

Scope and Perspectives of Neuroimaging and Neurostimulation to Develop the Theory of Systemic and Dynamic Localization of Higher Mental Functions

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The theory of systemic and dynamic localization of higher mental functions by Lev Vygotsky and Alexander Luria was based on the data obtained via an original method, syndrome analysis of deficits of higher mental functions in patients with local brain injury. When this theory was being constructed, technical methods for brain investigation were only in their early stages. Although in later years Luria and his disciples pointed out that such methods were prominent for further development of Soviet/Russian neuropsychology, they are still rarely used by the followers of these scientists. In this article, we focus on neuroimaging and neurostimulation methods that are both noninvasive and the most accessible in Russia: structural, diffusion-weighted, and functional magnetic resonance imaging, as well as transcranial magnetic stimulation. We discuss their scope and perspectives for addressing research questions in neuropsychology and describe possible designs for neuropsychological studies in patients with local brain injury and healthy individuals.

Keywords: neuropsychology, Luria, neuroimaging, neurostimulation, theory of systemic and dynamic localization of higher mental functions, structural MRI, diffusion-weighted MRI, functional MRI, transcranial magnetic stimulation.

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Возможности методов нейровизуализации и нейростимуляции для развития теории системной динамической локализации высших психических функций

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Теория системной динамической локализации высших психических функций была разработана Л.С. Выготским и А.Р. Лурией на основе данных, полученных с помощью оригинального метода — синдромного анализа нарушений высших психических функций у пациентов с локальными поражениями головного мозга. В период разработки этой теории аппаратные методы изучения головного мозга еще только зарождались. Хотя в более поздние годы А.Р. Лурия и его ученики указывали на важность применения таких методов для дальнейшего развития отечественной нейропсихологии, они до сих пор редко используются в работах последователей этих ученых. В данной статье мы обсудим возможности применения неинвазивных и наиболее доступных в России методов нейровизуализации (структурная, диффузионно-взвешенная и функциональная магнитно-резонансная томография) и нейростимуляции (транскраниальная магнитная стимуляция) для ответов на интересующие нейропсихологов исследовательские вопросы, а также опишем возможные планы нейропсихологических исследований с участием пациентов с локальными поражениями головного мозга и здоровых людей.

Ключевые слова: нейропсихология, Лурия, нейровизуализация, нейростимуляция, теория системной динамической локализации ВПФ, структурная МРТ, диффузионно-взвешенная МРТ, функциональная МРТ, транскраниальная магнитная стимуляция.

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Introduction

Neuropsychology, as a branch of science, appeared long before technical methods for the investigation of

brain structure and function began to develop intensively in the second half of the 20th century. For a considerable time, scientists had access to methods primarily associated with local brain injury — in animal experiments

and clinical observations of patients the exact injury location of whom was defined *post mortem*. From the 1930s, the intraoperative mapping technique invented by Wilder Penfield also became available to scientists.

Localization of mental processes in the human brain was and remains one of the core theoretical issues of neuropsychology. A prominent stage of its development was the theory of systemic and dynamic localization (TSDL) of higher mental functions (HMFs) proposed by the Soviet neuropsychologists Lev Vygotsky and Alexander Luria. This theory was a response to a scientific debate of the 18–19th centuries between narrow localizationists and equipotentialists, who either suggested localizing separate mental processes (or faculties) directly in the brain centers, or insisted on the equal impact of different brain regions in mental processes, respectively. None of these standpoints could explain the accumulated empirical data with any consistency (for a review, see [6]).

The TSDL is also based on data of local brain injury in humans. The location of injury was usually defined *in vivo* according either to the relative location of a skull fracture due to penetrating trauma or to the results of neurosurgery. However, the concept of function (i.e., what to localize) and the principles of its localization were revised within this theory. Vygotsky introduced the concept of HMFs as complex self-organizing processes in human activity (thinking, language, perception, etc.) which are voluntary, mediated by signs, and social in their origin. The TSDL rests on two basic principles.

