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Changes in Resting fMRI Networks in Patients with Severe Traumatic Brain Injury During Therapeutic Rhythmic Transcranial Magnetic Stimulation (Case Report)

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Summary

Severe traumatic brain injury (TBI) accompanied by impaired consciousness manifesting as prolonged postcoma unawareness (PCU) is one of the current medical and social problems causing high morbidity and mortality worldwide. Difficult recovery of such patients necessitates the development of additional neurorehabilitation approaches, including neuromodulation methods, as well as the search for objective markers of treatment efficacy.

Aim of the study: to evaluate the effect of therapeutic rhythmic transcranial magnetic stimulation (rTMS) on fMRI resting state networks (RSN) in PCU after severe TBI.

Materials and Methods. We analyzed individual fMRI RSN in three patients with PCU before and after a course of rTMS performed at different timepoints after severe TBI and with different efficacy of treatment. We assessed the topography and quantitative characteristics of the networks (DMN, sensorimotor, control functions, left and right fronto-parietal, auditory, and speech) known to be most significant for recovery of consciousness.

Results. We found a trend toward normalization of RSN topography as well as an increase in the integral index of network intensity in two of three patients with a distinct increase in consciousness after a course of rTMS.

Conclusion. Using case observations, we have demonstrated the therapeutic efficacy of rTMS and feasibility of using fMRI RSN as a reliable diagnostic approach in PCU following severe TBI.

Keywords: traumatic brain injury; unawareness; resting state networks; fMRI; rTMS

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Severe traumatic brain injury (STBI) associated with impaired consciousness and motor activity is one of the urgent medical and social issues causing high morbidity and mortality worldwide [1, 2]. Consciousness disorders such as coma and a high risk of prolonged (chronic) post-coma unawareness (PCU) are characteristic of STBI [3, 4]. Meanwhile, the assessment of cognitive functions and recovery potential for mental activity in general plays a crucial role in the integrated treatment and neurorehabilitation strategy.

PCU includes phases immediately following coma and succeeding each other, beginning with the first post-coma opening of the patient's eyes and ending with the reappearance of contact with him/her (most often as a clear compliance with the instructions) [3, 5–7]. Several clinical scales are

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used for quantitative assessment of PCU, and their relevance is determined by current perspectives and the research progress [7–10].

To date, several international guidelines for the treatment of this category of patients have been published [7, 11]. However, significant difficulties of patient rehabilitation provide a rationale for the search and development of additional neurorehabilitation approaches, which include neuromodulation methods [4]. Transcranial electrical and magnetic stimulation has been used in clinical practice for the past decade as a neuromodulatory intervention [12, 13]. The therapeutic use of rTMS is based on its ability to change the level of cortical excitability, causing depolarization of neurons with subsequent generation and propagation of action potential (AP) [14, 15]. Changes in hemodynamics, neurotrophic factor production, and neurotransmitter activity associated with rTMS have also been shown [13].

The use of rTMS seems very promising for the neurorehabilitation of patients with disorders of consciousness and motor function following STBI [16]. According to the literature, as well as our own research, stimulation of frontal hemispheres (zones Fz, F3–F4 or F3 according to the international scheme of electrode positioning 10–20% in electroencephalography) has significant positive effect [17–19]. The effectiveness of stimulation of these areas can be explained, among other things, by the fact that the frontal cortical areas are considered to be pivotal in providing the so-called executive functions that initiate, plan, regulate and control any purposeful activity [20, 21].

On the other hand, the rather complex mechanism of action of rTMS, especially in variable conditions of brain damage, determines possible individual differences in the brain responses of patients with a traumatic brain injury to this therapeutic intervention. The timing of rTMS integration into neurorehabilitation, in particular, in early period following traumatic brain injury during intensive therapy, is one of the controversial issues in this area. The study of systemic cerebral reactions, accompanying rTMS, as well as control of the effectiveness of stimulation necessitates the involvement of most informative parameters of brain performance.

The concepts of neural network structural and functional organization of brain activity [22], as well as the analysis of fMRI resting state networks [23] are currently widespread in neuroscience. The formation of resting state networks (RSN) is associated with high correlation in time of interregional hemodynamic signals [24]. There have been described 7 to 15 functional RSNs that are most typical for healthy people [23, 25], but are impaired in brain conditions, including traumatic brain injury [26]. A number of RSNs are considered in the literature to be the most significant for recovery of consciousness in PCU. They include such networks as default mode network (or DMN), executive functions, lateral frontoparietal, auditory, sensorimotor, visual, salience [27, 28], and probably speech network [29, 30] (Fig. 1).

In a series of our previous studies, we developed an algorithm for group and individual analysis of fMRI resting state networks (RSN) based on the ICA FSL software [31]. We have shown its informative value for the estimation of RSN in intact brain and in STBI [31, 32].

This study aims to investigate changes in the network organization of the brain in patients with STBI, accompanied by disorders of consciousness and motor activity, during therapeutic rTMS. The main focus was placed on RSNs shown in Fig. 1.

The aim was to evaluate the effect of therapeutic rhythmic transcranial magnetic stimulation (rTMS) on fMRI resting state networks (RSN) in PCU after STBI.

