Changes in Clinical and Network Functional Connectivity Parameters in Motor Networks and Cerebellum Based on Resting-State Functional Magnetic Resonance Imaging Data in Patients with Post-Stroke Hemiparesis Receiving Interactive Brain Stimulation Neurotherapy

Nadezhda A. Khrushcheva[1], Konstantin V. Kalgin[1], Andrey A. Savelov[2], Anastasia V. Shurunova[3], Elena V. Predtechenskaya[3], Mark B. Shtark[1]

[1]Federal Research Center of Fundamental and Translation Medicine, Novosibirsk, Russia;
[2]International Tomography Center, Novosibirsk, Russia;
[3]Novosibirsk State University, Novosibirsk, Russia

Abstract

Introduction. *Interactive brain stimulation (IBS) neurotherapy is an advanced neurofeedback technology (NFB) that involves the organization of a feedback "target" based on signals recorded by functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). The NFB allows patients to volitionally self-regulate their current brain activity and may therefore be a useful treatment option for diseases with altered activation and functional connectivity (FC) patterns.*

Our ***objective*** *was to assess the effects of IBS on the FC changes in motor networks and correlations between clinical and network parameters in patients with post-stroke hand paresis.*

Materials and methods. *Patients with a history of stroke < 2 months were randomized into a main group (n = 7) and a control group (n = 7). All the patients followed the stroke physical rehabilitation for 3 weeks. The main group received IBS training, where the patients learned to imagine movements of the paretic hand trying to amplify the fMRI signal from the primary motor cortex (M1) and the supplementary motor area (SMA) on the lesion side with simultaneous desynchronizing the μ- and β-2 EEG rhythms in the central leads. Clinical tests and MRI were performed prior to and immediately after the treatment. FC matrices were constructed using CONN software based on resting-state fMRI data.*

Results. *By the end of the training, M1–M1 functional connectivity in the control group weakened, while no changes were observed in the main group. The FC strength was positively correlated with the grip strength ($\rho = 0.69$; $p < 0.01$) and with the results of the Box and Blocks test (BBT score, $\rho = 0.72$; $p < 0.01$) and the Fugl-Meyer assessment for upper extremity (FM-UE score, $\rho = 0.87$; $p < 0.005$). Ipsilesional SMA connectivity with contralesional cerebellum weakened ($p < 0.05$ in the main group). Its strength was negatively correlated with the BBT and FM-UE scores (both tests $\rho = -0.44$; $p < 0.05$).*

Conclusions. *Volitional control of M1 and SMA activity in the lesion hemisphere during the post-stroke IBS training alters the architecture of the entire motor network affecting clinically significant FC types. We studied a possible mechanism of this technology and its potential use in treatment programs.*

Keywords: *interactive brain stimulation neurotherapy; neurofeedback; stroke rehabilitation; motor cerebral networks; functional connectivity*

Ethics approval. The study was approved by the Ethics Committee of Federal Research Center of Fundamental and Translational Medicine (protocol No. 8 dated March 15, 2021), all the patients signed informed consent prior to treatment.

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For correspondence: 630060, Russia, Novosibirsk, Timakova str., 2. Federal Research Center of Fundamental and Translational Medicine. E-mail: khrunks@mail.ru. Khrushcheva N.A.

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Клинико-сетевая динамика функциональных связностей моторной сети и мозжечка по данным функциональной магнитно-резонансной томографии покоя у пациентов с постинсультным гемипарезом в курсе интерактивной терапии (стимуляции) мозга

Н.А. Хрущева[1], К.В. Калгин[1], А.А. Савелов[2], А.В. Шурунова[3], Е.В. Предтеченская[3], М.Б. Штарк[1]

[1]Федеральный исследовательский центр фундаментальной и трансляционной медицины, Новосибирск, Россия;
[2]Международный томографический центр Сибирского отделения Российской академии наук, Новосибирск, Россия;
[3]Новосибирский национальный исследовательский государственный университет, Новосибирск, Россия

Аннотация

Введение. *Интерактивная терапия (стимуляция) мозга (ИСМ) – это развитие технологии нейробиоуправления (НБУ), предполагающее организацию обратной связи по сигналам функциональной магнитно-резонансной томографии (фМРТ) и электроэнцефалографии. НБУ позволяет испытуемым произвольно регулировать текущую мозговую активность и потому может быть полезным лечебным инструментом при заболеваниях с изменёнными паттернами активации и функциональных связностей (ФС).*

Цель *исследования – оценить влияние ИСМ на динамику ФС моторной сети и клинико-сетевые корреляции у больных с постинсультным парезом руки.*

