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Interactive Brain Stimulation Neurotherapy Based on BOLD Signal in Stroke Rehabilitation

*Nadezhda A. Khruscheva[1], Mikhail Ye. Mel'nikov[1], Dmitriy D. Bezmaternykh[1], Andrey A. Savelov[2], Konstantin V. Kalgin[3], Yevgeny D. Petrovsky[2], Anastasia V. Shurunova[3], Mark B. Shtark[1], and Estate M. Sokhadze[4]**

[1]Federal Research Center of Fundamental and Translational Medicine, Novosibirsk, Russia
[2]International Tomographic Center, Siberian Branch of Russian Academy of Science, Novosibirsk, Russia
[3]Novosibirsk State University, Novosibirsk, Russia
[4]Duke University, Durham, North Carolina, USA

Abstract

Interactive brain stimulation is a new generation of neurofeedback characterized by a radical change in the targets of cognitive (volitional, adaptive) influence. These targets are represented by specific cerebral structures and neural networks, the reconstruction of which leads to the brain functions' restoration and behavioral metamorphoses. Functional magnetic resonance imaging (fMRI) in the neurofeedback contour uses a natural intravascular tracer, a blood-oxygenation-level-dependent (BOLD) signal as feedback. The subject included into the "interactive brain contour" learns to modulate and modify his or her own cerebral networks, creating new ones or "awakening" pre-existing ones, in order to improve (or restore) mental, sensory, or motor functions. In this review we focus on interactive brain stimulation based on BOLD signal and its role in the motor rehabilitation of stroke, briefly introducing the basic concepts of the so-called "network vocabulary" and general biophysical basis of the BOLD signal. We also discuss a bimodal fMRI-EEG neurofeedback platform and the prospects of fMRI technology in controlling functional connectivity, a numerical assessment of neuroplasticity.

Keywords: interactive brain stimulation; cerebral networks; functional magnetic resonance imaging (fMRI); BOLD; bimodal fMRI-EEG neurofeedback platform.

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***Address correspondence to**: Estate Sokhadze, Duke University, Department of Neurology, Duke University Medical Center Box 3824, 40 Duke Medicine Circle, Durham, NC 27710, USA. Email: tato.sokhadze@duke.edu

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

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Introduction

Interactive brain stimulation (IBS) is a recently developed type of neurofeedback that involves the organization of a feedback "target" based on a hemodynamic response signal recorded by functional magnetic resonance imaging (fMRI). Biofeedback technologies in general, and neural interfaces in particular, have recently attracted increasing attention (Sulzer et al., 2013; Wang, Collinger, et al., 2010). The term "interactive brain" is closely related to neural interface technologies (or, in other words, neuro-prosthetics technologies), which are considered in the context of the prospects for creating algorithms for controlled neuroplasticity. The search for these neurofeedback algorithms is especially in demand for the recovery of the consequences of acute cerebrovascular accident, since stroke-induced motor, cognitive, and sensory impairments deprive survivors of independence for many years and increase the burden on their caregivers. It is generally accepted that the basis for motor functions recovery and improvement after a stroke is the innate anatomical and physiological plasticity of the brain enhanced by motor exercises and sensory stimulation (Kim & Kang, 2022; Kwakkel & Kollen, 2013; Nudo, 2003; Nudo et al., 1996; Schaechter et al., 2006; Sokolova et al., 2010;

Wang et al., 2006). This is the basis of the principle of poststroke rehabilitation, although it is known that even with intensive special training and general aerobic exercises recognized as the "gold standard" of poststroke rehabilitation, no more than 20% of surviving patients recover, and 33–60% of them remain disabled (Duncan et al., 2000; Feigin et al., 2016, 2017; Kwakkel & Kollen, 2013). In this regard, there is a strong need to identify the main involved brain structures and stimulation methods that can radically affect the current efficiency of the neurorehabilitation. The identification of such cerebral formations and, most importantly, their real-time interactions requires using modern technologies of functional noninvasive neuroimaging and neurofeedback systems.

Neuroimaging and Neurofeedback

FMRI of the Brain*.* FMRI is based on the fact that a decrease in blood oxygenation produces the increase of brain MRI image contrast (Ogawa & Lee, 1990; Ogawa et al., 1998). This contrast, which depends on the level of blood oxygenation (blood oxygenation level-dependent, BOLD), results from the conversion of diamagnetic oxyhemoglobin into paramagnetic deoxyhemoglobin. It is assumed that the observed signal changes are closely correlated with the neuronal activity (Bentley et al., 2016; Gauthier & Fan, 2019; Lecrux & Hamel, 2016; Miller et al., 2001), and, in fact, BOLD is a natural MRI contrast that indirectly reflects the level of oxidative processes in the brain tissue. At the same time, the fMRI experiment makes it possible to localize cerebral areas up to one cubic millimeter with high spatial resolution, including deep parts of the brain (Birn et al., 1999; Buckner, 1998; Matthews & Jezzard, 2004; Ogawa et al., 1998). Today, it can be argued that BOLD signal recording is the optimal tool of mapping the neuronal activity, precisely, the functional state of neural ensembles (NE) during volitional reconstruction of cerebral networks (Shtark et al., 2012).

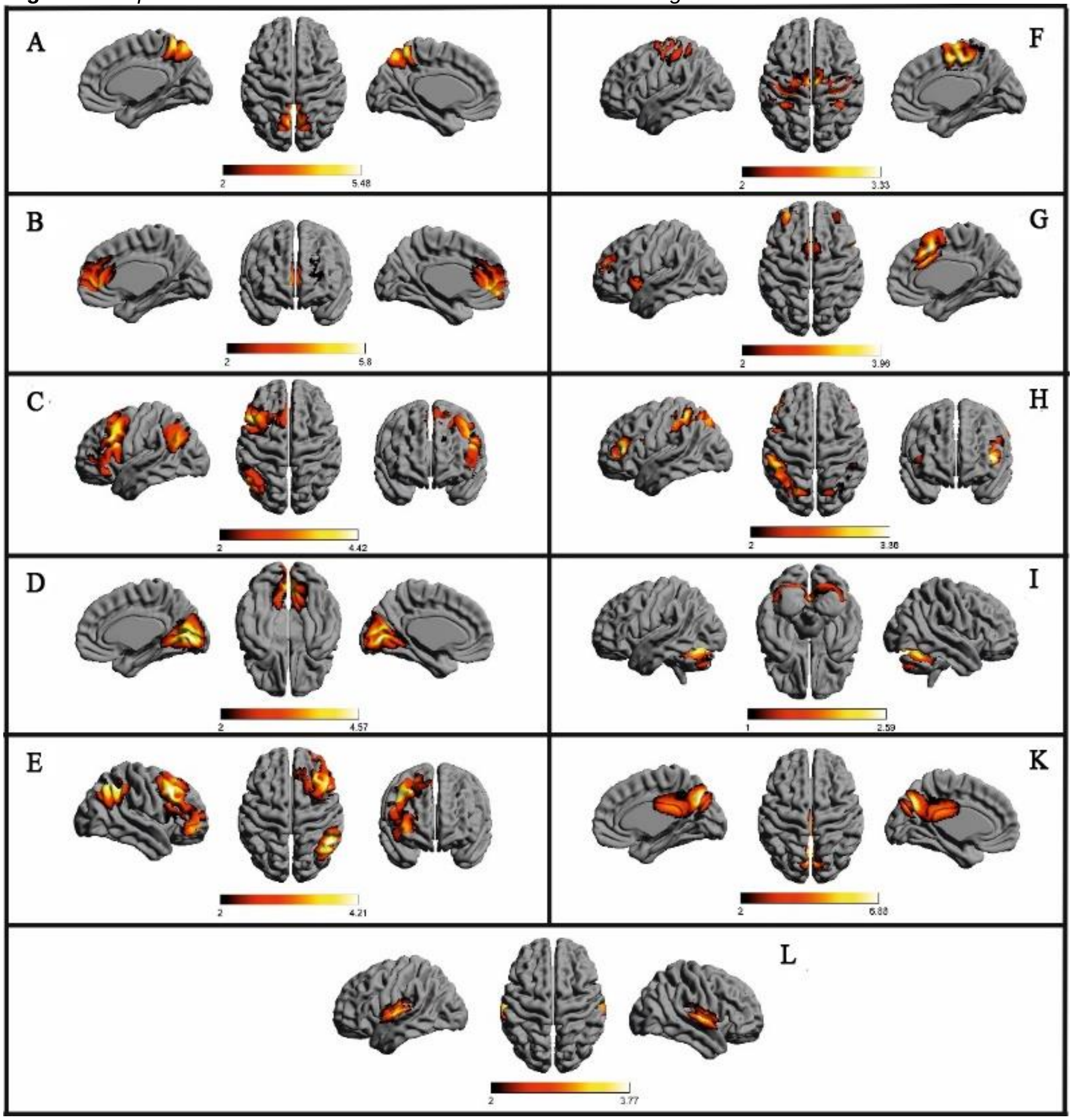
Electroencephalographic Neurofeedback; Bimodal fMRI-EEG Neuroimaging Platform EEG*.* The accuracy of mapping the brain activity zones based on electroencephalogram (EEG) recording from the surface of the scalp is very conditional, because the resultant is the sum of the signals from a huge number of neurons which is distorted due to the resistance of the cerebrospinal fluid, meninges, skull bones, muscles, and scalp. To some extent the problem is solved by increasing the number of EEG leads to 64 or even more (Luu et al., 2001), but in terms of spatial resolution the MRI technology, including fMRI, is beyond competition. Besides, applying correlation analysis in fMRI gives a clear idea of the relationship between distant brain regions (functional connectivity). However, its ability to determine the direction of the information flow (effective connectivity) in each NE is very limited. From this point of view, the EEG, which has a higher temporal resolution, is better suited for studying the dynamic processes of the brain (Lopes da Silva, 2013).

