRI,
- History of stroke (except lacunar one),
- History of epilepsy or epileptiform discharges on EEG,
- Use of antidepressants and antipsychotics,
- Decompensation of severe somatic disease,
- Mental disorder or alcohol and/or drug abuse.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Federal State Budgetary Scientific Institution "Research Center of Neurology" (Protocol No. 12-4/16 dated 14 December 2016). Prior to enrollment, all patients signed an informed consent form.

Design of the study

After enrollment, all patients were randomized using sealed envelope method in a 2:1 ratio to active stimulation (left DLPFC) or control stimulation (vertex area).

Prior to stimulation (T0), cognitive functions were assessed, and patients underwent task fMRI. Subsequently, 10 rTMS sessions (5 sessions per week) were performed. Cognitive functions were reassessed immediately (T1) and 3 months (T2) after the rTMS treatment. The investigator performing the initial clinical assessment for eligibility and repeated cognitive assessments at each stage was blinded to the stimulation protocols.

Cognitive function tests

The Montreal Cognitive Assessment Test (MoCA) was used to assess general cognitive status. Additional tests were used to assess EF and visuospatial functions [24]. EF was assessed using the Trail Making Test (TMT), with the TMT-A subtest assessing psychomotor speed and the TMT-B subtest assessing divided attention, and the Tower of London test assessing cognitive control. Visuospatial functions were assessed by copying the Rey–Osterrith Complex Figure Test (ROCF), and nonverbal memory was assessed by delayed recall of the CF 30 min after copying [25].

Neuroimaging

All patients had structural MRI and task fMRI on a 3T Magnetom Verio (Siemens) for determination of the stimulation target. The anatomical structure was visualized using a 3D-T1 gradient echo with multiplanar reconstruction (3D-T1 MPR) sequence consisting of 176 sagittal slices (TR = 1940 ms; TE = 308 ms; interslice interval = 0.5 mm; field of view = 250 mm; matrix = 256×256; slice thickness = 1 mm). The paradigm fMRI used an axial T2* gradient echo sequence (TR = 3000 ms; TE = 30 ms; slice thickness = 3 mm).

The paradigm had a block design and consisted of 4 activation blocks and 4 rest blocks, with each block lasting 30 s. Before the start and at the end of each activation block, subjects were verbally instructed to start or stop the task. They were asked to count silently starting from 1 and skipping multiples of 3. When the next activation block began, the patient repeated counting from 1 [26]. Before the MRI, the patient was trained to perform the task outside the scanner under the supervision of the investigator.

SPM12 for MATLAB R2018a (Mathworks) was used for preprocessing and statistical analysis of individual fMRI data to determine the stimulation target[1]. The first level analysis used a regressor with a value of 1 in the activation block, 0 in the rest block, and a T-contrast corresponding to the regressor with a voxel-wise significance threshold of 0.001 without correction. The data obtained were co-registered with the structural data and uploaded to the navigation system. The rTMS target was positioned within the left DLPFC (corresponding to the middle frontal gyrus) according to the visually detectable maximum activation.

Transcranial magnetic stimulation

The navigation system of the NBS eXimia Nexstim stimulator (Nexstim Plc) was used for fMRI-guided navigation rTMS. The target for active stimulation was located in the DLPFC while the control group used the vertex detected by visible anatomical landmarks. For rTMS, a Magstim Rapid 2 stimulator (Magstim Company Ltd.) was used with a figure-of-eight coil calibrated for navigation. Stimulation was performed at an intensity of 100% of the resting motor threshold of *m. abductor pollicis brevis*, determined using the Rossini–Rothwell algorithm [27]. In both groups, high-frequency rTMS was performed with a stimulation frequency of 20 Hz, 2-second trains with a 28-second intertrain interval, 2400 stimuli per session, for a total of 10 sessions. Patients completed standardized TMS tolerability questionnaires (adverse events (AEs) during stimulation and within 24 hours after the stimulation).

Statistical analysis

MATLAB R2018a (Mathworks) was used for statistical analysis. Normal distribution was tested using the Shapiro–Wilk test. The data were non-Gaussian distributed, so non-parametric methods were used. The Friedman test was used to determine changes in cognitive test scores between the 3 intra-group measurements. The Wilcoxon test was used for paired intra-group comparisons. The Mann–Whitney test was used to compare quantitative characteristics between groups (comparison of effects). The Fisher's test (for binary characteristics) and the Fisher–Freeman–Halton test (for 3 levels of the Fazekas scale) were used for comparing qualitative parameters. Changes were considered significant at $p < 0.05$.

Results

Patients

A total of 96 patients were screened for the study, of which 30 patients were included into the final analysis (Figure 1). There were no statistically significant differences in gender, age, severity of neurological symptoms, or cognitive test scores between two groups (Table 1).

All patients underwent paradigm fMRI with a target identification in the left DLPFC. Figure 2 shows the stimulation target localization for the active group.

