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# Methodical Approach to fMRI Assessment of Motor Connectome in Patients After Severe Traumatic Brain Injury

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## Summary

**The aim of the study**. To identify alterations of motor connectome in patients with varying degrees of hemiparesis after severe traumatic brain injury (TBI) versus healthy volunteers.

**Material and methods.** The study included 29 patients with TBI aged 18 to 35 years and 23 healthy volunteers aged 20 to 32 years. Participants underwent a comprehensive clinical and neuroimaging study. Motor impairment was evaluated via muscle strength assessment using a five-score scale. The fMRI data were processed using a dedicated CONN software package. Anatomical 3-D connection masks of the whole brain motor functional system in the predetermined regions of interest (ROIs) were used for the assessment. Then the group indicators of functional connectivity (statistical significance of the connection) were computed.

**Results.** It was established that the structure of connections in healthy individuals performing active movement with the right (leading) hand is determined by formation of focus in the cortical and subcortical ROIs in the contralateral hemisphere. With passive movement of the right hand the pale ball becomes functionally active in addition to the activated areas. The striopallidar system structures became active on both sides, and connectivity with the additional motor cortex and the motor cortex of the ipsilateral hemisphere emerged as the paresis increased during active movement. The focus of motor activity during passive movement was determined in the motor cortex and putamen, which makes it possible to use a passive test in patients with gross motor disorders or unconsciousness for a full assessment of the entire structural and functional brain connectome.

**Conclusion.** As hemiparesis increased in patients after severe traumatic brain injury, a decrease in the total number of connection appeared; simultaneous engagement of ancient primordial structures, such as bilateral activation of pale globes, demonstrated neuroplasticity.

***Keywords: traumatic brain injury; chronic critical illness; pathogenesis of motor connectome impairment; neuroplasticity***

**Conflict of interest.** The authors declare that there is no conflict of interest.

**Founding.** The study had no sponsorship.

## Introduction

Advances in critical care medicine improve patient survival even after severe traumatic brain injury (TBI) [1–4]. However, TBI is associated with severe impairment of movement, cognitive function and memory, alterations in the immune system, prolonged disorders of consciousness and the autonomic nervous system [1, 5–7]. The study of the function of cerebral systems is important both for the exploration of the pathogenesis of motor dysfunction and compensatory mechanisms [8, 9] and for the development of neurorehabilitation methods for patients after severe TBI [10, 11], including those in chronic critical illness with prolonged reduced consciousness. Functional magnetic resonance imaging with assessment of functional connectivity between specific regions is a contemporary diagnostic method for motor disorders [12, 13]. The advantages of this approach include the standardization of the «regions of interest» and the quantification of the connectivity parameters, which can be measured in the range from –1 to +1 [12]. This allows for a wide range of comparisons of group data regardless of the morphological characteristics of the brain. According to the literature, the parameters obtained from fMRI data can serve as markers of neuronal activity [14, 15]. Therefore, studying the connectivity of the motor functional system is a promising way to assess the survival of components of the human brain motor system after TBI.

The aim of the study was to identify changes in the patterns of the motor function system in healthy subjects and patients with varying degrees of hemiparesis after severe traumatic brain injury (TBI).

## Materials and Methods

Fifty-two subjects who met the inclusion criteria and had no exclusion criteria were included in the study (Fig. 1). The study was retrospective and observational.

Inclusion criteria:

— traumatic brain injury occurring 1-6 months earlier;

— right-sided hemiparesis;

— ability to follow instructions;

— right-handedness according to the Annette questionnaire [11].

Exclusion criteria:

— low level of consciousness;

— infectious complications and signs of acute infection;

— any contraindication to functional MRI and EEG;

— metal elements in the examined area (prostheses, clips, splinters);

— inappropriate patient behavior, such as panic attack, psychomotor agitation;

— inability to remain motionless during the examination;

— the need for continuous intensive care;

— the need for continuous monitoring of parameters such as ECG, blood pressure, respiratory rate.

Table 1 shows the general characteristics of the patients studied.

Patients were treated at the Neurotrauma Department of the N. N. Burdenko Scientific and Research Center for Neurosurgery. An fMRI study was performed simultaneously with the clinical examination.

