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fMRI Reactions in Motor Tasks Performed by Patients with Traumatic Brain Injury

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Abstract—The study included 22 healthy right-handed subjects (age 25.1 ± 3.9) and 9 patients with traumatic brain injury (TBI) (age 27.9 ± 7.3) without hemiparesis and local lesions in the sensorimotor cortex. The hemodynamical brain reactions were analyzed using functional magnetic resonance imaging (fMRI) during right- and left-hand movements. It was shown that reactive changes of responses have larger interindividual variability of the main topographic activation areas during left-hand movements as compared with right-hand movements in healthy subjects. In the TBI patients, the diffuse component of reactive changes was increased and involved a larger number of brain structures, both cortex areas and subcortical formations, including areas nonspecific for the motor analyzer. These changes were most clearly expressed in the dominant hemisphere (during movement of the right hand).

Keywords: fMRI, traumatic brain injury, right- and left-hand movements

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An important aspect in studying mechanisms of the brain function and its plasticity is analysis of reactive rearrangements in various types of pathology. Traumatic brain injury (TBI) is one of the most common forms of cerebral pathology, which is most frequent among young people of working age and results from road traffic accidents, sports injuries, etc. The statistics indicates that in Russia TBI affects about 600000 people annually; 60000 cases of these are the most severe and lead to social disadaptation of young people [1].

Post-traumatic disorders are typically multi-component and involve multiple injuries to conductive pathways, cortical and subcortical structures [2]. An important feature of TBI is frequent development of diffuse axonal injury [3], which slows down or completely arrests signal transmission along the conductive pathways [4, 5]. According to modern views, disintegration is a significant pathogenetic factor of TBI [5]. Therefore, TBI sequelae are frequently associated with disorders in various fields of human activity, including cognitive, emotional, and motor ones (e.g., post-traumatic hemiparesis). It is known that, even in the absence of apparent neurological disorders and hemiparesis, patients can experience various difficulties during quite a long period after the injury, e.g., in execution of professional activities [6]. However, the neurophysiological mechanisms of these disorders have not been studied sufficiently and require special research.

Many studies on the molecular and cellular mechanisms of brain function recovery following TBI and other injuries have been conducted in recent years. Some of the disintegrative processes developing in the brain after TBI are reversible and can be restored spontaneously due to the neuroplasticity potential of the brain [7, 8]. The effect of specific rehabilitation approaches, including active motor activities or their combination with cognitive activities, can facilitate the recovery of complete interaction between brain structures [9, 10]. It is possible that enhanced neurogenesis in conjunction with restoration (or involvement) of additional conductive pathways promotes functional recovery after TBI [11, 12].

Currently, different approaches are used to assess the functional state of the human brain in the norm and various forms of pathology. Electroencephalography is one of the first methods that began to be actively used in clinical practice. Advancement of new medical and neuroscience technologies has led to the popularization of neuroimaging techniques, which enable real-time monitoring of the processes occurring in the brain. Functional magnetic resonance imaging (fMRI) is neuroimaging technique that provides a high 3D resolution. fMRI analyzes the changes in blood oxygenation in activated brain regions during task execution and depicts the exact level of engagement of different cerebral structures in the implementation of a function [13–15]. Most studies that used fMRI were performed on healthy subjects and extended our understanding of the structural features involved in the reactive rearrangements of the human brain during implementation of various functions. For example, previous studies analyzed the hemodynamic brain reactions to motor tasks in healthy people [16–19]. In healthy subjects, the greatest locality and reproducibility of fMRI responses was detected during fist clenching compared to other motor tasks, such as fingerpicking [18]. Therefore, this motor paradigm was used as the most adequate in the study of patients with TBI.

The use of fMRI in the study of patients with TBI offers new opportunities for investigating the functional anatomy of the brain in TBI. Previous studies analyzed reactive fMRI rearrangements for the right hand in patients with TBI without hemiparesis [20]. In this study, the task was to compare the features of reactive rearrangements during the dominant and non-dominant hand movements by healthy subjects and then on the basis of these data to study the nature of these rearrangements in patients with TBI. Importantly, an analysis of hemodynamic rearrangements in patients without hemiparesis, without local lesions in the sensorimotor cortex and in other parts of the brain presents a particular interest since hemodynamic rearrangements represent an adequate model for studying the dynamics of development and recovery of cerebral functions in patients with traumatic brain injury. Furthermore, such analysis provides understanding into the basic mechanisms of brain injury in TBI. The available literature typically analyzes fMRI data for patients with more severe disorders, including hemiparesis. Therefore, the aim of this paper was to study the features of reactive rearrangements in fMRI responses during the right and left hand movements in patients with TBI without hemiparesis compared to healthy subjects.