[1] Statistical Parametric Mapping; Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK. URL: http://www.fil.ion.ucl.ac.uk/spm

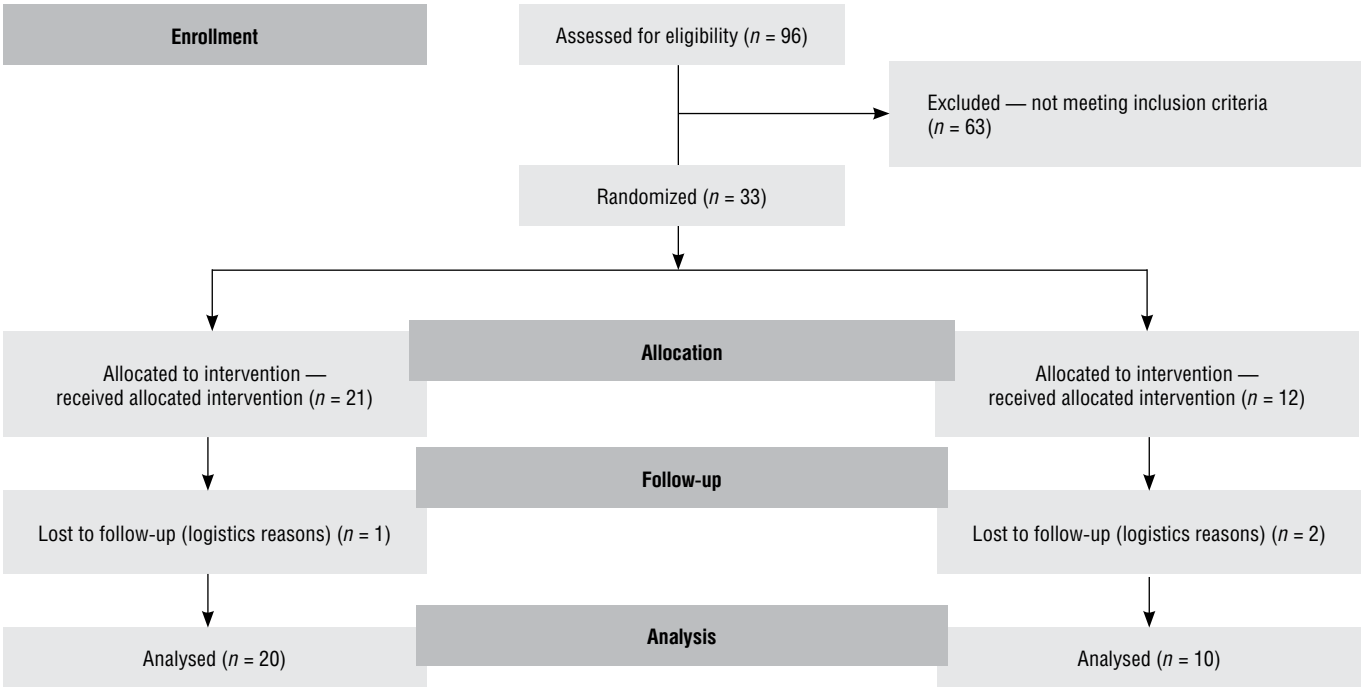

Рис. 1. Блок-схема отбора пациентов.
Fig. 1. Flow chart.

Table 1. Demographic, clinical, and neuroimaging characteristics of patients

Parameter	Active group (*n* = 20)	Control group (*n* = 10)	*p*
Sex (male), *n* (%)	10 (50%)	2 (20%)	0.24
Age, years, Me [Q1; Q3]	60 [57.5; 66.5]	58 [57.5; 69.0]	0.94
Gait disorder, *n* (%)	14 (70%)	6 (60%)	0.69
Pseudobulbar palsy, *n* (%)	5 (25%)	2 (20%)	1.00
White matter hyperintensity (Fazekas scale)			0.73
Fazekas I	2 (10%)	0	
Fazekas II	9 (45%)	4 (40%)	
Fazekas III	9 (45%)	6 (60%)	
White matter lacunes, *n* (%)	12 (60%)	4 (40%)	0.44
Lacunes in subcortical structures, *n* (%)	6 (30%)	5 (50%)	0.43
Brainstem lacunes, *n* (%)	9 (45%)	4 (40%)	1.00
Juxtacortical microbleeds, *n* (%)	5 (25%)	3 (30%)	1.00
Subcortical microbleeds, *n* (%)	11 (55%)	3 (30%)	0.26

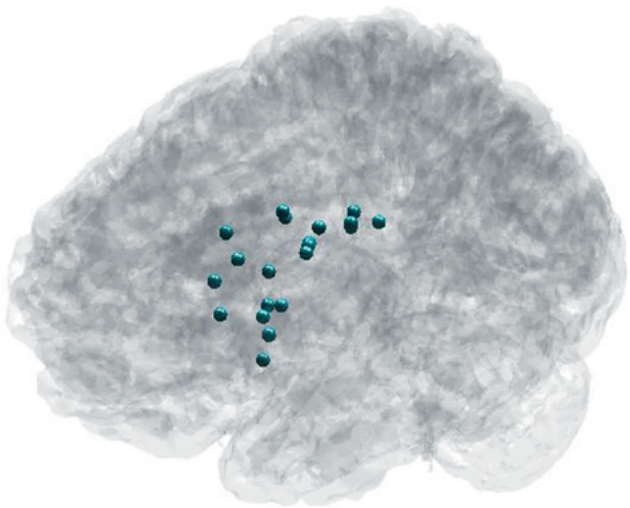

Fig. 2. Localization of stimulation target within the left DLPFC in the active group.