The principle of the systemic structure of HMFs implies that a HMF is a functional system consisting of a set of components, each of which provides a unique contribution to this HMF and relies on the functioning of particular brain structures. Consequently, a HMF may become impaired due to a functional deficit of any component, whereas the type of the impairment depends on the location of an injury. A component of a HMF, i.e., a structural and functional unit characterized by a particular type of functioning of a particular brain region, is called a neuropsychological factor. Therefore, the main objective of neuropsychology within the TSDL is articulated through the concept of HMFs as the investigation of their brain organization, i.e., the contribution of different brain regions and structures to the components of HMFs.

The main method of Soviet/Russian neuropsychology, syndrome analysis, is closely linked to the principle that HMFs have systemic structure. Syndrome analysis was developed by Luria, and the data which the TSDL is based on were obtained with this method. An examinee is asked to perform a set of tasks aimed at the assessment of a wide range of mental processes, then a neuropsy-

chologist analyzes the neuropsychological symptoms (i.e., impairments of HMFs) to identify the general cause (factor) the pathological change in which explains the origination of the former. The impairment of a factor and a set of symptoms caused by it constitute a neuropsychological syndrome. As long as technical methods for the diagnostics of brain injury were not accessible but data on the relations between injuries and deficits of HMFs were being accumulated, syndrome analysis was applied for topical diagnostics (identification of injury location, for instance, for surgical planning) and for functional diagnostics (qualification of the state of HMFs, inter alia, the hierarchical structure of deficits). Nowadays, syndrome analysis is used in practice and research only for functional diagnostics.

The principle that HMFs have a systemic structure can be seen in the functional role of several brain regions in language in right-handed individuals [2; 6; 12]. The left inferior frontal gyrus is involved in the motor and syntactic programming of speech and language. More anterior left frontal regions are associated with the generation of the idea of an utterance and development of the scheme of a sentence or text in inner speech. The posterior part of the superior temporal gyrus conducts phonemic analysis. The middle temporal gyrus supports the sufficient span of auditory verbal memory and word selection in the auditory form. The posterior inferior temporal regions store visual images linked to words. The inferior postcentral gyrus is involved in kinesthetic aspects of articulation. Regions at the temporal-parietal-occipital junction are relevant for the understanding of logical-grammatical constructions and word selection by meaning. The right hemisphere is implicated in pragmatic aspects of language (for instance, understanding of context; [1]). Subcortical structures support speech tempo, phonation, and verbal activity.

The second principle of the TSDL — the principle of the dynamic organization of HMFs — implies that HMFs and underlying functional brain systems can change in terms of their structure. First, the structure of HMFs changes in ontogeny and with skill automatization. For example, for a first grader, the act of writing activates visual, visuospatial, motor, auditory, and kinesthetic functions, whereas for a high school student, the technical operations are automatized, and the semantic organization of writing becomes the most attentionally demanding task [3]. Second, HMFs may be restructured through their variable components depending on the conditions and strategy of task performance. The variable components are present in the structure of HMFs along with invariant (i.e., constant, critically important) ones. For instance, when there are many people around speaking

loudly, to understand an interlocutor's speech, one needs to inhibit (filter out) the interfering messages, whereas in a quiet environment, such an additional mechanism is not required for language perception. Third, the reorganization of HMFs is also possible in patients with a brain injury [11]. In within-system reorganization, a HMF relies on its components being intact. For instance, writing impairments due to poor phonemic analysis may be partly compensated for by the kinesthetic components of writing (i.e., speaking aloud). In between-system reorganization, a HMF incorporates components from other functional systems. For example, to remediate visual perception of letters, a neuropsychologist may ask a patient to perform writing movements.

A study which addresses the dynamic reorganization of the brain's underpinnings of HMFs requires a longitudinal comparison of structural or functional brain characteristics in the same individual, or at least a comparison between groups with and without the expected reorganization. This was impossible before the emergence of noninvasive methods of brain investigation.