MATERIALS AND METHODS

This study included 20 healthy subjects (11 men and 9 women; the mean age was 25.1 ± 3.9 years). The group of patients included 9 subjects with TBI (6 men and 3 women, with a mean age of 27.9 ± 7.3 years) with the dominant right hand, without hemiparesis or local lesions in the sensorimotor cortex or other parts of the brain and without impaired consciousness at the moment of study. The prevalence of men in the group of TBI patients over women is consistent with the Russian and international statistics for patients with TBI [1]. Three patients of the total patient number had signs of mild destruction on MRI in the left hemisphere; three patients, in the right hemisphere; and three other patients, in both hemispheres. According to the Annett Hand Preference Questionnaire, all subjects were right-handed. Each subject signed an informed consent for the study approved by the Ethics Committee at the Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences. The patients were examined and treated at the Burdenko Neurosurgical Institute.

The fMRI study was performed with the eyes closed using a General Electric Signa HDxt MRI scanner (United States) with a magnetic field of 3 T. The functional test was fist clenching-unclenching separately by the right and left hands. The data were recorded according to the block paradigm consisting of alternating periods of rest and a motion test with a length of 30 s. The results of five tests were averaged. fMRI data were processed using the SPM8 software on the basis of Matlab R2014a individually and for the groups. Movement artifacts were corrected based on the generalized linear model (GLM). Statistical thresholds at the voxel level $p < 0.001$(*unc.*) were used to construct individual activation maps with corrected threshold of cluster significance level p(*FWE-corr*) < 0.01. The data were averaged for a group using one-way one-sample *t*-test. Two-sample *t*-test was used to compare independent samples with each other. Statistical thresholds at the voxel level $p < 0.001$(*unc.*) with corrected threshold of cluster significance level p(*FWE-corr*) < 0.05 were used to analyze activation maps separately for each group. When comparing groups of patients with TBI and healthy subjects, voxel threshold corresponded to $p < 0.001$(*unc.*) with corrected threshold of cluster significance level p(*FWE-corr*) < 0.01.

The activated areas were verified, their spatial location (*MNI*-coordinates) and volume of activation in voxels (Vox) were identified using the Automated Anatomical Labeling (AAL) application based on Matlab R2014a [19]. The structures in resultant tables were combined into larger structural and functional units. For example, the motor area included the gyrus precentralis and paracentral lobula; the frontal area included the frontal sup., supramargina, frontal mid., etc. The volumes of activated brain areas were compared between a group of healthy subjects and patients with TBI using the Statistica 6.0 software and Student's *t* test. In case of significant changes, the normalized increase in volumes in % was estimated for patients with TBI compared to healthy subjects.

RESULTS

Group analysis of hemodynamic changes in the brain in healthy subjects (Fig. 1a) showed that fist clenching by the right hand mainly activates (1) the sensorimotor cortex of the hemisphere contralateral to the working hand in the precentral and postcentral

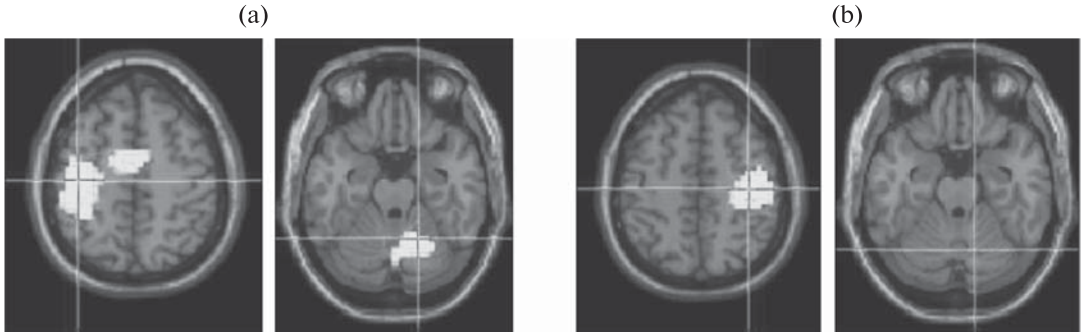

Fig. 1. Average fMRI responses for a group of healthy subjects in the (a) right- and (b) left-hand movements. $n = 20$, $t = 3.53$; $p(unc) < 0.001$, with cluster correction for multiple comparison $p(FWE\text{-}corr) < 0.05$.