The clinical observation included a comprehensive neurological examination. The level of consciousness was determined according to the Glasgow Coma Scale [16], using a five-point scale to assess movement disorders [17]. Right-sided hemiparesis in right-handed patients was chosen as a model because the majority of the population is right-handed and the function of the dominant and non-dominant hand differs in functional MRI characteristics in healthy subjects [19]. The focus was on the function and compensation mechanisms of the dominant hemisphere.

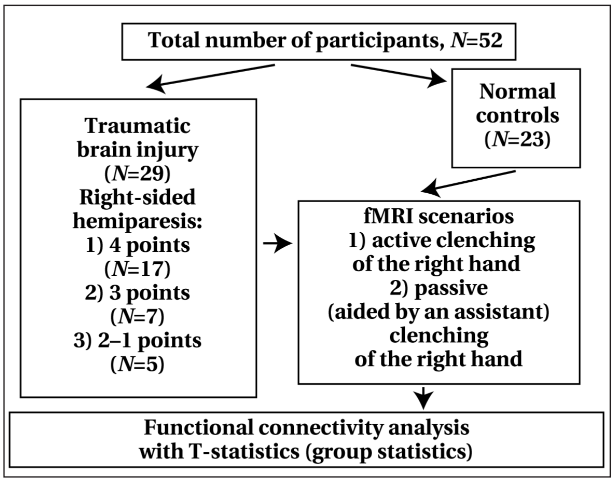


**Fig. 1. Flowchart of the study.**

Each participant underwent structural magnetic resonance imaging (MRI in T1 and T2 modes) and fMRI on a 3.0 Tesla GE Healthcare (General Electric, USA) magnetic resonance tomograph at the Department of X-ray and Nuclear Imaging of the Burdenko Scientific Research Center. The 3D FSPGR pulse sequence (BRAVO) was used to obtain structural data in the whole brain volume. The following parameters were used: 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, while an echoplanar sequence was used to obtain functional data. Spin echo (BOLD T2) had the following characteristics: 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 acquired, each containing 24–40 axial sections covering the entire brain. The scan time per functional volume was 2 seconds. The total number of slices in a functional series was 7000–12000. The signal-to-noise ratio was 1.0.

The fMRI with motor tests was performed with the subject's eyes closed using a block paradigm consisting of alternating periods of rest and movement, each lasting 30 seconds. The results of five repetitions of each test were averaged. Motor artifacts were corrected using a generalized linear model (GLM). The fMRI data (+BOLD response) were

**Table 1. Patient characteristics.**

| Parameter | Right-sided hemiparesisHealthy subjects | | | | Healthy subjects | P |
|---|---|---|---|---|---|---|
| | Total patient cohort | 4 points | 3 points | 2–1 points | | |
| Number of patients | 29 | 17 | 7 | 5 | 23 | |
| Age, years | 33±5.6 | 29±5 | 35±7 | 30±3 | 23.5±8 | 0.09 |
| Sex | M — 19, F — 10 | M — 10, F — 7 | M — 5, F — 2 | M — 3, F — 2 | M — 14, F — 9 | 0.15 |
| Consciousness level on CRS scale | Full 100% | Full 100% | Full 100% | Full 100% | Full 100% | |
| Average time after traumatic brain injury (days) | 46±13 | 35±7 | 52±8 | 32±10 | n/a | 0.07 |
| Right-handedness | 100% | 100% | 100% | 100% | 100% | |

processed according to a uniform protocol using SPM8 software in Mathlab 7.0 and Brainwave.

Two experimental situations were considered: an active test in which the fingers of the right hand were independently clenched/unclenched into a fist on command, and the performance of this movement with the help of an assistant. Each subject was instructed to remain in a quiet position. A structural MRI was also performed during the study to determine the comparability of the study groups. The study lasted 10 minutes and 12 seconds. A command was given (to the patient or assistant) to clench the hand into a fist for 30 seconds with a 30-second pause, and the subject performed 10 such series during the study.