Материалы и методы. *Больные с инсультом давностью до 2 мес рандомизированы в основную (n = 7) и контрольную (n = 7) группы. Все проходили курс физической реабилитации в течение 3 нед; основная группа в курсе ИСМ обучалась воображать движение паретичной руки так, чтобы добиться усиления сигнала фМРТ первичной моторной коры (M1) и дополнительной моторной области (SMA) на стороне поражения с одновременной десинхронизацией μ- и β-2 ритмов электроэнцефалограммы в центральных отведениях. Клинические и МРТ-исследования проводили до и сразу после лечения. Матрицы ФС строили в программе «CONN» по данным фМРТ покоя.*

Результаты. *К концу курса ФС M1–M1 в контрольной группе стала слабее, в основной – не изменилась. Сила её прямо коррелировала с динамометрией ($\rho = 0{,}69$; $p < 0{,}01$), результатом тестов «Box-n-Blocks» ($\rho = 0{,}72$; $p < 0{,}01$) и Фугл-Мейера для руки ($\rho = 0{,}87$; $p < 0{,}005$). Связность ипсилатеральной SMA с противоположным мозжечком ослабла (в основной группе – $p < 0{,}05$); сила её обратно коррелировала с результатом тестов «Box-n-Blocks» и Фугл-Мейера для руки (для обоих $\rho = -0{,}44$; $p < 0{,}05$).*

Заключение. *Волевое управление активностью M1 и SMA поражённого полушария в курсе ИСМ после инсульта меняет архитектуру всей моторной сети, влияя на клинически значимые ФС. Рассматривается возможный механизм действия технологии и перспектива освоения её в лечебных программах.*

Ключевые слова: *интерактивная терапия (стимуляция) мозга; нейробиоуправление; реабилитация после инсульта; моторная церебральная сеть; функциональная связность*

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Адрес для корреспонденции: 630060, Россия, г. Новосибирск, ул. Тимакова, д. 2. Федеральный исследовательский центр фундаментальной и трансляционной медицины. E-mail: khrunks@mail.ru. Хрущева Н.А.

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Introduction

Modern methods of neuroimaging and statistical analysis expand the possibilities to study the network mechanisms of the brain functioning in general and its plasticity in particular. Studying the effects of stroke lesions on the interactions between distant brain regions is possible using functional connectivity (FC), which is defined as a measure of the temporal correlation of the activation patterns in spatially separated cortex areas. Cerebral network modelling has shown that post-stroke changes in the neural activity are widely distributed throughout the whole brain [1], and cognitive and neurological recovery is associated with restoration of activation patterns and intra- and inter-network connectivity [2–7].

Stroke motor rehabilitation is typically focused on the affected limb, assuming that special exercises and sensory stimulation enhance innate structural and functional neuroplasticity, which compensates for lost functions. However, the existing approaches provide satisfactory rehabilitation results only in 30% of stroke survivors.[8] So, in the search of the ways to control neuroplasticity and to enhance the rehabilitation effects, brain-computer interface technology, namely neurofeedback (NFB) method [9–12] based on ideomotor learning, shows a lot of promise. Movement imagery activates various nodes of the brain's motor system [13], and targeted training in this mental skill helps restore motor function in stroke patients. Feedback on actual changes in the neural ensemble activity makes such training more efficient, enhancing its effects on local neuroplasticity.

Since desynchronization in μ- (8–13 Hz) and β-2 (18–26 Hz) EEG rhythms in central leads indicates the sensorimotor cortex activity, these rhythms are typically used as EEG-NFB targets in post-stroke rehabilitation [14]. However, mapping the activation area based on recordings from the scalp surface is imprecise because it records a cumulative signal from a large number of neurons, which is distorted by the transmission and resistance of the underlying tissues. In this regard, functional magnetic resonance imaging (fMRI) is the most adequate tool for visualizing spots from 1 mm^3, including those located in the deep parts of the brain. The fMRI technology is based on registering miniature magnetic field disturbances that depend on the level of blood oxygenation (blood oxygenation level dependent, BOLD). Activation of neurons is thought to increase local blood flow, a phenomenon known as neurovascular coupling, and alters the ratio of oxyhemoglobin to deoxyhemoglobin in the drainage venules. The BOLD signal amplified by increased oxyhemoglobin concentration is believed to indirectly indicate the activity of specific neural ensembles [15].

The NFB was proposed as a potentially useful tool for post-stroke rehabilitation over a decade ago [16]. Subsequent pilot studies demonstrated that patients can use the real-time fMRI signals to self-regulate the activity of various motor areas [17, 18]. However, the clinical effect and mechanism of this phenomenon are insufficiently studied.

The advancements in the systems for recording and processing electromagnetic signals allowed recording EEG directly in the magnetic field of an MR scanner. So, a new tool for research and rehabilitation emerged. It simultaneously captures electrical (EEG) and hemodynamic (fMRI) neuronal activity signals built in neurofeedback contour, and it serves as the basis for bimodal fMRI-EEG neurofeedback platform [19–21]. We address this NFB method as interactive brain stimulation neurotherapy (IBS) [22–24]. Several studies examined the feasibility of this method for chronic stroke patients [22, 25, 26], its potential for rehabilitation [27], changes in hierarchical communication within the motor networks [28], as well as their functional connections with non-motor structures involved in learning [29].