We focused on the determination of general trends in fMRI RSN changes in patients with STBI exposed to rTMS and identification of patterns of fMRI RSN associated with clinical effect of rTMS.

Material and Methods

We studied three patients (two men and one woman) who had suffered a traumatic brain injury resulting in post-coma unawareness state (Table 1). The current clinical status and level of consciousness were assessed using the CRS-R scale [9] as well as the consciousness recovery assessment scale [33]. According to this assessment, at the time of the 1st examination, one patient was in the unresponsive wakefulness syndrome (UWS) or vegetative state, two patients were in the MCS- or akinetic mutism (arbitrary fixation of gaze without executing instructions and speech production). Motor defect manifested as hemiparesis was assessed using a muscle strength scale [34]. All patients were not on ventilatory or oxygen support.

The current lack of generally accepted standards for therapeutic rTMS in patients with TBI [13] warrants the search for new and improved stimulation algorithms. In this study, we used a protocol developed earlier [19]. Stimulation was performed on a MagPro×100 device (MagVenture) using the ‘figure-of-eight' B-70 coil. Each patient underwent a course of rTMS on zones F3 and F4 according to the 10–20% EEG system (left and right dorsolateral prefrontal cortex, respectively). The duration of the TMS course varied from 5 to 10 sessions. One rTMS session included from 1000 to 4000 pulses with 50% maximum stimulator power (MSP). The threshold was determined according to the clinically accepted technique of diagnostic rTMS performed before the

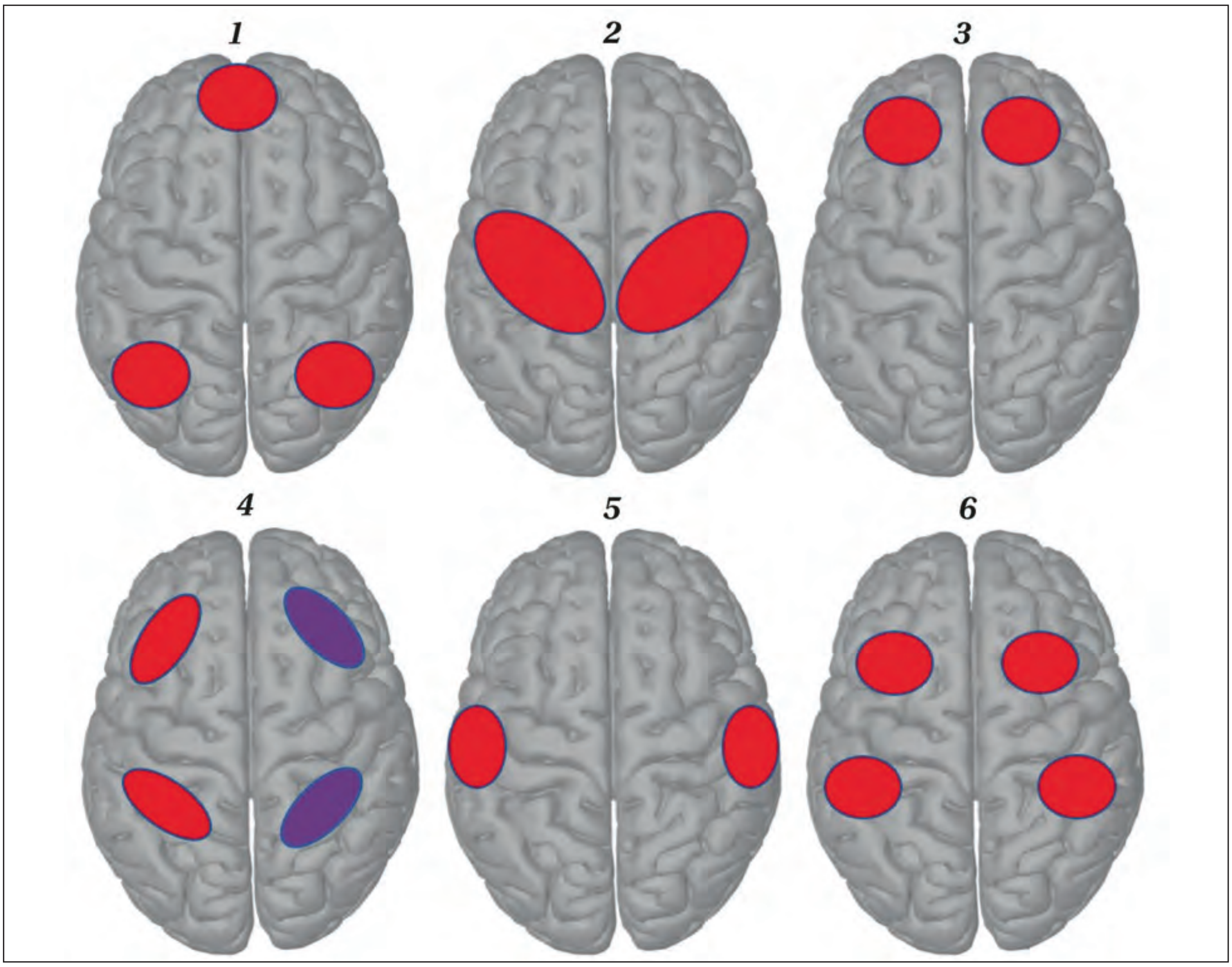

Fig. 1. Schematic representation of hemispheric projections of resting fMRI networks considered significant for recovery of reduced consciousness.
Note. *1* — DMN; *2* — sensorimotor network; *3* — executive functions; *4* — frontoparietal (left and right); *5* — auditory; *6* — speech.