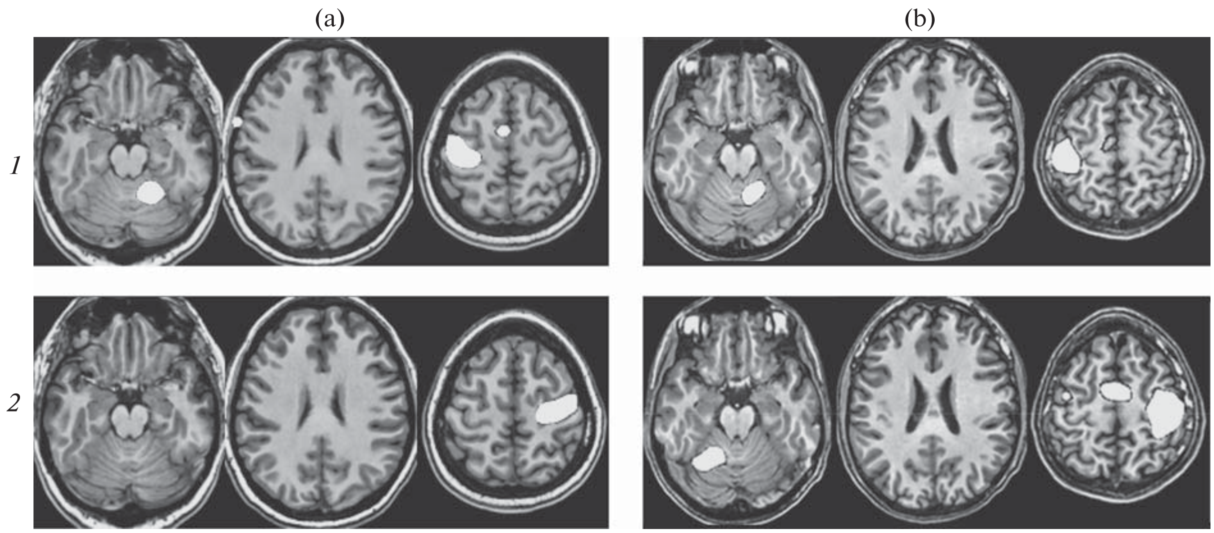

Fig. 2. Individual fMRI responses in healthy subjects in the (a) right- and (b) left-hand movements. (*1*) subject Shch.; (*2*) subject G. The other designations are the same as in Fig. 1.

gyri, (2) the supplementary motor area located in the medial parts of the superior frontal gyrus, and (3) the ipsilateral hemisphere of the cerebellum and the vermis. An analysis of the group mean fMRI responses in the left hand movement (Fig. 1b) revealed only one main activation area in the sensorimotor area of the contralateral right hemisphere. An explanation can be that individual fMRI responses are characterized by greater variability when moving the nondominant left hand than fMRI responses occurring in the right hand movement (Fig. 2). Some subjects do not have an activation area in the ipsilateral hemisphere of the cerebellum, while the sensorimotor cortex of the ispilateral hemisphere and the supplementary motor area were activated in other subjects. Noteworthy, an activation area was revealed in individual fMRI responses in most subjects in the ipsilateral hemisphere of the cerebellum but volumes and locations of the activation area were different.

Comparison of fMRI reactions between a group of patients and healthy subjects revealed the greatest differences in movement of the right dominant hand (Fig. 3a). A diffuse component of fMRI responses was present in group of patients, while the responses were more local in healthy subjects. Moreover, the subcortical structures and various nonspecific cortical areas of the contralateral hemisphere, which are not common for the motor response in the norm, were significantly more involved in responses in patients with TBI compared to healthy subjects.