Obviously, the combination of both methods seems attractive for observing spatiotemporal neural dynamics of the human brain (Herrmann & Debener, 2008). This became possible due to improvements in EEG recording devices and methods of processing the artifact noise generated in the magnetic field of an MR scanner (Bonmassar et al., 1999; Ives et al., 1993; Ullsperger & Debener, 2010). Studies have shown that EEG-fMRI "concordia" links electrophysiological and hemodynamic measurements together and generates new understanding of brain function, which is not possible if these technologies are used separately (Huster et al., 2012; Philiastides et al., 2021; Ritter & Villringer, 2006; Shtark et al., 2015). Considering that both EEG and fMRI signals are directly related to the activity of specific neural associations and act as physiological markers of the functional anatomy of the brain, these signals are of specific interest as neurofeedback targets either individually or together. Whereas EEG neurofeedback has a long history (Evans et al., 2019; Shtark, 2019), the IBS based on the fMRI signal is still evolving. However, before moving to the essence of IBS based on the BOLD signal in poststroke motor rehabilitation, it is feasible to discuss the network organization of the brain and its changes after a stroke.

Network Organization of the Brain and Its Reconstruction After Stroke

Major Cerebral Networks*.* Modern neurophysiology considers the brain macrostructural organization as a composition of interacting neural networks (fMRI products), each of which includes several areas that are functionally interconnected and have a certain specialization, which is manifested by activation or deactivation in response to a specific task. Network neuroscience was initiated in the 1990s, when the first cerebral network, the sensorimotor network (SMN), was described (Biswal et al., 1995; Golanov et al., 1994). Later other networks were discovered that determine different levels of brain organization, from small NE to large-scale networks, including widely spread areas of cortical and subcortical structures that provide mainly complex cognitive operations (Buckner & DiNicola, 2019; Marek & Dosenbach, 2018; Menon, 2011; Petersen & Sporns, 2015; Raichle et al., 2001). The main networks are frontal-parietal network (FPN) or central executive network, (CEN), salience network, cinguloopercular network (CON), default mode network (DMN), ventral and dorsal attention network (VAN, DAN), visual network (VN), and auditory network (AN), see Figure 1.

Figure 1. *Map of the Nodes of the Main Neural Networks According to fMRI Data.*



Note. A - default ventral network (vDMN): precuneus, superior parietal lobule; B - dorsal default network (dDMN): anterior cingulate, middle and superior frontal gyrus; C - left fronto-parietal network (LFPN): inferior, middle and superior frontal gyrus, infero-parietal lobule, supramarginal gyrus; D - primary visual network (PVN): wedge, lingual and posterior cingulate gyrus, precuneus; E - right fronto-parietal network (RFPN): middle, inferior and superior frontal gyrus, inferior parietal lobule, supramarginal gyrus; F - sensorimotor network (SMN): middle frontal, postcentral and precentral gyrus; G - anterior significant stimulus identification network (ASN): cingulate gyrus, superior, inferior and middle frontal gyrus, insular cortex; H - visuospatial information processing network (VSN): inferior and superior parietal lobule, inferior and middle frontal, postcentral gyrus; I - cerebellar network (CN): cerebellar clivus; K - precuneus network (PN): precuneus, posterior cingulate gyrus; L - auditory network (AN): superior temporal gyrus, insular cortex, postcentral gyrus, Heschl gyrus, precentral gyrus (Bezmaternykh et al., 2018).

The FPN includes the dorsolateral prefrontal and posterior parietal cortex, and it is one of the most important centers of cognitive control that ensures the alignment of goal-directed behavior that is relevant to the task. The FPN interacts closely with the attentional, visual, sensorimotor, and auditory networks, as well as with the cortical regions nearby, and its activity is characterized by a reciprocal relationship with DMN activity (Marek & Dosenbach, 2018).

One of the most extensive and well-studied is the DMN which, according to recent data, includes several subnetworks and has numerous connections with other cerebral networks (Buckner & DiNicola, 2019). The DMN belongs to the so-called “resting networks,” the activity of which is recorded in the state of calm wakefulness (Raichle et al., 2001). DMN is believed to provide "introspective" cognitive processes involving mental resources that are far beyond direct sensory perception of the environment, such as prediction, self-perception, and autobiographical memories, hypotheses about the thoughts and feelings of another person (Buckner & DiNicola, 2019; Molnar-Szakacs & Uddin, 2013; Raichle et al., 2001). One of the main properties of DMN is its deactivation in response to a task that requires concentration on external stimuli from the environment. In this view, there is a need of the whole variety of options mentioned above under the conditions of long-term "training" in the MRI tomograph.

Structural and Dynamic Parameters of Neural Networks*.* The modern neuroscience usually considers the brain network organization in terms of graph theory, the essence of which is the mathematical modeling of paired relationships between objects (Alionte et al., 2022). Bassett et al. (2006) described interactions within cerebral networks in view of the “small world” concept. From the small world perspective, the cerebral network model is a system of nodes and connections (vertices and edges) where most of the edges are assembled to form small amounts of strongly connected clusters, while the rest are involved in maintaining connections between them (Sporns & Honey, 2006). In a more conditional “neuroanatomical” language, nodes (clusters) in relation to neural networks are represented by neurons or anatomical regions of the brain, and edges (connections) are represented by axons (tracts). Thus, in the neural architecture any network can be defined as structurally separated areas of the brain that exhibit activation patterns that correlate over time (Alionte et al., 2022). These activation patterns can be measured using fMRI, and they necessarily have direct connections, which, by the way, can also be discovered using diffusion-weighted MRI methods.