These methods must have substantially enriched neuropsychology. Evgeniya Khomskaya noted that a new, psychophysiological line of research was established in experimental neuropsychology by Luria; and that he considered the development of psychophysiology which would focus on complex, conscious, and voluntary forms of mental activity to be the most pressing task in the field [10]. Thus, Luria and Khomskaya applied electroencephalography in their studies. Khomskaya also stated that further development of Russian neuropsychology was associated with advances in technical methods for the diagnostics of local brain injury (computed tomography, methods of nuclear magnetic resonance, and others) [10].

However, neuroimaging methods — which Khomskaya referred to — long served neuropsychology only as technical support for specification of the individual location of brain injury (and at the same time, freed neuropsychologists from the responsibility of topical diagnostics). For 45 years after Luria's death, research capabilities of these methods remained almost not demanded by the TSDL and are still insufficiently integrated into Russian neuropsychology.

We will further describe the scope of neuroimaging and neurostimulation methods in neuropsychology. We will focus on noninvasive methods that are the most accessible in Russia and seem the most prominent for the development of the TSDL. They are magnetic resonance imaging (MRI) — structural (sMRI), diffusion-weight-

ed (dMRI), and functional (fMRI), — and transcranial magnetic stimulation (TMS). Possible designs of studies on patients with local brain injury and healthy individuals that may inform neuropsychological theory in its different aspects will also be discussed.

Structural MRI

sMRI provides images of the brain wherein its tissues (gray and white matter and cerebrospinal fluid) have different intensity of pixels and voxels¹ on the gray scale due to the variable magnetic characteristics of hydrogen when it forms part of different molecules. With sMRI, the location of brain injury can be defined with an accuracy of fractions of a millimeter. Therefore, no description of a new clinical case important for neuropsychology is complete without sMRI [29]. Notably, sMRI also greatly adds to the understanding of historic cases. For instance, sMRIs of the preserved brains of two famous patients of Paul Broca demonstrated that their lesions extended into the insula and superior longitudinal fasciculus, in addition to lesions in the left inferior frontal gyrus (Broca's area) [20].

Converging data on the role of insular lesions in deficits of language production were obtained with another method which represents a natural extension of the traditional neuropsychological studies of local brain injury at a new technical level. This method, voxel-based lesion-symptom mapping (VLSM; [14]), allows researchers to analyze associations between quantitative neuropsychological data and data on lesion location in large clinical groups. Structural MRI images are labeled manually or automatically so that a binary 3D brain mask is obtained. In this mask, voxels corresponding to intact and damaged brain tissues have the values of 0 and 1, respectively. Then, statistical analysis of each voxel is carried out wherein the neuropsychological characteristics are compared between the patient groups with and without the lesions affecting this voxel. As a result, brain regions the injury of which contributes to the severity of a symptom may be revealed. In VLSM, there is also a procedure to test whether the lesion of another brain region is primary (i.e., has a direct causal role) for the symptom. It is important to prevent incorrect inferences because brain injury, especially of the vascular etiology, often involves adjacent brain structures (e.g., the inferior frontal gyrus and insula). Thus, VLSM conducted on a large clinical group has demonstrated that injury

¹ Voxel is a basic element of a 3D MR image of the brain.

to the inferior frontal gyrus *per se* causes speech fluency deficits with prominently less likelihood than injury to the anterior insula that had not been discovered in as long a time [14]. These results are fully consistent with the sMRI data on Broca's patients.

sMRI can also be applied in studies of the intact brain, wherein such a method as morphometry can be used. The most technically simple but laborious techniques imply manual segmentation of the brain structures in MR images with subsequent analysis of their volume. The voxel-based morphometry providing measures of gray and white matter volume in each voxel is fully automated and was popular for a long time, due to the relative simplicity of its implementation. However, it is strongly criticized for the biases associated with the possibility of imperfect spatial co-registration of brain images to one another and with the inability to clarify the reason for between-group differences — atrophy of tissue, a higher number of sulci, or an increase in the area of gyri or cortical thickness [15; 36]. These limitations can be overcome with surface-based morphometry which provides measures of the thickness, area, and gyrification in different brain regions. There are also methods for analyzing the volume of subcortical structures [24].