Assessment of the intra-group effect

In the active group, using the Friedman test, a statistically significant effect of time point was reported for MoCA test ($p < 0.001$), TMT-A ($p = 0.012$), TMT-B ($p < 0.001$), the Tower of London ($p < 0.001$), and delayed CF recall ($p = 0.009$) test. For CF copying, the effect was not statistically significant ($p = 0.929$). In the control group, the effect of time point was not statistically significant for all tests (MoCA, $p = 0.119$; TMT-A, $p = 0.368$; TMT-B, $p = 0.347$; the Tower of London, $p = 0.187$; copying and recall of CF, $p = 0.867$ and $p = 0.792$, respectively).

In a pairwise comparison using the Wilcoxon test, a statistically significant improvement was reported immediately after the stimulation and 3 months after the stimulation for the MoCA, TMT-B, and Tower of London tests, while for the TMT-A and delayed CF recall, a statistically significant improvement was reported only immediately after the stimulation, and no significant changes were observed when copying the CF (Table 2). In the control group, no statistically significant changes were observed in any of the tests used, either immediately or 3 months after the stimulation (Table 2).

Comparison of inter-group effects

When comparing the effects between the active and control groups, the active group showed a statistically significant greater effect on the MoCA, TMT-A, TMT-B, and the Tower of London tests immediately and 3 months after the stimulation. For delayed recall of CF, the active group showed a statistically significant greater effect only imme-

Table 2. Intra-group effect of rTMS, Me [Q_1; Q_3]

Test	Time points	Active group ($n = 20$)	p	Control group ($n = 10$)	p
MoCA, score	T0	24 [22; 26]	–	22 [22; 24]	–
	T1	26 [24; 28]	< 0.001	25 [22; 25]	0.094
	T2	26 [19.5; 27]	0.001	23 [21; 24]	0.329
TMT-A, sec	T0	69 [51.0; 91.5]	–	56 [47; 76]	–
	T1	53 [42.5; 72.5]	0.009	57 [52; 86]	0.91
	T2	58 [41; 87.5]	0.08	57 [52; 86]	0.093
TMT-B, sec	T0	162 [126.0; 256.5]	–	168 [135; 243]	–
	T1	138 [106.5; 219.5]	0.007	186 [109; 207]	0.071
	T2	119 [82; 173]	0.032	169 [138; 244]	0.889
The Tower of London Test, score	T0	12.5 [8.75; 16]	–	12 [11; 14].	–
	T1	13 [11.0; 18.5]	0.002	12 [11; 16]	0.083
	T2	14 [12.5; 16.5]	0.044	10 [9; 13]	0.724
Complex Figure, copying, score	T0	32 [27.5; 35]	–	34 [33; 34]	–
	T1	34 [27.5; 36]	0.279	33 [32; 35]	0.656
	T2	33 [28; 36]	0.612	27 [25; 31]	0.380
Complex Figure, delayed recall, score	T0	16 [8; 21.75]	–	15.5 [7; 21.5]	–
	T1	20 [10.25; 26.75]	0.003	17.5 [15.5; 26]	0.102
	T2	16 [9.75; 26.75]	0.690	14 [12; 21]	0.500

Note. T0, baseline testing; T1, testing immediately after the stimulation; T2, testing 3 months after the stimulation; p for T1 and T2 was calculated as a pairwise comparison for T1/T0 and T2/T0, respectively.

Table 3. Effect sizes of rTMS (difference in cognitive test scores between T1 and T0. T2 and T0) and comparison of active and control groups. Me [Q_1; Q_3]

Test	Time point	Active group (*n* = 20)	Control group (*n* = 10)	*p*
MoCA	T1	2 [1; 3]	1 [0; 2]	0.044
	T2	2 [0; 3]	1 [0; 1]	0.044
TMT-A	T1	–9 [–22.5; –3]	7 [–4; 12]	0.007
	T2	–5 [–26.5; 7.5]	7 [–4; 21]	0.041
TMT-B	T1	–15[–54; 6]	–5 [–10; 9]	0.014
	T2	–46 [–56.5; –18.5]	–5 [–10; 9]	0.006
The Tower of London Test	T1	2 [2; 3.5]	1 [0; 1].	0.019
	T2	3 [2; 5]	1 [0; 3].	0.046
Complex Figure. copying	T1	0 [–1; 3.5]	0 [–1; 1]	0.275
	T2	0 [–1.5; 3]	0 [–1; 1]	0.270
Complex Figure. delayed recall	T1	3 [0.75; 5.5]	1.5 [–0.5; 2.5]	0.043
	T2	1.5 [–1.75; 4]	0.5 [–0.5; 4]	0.480

Note. T0. baseline testing; T1. testing immediately after the stimulation; T2. testing 3 months after the stimulation. A negative value indicates a decline in the test scores. A positive score indicates an improvement for all tests except TMT. where improvements are indicated by a negative score and declines are indicated by a positive score.

diately after the stimulation. For copying CF, no statistically significant difference was found between the active and control groups (Table 3).

