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Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches

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The motor system comprises a network of cortical and subcortical areas interacting via excitatory and inhibitory circuits, thereby governing motor behaviour. The balance within the motor network may be critically disturbed after stroke when the lesion either directly affects any of these areas or damages-related white matter tracts. A growing body of evidence suggests that abnormal interactions among cortical regions remote from the ischaemic lesion might also contribute to the motor impairment after stroke. Here, we review recent studies employing models of functional and effective connectivity on neuroimaging data to investigate how stroke influences the interaction between motor areas and how changes in connectivity relate to impaired motor behaviour and functional recovery. Based on such data, we suggest that pathological intra- and inter-hemispheric interactions among key motor regions constitute an important pathophysiological aspect of motor impairment after subcortical stroke. We also demonstrate that therapeutic interventions, such as repetitive transcranial magnetic stimulation, which aims to interfere with abnormal cortical activity, may correct pathological connectivity not only at the stimulation site but also among distant brain regions. In summary, analyses of connectivity further our understanding of the pathophysiology underlying motor symptoms after stroke, and may thus help to design hypothesis-driven treatment strategies to promote recovery of motor function in patients.

Keywords: recovery of function; motor system; functional connectivity; effective connectivity; system theory
Abbreviations: SMA = supplementary motor area; TMS = transcranial magnetic stimulation

Introduction

The motor system consists of a complex network of cortical and subcortical areas in which neuronal populations interact with each other by both excitatory and inhibitory mechanisms. This highly dynamic system is modulated by external and internal factors that finely modulate sensory perception, attention and motor behaviour (Breakspear *et al.*, 2003). A structural lesion resulting from a stroke may critically disturb the complex balance of excitatory and inhibitory influences within the motor network. An ischaemic

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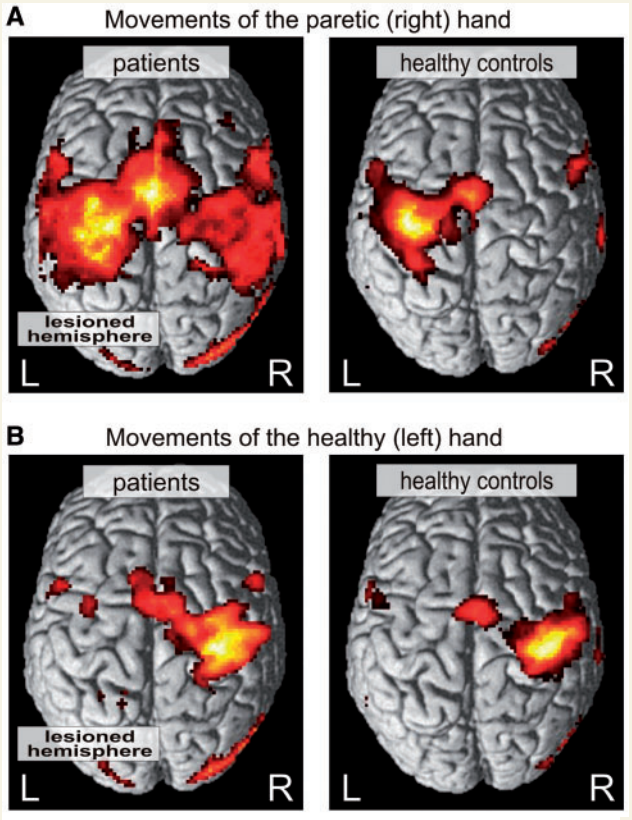

Figure 1 Neural activity during movement of the left or right hand in healthy subjects and in stroke patients with left-sided subcortical lesions ($P < 0.05$, corrected on the cluster level). Activation clusters were surface rendered onto a canonical brain. In stroke patients, movements of the impaired hand were associated with significant activations in ipsilateral (= contralesional) motor areas, which were absent in the healthy controls (**A**) or when moving the unaffected hand (**B**) (adapted from Grefkes *et al.*, 2008*b*, with permission).

lesion may not only directly affect the descending motor fibre pathways (i.e. the corticospinal tract), but may also affect the functional network architecture of cortical areas in both hemispheres distant from the lesion (Murase *et al.*, 2004; Hummel *et al.*, 2005; He *et al.*, 2007; Grefkes *et al.*, 2008*b*; Nomura *et al.*, 2010; Wang *et al.*, 2010). Functional MRI or PET studies have frequently shown that movements of the stroke-affected hand are associated with enhanced neural activity in the contralesional (i.e. 'healthy') hemisphere, which is not detected in healthy age-matched controls (Fig. 1) (Chollet *et al.*, 1991; Weiller *et al.*, 1992; Ward *et al.*, 2003; Grefkes *et al.*, 2008*b*). Importantly, however, the functional significance of areas in the unaffected hemisphere for moving the paretic hand—i.e. being supportive, unspecific or even disturbing—cannot be inferred from 'classical' neuroimaging experiments. Knowing where two functional conditions cause different levels of neural activity does not tell us how a particular region interacts with other regions, which modulate behaviour in concert (Stephan *et al.*, 2007*b*). In recent years, a number of studies have used models of functional or effective connectivity in stroke patients to demonstrate changes in functional interactions after stroke that relate to clinical deficits and recovery thereof. Such a systems perspective on brain networks allows new insights into the pathophysiology underlying stroke-induced deficits and may thus impact upon therapeutic strategies to interfere with pathological brain networks. Here, we review recent studies employing models of functional and effective connectivity on neuroimaging data to investigate how stroke influences the interactions of motor areas and how changes in connectivity relate to impaired motor behaviour and recovery of function.

System concepts in brain research

The brain can be regarded as a system of elements (e.g. neuronal populations in distinct cortical areas) that interact with each other in a temporally and spatially specific fashion. Functional neuroimaging can be used to investigate two fundamental dimensions of how the system 'brain' is organized (Friston, 2002*a*). The concept of 'functional specialization' assumes that a cortical area is specialized for certain aspects of perceptual or motor processing. This specialization allows for the anatomical segregation of an area from surrounding cortex. For example, the posterior wall of the precentral gyrus contains a microstructural entity coined 'area 4' by Korbinian Brodmann due to its distinct cytoarchitectonic appearance (Brodmann, 1909). Otfried Foerster was one of the first scientists to note that within this area 'stimulation of a given focus produces a single isolated movement of the corresponding part of the body' (Foerster, 1936, p. 137). Since then an overwhelming number of studies have used cortical stimulation approaches or functional neuroimaging techniques, and investigated in great detail the functional properties of that area, which was later termed 'primary motor cortex' (M1) (Penfield and Rasmussen, 1952; Fink *et al.*, 1997; Hallett, 2000; Schieber, 2000; Dum and Strick, 2002).