The left hand movement in general caused no significant differences in fMRI responses between the group of TBI patients and healthy subjects (Fig. 3b). However, slight differences were observed in the occipital cortex and subcortical structures. Furthermore, the volume of fMRI responses was slightly higher in the group of patients compared to healthy subjects.

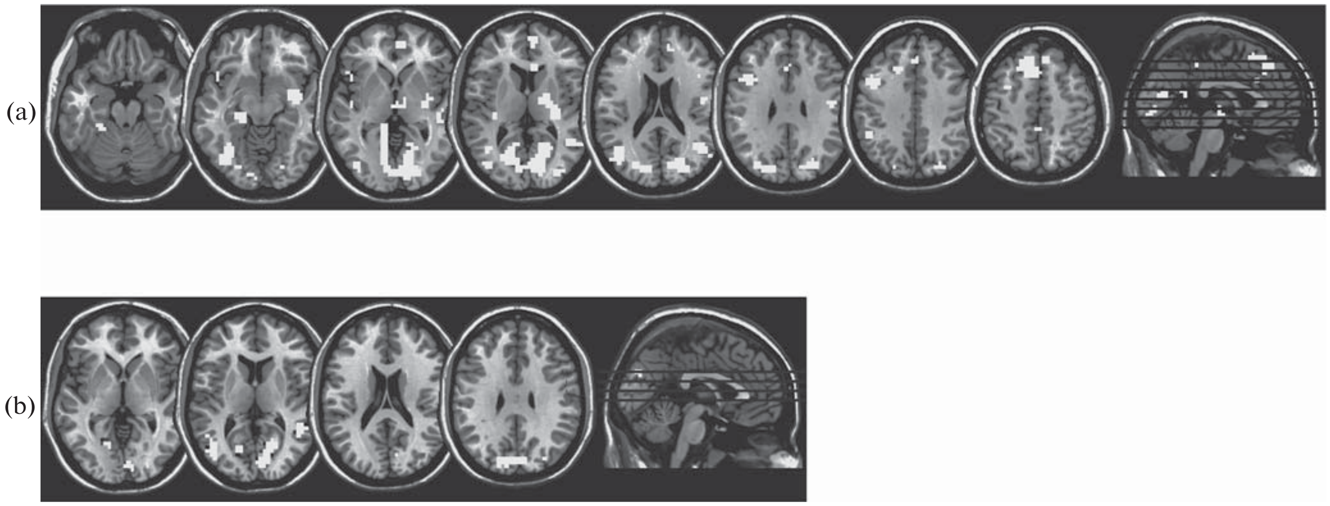

Fig. 3. Comparison of fMRI responses the (a) right- and (b) left-hand movements in TBI patients compared to healthy subjects. For the right hand, the comparison was performed at $p(unc) < 0.001$ and cluster correction for multiple comparisons $p(FWE\text{-}corr) < 0.01$ (patient group > group of healthy subjects). For designations, see Fig. 1.