Table 1. Characteristics of patients' level of consciousness before and after a course of rTMS.

Patient	Parameters							
	Sex	Age	Time after trauma	Post rTMS		Number of rTMS sessions	Post rTMS	
				On consciousness recovery assessment scale	On CRS-R		On consciousness recovery assessment scale	On CRS-R
M.	M	34	17 days	VS	UWS	5	AM-MSU	MCS+
B.	F	35	17 months	AM	MCS-	6	MSU	MCS+
Ya.	M	31	4.5 years	AM	MCS-	10	AM	MCS-

Notes. UWS — unresponsive wakefulness syndrome; MCS- — minimally conscious state without following commands; MCS+ — minimally conscious state able to follow commands; VS — vegetative state; AM — akinetic mutism; MSU — mutism with speech understanding.

course stimulation including bilateral stimulation of the motor cortex (M1) and neck region (CVII). The range of rTMS frequencies, which varied from 1 to 10 Hz, was selected for each patient individually depending on the lesion area anatomy and performance changes assessed using clinical examination and EEG data. Stimulation was performed along with a personalized, continuous and invariable treatment regimen, which included anticoagulants/antiaggregants, neurometabolic and gastroprotective drugs, as well as prophylactic doses of anticonvulsants.

After a course of rTMS, we recorded a qualitative improvement in two patients and no changes in the clinical condition were observed in one patient (Table 1).

Before and after the course of rTMS the fMRI was recorded using a General Electric Signa HDxt magnetic resonance tomograph (USA) at rest with eyes closed for 10 min and 12 sec in the Department of radiology and radioisotope diagnostics of the Burdenko Scientific Research Center of the Russian Ministry of Health.

A 3D FSPGR pulse sequence (BRAVO) was used to obtain structural data (whole brain volume) with the following parameters: TR = 8.8 ms, TE = 3.5 ms, slice thickness = 1 mm, FOV = 250 mm, image matrix 256×256, voxel size 0.97×0.97×1.0 mm. The echoplanar sequence Spin Echo (BOLD T2) was used to obtain functional data. TR = 2000 ms, TE = 30 ms, slice thickness = 3 mm, FOV 250 mm, image matrix 128×128, voxel size 1.95×1.95×3 mm. In each time series, 300 sets of functional volumes were obtained, each containing 24–40 axial slices capturing the entire brain. Scanning time per functional volume unit was 2 seconds. The total number of slices in a functional series was 7000–12000.

During fMRI registration the primary control of the quality of hemodynamic signals, automatic noise correction, as well as assessment of the quality of block recordings by the presence of motor artifacts (excellent, good, poor) were performed. In the latter case, the scanning was interrupted, and the study was started again. All studies were performed without anesthesia.

The output experimental data were recorded in DICOM format with subsequent conversion to NIFTI and processing in the FMRIB Software Library (FSL) [31].

Processing included removal of artifacts associated with low-frequency noise and correction of motion artifacts, then conversion of functional data to standard space (anatomical structure of the brain), and then, using the MELODIC-ICA tool, analysis of fMRI RS.

A series of special studies established the feasibility of limiting the number of networks at 60. With N > 60 or no limitation, the major RSNs normally became fragmented.

The data obtained were superimposed on individual brain images in axial, frontal, and sagittal planes.

As a result, several voxel groups (large-scale networks) with statistically independent BOLD-signal changes were distinguished in each patient. The significance level for the selection of independent components was P<0.01. Correction for multiple comparisons was performed automatically when the p value was lower than 0.05. The selected networks were then visualized in the three-dimensional image of the brain of each patient.

Three independent experts in neurophysiology, radiology, neurology participated in the verification of individual RSNs of patients, taking into account the experience of similar studies in healthy subjects [31] and patients with STBI [32]. The components of each network were verified using the AAL (Anatomical Automatic Labeling) software package.

To quantify the correlated activity of six resting fMRI networks (Fig. 1), we used such integral parameters recommended by the FSL developers as the number of voxels, their volume (cm^3) and maximum intensity. They were calculated automatically using a set of FSL console commands. Intensity refers to statistical indicators of network activity, which corresponds to the F value of Fisher criterion. Intensity has no units of measurement and is set automatically. F-value is displayed in accordance with graded color or black-and-white scale, where brightness or color corresponds to F-criterion value with the maximum intensity having maximal value and minimum value corresponding to the F-criterion value with P=0.01. F-values for p exceeding minimal level of significance are not displayed when anatomical and functional 3D data are combined.

The studies were performed in accordance with the principles of the Helsinki Declaration, after obtaining informed consent and approval by the ethical committee of Burdenko Scientific Research Center of the Russian Ministry of Health.