Possible designs of neuropsychological studies using morphometry may imply the search for correlations between morphometrical and neuropsychological characteristics. For instance, the volume of gray matter and cortical folding in the ventromedial, ventrolateral, and dorsolateral prefrontal cortices predicted three components of executive functions: common executive function, switching-specific, and updating-specific performance, respectively [34]. Experimental study designs are also possible, wherein the volume of a structure is measured before and after the intervention — training to improve a certain skill among the experimental group and another activity among the control group. For example, working memory training was shown to increase gyrification in the parietal regions [37].

Diffusion-weighted MRI

This method measures the direction of diffusion of water molecules in brain tissues in the magnetic field during MRI. As white matter fibers are organized in co-directional bundles, diffusion of water molecules occurs predominantly along but not across the fibers in the bundle. The simplest mathematical model

to describe the diffusion of water in tissues is a tensor model², for which diffusion tensor MRI, one of the types of dMRI, is named. In this model, diffusion is described by three eigenvectors (the direction of diffusion) and three eigenvalues (the magnitude of diffusion in the particular direction). These characteristics or their combinations may provide information on the white matter of the brain. Axial diffusivity, the value of the highest vector, reflects diffusion along the neural fibers, decreases in axonal injury, and increases with brain maturation in ontogeny. Radial diffusivity, the mean of the two vectors with lesser values, describes diffusion in the transverse direction and is sensitive to myelination. Radial diffusivity decreases in ontogeny and increases in neurodegenerative diseases. Fractional anisotropy reflects the degree of anisotropy (i.e., heterogeneity of directions) of diffusion of water molecules in each voxel³ and is sensitive to any changes in the white matter. However, this measure is non-specific, and for its precise interpretation, the measures of radial and axial diffusivity should also be considered [13]. The diffusion models allow researchers to conduct tractography, that is, a 3D reconstruction of the white matter tracts.

dMRI may complement the structural-functional model of the brain within the TSDL with data on the functional role of white matter tracts. This can be done through the analysis of correlations either between neuropsychological symptoms and injury to the tracts [26] or between white matter characteristics, in particular tracts and neuropsychological measures in healthy individuals [28]. The contribution of the brain's structural connections to mental processes was left under-studied in Soviet and later Russian neuropsychology (except the role of the corpus callosum in the interhemispheric interaction during different HMFs; e.g., [5]). When the TSDL was being developed, methods for the individual examination of white matter tracts *in vivo* were not available, while their identification in *post mortem* brains was laborious and required high proficiency. However, white matter tracts are the infrastructure which allows individual gray matter structures to unite in functional systems. Injury to the tracts and even their separate segments causes particular symptoms (e.g., semantic and phonological paraphasias induced by lesions in the inferior fronto-occipital and arcuate fascicles, respectively [21]). Therefore, the structural-functional organization of white matter should not be ignored by neuropsychological studies.

² More complex diffusion models such as the diffusion orientation distribution function overcome the limitations of the tensor model [22].

³ Diffusion is isotropic when eigenvalues are almost equal, and anisotropic when one of the eigenvalues is higher than the others.

Functional MRI

fMRI is a method for functional brain mapping which has a fairly high spatial resolution (usually 2–3 mm). It is based on neurovascular coupling, through which the enhancement of neuronal metabolism under neuronal activation increases the regional blood flow in the brain. Consequently, the ratio of oxy- to deoxyhemoglobin in the venous blood changes. This can be detected by an MR scanner as a local change of blood relaxation characteristics during MRI and is reflected in changes of the intensity of pixels and voxels in T2*-weighted images. This technique is known as BOLD (blood oxygenation level dependent) fMRI.

