BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

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

Christian Grefkes1,2 and Gereon R. Fink2,3

1 Neuromodulation and Neurorehabilitation, Max Planck Institute for Neurological Research, Gleueler Street 50, 50931 Köln, Germany
2 Department of Neurology, University Hospital Cologne, Kerpener Straße 62, 50937 Köln, Germany
3 Cognitive Neurology Section, Institute of Neuroscience and Medicine (INM-3), Research Centre Jülich, Leo-Brand-Straße 1, 52425 Jülich, Germany

Correspondence to: Dr Christian Grefkes,
Department of Neurology,
University Hospital Cologne,
Kerpener Straße 62,
50937 Cologne, Germany.
E-mail: christian.grefkes@uk-koeln.de

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...
Reorganization of cerebral networks after stroke

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, 2002a). 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). Offried 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, 2002a). 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., 2010b). 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 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.

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 (= contralateral) motor areas, which were absent in the healthy controls (A) or when moving the unaffected hand (B) (adapted from Grefkes et al., 2008b; with permission).
coordinating cross-neuronal interactions (Llinas et al., 1999; Buzsáki 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 homeostasis 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 (Erdős 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, 2002b; 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 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., 2007b). 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., 2004a; 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., 2004a). 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
prestroke returns to levels similar to those observed in healthy in both hemispheres, and then over the first 12 months
chaemia, neural activity is often enhanced in motor-related areas
Longitudinal functional MRI studies revealed that early after is-
2003; Gerloff
et al.
reported for the language domain in patients with aphasia (Saur
abnormal cortical activation patterns in the subacute to chronic
and physical therapy (Kwakkel
et al.
). Since in dynamic
causal modelling, the haemodynamic response function param-
eters are estimated individually for each region (Friston
et al.,
2003; Stephan
et al.,
2007a), deviations from the standard canon-
cal response, e.g. due to pathology affecting blood flow param-
eters, 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 prob-
lematic 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.,
2004b).
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 param-
eters 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 neuroima-
ging 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.,
2008b).
Longitudinal functional MRI studies revealed that early after is-
chaemia, 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.
(2002a) have demonstrated that training-induced improve-
ments in motor performance in chronic stroke patients (i.e. pa-
ients 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 hemi-
sphere may lead to a deterioration of motor performance in stroke
patients, but not in healthy controls (Johansen-Berg
et al.,
2002b;
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 recov-
ery 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 improve-
ment 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 con-
tralesional 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 con-
tralesional 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 con-
trolling 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 ex-
ample, 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 substi-
tute 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 SI 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).
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., 2008a). 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 cortico-cortical connectivity within and across hemispheres (Grefkes et al., 2008b). 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., 2008b). 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
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-interhemispheric 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;
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

---

**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.
modulates the neural responses of the cingulate motor area and subcortical regions following repetitive TMS over ipsi- or contral- sional M1, especially in patients with good therapy response. The network effects of such brain stimulation techniques can be inves- tigated 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 pre- motor cortex, M1 and other sensorimotor areas of the stimulated hemisphere, the authors also observed inter-hemispheric connectiv- ity changes for all studied frequency bands. These results demon- strate 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 demon- strated 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., 2010a). 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., 2010a). 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., 2010a). 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 condi- tions. 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, disrup- tions 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 cer- tain 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 prin- ciple governing physiological brain function is economical informa- tion 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 elu- cipated. Likewise, longitudinal studies employing different modalities covering the whole period from early post-ictal 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 symp- toms. Such information may help to decide when intervention therapies targeting the motor network should be performed to enhance motor recovery in patients.