Temporal correlations of activation of neural network nodes dispersed in the brain are described by the concept of functional connectivity (FC) which is defined as a statistical relationship between distant neurophysiological events (Friston, 2011). At the same time, integration paths in a complex hierarchically built system are better understood in terms of effective connectivity (EC) which explains both the correlation and vector components of the information flow between brain regions (Friston, 2011). Obviously, the basis for both dynamic characteristics of the neural networks viability is provided by structural connectivity (SC) represented by the corresponding signal conductors (paths), but it is neither sufficient nor a complete description of connectivity in relation to the purpose of the neural network (Friston, 2011). Understanding that the brain functions as a network of interconnected neural circuits is critical in determining approaches to the neurofeedback and IBS after a stroke, since structural damage to a single node (or several nodes) in a network can affect all the structures of this network, and vice versa, while the nods outside the affected network can take over the functions of the affected nods providing the recovery.

Cerebral Networks and Stroke*.* From the view of the brain network organization, stroke can no longer be considered as an exclusively focal disease of the central nervous system. The existence of various functional connections between nodes within a particular network (for example, motor areas of the sensorimotor network) and complex internetwork interactions can largely explain the global nature of changes in the brain and allows considering stroke as a disease of the whole brain, a "network disease."

On the one hand, damage to a certain area of the brain due to stroke results in a dysfunction of remote areas functionally related to the affected node; on the other hand, the remaining intact nodes of the damaged network are able to restore the impaired function (Carter, Astafiev, et al., 2010; Carter, Shulman, et al., 2012; Guggisberg et al., 2019). This was convincingly demonstrated in an experiment on mice where motor relearning after a stroke in the primary motor cortex (M1) was associated with activation of the medial premotor cortex (mPMC), which under normal conditions does not play a significant role in the implementation of movement, and ischemia of mPMC itself does not lead to paralysis (Zeiler et al., 2013). Modeling the network effects of damage showed that the lesions induce specific patterns of altered FC between distant cortical regions, often affecting both hemispheres. At the same time, the degree of these effects depends, among others, on localization and partially can be predicted by the properties of the structural network of the lesion site. In particular, lesions near the temporoparietal junction cause particularly severe and widespread changes in FC, while lesions in primary sensory or motor areas remain more localized (Alstott et al., 2009).

Functional neuroimaging based on the BOLD signal provides important information about the dynamics of the reorganization of cerebral networks after a stroke. It was shown that during one year after subcortical ischemic stroke, as movements are restored, the motor network gradually acquires a more complex, chaotic structure as compared to healthy people (Wang, Yu, et al., 2010). Apparently, such chaotic connections in a poststroke brain result from a formation of many new connections, or activation of preexisting connections, not active under normal conditions, that compensate for the destroyed nerve pathways. These new connections are less stable, but they are effective and provide at least partial restoration of the impaired function (Fornito et al., 2015; Guggisberg et al., 2019; Li et al., 2014; Rowe, 2010). In general, the poststroke reorganization of motor networks is reduced to a decreased inter- and intrahemispheric FC of the motor areas of the ipsilateral hemisphere (Carter et al., 2010; Larivière et al., 2018; Siegel et al., 2016; Tang et al., 2016; van Meer et al., 2010; Yuan et al., 2021) and an increased intra-hemispheric connectivity of contralateral motor areas (van Meer et al., 2010). It is noteworthy that the FC between motor areas and cognitive networks, specifically DMN, salience network, VAN, and DAN, weakens (Almeida et al., 2017; Cheng et al., 2021). At the same time, it was suggested that functional improvement after a stroke is provided by the preservation/restoration of the FC of motor and nonmotor networks (Almeida et al., 2017). Larivière and colleagues drew attention to the lack of proper reciprocal inhibition in the DMN after activation of the motor network, which is apparently associated with insufficient signal strength of the latter (Larivière et al., 2018). The evolution of the motor network poststroke reorganization is manifested as the restoration of the motor areas activity and an increase in their interhemispheric FC, which strongly correlates with the improvement in motor function (Carter et al., 2010; Guggisberg et al., 2019; van Meer et al., 2010; Zhang et al., 2016). Thus, by affecting the motor areas and/or their connections based on IBS it becomes possible to noninvasively and purposefully modulate the course of neuroplasticity after a stroke.

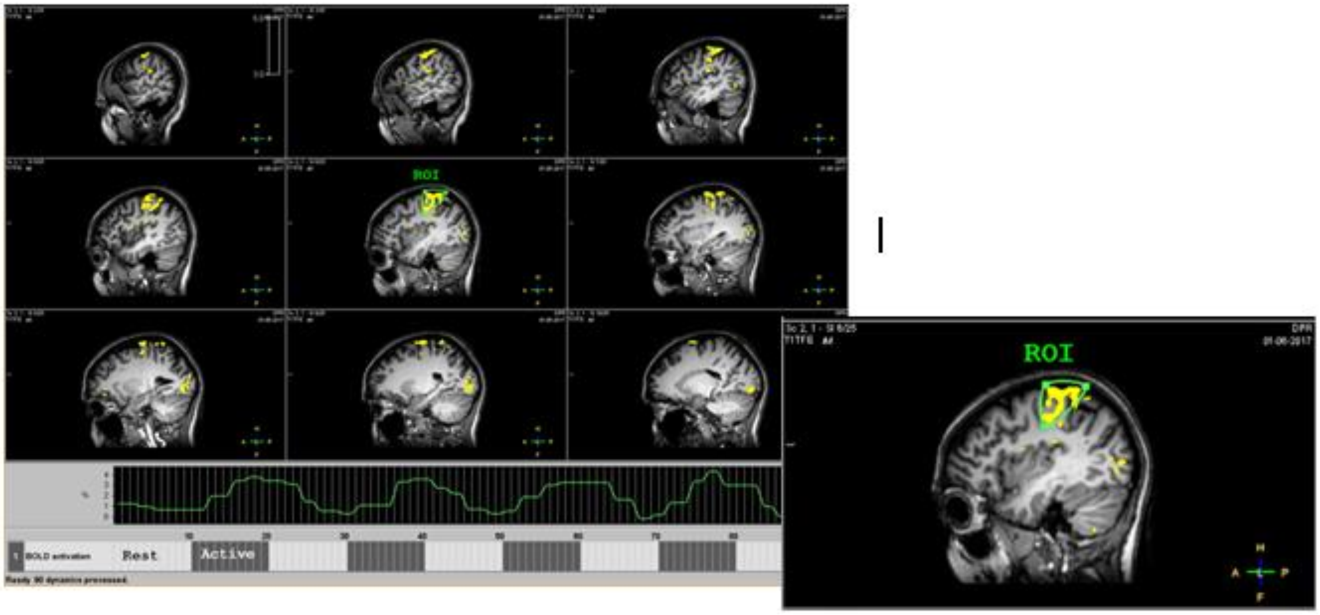
Neurofeedback Based on BOLD Signal in Poststroke Motor Rehabilitation

BOLD signal neurofeedback, or IBS, is a new generation of neurotherapy in the sense of a radical change of the target; from the traditional volitional influence on the peripheral domains characteristics (cardiovascular, respiratory, or muscular system) to the control of the brain region of interest (ROI). In the fMRI training paradigm, during performance of task the BOLD signal provides a subject information about the current brain activity almost in real time (response delay is only 4–6 s). At the same time, the fundamental advantage of fMRI over other methods of functional neuroimaging (EEG, functional near-infrared spectroscopy [fNIRS], magnetoencephalography [MEG]) is related to its high spatial resolution, which makes it possible to map activation patterns and show functional connections between cerebral network nodes with an accuracy up to several millimeters, including subcortical structures. At the same time, fMRI IMS not only allows to focus on the ROI in the research paradigm with good accuracy, but also provides “the necessary flexibility to adapt to frequent changes in brain network configurations that are typical for newly formed networks" (Paret et al., 2019). Here can be seen the prospects of controlling not only individual cerebral structures, but also the dynamics of functional connections between them, as well as the activity and coherence of neural networks, become well-formed (Mel'nikov et al., 2017). Without going into details of the technical and mathematical support of fMRI training, the next section will briefly touch on the methodological foundations of constructing sessions of IBS.

