Topical Review

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The Value of Resting-State Functional Magnetic Resonance Imaging in Stroke

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In the acute phase of stroke, the use of imaging techniques aims to provide pathophysiological information concerning vascular patency, areas of hypoperfusion, and metabolic and structural damage. Based on such information, therapeutic decisions such as the administration of reperfusion medications are made. After the acute phase, brain plasticity and reorganization are the main mechanisms underlying functional recovery, and improvement is determined by functional adaptations of distributed brain networks mediated by connectivity.[1] Accordingly, new therapeutic approaches, such as noninvasive brain stimulation, target the modulation of connectivity and network function.[2,3] At this stage, imaging-based biomarkers should reflect the status of cerebral networks. As the relevance of the network view of stroke becomes increasingly evident,[4] so does the usefulness of imaging techniques in the assessment of cerebral network function in clinical populations. Most notably is the use of resting-state functional MRI (rs-fMRI).

rs-fMRI is a task-independent functional neuroimaging approach based on intrinsic low-frequency fluctuations (typically <0.1 Hz) in the blood oxygenation level–dependent (BOLD) signal. This signal can be used to compute the temporal correlations between spatially remote areas, termed: functional connectivity. In the healthy brain, functional connectivity is increased between areas that are part of the same functional network even in the absence of task. The resulting spatial patterns closely resemble the activation patterns identified during specific tasks,[5] and these networks are referred to as resting-state networks.[6] Thus, rs-fMRI provides an approach for detailed investigation of functional networks, as well as a more general method for assessing changes in intrinsic neuronal activity. Unlike task-based methods, measures of intrinsic functional connectivity allow for flexible post hoc analyses that probe multiple functional networks. Additionally, the minimal demands on the patient during the scanning session make the technique an optimal choice for clinical settings.

rs-fMRI may offer the prospect of providing therapeutically useful information on both the focal vascular lesion and the connectivity-based reorganization and subsequent functional recovery. Here we provide an overview of recent applications of rs-fMRI to stroke diagnostics and prognostics and discuss future perspectives and considerations. We begin with methods used to characterize local alterations in acute stroke and proceed to describe studies of specific and general connectivity changes at various phases of the recovery process. For a detailed description of the studies reviewed here, see Table I in the online-only Data Supplement.

Local Intrinsic BOLD Activity as a Measure of Hypoperfusion

Correlation analyses based on the BOLD signal are thought to reflect neuronal synchronization.[7] However, the BOLD signal additionally contains information concerning local blood flow and oxygen consumption[8] and is, therefore, potentially useful for assessing pathophysiological events within the stroke lesion itself. Current stroke MRI approaches use MR angiography, fluid attenuated inversion recovery, as well as diffusion and perfusion imaging to identify the severely damaged infarct core and, most importantly, the potentially salvable tissue on appropriate reperfusion therapy. The necessity of susceptibility contrast agent application in perfusion imaging[9] is a major disadvantage because it can cause severe side effects (eg, nephrogenic systemic fibrosis). In addition, the use of a contrast agent prohibits the acquisition of repeated scans during the same session, which can be necessary in a clinical setting because of data loss (eg, from excessive motion). Alternative noninvasive approaches such as arterial spin labeling (ASL) have been suggested to replace contrast-based perfusion imaging.[10,11] ASL has the advantage of quantitatively assessing perfusion with no need of contrast agent. However, so far, it has not been widely used in clinical setting possibly because of low signal-to-noise ratio in areas with long transit times.[11] In a recent study, ASL failed to detect 7 of 39