References

Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. PLoS Comput Biol 2007; 3: e17.
Alstott J, Breakspear M, Hagmann P, Cammoun L, Sporns O. Modeling the impact of lesions in the human brain. PLoS Comput Biol 2009; 5: e1000408.
Bassett DS, Bullmore E. Small-world brain networks. Neuroscientist 2006; 12: 512–23.
Bartolomei F, Bosma I, Klein M, Baayen JC, Reijneveld JC, Postma TJ, et al. How do brain tumors alter functional connectivity? A magne- toencephalography study. Ann Neurol 2006; 59: 128–38.
Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Framh J. BOLD MRI responses to repetitive TMS over human dorsal premotor cortex. Neuroimage 2005; 28: 22–9.
Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Mag Res Med 1995; 34: 537–41.
Bollabas B. Random graphs. London: Academic Press; 1985.
Box GEP, Draper NR. Empirical model-building and response surfaces. Wiley: New York; 1987.
Breakspear M, Terry JR, Friston KJ. Modulation of excitatory synaptic coupling facilitates synchronization and complex dynamics in a bio- physical model of neuronal dynamics. Network 2003; 14: 703–32.
Brodmann K. Vergleichende Lokalisationslehre der Großhirrinde. Leipzig: Barth; 1909.
Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 2009; 10: 186–98.

Burge J, Lane T, Link H, Qiu S, Clark VP. Discrete dynamic Bayesian network analysis of fMRI data. Hum Brain Mapp 2009; 30: 122–37.

Buxton RB, Wong EC, Frank LR. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magn Reson Med 1998; 39: 855–64.

Buzsaki G, Draguhn A. Neuronal oscillations in cortical networks. Science 2004; 304: 1926–9.

Carter AR, Astafev SV, Lang CE, Connor LT, Renganachy J, Strube MJ, et al. Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. Ann Neurol 2010; 67: 365–75.

Chollet F, DiPiero V, Wise RJ, Brooks DJ, Dolan RJ, Frackowiak RS. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann Neurol 1991; 29: 63–71.

Chouinard PA, Leonard G, Paus T. Changes in effective connectivity of the primary motor cortex in stroke patients after rehabilitative therapy. Exp Neurol 2006; 201: 375–87.

Chouinard PA, Van Der Werf YD, Leonard G, Paus T. Modulating neural networks with transcranial magnetic stimulation applied over the dorsal premotor and primary motor cortices. J Neurophysiol 2003; 90: 1071–83.

Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A. Neural basis and recovery of spatial attention deficits in spatial neglect. Nat Neurosci 2005; 8: 1603–10.

Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. Ann Neurol 2008; 63: 272–87.

Crofts JJ, Higham DJ. A weighted communicability measure applied to complex brain networks. J R Soc Interface 2009; 6: 411–4.

David O, Cosmelli D, Friston KJ. Evaluation of different measures of functional connectivity using a neural mass model. Neuroimage 2004; 21: 659–73.

David O, Guillamein I, Saillet S, Reyt S, Deransart C, Segebarth C, et al. Identifying neural drivers with functional MRI: an electrophysiological validation. PLoS Biol 2008; 6: 2683–97.

De Vico Fallani F, Astolfi L, Cincotti F, Mattia D, la RD, Maksuti E, et al. Evaluation of the brain network organization from EEG signals: a preliminary evidence in stroke patient. Anat Rec 2009; 292: 2023–31.

Dong Y, Fukuyama H, Nabatame H, Yamauchi H, Shibasaki H, Yonekura Y. Assessment of benzodiazepine receptors using 17-2 labeled iodomazain single-photon emission computed tomography in patients with ischemic cerebrovascular disease. A comparison with PET study. Stroke 1997; 28: 1776–82.

Dum RP, Strick PL. Motor areas in the frontal lobe of the primate. Exp Neurol 2006; 201: 375–87.

Feldman EL, Grafton ST, Conture EG, Thompson KK, Kherif F, Numminen J, et al. Functional organization and plasticity within the human motor system. J Neurosci 2007; 27: 1407–16.

Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007; 8: 700–11.

Fridman EA, Hanakawa T, Chung M, Hummel F, Leiguarda R, Cohen LG. Reorganization of human premotor cortex after stroke recovery. Brain 2004; 127: 747–58.

Friston K. Beyond phrenology: what can neuroimaging tell us about distributed circuitry? Ann Rev Neurosci 2002a; 25: 221–50.

Friston K. Dynamic causal modeling and Granger causality. Comments on: The identification of interacting networks in the brain using fMRI: Model selection, causality and deconvolution. Neuroimage 2009; doi:10.1016/j.neuroimage.2009.09.031.

Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 1994; 2: 56–78.

