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Brain connectivity and neurological disorders after stroke

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Abstract

Purpose of review—An important challenge in neurology is identifying the neural mechanisms underlying behavioral deficits after brain injury. Here, we review recent advances in understanding the effects of focal brain lesions on brain networks and behavior.

Recent findings—Neuroimaging studies indicate that the human brain is organized in large-scale resting state networks (RSNs) defined via functional connectivity, that is the temporal correlation of spontaneous activity between different areas. Prior studies showed that focal brain lesion induced behaviorally relevant changes of functional connectivity beyond the site of damage. Recent work indicates that across domains, functional connectivity changes largely conform to two patterns: a reduction in interhemispheric functional connectivity and an increase in intrahemispheric functional connectivity between networks that are normally anticorrelated, for example dorsal attention and default networks. Abnormal functional connectivity can exhibit a high degree of behavioral specificity such that deficits in a given behavioral domain are selectively related to functional connectivity of the corresponding RSN, but some functional connectivity changes allow prediction across domains. Finally, as behavioral recovery proceeds, the prestroke pattern of functional connectivity is restored.

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Conflicts of interest

There are no conflicts of interest.

Summary—Investigating changes in RSNs may shed light on the neural mechanisms underlying brain dysfunction after stroke. Therefore, resting state functional connectivity may represent an important tool for clinical diagnosis, tracking recovery and rehabilitation.

Keywords

recovery; resting state functional connectivity; resting state network; stroke

INTRODUCTION

A fundamental challenge in neurology is to understand the effects of focal lesions on brain activity and subsequent behavioral impairments. Traditionally, anatomical damage of brain modules was thought to affect corresponding cognitive functions, leading to behavioral impairments. However, since the seminal paper of von Monakow on diaschisis [1], it has been shown that stroke also induces changes in function and physiology of brain regions distant from the site of anatomical damage (see a recent review by Carrera and Tononi [2]). A promising way to understand the widespread functional changes induced by stroke is to study the functional organization of brain networks. Measurements of the temporal correlation of blood-oxygenated-level-dependent (BOLD) signals between different brain regions in the absence of a task [3,4], that is resting-state functional connectivity, can be used to identify such networks, called resting state networks (RSNs). RSNs are associated with specific functions (e.g. vision, attention, motor) and their topography recapitulates that of networks activated during tasks [5–10]. Notably, a growing number of studies indicates that stroke induces changes of functional connectivity within and between RSNs [11–13] and that these changes correlate with behavioral impairment at acute [11,14,15] and chronic [11,16] phases (see Varsou *et al.* [17], for a review). Here, we review the latest reports showing behaviorally relevant stroke-induced changes of functional connectivity at acute and chronic phases after stroke and after rehabilitation.

BEHAVIORALLY RELEVANT CHANGES OF RESTING STATE FUNCTIONAL CONNECTIVITY AFTER STROKE AT ACUTE STAGE

In 2007, He *et al.* [11] demonstrated that the severity of spatial neglect, that is a deficit in processing stimuli on the body and in the space contralateral to the lesion, was correlated with the degree of reduction of the interhemispheric functional connectivity of regions of the so-called ‘dorsal attention network’ (DAN), which are involved in the control of visuo-spatial attention [18]. Similar results were obtained in another small sample study in 2010 [14]. Baldassarre *et al.* reexamined the relationship between neglect and functional connectivity across several RSNs in a large and heterogeneous (i.e. not only neglect) group of first ever stroke patients [15]. They observed that the severity of spatial and nonspatial deficits in neglect patients was associated with two correlated patterns of abnormal functional connectivity involving dorsal attention/sensory motor networks: a bilateral reduction of interhemispheric functional connectivity within these networks; an increase of functional connectivity between these networks and fronto-parietal/default mode networks in the right hemisphere, which normally are anticorrelated (Fig. 1). Therefore, neglect was related to the functional connectivity within and between (i.e. interaction) multiple RSNs.

Siegel *et al.* [19[■]] subsequently showed that these two patterns of behaviorally relevant functional connectivity are observed across many behavioral domains such as attention, language, motor function, verbal memory, and spatial memory.