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perfusion lesions.[12] In contrast, recent developments in ASL may improve its applicability.[10]

rs-fMRI, which also does not require the use of a contrast agent, has recently been used to identify the perfusion deficit.[13] Using time shift analysis, a high spatial correspondence has been found on the individual level with the area of hypoperfusion as defined by perfusion imaging (see Figure 1).[13] Time shift analysis was defined as the temporal shift necessary for maximum correlation with an average representative time series (ie, the global mean). These findings have been replicated in both acute patients after stroke and patients with chronic stenoocclusive vessel disease.[14] Given these results of time delay from the global mean, rs-fMRI could provide comparable results to those of conventional perfusion MRI without the need for contrast agents and may be of clinical value for diagnostic decisions, even in the acute phase after stroke. Although promising, this recent discovery should be further validated in larger cohorts, and issues such as motion artifacts and correlation with different perfusion parameters (ie, mean transient time and time to peak) should be further explored. In addition, scanning time used to obtain rs-fMRI–based results was longer in the 2 studies as compared with contrast-based perfusion scan. However, one of the studies demonstrated that reducing scanning time to 184 seconds still yielded similar results to those obtained using a full-length scan.[13] It is yet to be determined whether modification of scanning parameters (eg, faster repetition time afforded by newly developed multiband pulse sequences)[15] may be used to reduce scanning time without compromising the quality of the results.

Alterations in rs-fMRI Connectivity After Stroke

Evidence from animal studies suggests that processes such as axonal sprouting after ischemic lesions are induced by intrinsic patterns of synchronous low-frequency neuronal activity in areas connected to the infarct core.[16] This physiological role of intrinsic synchronous activity in areas capable of compensating for lost function, such as interhemispheric homologues, may underlie poststroke changes in functional connectivity. The impact of stroke on intrinsic BOLD activity has been widely characterized by describing such alterations in functional connectivity. The general effect reported thus far is a decrease in functional connectivity in areas that are structurally intact yet are connected to the lesion area. This phenomenon has been widely demonstrated in single networks, usually using a relatively small number of regions of interest (ROIs). In addition, perhaps the most promising finding is that changes in functional connectivity after stroke have been shown to correspond with the degree of behavioral deficit, emphasizing the prognostic value of rs-fMRI in stroke patients.

The advancement in our understanding of stroke as a network disorder dependent on global whole-brain communication and internetwork interaction, along with the development of methods in the wider field of functional connectivity, has created a shift in the methodological approaches applied to the study of stroke. As we will discuss in the following sections, early studies predominantly addressed alterations in specific networks, whereas more recent studies describe global graph-based changes.

Network-Specific Effects of Stroke

The sensorimotor network has been the most widely studied thus far, with a focus on interhemispheric functional connectivity. Interhemispheric connectivity between homologous regions is one of the prominent characteristics of resting-state connectivity patterns in healthy population and provides a stable and robust measure for the integrity of communication between the 2 hemispheres.[17] Alterations in connectivity between the arm subregions of the sensorimotor network have been found to correlate with the upper extremity motor impairment in patients with hemiparesis.[18] A decrease in interhemispheric functional connectivity was additionally reported for patients with corticospinal tract damage, further supporting the fact that the reduction in functional connectivity after stroke cannot be solely explained by structural damage and reflects distant effects of the lesion in areas that remain intact.[19]