Results

Case 1. Patient M., 34 years old, suffered a road traffic accident with STBI and severe cerebral contusion, diffuse axonal injury, multiple focal hemorrhages and subarachnoid hemorrhage (MRI evidence). Following the lesion, an 8-day coma developed which transformed into PCU state.

At the time of fMRI prior to rTMS (17 days after injury), neurological examination showed severe reduction of consciousness corresponding to UWS on the CRS-R or vegetative state according to the consciousness recovery scale [33]. The motor domain showed pyramidal tetraplegia with increased muscular tone in the left arm. Limb movements assessment was 2 points, slightly better on the right side. Brainstem signs corresponding to midbrain damage were observed.

The second fMRI examination was performed 34 days after injury, on day 5 after a course (5 sessions) of therapeutic rTMS of which 1 were done in the F3 area and other 4 bilaterally in F3–F4. The consciousness was assessed as MCS+ according to the CRS-R scale or intermediate between AM and MSU, according to the consciousness recovery assessment system [33]: voluntary fixation of gaze, unsteady following of commands. In the motor domain, the movement in the left arm was 3 points, in the right arm 2 points, in the legs 3 points, the patient performed better in keeping the right leg flexed.

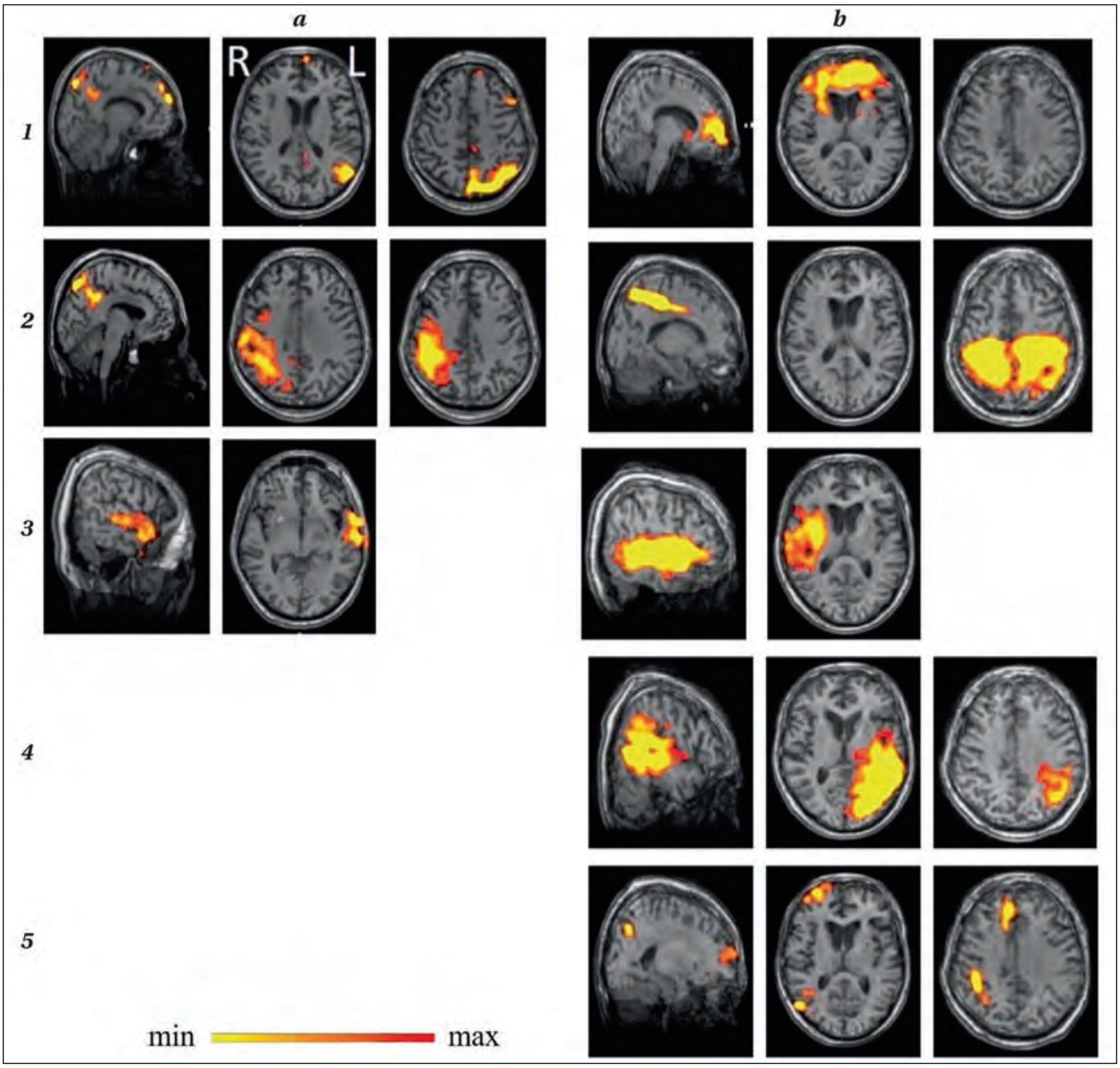

Fig. 2. Changes in RSN fMRI in patient M.
Note. *a* — prior to therapeutic rTMS; *b* — 5 days after the course of rTMS. *1* — DMN; *2* — sensorimotor; *3* — auditory; *4* — speech; *5* — frontoparietal networks.