A large number of studies have examined the relationship between behavioral deficits and changes in functional connectivity in the sensory motor domain. In 2010, a study in humans [14] and one in rodents [20] showed that motor deficits at the acute stage after stroke were correlated with the reduction of interhemispheric functional connectivity of the motor network. Similar observations have been recently reported in other studies [21–25]. In an interesting study, Rehme *et al.* [26[■]] used a multivariate fMRI approach to classify stroke patients with and without motor impairments. The authors studied 20 stroke patients, half with and half without deficits of hand function and a group of 10 healthy controls. Using functional connectivity between the ipsilesional primary motor cortex (M1) and the rest of the brain as the input features to a support vector machine, the authors classified patients with hand deficits compared with controls and patients without deficits with high accuracy (82.6–87.6%; Fig. 2). The classification was driven by a decrease of interhemispheric functional connectivity of M1 and an increase of functional connectivity between M1 and premotor areas.

Strokes often produce a cluster of correlated behavioral deficits [27]. For instance, patients with right hemisphere damage may exhibit unilateral spatial neglect, a general slowing of reaction time, spatial memory deficits, and motor impairments of the left side of the body (arm/limb) [27]. Accordingly, disentangling behavioral-specific patterns of functional connectivity might guide clinical and theoretical understanding. Baldassarre *et al.* [25] investigated this issue by studying the relationship between attention and motor deficits and interhemispheric functional connectivity of the dorsal attention and motor networks in a large group of right hemisphere damaged patients. A partial correlation technique that orthogonalized behavioral deficits and network functional connectivity was used to isolate the (relative) unique correlation between each deficit and network. For example, when the correlation between the attention deficit and the DAN was computed, both the motor deficit and motor network functional connectivity were regressed out. Using this procedure, a double dissociation was found that linked deficits of a given domain, for example attention, selectively and preferentially to the reduction of the interhemispheric functional connectivity of the corresponding network, for example the DAN. Therefore, this study provided evidence for the behavioral specificity of functional connectivity even for two related domains such as attention and motor, although only under circumstances in which correlated influences were removed. Conversely, Siegel *et al.* [19[■]] showed that some changes in functional connectivity predict behavioral deficits across a broad range of domains rather than being highly specific.

Although the above studies show the behavioral significance of resting state functional connectivity, they do not address the relative importance of functional connectivity and lesion topography for predicting behavioral deficits. Siegel *et al.* used machine-learning models to compare how well functional connectivity and lesion topography predicted behavioral deficits in each of six domains (attention, visual memory, verbal memory, language, motor, visual) in a large cohort of stroke patients ($n = 132$) [19[■]]. Although

sensory motor functions (visual and motor domains) were better predicted by lesion topography, associative functions (visual memory and verbal memory) were better predicted by functional connectivity. Attention and language deficits were well predicted by both.

Beyond correlation, a number of other measures based on the BOLD signal have been used to classify abnormalities after stroke. Graph theory, the mathematics of network organization, is one promising tool for understanding poststroke changes. In this framework, regions of interest (ROIs) in the brain are called ‘nodes’, whereas the pairwise relationships between nodes, indexed by functional connectivity, are defined as ‘ties’. An assemblage of nodes and ties represents a graph or network. In a recent study, Zhu *et al.* [28] found that, as compared to healthy individuals, patients showed higher nodal centrality as indexed by nodal degree (i.e., number of nodes exhibiting correlation with a given node) and nodal efficiency (i.e., how good is the communication between a node’s neighbors when the node is removed) in several regions of the default mode network. Critically, the altered nodal centrality of the middle frontal gyrus was associated with poor cognitive efficiency as indexed by a low mini-mental state examination score. The amplitude of low-frequency fluctuations (ALFFs), a measure of the BOLD signal within a region, also has been used to investigate the consequences of stroke. This metric, usually obtained by measuring the total power within a specific frequency band (i.e. 0.01–0.1 Hz), is an index of the strength of low frequency oscillations. Previous studies showed that ALFFs reflect physiological signals (3) and exhibit behavioral relevance in clinical [29] and healthy [30] populations. In the language domain, Yang *et al.* [31] reported that aphasic patients, compared to healthy individuals, showed increased ALFFs in contralesional mesial temporal cortex (hippocampus/parahippocampus). Changes in ALFFs were negatively correlated with the construction score in the Aphasia Battery of Chinese, i.e. low ALFFs were associated with poor language production.

Overall, these studies strongly argue in favor of a network-wide account of brain architecture in which structural damage produces abnormal interactions between distant areas leading to behavioral impairments of cognitive functions in a selective manner.