However, localizing activity in a distinct cortical region does not explain how spatially distributed areas are bound together for mediating and/or sustaining a perceptual or motor process. Functional specialization is therefore only meaningful in the context of 'functional integration' (Friston, 1994). The concept of functional integration assumes that sensory, motor or cognitive processes rely on context-dependent interactions between different brain regions mediated by specific anatomical connections (Friston, 2002*a*). For example, activity in M1 might be driven by facilitatory or inhibitory influences from premotor areas that themselves interact with activity in prefrontal, posterior-parietal or sensory areas (Rizzolatti *et al.*, 1998; Pascual-Leone *et al.*, 2000; Grefkes *et al.*, 2010*b*). It is conceivable, however, that the spatial separation of brain areas within or between functional networks might also constitute an important mechanism preventing potential interference during processing of competing information or tasks (Gee *et al.*, 2011). Furthermore, other concepts of brain organization, such as the theory of inter-hemispheric rivalry and competitive feedback inhibition (Kinsbourne, 1977, 2006), the concept of oscillatory patterns for supporting, propagating and

coordinating cross-neuronal interactions (Llinas *et al.*, 1999; Buzsaki and Draguhn, 2004; Logothetis *et al.*, 2007; Hoerzer *et al.*, 2010), the universal control system theory (Kazantsev *et al.*, 2003), and the concept of synaptic homoeostasis for the stabilization of neuronal circuits (Turrigiano, 2007) all underpin the relevance of a network perspective for describing and explaining brain function. Hence, a connectivity-based system perspective seems to be much closer to the neurobiology underlying brain function under both physiological and pathological conditions compared with approaches assigning specific behaviours (or clinical symptoms) to anatomically segregated regions.

Network models

Network models conceptualize brain organization on at least three distinct levels (Sporns *et al.*, 2005): (i) the level of individual neurons and synapses (microscale); (ii) the level of neuronal groups and populations (mesoscale); and (iii) the level of anatomically distinct regions and their corresponding inter-regional pathways (macroscale). Connectivity studies based on functional neuroimaging in humans usually work on the macroscale level of neural networks due to the limited spatial resolution of functional MRI data. Such neural networks can be formally described within the framework of graph theory (Erdös and Rényi, 1960; Bollobás, 1985; Watts and Strogatz, 1998; Bassett and Bullmore, 2006; Bullmore and Sporns, 2009). In graph theory, the brain is represented as a graph comprising a certain number of nodes (corresponding to brain regions) that are connected by edges (corresponding to anatomical connections or, more generally, some measure of inter-regional interaction). The arrangement and connection profiles of the nodes can then be interpreted in the light of communication efficiency. The basic assumption of this approach is that neural networks are optimized for high local and global information transfer while maintaining low wiring costs (Sporns *et al.*, 2007; Nomura *et al.*, 2010). This seems to be especially the case when networks display a 'small-world topology', which is characterized by a local clustering of connections and a short path length between any pair of nodes (Sporns *et al.*, 2005; Achard and Bullmore, 2007; Fornito *et al.*, 2010). As network efficiency can be strongly reduced after stroke, many connectivity studies have adopted a graph theoretical view to quantify network disturbances in stroke patients, as discussed later (Honey and Sporns, 2008; Wang *et al.*, 2010).

Models of functional network interactions

Functional interactions between areas constituting a network can be described in two ways: (i) functional connectivity; and (ii) effective connectivity. Functional connectivity is operationally defined as the temporal correlation (or covariance) between spatially remote neurophysiological processes (Friston, 1994). The assumption behind this connectivity approach is that areas are presumed to be components of the same network if their time courses are consistently correlated. A simple way of assessing functional connectivity in neuroimaging time series is to define a region of interest (e.g. primary motor cortex) that is used as a reference to identify those voxels in the brain showing correlated activity with this region (Horwitz *et al.*, 1998). Multivariate approaches, such as principal component analysis or independent component analysis, decompose neuroimaging data into a set of spatial modes that capture the greatest amount of variance expressed over time, thereby identifying functional networks (Friston *et al.*, 1993; Horwitz *et al.*, 1998; Friston, 2002*b*; Fox and Raichle, 2007). Both approaches are frequently used to study 'resting-state' connectivity (Biswal *et al.*, 1995), i.e. when subjects are scanned with functional MRI without any imposed task in order to identify brain regions that show synchronized blood oxygen level-dependent signal fluctuations at low frequencies (<0.1 Hz). A number of studies have demonstrated that brain regions showing correlated activity, while subjects lie in the scanner without performing any specific task, strongly overlap with the topography of multiple brain systems defined on the basis of task-related neuroimaging (Fox and Raichle, 2007). Resting-state functional MRI may hence reveal functional connectivity within various functional networks in a single functional MRI experiment. Disease associated changes in functional connectivity measures, such as connection strength (e.g. correlation between an index region and all other regions of the brain) and diversity of connectivity (e.g. the variance of correlations between an index region and all other regions of the brain), are often paralleled by changes in network topology metrics like clustering and small-worldness, rendering both approaches complementary (Lynall *et al.*, 2010; Wang *et al.*, 2010).

Non-linear functional connectivity can be established by means of mutual information analyses that (i) describe the amount of information in one area given the time series information in another area; and (ii) are sensitive to static non-linear dependencies (Roulston, 1999; David *et al.*, 2004). Well-established tools for analysing functional connectivity in EEG or magnetoencephalographic studies are time frequency analyses of phase synchronization or analyses of generalized synchronization in order to detect coupled oscillators in a broad range of structures (Pikovsky *et al.*, 2001). However, the sensitivity of measures of functional connectivity highly depends on the frequency specificity of coupling and whether such coupling is linear or non-linear. David *et al*. (2004), therefore, suggested that a battery of tests that are sensitive to different aspects of synchronization would to be more appropriate to investigate neural networks with electrophysiological signals.