The objective of our randomized clinical study was to analyze the effects of IBS on FC parameters in motor networks and evaluate the correlations between clinical and network characteristics in patients with hand paresis in the early post-stroke recovery period.

Patients and methods

The study included 14 patients (12 males and 2 females) with middle cerebral artery (MCA) stroke hemiparesis with hand paresis of $\geqslant$ 2 points (Medical Research Council Scale), and onset > 2 weeks and < 2 months, with Montreal Cognitive Assessment (MoCA test) $\geqslant$ 26. The patients were all right-handed and had an average age of 58.6 ± 8.7 years. All the patients were treated at the clinic of the Federal Research Center of Fundamental and Translational Medicine for three weeks. After the screening, they were randomized into the main (n = 7) and the control group (n = 7) in a blinded manner (Table 1). The treatment included massage to the paretic limb, physical therapy, reflex therapy, and therapeutic exercises (axial static load to the articular-ligamentous apparatus and dynamic aimed random movements) 3–5 times a week for 15–20 min depending on the patient's state determined by pulsoxymetrics. Rehabilitation in the main group was supported by 6 IBS sessions, where the patients followed movement imagery training to activate the primary motor cortex (M1) and supplementary motor area (SMA) and desynchronize the μ- (8–13 Hz) and β-2- (18–26 Hz) EEG rhythms in the central leads on the lesion side. The treatment strategy was generally presented as movement imagery training of the paretic limb. Each training session consisted of 16 parts: movement imagery/visual feedback (displayed on a digital scale from 0 to 100)/resting periods of 40/10/20 sec, respectively.

Table 1. Clinical and demographical characteristics of the study participants (n = 14)

Group	Index	Age, years	Gender	Stroke onset, weeks ago	Hemisphere	Lesion site	NIHSS score	Rankin score	MRC prox/ MRC dist*	Grip strength, kg*	BBT*, blocks/min	FM-UE* score	KVIQ vis/kin
Main group	P1	59	M	2	Right	Put; CE; LT	5	3	3/3	20,5	18	46	5/5
	P2	75	M	2	Right	CR; GP	2	3	4/3	21,4	47	44	10/5
	P3	58	M	3	Right	LF; LP	4	3	1/2	24,2	13	14	5/5
	P4	64	M	4	Left	GP	4	2	4/3	27,4	44	56	9/10
	P5	48	M	5	Right	NL; CE; Ins; LF; LP	3	3	4/3	20,6	41	49	8/5
	P6	48	M	2	Left	CR	5	3	3/3	24,6	31	49	8/8
	P7	47	F	4	Right	CR	3	4	4/2	8,8	16	38	15/10
Control group	P8	55	M	6	Left	Put; CE	5	4	1/1	3,7	8	19	21/22
	P9	65	M	2	Left	GP	5	3	4/2	9,1	17	34	5/5
	P10	71	M	6	Right	LF; LP; NB	3	3	3/3	0	8	32	5/5
	P11	55	M	6	Right	LF (lac)	3	3	3/2	8,5	27	34	5/5
	P12	65	M	3	Right	GP	3	3	3/2	1,6	0	38	20/16
	P13	51	F	2	Left	CR	3	3	3/4	14,6	45	55	20/20
	P14	59	M	6	Left	LP	4	3	3/2	14,5	19	32	5/5

Note. M — male; F — female; CE — *capsula externa*; CR — *corona radiata*; GP — *gyrus precentralis*; Ins — *insula*; KVIQ vis/kin Kinaesthetic and Visual Imagery Questionnaire, vis — visual subscale, kin — kinaesthetic subscale; lac — lacunar stroke; LF — *lobus frontalis*; LP — *lobus parietalis*; LT — *lobus temporalis*; MRC — Medical Research Council (MRC) Scale for Muscle Strength; MRC_{dist} — grip strength by MRC scale; MRC_{prox} — deltoid muscle strength by MRC scale; NB — *nuclei basales*; NIHSS — National Institutes of Health Stroke Scale; NL — *nucleus lentiformis*; Put — *putamen*; * — for the affected hand.

The fMRI was performed in the International Tomography Center of the Siberian branch of Russian Academy of Sciences (ITC SBRAS) using Ingenia 3.0T MR system (Philips). A reference anatomical brain image was obtained with T1-TFE sequence, voxel size of $1 \times 1 \times 1$ mm^3. Basic T2*-weighted images were obtained with EPI-FFE sequence (TR/TE = 2500/35 msec, voxel size of $2 \times 2 \times 5$ mm^3). FMRI neurofeedback sessions were supported by parallel EEG recording using BrainAmp128-channel EEG system (Brain Products). To pre-process the real-time fMRI images online, to compute the averaged signal level from the region of interest, and to organise the NFB target, OpenNFT software was used.