Tolerability

Data from 270 sessions were analyzed (180 sessions in the active group and 90 sessions in the control group). No serious adverse events were reported during rTMS in any group. Pain at the site of stimulation was observed in 11.7% of all rTMS sessions in the active group and in 9% of all rTMS sessions in the control group. Pain severity on the numerical rating scale was 1 in 61.9% of cases, 2 in 28.6%, 3 in 4.75%, and 5-6 in 4.75% in the active group and it was 2 in 62.5% of cases, 3 in 25%, 6 in 12.5% in the control group. Other discomfort sensations at the site of stimulation (muscle contractions, burning, itching, etc.) were observed in 15.5% of all sessions in the active group and in 2.2% in the control group. Patients reported somnolence in 11.7% of sessions in the active group and 17% of sessions in the control group. Headache within 24 hours of stimulation was reported in 3.9% of all sessions in the active group and 8.9% in the control group. When comparing the incidence of AEs between the active and control groups, there was no statistically significant difference for headache during ($p = 0.539$) and after the stimulation ($p = 0.08$), as for the somnolence ($p = 0.26$), and the statistically significant difference was found only for non-painful discomfort ($p < 0.001$).

Discussion

Our paper showed that 10 sessions of fMRI-guided rTMS of the left DLPFC significantly improved cognitive functions in CSVD patients with MCI. The active group showed the significantly greater effect compared to the control group, both at the general cognitive level and in specific domains (EF and non-verbal short-term memory), and this effect persisted across a range of tests for 3 months after the stimulation. The proposed rTMS protocol for MCI had a good safety and tolerability profile.

In our protocol, the left DLPFC was used as a stimulation target. The choice of the target area was based on the available data on the role of this area in vascular cognitive impairment [28, 29], as well as on previous studies showing the efficacy of stimulation of the left DLPFC in cognitive impairment of various etiologies [30]. The activity of the frontal lobes plays a key role in the EF, and in CSVD early decline in EF is observed [28]. Loss of frontal-parietal connectivity in white matter involvement is currently considered an important factor in the pathogenesis of cognitive impairment in CSVD [29]. A significant loss of interhemispheric and frontal connectivity in CSVD has been demonstrated by structural connectivity studies [28].

Along with the EF scores, nonverbal memory and overall cognitive level improved. However, no statistically significant changes in visuospatial functions (CF copying test) were found in our study, which may be due to the predominant role of the posterior parts of the cerebral cortex, such as the parietal and occipital cortex, for this domain [31]. Further studies are required to evaluate the efficacy of rTMS in cortical regions other than DLPFC or multisite TMS for the treatment of visuospatial deficits in MCI.

In our study, we analyzed individual paradigm fMRI data to determine target localization. fMRI-guided TMS is considered one of the potential methods to increase the efficacy of rTMS [32-34]. Comparing different approaches to

target detection (using a 10-20% electrode positioning system, using structural MRI, fMRI, or a target in Talairach space), determination of a significant effect of rTMS of the right DLPFC on fMRI reaction time requires a 10-fold smaller sample size compared to using the 10-20% system [33]. A recent meta-analysis showed that fMRI-guided navigation for rTMS in healthy volunteers had a higher online effect compared to other methods of target selection [20].

Our choice of paradigm is primarily based on the switching task, but also involves other components of EF and limits the effect of learning [35].

Limitations of target selection using individual paradigm fMRI data include the low reproducibility of fMRI results at the individual level [36]. It is unclear what impact this may have on clinical efficacy. However, we did not compare our method with other methods of target selection. Therefore, we cannot conclude on the advantage of a personalized approach and its appropriateness for real clinical practice.

It should be noted that the effect of rTMS on some of the tests persisted for at least 3 months after treatment. M. Sabbagh et al. reported a positive effect after TMS-COG treatment that was more significant 12 weeks after rTMS compared to that after 7 weeks, which is consistent with the data obtained in this study [37]. Given the progressive nature of cognitive impairment in CSVD, this suggests that rTMS may have an effect on the course of the disease. However, this statement requires further investigation in separate studies. It is also useful to study the effect of repeated rTMS courses or maintenance sessions after the main treatment. The latter approach has been shown to be effective in other conditions, such as depression and pain syndromes [38, 39].

One of the most promising areas for future research is the development of effective combined protocols for rTMS and cognitive training. The potential enhancement of neuromodulation effects by combining it with various methods of cognitive interventions is being actively studied in several neurological and mental disorders [40]. This approach has been shown to be effective in Alzheimer's disease [38] and requires further study in vascular cognitive impairment.

No serious AEs were reported during the rTMS treatment. The AEs reported by patients in the study were mild and did not affect treatment adherence. The profile of AEs was comparable to previously published data [41]. Therefore, our data confirm the safety and good tolerability of rTMS of the left DLPFC in vascular MCI.