Models of effective connectivity

A common feature of all correlative approaches to functional connectivity is that they do not provide any direct insight into how correlations are mediated. Therefore, functional integration within a distributed network is usually better described using measures of effective connectivity that refers explicitly to the influence that one neural system exerts over another (Friston, 1994). A general mathematical form of almost all established models of effective

connectivity is provided by the general state equation for non-autonomous deterministic systems, which allows a causal description of how dynamics in non-autonomous systems (i.e. systems that exchange energy or matter with their environment) result from system structure (Friston *et al.*, 2003; Stephan *et al.*, 2007*b*). Here, a system is defined as a set of interacting elements (e.g. single neurons or population of neurons in areas) with time-variant properties (e.g. neurophysiological properties such as membrane potentials or, more generally, neural activity) that are influenced by external inputs entering the system (e.g. sensory stimuli). Models of effective connectivity can be applied on the level of single synapses ('synaptic efficacy') as well as the level of large-scale networks such as the motor, sensory, language and other 'cognitive' systems of the brain.

A relatively simple approach to estimate effective connectivity from neuroimaging data is to model psycho-physiological interactions. This exploratory connectivity method explains responses of a cortical area by means of an interaction term between the influence of another area and some experimental or psychological parameter (Friston *et al.*, 1997; Stephan, 2004). Granger causality mapping of functional MRI time series identifies those voxels that are sources or targets of directed influence for any reference region, and can, therefore, also be used in an exploratory fashion (Roebroeck *et al.*, 2005). Non-linear effective connectivity can be explored by means of discrete dynamic Bayesian networks, which do not require a pre-definition of structure and do not make assumptions about the functional form of interactions between the nodes, i.e. whether they are stochastic, combinatorial or non-linear (Smith *et al.*, 2002, 2006). However, dynamic Bayesian networks gain this powerful flexibility at the cost of precision, i.e. they discard much of the information in continuously sampled neuroimaging data to obtain the discrete values they require (Burge *et al.*, 2009).

In contrast to these exploratory approaches, structural equation modelling and dynamic causal modelling are hypothesis-driven techniques requiring an *a priori* definition of a structural model (McIntosh and Gonzalez-Lima, 1994). Structural equation modelling is a multivariate approach, in which the strength of a connection between two areas (i.e. the 'path coefficient') indicates how the variance of area *X* depends on the variance of area *Y* if all other influences on area *X* are held constant (Stephan, 2004). Parameter estimation is achieved by minimizing the difference between the observed and implied covariance, i.e. by fitting the model to the data (Penny *et al.*, 2004*a*; Stephan, 2004). Importantly, structural equation models assume instantaneous correlations among regions. In contrast, dynamic causal modelling treats the brain as a deterministic system in which external inputs (e.g. an experimental condition) cause changes in neural activity that in turn lead to changes in the functional MRI signal (Friston *et al.*, 2003). In dynamic causal modelling, Bayesian model selection procedures are used to compare models of different connectivity in order to identify the model that best matches the measured functional MRI data (Penny *et al.*, 2004*a*). A particular strength of dynamic causal modelling is the use of a biophysical haemodynamic forward model that links estimated neuronal responses to haemodynamic signals by means of model inversion. The rationale behind this approach is that the functional MRI signal is an indirect measure of neuronal activity, which mainly reflects changes in blood volume and deoxyhaemoglobin content triggered by the metabolic demands of neurons (Buxton *et al.*, 1998; Logothetis, 2000). The haemodynamic response, however, is slow and regionally variable, which is of particular relevance for effective connectivity measures that assume temporal precedence, information transfer and prediction between time series. For example, David and colleagues (2008) demonstrated that coupling estimates directly computed on the blood oxygen level-dependent signal may lead to incorrect connectivity results in case of a large heterogeneity of the haemodynamic response waveforms (e.g. time-to-peak). Likewise, Smith *et al*. (2011) tested different connectivity approaches for a wide range of underlying networks, experimental protocols and problematic confounds, and found that lag-based approaches, like Granger causality implementations, performed relatively poorly in contrast to correlation-based or Bayesian approaches. The validity of haemodynamic (de-)convolution, however, crucially depends on the availability of and assumptions on hidden information (i.e. the input functions of experimental conditions) and the accuracy of the employed biophysical model (e.g. validity for different magnetic field strengths) (Roebroeck *et al.*, 2009).

Advantages and disadvantages of different connectivity approaches in stroke research

As discussed, each model of connectivity has certain limitations and no general model exists that can be considered optimal for all kinds of data and experimental conditions (Box and Draper, 1987). If the system is largely unknown, functional connectivity approaches are useful because they can be applied in an exploratory fashion (Stephan, 2004). Functional connectivity analyses of resting-state functional MRI data offer a way of inferring connectivity, especially in sick patients, as necessary functional MRI scans can be acquired in a relatively short period of time (usually <10 min) with minimal physical effort for the patient. Such designs also avoid any performance confound on connectivity measures, which is of particular relevance in longitudinal experiments or intervention studies when performance is likely to change between sessions (Carter *et al.*, 2010). Graph theoretical descriptions of such resting state networks may then provide useful information on how network efficiency changes during the process of recovery (Wang *et al.*, 2010).

In contrast to the approaches of functional connectivity, models of effective connectivity facilitate description of the causality of interactions among brain regions. Psycho-physiological interactions and Granger causality mappings can be used as exploratory tools to identify directional interactions between a given reference region (e.g. ipsilesional motor cortex) and all other regions in the brain. However, as only pair-wise interactions between the reference voxel and all other voxels are considered, psycho-physiological interactions have a limited capacity to represent complex neural systems (Stephan, 2004). Granger causality mappings (which are based on the concept of temporal

precedence) might be problematic in case of strong inter-regional variability of the haemodynamic response (David *et al.*, 2008), e.g. in stroke patients with vascular abnormalities. If someone is interested in neural interactions within a network defined *a priori* based on a certain hypothesis (e.g. effects of non-invasive motor cortex stimulation on movement-related interactions among premotor and primary motor areas), structural equation models and dynamic causal models are attractive options for modelling effective connectivity. In contrast to structural equation models, dynamic causal models are estimated on the neuronal rather than on the haemodynamic level (Friston *et al.*, 2003). Since in dynamic causal modelling, the haemodynamic response function parameters are estimated individually for each region (Friston *et al.*, 2003; Stephan *et al.*, 2007*a*), deviations from the standard canonical response, e.g. due to pathology affecting blood flow parameters, are more likely to be accommodated. An important prerequisite for dynamic causal modelling is that each region of a model is identified in each individual subject, which can be problematic for areas that show weak activation levels or inter-individual variability in spatial location. Furthermore, since model fitting in dynamic causal modelling is computationally demanding, the complexity of dynamic causal models is limited to structural models comprising up to eight regions (Penny *et al.*, 2004*b*). Importantly, dynamic causal models will not result in 'misleading' answers when regions are omitted in the model since the relay of neural information by brain regions not explicitly modelled in the connectivity matrix is captured implicitly in the coupling parameters between two regions (Friston *et al.*, 2003; Friston, 2009).