Test sessions with clinical assessment and MRI (3D T1 MP-RAGE sequences; resting state fMRI of real and imaginary hand movement) were conducted prior to and after the treatment (test 1 [T1] and test 2 [T2], respectively). Muscle strength was evaluated using Medical Research Council (MRC) Scale, where grade 0 means no movement and grade 5 means full strength, and grip strength dynamometer (normal values for males > 45 kg, for females > 31 kg). To assess motor functioning of the hand the Fugl-Meyer assessment (FM-UE) [30], Box and Blocks test (BBT), and the modified Rankin scale were used [31]. The Kinaesthetic and Visual Imagery Questionnaire (KVIQ-10) [32] was applied for diagnosis and daily self-training of the patients to develop correct and efficient motor imagery strategy.

For offline pre-processing of the results and display of the fMRI images Standard preprocessing pipeline of Matlab-based CONN software was used. The CONN Standard preprocessing pipeline enables functional frame realignment to eliminate motion artifacts, normalize images to the standard MNI brain , to correct motion artifacts, input of white matter and CSF signals profoundly, to remove the pronounced outliers with ASR function, and to smooth the data using isotropic Gaussian kernel. The data obtained from the patients with right-sided paresis were mirrored. FC matrices were generated using CONN toolbox with an a priori set of the regions of interest [23]: SMA, M1, and cerebellum (Cer) bilaterally. The FC matrices generated with the resting state fMRI data were compared within and between the groups using the Student's t-test. To identify general trends in the changes of clinical test results and FC parameters, Spearman's rank correlation coefficient was applied. Clinical data was computed in Microsoft Excel and Statistica v. 12.0 using descriptive statistics. To characterize the groups, median values (Me), 25th and 75th percentiles, mean values (M), and standard deviation (σ) were calculated. The groups were compared using the Mann–Whitney U test and the Pearson's χ^2 test. The intragroup changes of parameters were assessed using the Wilcoxon signed-rank test. The differences were recognized as significant at $p < 0.05$.

The study was approved by the Local Ethics Committee at the Federal Research Center of Fundamental and Translational Medicine (Protocol No. 8 dated March 15, 2021). All the patients signed informed consent prior to treatment.

Results

Clinical data

There were no intergroup differences by gender, age, stroke onset, Rankin, NIHSS and MRC scores for proximal and distal parts of the arm, nor in BBT and FM-UE scores prior to treatment (test 1). However, the baseline grip strength scores were lower in the control group (Table 2).

By the end of rehabilitation (test 2), all the clinical parameters in the main group, except MRCprox score, improved ($p < 0.05$). An increase in MRCprox and the BBT scores in the control group were recognized as significant ($p < 0.05$). We noticed that by the end of the treatment 4 patients (1 from the main group and 3 from the control group) lost 1.4–2.7 kg (1.9 kg in average) of their grip strength. The same patients showed either 1 point improvement or no improvement in their MRCdist scores (grip strength). Other test results showed no negative trends for individual values (Table 3). At the end of the treatment, the groups differed by the grip strength and BBT scores (Table 4).

Functional connectivity between motor network nodes

The motor network in the resting state (rs-fMRI) prior to treatment demonstrated medium intra-network connectivity: 0.18 in the main group and 0.15 in the control group ($p > 0.05$). There were no baseline intergroup differences in connectivity between specific nodes within the network. By the end of the treatment (test 2), the FC between ipsilesional SMA and contralesional Cer was significantly weaker in the main group; for other parameters only trends were observed (see the Figure). In the control group, we noticed the trend to diminished connectivity between ipsilesional M1 and contralesional M1, and between ipsilesional M1 and ipsilesional SMA (the upper row in the Figure). No changes in M1–M1 connectivity were observed in the main group; the connectivity between ipsilesional M1 and SMA in both hemispheres, and contralesional Cer became stronger (middle row in the Figure).

Correlations between clinical and network parameters

Correlation analysis of test 2 data revealed positive correlation between interhemispheric M1-M1 connectivity levels and FM-UE ($\rho = 0.87$; $p < 0.005$), BBT ($\rho = 0.72$; $p < 0.01$) and grip strength scores ($\rho = 0.69$; $p < 0.01$) in all the patients. Test 1 data demonstrated low correlation between M1–M1 connectivity levels and BBT score ($\rho = 0.45$; $p < 0.05$). By the end of the treatment, the connectivity between right-side

Table 2. Demographic and clinical characteristics of patients in the main and control groups prior to the treatment, median values [Q_1–Q_3]