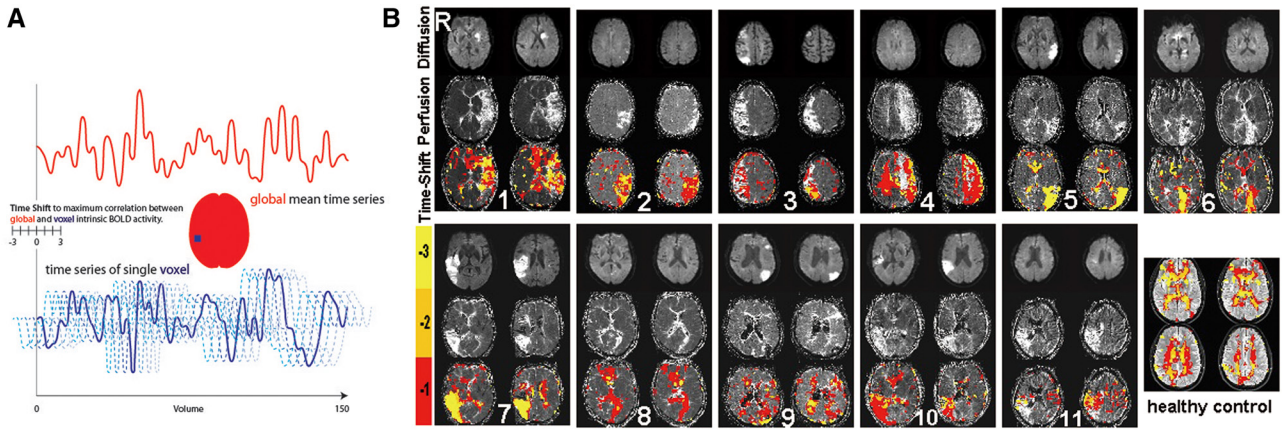

Figure 1. The resting-state functional MRI blood oxygenation level–dependent (BOLD) signal provides information similar to perfusion imaging. **A**, Time shift analysis. The time delay between the average whole-brain signal and each voxel was computed using time-lagged correlation. **B**, Areas of delayed BOLD from the global mean correspond to perfusion deficits, whereas diffusion depicts only the infarct core. Red-yellow scale colors reflect the delay in repetition time (TR). Adapted from Lv et al[13] with permission of the publisher. Copyright © 2013, John Wiley & Sons. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

The importance of interhemispheric connectivity has been further demonstrated in longitudinal studies. A decrease in interhemispheric connectivity in the motor cortex has been reported for patients scanned 4× during a 6-month period poststroke. The decrease in interhemispheric connectivity was accompanied by an increase in connectivity between the motor cortex and ipsilesional frontal and parietal cortex.[20] The reduction in interhemispheric functional connectivity has been reported even in the early stages after stroke in patients with motor deficits. Interestingly, connectivity between hemispheres recovered 7 days poststroke only in patients with recovered motor function, although the reduction in connectivity with subcortical regions remained after 90 days.[21] Animal studies have found similar results to those reported in humans. van Meer et al[22] explored the longitudinal changes in functional connectivity in rats after unilateral experimental stroke. A reduction of interhemispheric connectivity was found soon after stroke and was correlated with the sensorimotor deficit. Recovery of interhemispheric connectivity was associated with behavioral improvement (see Figure 2). The alterations in functional connectivity were later demonstrated to result from corresponding alterations in structural connectivity as measured by tracer uptake (manganese-enhanced MRI). A decrease in interhemispheric functional connectivity was associated with a decrease in transcallosal tracer transfer, whereas an increase in intrahemispheric functional connectivity was associated with a local increase in the tracer uptake. These results provide further support for a structural connectivity mechanism underlying changes in functional connectivity.[23]

The interhemispheric imbalance reported in the sensorimotor network is in accordance with findings from task-based fMRI and is the basis for the usage of noninvasive transcranial magnetic stimulation techniques for the treatment of patients with stroke.[2] However, it is yet to be determined how such stimulation affects the resting-state functional connectivity in patients with stroke, because most studies have made use of task-based connectivity techniques.