Changes in neural networks after stroke

In the acute phase of a stroke, over two-thirds of patients present with motor symptoms such as (hemi-)paresis or loss of dexterity (Kwakkel *et al.*, 2002). After acute ischaemic injury, recovery from motor deficits in the first few weeks and months post-stroke is predominantly driven by neuronal reorganization. Nevertheless, a large fraction of stroke patients exhibit a permanent motor deficit that impacts their activities of daily living despite intensive medical and physical therapy (Kwakkel *et al.*, 2002). Functional neuroimaging experiments using PET or functional MRI have demonstrated abnormal cortical activation patterns in the subacute to chronic phase after stroke during movements of the paretic hand (Fig. 1). Pathological activation patterns after stroke were also reported for the language domain in patients with aphasia (Saur *et al.*, 2006) and for the visuospatial attention network in patients with neglect (Corbetta *et al.*, 2005). In the motor domain, stroke patients typically show pathologically enhanced neural activity in a number of areas both in the lesioned (ipsilesional) and in the healthy (contralesional) hemisphere (Chollet *et al.*, 1991; Ward *et al.*, 2003; Gerloff *et al.*, 2006; Grefkes *et al.*, 2008*b*). Longitudinal functional MRI studies revealed that early after ischaemia, neural activity is often enhanced in motor-related areas in both hemispheres, and then over the first 12 months post-stroke returns to levels similar to those observed in healthy controls, in particular in patients with good motor recovery (Ward *et al.*, 2003; Tombari *et al.*, 2004; Rehme *et al.*, 2010). Activity levels in some regions of the motor system correlate with motor performance of the affected hand. For example, Johansen-Berg *et al.* (2002*a*) have demonstrated that training-induced improvements in motor performance in chronic stroke patients (i.e. patients at least 6 months after onset of the infarct) with cortical or subcortical lesions are associated with increases in neural activity in ipsilesional dorsal premotor cortex. Furthermore, disruption of dorsal premotor cortex activity by means of transcranial magnetic stimulation (TMS) over both the ipsilesional or contralesional hemisphere may lead to a deterioration of motor performance in stroke patients, but not in healthy controls (Johansen-Berg *et al.*, 2002*b*; Fridman *et al.*, 2004). These findings implicate premotor areas in recovery of function of the stroke-affected hand. To date, the role of the contralesional primary motor cortex (M1) for motor recovery remains controversial. Rehme *et al.* (2010) have shown that increases in contralesional M1 activity over the first 10 days after stroke correlate with the amount of spontaneous motor improvement in initially more impaired patients suggesting a supportive role for recovery of function in the very early phase after stroke. Furthermore, Lotze *et al.* (2006) have shown that disrupting contralesional M1 activity by means of TMS may cause a deterioration in motor performance of the stroke-affected hand of chronic stroke patients (>8 months) with internal capsule infarcts. However, other studies have demonstrated that inhibition of contralesional M1 excitability using repetitive TMS protocols may lead to improved motor performance of the stroke-affected hand in the subacute (Nowak *et al.*, 2008; 1–4 months post-stroke), subacute to chronic (Mansur *et al.*, 2005; <12 months) or chronic phase after an infarct (Takeuchi *et al.*, 2005; 7–54 months). A combined offline TMS-functional MRI study suggested that patients may benefit from contralesional M1 inhibition, which shows movement-related overactivity in the contralesional precentral gyrus, i.e. the cortex below the repetitive TMS stimulation site (Nowak *et al.*, 2008). Hence, enhanced activity in contralesional M1 might exert a negative influence on the motor network controlling the paretic hand and may thereby even impair recovery of function. A clear influence of the factors 'time after stroke' or 'lesion location' (e.g. cortical, subcortical) on the efficacy of low-frequency repetitive TMS applied over contralesional M1 remains to be demonstrated.

Stroke patients suffering from motor symptoms often show damage of the corticospinal tract. Invasive tract-tracing studies in non-human primates have shown that not only neurons in M1 but also neurons in higher motor areas such as the lateral premotor cortex and the supplementary motor area (SMA) have direct corticospinal connections to the alpha-motor neurons in the anterior horn of the spinal cord (Dum and Strick, 2002). For example, the proportion of axons originating from SMA neurons was estimated to be at least 10% of the entire corticospinal tract (Nachev *et al.*, 2008). Such pathways may at least in part substitute for damage to M1 neurons or their axons, respectively. This also suggests that the degree of motor impairment after stroke may depend on the extent of corticospinal tract damage caused by ischaemia. PET studies have shown that subcortical lesions may also cause changes in the metabolism and neurotransmitter layout

of cortical areas (Dong *et al.*, 1997; Kwan *et al.*, 1999), thereby interfering with cortical network dynamics and finally behaviour. Furthermore, the potential for motor recovery is related to how much of the corticospinal tract has been destroyed by the stroke. The more damage to fibres originating from M1, the less likely is a successful motor recovery and the stronger the recruitment of higher motor areas such as SMA or premotor cortex to compensate for M1 deficiency (Newton *et al.*, 2006; Ward *et al.*, 2006; Stinear *et al.*, 2007).

Changes in functional connectivity after stroke

A stroke-induced lesion not only affects connectivity between cortex and spinal cord, but may also impact on the interactions among cortical areas distant from the lesion. In 1914, the Russian-Swiss neurologist Constantin von Monakow introduced the concept of 'diaschisis' which refers to reduced activity (and hence function) observed in regions connected to the primary site of damage (von Monakow 1914; Feeney and Baron, 1986). Network simulation studies demonstrated that the degree of network disturbance following a lesion strongly depends on lesion location within a network. For example, Honey and Sporns (2008) investigated the theoretical impact of focal brain lesions on the synchronization of cortical networks based on the connectivity profiles of 47 areas (as established in macaque monkeys) with different oscillator models. The authors found that lesions to 'connector hubs' (i.e. regions like parietal areas 5, 7a and the frontal eye fields with long-range connections linking to nodes in different clusters) produced larger and more widespread disturbances on cortico-cortical interactions than lesions to 'provincial hubs' (i.e. regions like visual area V4 or somatosensory area SII that predominantly link to either neighbouring areas or areas within the same functional cluster). The authors concluded that lesions to parietal and (pre-)frontal areas are most likely to disrupt the system-wide integrative processes needed for the rapid de- and resynchronization of brain networks (Honey and Sporns, 2008). Similar results were reported by Alstott *et al*. (2009) who used structural connectivity data and graph theoretical measures to model the effects of focal lesions on whole-brain functional network topology based on a neural mass model. Crofts and Higham (2009) recently introduced the concept of 'weighted communicability' to account for the fact that two nodes that do not possess direct connections but have many common neighbours may exchange information more efficiently than two unconnected nodes that can only be joined through a long chain of edges (Estrada and Hatano, 2008; Crofts and Higham, 2009). Based on diffusion tensor imaging data, the authors found reduced communication among a number of brain regions in stroke patients compared with healthy controls (Crofts and Higham, 2009).