General Principles for Organizing IBS Sessions Based on the BOLD Signal. Defining a target (ROI) for BOLD IBS is determined by the specific therapeutic task and is usually based on the relationship of the selected brain structure with the target symptom(s). At the same time, the design of the fMRI-IBS training can be built specially to teach a patient to manage both "tonic" symptoms that are stabile (for example, hemiparesis, neglect, major depression episode, etc.), and "phasic," that are symptoms periodically and quickly developed (for example, hallucinations, obsessions, tics, etc.). Finally, IBS protocols can be aimed at enhancing the existing compensatory models (Fovet et al., 2015). The ROI for a particular subject is identified by selecting the desired structure according to MRI data or by functional localization during a separate short fMRI session aimed at determining the gray matter volume for an individual performing the task (Mel'nikov et al., 2017). A combination of the two methods is also possible. Some protocols use more than one target ROI (Rance, et al., 2014; Scharnowski et al., 2015). In addition to the target ROI, another one is recruited which obviously does not participate in the performance of the target function but serves to level the activation estimation error due to global processes in the brain. The network neurofeedback lexicon is presented more distinctly in the studies where the subject receives back the signal of the strength of the connection between the nodes of his/her cerebral network (Koush et al., 2013; Liew et al., 2016; Morgenroth et al., 2020).

Existing studies in the fMRI neurofeedback indicate the possibility of presenting a feedback signal in visual, auditory, and tactile modalities (Stoeckel et al., 2014). But perhaps the most common is the visual form. The signal metaphor can vary in complexity, from a simple graph or thermometer to game scenes and realistic maps of brain activation (Yoo & Jolesz, 2002). Before and after IBS sessions the subject passes behavioral and/or psychological tests depending on the symptom being studied, for a quantitative assessment of the dynamics of the trained skill. A number of research protocols suggest a follow-up in several months after training completion. Before the start of the training, a preliminary "calibration" MRI session is performed during which the subject’s individual brain structure is specified, the ROI is determined, and the equipment is adjusted for a particular participant (Figure 2).

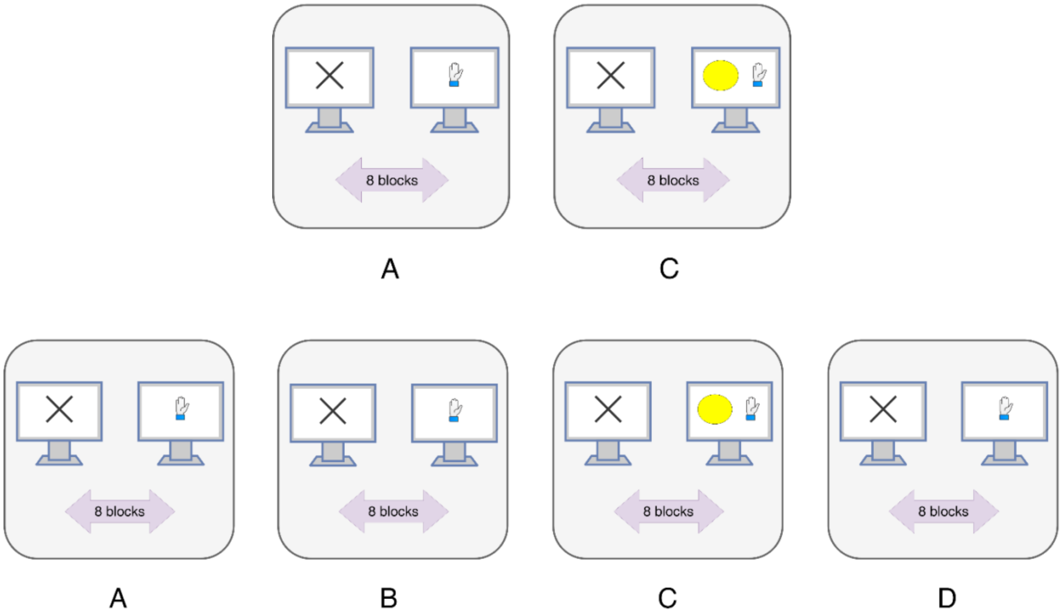
Figure 2. *Isolation of a ROI During an fMRI-IBS Calibration Session.*



Note. Actual hand work causes activation of the M1 (Brodmann area 4) which appears as a yellow area at the anatomical image of the brain. The operator can manually outline the ROI to later use it as a biofeedback target (green outline around the yellow area). The magnitude of the BOLD signal in the ROI is shown as a curve at the figure bottom (Savelov et al., 2019a).

In the first as well as in the final session, the characteristics of interest are measured for a subsequent detailed offline analysis. In the poststroke motor recovery paradigm, training sessions are performed daily or at 1- to 2-day intervals, typically for 3–4 weeks. During each session, the participant alternates periods of active regulation using a feedback signal and rest periods (Figure 3). One training session takes 40–60 min, including preparation. In several protocols, a “transfer run” can also be provided to test the independence of the trained skill compared to the experimental settings during which the subject does not receive feedback when performing the task.

Figure 3. *IBS Design Optimized for Teaching Self-Regulation Skills (Top) and for Demonstrating the Degree of Skill Formation (Bottom).*



Note. A - functional localization: eight 25-s cycles of "rest–work" (squeezing the ball with the hand). B, C, D - hand movement imagination with feedback (C) and without it (B, D): eight cycles of 25 s of rest / 75 s of work (Savelov et al., 2019a).

For most research and therapeutic tasks, the described monomodal training model is sufficient. However, the simultaneous registration and analysis of two neurophysiological signals at once leads to a qualitatively different level of understanding the mechanisms of neuroplasticity and reorganization of cerebral networks under the impact of IBS. Let us analyze the neurofeedback circuit based on the bimodal platform for fMRI-EEG signals recording.

Bimodal fMRI-EEG Neurofeedback Platform: Advantages and Prospects. Improvements in the mathematical and statistical processing of fMRI and EEG signals made it possible to combine the strengths of each of the technologies (meaning their high spatial and temporal resolution, respectively) and obtain more information about the current brain activity (Figure 4). To organize NFB based on the bimodal fMRI-EEG platform the key problem is to ensure a high level of synchronization between both platform subsystems and the protocol. If this requirement is fulfilled, the simultaneously arriving signals of each modality reflect the brain activity caused by the protocol task with minimal delay. In most studies involving the simultaneous fMRI and EEG recording the real-time feedback is presented only for one of the modalities, and the signals of the other modality are processed offline to assess the electrophysiological (EEG) and hemodynamic (BOLD) correlates of the NFB (Mano et al., 2017; Shtark et al., 2015; Zotev et al., 2014).