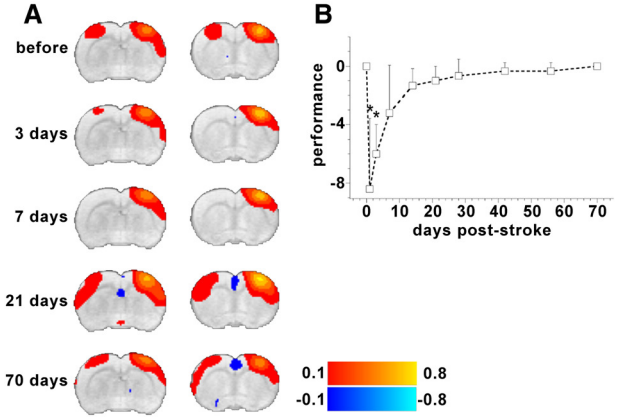

Figure 2. Correlation is decreased after stroke in areas that are structurally intact. Functional recovery correlates with the restoration of functional connectivity. **A**, Interhemispheric functional connectivity is reduced in structurally intact areas immediately after stroke and gradually recovers. Region of interest is located at the right forelimb region of the primary somatosensory cortex. **B**, Functional recovery as measured by sensorimotor performance is associated with recovery of functional connectivity. **P*<0.05 vs pre. Adapted from van Meer et al.[22] Copyright © 2010, The Authors (http://creativecommons.org/licenses/by-nc-sa/3.0/). Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Similar results to those found in the sensorimotor network have been reported for the attention network. Damage to the attention network and the corresponding symptoms of spatial neglect have been associated with decreased interhemispheric connectivity in structurally intact areas that are part of the attention network.[18,24] Importantly, functional connectivity correlates with the severity of symptoms.[24] rs-fMRI has also been used to demonstrate the effect of intraparietal sulcus lesions on functional connectivity in the attention network. Depending on the location of the lesion within the intraparietal sulcus, functional connectivity was impaired, emphasizing the importance of the intraparietal sulcus in spatial attention, in addition to the well-established roles of the inferior parietal lobule and temporoparietal junction.[25]

Another network that has been explored after stroke is the default-mode network. The default-mode network is a network of regions including the posterior cingulate and precuneus, the temporoparietal junction, and the medial prefrontal cortex. It has been widely implicated in various neurological and mental disorders and has been linked to tasks such as autobiographical memory retrieval and theory of mind functions.[26] After stroke, alterations in default-mode network functional connectivity have been associated with poststroke depression[27] and episodic memory dysfunction.[28]

Generalizing the Network Impact of Stroke

Our understanding of the complexity of symptoms after stroke, which usually involves >1 network, and the importance of whole-brain connectivity has led to a gradual shift in the methods of analysis used in this clinical population. A shift from single-network assessment to a multinetwork and eventually whole-brain level is currently underway. The assessment of multiple domains and the interaction between them is necessary for the development of meaningful biomarkers to assess recovery and potentially prognosis. Nomura et al[29] were the first to provide an approach that could be applied to populations with heterogeneous lesions affecting >1 network. The aim of this work was to determine whether the frontoparietal and cinguloopercular networks are dissociated cognitive control networks and to test their independence. rs-fMRI data were collected ≥5 months poststroke, and functional connectivity was assessed across predefined ROIs within and between network nodes. The percentage of network damage was found to negatively correlate with functional connectivity within the affected network and not within the unaffected network.

We have extended the findings of Nomura et al[29] in a longitudinal study starting at the acute phase after stroke. We aimed to explore whether heterogeneous lesions to 8 a priori–defined spatial networks covering most of the cortical surface demonstrate stronger alterations in functional connectivity during the course of recovery as compared with unaffected networks at the individual level. Twelve patients with ischemic stroke were studied using rs-fMRI acquired 1, 7, and 90

days poststroke. Dual regression[30] was used to create functional connectivity maps for each of the predefined networks. We applied whole-brain spatial concordance to measure the changes in connectivity over time.[31] Our findings indicate a preferential decrease in concordance in networks affected by the lesion, as compared with unaffected networks. This finding reflects a more robust change in the functional connectivity spatial maps of the affected networks during the course of recovery. The change in connectivity was correlated with clinical changes as assessed by the National Institutes of Health Stroke Scale. Our results provide additional support for the generalization of diaschisis-like effects to patients with multiple network damage. In addition, we demonstrated the feasibility of our approach for the study of heterogeneous lesions.[32] Figure 3 is representing a schematic illustration of network disruption after stroke based on these empirical findings. A multinetwork assessment of changes in functional connectivity may have the potential of better reflecting the complex clinical symptoms after stroke.