Parameter	Main group (*n* = 7)	Control group (*n* = 7)	*p*
Age, years	58.0 [48.0; 61.5]	59.0 [55.0; 65.0]	0.381
Males: Females	6 : 1	6 : 1	1.02
Stroke onset, weeks ago	3.0 [2.0; 4.0]	6.0 [2.5; 6.0]	0.211
Affected hand (left/right)	2/5	4/3	0.282
Modified Rankin score	3.0 [3.0; 3.0]	3.0 [3.0; 3.0]	0.461
NIHSS score	4.0 [3.5; 4.5]	3.0 [3.0; 4.5]	0.711
MRC_{prox} score*	4.0 [3.0; 4.0]	3.0 [3.0; 3.0]	0.261
MRC_{dist} score*	3.0 [2.5; 3.0]	2.0[2.0; 2.5]	0.261
Grip strength, kg*	21.4 [20.4; 24.4]	8.5 [2.7; 11.8]	0.0041
BBT, blocks/min*	31.0 [17.0; 42.5]	17.0 [8.0; 23.0]	0.211
FM-UE score*	46.0 [41.0; 49.0]	34.0 [32.0; 36.0]	0.131
KVIQ vis score	8.0 [6.5; 9.5]	5.0 [5.0; 20.0]	1.01
KVIQ kin score	5.0 [5.0; 9.0]	5.0 [5.0; 18.0]	0.621

Note. Here and in Tables 3 and 4: *values for the affected hand; MRC_{dist} — grip strength by MRC scale; MRC_{prox} — deltoid muscle strength by MRC scale; NIHSS — National Institutes of Health Stroke Scale. [1] — comparison using the Mann–Whitney U test; [2] — using the χ^2 test.

SMA and left-side Cer showed negative correlation with BBT and FM-UE scores (both $\rho = -0.44$; $p < 0.05$).

Discussion

We present the results of the first randomized study on the FC changes in the motor cerebral network compared with the hand mobility tests taken during interactive brain stimulation neurotherapy (fMRI-EEG-neurofeedback) in the ischemic stroke patients during the early recovery period.

By the end of the treatment, the patients in both groups showed clinical improvement, which was slightly more pronounced in the IBS group. The sample size allows no statements about specific impact of IBS on the success of motor learning; however, the trend appears promising. Previous fMRI-NFB [16–18] and fMRI-EEG-NFB [22–29] studies demonstrated that the participants were able to volitionally activate motor regions in the cortex, despite the stroke onset more than 6 months ago. Several studies [16, 27, 29] also demonstrated improvements in hand motor function in some patients. The IBS neurotherapy looks as an attractive treatment option because the BOLD-signal built in the neurofeedback contour allows to focus on a specific cerebral structure and to regulate its activity for treatment/research purposes in the assumption that long-term clinical effects would be mediated by structural and functional plasticity in the brain systems associated with learning. The concept of volitional reconstructing the neural networks during the post-stroke recovery period is based on this assumption.

The resting state fMRI registers basic activity of the brain caused by continuous transmission of neuronal signals at rest without any specific stimulation or active task execution. This registration is based on low-frequency filtration of spontaneous oscillations of the BOLD-signal [33]. Thus, this technology can be employed in the studies of network organization of the brain in patients with the broad range of neurological disorders.

Longitudinal observational studies showed that post-stroke motor executive networks become more complex and chaotic, inter- and intrahemispheric FC between motor regions in the lesioned hemisphere weakens, while intrahemispheric connectivity between motor regions on the "intact" side strengthens. In the meanwhile, the improvement in motor function correlates with the restoration of activity in the motor regions and an increase in their interhemispheric FC levels [2–4, 34, 35].

In our study, interhemispheric M1-M1 FC weakened in the control group by the end of the physical rehabilitation,

Table 3. Clinical data changes by the end of the treatment, median values [Q_1–Q_3]