Statistical analysis and connectivity construction were performed between the regions of interest (ROI) defined by the researcher. All obtained and saved ROIs in NIFTI format were transferred to MATLAB\toolbox\SPM\toolbox\CONN\rois system disk. The construction of functional relations was carried out in the CONN (Connectivity Toolbox) software based on MATLAB. This software allows to build graphical, 3D and 2D models of brain connectivity, as well as to estimate the strength, polarity and significance of connections. To determine the significant level of functional interaction between each pair of ROIs, we used Pearson correlation analysis followed by application of Fisher's bivariate transformation. Two-sample Student's t-test was used for intergroup analysis. The threshold of statistical significance was $P<0.05$ with correction for multiple comparisons.

The «mask» was designed based on literature data on subcortical and cortical support of voluntary movement [18], taking into account the multifaceted and multidirectional relationship of subcortical structures, as well as the density of the location of these entities. It combined all structures of interest: putamen, caudate nucleus, globus pallidus, precentral gyrus, amygdala, inferior frontal gyrus, supplementary motor cortex and cerebellum, thalamus, hippocampus. The connectivity of this mask was assessed in healthy subjects and patients with severe traumatic brain injury while performing active and passive right hand movements during an fMRI examination. Figure 2 shows the localization of the regions of interest between which functional connectivity was examined.

Given the multicomponent nature of this mask, all ROIs were grouped into networks reflecting their specific contribution to motor activity.

Network 1 included the caudate nucleus, putamen, globus pallidus and hypothalamus. In addition to memory, it also performs encoding and perception of external space. The interaction of the neostriatum

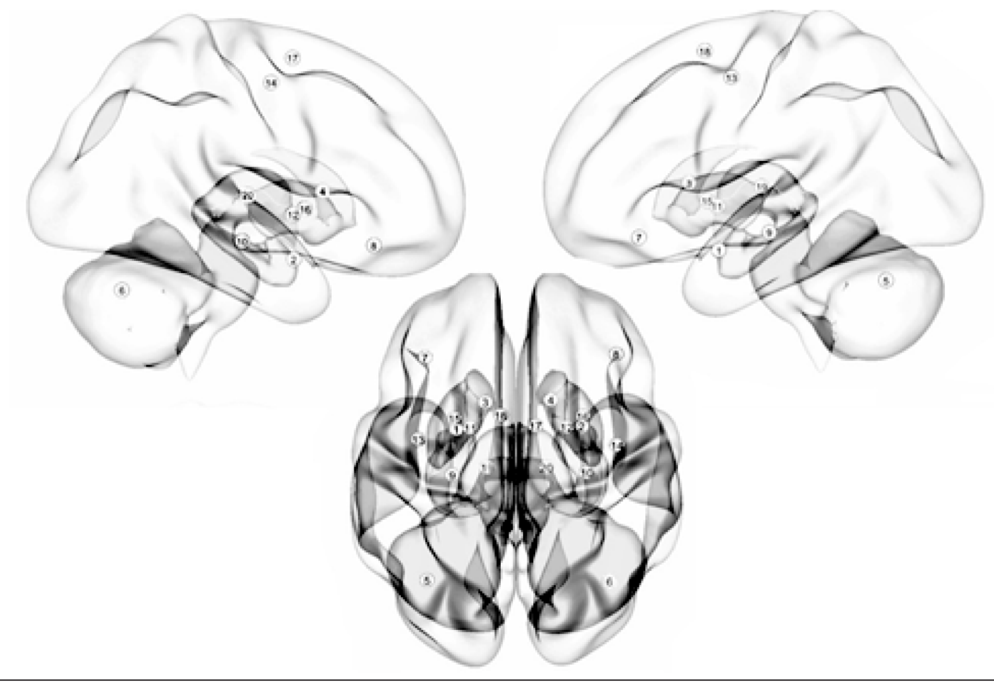

**Fig. 2. Scheme of «regions of interest» for the evaluation of fMRI connectivity in the system of subcortical support of voluntary movement.**

**Note.** «Regions of interest» according to the coordinates of the AAL atlas: 1 — left amygdala; 2 — right amygdala; 3 — left caudate nucleus; 4 — right caudate nucleus; 5 — left cerebellar hemisphere; 6 — right cerebellar hemisphere; 7 — left inferior frontal gyrus; 8 — right inferior frontal gyrus; 9 — left hippocampus; 10 — right hippocampus; 11 — left globus pallidus; 12 — right globus pallidus; 13 — left precentral gyrus; 14 — right precentral gyrus; 15 — left septum; 16 — right septum; 17 — right supplementary motor cortex; 18 — left supplementary motor cortex; 19 — left thalamus; 20 — right thalamus. Original drawing by the author.