Limitations of our study include the small sample size, therefore, our results should be validated in studies with larger samples. The diagnosis of vascular cognitive impairment was based on clinical and neuroimaging data according to the VASCOG criteria [23]; however, given the lack of cerebrospinal fluid testing for beta-amyloid, we cannot exclude the presence of mixed cognitive impairment in some patients. We used vertex TMS in the control group, which is a common approach in the study of cognitive function using TMS. However, it should be noted that one session of vertex theta burst stimulation had an effect on reaction time similar to that of stimulation of a functionally significant cortical area in the study by D. Pizem et al [42]. On the other hand, our study showed no significant differences in any of the test points in the control group, so we can to some extent ignore the significance of the effect of vertex stimulation. Another limitation of our study is the randomization procedure with unequal distribution ratio between groups. This resulted in a mismatch in number of subjects in the main and control groups. Such an approach increases the probability of the second type of error (reduces the probability of finding an effect, if any), but does not affect the probability of the first type of error (a false positive result). It should be noted that the aim of our study was not to identify the cognitive tests on which rTMS has the greatest effect, so the *p* values are given without adjustment for multiple comparisons. However, if the study results are used in work where such selection is required, a correction should be applied to control the possibility of false positives.

Conclusion

This study provides promising results on the potential efficacy of fMRI-guided rTMS for treatment of MCI in CSVD patients. However, given the above limitations, further larger studies are needed for more definitive conclusions.

References / Список источников

1. Wallin A., Nordlund A., Jonsson M. et al. The Gothenburg MCI study: design and distribution of Alzheimer's disease and subcortical vascular disease diagnoses from baseline to 6-year follow-up. *J. Cereb. Blood Flow Metab.* 2016;36(1):114–131.
DOI: 10.1038/jcbfm.2015.147
2. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol.* 2010;9(7):689–701. DOI: 10.1016/S1474-4422(10)70104-6
3. van der Flier W.M., Skoog I., Schneider J.A. et al. Vascular cognitive impairment. *Nat. Rev. Dis. Primers.* 2018;4:18003.
DOI: 10.1038/nrdp.2018.3
4. Ritter A., Pillai J.A. Treatment of vascular cognitive impairment. *Curr. Treat. Options Neurol.* 2015;17(8):367.
DOI: 10.1007/s11940-015-0367-0
5. Petersen R.C. Clinical practice. Mild cognitive impairment. *N. Engl. J. Med.* 2011;364(23):2227–2234. DOI: 10.1056/NEJMcp0910237