Friston KJ. Statistics I: Experimental design and statistical parametric mapping. In: Toga AW, Mazziotta JC, editors. Human brain function. San Diego: Academic Press; 2002b. p. 605–32.

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 1997; 6: 218–29.

Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab 1993; 13: 5–14.

Friston KJ, Harrison L, Penny W. Dynamic causal modelling. Neuroimage 2003; 19: 1273–302.

Gee DG, Biswal BB, Kelly C, Stark DE, Margulies DS, Shehzad Z, et al. Low frequency fluctuations reveal integrated and segregated processing among the cerebral hemispheres. Neuroimage 2011; 54: 517–27.

Gerloff C, Bushara K, Sailer A, Wassermann EM, Chen R, Matsuoka T, et al. Multimodal imaging of brain reorganization in motor areas of the contralateral hemisphere of well recovered patients after capsular stroke. Brain 2006; 129: 791–808.

Grefkes C, Eickhoff SB, Nowak DA, Dafotakis M, Fink GR. Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. Neuroimage 2008a; 41: 1382–94.

Grefkes C, Fink GR. Functional Neuroimaging and Neuromodulation: Effects of Transcranial Magnetic Stimulation on Cortical Networks in Healthy Subjects and Patients. Clin Neurophysiol 2009; 40: 239–47.

Grefkes C, Nowak DA, Eickhoff SB, Dafotakis M, Kust J, Karbe H, et al. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. Ann Neurol 2008b; 63: 236–46.

Grefkes C, Nowak DA, Wang LE, Dafotakis M, Eickhoff SB, Fink GR. Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. Neuroimage 2010a; 50: 234–43.

Grefkes C, Wang LE, Eickhoff SB, Fink GR. Noradrenergic modulation of cortical networks engaged in visuomotor processing. Cereb Cortex 2010b; 20: 783–97.

Hallett M. Transcranial magnetic stimulation and the human brain. Nature 2000; 406: 147–50.

He BJ, Snyder AZ, Vincent JL, Epstein A, Shulman GL, Corbetta M. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 2007; 53: 905–18.

Hoerzer GM, Liebe S, Schloegl A, Logothetis NK, Rainer G. Directed coupling in local field potentials of macaque v4 during visual short-term memory revealed by multivariate autoregressive models. Front Comput Neurosci 2010; 4: 14.

Honey CJ, Sporns O. Dynamical consequences of lesions in cortical networks. Hum Brain Mapp 2008; 29: 802–9.

Horwitz B, Rumsey JM, Donohue BC. Functional connectivity of the angular gyrus in normal reading and dyslexia. Proc Natl Acad Sci USA 1998; 95: 8939–44.

Hummel F, Celnik P, Giraux P, Fioel A, Wu WH, Gerloff C, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain 2005; 128: 490–9.
Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol 2006; 5: 708–12.

James GA, Lu ZL, VanMeter JW, Sathian K, Hu XP, Butler AJ. Changes in resting state effective connectivity in the motor network following rehabilitation of upper extremity poststroke paresis. Top Stroke Rehabil 2009; 16: 270–81.

Johansen-Berg H, Dawes H, Guy C, Smith SM, Wade DT, Matthews PM. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. Brain 2002a; 125: 2731–42.

Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. The role of ipsilateral premotor cortex in hand movement after stroke. Proc Natl Acad Sci USA 2002b; 99: 14518–23.

Kazantzis VB, Nekorkin VI, Makarenko VI, Llinas RR. Olivo-cerebellar cluster-based universal control system. Proc Natl Acad Sci USA 2003; 100: 13064–8.

Kinsbourne M. Hemi-neglect and hemisphere rivalry. In: Weinstein EA, Rpr, editor. Hemi-inattention and hemisphere specializa-

Kinsbourne M. From unilateral neglect to the brain basis of conscious-

Kwakkel G, Kollen BJ, Wagenaar RC. Long term effects of intensity of upper and lower limb training after stroke: a randomised trial. J Neurol Neurosurg Psychiatry 2002; 72: 473–9.

Kwan LT, Reed BR, Eberling JL, Schuff N, Tanabe J, Norman D, et al. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. Brain 2002a; 125: 2731–42.