Changes in Network Topology in Single Networks

Recently, methods from the mathematical field of graph theory have been applied to rs-fMRI data and structural data.[33] Although functional connectivity between predefined ROIs (seed-based ROI) has been proven valuable in investigating synchronization between specific regions, it does not provide us with information concerning the integrative ability of different regions, or nodes, within the network. Measures of graph theory can contribute to our understanding of topological organization of single and even multiple networks. Edges are determined based on connection described by correlation matrices. Various measures representing network structure and effectiveness can be computed, among them centrality, path length, clustering coefficient, and modularity.[33] Initially, measures of graph theory were used to study a single network after stroke, namely the motor network. In a 1-year longitudinal follow-up on patients having had subcortical stroke, a gradual shift in the motor network topology to a random mode has been reported, suggesting less efficient communication within the network. These changes were accompanied by a gradual increase in interhemispheric functional connectivity.[34] Interestingly, contradicting results were reported in a similar study conducted in rats. During the course of recovery, a gradual re-establishment of network properties was accompanied by normalization of interhemispheric functional connectivity.[35] These conflicting results may be explained by differences in scanning time, model type (ie, animal versus human), and bases for the graph reconstruction. In the study by Wang et al,[34] the network was built based on functional connectivity between ROIs, whereas in the study by van Meer et al,[35] the graph was computed for single voxels.

With the continuing advancement in computational capabilities, network properties can be examined using a larger number of regions, thereby creating more realistic graphs that better reflect the global properties of communication in the brain.[36]

Lesion Topology

Modeling studies on the impact of lesions on functional connectivity have provided similar results to those found in empirical data. The effect of simulated lesions extends beyond the immediate lesion environment to structurally intact areas. In addition, modeling studies suggest that the topological properties of the lesion itself have a meaningful effect on the