These theoretical data on network disturbances after stroke are supported by functional MRI studies analysing the impact of a stroke on functional connectivity. For example, van Meer *et al.*, (2010) investigated resting-state functional connectivity in the sensorimotor system of rats recovering from experimentally induced stroke. They found that the decline in sensorimotor performance in the first few days after stroke was paralleled by a loss of coherence of low-frequency blood oxygen level-dependent fluctuations between ipsilesional and contralesional sensorimotor regions outside the ischaemic lesion zone. Interestingly, while contralesional functional connectivity was enhanced in animals with larger lesions extending onto the cortical surface, intra-hemispheric functional connectivity remained intact in the lesioned hemisphere independent from lesion extent and despite significant behavioural deficits. Moreover, improvements in sensorimotor functions over time correlated with the consolidation of inter-hemispheric connectivity between sensorimotor regions (van Meer *et al.*, 2010). These results are paralleled by a recent resting-state functional MRI study with human stroke patients (Carter *et al.*, 2010) in which the loss of coherence in inter-hemispheric blood oxygen level-dependent fluctuations between homologous motor regions predicted behavioural deficits, while changes in intra-hemispheric coupling were not correlated with motor performance of the patients. Preserved inter-hemispheric connectivity was also indicative of better performance of aphasic stroke patients in language tasks (Warren *et al.*, 2009). Furthermore, recovery from visuospatial neglect was shown to be correlated with a restitution of inter-hemispheric functional connectivity between left and right dorsal parietal cortex (He *et al.*, 2007). Stroke-induced changes within a functional network seem to be primarily dependent on lesion localization. Nomura *et al.* (2010) investigated the impact of stroke lesions on two functionally distinct resting-state networks engaged in cognitive control, and found that local information processing (i.e. 'small-worldness') among non-lesioned nodes was reduced when compared with other networks whose nodes were unaffected by the lesion. This suggests that the effects of anatomical damage extend beyond the lesioned area, but remain within the borders of existing network connections (Nomura *et al.*, 2010).

Taken together, resting-state functional MRI data sampled across different functional systems and species strongly suggest that functional outcome after stroke can be predicted by how both hemispheres are coupled in the absence of any active task. However, a recent resting-state functional MRI study implies that stronger engagement of the contralesional hemisphere is not necessarily a good indicator for efficient cortical reorganization. In this study, Wang *et al.* (2010) used graph theory to assess changes in the topological configuration of the motor network from the acute phase to the chronic phase after subcortical stroke. A key finding was that over a year of recovery motor execution networks showed lower normalized clustering within the network (indicated by the Gamma index, which quantifies the efficiency of local information transfer within a network) suggesting a shift towards a non-optimal network configuration with less functional segregation. The overall decrease in network efficiency was paralleled by a stronger betweenness centrality of ipsilesional M1, the latter being a measure of the functional importance of a node for information processing. The increased importance of ipsilesional M1 within the motor network after recovery was also indicated by stronger functional connectivity of this area with contralesional motor areas (Wang *et al.*, 2010). A

similar finding was reported by De Vico Fallani *et al*. (2009) who used graph theoretical measures on EEG data to investigate functional connectivity during preparation and execution of a finger tapping task. Compared with healthy controls, the capacity to integrate information between distant brain regions was significantly reduced after subcortical stroke (indicated by a lower global-efficiency index E_g). The analysis also showed that these changes were associated with significant increases in the number of (i) disconnected nodes and (ii) links within other nodes. The authors concluded that overall connectivity after stroke was governed by a lower number of brain regions in which increased connectivity could not compensate for the drastic reduction in information propagation (De Vico Fallani *et al.*, 2009). Reduced cortico-cortical connectivity in the lesioned hemisphere and relatively increased connectivity in the contralesional hemisphere was also suggested by coherence analyses of EEG data recorded in well-recovered stroke patients in the chronic phase after stroke (Gerloff *et al.*, 2006). These findings converge with the observation that the contralesional hemisphere may show disinhibition phenomena such as increased task-related blood oxygen level-dependent activity or reduced intra-cortical excitability, especially in patients with more pronounced motor deficits (Ward *et al.*, 2003; Talelli *et al.*, 2008). Wang *et al*. (2010) suggest that the neurobiological changes underlying reduced network efficiency during stroke recovery might encompass both degeneration phenomena and mechanisms of plasticity, such as random sprouting axons and changes in synaptic processing (Cramer, 2008).

In summary, the results of the functional connectivity studies in stroke thus far discussed imply that recovery of motor function depends on reorganization processes within both hemispheres leading to enhanced inter-hemispheric connectivity which might occur, however, at the cost of network efficiency underlying recovered function. This might explain the clinical observation that a second stroke sometimes re-instates recovered symptoms from a first stroke, even if the opposite (previously 'healthy') hemisphere is affected (Yamamoto *et al.*, 2007).