RESTING STATE FUNCTIONAL CONNECTIVITY AT CHRONIC STAGE

Although the studies described above have investigated the effects of stroke on functional connectivity at the acute phase, three recent reports examined the patterns of abnormal functional connectivity at the chronic stage, for example ~3–4 months after stroke onset. Tang *et al.* [32] reported that as compared to healthy individuals, chronic patients with subcortical stroke exhibited reduced homologous interhemispheric functional connectivity of the precentral gyrus, postcentral gyrus, inferior frontal gyrus, middle temporal gyrus, thalamus, cerebellum anterior lobe, and cerebellum posterior lobe (CPL). Notably, the interhemispheric functional connectivity of the CPL was correlated with the Fugl–Meyer score of hand (FMA-H) and illness duration such that patients with low functional connectivity exhibited poor FMA-H and longer duration of impairment. These findings suggest that the functional connectivity of the CPL may represent a good indicator of motor functions at the chronic stage.

Almeida *et al.* [33] showed reduced functional connectivity between motor and executive control and visuospatial networks in patients with motor deficits vs. healthy controls, indicating that chronically, poor motor outcome is associated with abnormal functional connections across multiple networks.

Finally, Liu *et al.* [34] found higher interhemispheric functional connectivity of M1 in chronic stroke patients with well recovered motor functions as compared to healthy individuals. This increased functional connectivity was negatively correlated with the degree of damage of the cortical spinal tract and M1–M1 anatomical fibers, suggesting a compensatory mechanism of functional connectivity restoration when motor functions have recovered.

CHANGES OF RESTING STATE FUNCTIONAL CONNECTIVITY AND RECOVERY

Previous work in humans [11] and rodents [20] indicated that behavioral recovery proceeds in parallel with the restoration of normal resting state functional connectivity. More recent studies have primarily focused on recovery in the domains of attention and language function. We briefly consider each domain below.

For patients with acute neglect, recovery appears dependent on the normalization of connectivity in attention and motor areas. Ramsey *et al.* [16[■]] investigated the mechanisms underlying neglect recovery by studying longitudinally the resting state functional connectivity of a large cohort of stroke patients. Beginning with a-priori knowledge of disruptions associated with acute neglect, they correlated longitudinal changes (at 0.5, 3, and 12 months) of spatial and nonspatial deficits with changes in the functional connectivity of dorsal attention/sensory motor networks [16[■]] (Fig. 3). A whole-brain data-driven analysis was also conducted to identify patterns of functional connectivity behavior correlations related to neglect recovery. Both analyses indicated that recovery of neglect, mostly complete by 3 months, was associated with restoration of interhemispheric functional connectivity across attention, sensory, and motor networks as well as with the return of normal anticorrelation functional connectivity patterns in the right hemisphere.

In the language domain, two recent reports investigated the changes of functional connectivity at the chronic phase after stroke onset. In a small sample study ($n = 4$), Sebastian *et al.* [35] showed that recovery of naming deficits at 5–7 months after stroke in three out of four patients was mirrored by increased functional connectivity within the language network, whereas a patient with no recovery exhibited decreased functional connectivity. Although based on few cases, the study suggests that restoration of functional connectivity of language network may track the recovery of language production. Nair *et al.* [36] reported that, acutely, patients without documented clinical deficits of language as compared to healthy controls exhibited decreased functional connectivity of the language network, which then recovered at the chronic stage. Moreover, longitudinal changes in functional connectivity between left putamen and right superior parietal cortex were positively correlated with improved verbal fluency scores. These findings indicate that even

in patients without a clear diagnosis of aphasia, both language network and functions can be impaired and recover in parallel.

The reports reviewed above indicate that longitudinal changes in behavioral performance are parallel to the restoration of the patterns of resting state functional connectivity, suggesting that RSNs may be used to track recovery after focal brain injury.

NEW INSIGHT FOR REHABILITATION?