Figure 2 shows RSN fMRI images (from those listed in the technique) of patient M. revealed before (Fig. 2, *a*) and after rTMS (Fig. 2, *b*) on identical brain slices (sagittal and horizontal).

Prior to stimulation, only 3 out of the 6 networks under study could be verified, i. e., DMN, sensorimotor, and auditory networks. Meanwhile, even the identified networks were different from normal, primarily because of their asymmetry. In the DMN (Fig. 2, *a 1*), the left hemispheric occipital component was dominant, with a pronounced reduction of the frontal component. The sensorimotor network (Fig. 2, *a 2*) was represented by activated components in the deep parts of the right hemisphere. The auditory network (Fig. 2, *a 3*) was represented by left-sided activation in the basal parts.

After stimulation, we noticed a quantitative increase in the intensity of the already existing RSNs (Table 2), with changes in their spatial organization. Thus, there was an increased bilateral activation of the anterior (frontal) component of the DMN (Fig. 2, *b 1*), as well as of the motor cortex of both hemispheres of the sensorimotor network (Fig. 2, *b 2*). We observed widespread activation of the right hemispheric component of the auditory network (Fig. 2, *b 3*). In addition, components of two RSNs that were absent before stimulation were identified: the left hemispheric posterior temporal corresponding to the speech network (Fig. 2, *b 4*), as well as the main components of the right frontoparietal network (Fig. 2, *b 5*). All of the observed changes in RSN activation due to synchronization of hemodynamic signals relate to the network components close to the stimulation zones.

Case 2. Patient B., a 35-year-old female with a right-sided traumatic brain injury (severe contusion with intracerebral hematoma of the right frontal lobe followed by decompressive cranial trepanation in the right fronto-temporo-parietal region and hematoma removal), subsequent inflammatory process (meningoencephalitis, ventriculitis resulting in posttraumatic postinflammatory multilocular hydrocephalus followed by ventriculo-peritoneal shunting), who still remained in a long-term PCU 17 months after injury.

At the time of the examination before rTMS, the level of consciousness on the CRS-R scale was assessed as MCS-, manifested as AM (arbitrary fixation of gaze without following instructions and verbal production) [33]. Gross tetraparesis with increased muscular tone and decreased reflexes were revealed in the motor domain. MR tomograms (Fig. 3) visualized abnormalities predominantly in the right hemisphere (expansion of the right lateral ventricle and moderate lateral dislocation of the lateral ventricles to the right) with disruption of the anatomical relations of the brain structures. In the left frontal lobe, in the projection of the anterior border of the precentral gyrus, a small area of altered cerebral tissue, probably of hemorrhagic nature, was also identified.

After 9 days and 6 sessions of rTMS (5 in the F3 zone, 1 in the F4 zone), positive changes in consciousness were noted: MCS+ on the CRS-R scale, or transition to mutism with speech understanding (i.e., following selected commands) according to the consciousness recovery assessment system [33]. In the motor domain, gross tetraparesis persisted, but with a slight increase in muscular tone and reflexes. For the first time since the injury, patient B. was able to raise and lower her right arm upon request.

Fig. 3 shows the fMRI images listed in the RSN procedure of Patient B. before (Fig. 3, *a*) and after rTMS (Fig. 3, *b*) on identical brain slices (sagittal and horizontal).

Before stimulation, 6 RSNs under study were revealed including DMN, sensorimotor, executive functions, auditory, and frontoparietal, which, however, differed sharply from the normal ones. The pronounced asymmetry of all networks, with activation of components mainly in the left (structurally more intact) hemisphere, as well as their disorganization, was remarkable. The DMN was characterized by time-differentiated synchronization of the anterior (frontal) (Fig. 3, *a 1*) and posterior components, which are normally activated simultaneously. The sensorimotor network (Fig. 3, *a 2*) was represented only by the left-hand motor component, the executive function network (Fig. 3, *a 3*) by the frontal one, and the auditory network (Fig. 3, *a 5*) by the temporal one, also in the left hemisphere. The frontal-parietal network (Fig. 3, *a 4*) was activated solely superficially, in the right hemisphere, with a slight partitioning into the parietal and frontal components.

After stimulation, certain changes in resting networks were seen corresponding to positive clinical progress. All RSNs were still asymmetrically activated in the left (more morphologically intact) hemisphere. Meanwhile, greater (simultaneous) coherence of activation of the anterior and posterior components was noted in the DMN (Fig. 3, *b 1*). The left hemispheric components of the sensorimotor network (Fig. 3, *b 2*) were represented at all levels of the hemisphere, with increased intensity (Table 2), approaching normal topography. Bilateral activation of the frontal components was observed in the executive functions network (Fig. 3, *b 3*). The left frontoparietal network (Fig. 3, *b 4*) with a clear activation of both of its components was seen. While there were no significant changes in the auditory network (Fig. 3, *b 5*), the presence of fragments of the speech RSN (Fig. 3, *b 6*), undetectable prior to rTMS, was noted.