The most common application of fMRI in science is that used to investigate brain activation in healthy individuals during task performance. Development of the tasks loading particular neuropsychological factors is of great interest for neuropsychology – this has not been done so far. To reveal activations specific for each mental process, it is necessary to use at least two tasks, main and control. The control and main conditions should differ only in the content of the mental process of interest. For instance, the main condition for a task aimed to load the semantic processing of language may include the reading of sentences, while the control condition may be the reading of syllables; or listening to an audiobook versus listening to the same recording played backwards [9].

Other important opportunities that the fMRI gives to neuropsychology are the research of age-related changes (e.g., [30]) and individual differences in the brain's underpinnings of HMFs. Brain localization of HMFs is characterized by high interindividual variability (e.g., language [23], executive functions [33]).

Within the framework of the TSDL, fMRI can reveal functional networks which include invariant and variable components of HMFs. However, in contrast to sMRI and dMRI studies of local brain injury, invariant components can be hard to isolate based on the data obtained from brain activation studies. The presence of local activation *per se* does not indicate that this activation is necessary for the mental function. To identify invariant components, a combined task analysis can be used. An examinee is asked to perform several tasks aimed to load the same mental process, and the invariant components are expected to be present in all activation maps [9]. For example, common components of activation in the tasks addressing inhibition [17; 25] are seen in the left dorsolateral prefrontal and right insular cortices, as well as the cingulate and inferior frontal gyri. Activation in the left fusiform gyrus specific for the Stroop test may be related to word recognition. Activation of the ventral attention network exclusive for

the Go/No-go task may be explained by the detection of unexpected salient stimuli.

Apart from the analysis of brain activation, fMRI provides the crucial opportunity for neuropsychology to investigate functional connectivity (FC), through which separate brain regions become the components of a single functional system [7]. The functional integration between different brain regions is one of the core ideas of the TSDL. HMFs can exist only due to the interaction between highly differentiated brain structures, each of which provides a unique contribution to the dynamic functional systems [6]. Syndrome analysis, in contrast to fMRI, is not able to reveal changes in the FC between components of a functional system but only to assume that the FC is impaired due to a deficit of a particular component of a HMF.

Technically, the FC in fMRI is defined as a statistical correlation between low-frequency (<0.1 Hz) fluctuations of the BOLD-signal in different brain regions and subcortical structures. The FC can be studied not only during task performance but also at rest. In this case, the intrinsic functional brain architecture is supposed to be analyzed. Thus, a number of networks can be identified based on resting-state fMRI data, including the frontoparietal network, the default mode network, and the dorsal and ventral attention networks [38]. Associations between the results of outside-of-scanner neuropsychological assessment and characteristics of the resting-state FC seem the most interesting for neuropsychology. For instance, the FC of the dorsolateral prefrontal cortex with different brain regions was shown to be related to the switching, inhibition, and verbal components of executive functions [32]. In the same way, correlations between neuropsychological parameters and FC, or activation during task performance, can be analyzed. Another perspective approach is lesion network mapping wherein a single study includes sMRI in patients with brain injury to reveal regions that are crucially important for a particular function, and fMRI in healthy individuals to identify the FC of these regions [16].

Activation or FC during task performance and FC at rest can also be analyzed in patients with local brain injury – to explore compensatory reorganization of brain functioning during the development of a disease or during neuropsychological rehabilitation. Longitudinal designs are perfect for such studies. For further direct comparison, neurophysiological data should be obtained under the same conditions for each patient before, during, and after the rehabilitation, or before and after the onset of a disease. As the latter design can be implemented only in large screening studies, more feasible designs imply the comparison of activation or FC between patients and healthy individuals and the analysis of cor-

relations between neurophysiological and neuropsychological characteristics [35].