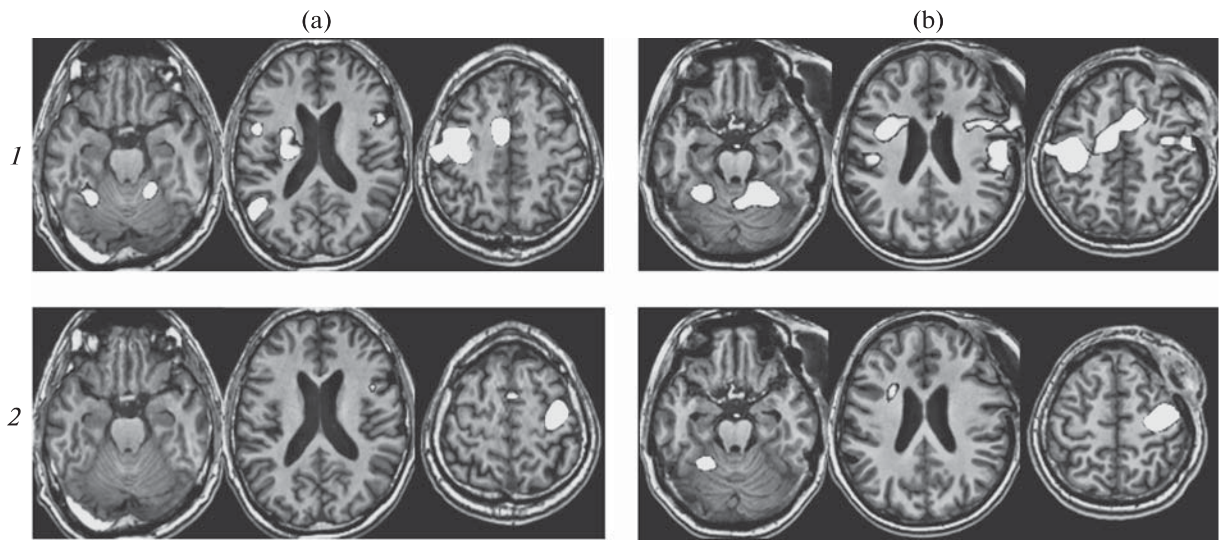

Fig. 4. Individual fMRI responses in patients with TBI in the (a) right- and (b) left-hand movements. (*1*) patient K.; (*2*) patient S. $p < 0.001(unc.)$ with cluster correction $p(FWE\text{-}corr) < 0.01$. For designations, see Fig. 1.

Individual fMRI responses in TBI patients exhibited high interindividual variation, but the diffuse form of brain response was detected in all patients, in contrast to healthy subjects, which was more distinctly expressed in movements of the right dominant hand (Fig. 4). In patients, execution of this task involved a larger number of cerebral structures compared to the norm; this effect was expressed both in the contralateral and ipsilateral hemispheres. A lower number of distinctive features were detected in fMRI responses in the left hand movement in patients with TBI compared to healthy subjects (Fig. 4b).

Statistical analysis of fMRI responses in different brain structures also showed the greatest changes in the contralateral hemisphere in the right hand movement. In patients, the volume of response from the motor cortex, the supplementary motor area, and the vermis was much larger than in healthy subjects. Moreover, areas such as the subcortical nuclei, thalamus, limbic system, and some areas of the cerebral cortex that are nonspecific for the motor analyzer (temporal and occipital) in healthy subjects were more involved in the patients (Fig. 5a-I, Table 1). In contrast, patients had a small increase in the volume of