Case 3. Patient Ya., 31 years old, suffered a traumatic brain injury with severe left frontal lobe contusion, diffuse axonal damage, multiple small cortical-subcortical hemorrhagic foci, intraventricular and subarachnoid hemorrhages and subsequently developed hyporesorptive hydrocephalus according to MRI.

At the time of the examination before rTMS, 4.5 years after injury, the patient's consciousness was assessed as MCS- according to the CRS-R scale, manifested as akinetic mutism according to the consciousness recovery assessment system [33]. In the motor domain, we detected predominantly right-sided tetraparesis with increased muscular tone in the arms; brainstem signs from the midbrain level and gross pseudobulbar syndrome. MRI scans (Fig. 4) showed enlargement of the lateral ventricles, more pronounced in the anterior horns, amid brain atrophy prevailing in the frontal lobes.

Seventeen days after the course of rTMS (10 sessions in the F3–F4 areas), the patient's condition did not change, and he was still rated as MCS on the CRS-R scale. Though when asssessed according to the alternative classification [33], the patient became emotionally reactive while still having akinetic mutism. Pyramidal tetraplegia persisted, but without a significant increase in muscle tone; there were brainstem signs corresponding to the midbrain lesion, as well as a gross pseudobulbar syndrome.

Fig. 4 depicts the studied RSN fMRI of patient Ya. before (Fig. 4, *a*) and after rTMS (Fig. 4, *b*).

Before stimulation, components of 5 of the 6 resting fMRI networks under study were detected

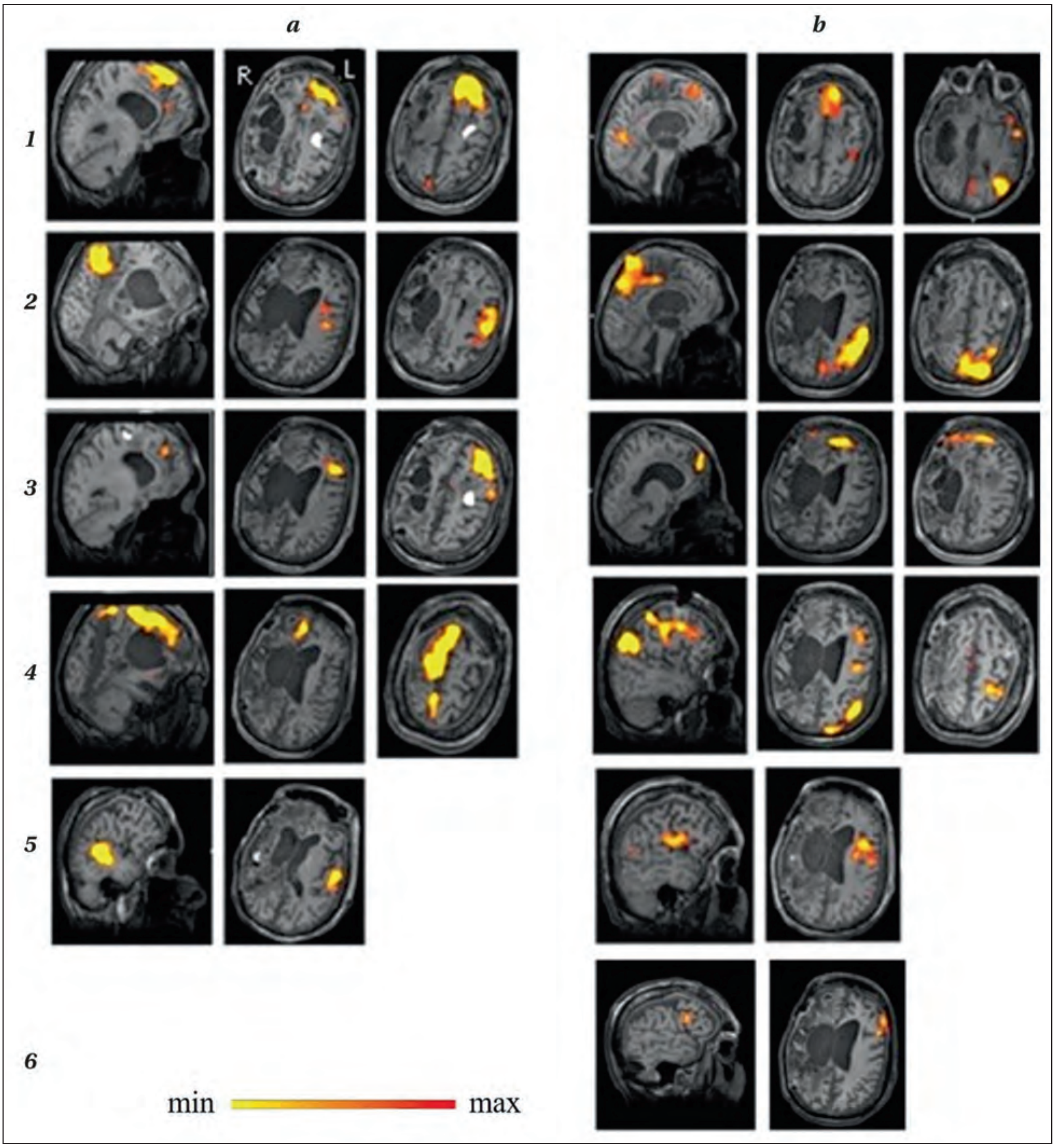

Fig. 3. Changes in RSN fMRI of patient B.
Note. *a* — before the therapeutic rTMS course; *b* — after stimulation. The RSN fMRI: *1* — DMN; *2* — sensorimotor; *3* — executive functions; *4* — frontoparietal; *5* — auditory; *6* — speech, frontal component.