**Table 2. Severity of paresis in traumatic brain injuries of various brain regions (according to structural MRI).**

| Damaged structure | Frequency of paresis development in structure damage, % | | | P |
|---|---|---|---|---|
| | Paresis 4 points | Paresis 3 points | Paresis 2 points | |
| Brainstem | 0 | 0 | 62.5 | >0.05 |
| Pons | 17 | 0 | 50 | >0.05 |
| Left cerebral peduncle | 0 | 0 | 25 | >0.05 |
| Right cerebral peduncle | 17 | 20 | 25 | >0.05 |
| Both peduncles | 0 | 0 | 25 | >0.05 |
| Corpus callosum | 33 | 20 | 50 | >0.05 |
| Right thalamus | 0 | 20 | 12.5 | >0.05 |
| Left thalamus | 0 | 0 | 12.5 | >0.05 |
| Right subcortical nuclei | 33 | 0 | 37.5 | >0.05 |
| Left subcortical nuclei | 33 | 0 | 37.5 | >0.05 |
| Basal areas | 0 | 20 | 50.0 | >0.05 |
| Right frontal lobe | 50 | 60 | 87.5 | >0.05 |
| Left frontal lobe | 50 | 60 | 87.5 | >0.05 |
| Right parietal lobe | 33 | 80 | 62.5 | >0.05 |
| Left parietal lobe | 33 | 40 | 62.5 | >0.05 |
| Right temporal lobe | 50 | 60 | 62.5 | >0.05 |
| Left temporal lobe | 33 | 60 | 87.5 | >0.05 |
| Right occipital lobe | 17 | 20 | 37.5 | >0.05 |
| Left occipital lobe | 0 | 0 | 50 | >0.05 |
| Diffuse axonal injury | 33 | 20 | 87.5 | >0.05 |

(caudate nucleus and putamen) and the paleostriatum (globus pallidus) allows the maintenance of position at rest. Thus, this network integrates subcortical structures of the motor functional system (MFS), which are functionally related to the maintenance of a certain posture in space.

Network 2 included thalamus, hippocampus, inferior frontal gyrus — structures of mesolimbic part of dopaminergic system and sites of its projection to cortex. In the motor system they form the afferent cluster.

Network 3 included precentral gyrus, caudate nucleus, putamen, amygdala, globus pallidus, which are part of extrapyramidal and motivational systems. Thus, this network contains MFS components responsible for voluntary state of rest or coordinated movement and motivation.

Network 4 included the precentral gyrus, supplementary motor cortex, amygdala and cerebellum, which are the components of the MFS that directly provide the precise motor act.

Paired $t$-statistics based on the selection of appropriate covariance matrices were used to analyze functional connectivity. A color scale was used to conveniently display the direction of connectivity. The color scale corresponded to the effect size ($T$-value). That is, the color indicated the highest significance, and deviations from red or blue indicated the «direction» of activation. Red was positive and blue was negative.

The studies were conducted in accordance with the principles of the Declaration of Helsinki, after obtaining informed consent from the subjects and approval from the ethics committees of the relevant institutions and the Scientific Research Center of Neurosurgery.

## Results and Discussion

First, we analyzed the fMRI connectivity of the motor functional system of healthy subjects during active and passive movements of the right hand in healthy subjects. In Fig. 3 they are shown as schematic diagrams reflecting the level of significant connections (p-FDR corr <0.05) between the specified regions of interest. Obviously, the performance of active movement (Fig. 3, *I*) is associated with the formation of a «focus» of functional activity that includes both cortical and subcortical structures. The correlation between the structures of the subcortical (caudate nucleus, septum, globus pallidus) and cortical (motor, supplementary motor cortex and inferior frontal gyrus) levels of the motor functional system was recorded.

The subcortical nuclei (caudate, septum) form most of the interhemispheric as well as intrahemispheric connections. The lack of symmetrical frontal interaction indicates that this movement is automated. At the same time, the large number of bilateral connections of the amygdala, whose main function is to induce action, attracted attention.