As far as we know, the first experimental online integration of signals of both modalities for the purposes of NFB was performed by Zotev et al. (2014). In Zotev's experiment (2014) healthy volunteers practiced emotional self-regulation by simultaneously controlling the BOLD fMRI signal in the ROI of the left amygdala and EEG frontal power asymmetry in the high beta range (21–30 Hz). In this research the participants were asked to evoke positive emotions using happy autobiographical memories. The integrated signal flow of both modalities was presented to the participants at the screen as a red bar, the level of which had to be raised to the target (blue line). The results of this study showed the fundamental feasibility of simultaneous regulation of hemodynamic (BOLD) and electrophysiological (EEG) activity of the human brain and inspired optimistic prospects for the development of new research paradigms and cognitive approaches to the treatment of major neuropsychiatric disorders (Zotev et al., 2014). Later, the results of using the bimodal NFB fMRI-EEG platform in the stroke rehabilitation were published, which we discuss in the next section.

Figure 4. *IBS Session on the Bimodal fMRI-EEG Platform.*

Note. The patient in the MRI tomograph is asked to imagine the movement of the paretic hand. The monitor in the center of the picture shows a hand-shaped hint and a feedback metaphor (a yellow circle), the size of which depends on the success of the hand movement imagination task, being proportional to the magnitude of the BOLD signal in ROI. The same image is duplicated on the patient's monitor behind the tomograph. The monitor on the left displays brain activation zones according to the BOLD fMRI signal; right monitor shows simultaneous EEG recording (Savelov et al., 2019a).

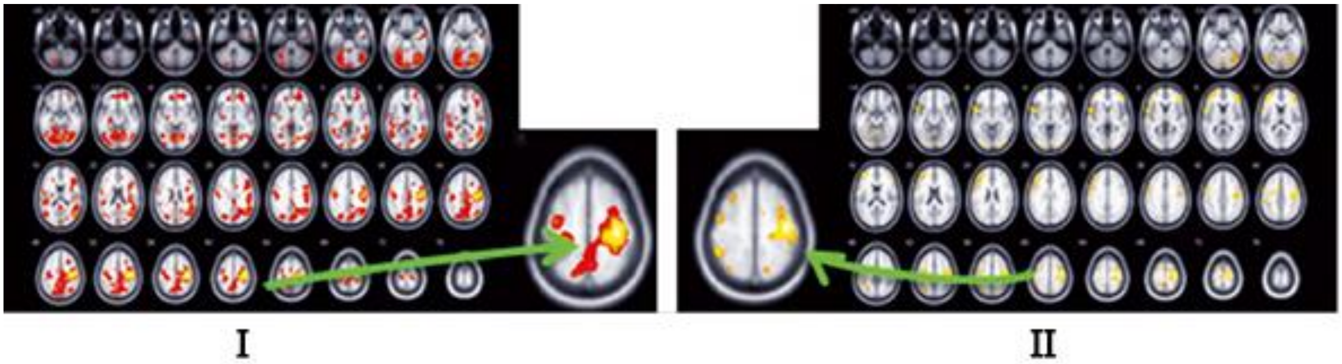
***Neurofeedback by BOLD Signal After a Stroke: "Birth" of an Interactive Brain**.* The first study that confirmed the possibility of poststroke restoring of the functions of the brain motor areas using fMRI NFB was published in 2012. Six subjects (two patients with hemiparesis after a subcortical stroke in more than one year and four healthy volunteers with an average age of 25.3 years) during three training sessions were instructed to increase the activity of the ventral premotor cortex (vPMC), one of the secondary motor areas. All participants learned to voluntarily increase the BOLD signal in the vPMC, however, the strength of the pinch grip (assessed as a behavioral end point) remained unchanged in one patient and one volunteer. An interesting finding of this study was revealed while comparing the levels of intracortical inhibition/facilitation with the degree of change in the BOLD signal during training. It turned out that initially high level of intracortical facilitation or a low level of intracortical inhibition assessed using transcranial magnetic stimulation (TMS) correlated with the success of self-regulation of the BOLD signal in vPMC. Moreover, the increase of the BOLD signal in vPMC, in turn, suppressed intracortical inhibition, revealing the reciprocal relationship of these two processes. Since the study was conducted during the development of the method and the main aim was to study the feasibility of learning the self-regulation of vPMC activity, the relationship of the studied neurophysiological changes with the functional outcomes was not evaluated. In addition, the limitations of the applied TMS protocol did not allow the authors to understand whether the increase of M1 excitability during fMRI IBS training was direct or indirect, through the modulating effects of vPMC (Sitaram et al., 2012).

Another study included four patients who had a stroke more than 6 months before the start of the training (two 2-hour sessions during 1 week). Participants practiced increasing the strength of the functional connections of two regions: 1) the motor cortex at the border of the affected area and 2) the thalamus of the same hemisphere. Three patients showed a significant increase of the characteristic value; two patients were able to reproduce this effect without feedback during a special test (transfer run), which confirmed the formation of the self-regulation skill. At the same time, the training was found to be most effective in subjects who demonstrated the most severe impairments of motor functions before the start of the training (Liew et al., 2016). Regretfully, the relations between neurobiological and behavioral characteristics were not considered in these studies. However, it should be emphasized that it was the first study of using fMRI NFB in stroke rehabilitation where network vocabulary was used and patients were trained to control not the signal from the motor areas, but the FC between them.

A recent pilot study by Lioi et al. (Lioi, Butet, et al., 2020; Lioi, Fleury, et al., 2018) was aimed to educate patients with poststroke hemiparesis to self-regulate the activity in the ipsilateral supplementary motor area (SMA) using both the BOLD signal and the EEG signal (in case the EEG signal of the event-associated cortical rhythm desynchronization [ERD] was assessed). The study included two patients with left-sided hemiparesis after a stroke that occurred more than 6 months before the start of the training. During two training sessions (5 min each) the patients were instructed to imagine the movement of the paretic arm, while the result of ROI activation was presented to them in the form of a visual signal. The first part of the study (Lioi et al., 2018) proved the feasibility of such a paradigm in patients with hemiparesis and revealed their high motivation to participate in training sessions based on animation and feedback. In the second part (Lioi et al., 2020) the study protocol was extended: after the first bimodal training session three NFB EEG sessions were conducted, followed by fMRI-EEG bimodal training (five training sessions in total). Motor functions were assessed before and after the training. A very important feature of the NFB design, in our opinion, was an adaptive character of training, specifically, the reward for the activation of each of the two ROIs chosen by the researchers changed consequently: at the first training session SMA activation was rewarded higher, and at subsequent sessions the reward for M1 activation was greater. For all four patients (stroke at least 1 year before the training; two of them had ischemic stroke) their work on the strategy of paretic arm movement pattern resulted in an increase in the and ERD signals in the SMA and M1 (according to the Wilcoxon test p = 0.004 and 0.006, respectively). For two patients who showed the most significant increase in M1 activation in the ipsilateral cortex at the end of training there was also a functional improvement according to the Fugle-Meyer test (hand subscale): from 19 to 25 points for one patient and from 50 to 53 for the other. The patient with less marked activation of M1 showed no changes in hand function after training. This outcome may have been affected by a significant impairment of the corticospinal tract (CST) integrity—the fractional anisotropy (FA) asymmetry index was 0.105. It is relevant to note that the two patients mentioned above had relatively intact CST, with FA asymmetry index 0.04 and 0.06, respectively. However, for the fourth patient the CST preservation (FA index = 0.05) was not sufficient for the motor function progress: the Fugle-Meyer score decreased from 41 to 37, and M1 activation in NBU sessions was found weak (although SMA was activated well). It can be assumed that this failure is associated with the cortical localization of the lesion (three other patients suffered a subcortical stroke).