6. Ward A., Arrighi H.M., Michels S., Cedarbaum J.M. Mild cognitive impairment: disparity of incidence and prevalence estimates. *Alzheimers Dement*. 2012;8(1):14–21. DOI: 10.1016/j.jalz.2011.01.002
7. Hussenoeder F.S., Conrad I., Roehr S. et al. Mild cognitive impairment and quality of life in the oldest old: a closer look. *Qual. Life Res.* 2020;29(6):1675–1683. DOI: 10.1007/s11136-020-02425-5
8. Lefaucheur J.P., Aleman A., Baeken C. et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). *Clin. Neurophysiol.* 2020;131(2):474–528. DOI: 10.1016/j.clinph.2019.11.002
9. Chervyakov A.V., Chernyavsky A.Y., Sinitsyn D.O., Piradov M.A. Possible mechanisms underlying the therapeutic effects of transcranial magnetic stimulation. *Front. Hum. Neurosci.* 2015;9:303. DOI: 10.3389/fnhum.2015.00303
10. Lin Y., Jiang W.J., Shan P.Y. et al. The role of repetitive transcranial magnetic stimulation (rTMS) in the treatment of cognitive impairment in patients with Alzheimer's disease: A systematic review and meta-analysis. *J. Neurol. Sci.* 2019;398:184–191. DOI: 10.1016/j.jns.2019.01.038
11. Drumond Marra H.L., Myczkowski M.L., Maia Memória C. et al. Transcranial magnetic stimulation to address mild cognitive impairment in the elderly: a randomized controlled study. *Behav. Neurol.* 2015;2015:287843. DOI: 10.1155/2015/287843
12. Rektorova I., Megova S., Bares M., Rektor I. Cognitive functioning after repetitive transcranial magnetic stimulation in patients with cerebrovascular disease without dementia: a pilot study of seven patients. *J. Neurol. Sci.* 2005;229-230:157–161. DOI: 10.1016/j.jns.2004.11.021
13. Sedlackova S., Rektorová I., Fanfrdlová Z., Rektor I. Neurocognitive effects of repetitive transcranial magnetic stimulation in patients with cerebrovascular disease without dementia. *J. Psychophysiol.* 2008;22(1):14–19. DOI: 10.1027/0269-8803.22.1.14
14. Лагода Д.Ю., Добрынина Л.А., Супонева Н.А. и др. Ритмическая транскраниальная магнитная стимуляция в терапии умеренных когнитивных расстройств при церебральной микроангиопатии. *Анналы клинической и экспериментальной неврологии.* 2021;15(4):5–14. DOI: 10.54101/ACEN.2021.4.1
Lagoda D.Y., Dobrynina L.A., Suponeva N.A. et al. Repetitive transcranial magnetic stimulation in the treatment of mild cognitive impairment due to cerebral small vessel disease. *Annals of Clinical and Experimental Neurology*. 2021;15(4):5–14. DOI: 10.54101/ACEN.2021.4.1
15. Modak A., Fitzgerald P.B. Personalising transcranial magnetic stimulation for depression using neuroimaging: a systematic review. *World J. Biol. Psychiatry.* 2021;22(9):647–669. DOI: 10.1080/15622975.2021.1907710
16. Barbour T., Lee E., Ellard K., Camprodon J. Individualized TMS target selection for MDD: clinical outcomes, mechanisms of action and predictors of response. *Brain Stimul.* 2019;12(2):516. DOI: 10.1186/s12888-020-03030-z
17. Cash R.F.H., Weigand A., Zalesky A. et al. Using brain imaging to improve spatial targeting of transcranial magnetic stimulation for depression. *Biological Psychiatry*. 2020;7:S0006-3223(20)31668-1. DOI: 10.1016/j.biopsych.2020.05.033
18. Пойдашева А.Г., Синицын Д.О., Бакулин И.С. и др. Определение мишени для транскраниальной магнитной стимуляции у пациентов с резистентным к фармакотерапии депрессивным эпизодом на основе индивидуальных параметров функциональной магнитно-резонансной томографии покоя (пилотное слепое контролируемое исследование). *Неврология, нейропсихиатрия, психосоматика.* 2019;11(4):44–50. DOI: 10.14412/2074-2711-2019-4-44-50
Poydasheva A.G., Sinitsyn D.O., Bakulin I.S. et al. Target determination for transcranial magnetic stimulation in patients with a pharmacotherapy-resistant depressive episode based on the individual parameters of resting-state functional magnetic resonance imaging (a pilot blind controlled trial). *Neurology, Neuropsychiatry, Psychosomatics.* 2019;11(4):44–50. DOI: 10.14412/2074-2711-2019-4-44-50
19. Cole E.J., Phillips A.L., Bentzley B.S. et al. Stanford Neuromodulation Therapy (SNT): a double-blind randomized controlled trial. *Am. J. Psychiatry*. 2021;appiajp202120101429. DOI: 10.1176/appi.ajp.2021.20101429
20. Beynel L., Appelbaum L.G., Luber B. et al. Effects of online repetitive transcranial magnetic stimulation (rTMS) on cognitive processing: A meta-analysis and recommendations for future studies. *Neurosci. Biobehav. Rev.* 2019;107:47–58. DOI: 10.1016/j.neubiorev.2019.08.018
21. Szaflarski J.P., Vannest J., Wu S.W. et al. Excitatory repetitive transcranial magnetic stimulation induces improvements in chronic post-stroke aphasia. *Med. Sci. Monit.* 2011;17(3):CR132–CR 139. DOI: 10.12659/msm.881446
22. Wardlaw J.M., Smith E.E., Biessels G.J. et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 2013;12(8):822–838. DOI: 10.1016/S1474-4422(13)70124-8
23. Sachdev P., Kalaria R., O'Brien J. et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis. Assoc. Disord.* 2014;28(3):206–218. DOI: 10.1097/WAD.0000000000000034
24. Salvadori E., Poggesi A., Pracucci G. et al. Development and psychometric properties of a neuropsychological battery for mild cognitive impairment with small vessel disease: the VMCI-Tuscany Study. *J. Alzheimers Dis.* 2015;43(4):1313–1323. DOI: 10.3233/JAD-141449
25. Lezak M.D., Howieson D.B., Loring D.W., Fischer J.S. Neuropsychological assessment. N.Y., 2012:499–504.
26. Gadzhieva Z., Kremneva E., Morozova S. et al. fMRI of healthy elderly during Stroop test and the serial count test: Comparative analysis. *J. Alzheimers Dis. Parkinsonism.* 2018;8:52. DOI: 10.4172/2161-0460-C1-037
27. Rossini P.M., Barker A.T., Berardelli A. et al. Noninvasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr. Clin. Neurophysiol.* 1994;91:79–92. DOI: 10.1016/0013-4694(94)90029-9
28. Ter Telgte A., van Leijsen E.M.C., Wiegertjes K. et al. Cerebral small vessel disease: from a focal to a global perspective. *Nat. Rev. Neurol.* 2018;14(7):387–398. DOI: 10.1038/s41582-018-0014-y
29. Dey A.K., Stamenova V., Turner G. et al. Pathoconnectomics of cognitive impairment in small vessel disease: a systematic review. *Alzheimers Dement.* 2016;12(7):831–845. DOI: 10.1016/j.jalz.2016.01.007
30. Guse B., Falkai P., Wobrock T. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. *J. Neural. Transm (Vienna).* 2010;117(1):105–122. DOI: 10.1007/s00702-009-0333-7
31. Pisella L. Visual perception is dependent on visuospatial working memory and thus on the posterior parietal cortex. *Ann. Phys. Rehabil. Med.* 2017;60(3):141–147. DOI: 10.1016/j.rehab.2016.01.002
32. Rosen A.C. Targeting location relates to treatment response in active but not sham rTMS stimulation. *Brain Stimul.* 2021;14(3):703–709. DOI: 10.1016/j.brs.2021.04.010
33. Sack A.T., Cohen Kadosh R., Schuhmann T. et al. Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods. *J. Cogn. Neurosci.* 2009;21(2):207–221. DOI: 10.1162/jocn.2009.21126
34. Bakulin I., Zabirova A., Lagoda D. et al. Combining HF rTMS over the left DLPFC with concurrent cognitive activity for the offline modulation of working memory in healthy volunteers: a proof-of-concept study. *Brain Sci.* 2020;10(2):83. DOI: 10.3390/brainsci10020083
35. Добрынина Л.А., Гаджиева З.Ш., Морозова С.Н. и др. Управляющие функции мозга: функциональная магнитно-резонансная томография с использованием теста Струпа и теста серийного счета про себя у здоровых добровольцев. *Журнал неврологии и психиатрии им. С.С. Корсакова.* 2018;118(11):64–71. DOI: 10.17116/jnevro201811811164
Dobrynina L.A., Gadzhieva Z.S., Morozova S.N. et al. Executive functions: fMRI of healthy volunteers during Stroop test and the serial count test. *Zhurnal nevrologii i psihiatrii im. S.S. Korsakova.* 2018;118(11):64–71. DOI: 10.17116/jnevro201811811164
36. Elliott M.L., Knodt A.R., Ireland D. et al. What is the test-retest reliability of common task-functional MRI measures? New empirical evidence and a meta-analysis. *Psychol Sci.* 2020;31(7):792–806. DOI: 10.1177/0956797620916786
37. Sabbagh M., Sadowsky C., Tousi B. et al. Effects of a combined transcranial magnetic stimulation (TMS) and cognitive training intervention in patients with Alzheimer's disease. *Alzheimers Dement.* 2020;16(4):641–650. DOI: 10.1016/j.jalz.2019.08.197
38. Hodaj H., Alibeu J.P., Payen J.F., Lefaucheur J.P. Treatment of chronic facial pain including cluster headache by repetitive transcranial magnetic stimulation of the motor cortex with maintenance sessions: a naturalistic study. *Brain Stimul.* 2015;8(4):801–807. DOI: 10.1016/j.brs.2015.01.416
39. Chang J., Chu Y., Ren Y. et al. Maintenance treatment of transcranial magnetic stimulation (TMS) for treatment-resistant depression patients responding to acute TMS treatment. *Int. J. Physiol. Pathophysiol. Pharmacol.* 2020;12(5):128–133.
40. Sathappan A.V., Luber B.M., Lisanby S.H. The dynamic duo: combining noninvasive brain stimulation with cognitive interventions. Prog. Neuropsychopharmacol. *Biol. Psychiatry.* 2019;89:347–360. DOI: 10.1016/j.pnpbp.2018.10.006
41. Rossi S., Hallett M., Rossini P.M., Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin. Neurophysiol.* 2009;120(12):2008–2039. DOI: 10.1016/j.clinph.2009.08.016
42. Pizem D., Novakova L., Gajdos M., Rektorova I. Is the vertex a good control stimulation site? Theta burst stimulation in healthy controls. *J. Neural. Transm (Vienna).* 2022;129(3):319–329. DOI: 10.1007/s00702-022-02466-9