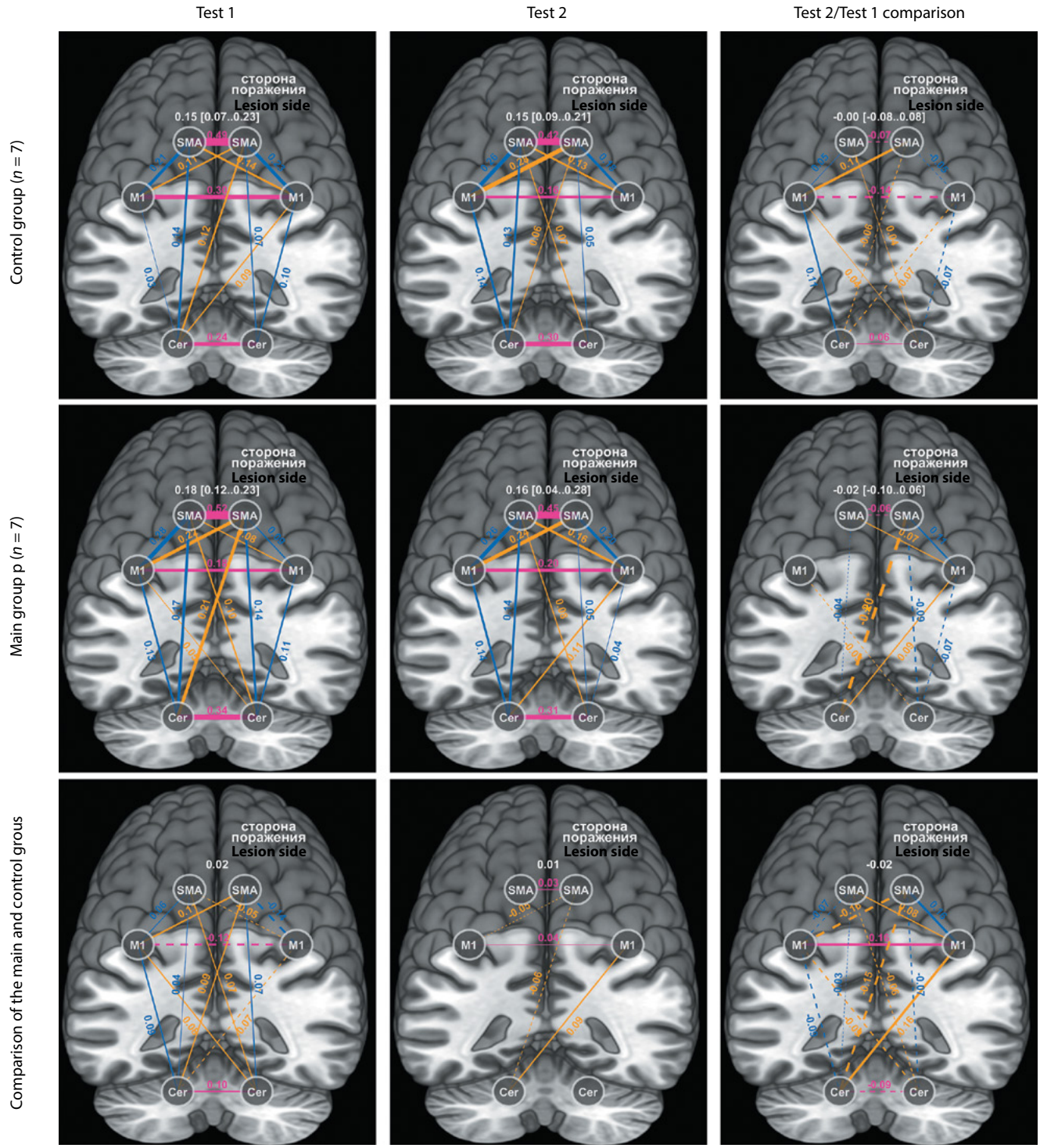
Parameter	Main group (*n* = 7)		Control group (*n* = 7)	
	test 1	test 2	test 1	test 2
Modified Rankin score	3.0 [3.0; 3.0]	2.0# [2.0; 2.0]	3.0 [3.0; 3.0]	2.0 [2.0; 3.0]
NIHSS score	4.0 [3.5; 4.5]	3.0# [1.5; 3.0]	3.0 [3.0; 4.5]	2.0 [2.5; 3.5]
FM-UE score*	46.0 [41.0; 49.0]	51.0# [45.5; 55.0]	34.0 [32.0; 36.0]	36.0 [31.5; 44.0]
MRC_{prox} score*	4.0 [3.0; 4.0]	4.0 [4.0; 4.0]	3.0 [3.0; 3.0]	4.0# [3.5; 4.0]
MRC_{dist} score*	3.0 [2.5; 3.0]	4.0# [3.5; 4.0]	2.0 [2.0; 2.5]	3.0 [2.5; 3.5]
Grip strength, kg*	21.4 [20.4; 24.4]	27.6# [22.8; 28.6]	8.5 [2.7; 11.8]	5.8# [5.0; 15.1]
BBT, blocks/min*	31.0 [17.0; 42.5]	47.0# [38.5; 52.0]	17.0 [8.0; 23.0]	27.0 [15.0; 34.0]
KVIQ vis score	8.0 [6.5; 9.5]	17.0# [13.5; 20.0]	5.0 [5.0; 20.0]	14.0 [7.5; 18.0]
KVIQ kin score	5.0 [5.0; 9.0]	15.0# [12.5; 17.5]	5.0 [5.0; 18.0]	5.0 [5.0; 17.0]

Note. #$p < 0.05$ compared with test 1 results (Wilcoxon signed-rank test).

Table 4. Clinical data in the main group vs.control group at the end of the treatment, median values [Q_1–Q_3]

Parameter	Main group (*n* = 7)	Control group (*n* = 7)	*p*
Modified Rankin score	2.0 [2.0; 2.0]	2.0 [2.0; 3.0]	0.26
NIHSS score	3.0 [1.5; 3.0]	2.0 [2.5; 3.5]	0.32
MRC_{prox} score*	4.0 [4.0; 4.0]	4.0 [3.5; 4.0]	0.80
MRC_{dist} score*	4.0 [3.5; 4.0]	3.0 [2.5; 3.5]	0.21
Grip strength. kg*	27.6 [22.8; 28.6]	5.8 [5.0; 15.1]	0.001#
BBT. blocks/min*	47.0 [38.5; 52.0]	27.0 [15.0; 34.0]	0.026#
FM-UE score*	51.0 [45.5; 55.0]	36.0 [31.5; 44.0]	0.13
KVIQ vis score	17.0 [13.5; 20.0]	14.0 [7.5; 18.0]	0.38
KVIQ kin score	15.0 [12.5; 17.5]	5.0 [5.0; 17.0]	0.32

Note. #$p < 0.05$ compared with test 1 results (Wilcoxon signed-rank test).