A fundamentally different research, treatment and rehabilitation approach characterized by a change the targets, from cognitive impact of specific brain areas to a more global and holistic view of cerebral networks, was demonstrated in the works of Savelov et al. (Savelov, Shtark, Kozlova, et al., 2019; Savelov, Shtark, Mel'nikov, et al., 2019b). The outcome of IBS on the bimodal fMRI-EEG platform was assessed not only in terms of restoration of the paretic arm functioning, but mainly in terms of FC dynamics and remodeling of cerebral network elements dispersed throughout the brain (Figures 5–8).

Figure 5. *Distribution of Activated Voxels in the Patient's Brain During Actual Work with the Paretic Limb at Different Stages of the IBS Course*



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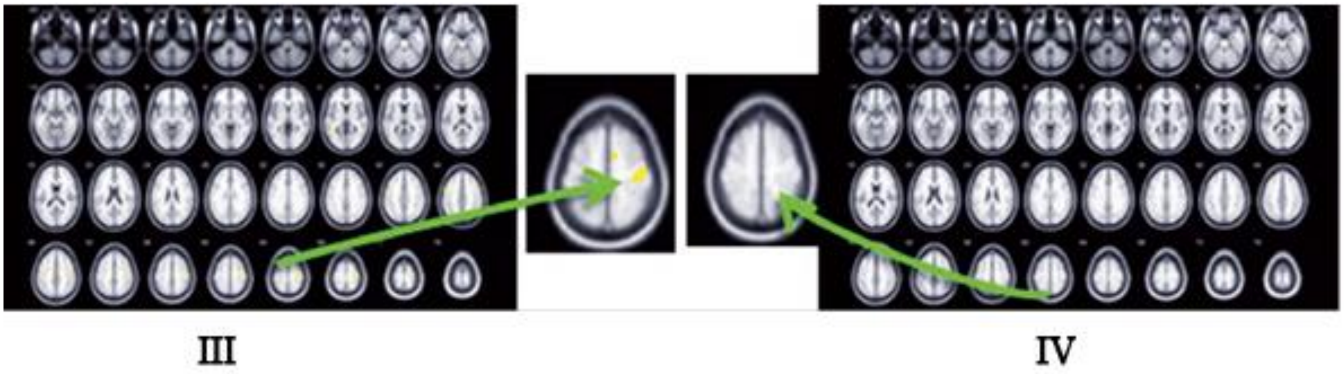
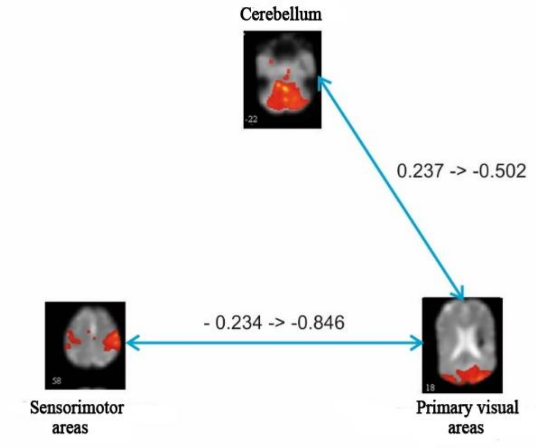


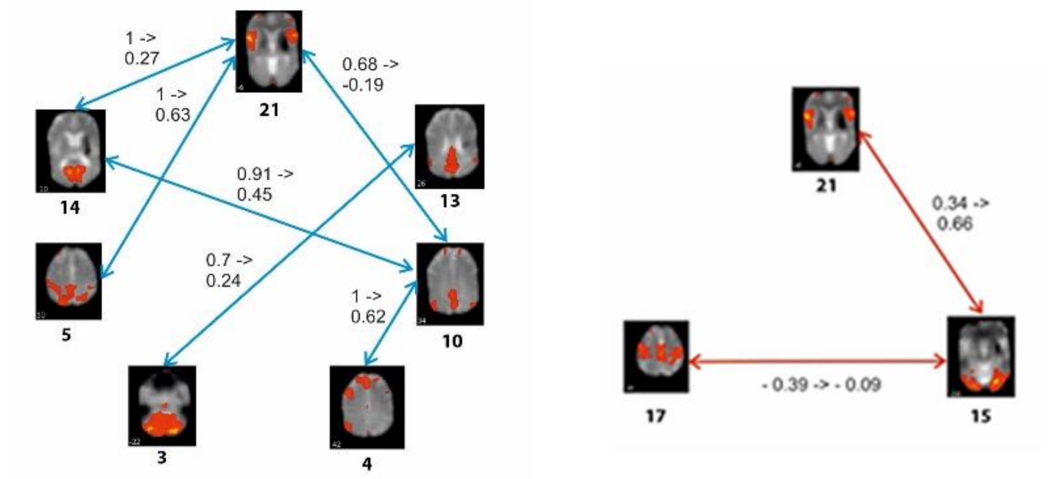
Note. During the IBS course (stages I, II, III, and IV), while performing a real hand movement, the activity of irrelevant cerebral regions (in particular, the occipital lobes) decreases, as well as the intensity of the ROI signal, which, apparently, is associated with the skill acquisition and ability to perform with less energy consumption (Savelov et al., 2019b).

Figure 6. *Evolution of Functional Relationships of Independent Components from First to Fifth IBS Session in a Patient with Left-Sided Hemiparesis.*



Real grip of left (paretic)

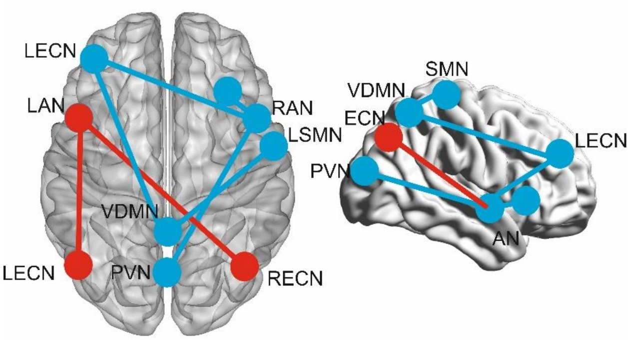
Note. The patient demonstrated reciprocal connections between the primary visual and sensorimotor areas and the cerebellum during a real grip of the left (paretic) hand. This was probably due to a patient's poor proprioception, as a result of which precise movements can only be performed under visual control. During training the proprioceptive function is restored, and vision does not play a leading role in the coordination of movements (see also Figure 5). Arrows - statistically significant change of FC in a pair of components during training (correlation coefficient of temporal dynamics in a pair of networks for 1 and 5 sessions, respectively). Each component corresponds to a number: 3 - cerebellum (cerebellar network); 4 - lateral frontal region (FPN on the left); 5 - precentral gyrus, precuneus (network of spatial perception); 10 - lateral frontal region, posterior cingulate gyrus, precuneus (dorsal network of passive work); 13 - precuneus, wedge (precuneus network); 14 - posterior cingulate gyrus, precuneus (primary visual network); 15 - lingual gyrus, wedge (network of the highest level of visual processing); 17 - pre- and postcentral gyrus (sensorimotor network); 21 - superior temporal, inferior frontal gyrus (search network for significant stimuli) (Savelov, Shtark, Kozlova, et al., 2019).