Information about the authors

Dmitry Yu. Lagoda – Cand. Sci. (Med.), researcher, Noninvasive neuromodulation group, Institute of Neurorehabilitation and Rehabilitation Medicine, Research Center of Neurology, Moscow, Russia,
https://orcid.org/0000-0002-9267-8315
Ilya S. Bakulin – Cand. Sci. (Med.), senior researcher, Head, Noninvasive neuromodulation group, Institute of Neurorehabilitation and Rehabilitation Medicine, Research Center of Neurology, Moscow,
Russia, https://orcid.org/0000-0003-0716-3737
Alexandra G. Poydasheva – Cand. Sci. (Med.), researcher, Noninvasive neuromodulation group, Institute of Neurorehabilitation and Rehabilitation Medicine, Research Center of Neurology, Moscow,
Russia, https://orcid.org/0000-0003-1841-1177
Dmitry O. Sinitsyn – Cand. Sci. (Physics and Math.), researcher, Institute of neurorehabilitation and rehabilitation medicine, Research Center of Neurology, Moscow, Russia, https://orcid.org/0000-0001-9951-9803
Alfiia Kh. Zabirova – postgraduate student, neurologist, Research Center of Neurology, Moscow, Russia,
https://orcid.org/0000-0001-8544-3107
Zukhra Sh. Gadzhieva – Cand. Sci. (Med.), neurologist, 3rd Neurological department, Institute of Clinical and Preventive Neurology, Research Center of Neurology, Moscow, Russia, https://orcid.org/ 0000-0001-7498-4063
Maryam R. Zabitova – Cand. Sci. (Med.), researcher, 3rd Neurological department, Institute of Clinical and Preventive Neurology, Research Center of Neurology, Moscow, Russia,
https://orcid.org/0000-0003-2523-333X
Kamila V. Shamtieva – Cand. Sci. (Med.), researcher, 3rd Neurological department, Institute of Clinical and Preventive Neurology, Research Center of Neurology, Moscow, Russia, https://orcid.org/ 0000-0002-6995-1352
Larisa A. Dobrynina – D. Sci. (Med.), chief researcher, Head, 3rd Neurological department, Institute of Clinical and Preventive Neurology, Research Center of Neurology, Moscow, Russia,
https://orcid.org/0000-0001-9929-2725
Natalia A. Suponeva – D. Sci. (Med.), Corresponding Member of the Russian Academy of Sciences, Director, Institute of Neurorehabilitation and Restorative Technologies, Research Center of Neurology, Moscow, Russia,
https://orcid.org/0000-0003-3956-6362
Michael A. Piradov – D. Sci. (Med.), Academician of the Russian Academy of Sciences, Director, Research Center of Neurology, Moscow, Russia,
https://orcid.org/0000-0002-6338-0392