Passive movement in normal subjects (Fig. 3, *II*) is characterized by a greater number of connections of subcortical structures than of cortical ones in network 3 (Fig. 3, *II, b*). This fact indicates the crucial role of subcortical structures (caudate nucleus and globus pallidus) in the regulation of muscle tone. The activity of the cortical regions and the activation of the structures of the corticospinal pathway (motor cortex and supplementary motor cortex) confirm the assumption that this test can be used to verify the functional integrity of this pathway.

Table 3 shows the matching pairs of subcortical connections and their significance ($T$-value) for both studied scenarios of right hand movements, reflecting specific behavior of subcortical structures of the functional motor system. Of the 6 pairs, three (involving the caudate nucleus) showed a decrease in significance from the active to the passive test. This is most likely due to the fact that the passive test requires maximum relaxation, i. e., a conscious reduction of postural control. However, two amygdala connections had maximum significance during the active movement compared to the passive movement, reflecting the importance of motivation to perform the active movement. The largest number of connections was registered from the left globus pallidus area and the left motor cortex.

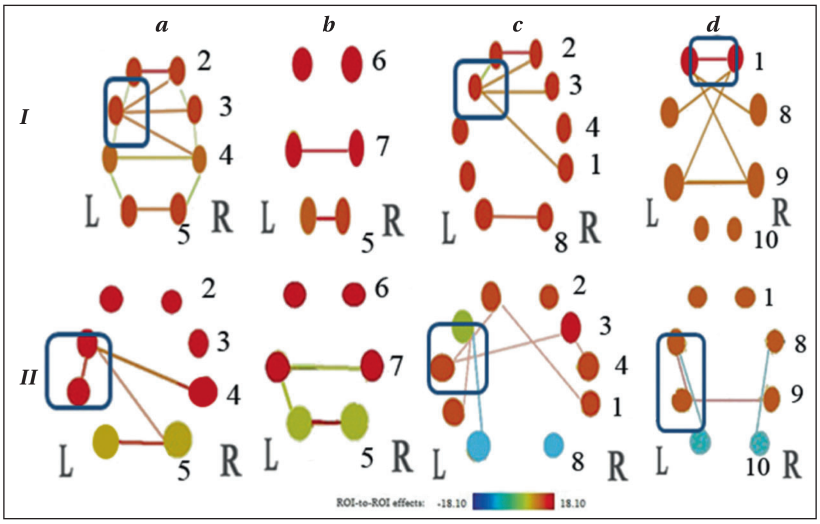


**Fig. 3. Functional connections of subcortical and cortical-subcortical segments of the motor functional system according to fMRI data.**
**Note.** *I* — with active right hand movement (*N*=23); *II* — with passive right hand movement (*N*=23). *a* — network 1; *b* — network 2; *c* — network 3; *d* — network 4. 1 — amygdala; 2 — caudate nucleus; 3 — cortex; 4 — globus pallidus; 5 — hippocampus; 6 — lower frontal gyrus; 7 — thalamus; 8 — motor cortex; 9 — supplementary motor cortex; 10 — cerebellum. Original drawing by the author.

In patients with TBI, the number of significant connectivity components of the MFS and changes in connectivity structure were found to decrease with increasing severity of hemiparesis compared to normal subjects during active movement of the right hand (Fig. 4). Thus, in patients with mild right hemiparesis during active movement of the paretic arm (Fig. 4, *II*), the putamen nuclei of both hemispheres were the foci of predominant subcortical activity, with a greater number of interactions on the right side (network 4, Fig. 4, *b*). The latter fact can be regarded as evidence for the involvement of the right subcortical nuclei in the compensatory activity. The interaction of the symmetric areas of the motor and supplementary motor cortices, as well as their bilateral connections, which are not normally seen, can also be attributed to this fact. In the group of patients with severe (3 points) right-sided hemiparesis who were able to move independently, the pattern of MFS connectivity (Fig. 4, *III*) showed a reduction of connections between the putamen and the caudate nucleus as well as motor cortical regions, predominantly left hemispheric ones (Fig. 4, *a, b, d*). Meanwhile, we detected an increase in connectivity, mainly of the globus pallidus (an older subcortical structure), both unilaterally to the left and diagonally with the subcortical nuclei of the right hemisphere. The connectivity of the left motor cortex and cerebellum, uncharacteristic of other groups, appeared (Fig. 4, *d*). We also tend to consider the above qualitative changes in the pattern of MFS connections as compensatory cerebral rearrangements [4].