Although the studies described above have investigated the relationship between resting state functional connectivity and (relatively) spontaneous recovery, several investigations have focused on functional connectivity as related to rehabilitation after behavioral and brain stimulation treatment. In a longitudinal study, Volz *et al.* [37[■]] investigated the effects of intermittent theta-burst stimulation (iTBS) over ipsilesional primary motor cortex on motor function and resting state functional connectivity in a group of acute stroke patients prior to physiotherapy treatment. Patients with hand motor deficits were pseudo-randomized into two matched groups in which iTBS was delivered for 5 days either over ipsilesional primary motor cortex (M1-stimulation group) or parieto-occipital vertex (control-stimulation group). Whole brain resting state functional connectivity of ipsilesional M1 and motor functions as indexed by grip strength and the Jebsen–Taylor Hand Function Test, were measured at two time points: one day before the first iTBS session (baseline) and one day after the last iTBS session (posttreatment). Although both groups recovered over timepoints, the M1-stimulation group exhibited a significantly better outcome than the control-stimulation group. Notably, although the control-stimulation group showed a significant reduction of interhemispheric functional connectivity of ipsilesional M1 with several motor areas, the M1-stimulation group did not exhibit such decrease of motor network functional connectivity (Fig. 4) between pretreatment and posttreatment time points. Furthermore, changes in functional connectivity were correlated with improvement of motor functions. These findings indicate that iTBS mitigates the disruption of motor network as well as facilitates a good behavioral outcome.

Another stimulation tool for improving behavioral performance after stroke is transcranial direct current stimulation (tDCS). Two recent studies investigated the effects of tDCS on motor and language functions and on resting state functional connectivity after stroke. In a pilot study on a small sample of stroke patients ($n = 5$), Chen and Schlaug [38] employed tDCS for 10 sessions within 2 weeks, with the anode and cathode electrodes placed over the ipsilesional and contralesional motor cortex, respectively. The treatment induced significant behavioral amelioration of motor functions as well as increased functional connectivity of ipsilesional motor cortex with contralateral premotor cortex and bilateral precuneus. Similarly, in the language domain, Marangolo *et al.* [39] investigated the effects of tDCS on language recovery and resting state functional connectivity in a small group ($n = 9$) of aphasic patients with articulatory deficits. Patients underwent two 15-day sessions of language therapy and real or sham tDCS treatment with a 14-day intersession interval between the real and the sham condition. As compared to sham, tDCS stimulation induced a significant improvement in syllable and word production. Resting state functional connectivity was indexed by eigenvector centrality, a graph-based metric that quantitatively

identifies network profiles across the whole brain [40]. A high eigenvector centrality score is assigned to nodes exhibiting several connections with nodes that in turn are highly connected with many other nodes. Accordingly, this topological measure captures the influence of a given node across multiple networks. Between-session analyses revealed that several regions of motor, default, and control network exhibited increased eigenvector centrality after tDCS treatment as compared to sham tDCS. Interestingly, these changes were correlated with the improvement of syllables repetition accuracy after treatment.

Taken together, these studies indicate that treatment leading to recovery of behavioral functions is correlated with the restoration of patterns of resting state functional connectivity of multiple RSNs, suggesting that intrinsic brain activity may represent a biomarker for tracking rehabilitation.

CONCLUSION

The findings reviewed here have important clinical and theoretical implications. First, functional connectivity measurements of resting state activity can predict behavioral deficits after stroke. Second, changes in resting state functional connectivity may be used to track behavioral recovery longitudinally. Finally, functional connectivity may serve as a marker to better understand effects of rehabilitation paradigms. Future studies should aim at understanding the degree to which specific patterns of behavioral deficits are selectively related to patterns of abnormal functional connectivity. Understanding this relationship will facilitate the development of targeted/individualized treatments in clinical practice, because the functional connectivity score of a patient can be used in parallel with anatomical images to formulate an early diagnosis after stroke. Finally, from a theoretical point of view, these studies suggest that interindividual variability in complex behavior is partially accounted for by individual differences in patterns of spontaneous activity.

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KEY POINTS

- The human brain is organized in large-scale resting state networks (RSNs).
- Stroke induces behaviorally relevant changes of resting state functional connectivity within and across RSNs.
- Longitudinal changes of resting state functional connectivity reflect spontaneous recovery and rehabilitation outcome.
- Resting state functional connectivity can be used to predict behavioral deficits, track recovery and monitor the rehabilitation.

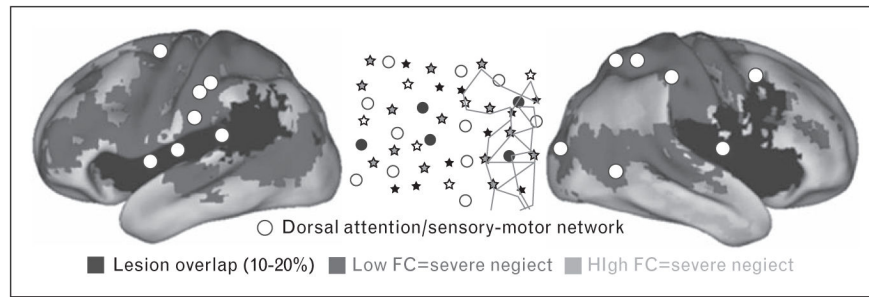


FIGURE 1.