Changes in effective connectivity after stroke

As outlined above, in contrast to functional connectivity, where interactions between areas are inferred from correlated activity (and hence do not provide directional information), models of effective connectivity estimate the causal influences that one area exerts over the activity of another area. Such information allows us to investigate the specific role of a cortical region during a given task. For example, analysing effective connectivity in healthy subjects performing rhythmic fist closures with the left or right hand showed that neural coupling among key motor areas is symmetrically organized (Fig. 2A). The analysis by means of dynamic causal modelling revealed that, irrespective of hand movements, motor areas such as SMA, premotor cortex and M1 showed a strong positive coupling with each other, especially between SMA and M1 (Grefkes *et al.*, 2008*a*). The inter-hemispheric coupling parameters between left and right M1 were negative, suggesting mutual inhibition in the absence of a particular hand movement (Fig. 2A). In contrast, moving the left or the right hand induced a side-specific modulation of inter-regional connectivity. Neural coupling was strongly enhanced in the hemisphere contralateral to the moving hand, while ipsilateral areas, especially ipsilateral M1, were inhibited (Fig. 2B). Patients suffering from stroke-induced motor deficits in the subacute phase (i.e. in the first few weeks and months post-stroke) showed several changes in this pattern of normal cortical connectivity within and across hemispheres (Grefkes *et al.*, 2008*b*). In particular, intrinsic (i.e. movement-independent) coupling between ipsilesional SMA and ipsilesional M1 was significantly reduced compared with healthy control subjects (Fig. 2A, right). Importantly, the amount of 'hypo-connectivity' between SMA and M1 correlated with the individual motor deficit suggesting that reduced motor performance may, at least to some extent, be caused by ineffective processing between ipsilesional SMA and M1. Likewise, the negative coupling with contralesional SMA was significantly reduced in the group of stroke patients (Fig. 2A, right). As these disturbances in effective connectivity were independent from which hand was moved by the patients, they might explain the finding that the unaffected hand of stroke patients often shows subtle motor deficits when compared with healthy control subjects (Nowak *et al.*, 2007). Apart from changes in movement-independent coupling, the dynamic causal modelling analysis also revealed significant changes in the modulation of inter-regional coupling evoked by moving the paretic or non-paretic hand. While in healthy subjects, contralateral M1 exerted an inhibitory influence on M1 activity ipsilateral to the moving hand, stroke patients showed an additional inhibitory influence on ipsilesional M1 originating from contralesional M1, which was not present in healthy subjects or when patients moved their unaffected hand (Fig. 2B, right). Importantly, the strength of this pathological inhibition from contralesional M1 correlated with the motor impairment of the paretic hand (Grefkes *et al.*, 2008*b*). This means that, especially in patients with stronger motor deficits, ipsilesional M1 activity was negatively influenced by contralesional M1, which thereby might exert a detrimental effect on motor performance of the paretic hand.

The above findings are supported by TMS studies using the double-pulse protocol for assessing inter-hemispheric inhibition. Here, a conditioning TMS pulse is delivered over M1 some milliseconds (typically 10–15 ms) before applying a test pulse over M1 of the other hemisphere (Ferbert *et al.*, 1992). At rest, this scenario leads to a reduction of the amplitude of the motor evoked potential following the test stimulus, which has been interpreted to result from transcallosal inhibitory influences induced by the conditioning pulse applied over the other hemisphere. In healthy subjects, these inhibitory effects at rest turn into facilitation when the subject prepares a hand movement just a few milliseconds before the movement starts (Murase *et al.*, 2004). Such facilitatory effects between the hemispheres are believed to support accurate motor control underlying lateralized voluntary movements. In contrast, patients with motor deficits do not show this release of inter-hemispheric inhibition for movements of the stroke affected hand, but rather a persistent inhibitory influence on ipsilesional M1 (Murase *et al.*, 2004). Similar to the findings of the

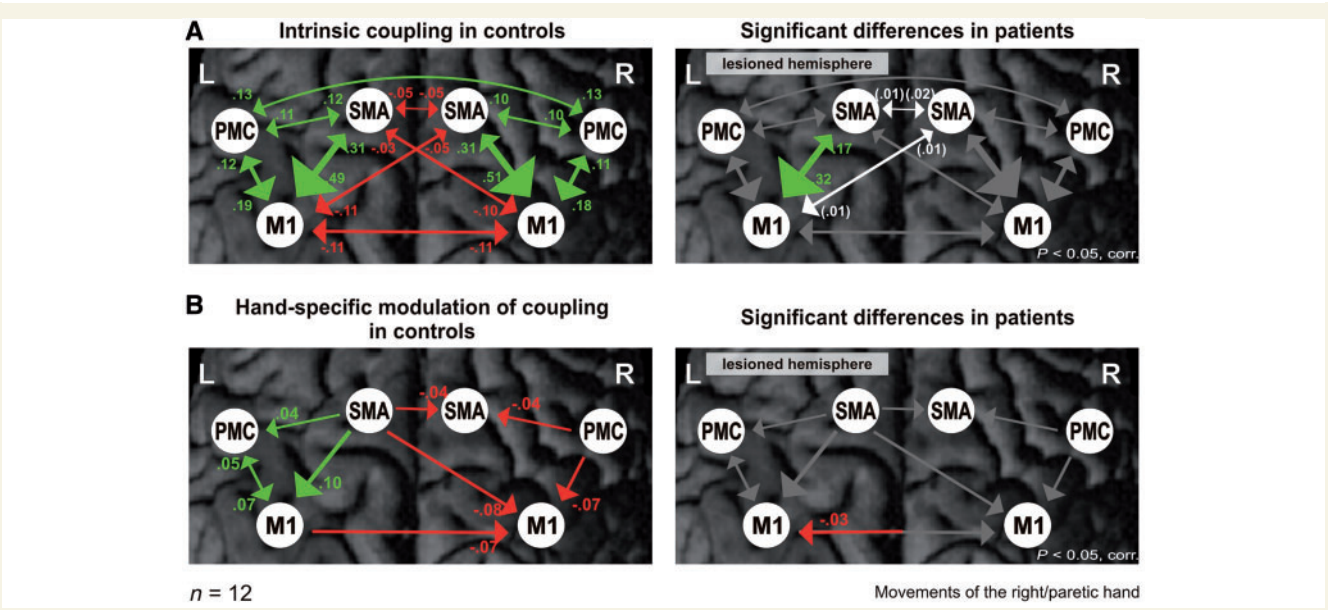

Figure 2 Connectivity among motor regions in healthy subjects and patients with hemiparesis caused by subcortical stroke. Coupling parameters (rate constants in 1/s) indicate connection strength, which is also coded in the size and colour of the arrows representing effective connectivity. Positive (green) values represent facilitatory, negative (red) values inhibitory influences on neuronal activity. The greater the absolute value, the more predominant the effect one area has over another. (**A**) Neural coupling in healthy subjects. In healthy subjects, the intrinsic coupling of motor areas is well balanced within and across hemispheres, while movements of the right hand induce a hemispheric-specific modulation of inter-regional coupling. (**B**) Significant changes of coupling parameters in stroke patients. Grey arrows denote no significant difference to healthy control subjects, while white arrows indicate a loss of coupling in the patient group. Patients with subcortical stroke show a significant reduction in intrinsic SMA-M1 coupling in the lesioned hemisphere, and a decoupling of ipsilesional areas from contralesional SMA (white arrows). Movements of the paretic hand are associated with a pathological inhibition of ipsilesional M1 exerted by contralesional M1, which does not occur in healthy subjects and correlates with the motor deficit of the paretic hand (adapted from Grefkes *et al.*, 2008*b*, with permission). PMC = ventral premotor cortex

dynamic causal modelling analyses, these pathological effects were especially present in patients with stronger deficits, and might hence contribute to the reduced performance of the stroke-affected hand (Murase *et al.*, 2004; Duque *et al.*, 2005). However, whether and to what extent pathological TMS-inter-hemispheric inhibition is related to pathological M1–M1 couplings, as demonstrated by dynamic causal modelling, remains to be further elucidated in future studies.