BS at right Brodmann area 4

IBS at left Brodmann area 4

Figure 7. *Evolution of the Coefficients of the Strength of Functional Connections of the Components From the First to the Fourth Biofeedback Session in the Right Motor Zone (No Significant Connections on the Left) in a Patient with Left-Sided Hemiparesis.*

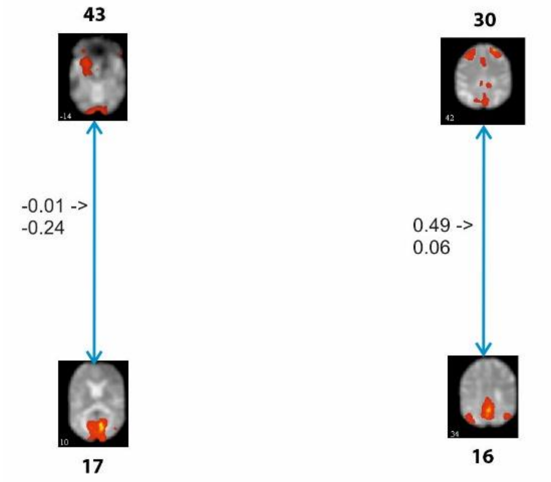


Note. Red lines - increase in the strength of functional connections, blue lines - decrease. L(R)ECN - left (right) CEN (FPN); VDMN - default network; L(R)AN - left (right) auditory network; PVN, primary visual network; SMN - sensorimotor network (Savelov, Shtark, Kozlova, et al., 2019).

In the study (Savelov et al., 2019b) dynamics of the BOLD and EEG signals was evaluated: the values of spectral power and coherence were calculated in the standard ranges of α, β, and θ separately for the attempts of paretic hand actual move and of imagining this action. At the end of the training (eight IBS sessions with an interval of 3–4 weeks) a significant clinical improvement was demonstrated in parallel with the reorganization of the Brodmann areas (BA) activities considering the power of the EEG rhythms (Figure 9). In general, the EEG and fMRI characteristics indicated an increasing similarity between the fragments of functional communications realized during real and imaginary movements during the training course. According to the authors opinion, the observed patterns revealed a “common neural pathway” that can be used in IBS to restore the skill of hand physical contraction with the lowest energy costs (Savelov et al., 2019b).

Another study attempted to compare the clinical and neurophysiological effects of a mono- and bimodal IBS platform (i.e., fMRI IBS and fMRI EEG IBS) in motor stroke rehabilitation (Bezmaternykh et al., 2021). Assessing the sample as nonrepresentative (one patient for each method), the authors concluded that both patients learned to increase C3/C4 coherence with other central leads in the EEG μ-band on the basis of feedback, and both of them improved their functional performance. However, the patient who trained on the bimodal platform mastered the regulation of EEG activity to a greater extent. This seems logical at first glance, although further research is certainly needed to explain the significance of the observation for the restoration of function.

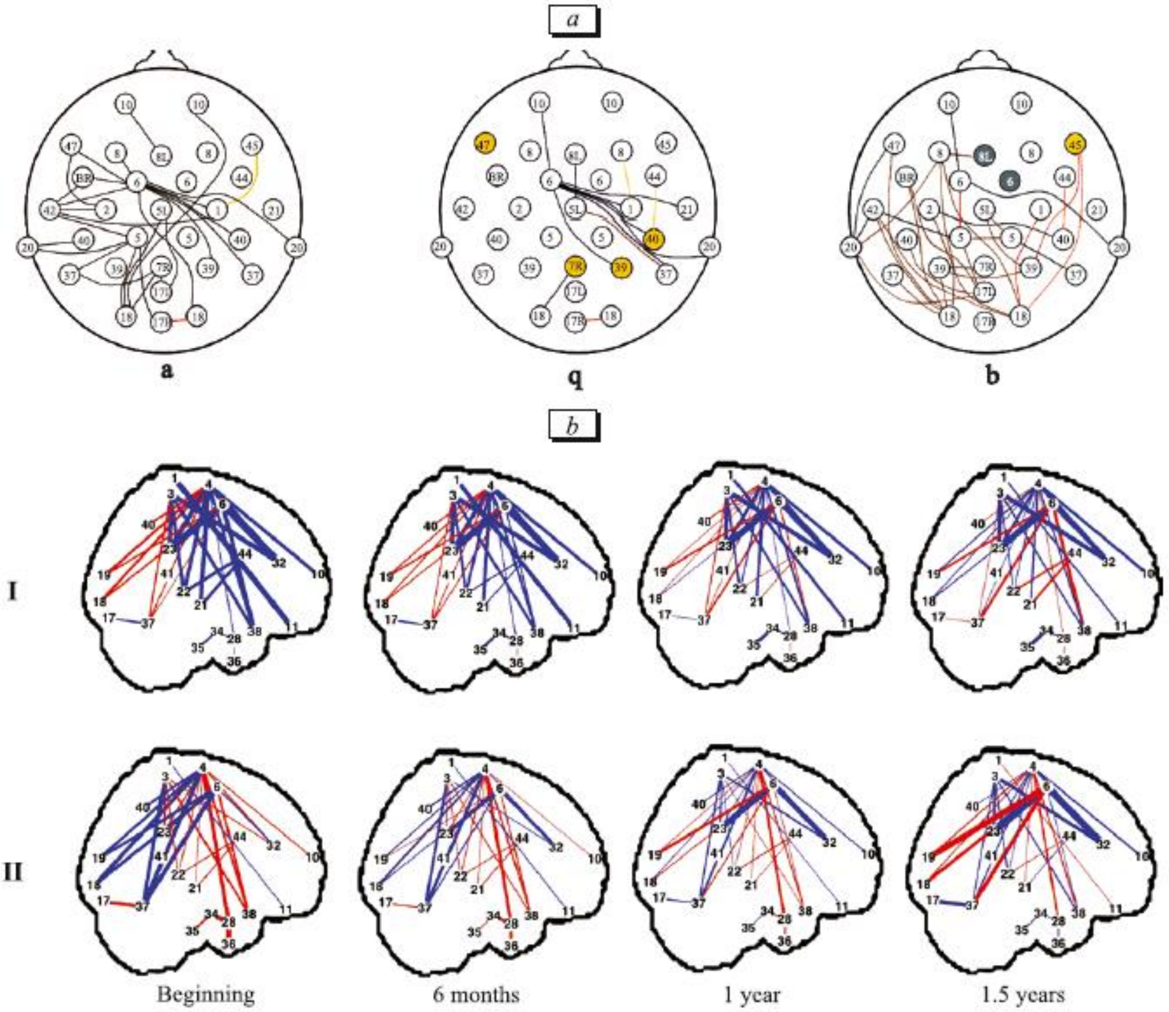
Figure 8. *Evolution of the Coefficients of Functional Connections of the Components from the First to the Fifth Biofeedback Session Along the Left (Left) and from the First to the Fourth Session Along the Right (Right) Brodmann Zone 4.*



Note. In the context of ISM in the left motor area, there was an increase in desynchronization of the primary visual network with a component that included the lingual and inferior frontal gyrus; i.e., reduced integration in the processing of visual stimuli. The biofeedback of the right Brodmann zone 4 was accompanied by a decrease in the connectivity strength of the passive mode network and the relevant stimulus search network, which corresponds to the normal relationship of these systems and may reflect a decrease in cognitive control over the task. Arrows - statistically significant change in FC in a pair of components during the course (correlation coefficient of temporal dynamics in a pair of networks for 1 and 5 sessions, respectively). A number is indicated for each component: 16 - precuneus, posterior cingulate gyrus (passive mode network); 17 - wedge, lingual gyrus (primary visual network); 30 - superior and middle frontal gyrus, precuneus (relevant stimulus search network); 43 - lingual, inferior frontal gyrus (Savelov, Shtark, Kozlova, et al., 2019).