Patterns of resting state functional connectivity associated to spatial neglect at acute stage. The white circles indicate the regions of interest (ROIs) belonging to dorsal attention/sensory motor networks, whose functional connectivity is associated to the degree of the rightward spatial biases in attention typical of neglect patients (schematically illustrated in central inset, in a large sample of stroke patients ($n = 84$)). Spatial neglect is associated with two abnormal patterns of functional connectivity derived from the white ROIs: reduced interhemispheric functional connectivity with regions of dorsal attention/sensory motor networks in the opposite hemisphere (blue voxels); increased functional connectivity (reduced segregation) with regions of default mode/fronto-parietal networks (orange voxels). Note that dorsal attention/sensory motor and default mode/fronto-parietal networks are typically anticorrelated in healthy individuals, hence, the increased functional connectivity should be read as reduction of ‘segregation’ between two sets of networks. Black color indicates voxels damaged in 10–20% of patients. Reproduced with permission [15].

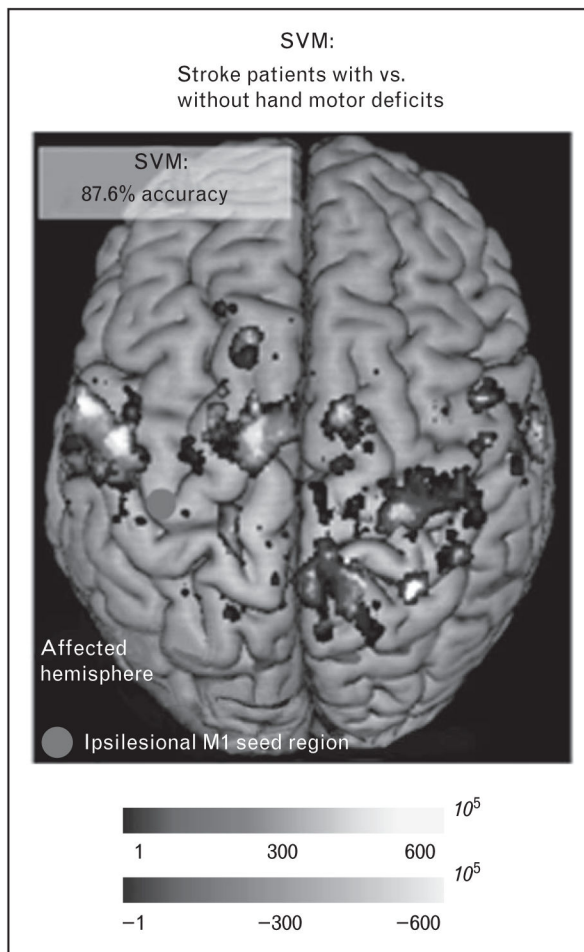


FIGURE 2.

Multivariate SVM classification distinguishes patients with versus without motor deficits. Resting-state functional connectivity of ipsilesional M1 provided 87.6% mean accuracy for the classification of stroke patients into hand motor impairment groups. Blue: areas of voxelwise resting-state connectivity, which contribute to the classification of stroke patients without hand motor deficit (i.e. stroke patients with hand motor impairment were characterized by reduced connectivity with these areas). Red: areas of voxelwise resting-state connectivity, which contribute to the classification of stroke patients with hand motor impairment. The scaling of the weights reflects the relative contribution of voxelwise resting-state connectivity with ipsilesional M1 to group classification. The green dot indicates the seed voxel coordinate in ipsilesional M1. SVM, Support Vector Machine. Reproduced with permission [26¹¹].