Analyses of effective connectivity also identified altered couplings of cortical areas in stroke patients during motor imagery. Sharma *et al.* (2009) investigated well recovered stroke patients performing a motor imagery task, and found no difference in regional blood oxygen level-dependent activity compared with healthy controls. In contrast, effective connectivity analyses by means of structural equation modelling revealed that neural coupling within an extended motor network was abnormal in the patients' group. Here, patients showed abnormally enhanced effective connectivity between both ipsilesional prefrontal cortex and ipsilesional SMA, and between ipsilesional prefrontal cortex and lateral premotor cortex. Sharma *et al.* (2009) also reported significantly weaker couplings among SMA and lateral premotor cortex, which correlated with the degree of motor impairment. The authors suggested that enhanced coupling of premotor areas with prefrontal areas might reflect cortical reorganization processes facilitating movement planning to overcome the functional deficits caused by the damage to the central motor pathways (Sharma *et al.*, 2009). Interestingly, the 'classical' analysis of the regional blood oxygen level-dependent signal in that study did not reveal pathological differences between patients and controls. Hence, analyses of connectivity may detect stroke-induced pathological changes of neural activity in motor-related cortical networks with higher sensitivity than conventional analyses of neuroimaging data.

Synopsis of stroke-induced changes in connectivity

The connectivity studies reviewed here consistently demonstrated system-wide network disturbances following stroke. Depending on lesion location, stroke-induced malfunction of a brain region may spread to undamaged areas connected to that node in both hemispheres (Honey and Sporns, 2008; Alstott *et al.*, 2009; Crofts and Higham, 2009; Nomura *et al.*, 2010). Enhanced inter-hemispheric coupling between homotopical areas seems to be a common feature of reorganized resting-state networks after stroke (He *et al.*, 2007; Warren *et al.*, 2009; van Meer *et al.*, 2010;

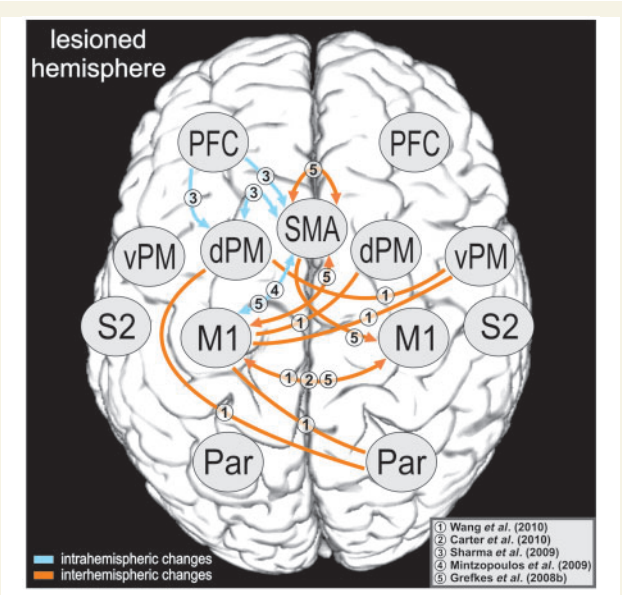

Figure 3 Synopsis of altered connectivity between cortical areas after stroke. To date, five studies have reported changes in cortical connectivity in patients suffering from motor deficits after stroke. The figure summarizes those regions that were included in the respective connectivity models: primary motor cortex (M1), dorsal and ventral premotor cortex (dPM, vPM), supplementary motor area (SMA), parietal cortex (PAR, including postcentral gyrus), secondary somatosensory cortex (S2) and prefrontal cortex (PFC). Among these regions of interest, a number of intra-hemispheric (blue-coloured) and inter-hemispheric (orange-coloured) connections were identified to be altered in stroke patients and/or to correlate with motor symptoms. Numbers on connections refer to the publication in which a change in neural coupling was reported. Arrow heads were added to the connections whenever directional information was available (i.e. in studies assessing effective connectivity). Strongest convergence across studies was found for the inter-hemispheric interactions between the primary motor cortices.

Wang *et al.*, 2010), but is often paralleled by a reduced network efficiency in these patients (De Vico Fallani *et al.*, 2009; Wang *et al.*, 2010). This conclusion is supported by studies investigating effective connectivity in the motor system that demonstrated reduced (and presumably less effective) coupling among different premotor regions (Sharma *et al.*, 2009) or between SMA and M1 (Grefkes *et al.*, 2008*b*) during finger/hand movements.

The limited number of studies published thus far on the topic of altered functional/effective connectivity in stroke is methodologically too heterogeneous to allow for a statistically founded meta-analysis. We rather provide a tentative synopsis (Fig. 3) that demonstrates which connections showed stroke-related changes in one or more of the hitherto published functional MRI studies on functional or effective connectivity of the cortical motor system. Note that the respective studies vary in tasks, regions of interests and model of connectivity. Nevertheless, this synopsis shows that a relatively large number of ipsilesional and contralesional interactions are altered in stroke patients suffering from motor deficits. In the ipsilesional hemisphere, basically all stages of the extended motor network, including prefrontal areas down to the primary motor cortex, may show changes in (effective) connectivity after stroke. The figure also shows that inter-hemispheric interactions seem to be altered after stroke, in particular those concerning ipsilesional M1. Here, strongest convergence across studies is found for the homotopic M1–M1 connection. However, while analyses of resting-state functional connectivity suggested enhanced inter-hemispheric positive coupling between these two regions (Carter *et al.*, 2010; Wang *et al.*, 2010), studies investigating activity-dependent effective connectivity reported no change in M1–M1 coupling (Sharma *et al.*, 2009) or even negative coupling suggesting inhibitory influences (Grefkes *et al.*, 2008). While discrepancies across studies might be due to differences in patient characteristics such as severity of residual deficits or time since stroke, they might also reflect fundamental differences in network dynamics between rest and activity. Functional coupling among neuronal populations changes as a function of processing demands, which implies that connectivity is context-dependent and dynamic (Stephan *et al.*, 2008). Therefore, to what degree stroke-induced changes in resting state networks are paralleled by changes in task-dependent effective connectivity must be elucidated in future studies.