Recently preliminary data from the proof-of-concept (PoC) study of a new paradigm were published where participants practiced not only to activate the ROI, but also to regulate the degree of this activation—the so-called "graded fMRI neurofeedback" (Mehler et al., 2020). This paradigm was previously tested in healthy volunteers (Mehler et al., 2019; Sorger et al., 2018), then transferred later to the stroke population (Mehler et al., 2020).

Figure 9. *Representation of Linear Trends in the Changes of (A) EEG Parameters and (B) the Strength of fMRI-Reported Functional Connections During Neurofeedback Course.*



Note. a) α, β, and θ EEG rhythms. The numbers indicate (BA) corresponding to EEG leads. The colored circle (BA) marks a trend in the power of EEG rhythm at the corresponding lead. The lines between circles (BA) illustrate the trends of coherence within the given frequency range between two leads. The red (black) color marks the coherences and spectrum powers which respectively increased (decreased) during imaginary or real work with the paretic wrist. The brown (yellow) color marks the coherences and spectrum powers which respectively increased (decreased) during real work and decreased (increased) during the imaginary one. b) The numbers indicate BA. The red and blue lines mark the positive and negative connections, respectively, while the line thickness corresponds to connection strength. I and II: patterns of real and imaginary wrist clench, respectively (Savelov et al., 2019b).

The hypothesis was that using the fMRI NFB contour a poststroke patient was able to create an image of the paretic arm movement in such a way as to 1) steadily activate the SMA of the ipsilateral hemisphere and 2) independently control SMA activity to achieve the discrete (high and low) target levels. Following strict selection criteria of the study five patients were recruited, heterogeneous in terms of the severity of upper limb dysfunction, including one patient with complete motor recovery. The patients underwent two training sessions of movement imagination of the paretic hand based on the BOLD feedback signal from the SMA at the lesion side and learned to activate the signal from the SMA. The authors keep open the confirmation of the hypothesis of the ability to regulate the degree of this activation and invite to discuss this topic (Mehler et al., 2020). We would like to emphasize the boldness of the declared paradigm that considers the model of neurofeedback as reinforcing the "interactive brain" concept.

Table 1

IBS in Poststroke Motor Rehabilitation

№	Автор	Patients/ control, *n*	Platform Modality	ROI	Number of Sessions	Outcome
1	Sitaram et al., 2012	2/4	fMRI	vPMC	3	All participants learned to activate ROI signal. Pinch grip strength increased in four subjects (three healthy subjects and one patient).
2	Liew et al., 2016	4/0	fMRI	FC iM1 - iThal	2	Three participants learned to activate ROI signal, activation more manifested in patients with severe paresis. Skills were tested at transfer run. Motor function was not assessed.
3	Lioi et al., 2018	2/0	fMRI-EEG	iSMA	2	All participants learned to activate ROI signal.
4	Savelov, Shtark, Mel'nikov, et al., 2019b	1/0	fMRI-EEG	iM1; ERD at BA	8	Activity zones were reorganized throughout the brain. Hand motor function improved.
5	Savelov, Shtark, Kozlova, et al., 2019	12/0	fMRI-EEG	iM1	3–8	Formation of reciprocal connections between primary visual areas, cerebellum and sensorimotor areas with real grip of the paretic hand.
6	Lioi et al., 2020	4/0	fMRI-EEG	iM1 and iSMA	2+3*	Neurofeedback adaptive model. All participants learned to activate ROI signal. Motor function restoration was better in case of relatively intact CST and subcortical stroke.
7	Mehler et al., 2020	5/0	fMRI	iSMA	2	All participants learned to activate ROI signal.
8	Bezmaternykh et al., 2021	2/0	fMRI-EEG	iPreM, iSMA, cSMA	6	Both participants learned to activate ROI signal. C3/C4 coherency with other central leads in EEG μ-band. Both participants also improved their ability to imagine movements.

Note. *n* - number of observations; ROI - region of interest; fMRI - functional magnetic resonance imaging; EEG - electroencephalography; vPMC, ventral premotor cortex; SMA - supplementary motor area; CST - corticospinal tract; FC - functional connectivity; Thal - thalamus; M1 - primary motor cortex; i - ipsilateral; c - contralateral; ERD - event-related cortical rhythm desynchronization; BA - Brodmann area; PreM - premotor cortex * - two sessions were conducted on a bimodal fMRI-EEG platform and three sessions on an EEG-monomodal platform

Conclusion

In February 2015, a conference was held in Gainesville (Florida, USA) dedicated to the "birth" of the trimodal platform; that is, integration of the fMRI-EEG tandem into the adaptive (cognitive, etc.) feedback contour (Sulzer et al., 2013). The targets of the neurofeedback were cerebral structures and neural networks. We called this entire methodological structure an interactive therapy (stimulation) of the brain (Mel'nikov et al., 2017). Thanks to the IBS a person, healthy or sick, has an opportunity to learn, being in a tomograph, to control the characteristics of visualized intracerebral formations; that is, cognitively rebuild the stereometry of neural networks, that leads to therapeutic and behavioral metamorphoses. The authors of the article participated in a conference in the United States and then entered the circle of this continually developing scientific community (Maastricht - Aachen, the Netherlands - Germany, 2017; Nara, Japan, 2019). Today, this direction is an undoubted trend in neurosciences that provides methodology, neurotechnology, and tools for modern neurobiological problems of any complexity.

What can be attributed to the basic knowledge of this direction?

1. First of all, the phenomenon of a polymodal platform that allows solving problems of

spatial and temporal resolution. Built into the feedback contour, this format allows combining online volitional control of cerebral hemodynamics and electrogenesis using both modalities simultaneously.

2. New essence: FC becomes the target of the interactions, drawing the recovery process (for example, after stroke) to *in vitro* situation. We assume that the development of this option will provide a basis for the “transplantation” of a neural network created on a 3D printer in the future.
3. The concept of "network neurology", largely a product of fMRI, that allows us considering stroke and its consequences as "network diseases," which changes the view on many stroke aspects: diagnosis, treatment, recovery, and prognosis. The patient's medical history involves a new lexical and semantic vocabulary, and FC becomes a numerical expression of brain neuroplasticity.
4. The so-called phenomenon of BOLD-dependent EEG that arose in connection with the need to expand the applicability of the IBS, which was prevented by two complicating circumstances: a close "local" binding with a tomograph and, of course, the commercial component of the whole technology. The studies in this direction appeared in Israel and were conducted in the frameworks of the fMRI-EEG tandem, demonstrating a real transition to BOLD-dependent EEG using the example of affective disorders (Meir-Hasson, Keynan, et al., 2016; Meir-Hasson, Kinreich, et al., 2014; Keynan, Cohen, et al., 2019; Keynan, Meir-Hasson, et al., 2016) and similar transformations in relation to stroke (Rudnev et al., 2021).
5. Finally, diffusion characteristics reflecting the transformations of the brain microstructure (in terms of "network vocabulary," the dynamics of neural networks SC) are being considered as possible predictors of stroke itself (Alves et al., 2022; Zhuravleva et al., 2022) and its outcomes (Spampinato et al., 2017; Yu et al., 2020), and become one of the potentially “controllable” characteristics.

Thus, due to fMRI, neurofeedback technology is now undergoing a period of “revolutionary” reformation moving into a coordinate system of network neuroscience that promises a new understanding of the structural and functional organization of the brain.

Author Declaration and Acknowledgement

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