FC matrices of motor networks in the main and the control groups prior to and after the treatment.
The white circles designate the regions of interest, the colored lines indicate their connections. The rose lines represent interhemispheric cross-lateral connections, the orange lines represent interhemispheric diagonal connections, and the blue lines represent intrahemispheric connections. The strength of the functional connections is proportional to the width of the lines, with weaker connections indicated by dotted lines. The correlation coefficient (ρ) is shown above the lines. The results of FC comparison before and after the treatment are presented on the right and on the lower panels, within and between the groups, respectively.
Digits in white above each matrix reflect the mean value of the intranetwork connectivity or the difference in its level within or between the groups: on the right and on the lower panels, respectively. The confidence interval of 0.95 for this mean value is shown in the brackets. *$p < 0.05$ (using Student's t-test).

while in the main group it did not change or tended to increase. At the same time, the intrahemispheric functional connectivity M1–SMA on the lesion side became stronger in the IBS group, while in the control group no similar trend was observed (see the Figure). The functional test results (BBT, FM-UE, and grip strength scores) showed positive correlation with M1–M1 interhemispheric connectivity levels.

The cerebellum is involved in the motor learning and further in motor control of the developed movement imagery skills [36]. We observed an increase in connectivity between ipsilesoinal M1 and contralesional Cer in the main group and a decrease in FC between the ipsilateral SMA and both Cer in all the patients (see the Figure). To what extent such trends determine the success of post-stroke motor learning is not entirely clear, although we have found a negative correlation between the results of functional tests and the levels of connectivity between SMA in the lesioned hemisphere and the contralesional Cer.

There is a controversy between the results obtained in our study and in the previous studies, and the data of some recent studies, where the clinical improvement was not associated with the changes in the motor network FC [37, 38]. In one of the studies [38], the activation patterns and FC in stroke patients showed no difference from the same parameters in healthy controls in none of the recovery stages for one year. These data may indicate that cortical reorganization is not the only (and, possibly, not the main) mechanism for restoring lost movements. This assumption is supported by our data showing no significant intragroup changes in connectivity matrices by the end of the treatment, while the improvement in hand motor function during the treatment was obvious. Perhaps, it can be explained by a relatively short duration of the study (3 weeks). However, this time was sufficient to notice the trends in the changes of interactions between certain motor network nodes, and these trends were different in the main and in the control groups. Apparently, IBS additionally recruits cerebral structures associated with motor learning, and this, together with volitional control of the activity of the motor network cortical nodes on the lesioned side, leads to secondary changes in the pyramidal tracts. We came to this assumption based on the results of the recent study carried out by Z.B. Sanders et al.: after three sessions of real-time fMRI NFB in the remote period of stroke onset, the patients learned to increase the laterality of motor cortex activity in the lesioned hemisphere during movements of the stroke-affected hand. No differences in FM-UE scores were observed between the groups receiving real or sham neurofeedback, although real fMRI-NFB group demonstrated better gross hand motor performance in subtasks in the Jebsen–Taylor hand function test [39]. In the same group, the data of diffusion tensor imaging tractography collected one month after the treatment showed decreased corticospinal tract asymmetry, which was positively correlated with participants neurofeedback performance [39]. It can be assumed that volitional modulation of cortical activity might have a specific impact on both functional and structural neuroplasticity, potentially leading to favorable clinical outcomes.

Study limitations. The study enrolled patients with a wide range of stroke localizations and individual differences in screening results, so we aimed to focus on intragroup changes avoiding inter-group comparisons. Analysis of EEG data recorded during the training sessions, where possible effects of the treatment on each modality of bimodal fMRI-EEG platform were assessed separately and/or interchangeably, was not included in this article, although it was a significant part of the study. The fMRI-EEG-NFB sessions were carried out in the early post-stroke recovery period, when the innate neuroplasticity mechanisms are still active. On one hand, drawing conclusions about the real effects of our intervention is difficult. On the other hand, this supports the hypothesis that targeted self-regulation of activity in motor cortical regions through IBS neurotherapy during this period can provide the necessary impulse for neural network improvement. A small sample size (in our case, n = 14) is a common weak point of an fMRI and fMRI-EEG research. However, the NFB neurotherapy based on bimodal fMRI-EEG platform is a conceptual trend that allows accumulating data in order to achieve correlations sufficient to serve the needs of practical medicine. A larger sample size might provide conclusive evidence of the effects of IBS on motor learning efficacy. However, we have found correlations between clinical parameters and changes in specific connectivities within the motor networks, and these changes differed between the study groups.