such as DMN, sensorimotor, executive functions, fronto-parietal, temporal, and even speech. Similarly to Patient B., the network activation was fragmentary and predominantly unilateral, asymmetrical in nature. We detected a frontal component of the DMN, activation of the left motor cortex sensorimotor network, the left frontal cortex executive functions network, the parietal component of the right fronto-parietal network, and the left parietal component of the speech network (Fig. 4, *a 1–5*, respectively).

After stimulation, RSNs were still represented only by separate components, predominantly in the left hemisphere. The topography of the sensorimotor and executive networks did not change (Fig. 4 *b 2, 3,* respectively). The parieto-occipital component of the DMN (Fig. 4, *b 1*), the parietal component of the frontal-parietal network (Fig. 4, *b 4*), and the frontal component of the speech network (Fig. 4, *b 5*) were activated, all in the left hemisphere. Noteworthy is the appearance of a near-normal configuration

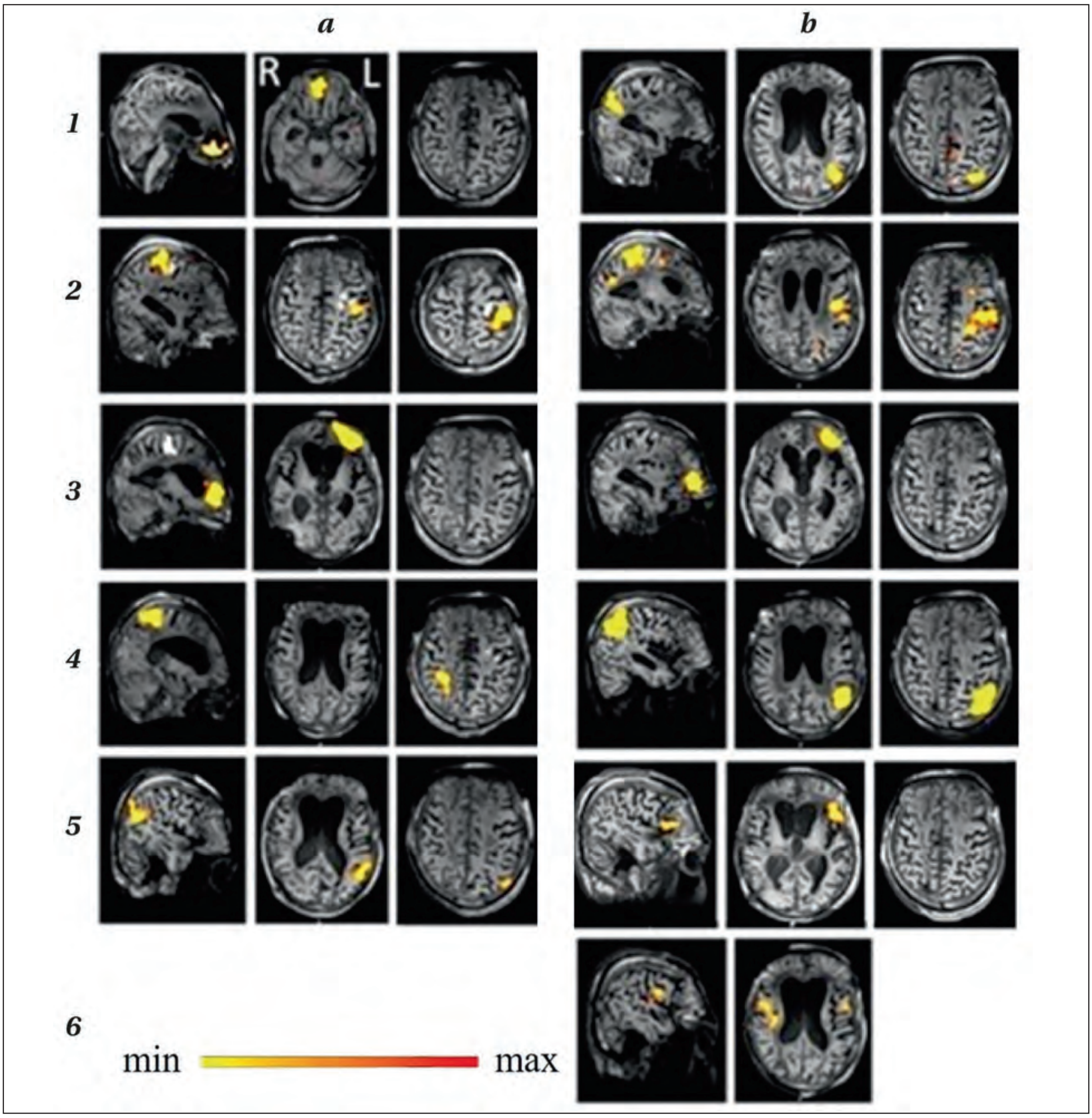

Fig. 4. Changes in RSN fMRI of patient Ya.
Note. *a* — before the rTMS course; *b* — after stimulation. RSN fMRI: *1* — DMN; *2* — sensorimotor; *3* — executive functions; *4* — fronto-parietal; *5* — speech; *6* — auditory.