Intervention effects on connectivity

Analyses of connectivity were also used to investigate the network effects of interventions aiming at restoring physiological patterns of inter-hemispheric interactions in order to promote recovery of motor functions (Hummel and Cohen, 2006; Grefkes and Fink, 2009). James *et al*. (2009) investigated the impact of 3 weeks of upper limb rehabilitation therapy on effective connectivity among motor areas in hemiparetic stroke patients (James *et al.*, 2009). Structural equation modelling of the resting state functional MRI data before and after therapy revealed a stronger influence of ipsilesional dorsal premotor cortex on its contralesional homologue, which was paralleled by improvements in behavioural performance. The finding that improvements in motor performance were associated with enhanced inter-hemispheric communication resembles those data discussed above for functional connectivity analyses (Carter *et al.*, 2010; van Meer *et al.*, 2010). Other strategies for improving motor performance in patients make use of brain stimulation techniques. For example, repetitive TMS protocols can be used to modulate cortical excitability with effects outlasting the end of the stimulation (Hummel *et al.*, 2005). Depending on pulse frequency, cortical excitability underneath the TMS coil can be increased (e.g. with frequencies between 5 and 20 Hz) or decreased (e.g. with frequencies ~1 Hz). Nevertheless, repetitive TMS applied over M1 does not only evoke metabolic changes in cortex underneath the stimulation coil, but also in brain regions interconnected with the stimulation site (Chouinard *et al.*, 2003; Lee *et al.*, 2003; Bestmann *et al.*, 2005). Chouinard *et al*. (2006) demonstrated that in chronic stroke patients, 3 weeks of upper limb rehabilitation therapy

modulates the neural responses of the cingulate motor area and subcortical regions following repetitive TMS over ipsi- or contralesional M1, especially in patients with good therapy response. The network effects of such brain stimulation techniques can be investigated with analyses of connectivity. Polania *et al*. (2010) used EEG to investigate the network effects of anodal transcranial direct current stimulation applied over M1 in healthy subjects. In addition to significantly increased functional connectivity within premotor cortex, M1 and other sensorimotor areas of the stimulated hemisphere, the authors also observed inter-hemispheric connectivity changes for all studied frequency bands. These results demonstrate that stimulating a certain anatomical region may have system-wide consequences in neural processing. Also, studies on effective connectivity converge with these data since they demonstrated remote effects of focal non-invasive stimulation. For example, inhibitory repetitive TMS applied over the contralesional M1 was associated with a significant reduction of pathological coupling between contra- and ipsilesional M1 compared with a repetitive TMS control stimulation site (Grefkes *et al.*, 2010*a*). In addition, neural coupling between ipsilesional SMA and ipsilesional M1 was significantly enhanced after repetitive TMS applied over contralesional M1, and the increase in coupling correlated with the increase in motor performance of the paretic hand (Grefkes *et al.*, 2010*a*). Hence, a focal stimulation by means of TMS does not only alter connectivity of the region stimulated, but also of areas distant to the stimulation site. This also implies that behavioural effects evolving after stimulation are based on a remodelling of the whole network rather than being caused by excitability changes of a single motor region. In particular, a more effective integration of ipsilesional M1 into the motor network architecture might constitute a key factor for improving motor performance of stroke patients by means of repetitive TMS (Grefkes *et al.*, 2010*a*). Such a conclusion is in line with the observation that spontaneous recovery over time is associated with increased connectivity of ipsilesional M1 in resting state functional MRI analyses (Wang *et al.*, 2010).

Conclusions

A connectivity-based approach of analysing functional imaging data allows hypothesis-driven investigations of the interactions among brain regions under physiological and pathological conditions. In contrast to 'classical' voxel-wise analyses of functional MRI data applying *t*-statistics to localize neural activity, models of connectivity make use of a network perspective in which the change of neural activity of a given brain region is explained by interactions with other brain regions. Network disturbances were also reported for a number of other neurological and psychiatric conditions (Bassett and Bullmore, 2009). For example, deficits in attentional modulation of motor performance in patients with Parkinson's disease were found to be associated with reduced effective connectivity between prefrontal cortex and premotor areas (Rowe *et al.*, 2002). Network topology in patients suffering from brain tumours were reported to be close to a random (i.e. less efficient) configuration (Bartolomei *et al.*, 2006). Likewise, disruptions of the small-world topology of brain networks were found in patients suffering from Alzheimer's disease (Stam *et al.*, 2007), schizophrenia (Liu *et al.*, 2008) and even in normal ageing (Achard and Bullmore, 2007). By showing how damage to a certain brain region affects system-wide connectivity, we can learn something about the intrinsic architecture of cortical circuits engaged in sensory, motor or cognitive functions (Nomura *et al*., 2010). Taken together, the connectivity data obtained in different clinical states support the hypothesis that one key principle governing physiological brain function is economical information exchange, which is achieved in a small-world topology supporting efficient parallel information transfer at relatively low wiring cost (Achard and Bullmore, 2007). The finding that normal ageing interferes with network topology may help to explain why network disturbance after stroke may have stronger clinical impact and less potential of recovery in older subjects compared with younger subjects.

Stroke and other neurological diseases typically affect the entire 'brain' system, and hence a network approach is likely to be better suited to investigate the pathophysiology underlying neurological deficits in the diseased brain than conventional functional MRI studies. To date, much of the neurobiological mechanisms leading to changes in cortical connectivity after stroke remain to be elucidated. Likewise, longitudinal studies employing different modalities covering the whole period from early post-ischaemic changes to the chronic stage are needed to further our understanding of how pathological interactions among brain areas develop after stroke and how they relate to neurological deficits and clinical outcome. Analyses of connectivity may offer new insights into the pathophysiology underlying stroke-induced neurological symptoms. Such information may help to decide when intervention therapies targeting the motor network should be performed to enhance motor recovery in patients.

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