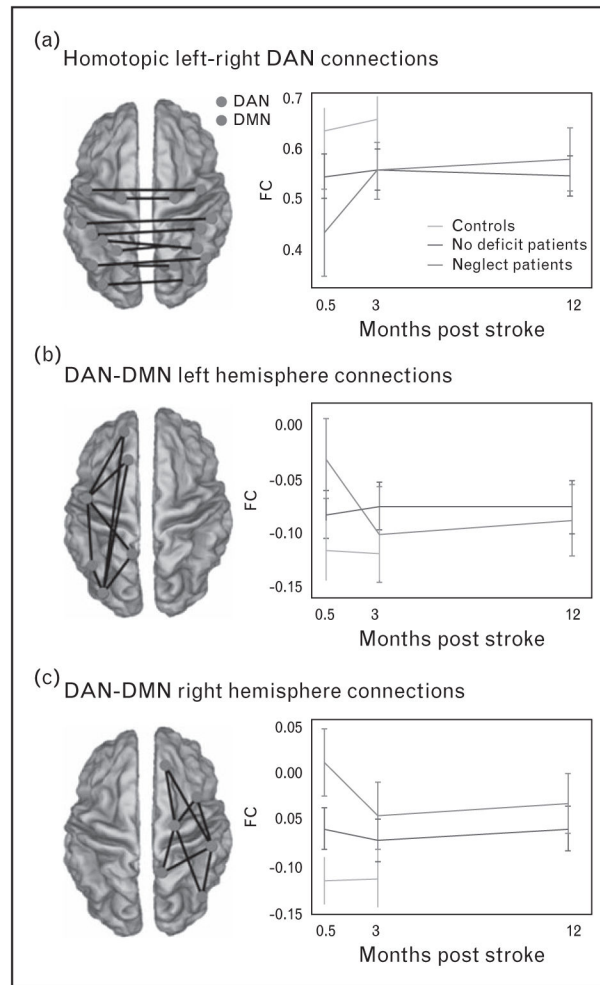


FIGURE 3.

Recovery of spatial neglect is associated to restoration of the interhemispheric functional connectivity of DAN and anticorrelation between DAN and default mode network (DMN). Interhemispheric dorsal attention network (DAN) (a), left hemisphere DAN to DMN (b) and right hemisphere DAN to DMN (c) functional connectivity over time for the deficit (red) and no deficit (blue) patients and controls (green). The brain figures show a subset of the connections that were averaged in the graphs (blue dots represent DAN ROIs and red dots DMN ROIs). Reproduced with permission [16[■]].

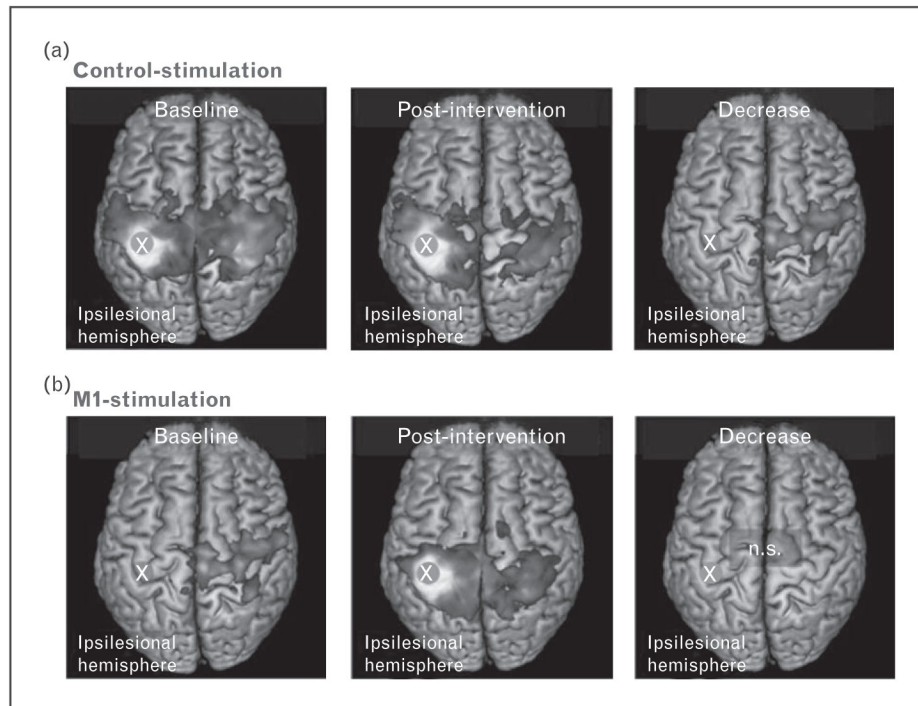


FIGURE 4.

iTBS treatment increases inter-hemispheric functional connectivity of motor network after stroke. Interhemispheric resting-state connectivity of ipsilesional M1 decreased in the early subacute phase in control-stimulated patients (a). Interestingly, no significant decrease was evident in the M1-stimulation group (b). Reproduced with permission [37[■]].