Author contribution: *Lagoda D.Yu.* – creating a research concept, conducting research, curating data, analyzing data, preparing a draft manuscript; *Dobrynina L.A., Suponeva N.A., Piradov M.A.* – creation of the research concept, management of research work, revision and editing of the manuscript; *Bakulin I.S., Poydasheva A.G.* – methodology development, research, preparation of a draft manuscript, revision and editing of the manuscript; *Sinitsyn D.O., Zabirova A.Kh.* – data analysis, preparation of a draft manuscript, revision and editing of the manuscript; *Gadzhieva Z.Sh., Zabitova M.R., Shamtieva K.V.* – conducting research, data curation, revision and editing of the manuscript.

Информация об авторах

Лагода Дмитрий Юрьевич – к.м.н., н.с. группы неинвазивной нейромодуляции Института нейрореабилитации и восстановительных технологий Научного центра неврологии, Москва, Россия,
https://orcid.org/0000-0002-9267-8315
Бакулин Илья Сергеевич – к.м.н., с.н.с., рук. группы неинвазивной нейромодуляции Института нейрореабилитации и восстановительных технологий Научного центра неврологии, Москва, Россия,
https://orcid.org/0000-0003-0716-3737
Пойдашева Александра Георгиевна – к.м.н., н.с. группы неинвазивной нейромодуляции Института нейрореабилитации и восстановительных технологий Научного центра неврологии, Москва, Россия,
https://orcid.org/0000-0003-1841-1177
Синицын Дмитрий Олегович – к.ф.-м.н., н.с. Института нейрореабилитации и восстановительных технологий Научного центра неврологии, Москва, Россия, https://orcid.org/0000-0001-9951-9803
Забирова Альфия Ходжаевна – аспирант, врач-невролог Научного центра неврологии, Москва, Россия, https://orcid.org/0000-0001-8544-3107
Гаджиева Зухра Шарапутдиновна – к.м.н., врач-невролог 3-го неврологического отделения Института клинической и профилактической неврологии Научного центра неврологии, Москва, Россия,
https://orcid.org/0000-0001-7498-4063
Забитова Марьям Руслановна – к.м.н., н.с. 3-го неврологического отделения Института клинической и профилактической неврологии Научного центра неврологии, Москва, Россия,
https://orcid.org/0000-0003-2523-333X
Шамтиева Камила Витальевна – к.м.н., н.с. 3-го неврологического отделения Института клинической и профилактической неврологии Научного центра неврологии, Москва, Россия,
https://orcid.org/0000-0002-6995-1352
Добрынина Лариса Анатольевна – д.м.н., рук. 3-го неврологического отделения Института клинической и профилактической неврологии Научного центра неврологии, Москва, Россия,
https://orcid.org/0000-0001-9929-2725
Супонева Наталья Александровна – д.м.н., член-корреспондент РАН, директор Института нейрореабилитации и восстановительных технологий Научного центра неврологии, Москва, Россия,
https://orcid.org/0000-0003-3956-6362
Пирадов Михаил Александрович – д.м.н., профессор, академик РАН, директор Научного центра неврологии, Москва, Россия,
https://orcid.org/0000-0002-6338-0392

Вклад авторов: *Лагода Д.Ю.* – создание концепции исследования, проведение исследования, курирование данных, анализ данных, подготовка черновика рукописи; *Добрынина Л.А., Супонева Н.А., Пирадов М.А.* – создание концепции исследования, руководство научно-исследовательской работой, доработка и редактирование рукописи; *Бакулин И.С., Пойдашева А.Г.* – разработка методологии, проведение исследования, подготовка черновика рукописи, доработка и редактирование рукописи; *Синицын Д.О., Забирова А.Х.* – анализ данных, подготовка черновика рукописи, доработка и редактирование рукописи; *Гаджиева З.Ш., Забитова М.Р, Шамтиева К.В.* – проведение исследования, курирование данных, доработка и редактирование рукописи.