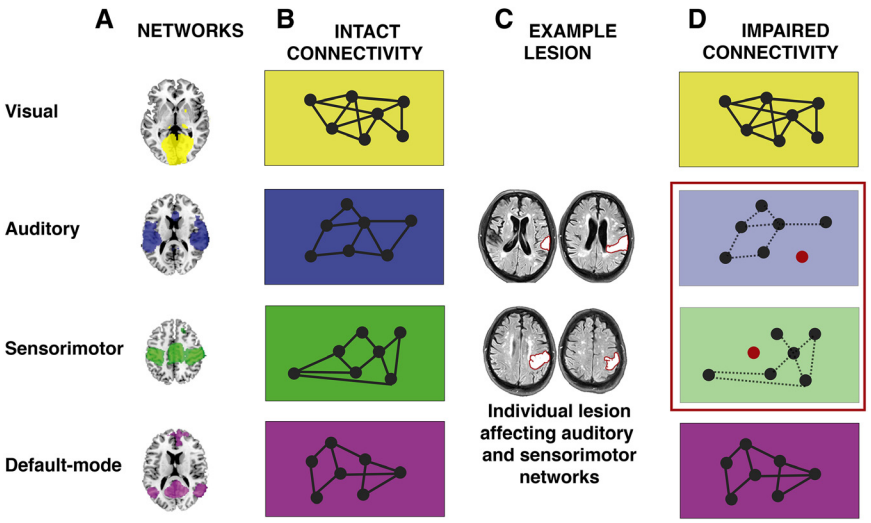

Figure 3. Schematic illustration of network disruption after stroke. **A**, Functional networks are correlated even in the absence of task. Here, an example of 4 functional networks based on resting-state functional MRI functional connectivity in healthy controls. **B**, Intact connectivity structure in healthy controls is reflected in the high correlation (solid black lines) between functionally relevant nodes of a specific network. **C**, Anatomic location of an individual lesion in a patient with a recent ischemic stroke (white areas outlined in red). The lesion affects the auditory and the sensorimotor networks, sparing the visual and default-mode networks. **D**, After stroke, structural damage to specific nodes (red circles) in the network leads to global disruption in connectivity in the affected networks (red rectangle), even in structurally intact regions. Connectivity is interrupted from the lesion area and altered among the structurally intact nodes of the network (black dotted lines). The disruption of connectivity after a local stroke is network-specific and largely spares the unaffected functional networks. A multinetwork assessment of changes in functional connectivity has better potential for reflecting complex clinical symptoms, which often involve >1 functional network.

amplitude of alterations in functional connectivity. More central connected regions (ie, hub regions) have a larger effect on functional connectivity after stroke.[37,38]

Hub regions can be defined by their role within the graph. Connector hubs connect different modules (eg, visual and motor network), whereas provincial hubs connect nodes within a single module (eg, within the visual network).[33] Gratton et al[39] empirically tested the influence of lesion topology on network integrity in patients after stroke using rs-fMRI. Whole-brain modularity was used as a measure of network integrity and was computed for both the affected and the unaffected hemispheres. Modularity was defined as a comparison between the number of connections within a module and the number of connections between different modules. In patients with stroke, a widespread decrease in modularity, even in the unaffected hemisphere, was found. The decrease in modularity was found to correlate with the increase in damage to connector hubs (high connector damage) and not to provincial hubs (low connector damage; Figure 4). The association between connector hub damage and modularity could not be explained by the lesion size alone. This study demonstrates the importance of connector hubs to the integrity of network structure; however, the link between hub damage and behavioral outcome after stroke is yet to be explored.

Conclusions, Considerations, and Future Perspectives

In summary, rs-fMRI has been successfully applied in patients with acute and chronic stroke. In acute stroke, time shift analysis based on rs-fMRI could potentially replace classic perfusion measurements without the need for contrast agent application. We are currently evaluating this approach in a larger clinical study. Using connectivity analysis based on rs-fMRI, focal infarcts have been shown to influence connectivity within the affected networks as well as disrupt whole-brain topology. These changes have been shown to correlate with behavioral measures as well as behavioral outcome.

Certain limitations should be taken into account when using rs-fMRI in patients with stroke. Functional connectivity is highly susceptible to motion-related artifacts, and because patients tend to move more than controls, there is a need for either real-time motion correction or improved post hoc removal of motion artifacts.[40] In addition, given that white matter lesions affect brain connectivity[41,42] and are reported to relate to behavioral deficits after stroke,[43] the variance explained by this factor needs to be accounted for when conducting functional connectivity analyses.

An additional challenge in using rs-fMRI is the interpretability of changes in the BOLD signal given the state of vascular pathology in patients with stroke. The BOLD signal mainly reflects changes in the concentration of deoxyhemoglobin and, as such, is an indirect measure of neuronal activity.[8,44] Comparing stroke patients' data to those obtained from healthy controls is assuming similar neurovascular coupling; however, in the case of local ischemia or other pre-existing vascular disease (such as stenosis), this assumption may not be justified.[45] Such decoupling poses difficulties in interpreting the pathophysiological basis for differences between the groups (ie, neuronal or vascular). Alterations in the BOLD signal (eg, decreased amplitude) that result from mere vascular changes have been shown in patients with cerebrovascular disease.[46–48] Thus far, all studies examining the effect of changes in neurovascular coupling have used task-based fMRI. It is yet to be determined how such changes affect functional connectivity based on rs-fMRI. A multimodal approach including electroencephalography/magnetoencephalography as well as methods to assess cerebral blood flow quantitatively, such as ASL, may be used to separate neuronal from vascular changes. In addition, shifting from group comparisons of healthy controls and patients to longitudinal studies with single patient–based analysis could further minimize this limitation. Linking the observed changes in functional connectivity after stroke to relevant behavioral measures is another crucial factor, which would support neuronal bases for changes observed.