Transcranial magnetic stimulation

During TMS, a selected brain region is stimulated with an alternating magnetic field generated by a coil. The depth of stimulation is usually 2-3 cm, however, with the application of some coils, this can be increased up to 6 cm. Structural and functional MRI data can be used to choose the brain region for stimulation. Depending on the parameters of stimulation, the neuronal activity in this region may either be facilitated or inhibited. It is even possible to induce a so-called virtual lesion of a particular brain region in healthy individuals. The virtual lesion is an impairment of function of a stimulated region that is similar to symptoms of a real lesion but lasts only for several seconds and is fully reversible [4]. When the immediate effect of TMS (inhibitory or facilitatory) persists, a researcher may compare the task performance carried out by an examinee with her or his performance without stimulation, during stimulation of another brain region, or during sham (i.e., placebo) stimulation. Sham stimulation causes the same auditory and tactile sensations as that in TMS but does not stimulate the brain [4].

TMS studies demonstrating the improvement of task performance in healthy individuals [18] and possibilities of therapy of cognitive impairments in local brain injury [31] are also interesting for neuropsychology.

General discussion and conclusions

As can be concluded from the brief review presented above, neuroimaging and neurostimulation methods can be effectively implemented for the investigation of brain organization of HMFs considered as multicomponent functional systems with invariant and variable components. These methods can complement the information obtained through a neuropsychological syndrome analysis using the data on brain phenomena. They can also be applied in more specific objectives of neuropsychology — for the research of the structural-functional reorganization of HMFs in ontogeny, after local brain injury, and due to neuropsychological rehabilitation; and for the investigation of individual differences in the brain mechanisms of HMFs. Neuroimaging methods have a high spatial accuracy that was non-existent during the early development of the TSDL and provide opportunities crucial for neuropsychology — to analyze the functional (fMRI) and structural (dMRI) connectivity of the brain.

In this article, we suggested some examples of neuropsychological studies that apply neuroimaging and neurostimulation methods. They are summarized in Table 1.

Studies of the intact brain overcome a number of fundamental problems that arise during the examination of patients with local brain injury. The main problem is associated with the non-specific effects of brain injury that always accompany brain diseases: alterations in the vascular blood flow and dynamics of the circulation of cerebrospinal fluid, inflammatory processes, and hypertension-dislocation phenomena leading to abnormal dynamics of neural processes and an altered relationship between processes of excitation and inhibition [6]. Furthermore, examination of healthy individuals provides more opportunities for the investigation of subcortical brain structures. In patients with subcortical brain injury, this is complicated with high morbidity, altered states of consciousness [6], and severe motor symptoms that may mask cognitive symptoms. Finally, a sample of healthy individuals sufficient for the analysis is easier to draw in contrast to several clinical groups matched by sex, age, level of education; location, volume, and etiology of a lesion; and time post-onset of the disease.

A prominent research issue is what hypotheses can be tested in the study designs described above. One of the main hypotheses for neuropsychology is a causal hypothesis of the type “functioning of a brain region (X) is necessary for HMF component (Y)”. The majority of designs of intact brain studies (2, 4, 6, 8, 10; Table 1) are able to test only hypotheses of type “X is related to Y” but not necessarily critically important for Y. Research on local brain injury (1, 3) brings us closer to the identification of the “X necessary for Y”, however, only quasi-experimental study designs are possible in this case. A researcher cannot control to whom and when different levels of the independent variable (injury / its absence) are presented, does not have complete information on the effects of injury on the brain (e.g., diaschisis and neuroplasticity), and is not able to assess mental functions before the injury. Therefore, strictly speaking, the above causal hypothesis cannot be tested in such studies either. When the data obtained on patients with brain injury and on healthy individuals are interpreted in combination, a stronger level of inference is provided [19]. TMS studies (12), in turn, are able to test the hypothesis on causal relationships between the functioning of a number of cortical brain regions and components of HMFs through a true experiment wherein the independent variable (intervention) is controlled. Designs 11, 13, 14 are able to test causal hypotheses but of another kind: on the change of a brain region due to learning aimed at im-

Table 1

Designs of neuropsychological studies applying neuroimaging and neurostimulation methods