of the auditory network with its bilateral components (Fig. 4, *b 6*). The intensity of the majority of the network signals visually manifested itself without pronounced changes, but with a trend toward a quantitative decrease after rTMS (Table 2). Only for the left frontoparietal network did this parameter increase.

Discussion

In all three patients with PCU states, resting fMRI networks significantly differed from normal ones both in the number of RSNs detected (reduced quantity) and in their spatial organization. They were asymmetric and had abnormal temporal synchronization of the activity of intra-network components. These results agree with the available literature data [32, 35]. Characteristic abnormalities also include the reduction in some network components, primarily cortical ones, while stem and basal components remain intact [36]. The lowest number of RSNs was detected in patient M., who was in a vegetative state before rTMS. In two ceses with akinetic mutism, the network abnormalities

Table 2. Maximal intensity of RSN fMRI before and after stimulation.

Patient	Network											
	DMN		Sensorimotor		Salience		Frontoparietal		Temporal		Speech	
	before	after	before	after	before	after	before	after	before	after	before	after
M.	11.3	17.8	13	19.1		10.3		12.8	9.4	14.3		14.3
B.	11.4	29.6	15.7	20.4	12	17.4	21	30.7		9.4	9.2	15.4
Ya.	22.2	18.6	15.7	14	33.3	11.2	12.5	20.7		11.3	11.3	10.8

mainly concerned spatial organization of the cortical components, which had been previously reported in the literature [37].

These topographic network abnormalities were essentially similar in patients B. and Ya. who were in the AM before rTMS, but with different stimulation efficiencies. In this regard, the results of the study, as well as our earlier evaluation of fMRI motor network connectivity [38], indicate significant diagnostic yield of resting fMRI parameters. The combination of fMRI recorded at rest and during any activity seems to be more efficient for prognostic purposes [38, 39]. In this study, rTMS served as test activation to a certain extent.

The common effects of rTMS in all patients include greater reactivity of the left hemisphere, regardless of the lateralization of the predominant brain lesion in patients with STBI (which we previously observed in healthy subjects as well [17]) and marked functional changes primarily in the components close to the stimulation areas (left frontal and anterior temporal areas) which were significant for the formation of almost all of the RSNs studied.

Positive neural network effects of rTMS, accompanying improvement of M. and B. patients to MCS+, manifested as a trend to normalization of spatial organization of RSNs significant for PCU state. This normalization included simultaneous synchronisation of all components with one network and appearance of networks not detected before stimulation (probably «sleeping» in lower levels of consciousness). Mainly it concerns bilateral activation of symmetric frontal or motor areas, as well as frontal and parietal regions of the left hemisphere. We believe that these changes are caused by restoration of some interhemispheric and extended intrahemispheric (fronto-parietal, etc.) functional connections. Significance of these functional and structural connectivities for development and regression of PCU was shown in several multidisciplinary studies [40–43]. Quantitatively confirmed Increase in intensity of resting networks after a course of rTMS was revealed in patients with a positive clinical effect of rTMS (qualitative improvement of the status). However, the assessed RSN fMRI «total volume» parameter did not change in parallel with the clinical evolution.

A qualitative improvement in the consciousness of patient M., who had a short-term course of rTMS early after traumatic brain injury while receiving continuous drug therapy, was remarkable. This result indicates the promising use of rTMS to activate the natural processes of neuroplasticity. Additional placebo-controlled studies are required to clarify the effect of rTMS in accelerating recovery in the early posttraumatic periods.

Less prominent consciousness recovery in patient Ya. (within the MCS-level) was manifested by activation of additional neural network components of the RSN without normalization of the spatial organization of each network (i. e., without signs of restoration of extended intrahemispheric connectivity), but with activation of symmetrical components of the temporal network, reflecting probable restoration of individual interhemispheric connections.

The feasibility of functional cerebral interactions development is largely determined by the morphology of the STBI, i. e., the conduction pathways and brain substance [44], which is confirmed by MRI data from the above patients. In this regard, the timing after injury is crucial. The striking clinical and neural network positive result of rTMS was shown in patient M. early after the STBI. Stimulation of patient Ya. 4.5 years after trauma has been the least effective.

Conclusion

Therapeutic rTMS of the frontal hemispheres can activate resting neural networks or their individual components with a tendency to normalize the RSN topology.

Our observations showed the promise of rTMS as a therapeutic intervention, as well as the feasibility of using RSN fMRI for diagnostic purposes in PCU following STBI.

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