As TBI is often associated with severe hemiparesis (2-1-0), as well as speech disturbances or reduced consciousness [1], the use of an active motor test to investigate the functional connectivity of the DFS is not feasible. However, a passive motor test is possible in all categories of patients. Therefore, we performed a comparative analysis of fMRI connectivity in groups of healthy subjects as well as in

**Table 3. *T*-statistics of matched pairs of connections at rest, during active and passive movement of subcortical connections in healthy subjects.**

| Area of analysis | Right hand movement | | | |
|---|---|---|---|---|
| | active | | passive | |
| | *T*-value | *P*-unc | *T*-value | *P*-unc |
| Left caudate nucleus — left globus pallidus | 5.51 | 0.0003 | 3.44 | 0.0003 |
| Left caudate nucleus — left putamen | 3.27 | 0.0085 | 2.56 | 0.0005 |
| Left amygdala — left putamen | 9.17 | 0.0002 | 8.17 | 0.0001 |
| Right caudate nucleus — right putamen | 4.35 | 0.0007 | 3.16 | 0.0003 |
| Right caudate nucleus — right globus pallidus | 2.22 | 0.0048 | 1.18 | 0.0032 |
| Right amygdala — right putamen | 5.59 | 0.0079 | 4.39 | 0.0029 |

**Note.** *T*-value is the cut-off point of *t*-distribution, a measure of significance recommended for use with samples of less than 30 subjects with an unknown standard deviation.

patients with mild, severe and gross right-sided posttraumatic hemiparesis using the system described above (Fig. 5).

Analysis of MFS networks during passive movement (Fig. 5) showed that connectivity in all groups was characterized by a slightly lower number of significant connections, especially cortical ones (Fig. 4, *d*), compared to active movement.

Furthermore, the pattern of rearrangements was similar to that of the active test, with denser connections (foci of activity) in the motor cortex and putamen. We also found specific changes in MFS connectivity that are characteristic of passive movement in patients with hemiparesis. For example, the role of the ipsilateral right motor cortex in the formation of cortical-subcortical connections was prominent in all hemiparesis groups (Fig. 5, *b*). In addition, we observed an increased importance of the left globus pallidus (paleostriatum), contralateral to the movement, in the formation of subcortical connectivity with increasing hemiparesis (Fig. 5, *a*). These features could also be considered a manifestation of compensatory neuroplastic rearrangements.