Method	Object of study	Study design	Research questions in neuropsychology
sMRI	Local brain injury	(1) Voxel-based comparisons of the severity of symptoms between patient groups with and without lesions in a voxel (VLSM)	Localization of the invariant components of HMFs in the brain and the functional role of the white matter tracts
	Intact brain	(2) Correlations between morphometric measurements and data on cognitive functions. Comparison of these correlations between groups or hemispheres	Functional role of gray matter regions, individual and age-related differences, hemispheric asymmetry
dMRI	Local brain injury (3), intact brain (4)	(3,4) Correlations between characteristics of white matter tracts and results of neuropsychological assessment. Comparison of these correlations between groups / hemispheres	3,4: Functional role of the tracts 4: Individual and age-related differences, hemispheric asymmetry
tbfMRI	Local brain injury (5,7), intact brain (6,8)	(5,6) Investigation of brain activation or FC during task performance (7,8) Correlations between activation or FC during task performance and results of neuropsychological assessment. Comparison of these correlations between groups or points in time	6,8: Localization of invariant + variable components of HMFs in the brain, interhemispheric interaction, individual and age-related differences in FC, volume of activation and localization of HMFs 5,7: Compensatory reorganization of brain function due to disease or after rehabilitation
rsfMRI	Local brain injury (9), intact brain (10)	(9,10) Correlations between FC at rest and the results of neuropsychological assessment. Comparison of these correlations between groups, conditions, or points in time	9: Compensatory brain reorganization 10: Contribution of the FC to HMFs, individual and age-related differences
sMRI, dMRI, tbfMRI, rsfMRI	Intact brain	(11) Comparison of MRI measures between the experimental group (which undergoes training aimed at enhancing a particular function) and the control group (another activity), before and after the experimental intervention	Reorganization of functional systems in learning
TMS	Intact brain	(12) Description of impairments of HMFs during task performance with virtual lesions of brain regions compared to sham stimulation	Localization of invariant components of HMFs in the brain
		(13) Description of the effects of stimulation of brain regions to enhance task performance compared to sham stimulation	Functional role of a number of cortical brain regions, hemispheric asymmetry, plasticity of HMFs in healthy individuals
	Local brain injury	(14) Description of the effects of stimulation of brain regions to remediate deficits of HMFs, compared to sham stimulation	Compensatory brain reorganization

Note: tbfMRI is a task-based fMRI; rsfMRI is a resting-state fMRI.

proving a particular HMF (11) and on the contribution of a brain region to the plasticity of HMFs in healthy individuals (13) or during the compensatory reorganization of HMFs (14).

An important problem that researchers will face in studies with designs 1–4 and 7–10 is associated with the necessity to present neuropsychological data in quantitative scales. The elaboration of integrative quantitative indices reflecting the state of neuropsychological factors is required to explore their brain organization. This demands substantial consideration due to the multicausality of a symptom – the same symptom can be caused by the impairment of different factors.

For instance, anomia may occur due to either poor visual perception, language impairments, or executive deficits. This problem can be largely resolved with the elaboration of a detailed classification of errors in each task (based on their nature) and with the evaluation of neuropsychological data by qualified and skilled neuropsychologists. Another problem, the subjective nature of syndrome analysis, may be overcome through the development of precise evaluation criteria. A system for the quantitative estimation of the results of neuropsychological assessment has already been developed by the research group of Tatiana Akhutina in Russian child neuropsychology. This complex system combines the

qualitative analysis of a symptom with its scoring based on its severity [8]. As a result, the integrative indices of executive functions, serial organization of movements and language, processing of kinesthetic, auditory, visual, and visuospatial information, as well as the indices of hyperactivity/impulsivity and fatigue/slow tempo are derived from a set of single symptoms [27]. The composition of these indices is based on the theoretical considerations, experience of syndrome analysis, and the results of confirmatory factor analysis. The indices are

calculated through the summation of the corresponding standardized measures of performance in different tasks, such as productivity and specific errors.

To conclude, a rich arsenal of up-to-date neuroimaging and neurostimulation methods, in combination with statistical data analysis, provide opportunities to verify, detail, and continue the development of the model of structural-functional brain organization within the TSDL using the data obtained on patients with brain injury and on healthy individuals.

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