Liu Y, Liang M, Zhou Y, He Y, Hao Y, Song M, et al. Disrupted small-world networks in schizophrenia. Brain 2008; 131: 945–61.

Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syn-

Logothetis NK, Kayser A, Frith C, Bressler SL, Lebedev MA, Grechko AV, et al. Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. J Neurosci 2003; 23: 5308–17.

Liu Y, Liao M, Zhou Y, He Y, Hao Y, Song M, et al. Disrupted small-world networks in schizophrenia. Brain 2008; 131: 945–61.

Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syn-

Logothetis NK, Kayser A, Oeltermann A. In vivo measurement of cortical connectivity in the macaque monkey. Proc Natl Acad Sci USA 1999; 96: 15222–7.

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Muraue N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Murase N, Duque J, Mazocchio R, Cohen LG. Influence of interhemi-

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005; 64: 1802–4.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.
Stephan KE, Fink GR, Marshall JC. Mechanisms of hemispheric specialization: insights from analyses of connectivity. Neuropsychologia 2007a; 45: 209–28.

Stephan KE, Harrison LM, Kiebel SJ, David O, Penny WD, Friston KJ. Dynamic causal models of neural system dynamics: current state and future extensions. J Biosci 2007b; 32: 129–44.

Stephan KE. On the role of general system theory for functional neuroimaging. J Anat 2004; 205: 443–70.

Stephan KE, Kasper L, Harrison LM, Daunizeau J, den Ouden HE, Breakspear M, et al. Nonlinear dynamic causal models for fMRI. Neuroimage 2008; 42: 649–62.

Stephan KE, Weiskopf N, Drysdale PM, Robinson PA, Friston KJ. Comparing hemodynamic models with DCM. Neuroimage 2007; 38: 387–401.

Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. Brain 2007; 130: 170–80.

Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke 2005; 36: 2681–6.

Talelli P, Greenwood RJ, Rothwell JC. Arm function after stroke: neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. Clin Neurophysiol 2008; 117: 1641–59.

Tombari D, Loubinoux I, Pariente J, Gerdelat A, Albucher JF, Tardy J, et al. A longitudinal fMRI study: in recovering and then in clinically stable sub-cortical stroke patients. Neuroimage 2004; 23: 827–39.

Turrigiano G. Homeostatic signaling: the positive side of negative feedback. Curr Opin Neurobiol 2007; 17: 318–24.

van Meer MP, van der Marel K, Wang K, Otte WM, El BS, Roeling TA, et al. Recovery of sensorimotor function after experimental stroke correlates with restoration of resting-state interhemispheric functional connectivity. J Neurosci 2010; 30: 3964–72.

von Monakow C. Die Lokalisation im Grosshirn und der Abbau der Funktion durch kortikale Herde. Wiesbaden/Germany: JF Bergmann; 1914.

Wang L, Yu C, Chen H, Qin W, He Y, Fan F, et al. Dynamic functional reorganization of the motor execution network after stroke. Brain 2010; 133: 1224–38.

Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain 2003; 126: 2476–96.

Ward NS, Newton JM, Swayne OB, Lee L, Thompson AJ, Greenwood RJ, et al. Motor system activation after subcortical stroke depends on corticospinal system integrity. Brain 2006; 129: 809–19.

Warren JE, Crinion JT, Lambon Ralph MA, Wise RJ. Anterior temporal lobe connectivity correlates with functional outcome after aphasic stroke. Brain 2009; 132: 3428–42.

Watts DJ, Strogatz SH. Collective dynamics of ‘small-world’ networks. Nature 1998; 393: 440–2.

Weiller C, Chollet F, Friston KJ, Wise RJ, Frackowiak RS. Functional reorganization of the brain in recovery from striatocapsular infarction in man. Ann Neurol 1992; 31: 463–72.

Yamamoto S, Takasawa M, Kajiyama K, Baron JC, Yamaguchi T. Deterioration of hemiparesis after recurrent stroke in the unaffected hemisphere: Three further cases with possible interpretation. Cerebrovasc Dis 2007; 23: 35–9.