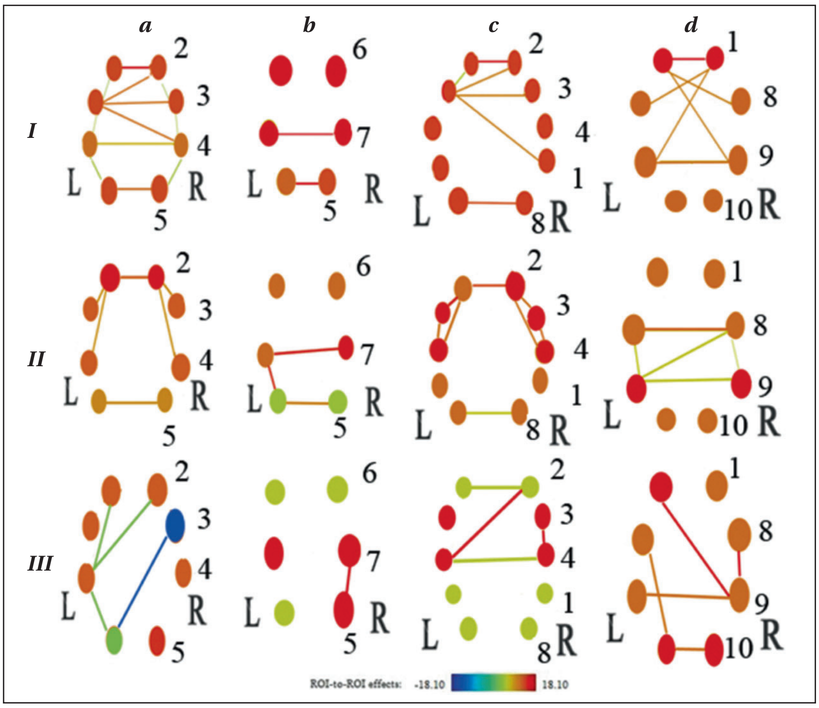


**Fig. 4. Important functional connections of subcortical and cortical-subcortical segments of the motor functional system during active movement of the right hand in healthy subjects and patients with TBI according to fMRI data.**

**Note.** *I* — healthy subjects (*N*=23); *II* — patients with mild right-sided posttraumatic hemiparesis, 4 points (*N*=18); *III* — patients with severe right-sided posttraumatic hemiparesis, 3 points (*N*=7). *a* — network 1; *b* — network 2; *c* — network 3; *d* — network 4. 1 — amygdala; 2 — caudate nucleus; 3 — cortex; 4 — globus pallidus; 5 — hippocampus; 6 — lower frontal gyrus; 7 — thalamus; 8 — motor cortex; 9 — supplementary motor cortex; 10 — cerebellum. Original drawing by the author.

In patients with mild hemiparesis, intrahemispheric lateralized interactions were found to be more significant than in normal subjects. Analyzing passive movements of the paretic right hand in the same group revealed a similar pattern of connectivity. However, connectivity between caudate nuclei and symmetric cortical areas (supplementary motor cortex, precentral gyrus) was more significant than during independent fist clenching (Table 4). With increasing paresis, a progressive reduction in the level of connectivity during active movement was observed. Meanwhile, a comparison of active and passive motor tests showed higher connectivity values during passive movement, which may reflect the functional capabilities of the motor system and, accordingly, functional integrity.

Our data confirm the informative value of passive motor testing in patients with gross motor impairment to assess functional motor integrity at any level [19, 20]. The results obtained are in

**Table 4. *T*-statistics of matched pairs of connections at rest, during active and passive movement of subcortical connections in the group of post-TBI patients.**

| | 4 points | | | | 3 points | | | | 2–1 points | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Active | | Passive | | Active | | Passive | | Active | | Passive | |
| Area of analysis | *T*-value | *P*-unc | *T*-value | *P*-unc | *T*-value | *P*-unc | *T*-value | *P*-unc | *T*-value | *P*-unc | *T*-value | *P*-unc |
| Lest septum — left thalamus | 6.44 | 0.0015 | 5.11 | 0.015 | 5.25 | 0.0045 | 12.50 | 0.0063 | 3.73 | 0.016 | 6.87 | 0.005 |
| Left septum — left caudate nucleus | 4.20 | 0.0015 | 3.90 | 0.0437 | 6.54 | 0.0028 | 12.59 | 0.0063 | 4.31 | 0.049 | 10.49 | 0.006 |
| Left caudate nucleus — right caudate nucleus | 8.54 | 0.0028 | 6.60 | 0.0066 | 5.19 | 0.052 | 12.15 | 0.006 | 6.51 | 0.005 | 13.87 | 0.033 |
| Left septum — left globus pallidus | 4.64 | 0.0049 | 3.59 | 0.0348 | 4.25 | 0.0025 | 10.70 | 0.0033 | 7.17 | 0.024 | 9.18 | 0.010 |
| Left supplementary motor cortex — right supplementary motor cortex | 12.83 | 0.004 | 10.15 | 0.006 | 6.74 | 0.002 | 14.5 | 0.006 | 10.3 | 0.004 | 16.22 | 0.024 |
| Right globus pallidus — right septum | 2.90 | 0.0518 | 1.19 | 0.0345 | 3.19 | 0.005 | 11.35 | 0.008 | 9.40 | 0.003 | 12.26 | 0.025 |

**Note.** The names of the structures are labeled according to the AAL atlas. *T*-value is the cut-off point of *t*-distribution, a measure of significance recommended for use with samples of less than 30 subjects with an unknown standard deviation.