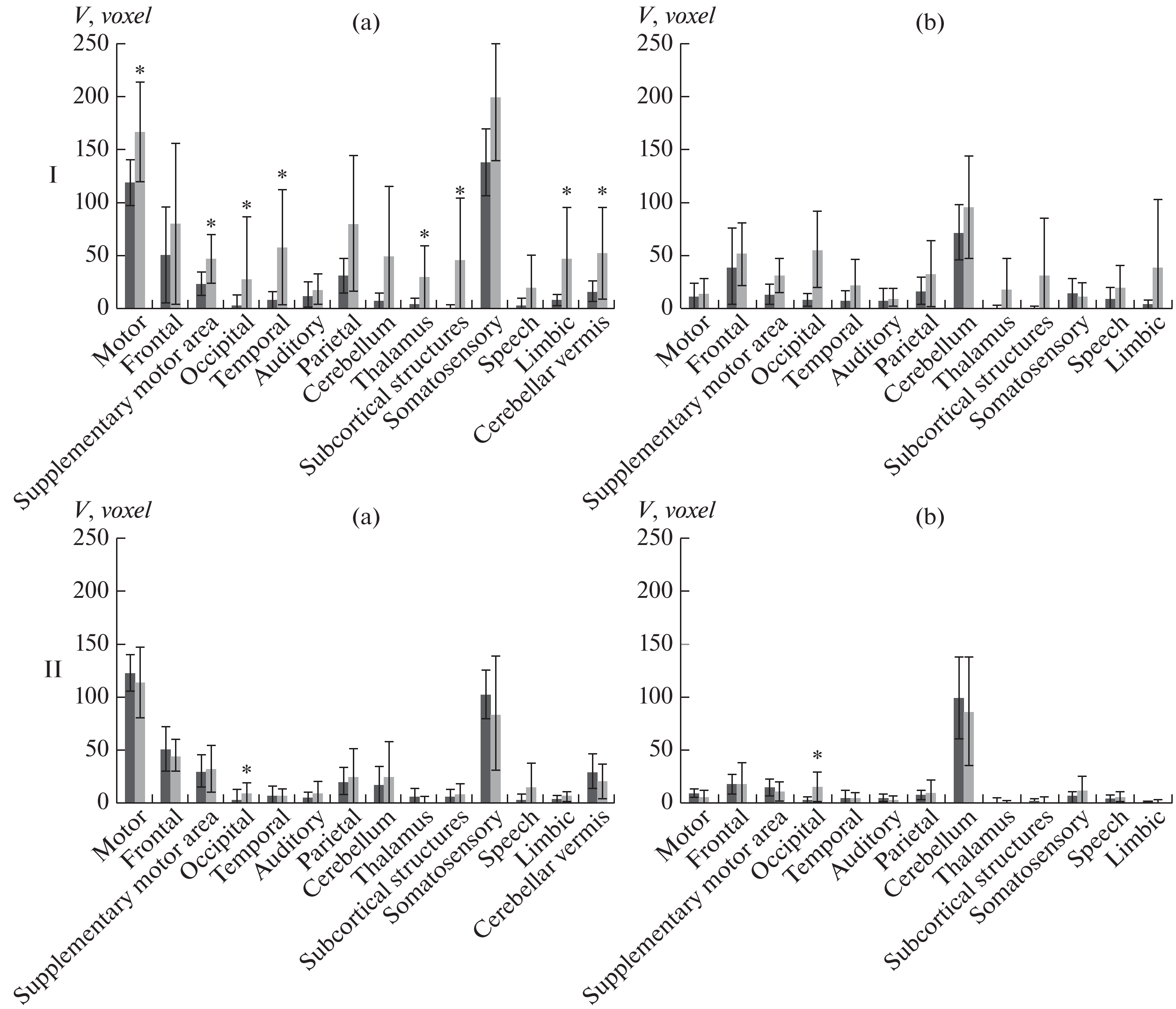

Fig. 5. Mean volumes of fMRI activation in some cerebral structures in patients with TBI compared to the norm. I, mean volumes of fMRI responses in the right hand movement; II, mean volumes of fMRI responses in the left hand movement; (a) contralateral hemisphere; (b) ipsilateral hemisphere; * $p < 0.05$. Black bars, healthy subjects; gray bars, patients with TBI.

fMRI response from many structures in the ipsilateral hemisphere but these differences were insignificant (Fig. 5b-I). In the left hand movement, the changes were insignificant in both the contralateral and ipsilateral hemispheres for most parts of the brain in patients compared to the norm; volume of fMRI responses significantly increased only in the occipital region of both hemispheres (Fig. 5, II, Table 2).

Furthermore, we estimated the degree of changes in patients with TBI compared to healthy subjects and the normalized increase in fMRI response volume for different areas of the cortex and subcortical structures (Tables 1 and 2). It was shown that, in patients, the changes in fMRI responses were more expressed in the subcortical structures and nonspecific cortex areas than in the cortical projection areas. Thus, in the right hand movement, volume of fMRI responses in the motor and supplementary motor areas of the contralateral hemisphere increased by 20% and 33%, respectively, in patients compared to the control group, and volume of fMRI responses from nonspecific cortical areas (temporal and occipital) and subcortical nuclei increased by 70% and 90% (Table 1). In the left hand movement, volume of fMRI responses in the occipital region of the contralateral and ipsilateral hemisphere increased by 80% and 70%, respectively, in patients with TBI (Table 2).

DISCUSSION

In healthy subjects, left hand movement produces a large interindividual variation of fMRI responses compared to the right-hand movement. It is assumed that movement of the left hand that is less common to

Table 1. Comparison of fMRI response volumes in different brain structures (in voxels) according to Student's test between healthy subjects and patients with TBI in the right hand movement (differences at the 5% level are shown)

Brain region	Mean for healthy subjects	Mean for patients	t	p	Normalized volume increase in %
Motor cortex (contralateral)	118.6375	166.5468	–2.07764	0.046703	20
Supplementary motor area (contralateral)	23.0411	46.8741	–2.11152	0.043464	33
Occipital cortex (contralateral)	7.2726	55.8213	–2.39719	0.023187	70
Temporal cortex (contralateral)	8.0861	57.6505	–2.68583	0.011844	70
Cerebellar vermis	15.9089	52.0101	–2.28924	0.029534	50
Thalamus (contralateral)	3.8184	28.7676	–2.31113	0.028132	75
Subcortical nuclei (contralateral)	1.5001	45.4359	–2.34546	0.026054	90
Limbic system (contralateral)	8.1834	46.7075	–2.38106	0.024048	70