Conclusion

Neurological deficits and post-stroke recovery depend on the intensity of processes running all over the brain. This is the reason why the search for cerebral structures, which can respond to non-invasive treatment allowing directly or indirectly optimize the neuroplasticity of the brain, is so much in trend nowadays. One of such research and therapeutic tools is neurofeedback neurotherapy based on BOLD-signal (that is, interactive brain stimulation based on fMRI- or fMRI-EEG-neurofeedback). It allows patients to evolve from a passive recipients of therapeutic intervention into active participants capable of reconstructing neural connections between distant areas of their own brain, resulting in efficient clinical progress.

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Information about the authors

Nadezhda A. Khrushcheva – Cand. Sci. (Med.), senior researcher, Laboratory of clinical and experimental neurology, neurologist, Head, Neurological clinical department, Federal Research Center of Fundamental and Translation Medicine, Novosibirsk, Russia, https://orcid.org/0000-0003-4657-2947
Konstantin V. Kalgin – Cand. Sci. (Phys.-Math.), doctor resident of the second year of study, Federal Research Center of Fundamental and Translation Medicine, Novosibirsk, Russia, https://orcid.org/0000-0002-1873-4454
Andrey A. Savelov – Cand. Sci. (Phys.-Math.), senior researcher, MRI Technology Laboratory, Head, MR biophysics group, International Tomography Center of the Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia, https://orcid.org/0000-0002-5332-2607
Anastasia V. Shurunova – doctor resident, Zelman Institute of Medicine and Psychology, Novosibirsk State University, Novosibirsk, Russia, https://orcid.org/0009-0006-4866-6372
Elena V. Predtechenskaya – D. Sci. (Med.), Professor, Department of neurology, Zelman Institute of Medicine and Psychology, Novosibirsk State University, Novosibirsk, Russia, https://orcid.org/0000-0003-3750-0634
Mark B. Shtark – D. Sci. (Med.), Professor, Academician of the Russian Academy of Sciences, main researcher, Federal Research Center of Fundamental and Translation Medicine, Novosibirsk, Russia, https://orcid.org/0000-0002-2326-4709

Author contribution: *Khrushcheva N.A.* – concept creation and conducting the research, data curation and analysis; *Kalgin K.V.* – software, data curation and analysis; *Savelov A.A.* – development of the research methodology, management of the research work, conduction of the research, data curation; *Shurunova A.V.* – conducting of the research, data curation; *Predtechenskaya E.V.* – creation of the research concept, data analysis; *Shtark M.B.* – seeking funding, developing of the research methodology, management of the research work, creating a research concept. All authors made final approval of the version to be published.

Информация об авторах

Хрущева Надежда Алексеевна – к.м.н., с.н.с. лаб. клинической и экспериментальной неврологии, врач-невролог, зав. неврологическим отделением клиники Федерального исследовательского центра фундаментальной и трансляционной медицины, Новосибирск, Россия, https://orcid.org/0000-0003-4657-2947
Калгин Константин Викторович – к.ф.-м.н., ординатор 2-го года обучения Федерального исследовательского центра фундаментальной и трансляционной медицины, Новосибирск, Россия, https://orcid.org/0000-0002-1873-4454
Савелов Андрей Александрович – к.ф.-м.н., с.н.с. лаб. «МРТ Технологии», руководитель группы магнитно-резонансной биофизики Международного томографического центра СО РАН, Новосибирск, Россия, https://orcid.org/0000-0002-5332-2607
Шурунова Анастасия Владимировна – врач-ординатор по направлению «Неврология» Центра постдипломного образования Института медицины и психологии В. Зельмана Новосибирского национального исследовательского государственного университета, Новосибирск, Россия, https://orcid.org/0009-0006-4866-6372
Предтеченская Елена Владимировна – д.м.н., профессор каф. неврологии Института медицины и психологии В. Зельмана Новосибирского национального исследовательского государственного университета, Новосибирск, Россия, https://orcid.org/0000-0003-3750-0634
Штарк Марк Борисович – д.м.н., профессор, академик РАН, г.н.с. Федерального исследовательского центра фундаментальной и трансляционной медицины, Новосибирск, Россия, https://orcid.org/0000-0002-2326-4709

Вклад авторов: *Хрущева Н.А.* – создание концепции и проведение исследования, курирование и анализ данных; *Калгин К.В.* – программное обеспечение, курирование и анализ данных; *Савелов А.А.* – разработка методологии исследования, руководство научно-исследовательской работой, проведение исследования, курирование данных; *Шурунова А.В.* – курирование данных, проведение исследования; *Предтеченская Е.В.* – создание концепции исследования, анализ данных; *Штарк М.Б.* – поиск финансирования, разработка методологии исследования, руководство научно-исследовательской работой, создание концепции исследования. Все авторы прочли и одобрили финальную версию перед публикацией.