Changes in local perfusion and metabolism after stroke are most pronounced in the early acute phase (<24 hours after ictus). These complex hemodynamic changes are reflected in the BOLD signal because of dependency on cerebral blood flow, cerebral blood volume, and cerebral metabolic rate of oxygen.[8] Since the effects of hyperacute hemodynamic changes on functional connectivity rs-fMRI have not been explored thus far, results obtained at this stage should

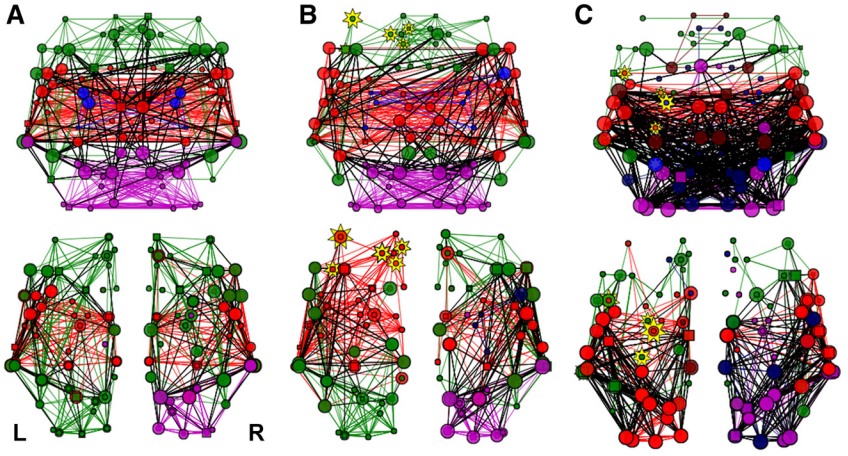

Figure 4. The topological role of the lesion has a crucial impact on the whole-brain network integrity. **A**, A healthy control template demonstrating an intact modular organization on the whole brain (**top**) and for each hemisphere separately (**bottom**). **B**, Patient with low connector damage demonstrating a relatively preserved modular organization. **C**, Patient with high connector damage demonstrating a highly disrupted modular organization at the whole-brain level as well as in both hemispheres. Yellow stars depict lesioned nodes, with the size of the star proportional to the percent damage to that node. Adapted from Gratton et al[39] with permission of the publisher. Copyright © 2012, The MIT Press. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

be considered with caution. To minimize the effects of local perfusion changes, most studies explore patients after the first 24 hours and remove the lesion area from the analysis. These studies demonstrate that the changes in functional connectivity are not solely dependent on the lesion area.

Current methodological developments in the field of rs-fMRI are concerned with changes in functional connectivity during the rs-fMRI scan. All studies investigating functional connectivity in stroke published thus far have provided stationary information concerning the interaction between different brain regions. However, supported by findings demonstrating a link between different resting-state networks and specific combinations of electrophysiological rhythms,[49] recent studies have explored the dynamics of intrinsic BOLD fluctuations in healthy subjects as well as in schizophrenia, depression, and Alzheimer disease.[50] Such analysis requires longer scanning time, which could pose difficulties when applied to patients with stroke. Nonetheless, future studies exploring changes in dynamic connectivity may shed light on the underlying mechanisms of reported connectivity changes and behavioral deficits after stroke.

Based on the promising results obtained to date, more systematic validation studies in larger clinical populations with thorough clinical description are an important next step. This should allow for a validation of the multinetwork approach for an optimal description of neurological symptoms, as well as improved prognostic accuracy. The diagnostic assessment of connectivity changes in multiple networks finds a therapeutic counterpart in transcranial stimulation approaches, which have been shown to successfully modulate connectivity in cerebral networks.[2,3] In future studies, rs-fMRI connectivity patterns may be used to tailor stimulation protocol to individual patients.

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Disclosures

None.

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