Table 2. Comparison of fMRI response volumes in different brain regions (in voxels) using Student's test between groups of healthy subjects and patients with TBI in the left hand movement (differences at the 5% level are shown)

Brain region	Mean for healthy subjects	Mean for patient	t	p	Normalized volume increase in %
Occipital cortex (contralateral)	1.4539	9.3351	–2.52321	0.017367	80
Occipital cortex (ipsilateral)	2.6352	14.6665	–2.39777	0.023156	70

the right-handed subjects leads to less structural determinism in response formation.

An analysis of the hemodynamic changes in the brain during physical exercises in patients with TBI without hemiparesis revealed impairment in control of movements at multiple levels involving different cerebral structures upon TBI. The results of fMRI analysis in the patients revealed transition to a diffuse form of fMRI responses that involves more structures than in the norm. The transition from the local form of brain response to the diffuse form was noted earlier by other authors, e.g., in motor [19] and spatial [18] tasks in patients with TBI. Similar reactive changes were revealed in other forms of cerebral pathology, such as brain tumors [21, 22] and in patients with speech disorders of different origins [23].

Analysis of brain structures involved in motor task execution with the right and left hands in patients with TBI without hemiparesis showed that nonspecific cortical and, especially, subcortical structures were more involved in the patients than in healthy subjects. Probably, this reflects the specifics of the inclusion of compensatory processes necessary for motor tasks in patients with this form of cerebral pathology. According to Bechtereva, the central nervous system has both rigidly fixed functional connections and more flexible connections having significant degrees of freedom that are activated in pathology [24]; hence, it is assumed that the revealed features in the formation of reactive rearrangements in patients with TBI reflect a greater extent of compensatory engagement of the deep cerebral structures in rearrangements.

Interestingly, in this paper, in TBI with focal lesions without any specific location, the greatest structural and functional pathological changes were detected in the dominant hemisphere (as judged by handedness). A similar pattern was noted earlier for patients with strokes that were more likely to appear in the left hemisphere [25]. The left hemisphere was also the most sensitive to the effects of such adverse factors as low doses of radiation. For example, the hemispheric brain asymmetry decreased in young subjects involved in elimination of the Chernobyl disaster consequences compared to the age-appropriate norm. These changes occurred mainly due to a decreased left hemispheric functional state [26]. Furthermore, healthy right-handed subjects experience an age-related decrease in brain asymmetry mainly due to a reduced reactivity of the dominant left hemisphere [25]. The HAROLD hypothesis of aging (hemispheric asymmetry reduction at old age) of the human brain was proposed by Cabeza [27], which also explains the aging process of the human brain due to the predominant reduction of the left hemispheric functional activity.

Thus, the impaired reactive fMRI rearrangements in motor tasks in patients with TBI sequelae suggest that the cortical areas that represent the most recent structures of the brain are primarily affected by injury. Moreover, fMRI data indirectly indicate that the dominant left hemisphere is more affected in the right-handed subjects, a structure that is also ontogenetically younger compared to the right hemisphere. The data require further studies using different functional tasks and a more detailed study of structural

MRI. More research involving a larger group of subjects with TBI is needed for more evidences of the results. However, it is suggested yet at this stage of research that an increase in volume and number of activated brain structures in pathology can reflect the involvement of compensatory processes necessary for motor function execution in patients with TBI sequelae.

In summary, it is suggested that in the right-handed subjects with TBI, the pathological fMRI response was most expressed in the dominant left hemisphere and the changes of fMRI responses occurred in a larger number of brain structures, both cortex areas and subcortical formations, including areas nonspecific for the motor analyzer. This agrees with the results of other studies and confirms the idea on general biological nature of the response in ontogenetically younger brain structures to adverse environmental factors.

CONCLUSIONS

(1) In healthy subjects, a large interindividual variability of the topography of the main activation areas in fMRI responses was revealed in the left-hand movement compared to the right-hand movement.

(2) In right-handed patients with TBI, the diffuse component of reactive changes was increased and involved a larger number of brain structures, both cortex areas and subcortical formations, including areas nonspecific for the motor analyzer. These changes were most clearly expressed in the dominant hemisphere (during movement of the right hand).

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