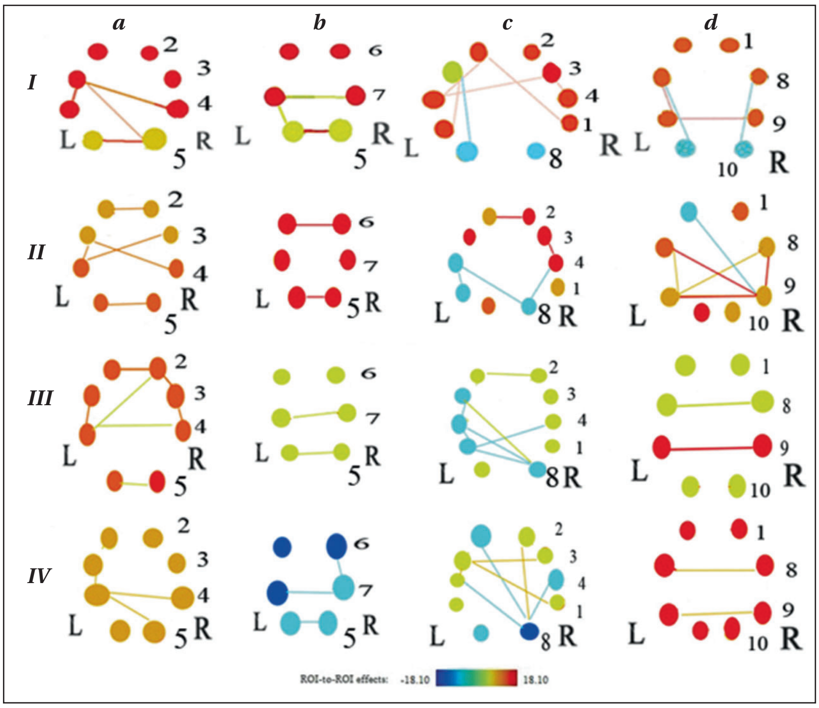


**Fig. 5. Significant functional connections of subcortical and cortical-subcortical segments of the motor functional system during passive movement of the right hand in healthy subjects and patients with CHMT according to fMRI data.**

**Note.** *I* — healthy subjects (*n*=23); *II* — patients with mild right-sided posttraumatic hemiparesis, 4 points (*n*=18); *III* — patients with severe right-sided posttraumatic hemiparesis, 3 points (*n*=7); *IV* — patients with severe posttraumatic hemiparesis, 1–2 points (*n*=5). *a* — network 1; *b* — network 2; *c* — network 3; *d* — network 4. 1 — amygdala; 2 — caudate nucleus; 3 — cortex; 4 — globus pallidus; 5 — hippocampus; 6 — lower frontal gyrus; 7 — thalamus; 8 — motor cortex; 9 — supplementary motor cortex; 10 — cerebellum. Original drawing by the author.

agreement with those of Hallett M. L. et al. [12], who showed that as the motor deficit worsens in patients with cerebral circulation impairment, the number of interhemispheric functional connections and intrahemispheric connectivity decreases, while the activity of bilateral areas of supplementary motor cortex increases. Our findings add to the current understanding of the main cortical response to the performance of active and passive tests, which is seen in the sensorimotor area of the contralateral hemisphere, the supplementary motor cortex, and the cerebellum [21–23]. An important feature of motor fMRI responses in patients with severe TBI, noted in many publications, is an increase in diffuse hemodynamic changes with activation of brain regions uncharacteristic of healthy individuals [24–27], whereas connectivity data suggest that this may be due to activation of subcortical structures.

## Conclusion

The obtained data on rearrangements of fMRI connectivity of the motor functional system significantly extend our knowledge of the pathogenetic relevance of movement disorders in traumatic brain disease. Patterns of motor system connectivity during right hand movement in normal subjects usually reflect the specific type of motor activity. With increasing hemiparesis in post-TBI patients, multidirectional changes in MFS connectivity were observed. On the one hand, the total number of functional connections decreased, and on the other hand, the involvement of older structures (globus pallidus) and ipsilateral regions was observed in response to the reduction of significant interhemispheric interactions. In our opinion, the revealed patterns represent compensatory pathways of neuroplasticity in patients after severe traumatic brain injury.

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